Published in final edited form as:

Mol Biosyst. 2016 July 19; 12(8): 2318–2341. doi:10.1039/c6mb00240d.

Molecular and Genetic Inflammation Networks in Major Human Diseases

Yongzhong Zhao^{1,2}, Christian V. Forst^{1,2}, Camil E. Sayegh³, I-Ming Wang^{4,*}, Xia Yang^{5,*}, and Bin Zhang^{1,2,*}

¹Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, 1425 Madison Avenue, NY 10029, USA

²Institute of Genomics and Multiscale Biology, Mount Sinai School of Medicine, 1425 Madison Avenue, NY10029, USA

³Vertex Pharmaceuticals (Canada) Incorporated, 275 Armand-Frappier, Laval, Quebec, H7V 4A7

⁴Informatics and Analysis, Merck Research Laboratories, Merck & Co., Inc., 770 Sumneytown Pike, West Point, PA 19486, USA.

⁵Department of Integrative Biology and Physiology, University of California, Los Angeles, CA 90025, USA

Abstract

It has been well-recognized that inflammation alongside tissue repair and damage maintaining tissue homeostasis determines the initiation and progression of complex diseases. Albeit with the accomplishment of having captured most critical inflammation involved molecules, genetic susceptibilities, epigenetic factors, and environmental exposures, our schemata on role of inflammation in complex disease, remain largely patchy, in part due to the success of reductionism in terms of research methodology per se. Omics data alongside the advances in data integration technologies have enabled reconstruction of molecular and genetic inflammation networks which shed light on the underlying pathophysiology of complex diseases or clinical conditions. Given the proven beneficial role of anti-inflammation in coronary heart disease as well as other complex diseases and immunotherapy as a revolutionary transition in oncology, it becomes timely to review our current understanding of the inflammation molecular and genetic networks underlying major human diseases. In this Review, we first briefly discuss the complexity of infectious diseases and then highlight recently uncovered molecular and genetic inflammation networks in other major human diseases including obesity, type II diabetes, coronary heart disease, late onset Alzheimer Disease, Parkinson disease, and sporadic cancer. The commonality and specificity of these molecular networks are addressed in the context of genetics based on genome-wide association study (GWAS). The double-sword role of inflammation, such as how the aberrant type 1 and/or

*Correspondence to bin.zhang@mssm.edu, xyang123@ucla.edu or i_ming_wang@merck.com.

Author Contributions Statement

BZ, XY and IMW conceived the idea. BZ, CF, XY, YZ and IMW collected the data, BZ, XY, CES, CF, YZ and IMW wrote the manuscript together. All authors read, edited and approved the final manuscript.

Additional Information

The authors have no competing financial interests.

type 2 immunity leads to chronic and severe clinical conditions, remains open in terms of the inflammasome and the core inflammatome network features. Increasingly available large Omics and clinical data in tandem with systems biology approaches have offered an exciting yet challenging opportunity toward reconstruction of more comprehensive and dynamic molecular and genetic inflammation networks, which hold a great promise in transiting network snapshots to video-style multi-scale interplays of disease mechanisms, in turn leading to effective clinical intervening.

Keywords

complex disease; inflammation; immune response; systems biology; genome-wide association; gene coexpression network; gene regulatory networks; gene signature; gene networks; obesity; diabetes; coronary heart disease; Alzheimer Disease; Parkinson disease; cancer

Introduction

A vast majority of human diseases fall into the complex diseases categories, which are caused by a combination of genetic, epigenetic, and environmental exposure, most of which yet to be identified elaborately. Most common life-threatening and life-quality-impact diseases or clinical conditions, including obesity (OB), Type 2 diabetes mellitus (T2DM), coronary heart disease (CHD), Alzheimer's disease (AD) and Parkinson's disease (PD), and cancer fully meet the criteria of the definition of complex disease, which in general does not obey the standard Mendelian patterns of inheritance but can be studied by a means of genetic predisposition such as genome-wide association study (GWAS).

The progress of these complex disease phenotypes depends largely on environmental exposure and lifestyle. Thus, the interplay between gene products/by-products and environmental exposure at the molecular level is a general scenario underlying complex diseases. Naturally, such interplays invoke inflammation, which comes from the Latin “*inflammo*”, meaning “*I set alight, I ignite*”. Inflammation, part of the body's immune response, is beneficial initially but can become self-perpetuating as more inflammation is created in response to the existing inflammation. If not stopped, it becomes chronic inflammation, which is linked to complex diseases, e.g., plaque in AD and genome instability in tumor cells.

Vertebrates including humans deploy two types of immunity to defend themselves against two distinct types of ‘insult’, namely, the type 1 – invasion of rapidly replicating microorganisms, such as bacteria, viruses, protozoa and fungi, and the type 2 – breach of the protective barriers of the body by physical trauma. For the first scenario, an antimicrobial type 1 immune response characterized by the T helper 1 (TH1) cell-associated cytokines interferon- γ and interleukin-12 (IL-12) is invoked, and is directed and enhanced through cytokines that are produced by TH1 and TH17 cells of the adaptive immune system; however, there is a risk leading to the induction of highly toxic antimicrobial products which are capable of damaging consequences for the host tissue. The Type 2 immunity involves innate immune cells, such as basophils, eosinophils, mast cells, M2 macrophages (also

known as alternatively activated macrophages) and group 2 innate lymphoid cells, with TH2 cells functioning as the central mediators of the adaptive immune response¹.

In-depth one-gene-one-protein-one-lab research has been offering great insights into such links. Encouragingly, recent technological advances have led to the generation of large amount of high throughput and high dimensional molecular data to study inflammation in a more systematic and comprehensive way²⁻⁴. Forward genetics discoveries have dissected pivotal genetic components, e.g., Mendelian disease genes⁵ and GWAS⁶ susceptibility genes. Both catalogs could provide meaningful targets for detailed molecular genetic explorations. Likewise, genome-wide expression studies (GWES) have revealed many molecular phenotypes that are directly linked to disease phenotypes⁷. Moreover, nuanced model based molecular studies that leverage diverse types of large scale molecular data have become available for modeling tissue-specific regulatory networks and pinpointing key regulators and have advanced our in-depth understanding of molecular mechanisms underlying disease progression⁸. These efforts have been driving an emerging network biology of complex diseases, in which pro-inflammatory response is of primary importance. Network biology aims to holistically reconstruct interactions, associations, or causal relationships among a large number of variables such as genes and proteins in biological processes, systems, or pathophysiologic states. As such, network biology has the potential to identify novel key variables and interacting pathways underlying a biological function, system or state under examination. As an example, the recently uncovered genome-wide genetic and transcriptomic data from brain tissues and demonstrated that an inflammation/microglial enriched subnetwork is most causally linked to AD and further validated that its key driver *TYROBP* was involved in amyloid- β (A β) turnover and neuronal damage⁹. Similarly, a causal role of a similar inflammation/macrophage enriched network in association with obesity and diabetes has been established and a number of key drivers of the network have been validated *in vivo*^{4,10,11}. Further, the study of the transcriptome of nine different tissues from eleven disease models revealed a shared inflammatome signature that appears to play causal roles in multiple diseases¹².

Infectious diseases remain a significant threat to human health and a major cause of death, especially in developing countries. The top three most challenging infectious diseases including AIDS, malaria and tuberculosis generate more than 235 million new cases and cause more than five million deaths per year¹³. Although effective therapeutics have been developed for the top three infectious diseases, there are issues in prevention, drug resistance and availability. Similar situations exist for other infectious diseases caused by respiratory syncytial virus (RSV)¹⁴, cytomegalovirus (CMV)¹⁵, dengue virus¹⁶, *Clostridium difficile* and *Staphylococcus aureus*¹⁷. Since the etiology of infectious diseases are known from the pathogen perspective, it has been crucial to elucidate the core component of the inflammation system by rigorous study infectious diseases especially with a means of focusing on host-pathogen interactions.

Here we review the mechanisms of inflammation in major human diseases including infectious disease, OB, T2DM, CHD, AD, PD, and CA in the context of molecular networks with identification of several big challenges in understanding the inflammation networks in complex diseases.

Recognition of pathogens by the innate immune system

The innate immune system plays an essential role in controlling pathogen infection and initiating specific adaptive immune response by recognizing microbial pathogen-associated molecular patterns (PAMPs) such as viral-/bacterial-nucleic acids and bacterial cell wall components¹⁸. Five main families of host germline-encoded pattern-recognition receptors (PRRs) have been identified including C-type lectin receptors (CLRs), nucleotide oligomerization and binding domain (NOD)-like receptors (NLRs), Pyrin-HIN (PYHIN) domain containing receptors (e.g. AIM2), retinoic acid inducible gene-I (RIG-I)-like receptors (RLRs), and Toll-like receptors (TLRs)¹⁹. These innate receptors closely interact with one another and many other signaling pathways (e.g. MAPK, NF- κ B and IRFs²⁰) including a recently found connection with autophagy, an eukaryotic pathway induced by PRRs to eliminate intracellular microorganisms²¹. An association between genetic variants in the regulatory region of parkin gene (*PARK2*), a ubiquitin ligase, and susceptibility to intracellular pathogen infection was established earlier²² and more recent data suggested that parkin actually plays a key role in mediating autophagy of *Mycobacterium tuberculosis* and perhaps other intracellular pathogens since mice deficient in *PARK2* are sensitive to various intracellular bacterial infections²³.

Close interactions between PRRs are further substantiated by the two-signal model mediated by TLRs and NLRs for the production of two of the most important pro-inflammatory cytokines, *IL-1 β* and *IL-18*. In this model, TLR agonists stimulate transcription whereas NLR agonists activate the inflammasome to release active *IL-1 β* and *IL-18*²⁴. For examples, *TLR2* signaling has been shown to activate inflammasome and release *IL-1 β* and *IL-18* in infection by RSV²⁵ and *Francisella novicida*²⁶ infection, respectively. In the former case, *NLRP3* gene expression was induced by RSV infection and two additional signals, potassium (K⁺) efflux and reactive oxygen species (ROS) were required subsequently to promote inflammasome activation for *IL-1 β* secretion. Negash AA et al.²⁷ found that HCV viral RNA induces TLR7 signaling and a potassium efflux to promote *IL-1 β* secretion via a *NLRP3*-containing inflammasome. By performing RNA sequencing analysis of liver from chronic hepatitis C patients and HCV-infected THP-1 macrophage cell line, they were able to show that intrahepatic *IL-1 β* production by macrophage modulates gene expression networks of proinflammatory mediators and is the key driver of liver inflammation.

In addition to detecting pathogen infection by PRRs, cells also express multiple antiviral restriction factors which could block virus replication at different stages and in response, many viruses develop a plethora of mechanisms to evade host detection²⁸. For examples, two genes or open reading frames (ORFs) encoded by varicella-zoster virus (VZV), *ORF47*²⁹ and *ORF61*³⁰, have been shown to interfere with the host innate immunity by inhibiting the activation of IRF3. Recently expression of many antiviral restriction factors such as *ADAR-1*, *APOBEC3*, *IFITM1/3*, *SAMHD1*, Tetherin and *TRIM5* were all down-regulated in VZV-infected MRC-5 cells (Wang IM et al. unpublished results). The type I interferon (IFN) family plays a key role in protecting cells from viral infection by stimulating hundreds of interferon-stimulated genes (ISGs)³¹. A lentiviral over-expression system was adopted to test the ability of more than 380 ISGs in inhibiting the replication of multiple important viruses and the results indicated *IRF-1*, *RIG-I/DDX58*, *MDA5/IFIH1*,

and *IFITM3* as being broadly acting inhibitors against multiple viruses whereas *DDX60*, *IFI6*, *IFITM2*, *OASL*, *TREX1* and *IFI44L* possess more targeted antiviral activity^{32,33}. Consistent with the above finding, Goulet et al.³³ showed that a synthetic *RIG-I* agonist activated inflammatory and interferon-stimulated genes including *IRF3*, *IRF7* and *STAT1* in human lung epithelial A549 cells and protected mice from a lethal challenge with H1N1 influenza virus at the picomolar range. This *RIG-I* specific effect offered partial protection from influenza-challenged mice in the absence of IFN signaling. Interestingly, a genome-wide RNAi screening using a similar lentiviral expression system described above identified a new negative regulatory role of virus-mediated innate immunity for the WNT/CTNNB1 signaling pathway³⁴. The information could be used for selecting broad-spectrum antiviral agents for preventing inflammatory diseases caused by viral infection.

Immune dysfunction caused by chronic viral infection

Chronic infection by viruses such as anellovirus, circovirus, adeno-associated virus (AAV), polyomavirus, different types of herpesviruses including HHV-6, HHV-7, varicella zoster virus (VZV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV) is common in humans. Some viruses infect more than 90% of the population surveyed and estimated at 8-12 chronic infections in each person³⁵. Most chronic infections mentioned above do not result in discernible disease, at least in healthy hosts but others such as papilloma virus, HBV, HCV and HIV could create a persistent low grade inflammation or immune dysfunction which predisposes susceptible hosts to other ailments including cardiovascular disease, type 2 diabetes³⁶ and cancer³⁷. Most discussion in this section will focus on HIV since it's one of the best characterized examples of chronic viral infection. Evidences accumulated from the past decade indicated that although AIDS-related symptoms are well under control and patients' life expectancies significantly prolonged since highly active anti-retroviral therapies (HAART) became available, patients' overall well-beings are still at risk with several complications reminiscent of aging. This is due to the latently-infected HIV which maintains a low-level systemic inflammation. To achieve a better life span and quality, novel treatment approaches targeting this chronic inflammation need to be in place³⁸.

Several key immune signaling pathways involved in shaping a normal physiological state are disrupted during viral infection. In the HIV-infected hosts, IFN signaling (and ISG genes), cell cycle and proteasome gene networks were perturbed but the transcriptome could be reverted in a way comparable to that of uninfected subjects with HAART treatment. By combining genome-wide gene expression and single-nucleotide polymorphism (SNP) data, it was found that expression of 190 genes was driven by cis-acting genetic variants or expression SNP (eSNP) and among them, one of the ISGs, *OAS1* was associated with viral load³⁹. *OAS1* is involved in the innate immunity against viral infection; genetic variants in *OAS1* have previously been shown to associate with controlling West Nile virus infection⁴⁰ and clinical outcome of dengue virus infection⁴¹.

Non-human primate (NHP) species such as sooty mangabey and African green monkeys are natural host for simian immunodeficiency viruses (SIV) and remain asymptomatic upon viral infection even in the presence of high viremia. In contrast, SIV-infected rhesus macaques, like HIV-infected humans, have depleted CD4⁺ T cells; elicit generalized

immune activation and develop AIDS⁴². Sooty mangabeys have substantially reduced levels of innate immune response upon SIV infection and their plasmacytoid dendritic cells (pDCs) produce significantly less type 1 IFN in response to SIV *in vivo* and TLR7/TLR9 ligands *in vitro*⁴³. Comprehensive transcriptome analysis of human rapid progressors (RPs) and nonprogressors (NPs) upon HIV infection showed a clear resemblance of RP gene signature to symptomatic SIV-infected rhesus macaques whereas NP signature was more similar to that of asymptomatic SIV-infected sooty mangabeys⁴⁴.

Veazey et al.⁴⁵ first indicated that gastrointestinal tract was enriched with CD4⁺ T cells but there was a profound and selective depletion of this cell population in rhesus macaques within days after SIV infection. It was later discovered that in both chronically HIV-infected human and SIV-infected rhesus macaques, circulating microbial products such as lipopolysaccharide (LPS), an agonist for TLR4, was significantly increased and correlated to levels of innate and adaptive immune response⁴⁶. These microbial products were derived from the gastrointestinal tract in a process called microbial translocation⁴⁷ due to damage in the gut epithelium caused only by the pathogenic infection since the process did not occur in nonpathogenic SIV infection of sooty mangabeys and could be partially reversed by antiretroviral therapy. Mucosal Th17 cell plays a key role in maintaining the integrity of gut epithelial barrier⁴⁸ but its number is reduced and function altered during HIV infection⁴⁹; however, in SIV-infected rhesus macaques, these abnormalities could be corrected by *IL-21* treatment⁵⁰. Using next-generation sequencing (NGS) in SIV-infected rhesus monkeys⁵¹ and high-resolution bacterial community profiling in HIV-infected humans⁵², it was found that pathogenic (but not nonpathogenic) SIV infection was correlated to a significant broadening of the enteric virome with 32 previously undocumented viruses confirmed by independent assays. In this case, no association was evident between the family-level of bacteria and pathogenic SIV infection⁵¹. In the HIV-infected patients, markers of chronic inflammation, T cell activation and disruption of mucosal immunity was associated with enriched Proteobacteria and depleted Bacteroidia members and the level of dysbiosis was proportional to two established disease progression markers, tryptophan catabolism and *IL-6*⁵². The different results

Functional virus-specific T cells are generated during the early stage of infection but they gradually lose their immune competence when the infection becomes chronic – a process termed T cell exhaustion⁵³. Several mechanisms for modulating immune response during chronic infections have been proposed based on results from high through-put genome-wide analysis. Gene expression of CD8 T cells derived from mice chronically infected with lymphocytic choriomeningitis virus (LCMV) was compared with normal functional CD8⁺ T cells and CD8⁺ T cells from acutely infected mice⁵⁴. The results indicated that expression of several inhibitory receptors including *PD-1*, *CTLA-4*, *2B4*, *CD160* and *LAG-3* were up-regulated by the exhausted T cells. *In vivo* administration of antibodies blocking the interaction of *PD-1* with its ligand, *PD-L1* decreased LCMV viral load and restored T-cell function of cytokine secretion, cell proliferation and cytotoxic capacity. Other significantly modulated pathways include T cell receptor signaling, cytokine signaling and chemotactic pathways as well as down-regulation of several metabolic and bioenergetics pathways. The finding was then extended to HIV-infected patients⁵⁵ and HCV-infected chimpanzees⁵⁶. *PD-1* was significantly up-regulated in CD8⁺ cells from HIV-infected humans and its expression level was positively correlated to viral load and negatively correlated to CD4⁺ T

cell count. Blocking *PD-1/PD-L1* interaction increased HIV-specific CD4 and CD8 function and improved disease outcome⁵⁵. In HCV-infected chimpanzees, *PD-1* blockade could reduce HCV viremia but the effect was more significant in animals with a broader T cell response to HCV.⁵⁶ It was proposed that *PD-1* immunotherapy could also be applied to treat other chronic viral infections such as hepatitis B virus and in fact, several anti-*PD-1*-related clinical programs are being actively pursued to treat multiple types of human cancers including melanoma, colon and lung cancer^{57,58}.

The profound change in the immune system caused by chronic pathogens such as HIV suggests the involvement of pleiotropic factors that affect immune cell life span, proliferation, differentiation and maturation. One such factor is *FOXO3a* which was originally characterized by an integrated transcriptomic, proteomic and functional analysis as being the key transcription factor involved in survival of central memory CD4+ T cells (Tcm)⁵⁹. Specifically, it was the phosphorylated and hence transcriptionally inactive form of FOXO3a which provided protection of Tcm from apoptosis. Roles of *FOXO3a* include transcriptional induction of pro-apoptotic⁶⁰, anti-proliferative genes⁶¹, genes regulate carbohydrate metabolism⁶² and reactive oxygen species (ROS)-related detoxification⁶³. It was subsequently demonstrated that down-regulation of *FOXO3a* either by small interfering RNA (siRNA) or by a dominant-negative form of *FOXO3a* could extend the life span of Tcm cells⁶⁴ and increased *FOXO3a* transcriptional activity resulted in a loss of memory B cells via *TRAIL*-mediated apoptosis⁶⁵. The immune dysfunction mediated by *FOXO3a* is reversible even after long-term infection so the pathway could be explored for the development of new therapeutics⁶⁶.

Host response to vaccination and infection

Significant progress in systems analysis of host response to vaccination and pathogen infection has been made in the past few years due to 1) the advancement in whole blood/leukocyte transcriptome analysis^{67, 68, 69, 70, 71, 72}; and 2) the availability of high-throughput technologies such as DNA microarray, single nucleotide polymorphism (SNP) profiling and next-generation sequencing (NGS)-based platforms^{73, 74, 75}. Instead of using single genes, an algorithm was developed by grouping co-expressed blood or PBMC genes from large disease data sets into modules which could be easily quantitated and used as potential biomarkers for predicting clinical outcomes such as antibody response^{76, 77}. Advantages of the module analysis approach include reduction of data dimensionality and facilitating data interpretation since each module usually is associated with a particular biological pathway or function. For example, with respect to *Staphylococcus aureus* infections, Banchereau et al.⁷⁷ were able to identify gene-network modules related to (i) neutrophil myeloid lineage inflammation, (ii) hematopoiesis cell cycle, and (ii) T-cell cytotoxicity lymphoid lineage that are correlated with clinical traits. The major transcriptional patterns identified included pro-inflammatory myeloid signature, linked to sampling early in the course of infection, high neutrophil and monocyte counts and elevated C-reactive protein. Inflammatory response, for example, is mediated by calmodulin B, interleukin and TLR signaling targeting NF- κ B and TNF α -mediated pro-inflammatory pathways.

Similar progress has been made with respect to cell-based model systems. In particular advancements in high-throughput RNAi screens are instrumental to decipher molecular host-pathogen interaction networks. Watanabe et al. compared published RNAi studies on host-factors required for influenza infections and identified 128 targets common between at least two of each screens⁷⁸. Novel host processes, such as, V-type ATPases important for endocytosis, *COPI* vesicular transport or the pre-mRNA splicing machinery with *PTBPI* and splicing factors *SF3A1/SF3B1* have been identified. Host-response is certainly gene-context dependent, as Ward et al. demonstrated with respect to influenza H1N1 infection. By combining RNAi screening data from influenza replication assays with cell viability data, Ward et al.⁷⁹ identified a pharmacologically addressable network involving cell cycle/DNA damage checkpoint protein *CHEK1*. Employing SB218078, an investigational *CHEK1* inhibitor, severely limited viral protein production in nontransformed bronchial epithelial cell lines at single cell resolution. Remarkably, SB218078 had no consequence on H1N1 replication in A549 cells, a cancer cell line often employed to test for modulators of viral replication and host responses (Figure 1A).

Another example of a cancer related molecular network relevant for infectious disease has been identified by Mata et al.⁸⁰ By chemical screening a class of naphthalimides has been identified that activates a novel host-defense factor *REDD1* (or *DDIT4*). When activated, *REDD1* inactivates the mTORC1 pathway which is required for viral replication, thus essentially preventing viral protein production (Figure 1B).

A web-based interactive software tool has been designed for data analysis/visualization and was applied for comparative analysis of two vaccines, the trivalent influenza vaccine (TIV) and 23-valent pneumococcal vaccine covering polysaccharide components from 23 most widely encountered strains of *Pneumococcus pneumoniae*⁸¹. More recently, Li et al.⁸² conducted a similar blood transcription module (BTM) analysis of five vaccines (yellow fever YF-17D, trivalent inactivated influenza virus [TIV], live attenuated influenza virus [LAIV], meningitis quadrivalent polysaccharide vaccine [MPSV4] and meningitis quadrivalent conjugate vaccine [MCV4-PS] which is conjugated to diphtheria toxoid [MCV4-DT]) in three different categories (naïve attenuated viral, recall peptide and anti-polysaccharide vaccines) by using an integrated large-scale network approach employing public human blood transcriptome data from 500 studies with more than 30,000 samples. The results indicated correlations between antibody titers and 1) type I interferon modules for YF-17D vaccine, 2) dendritic cell and complement activation modules for MCV4-PS and MPSV4, and 3) BCR signaling/plasma cells–immunoglobulins modules for peptide recall responses (i.e. TIV and MCV4-DT). These authors also identified previously unknown innate immune networks which should be further investigated to enhance our understanding of the vaccine response⁸³. The identification of genes such as *TLR5*, *CASPI*, *PYCARD*, *NOD2* and *NAIP* suggested previously unknown mechanistic links between host innate immunity and humoral responses. The implication from these analyses is that each category of vaccine induces immunogenicity by a different mode of action (MOA) and there is probably no consensus gene expression predictor for antibody response.

The inflammasome

Inflammasome is the signaling platform of the innate immune system that activates proinflammatory cytokines after microbial pathogens are sensed or sterile danger is detected. The kinases Syk and Jnk control inflammasome activation by mediating phosphorylation of the inflammasome adaptor ASC. Inflammasomes are large intracellular multiprotein complexes that control activation of the protease caspase-1, which in turn mediates the proteolytic maturation of the highly inflammatory cytokines *IL-1 β* and *IL-18*^{84,85}. Several types of inflammasomes have been identified that can respond to distinct bacterial, viral or fungal infections, to sterile cell damage or to other stressors such as metabolic imbalances. Inflammasomes are composed of a sensor (such as *NLRP3*, *AIM2* or *NLRC4*), the adaptor ASC and caspase-1. Whereas *NLRP3* and *AIM2* depend critically on *ASC* for engagement of caspase-1, the inflammasome sensor *NLRC4* can directly interact with caspase-1. The regulated activation of inflammasomes after microbial infection or injury is critical for the maintenance of tissue homeostasis, but deregulated inflammasome activity has emerged as a major contributor to the pathogenesis of prevalent diseases, including inflammatory bowel disease, coronary heart disease and cancer. Therefore, it is importance to understand how the activities of inflammasomes are regulated⁸⁶.

The core inflammatome

Given the inflammatory nature of many common chronic diseases, a recent study of multiple disease models further demonstrates that chronic diseases share a common inflammatome gene signature and network structure¹². Specifically, a representative gene signature was identified by an integrated analysis of 12 expression profiling data sets derived from 9 different tissues of 11 rodent inflammatory disease models. This “inflammatome” signature significantly overlaps with coexpressed gene modules linked to metabolic disorders, cancer, neuron-degenerative diseases. Moreover, the inflammatome signature is highly enriched for immune response-related genes tested causal for adiposity, adipokine, diabetes, aortic lesion, bone, muscle, and cholesterol traits, suggesting the causal nature of the inflammatome. Integration of this inflammatome signature and gene regulatory networks reconstructed based on multiple independent mouse and human cohorts uncovered a set of key regulators, which appeared to be more biologically important than the non-drivers in terms of the impact on mutant phenotypes. At the conceptual level, the inflammasome is distinct to the inflammatome as illustrated in **Fig. 2**. However, both substantially overlap with the innate immunity genes⁸⁷ (the statistical test result of the intersection of the three sets by SuperExactTest, $P=2.74E-33$). Further, whether such inflammation core gene sets are overlapped with infectious disease and complex disease signatures has been examined. For influenza virus related signatures, two gene sets were generated, one from a combined RNAi-screening data from six studies on host-factors required by the influenza virus for replication (I1)⁷⁸, and a consensus response of 487 (12, 73 up- and 414 down-regulated) genes inferred by an in-house integration of gene-expression profiles (GSE19392, GSE28166, GSE31524, GSE33142, GSE36555, GSE37571, GSE37951, GSE40844). **Fig.3** illustrates interested intersections among the GWAS gene sets of the six common complex diseases (OB, T2DM, CHD, PD, AD, CA)⁸⁸, the inflammatory gene signatures (the innate immunity and the inflammatome gene sets), and the two influenza signatures. Of

particularly interest, the I2 signature is significantly overlapped with the Inflammome and Innate Immunity sets ($P=5.40E-05$) involving eleven overlapped genes, *ABCA1*, *CCL5*, *CTSB*, *CXCL10*, *GRN*, *IFITM2*, *IFITM3*, *MYH9*, *OAS1*, *OAS2*, and *PRKCA*. Moreover, three genes, *AIG1*, *B2M*, *C21orf33* have been observed in the intersection of the inflammome, I1 and I2 ($P=4.10E-3$). Intriguingly, the *CDKN2A* gene is the element of innate immunity, CA, T2DM, as well as CHD. Eight genes, *NR*, *BMP4*, *SLC41A1*, *HLA*, *CNNM2*, *C10orf32*, *CYP17A1*, and *SFXN2*, consist of the intersection of CA and PD GWAS sets ($P=7.27E-05$). Meanwhile, there are fourteen genes, including *ADSS*, *BCAS3*, *SLC8A1*, *CNTNAP2*, *TTL7*, *RFC3*, *CSMD1*, *GPC6*, *HECW1*, *LIPC*, *MYO16*, *PLEKHG1*, *DYNC1I1*, and *SLCO3A1*, overlapped between AD and OB ($P=1.51E-05$). These data suggest the instrumental role of inflammation in the molecular and genetic pathogenesis of complex diseases connected by the inflammome. Further, **Fig. 4** shows a core gene causal network conserved across tissues and species and its key drivers. Highly consistent driver genes such as *HCK*, *CD53* and *TYROBP* have been found being involved in many inflammation-related disorders. The discovery of the data-driven “inflammome” gene signature and its corresponding regulatory networks provide a general framework to not only study the common mechanisms underlying complex chronic diseases but also identify key intervention points as therapeutic targets.

Molecular and genetic inflammation networks underlying complex metabolic diseases

In the context of metabolic disorders, inflammation is considered to be primarily induced by nutritional or metabolic perturbations and is of low-grade and chronic nature, in contrast to the strong and short-term classic inflammatory response associated with injury and infection. The metabolism-induced inflammation is attributable to the tight connection and coevolution between metabolism and immune systems, two fundamental and conserved mechanisms to ensure survival³⁶. When the delicate balance between the two processes is disrupted by nutrient overAD, as in the typical case of long-term consumption of high fat high fructose diet in the modern society, inflammatory processes enter the stage via mechanisms that are shared between nutrient sensing and the immune system in central metabolic tissues like white adipose tissue (WAT) and liver. Although conventionally perceived as an energy and fat storage tissue, WAT is also tightly connected to the immune system due to its ability to secrete adipokines with pro- or anti-inflammatory properties⁸⁹, presence of resident T cells regulating metabolic and inflammatory response^{90,91}, and accumulation of macrophage upon adipocyte expansion⁹².

In order to better understand the mechanisms of molecular processes involved in the onset of inflammation and the downstream events, major research efforts have been focused on investigating individual inflammatory mediators and their respective signaling pathways using classic molecular biology techniques. Such studies have provided strong evidence supporting the causal roles of cytokines, chemokines, and receptors such as tumor-necrosis factor alpha (TNF- α), interleukin 6 (IL6), interleukin 18 (IL18), and toll-like receptors (TLRs) in mediating metabolic cues such as lipid overAD in the WAT. The detailed inflammatory signaling cascades involved have been well illustrated and documented³⁶.

However, the complexity of metabolic disorders that involve multiple organ systems, tissue types, and multiple molecular pathways demand a systems view of how inflammation interplays with other processes throughout the organism to induce disease onset. In this section, we review the recent attempts to obtain such comprehensive views using integrative and systems biology approaches that involve objective screening of tissue-specific, genome-scale molecular information.

Obesity

Obesity reflects increased adiposity, primarily visceral WAT, in the body. A large number of animal and epidemiological studies have consistently revealed low-grade chronic and systemic inflammation as a major characteristic of obesity⁹³. However, the extent of inflammatory signals in individual obesity-related tissues was poorly evaluated. In a genetic and genomic study of an extreme obese population comprising ~1000 individuals who underwent gastric bypass surgery, Greenawalt et al. systematically investigated the genetics of gene expression, gene-disease correlations, and the gene regulatory network structures in four individual tissues including liver, omental adipose tissue, subcutaneous adipose tissue, and stomach⁹⁴. They found that genes correlated with multiple obesity traits such as BMI and leptin levels in liver, omental adipose tissue, and subcutaneous adipose tissue were significantly enriched for inflammatory signals including macrophage- and spleen-related inflammatory genes, immunoglobulins, and genes involved in B-cell and antibody mediated immunity. Based on a weighted gene coexpression network analysis, they also identified coexpression modules from liver and subcutaneous adipose tissues that were highly correlated with obesity traits. Similarly, these modules were primarily enriched for immune and inflammatory response genes. This systems genetic study objectively uncovered inflammation in liver and WAT (but not in stomach) as the central player in obesity through large-scale systems screening. However, the causal nature of inflammatory was not clear through these correlative analyses.

To tackle the causal versus reactive nature of inflammation, Kwon et al. conducted a time-course with 8 time points over 24 weeks to assess changes in adipocyte morphology, adipokines and transcriptome in visceral WAT from four depots (epididymal, perirenal, retroperitoneum, mesentery) during the course of high fat diet-induced obesity⁹⁵. Through gene expression microarray analysis, they identified early and sustained activation of the immune response and inflammatory genes including multiple TLRs, *Irf5* and *Cd14* that are involved in metabolism-induced inflammatory signaling and their downstream pro-inflammatory cytokines such as *Tnf*, *Il1rn*, *Saa3*, *Emr1*, *Adam8*, *Irgam*, and chemokine (C-C motif) ligand genes. These changes were mainly observed in epididymal and mesenteric depots and preceded morphological onset of obesity. The early activation of TLR-mediated inflammatory signaling cascades revealed from this time course study convincingly placed inflammation in visceral WAT into the causal position. Using a similar time course design, Oh et al. combined liver gene expression profiles with gene network analysis to identify gene networks and key regulators (hubs) of high-fat diet induced obesity and liver non-alcoholic steatohepatitis. A network associated with inflammatory response was among the five core networks uncovered; *Tlr2*, *Cd14*, and *Ccnd1* were found to be the central regulators of this network and these genes appear to interact through the ErbB/insulin signaling

pathway. Taken together, these new systems-level genomic studies clearly and consistently confirm the central causal role of inflammation in WAT and liver in inducing obesity.

T2 Diabetes Mellitus

T2DM is often associated with obesity as a consequence of overnutrition with or without genetic susceptibility. Impaired insulin signaling, or insulin resistance, usually follows obesity onset and precedes T2DM. Evidence has been converging on inflammation as a primary cause for insulin resistance as well as for pancreatic islet β -cell deterioration and failure, two key events leading to T2DM. Considering the critical role of inflammatory in obesity as discussed above, it is intuitive to understand why obesity is a risk factor for T2DM. Through analysis of key tissues involved in insulin resistance and insulin secretion – adipose, liver, islet and muscle, Imai et al. recently discovered that hormone and cytokine production by adipose tissue and infiltration of immune cells such as macrophages in liver, adipose, and islet (but not in muscle) are partially responsible for impaired insulin signaling and β -cell failure in T2DM^{96,97}.

Recent systems studies have uncovered many inflammatory genes as playing causal roles in T2DM development and highlight the key role of adipose tissue inflammation in T2DM development. In a series of studies, Butte and colleagues conducted systematic analysis of gene expression datasets across 130 independent experiments that included a total of 1,175 T2DM case-control microarrays, they identified CD44, encoding a T cell-related cell adhesion molecule, as the top differentially expressed gene across studies and experimentally confirmed its role in modulating adipose tissue inflammation, insulin sensitivity, and glycemic control⁹⁸. In an integrative analysis involving T2DM GWAS, genetic of gene expression in liver and adipose tissues, and biological pathways, Zhong et al identified complement and coagulation, and antigen processing and presentation as key pathways contributing to T2DM pathogenesis⁹⁹. Recently, Mori et al. conducted an extensive comparison between two mouse strains with different susceptibility to T2DM. They integrated metabolic characterization, gene expression, protein-protein interaction networks, and other analyses of adipose, skeletal muscle, and liver tissue of the two mouse strains at two different time points, and identified an inflammation- and immune system-related adipose subnetwork that predicts and contributes to the differences in T2DM risk¹⁰⁰. Particularly, increases in T-cell related molecules such as SDF1 α , CCL5/RANTES, IFN γ and CD80 are accompanied by T-cell and macrophage infiltration in adipose tissue. In another study, Gao et al. screened six tissues of two strains of mice at two obesity status and two ages. Again inflammatory pathways especially the T cell receptor signaling pathway, autoimmune processes, and focal adhesion were predominant in adipose tissue in T2DM, whereas metabolic pathways are more prominent in other tissues (e.g., glycolysis/ gluconeogenesis in liver and insulin signaling in muscle)¹⁰¹.

Coronary Heart Disease

The role of inflammation in coronary heart disease (CHD) was first captured by C-reactive protein (CRP), an acute phase protein released from liver and adipose tissues and a strong indicator of coronary heart disease risk¹⁰². Through studies of coronary heart disease, a condition characterized by the hardening and narrowing of arteries that is the key feature to

coronary heart disease development, increasing evidence supports an important role for inflammation in all phases of coronary heart disease, from initiation of the fatty streak to final culmination in acute coronary syndromes¹⁰³. Numerous inflammatory biomarkers including cell adhesion molecules, cytokines, chemokines, and acute-phase reactants such as fibrinogen, serum amyloid A, and CRP have been shown to predict coronary heart disease events. TLRs, pattern recognition receptors and members of the innate immune system, contribute to inflammation and appear to play key roles in coronary heart disease. Similar to obesity and T2DM discussed above, coronary heart disease and coronary heart disease are also highly complex and involve the interactions among diverse biological processes in various tissues and organs. In the past few years, systems biology and integrative genomics approaches that aim to provide a comprehensive view of molecular mechanisms underpinning coronary heart disease have again highlighted inflammation as a key causal mechanism that tightly interact with lipid metabolism^{104,105}.

In a study involving more than 300 F2 mice derived from a cross between the strains C3H/HeJ and C57BL/6J on a hyperlipidemic apolipoprotein E-null background, Wang et al. conducted a genetical genomic analysis of coronary heart disease, aiming to objectively identify genetic loci and tissue-specific biological processes contributing to coronary heart disease. By correlating DNA genotyping with coronary heart disease traits, they identified 10 quantitative trait loci for lesion size; by performing expression analysis for 23,574 transcripts of the livers and adipose tissues, they identified genetic loci regulating gene expression and genes correlated with atherosclerotic lesion development. Genes involved in cholesterol metabolism, mitochondrial oxidative phosphorylation, and inflammation was found to be highly over-represented among the lesion-correlated genes¹⁰⁶. Taking one step further to go beyond correlation into causation, Yang et al. employed a likelihood-based causality test¹⁰⁷ to identify causal genes for atherosclerotic lesions¹⁰⁸. A total of 292 causal genes were identified from liver and adipose tissues and these genes were highly enriched for inflammatory genes involved in lymphocyte activation and B cell receptor signaling¹⁰⁸. Validation experiments in two plaque progression mouse models, in a knockout mouse model of C3ar1 (a gene involved in complementation), and via cross-checking with human genome-wide association studies (GWAS) confirmed the causal nature of these genes.

Similar systems analyses have been conducted in human populations and inflammation related processes were consistently pinpointed as the causal factors of coronary heart disease. For instance, Huan et al. carried out an integrative analysis using whole blood gene expression profiling data obtained from 188 pairs of coronary heart disease case-control individuals in the Framingham Heart Study¹⁰⁹. Although few differentially expressed genes between cases and controls were identified, gene coexpression network analysis revealed a network module comprising genes involved in B cell activation to be highly coexpressed in controls but disrupted in coronary heart disease cases. This module was further demonstrated to be enriched for genes whose functional genetic variants exhibit association with coronary heart disease in the GWAS from the CARDIoGRAM consortium¹¹⁰, thus supporting a causal role in coronary heart disease. In two parallel studies of a Finnish cohort with ~500 individuals¹¹¹, Inouye et al. integrated blood transcriptomic, metabolomics, and genetic data and constructed gene co-expression networks to capture the molecular interactions. They linked network modules to >80 blood metabolites that are relevant to

coronary heart disease, such as lipoprotein subclasses and lipids¹¹¹. A lipid-leukocyte module comprising primarily inflammatory genes was highly associated with and largely reactive to blood metabolites, and was genetically linked to variants controlling serum immunoglobulin IgE levels. The authors postulate that this immune response module is a key mediator that senses metabolite variations and then translates metabolic signals into inflammatory signals, which in turn contribute to atherogenesis. In one recent comprehensive investigation of the genetically perturbed molecular mechanisms of coronary heart disease, we systematically integrated diverse types of genomic data including genetic associations from GWAS, tissue-specific genetic regulation of gene expression, biological pathways, and tissue-specific gene regulatory networks. As a result we identified tens of molecular pathways, both known and novel, to be involved in coronary heart disease development¹¹². Multiple immune/inflammation related pathways such as immunoregulation, antigen processing and presentation, Th1/Th2 differentiation, and adhesion and diapedesis of lymphocytes are among the top signals. Furthermore, this study identified tens of potential key regulators of the significant processes using data-driven approaches including *PTPRC*, *NCKAP1L*, *FCGR1A*, *FYB*, and *FCER1G* for the inflammation gene network and *VPS52*, *PPIL1*, *GLO1*, *GFER*, and *DECR2* for the antigen-related gene network. These systems studies in both human and mouse revealed tissue-specific causal genes and unanimously pointed to the central role of inflammation in coronary heart disease.

As discussed above, when analyzing individual metabolic disorders separately, inflammation emerges as a causal mechanism shared among these diseases. The conclusion remains true when these diseases are assessed together. In fact, in two seminal systems biology studies, one focusing on data generated from a mouse F2 cross and the other studying an Icelandic human population, Chen et al. and Emilsson et al. identified a co-expression network module that is conserved between liver and adipose tissues, conserved between human and mouse, highly enriched for macrophage- and spleen-related inflammatory genes, and linked to various metabolic phenotypes including adiposity, coronary heart disease, and plasma lipids, insulin and glucose levels, all essential traits of metabolic disorders^{4,113}. In our recent study, we analyzed 12 tissue-specific gene expression profiling data of eleven different mouse and rat disease models of metabolic disorders and other common diseases and identified a consistent inflammatome signature that are not only shared among all diseases but also demonstrate causal properties¹¹⁴. Therefore, inflammation serves as an attractive targeting point for therapeutics. In fact, recent attempts to alleviate metabolic diseases by targeting the inflammatory pathways have proven to be successful^{115,116}. Kiechl et al. targeted RANKL, the receptor activator of NF- κ B signaling and observed the preventative potential of the treatment for T2DM. In parallel, Reilly et al. used amlexanox, a drug approved for asthma and aphthous ulcers and an inhibitor of I κ B kinases TBK1 and IKK- ϵ to treat obese mice and found overall improvement of metabolic profiles.

Molecular and genetic inflammation networks underlying neurodegenerative diseases

Complex neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), and amyotrophic lateral sclerosis (ALS) share common molecular pathological mechanistic networks involving misfolded proteins, especially those prion-like proteins. The aggregation, deposition and propagation of prion-like proteins is tightly connected to immune response pathways¹¹⁷. However, the types of aggregated proteins and affected neuron cells vary from disease to disease^{5,118-121}. A line of Prion-like proteins such as α -synuclein, tau, TDP-43, FUS, and C9orf72, have been characterized, with the former two specific to PD and AD respectively while the latter three mainly involved in FTD and ALS¹²⁰.

Blood-brain barrier (BBB) is critical to the brain's normal function. Accordingly, a compromise of BBB accompanies many neurologic disorders, and is tightly associated with brain inflammatory processes initiated by both infiltrating leukocytes from the blood, and activation of glial cells. Those inflammatory processes contribute to determining the severity and prognosis of numerous neurologic disorders, and can both cause, and result from BBB dysfunction¹²²⁻¹²⁷.

A pathological hallmark of AD, aggregation and deposition of amyloid- β peptides, has been recognized as a potent activator of microglia-mediated neuroinflammation and neuronal dysfunction. Autophagy is a major cellular pathway leading to the removal of aggregated proteins of amyloid- β (A β) peptides and tau protein. Autophagy not only reduces intracellular components to compensate for nutrient deprivation but also selectively eliminates organelles to regulate their number and maintain quality control¹²⁸⁻¹³⁰. Mitophagy, the specific autophagy elimination of mitochondria, has been identified in yeast, mediated by autophagy-related 32 (Atg32) and in mammals during red blood cell differentiation, mediated by NIP3-like protein X (NIX; also known as BNIP3L)¹³¹⁻¹³⁵. Moreover, mitophagy is regulated in many metazoan cell types by PARKIN and PTEN-induced putative kinase protein (PINK1), and mutations in the gene encoding these proteins have been linked to forms of Parkinson's disease^{132,133,136}. Neoechinulin A can significantly suppress the production of neurotoxic inflammatory mediator tumour necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and prostaglandin E2 (PGE2) in activated BV-2 cells. Activated microglia-mediated apoptosis of PC-12 pheochromocytoma cells was significantly repressed by neoechinulin A¹³⁷. The molecular mechanism studies suggested that neoechinulin A may block the phosphorylation of mitogen-activated protein kinase (MAPK) molecule p38, apoptosis signal-regulating kinase 1 (ASK-1) and nuclear translocation of nuclear factor- κ B (NF- κ B) p65 and p50 subunits.

Microglial cells constitute the first line of defense of the central nervous system (CNS) against microbial invasion. Pathogens are detected thanks to an array of innate immune receptors termed pattern recognition receptors (PRRs). PRRs have been thoroughly characterized in bone marrow-derived macrophages, but the PRRs repertoire and functionality in microglial cells remain largely unknown. Microglial cells express various Toll-like Receptors and the Nod1/2 receptors. Recently, a novel innate immune signalling

pathway, the inflammasome pathway has been uncovered. Inflammasome activation leads to caspase-1 activation, release of the proinflammatory cytokines, IL-1 β and IL-18 and cell death in a process termed pyroptosis. One inflammasome receptor, NLRP3, has been characterized in microglial cells and associated with response to infections and in the initiation of neuro-degeneration in an Alzheimer's disease model, illustrating that microglial cells detect *L. pneumophila* infection in a flagellin-dependent manner leading to caspase-1-mediated bacterial growth restriction, infected cell death and secretion of the proinflammatory cytokines IL-1 β and IL18. Overall, these data demonstrate that microglial cells have a functional Naip5-NLRC4 inflammasome likely to be important to monitor and clear CNS infections by flagellated bacteria. A more complete inflammation response pathway has been proposed based on data-driven molecular networks⁹.

Autophagy, a fundamental eukaryotic pathway with multiple effects on immunity, can be induced by pattern recognition receptors and, through autophagic adaptors. Detailed mechanisms for the elimination of intracellular microorganisms involve controlling inflammation through regulatory interactions with innate immune signaling pathways, by removing endogenous inflammasome agonists and through effects on the secretion of immune mediators¹³⁸.

Autophagy is an intracellular degradation process that clears long-lived proteins and organelles from the cytoplasm (28). It involves the formation of double-membraned structures called autophagosomes that can engulf portions of cytoplasm containing oligomeric protein complexes and organelles, such as mitochondria. Autophagosomes fuse with lysosomes and their contents then are degraded. Failure of autophagy in neurons can result in the accumulation of aggregate-prone proteins and neurodegeneration. Pharmacological induction of autophagy can enhance the clearance of intracytoplasmic aggregate-prone proteins, such as mutant forms of huntingtin, and ameliorate pathology in cell and animal models of neurodegenerative diseases. The ways in which dysfunctions at multiple stages in the autophagic pathways contribute to numerous neurological disorders are highlighted through the use of examples of Mendelian and complex conditions, including Alzheimer disease, Parkinson disease and forms of motor neuron disease. The different ways in which autophagic pathways might be manipulated for the therapeutic benefit of patients with neurodegenerative disorders are also considered. As mitochondrial dysfunction is a common observation in these and other neurodegenerative diseases, the available data on AD and PD can be incorporated into a single integrated paradigm based on mitochondrial genetics and pathophysiology. Rare chromosomal cases of AD and PD can be interpreted as affecting mitochondrial function, quality control, and mitochondrial DNA (mtDNA) integrity. mtDNA lineages, haplogroups, such haplogroup H5a which harbors the mtDNA tRNA(Gln) A8336G variant, are important risk factors for AD and PD. Somatic mtDNA mutations are elevated in AD, PD, and Down Syndrome and Dementia (DSAD) both in brains and also systemically. AD, DS, and DSAD brains also have reduced mtDNA ND6 mRNA levels, altered mtDNA copy number, and perturbed Abeta metabolism. Classical AD genetic changes incorporated into the 3XTg-AD (APP, Tau, PS1) mouse result in reduced forebrain size, life-long reduced mitochondrial respiration in 3XTg-AD males, and initially elevated respiration and complex I and IV activities in 3XTg-AD females which

markedly declines with age. Mitochondrial dysfunction provides a unifying genetic and pathophysiology explanation for AD, PD, and other neurodegenerative diseases.

Key molecular pathways and modules in neurodegenerative diseases are typically pro-inflammatory

Recent advent highlighted the key role of over-activated NALP3 inflammasome linking IL-1 β and IL-18 pathways in the molecular pathophysiology of Alzheimer's disease¹³⁹. Deposition of A β peptide drives cerebral neuroinflammation by activating microglia. Indeed, A β activation of the NLRP3 inflammasome in microglia is fundamental for interleukin-1 β maturation and subsequent inflammatory events. They demonstrated strongly enhanced active caspase-1 expression in human mild cognitive impairment and brains with Alzheimer's disease, suggesting a role for the inflammasome in this neurodegenerative disease. *Nlrp3*^{-/-} or *Casp1*^{-/-} mice carrying mutations associated with familial Alzheimer's disease were largely protected from loss of spatial memory and other sequelae associated with Alzheimer's disease, and demonstrated reduced brain caspase-1 and interleukin-1 β activation as well as enhanced amyloid- β clearance. Furthermore, NLRP3 inflammasome deficiency skewed microglial cells to an M2 phenotype and resulted in the decreased deposition of amyloid- β in the APP/PS1 model of Alzheimer's disease. These results show an important role for the NLRP3/caspase-1 axis in the pathogenesis of Alzheimer's disease, and suggest that NLRP3 inflammasome inhibition represents a new therapeutic intervention for the disease.

While dysregulated CD36/TLR4-6 innate immune pathway related to endoplasmic reticulum (ER) stress are crucial to common inflammatory disease, it has been underscored that CD36/TLR4-6 are tightly connected to AD disease pathology^{92,140-147}. Particulate ligands, including cholesterol crystals and amyloid fibrils, induce production of interleukin 1 β dependent on the cytoplasmic sensor NLRP3 in coronary heart disease, AD and diabetes. Soluble endogenous ligands, including oxidized low-density lipoprotein (LDL), amyloid-beta and amylin peptides, accumulate in such diseases. Here we identify an endocytic pathway mediated by the pattern-recognition receptor CD36 that coordinated the intracellular conversion of those soluble ligands into crystals or fibrils, which resulted in lysosomal disruption and activation of the NLRP3 inflammasome. Consequently, macrophages that lacked CD36 failed to elicit IL-1 β production in response to those ligands, and targeting CD36 in atherosclerotic mice resulted in lower serum concentrations of IL-1 β and accumulation of cholesterol crystals in plaques. The importance of CD36 in the accrual and nucleation of NLRP3 ligands from within the macrophage and position CD36 as a central regulator of inflammasome activation in sterile inflammation has been underscored. Phagocytosis controls CNS homeostasis by facilitating the removal of unwanted cellular debris. Accordingly, impairments in different receptors or proteins involved in phagocytosis result in enhanced inflammation and neurodegeneration. They show that the autophagy protein beclin 1 is required for efficient phagocytosis in vitro and in mouse brains; beclin 1-mediated impairments in phagocytosis are associated with dysfunctional recruitment of retromer to phagosomal membranes, reduced retromer levels, and impaired recycling of phagocytic receptors CD36 and Trem2. Interestingly, in the study, microglia isolated from human AD brains show significantly reduced beclin 1 and retromer protein levels. These

findings position beclin 1 as a link between autophagy, retromer trafficking, and receptor-mediated phagocytosis and provide insight into mechanisms by which phagocytosis is regulated and how it may become impaired in AD. The mechanisms linking A β to NADPH oxidase-dependent vascular oxidative stress have not been identified, however. The scavenger receptor CD36, a membrane glycoprotein that binds A β , is essential for the vascular oxidative stress and neurovascular dysfunction induced by A β 1-40. Thus, topical application of A β 1-40 onto the somatosensory cortex attenuates the increase in cerebral blood flow elicited by neural activity or by endothelium-dependent vasodilators in WT mice but not in CD36-null mice (CD36(0/0)). The cerebrovascular effects of infusion of A β 1-40 into cerebral arteries are not observed in mice pretreated with CD36 blocking antibodies or in CD36 (null/null) mice. Meanwhile, CD36 deficiency prevents the neurovascular dysfunction observed in transgenic mice overexpressing the Swedish mutation of the amyloid precursor protein Tg2576 despite elevated levels of brain A β 1-40. Thus, CD36 is also required for the vascular oxidative stress induced by exogenous A β 1-40 or observed in Tg2576 mice. These observations have established CD36 as a key link between A β 1-40 and the NADPH oxidase-dependent vascular oxidative stress underlying the neurovascular dysfunction and suggest that CD36 is a potential therapeutic target to counteract the cerebrovascular dysfunction associated with A β .

The mixed results from anti-inflammatory drugs for ameliorating AD or amyotrophic lateral sclerosis may suggest both local cytotoxic inflammation and protective systemic immune response occurs in these disease conditions¹⁴⁸. Very recently, a new study offered evidence that PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of AD¹⁴⁹. It appears that both systemic and local inflammation plays double-sword roles. Taken together, these results highlight the importance of complex immune responses both locally and systemically during of the progression of neurodegenerative diseases. To dissect the complexity of local and systemic immune responses in the initiation and development of complex diseases, systems immunology approaches need be adopted by leveraging multiscale network biology schemata and technologies.

Molecular and genetic inflammation networks underlying cancer

There is an emerging consensus that inflammation and cancer are tightly coupled together and mutually causal throughout all carcinoma progression stages spanning from normal epithelium, carcinoma *in situ*, local invasion, to distant metastasis¹⁵⁰. Due to the complexities of cancer and inflammation, more explicit mechanisms remain elusive. Albeit solid epidemiological data revealed on the efficacy of anti-inflammatory drug, such as salicylate including aspirin, to preventing cancer¹⁵¹⁻¹⁵⁷, the arising precision medicine requires nuanced rational upon pinpointing in-depth mechanistic connections between inflammation and cancer^{158,159}, rather than completely depending on clinical cohort studies. In this section, we seek to underscore key principles that govern the functional links between inflammation and cancer. This holistic view via molecular networks is intended to convey systems molecular pathophysiology insights by highlighting crucial interplays between key modules of inflammation and cancer networks^{12,160}.

Cancer as a complex disease has been gaining more attentions as a malignant system rather than a bag of evil tumor cells solely, leading to substantial emphasis on tumor evolution micro-environment^{161,162}. Such a malignant system is essentially consisted of active innate and adaptive immune cells which can promote or suppress cancer cell growth, thereby coupling cancer and inflammation together tightly^{37,150,159,163-167}. This cellular composition heterogeneity appears to be underpinned by genetically and biochemically sophisticated molecular networks. Naturally it has been reaching agreement that tumor is generally heterogeneous at all levels¹⁶⁸⁻¹⁷². These types of complex and heterogeneous systems generally result from a multistep development involving newly acquired cellular phenotypes, such as sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis^{173,174}. Moreover, two fundamental cancer hallmarks recently highlighted, reprogramming of energy metabolism and evading immune destructions, are thought to be crucial to drive cancer^{173,174}. All of these cellular phenotypes are connected to molecular inflammation. Indeed, at the molecular level, both the extrinsic inflammation and the intrinsic oncogene activation can lead to activation of pivotal transcription factors, such as NF- κ B, STAT3, and HIF1 α in tumor cells as well, resulting in the secretion of chemokines, cytokines, and prostaglandins³⁷. These secreted factors further enable recruiting a variety of inflammatory cells, including macrophages, mast cells, neutrophils, eosinophils, as well as myeloid-derived suppressor cells. Intriguingly, these recruited cells, especially macrophages¹⁷⁴, have their essential function producing growth factors, chemokines, adhesion molecules, as well as proteases. Thus, intercellular positive feedback loops can be formed, supporting the mutual causality between inflammation and cancer. Furthermore, these secreted macromolecules have been shown actively participating in cancer progression via a set of complex mechanisms, including promoting cancerous cells transformation, carcinoma in situ formation, local invasion, cancer cell homing, as well as tumor angiogenesis³⁷. Apparently, such knowledge underpins the rationale for anti-inflammatory intervention. Canonical reductionist wisdoms that have been deployed in uncovering crucial molecular pathways, such as integrin based cell signaling, metabolic switching controlled by AMPK and mTOR pathways, yet have been facing formidable challenges to dissect such complexities in terms of reaching a systematic fine-resolution. Therefore, systems biology approaches have been holding a great promise to detangle those sophisticated interplays between cancer and inflammation. Thus, how to pinpoint rate-limiting network modules has been emerging crucial to hold more promises in underpinning nuanced molecular mechanisms underlying cancer progression. Recent network biology advances have been further illuminating the power of filtering and integrating of large data sets in pinpointing key modules and driver genes, as well as novel anti-cancer potentials of classical anti-inflammatory or anti-diabetes drugs.

There are many lines of compelling evidence indicating the connection between carcinogenesis and inflammation in mouse models¹⁷⁵. Genetic architecture of mouse skin inflammation and tumor susceptibility has illuminated the crucial role of *Lgr5* and *Vdr* in coordinated control of epidermal barrier function, inflammation, and tumor susceptibility¹⁷⁶. Further expression quantitative trait locus (eQTL) analysis from the same research group further highlighted the critical role of tumor microenvironment, mitogen-activated protein,

kinase signaling, inflammation, and cancer susceptibility¹⁷⁵. In ovarian cancer, network of inflammatory cytokine interactions appeared crucial to tumor progression¹⁶². Furthermore, in the prostate carcinogenesis, a hypothesis referred as proliferative inflammatory atrophy (PIA) has been proposed, with a specific emphasis on molecular mechanisms of inflammation-induced cancers¹⁶⁵.

Recently, by exploiting twelve expression data sets profiled from nine distinct types of tissues in eleven rodent inflammatory disease models, an inflammatome gene signature has been found in which around 2,500 genes and 151 key drivers and the network architecture therein are crucial to progressions of eleven representative complex diseases including asthma, emphysema, pulmonary fibrosis, lipopolysaccharide (LPS) induced sepsis, neuropathic pain, coronary heart disease, stroke, obesity, diabetes, and age-related sarcopenia¹². Intriguingly, two most consensus drug targets are *Ppara* and *Prkaa*, both of which are pivotal during cancer progression¹². AMPK encoded by *Prkaa* in mouse, has been demonstrated as a key kinase regulating metabolism and information flux, especially on cancer and inflammatory cells metabolism switching (Warberg effect)¹⁵⁹, as well as linking epigenetic modification¹⁶⁴. Such efforts offer an opportunity to infer and rank key driver modules and genes that underlie the awry cancer genetic architectures. Nonetheless, both cancer and inflammatory are driven by highly dynamic signaling networks, shared by key network attractors¹⁷⁷. This raises a grand challenge to disclose the in-depth fine-resolution mapping of the molecular pathophysiology links between inflammation and cancer. Diagnostic or prognostic biomarker and lead compounds discover, as well as novel druggable targets ranking, have been practically adapted to next generation technologies by utilizing large data sets. Epigenetic modification may play key roles in bridging a variety of inflammation and cancer mechanistic links. For the long run, it will be exceptionally interesting on how to integrate those emerging large data sets (for example, the one million cancer genome warehouse) guided by explicit biomedical hypothesis and how to uncover sophisticated mechanisms linking information metabolism and metabolite influx by borrowing conceptual innovations from those arising mathematical framework on network properties, including stability^{178,179}, resilience¹⁸⁰, as well as dynamics^{181,182}. In light of network biology, more exciting molecular pathophysiology mechanisms that underlie the inflammation-cancer axis have been emerging, thereby favoring the arising of next generation precise medicine upon complex diseases.

Immune Repertoire Sequencing

Recent advancement in massively parallel or next-generation sequencing (NGS) technology has revolutionized the way to conduct biological and medical research^{183,184,185}. Among the active inflammation-related research fields which benefit from these high-throughput sequencing platforms are metagenomic analysis of microbial flora and immune repertoire sequencing (Rep-seq)^{186,187,188}. Many excellent reviews about impacts of microbiome on health and disease have been published the past few years¹⁸⁹⁻¹⁹². This section will focus only on applying Rep-seq in addressing key inflammation-related issues.

The adaptive immune responses mediated by B and T lymphocytes are keys to host defense against microbial pathogens and transformed cells or cancers. B cell receptor

(immunoglobulin) and T cell receptor are encoded by multiple V (variable), D (diversity) and J (Joining) gene segments. The enormous diversity of the immune repertoire required for providing protection is generated via a somatic rearrangement of the germline V, D, J genes and addition or deletion of nucleotides at the junctional regions during lymphocyte development. Traditional Sanger sequencing can at most sequence hundreds of immune receptors at a time and it is only when NGS technology become available that a comprehensive analysis of the immune repertoire can be achieved¹⁹³. In oncology area, due to the aberrant oligoclonal expansion of T/B lymphocytes in hematological malignancies, Rep-seq has been applied to monitor disease progression and response to therapy in lymphoma/leukemia^{194,195} and demonstrated better sensitivities in detecting minimal residual disease (MRD) than more traditional flow cytometry-based methods^{196,195}. For a separate application, a strong correlation has been established between tumor-infiltrating T lymphocytes (TILs) and increased survival in multiple cancer types but the current anti-CD3 immunohistochemistry (IHC) assay to identify TILs is suboptimal in terms of interpretability and quantifiability. By using multiple PCR primer sets targeting all functional TCR V segments, Robins et al.¹⁹⁷ introduced a Rep-seq based digital DNA assay to count and assess TILs and their clonalities in tumor tissues and were able to confirm, in ovarian cancer, an positive association between TIL counts and survival. They also made an observation that TIL repertoire is diverse with no obvious oligoclonal expansions. When the same approach was employed to examine lesions in cervical intraepithelial neoplasias caused by human papillomavirus (HPV16), it was found that intensity of CD8+ TILs increased significantly in patients receiving a therapeutic vaccine targeting HPV antigens and unlike the situation in untreated TILs¹⁹⁷ in other tumors, these CD8+ TILs showed clonal expansions, presumably as a result of recognizing cognate antigens¹⁹⁸.

It has been suggested that during CMV infection, T cell diversity rather than abundance could be more important in conferring protection to pathogen infection. In fact, CD8+ T cell diversity but not the size of CD8+ T cell response, was negatively correlated to CMV-specific antibody titers in the infected human subjects¹⁰⁶. In this case, high anti-CMV antibody levels (and therefore low T cell repertoire diversity) were found to be associated with increased viral ADs and mortality risks. Patients suffered from septic shock were also reported to have a lower T cell repertoire diversity which was predictive of higher mortality rate and the development of nosocomial infections¹⁹⁹. Combining transcriptional profiling and Rep-seq on genital skin and mucosal tissues at the neuronal release sites acquired by laser capture micro-dissection (LCM), it was shown that CD8+ T cells play a key immune surveillance role in responding to herpes simplex virus 2 (HSV-2) infections and express diversified TCR-V region genes with dominant clonotypes overlapping multiple infection episodes over extended period of time¹⁰⁸.

B cell response to vaccination is critical in providing protective immunity but detailed analysis of molecular nature of antibodies present in serum after vaccination remains lacking. Lavinder et al. applied high resolution MS proteomic and Rep-seq analysis following tetanus toxoid booster vaccination and detected ~100 antibody clonotypes with 3 constitutes more than 40% of all antibodies. The results also suggested that a small proportion of peripheral blood plasmablasts at day 7 post-vaccination and an even smaller proportion of memory B cells encode antigen-specific antibodies 9 months later²⁰⁰. Recent

published reports indicated that people 65 years or older have significantly lower antibody titers and repertoire diversity than younger population in response to pneumococcal²⁰¹ and influenza vaccines²⁰². Although IgG is the most prevalent antibody isotype in serum and is most often correlated to vaccine protection, it is IgA, and to a lesser extent IgM, that show the most significant age-dependent titer decrease in the elderly post-vaccination; the significance of this observation is yet to be further explored¹⁹⁵. It is interesting to note that inclusion of a Toll-like receptor (TLR) agonist (as an adjuvant therapy) in a malaria vaccine formulation not only increased the antibody diversity but also improved antigen neutralization²⁰³.

Another large scale analysis has been conducted within the ImmVar project, where the impact of genetic variation on the ability of the immune system to protect against pathogen has been studied²⁰⁴. Although not by complete genome sequencing but by genotyping, the population variation of a cohort of 600 healthy individuals have been assessed and mapped to transcriptional responses of peripheral blood mononuclear cells (PBMCs). Transcriptional baseline as well as response against IFN β , influenza virus and lipopolysaccharide (LPS) have been analysed. A number of SNPs are cis-eQTLs that are associated with the expression of genes encoding regulators, i.e. transcription factors (TFs), in pathways that were stimulated. Of these, rs2805435 was the most significant, associating with the expression of the master antiviral TF *IRF7* in cis only after influenza, IFN β , or LPS stimulation. Seven more genes were associated with this SNP in trans (*IFNA4*, *IFNA5*, *IFNA10*, *IFNA13*, *IFNA17*, *IFNA21*, *NMI*)²⁰⁵.

Perhaps the most advanced and productive immune repertoire analysis was conducted in studying the HIV broad neutralizing antibodies²⁰⁶. Combining B cell cloning, antibody isolation, B cell Rep-seq, structural analysis and viral genome sequencing, broad neutralizing antibodies (BnAbs) defined as cross-reactive antibodies capable of neutralizing the majority of HIV-1 strains which are generated in ~20% of HIV patients 2-3 years post-infection) targeting HIV gp120²⁰⁷ and V1V2 region of the HIV-1 envelope²⁰⁶ were identified and characterized in details. These antibodies contain long complementarity-determining region 3 (CDR3) and are hyper-mutated. Longitudinal sequencing of BnAbs (and their unmutated ancestors) and viral genomes suggested a co-evolutional relationship started with a diversified viral population followed by antibody affinity maturation. These findings would not have been made without the availability of NGS technology and could be integrated into future HIV vaccine development. However, immune repertoire analysis is still at its infancy and will require more collaboration among researchers to share best practice and to standardize experimental protocols so results obtained from different labs can be compared and analyzed together.

Computational Approaches for Modeling Inflammation and Immune Response

Computational approaches have been long developed to model inflammation and immunology so as to derive a holistic understanding of immune systems. Seminal studies of dynamic models of immune systems by Perelson *et al.*²⁰⁸, DeBoer *et al.*²⁰⁹ and Nowak and

May²¹⁰ were based on differential equations. Early network models of host-pathogen systems utilized pre-existing knowledge of metabolic pathways. For example, the tryptophan biosynthesis pathway was investigated in the case of Chlamydia infection²¹¹. Metabolic network databases such as KEGG²¹², MetaCyc²¹³ or WIT²¹⁴, were used in tandem with the comparative analysis of metabolic networks²¹⁵ to identify the interdependence and connectivity between the pathogen and the host that helped to explain the development of the chronic disease caused by the pathogen.

Early predictive multi-scale models have been conducted by Stokes and coworkers at the same time. Using the Entelos PhysioLab framework for simulating disease physiology, Stokes *et al.* developed a computation model of asthma²¹⁶, by combining organ level physiological responses with biological pathways and molecular networks. Different steady states of this disease, such as chronic asthma including chronic eosinophilic inflammation, chronic airway obstruction, airway hyper-responsiveness and elevated IgE levels, can be induced in the model. These *in silico* asthmatic models respond as expected to various drugs, such as β 2-agonists, glucocorticoids and leukotriene antagonists.

The Ingenuity Pathway Analyzer (IPA) is another commercial tool. It has been successfully applied to the network based analysis of systemic inflammation in humans. As discussed in the metabolic network based approach, such an approach requires pre-existing knowledge of pathways and interactions for network analysis. Identified targets were superimposed with network information from the Ingenuity knowledge base. Pathways of highly interconnected genes were identified by statistical likelihood calculation²¹⁷.

Complementary to these model based computational approaches that rely on a priori knowledge are *de novo* network construction methods. A well-established approach in this direction is weighted gene co-expression networks (WGCNA)²¹⁸. The method is based on gene-gene correlation using soft-thresholding (weighted) similarity measures to define a co-expression similarity between genes. Coexpressed gene modules are identified by average linkage hierarchical clustering of a topological overlap matrix of the transformed coexpression similarity matrix. A recent application of WGCNA showed that inflammatory response triggered downregulation of a gene (ADAR2) leading to a decrease in mRNA editing of serotonin receptor after spinal cord injury (SCI), which further contributes to a post-SCI spasticity²¹⁹. However, WGCNA enforces the connectivity to exhibit a power-law distribution and it doesn't explicitly define more intuitive unweighted coexpression networks. To address these issues, Multiscale embedded Gene co-Expression Network Analysis (MEGENA)²²⁰, an advanced version of Planar Filtered Network Analysis (PFNA)^{221,222}, have been developed. MEGENA first employs network embedding technique on topological sphere to construct unweighted coexpression network and then identifies multi-scale organizations of coherently co-expressed modules of genes²²⁰. MEGENA shows superior performance over many existing coexpression network analysis approaches. MEGENA revealed a group of multiscale immune response modules that are associated with breast cancer²²⁰.

For experiments under multiple conditions such as studying gene expression response at multiple time points in infectious diseases, cMonkey, which performs biclustering of co-

regulated genes together with observed experimental conditions²²³, would be a more suitable tool. In cMonkey, each bicluster is modeled via an iterative Markov chain Monte Carlo process. The method uses simulated annealing to add genes or conditions to the bicluster with high probability of membership and drops genes or conditions from the bicluster with low probability of membership. cMonkey has been discussed in an review on Systems Biology of Innate Immunity, by Zak and Aderem²²⁴.

While the above coexpression network analysis approaches can reveal biologically meaningful clustering structures, they are not capable of determining causal relationships between genes, which is critical for identification of key causal regulators. Bayesian network inference is a natural framework for integrating high throughput multi-omics data as well as a priori information into probabilistic causal networks. Integration of large genetic and gene expression data has systematically revealed novel causal relationships among genes and key causal regulators in complex human diseases such as diabetes and obesity^{4,107,113,225}, Alzheimer's disease²²⁶. Given the high complexity of Bayesian network construction, an emerging trend is to integrate both coexpression and causal networks by performing causal network inference on coexpressed gene modules²²⁷.

Summary

Tremendous progresses have been made in exploring the roles of inflammation response in complex human diseases in the past two hundred years but only in the last 40 years we are able to pinpoint particular specific mechanisms at the molecular level thanks to the emergence of genomics. We curated a table (supplement Table S1), in which gene symbol, name, function accession including OMIM and COSMIC gene name, as well as relevant drugs from a variety of data setting, were cataloged²²⁸⁻²³⁰. However, we are still at the early stage of depicting a complete inflammation response pathway map because molecular mechanisms and physiological functions of inflammation still remain most unknown²³¹. Recent progresses in system biology built up upon large-scale genomic, genetic, epigenetic, proteomic and pathophysiological data have substantially accelerated the process by reconstructing molecular networks in an unbiased manner. For example, for the first time in AD research, we could put together genetic, gene expression and pathological data to construct and prioritize gene networks that are causally linked to AD⁹. These predictive data-driven networks provide a blueprint to reconstruct inflammation and other pathway maps for subsequent hypothesis development and biological validation.

On the other hand, we should keep in mind that inflammation response is only one of many pathways contributing to complex human diseases. So, exploration of molecular mechanisms and physiological functions of inflammation should be carried out in a more global context of pathway-pathway interactions. Again systems/network biology holds the key to the success given its unbiased and more disease-relevant nature.

A fundamental goal of understanding inflammation in complex human diseases is to identify novel therapeutic targets and effective treatments²³². The inflammatome signature previously identified was highly enriched with current marketed drug targets²³³ and could be a resource for identifying additional new drugs. Discovery of common features of

inflammation related regulation in major human diseases will facilitate the development of drugs targeting many inflammatory diseases rather than only in a limited spectrum of diseases. Core molecular networks in inflammation and their drivers can be used to identify existing drugs that could be used to reverse the states of the networks and drivers.

Recent advances in high-throughput technologies, data analysis algorithm development have made integrated Omics analysis an achievable goal, especially in the immunology/inflammation area²³⁴. A well-cited example by Chen et al. performed an integrated personal omics profile (iPOP) analysis combining longitudinal genomic, transcriptomic, proteomic, metabolomics and autoantibody data from a single individual during healthy and viral-infected states²³⁵. An NIH-sponsored Human Immunology Project Consortium (HIPC) generated a large repository of multiple data types including enzyme-linked immunosorbent assay (ELISA), enzyme-linked immunospot (ELISPOT), flow cytometry and gene expression. HIPC also created a software analysis tool for researchers to use this resource (<https://import.niaid.nih.gov/>). The other example recently announced by Institute of Systems Biology (ISB) is even more ambitious - in addition to key genomics analysis, the 100 participants involved in the first phase will be asked to continuously record multiple physical/biochemical activities including blood glucose, ~100 protein levels (for monitoring organ health), immune cell activities, heart rate and sleep patterns. The stool samples will also be collected for sequencing major microbial species in the gut. ISB planned on expanding the study to 100,000 subjects for up to 25 years if the results from first phase look promising²³⁶. Although not without significant challenges, these efforts will no doubt bring us closer to the goal of achieving personalized medicine in a way envisioned as predictive, personalized, preventive and participatory (P4)²³⁷.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

This work was supported by in part the grants R01AG046170 (to B.Z.) from the NIH/National Institute on Aging (NIA, <http://www.nia.nih.gov/>), R01CA163772 (to B.Z.) from NIH/National Cancer Institute (NCI, <http://www.cancer.gov/>), and U01AI11598-01 (to B.Z.) from NIH/National Institute of Allergy and Infectious Diseases (NIAID, <http://www.niaid.nih.gov/>). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Reference

1. Gause WC, Wynn TA, Allen JE. Type 2 immunity and wound healing: evolutionary refinement of adaptive immunity by helminths. *Nature reviews. Immunology*. 2013; 13:607–614. doi:10.1038/nri3476.
2. Newell EW, Davis MM. Beyond model antigens: high-dimensional methods for the analysis of antigen-specific T cells. *Nature biotechnology*. 32:149–157.
3. Huan T, et al. A systems biology framework identifies molecular underpinnings of coronary heart disease. *Arteriosclerosis, thrombosis, and vascular biology*. 33:1427–1434.
4. Chen Y, et al. Variations in DNA elucidate molecular networks that cause disease. *Nature*. 2008; 452:429–435. [PubMed: 18344982]

5. Kim HJ, et al. Mutations in prion-like domains in hnRNPA2B1 and hnRNPA1 cause multisystem proteinopathy and ALS. *Nature*. 2013; 495:467–473. doi:10.1038/nature11922. [PubMed: 23455423]
6. Solomon BD, Nguyen AD, Bear KA, Wolfsberg TG. Clinical genomic database. *Proceedings of the National Academy of Sciences of the United States of America*. 2013; 110:9851–9855. doi:10.1073/pnas.1302575110. [PubMed: 23696674]
7. Lagier-Tourenne C, et al. Targeted degradation of sense and antisense C9orf72 RNA foci as therapy for ALS and frontotemporal degeneration. *Proceedings of the National Academy of Sciences of the United States of America*. 2013; 110:E4530–4539. doi:10.1073/pnas.1318835110. [PubMed: 24170860]
8. Imai Y, et al. An unfolded putative transmembrane polypeptide, which can lead to endoplasmic reticulum stress, is a substrate of Parkin. *Cell*. 2001; 105:891–902. [PubMed: 11439185]
9. Zhang B, et al. Integrated Systems Approach Identifies Genetic Nodes and Networks in Late-Onset Alzheimer's Disease. *Cell*. 2013; 153:14. [PubMed: 23540687]
10. Emilsson V, et al. Genetics of gene expression and its effect on disease. *Nature*. 2008; 452:423–428. [PubMed: 18344981]
11. Yang X, et al. Validation of candidate causal genes for abdominal obesity which affect shared metabolic pathways and networks. *Nature Genetics*. 2009 In Press.
12. Wang IM, et al. Systems analysis of eleven rodent disease models reveals an inflammatome signature and key drivers. *Mol Syst Biol*. 2012; 8:594. doi:10.1038/msb.2012.24. [PubMed: 22806142]
13. Rappuoli R, Aderem A. A 2020 vision for vaccines against HIV, tuberculosis and malaria. *Nature*. 473:463–469. [PubMed: 21614073]
14. Karron RA, Buchholz UJ, Collins PL. Live-attenuated respiratory syncytial virus vaccines. *Current topics in microbiology and immunology*. 372:259–284. [PubMed: 24362694]
15. Sung H, Schleiss MR. Update on the current status of cytomegalovirus vaccines. *Expert review of vaccines*. 9:1303–1314. [PubMed: 21087108]
16. Rothman AL. Immunity to dengue virus: a tale of original antigenic sin and tropical cytokine storms. *Nature reviews. Immunology*. 11:532–543.
17. Kaslow DC, Shiver JW. Clostridium difficile and methicillin-resistant Staphylococcus aureus: emerging concepts in vaccine development. *Annual review of medicine*. 62:201–215.
18. Kumar H, Kawai T, Akira S. Pathogen recognition by the innate immune system. *International reviews of immunology*. 30:16–34. [PubMed: 21235323]
19. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nature immunology*. 11:373–384. [PubMed: 20404851]
20. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell*. 140:805–820. [PubMed: 20303872]
21. Deretic V. Autophagy: an emerging immunological paradigm. *Journal of immunology*. 189:15–20.
22. Mira MT, et al. Susceptibility to leprosy is associated with PARK2 and PACRG. *Nature*. 2004; 427:636–640. [PubMed: 14737177]
23. Manzanillo PS, et al. The ubiquitin ligase parkin mediates resistance to intracellular pathogens. *Nature*. 501:512–516. [PubMed: 24005326]
24. Netea MG, van de Veerdonk FL, Kullberg BJ, Van der Meer JW, Joosten LA. The role of NLRs and TLRs in the activation of the inflammasome. *Expert opinion on biological therapy*. 2008; 8:1867–1872. [PubMed: 18990074]
25. Segovia J, et al. TLR2/MyD88/NF-kappaB pathway, reactive oxygen species, potassium efflux activates NLRP3/ASC inflammasome during respiratory syncytial virus infection. *PloS one*. 7:e29695. [PubMed: 22295065]
26. Jones CL, Weiss DS. TLR2 signaling contributes to rapid inflammasome activation during F. novicida infection. *PloS one*. 6:e20609. [PubMed: 21698237]
27. Negash AA, et al. IL-1beta production through the NLRP3 inflammasome by hepatic macrophages links hepatitis C virus infection with liver inflammation and disease. *PLoS pathogens*. 9:e1003330. [PubMed: 23633957]

28. Goubau D, Deddouche S, Reis e Sousa C. Cytosolic sensing of viruses. *Immunity*. 38:855–869. [PubMed: 23706667]
29. Vandevenne P, et al. The varicella-zoster virus ORF47 kinase interferes with host innate immune response by inhibiting the activation of IRF3. *PloS one*. 6:e16870. [PubMed: 21347389]
30. Zhu H, et al. Varicella-zoster virus immediate-early protein ORF61 abrogates the IRF3-mediated innate immune response through degradation of activated IRF3. *Journal of virology*. 85:11079–11089. [PubMed: 21835786]
31. Diamond MS, Farzan M. The broad-spectrum antiviral functions of IFIT and IFITM proteins. *Nature reviews. Immunology*. 13:46–57.
32. Schoggins JW, et al. A diverse range of gene products are effectors of the type I interferon antiviral response. *Nature*. 472:481–485. [PubMed: 21478870]
33. Goulet ML, et al. Systems analysis of a RIG-I agonist inducing broad spectrum inhibition of virus infectivity. *PLoS pathogens*. 9:e1003298. [PubMed: 23633948]
34. Baril M, et al. Genome-wide RNAi screen reveals a new role of a WNT/CTNNB1 signaling pathway as negative regulator of virus-induced innate immune responses. *PLoS pathogens*. 9:e1003416. [PubMed: 23785285]
35. Virgin HW, Wherry EJ, Ahmed R. Redefining chronic viral infection. *Cell*. 2009; 138:30–50. [PubMed: 19596234]
36. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006; 444:860–867. doi:10.1038/nature05485. [PubMed: 17167474]
37. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008; 454:436–444. doi:10.1038/nature07205. [PubMed: 18650914]
38. Deeks SG. HIV: How to escape treatment. *Nature*. 477:36–37. [PubMed: 21886150]
39. Rotger M, et al. Comparative transcriptomics of extreme phenotypes of human HIV-1 infection and SIV infection in sooty mangabey and rhesus macaque. *The Journal of clinical investigation*. 121:2391–2400. [PubMed: 21555857]
40. Lim JK, et al. Genetic variation in OAS1 is a risk factor for initial infection with West Nile virus in man. *PLoS pathogens*. 2009; 5:e1000321. [PubMed: 19247438]
41. Alagarasu K, et al. Polymorphisms in the oligoadenylate synthetase gene cluster and its association with clinical outcomes of dengue virus infection. *Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases*. 14:390–395.
42. Silvestri G. AIDS pathogenesis: a tale of two monkeys. *Journal of medical primatology*. 2008; 37(Suppl 2):6–12. [PubMed: 19187426]
43. Mandl JN, et al. Divergent TLR7 and TLR9 signaling and type I interferon production distinguish pathogenic and nonpathogenic AIDS virus infections. *Nature medicine*. 2008; 14:1077–1087.
44. Rotger M, et al. Genome-wide mRNA expression correlates of viral control in CD4+ T-cells from HIV-1-infected individuals. *PLoS pathogens*. 6:e1000781. [PubMed: 20195503]
45. Veazey RS, et al. Gastrointestinal tract as a major site of CD4+ T cell depletion and viral replication in SIV infection. *Science*. 1998; 280:427–431. [PubMed: 9545219]
46. Brenchley JM, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nature medicine*. 2006; 12:1365–1371.
47. Marchetti G, Tincati C, Silvestri G. Microbial translocation in the pathogenesis of HIV infection and AIDS. *Clinical microbiology reviews*. 26:2–18. [PubMed: 23297256]
48. Dandekar S, George MD, Baumler AJ. Th17 cells, HIV and the gut mucosal barrier. *Current opinion in HIV and AIDS*. 5:173–178. [PubMed: 20543596]
49. Kim CJ, et al. Mucosal Th17 cell function is altered during HIV infection and is an independent predictor of systemic immune activation. *Journal of immunology*. 191:2164–2173.
50. Pallikkuth S, et al. Maintenance of intestinal Th17 cells and reduced microbial translocation in SIV-infected rhesus macaques treated with interleukin (IL)-21. *PLoS pathogens*. 9:e1003471. [PubMed: 23853592]
51. Handley SA, et al. Pathogenic simian immunodeficiency virus infection is associated with expansion of the enteric virome. *Cell*. 151:253–266. [PubMed: 23063120]

52. Vujkovic-Cvijin I, et al. Dysbiosis of the gut microbiota is associated with hiv disease progression and tryptophan catabolism. *Science translational medicine*. 5:193ra191.
53. Wherry EJ. T cell exhaustion. *Nature immunology*. 12:492–499. [PubMed: 21739672]
54. Wherry EJ, et al. Molecular signature of CD8+ T cell exhaustion during chronic viral infection. *Immunity*. 2007; 27:670–684. [PubMed: 17950003]
55. Day CL, et al. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. *Nature*. 2006; 443:350–354. [PubMed: 16921384]
56. Fuller MJ, et al. Immunotherapy of chronic hepatitis C virus infection with antibodies against programmed cell death-1 (PD-1). *Proceedings of the National Academy of Sciences of the United States of America*. 110:15001–15006. [PubMed: 23980172]
57. Hamid O, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *The New England journal of medicine*. 369:134–144. [PubMed: 23724846]
58. Wolchok JD, et al. Nivolumab plus ipilimumab in advanced melanoma. *The New England journal of medicine*. 369:122–133. [PubMed: 23724867]
59. Riou C, et al. Convergence of TCR and cytokine signaling leads to FOXO3a phosphorylation and drives the survival of CD4+ central memory T cells. *The Journal of experimental medicine*. 2007; 204:79–91. [PubMed: 17190839]
60. Brunet A, et al. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. *Science*. 2004; 303:2011–2015. [PubMed: 14976264]
61. Calnan DR, Brunet A. The FoxO code. *Oncogene*. 2008; 27:2276–2288. [PubMed: 18391970]
62. Greer EL, et al. The energy sensor AMP-activated protein kinase directly regulates the mammalian FOXO3 transcription factor. *The Journal of biological chemistry*. 2007; 282:30107–30119. [PubMed: 17711846]
63. Nakamura T, Sakamoto K. Forkhead transcription factor FOXO subfamily is essential for reactive oxygen species-induced apoptosis. *Molecular and cellular endocrinology*. 2008; 281:47–55. [PubMed: 18035477]
64. van Grevenynghe J, et al. Lymph node architecture collapse and consequent modulation of FOXO3a pathway on memory T- and B-cells during HIV infection. *Seminars in immunology*. 2008; 20:196–203. [PubMed: 18757210]
65. van Grevenynghe J, et al. Loss of memory B cells during chronic HIV infection is driven by Foxo3a- and TRAIL-mediated apoptosis. *The Journal of clinical investigation*. 121:3877–3888. [PubMed: 21926463]
66. van Grevenynghe J, et al. Foxo3a: an integrator of immune dysfunction during HIV infection. *Cytokine & growth factor reviews*. 23:215–221. [PubMed: 22748238]
67. Asare AL, et al. Differential gene expression profiles are dependent upon method of peripheral blood collection and RNA isolation. *BMC genomics*. 2008; 9:474. [PubMed: 18847473]
68. Vartanian K, et al. Gene expression profiling of whole blood: comparison of target preparation methods for accurate and reproducible microarray analysis. *BMC genomics*. 2009; 10:2. [PubMed: 19123946]
69. Parrish ML, et al. cDNA targets improve whole blood gene expression profiling and enhance detection of pharmacodynamic biomarkers: a quantitative platform analysis. *J Transl Med*. 8:87. [PubMed: 20868515]
70. Chaussabel D, Pascual V, Banchereau J. Assessing the human immune system through blood transcriptomics. *BMC biology*. 8:84. [PubMed: 20619006]
71. Mohr S, Liew CC. The peripheral-blood transcriptome: new insights into disease and risk assessment. *Trends in molecular medicine*. 2007; 13:422–432. [PubMed: 17919976]
72. Buonaguro L, Pulendran B. Immunogenomics and systems biology of vaccines. *Immunological reviews*. 239:197–208. [PubMed: 21198673]
73. Luciani F, Bull RA, Lloyd AR. Next generation deep sequencing and vaccine design: today and tomorrow. *Trends in biotechnology*. 30:443–452. [PubMed: 22721705]
74. Prachi P, Donati C, Masciopinto F, Rappuoli R, Bagnoli F. Deep sequencing in pre- and clinical vaccine research. *Public health genomics*. 16:62–68. [PubMed: 23548719]

75. Lawrence M, et al. Software for computing and annotating genomic ranges. *PLoS Comput Biol*. 2013; 9:e1003118. doi:10.1371/journal.pcbi.1003118. [PubMed: 23950696]
76. Chaussabel D, et al. A modular analysis framework for blood genomics studies: application to systemic lupus erythematosus. *Immunity*. 2008; 29:150–164. [PubMed: 18631455]
77. Banchereau R, et al. Host immune transcriptional profiles reflect the variability in clinical disease manifestations in patients with *Staphylococcus aureus* infections. *PloS one*. 2012; 7:e34390. doi: 10.1371/journal.pone.0034390. [PubMed: 22496797]
78. Watanabe T, Watanabe S, Kawaoka Y. Cellular networks involved in the influenza virus life cycle. *Cell host & microbe*. 2010; 7:427–439. doi:10.1016/j.chom.2010.05.008. [PubMed: 20542247]
79. Ward SE, et al. Host modulators of H1N1 cytopathogenicity. *PLoS One*. 2012; 7:e39284. doi: 10.1371/journal.pone.0039284. [PubMed: 22876275]
80. Mata MA, et al. Chemical inhibition of RNA viruses reveals REDD1 as a host defense factor. *Nature chemical biology*. 2011; 7:712–719. doi:10.1038/nchembio.645. [PubMed: 21909097]
81. Obermoser G, et al. Systems scale interactive exploration reveals quantitative and qualitative differences in response to influenza and pneumococcal vaccines. *Immunity*. 38:831–844. [PubMed: 23601689]
82. Li S, et al. Molecular signatures of antibody responses derived from a systems biology study of five human vaccines. *Nature immunology*. 2014; 15:195–204. doi:10.1038/ni.2789. [PubMed: 24336226]
83. Nakaya HI, et al. Systems biology of vaccination for seasonal influenza in humans. *Nature immunology*. 2011; 12:786–795. doi:10.1038/ni.2067. [PubMed: 21743478]
84. Shi J, et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. *Nature*. 2015; 526:660–665. doi:10.1038/nature15514. [PubMed: 26375003]
85. Kayagaki N, et al. Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. *Nature*. 2015; 526:666–671. doi:10.1038/nature15541. [PubMed: 26375259]
86. Triantafilou M, Hughes TR, Morgan BP, Triantafilou K. Complementing the inflammasome. *Immunology*. 2015 doi:10.1111/imm.12556.
87. Breuer K, et al. InnateDB: systems biology of innate immunity and beyond--recent updates and continuing curation. *Nucleic acids research*. 2013; 41:D1228–1233. doi:10.1093/nar/gks1147. [PubMed: 23180781]
88. Welter D, et al. The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. *Nucleic acids research*. 2014; 42:D1001–1006. doi:10.1093/nar/gkt1229. [PubMed: 24316577]
89. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nature reviews. Immunology*. 2011; 11:85–97. doi:10.1038/nri2921.
90. Osorio J. Obesity: MHC class II pathway mediates adipose inflammation. *Nature reviews. Endocrinology*. 2013; 9:252. doi:10.1038/nrendo.2013.59.
91. Deng T, et al. Class II major histocompatibility complex plays an essential role in obesity-induced adipose inflammation. *Cell metabolism*. 2013; 17:411–422. doi:10.1016/j.cmet.2013.02.009. [PubMed: 23473035]
92. Neculai D, et al. Structure of LIMP-2 provides functional insights with implications for SR-BI and CD36. *Nature*. 2013 doi:10.1038/nature12684.
93. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. *Physiological reviews*. 2013; 93:359–404. doi:10.1152/physrev.00033.2011. [PubMed: 23303913]
94. Greenawalt DM, et al. A survey of the genetics of stomach, liver, and adipose gene expression from a morbidly obese cohort. *Genome Res*. 2011; 21:1008–1016. doi:gr.112821.110 [pii] 10.1101/gr.112821.110. [PubMed: 21602305]
95. Kwon EY, et al. Time-course microarrays reveal early activation of the immune transcriptome and adipokine dysregulation leads to fibrosis in visceral adipose depots during diet-induced obesity. *BMC genomics*. 2012; 13:450. doi:10.1186/1471-2164-13-450. [PubMed: 22947075]
96. Lontchi-Yimagou E, Sobngwi E, Matsha TE, Kengne AP. Diabetes Mellitus and Inflammation. *Current diabetes reports*. 2013 doi:10.1007/s11892-013-0375-y.
97. Imai Y, Dobrian AD, Morris MA, Nadler JL. Islet inflammation: a unifying target for diabetes treatment? *Trends in endocrinology and metabolism: TEM*. 2013 doi:10.1016/j.tem.2013.01.007.

98. Kodama K, et al. Expression-based genome-wide association study links the receptor CD44 in adipose tissue with type 2 diabetes. *Proceedings of the National Academy of Sciences of the United States of America*. 2012; 109:7049–7054. doi:10.1073/pnas.1114513109. [PubMed: 22499789]
99. Zhong H, Yang X, Kaplan LM, Molony C, Schadt EE. Integrating pathway analysis and genetics of gene expression for genome-wide association studies. *Am J Hum Genet*. 2010; 86:581–591. doi:S0002-9297(10)00102-3 [pii] 10.1016/j.ajhg.2010.02.020. [PubMed: 20346437]
100. Mori MA, et al. A systems biology approach identifies inflammatory abnormalities between mouse strains prior to development of metabolic disease. *Diabetes*. 2010; 59:2960–2971. doi: 10.2337/db10-0367. [PubMed: 20713682]
101. Gao S, Roberts HK, Wang X. Cross tissue trait-pathway network reveals the importance of oxidative stress and inflammation pathways in obesity-induced diabetes in mouse. *PloS one*. 2012; 7:e44544. doi:10.1371/journal.pone.0044544. [PubMed: 23028558]
102. Rifai N. High-sensitivity C-reactive protein: a useful marker for cardiovascular disease risk prediction and the metabolic syndrome. *Clinical chemistry*. 2005; 51:504–505. doi:10.1373/clinchem.2004.044990. [PubMed: 15738514]
103. Siegel D, et al. Inflammation, atherosclerosis, and psoriasis. *Clinical reviews in allergy & immunology*. 2013; 44:194–204. doi:10.1007/s12016-012-8308-0. [PubMed: 22359071]
104. Meng Q, Makinen VP, Luk H, Yang X. Systems Biology Approaches and Applications in Obesity, Diabetes, and Cardiovascular Diseases. *Current cardiovascular risk reports*. 2013; 7:73–83. doi:10.1007/s12170-012-0280-y. [PubMed: 23326608]
105. Nikolsky Y, Kleemann R. Systems biology approaches to the study of cardiovascular drugs. *Methods Mol Biol*. 2010; 662:221–243. doi:10.1007/978-1-60761-800-3_11. [PubMed: 20824474]
106. Wang SS, et al. Identification of pathways for atherosclerosis in mice: integration of quantitative trait locus analysis and global gene expression data. *Circ Res*. 2007; 101:e11–30. [PubMed: 17641228]
107. Schadt EE, et al. An integrative genomics approach to infer causal associations between gene expression and disease. *Nat Genet*. 2005; 37:710–717. [PubMed: 15965475]
108. Yang X, et al. Identification and validation of genes affecting aortic lesions in mice. *J Clin Invest*. 2010; 120:2414–2422. doi:42742 [pii] 10.1172/JCI42742. [PubMed: 20577049]
109. Huan T, et al. A systems biology framework identifies molecular underpinnings of coronary heart disease. *Arteriosclerosis, thrombosis, and vascular biology*. 2013; 33:1427–1434. doi:10.1161/ATVBAHA.112.300112.
110. Schunkert H, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet*. 2011; 43:333–338. doi:10.1038/ng.784. [PubMed: 21378990]
111. Inouye M, et al. An immune response network associated with blood lipid levels. *PLoS genetics*. 2010; 6 doi:10.1371/journal.pgen.1001113.
112. Makinen VP, et al. Integrative genomics reveals novel molecular pathways and gene networks for coronary artery disease. *PLoS genetics*. 2014; 10:e1004502. doi:10.1371/journal.pgen.1004502. [PubMed: 25033284]
113. Emilsson V, et al. Genetics of gene expression and its effect on disease. *Nature*. 2008; 452:423–428. doi:10.1038/nature06758. [PubMed: 18344981]
114. Wang IM, et al. Systems analysis of eleven rodent disease models reveals an inflammatome signature and key drivers. *Molecular systems biology*. 2012; 8:594. doi:10.1038/msb.2012.24. [PubMed: 22806142]
115. Kiechl S, et al. Blockade of receptor activator of nuclear factor-kappaB (RANKL) signaling improves hepatic insulin resistance and prevents development of diabetes mellitus. *Nature medicine*. 2013; 19:358–363. doi:10.1038/nm.3084.
116. Reilly SM, et al. An inhibitor of the protein kinases TBK1 and IKK-varepsilon improves obesity-related metabolic dysfunctions in mice. *Nature medicine*. 2013; 19:313–321. doi:10.1038/nm.3082.
117. Kazantsev AG. Cellular pathways leading to neuronal dysfunction and degeneration. *Drug news & perspectives*. 2007; 20:501–509. doi:10.1358/dnp.2007.20.8.1157616. [PubMed: 18080037]

118. Cisse M, Mucke L. Alzheimer's disease: A prion protein connection. *Nature*. 2009; 457:1090–1091. doi:10.1038/4571090a. [PubMed: 19242462]
119. Nussbaum JM, et al. Prion-like behaviour and tau-dependent cytotoxicity of pyroglutamylated amyloid-beta. *Nature*. 2012; 485:651–655. doi:10.1038/nature11060. [PubMed: 22660329]
120. Jucker M, Walker LC. Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. *Nature*. 2013; 501:45–51. doi:10.1038/nature12481. [PubMed: 24005412]
121. Polymenidou M, Cleveland DW. The seeds of neurodegeneration: prion-like spreading in ALS. *Cell*. 2011; 147:498–508. doi:10.1016/j.cell.2011.10.011. [PubMed: 22036560]
122. Wright JW, Harding JW. Importance of the brain Angiotensin system in Parkinson's disease. *Parkinson's disease*. 2012; 2012:860923. doi:10.1155/2012/860923.
123. Nicoletti F, et al. 17alpha-Ethynyl-androst-5-ene-3beta,7beta,17beta-triol (HE3286) Is Neuroprotective and Reduces Motor Impairment and Neuroinflammation in a Murine MPTP Model of Parkinson's Disease. *Parkinson's disease*. 2012; 2012:969418. doi:10.1155/2012/969418.
124. Paganetti P, et al. Increased Efflux of Amyloid-beta Peptides through the Blood-Brain Barrier by Muscarinic Acetylcholine Receptor Inhibition Reduces Pathological Phenotypes in Mouse Models of Brain Amyloidosis. *Journal of Alzheimer's disease : JAD*. 2013 doi:10.3233/JAD-131091.
125. Saresella M, et al. A complex proinflammatory role for peripheral monocytes in Alzheimer's disease. *Journal of Alzheimer's disease : JAD*. 2014; 38:403–413. doi:10.3233/JAD-131160. [PubMed: 23979026]
126. Parham C, Auckland L, Rachwal J, Clarke D, Bix G. Perlecan Domain V Inhibits Amyloid-beta Induced Brain Endothelial Cell Toxicity and Restores Angiogenic Function. *Journal of Alzheimer's disease : JAD*. 2014; 38:415–423. doi:10.3233/JAD-130683. [PubMed: 23979025]
127. Cook C, et al. Acetylation of the KXGS motifs in tau is a critical determinant in modulation of tau aggregation and clearance. *Human molecular genetics*. 2013 doi:10.1093/hmg/ddt402.
128. Maejima Y, et al. Mst1 inhibits autophagy by promoting the interaction between Beclin1 and Bcl-2. *Nature medicine*. 2013; 19:1478–1488. doi:10.1038/nm.3322.
129. Torisu T, et al. Autophagy regulates endothelial cell processing, maturation and secretion of von Willebrand factor. *Nature medicine*. 2013; 19:1281–1287. doi:10.1038/nm.3288.
130. Nixon RA. The role of autophagy in neurodegenerative disease. *Nature medicine*. 2013; 19:983–997. doi:10.1038/nm.3232.
131. Hasson SA, et al. High-content genome-wide RNAi screens identify regulators of parkin upstream of mitophagy. *Nature*. 2013 doi:10.1038/nature12748.
132. Manzanillo PS, et al. The ubiquitin ligase parkin mediates resistance to intracellular pathogens. *Nature*. 2013; 501:512–516. doi:10.1038/nature12566. [PubMed: 24005326]
133. Sarraf SA, et al. Landscape of the PARKIN-dependent ubiquitylome in response to mitochondrial depolarization. *Nature*. 2013; 496:372–376. doi:10.1038/nature12043. [PubMed: 23503661]
134. Hughes AL, Gottschling DE. An early age increase in vacuolar pH limits mitochondrial function and lifespan in yeast. *Nature*. 2012; 492:261–265. doi:10.1038/nature11654. [PubMed: 23172144]
135. Orvedahl A, et al. Image-based genome-wide siRNA screen identifies selective autophagy factors. *Nature*. 2011; 480:113–117. doi:10.1038/nature10546. [PubMed: 22020285]
136. Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. *Nature*. 2011; 469:221–225. doi:10.1038/nature09663. [PubMed: 21124315]
137. Dewapriya P, Li YX, Himaya SW, Pangestuti R, Kim SK. Neoechinulin A suppresses amyloid-beta oligomer-induced microglia activation and thereby protects PC-12 cells from inflammation-mediated toxicity. *Neurotoxicology*. 2013; 35:30–40. doi:10.1016/j.neuro.2012.12.004. [PubMed: 23261590]
138. Deretic V, Saitoh T, Akira S. Autophagy in infection, inflammation and immunity. *Nature reviews. Immunology*. 2013; 13:722–737. doi:10.1038/nri3532. [PubMed: 24064518]
139. Heneka MT, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature*. 2013; 493:674–678. doi:10.1038/nature11729. [PubMed: 23254930]

140. Lucin KM, et al. Microglial beclin 1 regulates retromer trafficking and phagocytosis and is impaired in Alzheimer's disease. *Neuron*. 2013; 79:873–886. doi:10.1016/j.neuron.2013.06.046. [PubMed: 24012002]
141. Kagan JC, Horng T. NLRP3 inflammasome activation: CD36 serves double duty. *Nature immunology*. 2013; 14:772–774. doi:10.1038/ni.2668. [PubMed: 23867926]
142. Sheedy FJ, et al. CD36 coordinates NLRP3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation. *Nature immunology*. 2013; 14:812–820. doi:10.1038/ni.2639. [PubMed: 23812099]
143. Park L, et al. Innate immunity receptor CD36 promotes cerebral amyloid angiopathy. *Proceedings of the National Academy of Sciences of the United States of America*. 2013; 110:3089–3094. doi:10.1073/pnas.1300021110. [PubMed: 23382216]
144. Yamanaka M, et al. PPARgamma/RXRalpha-induced and CD36-mediated microglial amyloid-beta phagocytosis results in cognitive improvement in amyloid precursor protein/presenilin 1 mice. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2012; 32:17321–17331. doi:10.1523/JNEUROSCI.1569-12.2012. [PubMed: 23197723]
145. Wilkinson K, Boyd JD, Glicksman M, Moore KJ, El Khoury J. A high content drug screen identifies ursolic acid as an inhibitor of amyloid beta protein interactions with its receptor CD36. *The Journal of biological chemistry*. 2011; 286:34914–34922. doi:10.1074/jbc.M111.232116. [PubMed: 21835916]
146. Kuda O, et al. CD36 protein is involved in store-operated calcium flux, phospholipase A2 activation, and production of prostaglandin E2. *The Journal of biological chemistry*. 2011; 286:17785–17795. doi:10.1074/jbc.M111.232975. [PubMed: 21454644]
147. Stewart CR, et al. CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. *Nature immunology*. 2010; 11:155–161. doi:10.1038/ni.1836. [PubMed: 20037584]
148. Schwartz M, Shechter R. Systemic inflammatory cells fight off neurodegenerative disease. *Nature reviews. Neurology*. 2010; 6:405–410. doi:10.1038/nrneurol.2010.71. [PubMed: 20531383]
149. Baruch K, et al. PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of Alzheimer's disease. *Nature medicine*. 2016; 22:135–137. doi:10.1038/nm.4022.
150. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002; 420:860–867. doi:10.1038/nature01322. [PubMed: 12490959]
151. Rothwell PM, et al. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet*. 2012; 379:1591–1601. doi:10.1016/S0140-6736(12)60209-8. [PubMed: 22440947]
152. Rothwell PM, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and nonvascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet*. 2012; 379:1602–1612. doi:10.1016/S0140-6736(11)61720-0. [PubMed: 22440946]
153. Burn J, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet*. 2011; 378:2081–2087. doi:10.1016/S0140-6736(11)61049-0. [PubMed: 22036019]
154. Li C, et al. Host regulatory network response to infection with highly pathogenic H5N1 avian influenza virus. *Journal of virology*. 2011; 85:10955–10967. doi:10.1128/JVI.05792-11. [PubMed: 21865398]
155. Elwood PC, Gallagher AM, Duthie GG, Mur LA, Morgan G. Aspirin, salicylates, and cancer. *Lancet*. 2009; 373:1301–1309. doi:10.1016/S0140-6736(09)60243-9. [PubMed: 19328542]
156. Wunsch H. COX provides missing link in mechanism of aspirin in colon cancer. *Lancet*. 1998; 351:1864. doi:10.1016/S0140-6736(05)78812-7. [PubMed: 9652680]
157. Powles TJ, Dowsett M, Easty GC, Easty DM, Neville AM. Breast-cancer osteolysis, bone metastases, and anti-osteolytic effect of aspirin. *Lancet*. 1976; 1:608–610. [PubMed: 55892]
158. Hawley SA, et al. The ancient drug salicylate directly activates AMP-activated protein kinase. *Science*. 2012; 336:918–922. doi:10.1126/science.1215327. [PubMed: 22517326]
159. O'Neill LA, Hardie DG. Metabolism of inflammation limited by AMPK and pseudo-starvation. *Nature*. 2013; 493:346–355. doi:10.1038/nature11862. [PubMed: 23325217]

160. Kuilman T, et al. Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. *Cell*. 2008; 133:1019–1031. doi:10.1016/j.cell.2008.03.039. [PubMed: 18555778]
161. Sanz-Moreno V, et al. ROCK and JAK1 signaling cooperate to control actomyosin contractility in tumor cells and stroma. *Cancer Cell*. 2011; 20:229–245. doi:10.1016/j.ccr.2011.06.018. [PubMed: 21840487]
162. Goldberg J. Decoding of sorting signals by coatamer through a GTPase switch in the COPI coat complex. *Cell*. 2000; 100:671–679. [PubMed: 10761932]
163. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. *N Engl J Med*. 2011; 364:656–665. doi: 10.1056/NEJMr0910283. [PubMed: 21323543]
164. Belkina AC, Denis GV. BET domain co-regulators in obesity, inflammation and cancer. *Nat Rev Cancer*. 2012; 12:465–477. doi:10.1038/nrc3256. [PubMed: 22722403]
165. De Marzo AM, et al. Inflammation in prostate carcinogenesis. *Nat Rev Cancer*. 2007; 7:256–269. doi:10.1038/nrc2090. [PubMed: 17384581]
166. Gyrð-Hansen M, Meier P. IAPs: from caspase inhibitors to modulators of NF-kappaB, inflammation and cancer. *Nat Rev Cancer*. 2010; 10:561–574. doi:10.1038/nrc2889. [PubMed: 20651737]
167. Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. *Nat Rev Cancer*. 2009; 9:798–809. doi:10.1038/nrc2734. [PubMed: 19851315]
168. Suva ML, Riggi N, Bernstein BE. Epigenetic reprogramming in cancer. *Science*. 2013; 339:1567–1570. doi:10.1126/science.1230184. [PubMed: 23539597]
169. Vogelstein B, et al. Cancer genome landscapes. *Science*. 2013; 339:1546–1558. doi:10.1126/science.1235122. [PubMed: 23539594]
170. Kreso A, et al. Variable clonal repopulation dynamics influence chemotherapy response in colorectal cancer. *Science*. 2013; 339:543–548. doi:10.1126/science.1227670. [PubMed: 23239622]
171. Krivtsov AV, Armstrong SA. Cancer. Can one cell influence cancer heterogeneity? *Science*. 2012; 338:1035–1036. doi:10.1126/science.1231594. [PubMed: 23180850]
172. Shibata D. Cancer. Heterogeneity and tumor history. *Science*. 2012; 336:304–305. doi:10.1126/science.1222361. [PubMed: 22517848]
173. Hein LK, Duplock S, Fuller M. Selective reduction of bis(monoacylglycerol)phosphate ameliorates the storage burden in a THP-1 macrophage model of Gaucher disease. *J Lipid Res*. 2013 doi:10.1194/jlr.M038232.
174. Deng H, Maitra U, Morris M, Li L. Molecular mechanism responsible for the priming of macrophage activation. *J Biol Chem*. 2013; 288:3897–3906. doi:10.1074/jbc.M112.424390. [PubMed: 23264622]
175. Quigley DA, et al. Network analysis of skin tumor progression identifies a rewired genetic architecture affecting inflammation and tumor susceptibility. *Genome Biol*. 2011; 12:R5. doi: 10.1186/gb-2011-12-1-r5. [PubMed: 21244661]
176. Quigley DA, et al. Genetic architecture of mouse skin inflammation and tumour susceptibility. *Nature*. 2009; 458:505–508. doi:10.1038/nature07683. [PubMed: 19136944]
177. Creixell P, Schoof EM, Erler JT, Linding R. Navigating cancer network attractors for tumor-specific therapy. *Nat Biotechnol*. 2012; 30:842–848. doi:10.1038/nbt.2345. [PubMed: 22965061]
178. Allesina S, Tang S. Stability criteria for complex ecosystems. *Nature*. 2012; 483:205–208. doi: 10.1038/nature10832. [PubMed: 22343894]
179. Neutel AM, et al. Reconciling complexity with stability in naturally assembling food webs. *Nature*. 2007; 449:599–602. doi:10.1038/nature06154. [PubMed: 17914396]
180. Vandermeer J, Perfecto I, Philpott SM. Clusters of ant colonies and robust criticality in a tropical agroecosystem. *Nature*. 2008; 451:457–459. doi:10.1038/nature06477. [PubMed: 18216853]
181. Luscombe NM, et al. Genomic analysis of regulatory network dynamics reveals large topological changes. *Nature*. 2004; 431:308–312. [PubMed: 15372033]
182. Azaele S, Pigolotti S, Banavar JR, Maritan A. Dynamical evolution of ecosystems. *Nature*. 2006; 444:926–928. doi:10.1038/nature05320. [PubMed: 17167485]

183. Soon WW, Hariharan M, Snyder MP. High-throughput sequencing for biology and medicine. *Molecular systems biology*. 9:640. [PubMed: 23340846]
184. Koboldt DC, Steinberg KM, Larson DE, Wilson RK, Mardis ER. The next-generation sequencing revolution and its impact on genomics. *Cell*. 155:27–38. [PubMed: 24074859]
185. Shapiro E, Biezuner T, Linnarsson S. Single-cell sequencing-based technologies will revolutionize whole-organism science. *Nat Rev Genet*. 14:618–630. [PubMed: 23897237]
186. Six A, et al. The Past, Present, and Future of Immune Repertoire Biology - The Rise of Next-Generation Repertoire Analysis. *Frontiers in immunology*. 4:413. [PubMed: 24348479]
187. Robins H. Immunosequencing: applications of immune repertoire deep sequencing. *Current opinion in immunology*. 25:646–652. [PubMed: 24140071]
188. Georgiou G, et al. The promise and challenge of high-throughput sequencing of the antibody repertoire. *Nature biotechnology*. 32:158–168.
189. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. *Cell*. 148:1258–1270. [PubMed: 22424233]
190. Cox MJ, Cookson WO, Moffatt MF. Sequencing the human microbiome in health and disease. *Human molecular genetics*. 22:R88–94. [PubMed: 23943792]
191. Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JI. Human nutrition, the gut microbiome and the immune system. *Nature*. 474:327–336. [PubMed: 21677749]
192. Yatsunenko T, et al. Human gut microbiome viewed across age and geography. *Nature*. 486:222–227. [PubMed: 22699611]
193. Weinstein JA, Jiang N, White RA 3rd, Fisher DS, Quake SR. High-throughput sequencing of the zebrafish antibody repertoire. *Science*. 2009; 324:807–810. [PubMed: 19423829]
194. Boyd SD, et al. Measurement and clinical monitoring of human lymphocyte clonality by massively parallel VDJ pyrosequencing. *Science translational medicine*. 2009; 1:12ra23.
195. Wu D, et al. High-throughput sequencing detects minimal residual disease in acute T lymphoblastic leukemia. *Science translational medicine*. 4:134ra163.
196. Logan AC, et al. High-throughput VDJ sequencing for quantification of minimal residual disease in chronic lymphocytic leukemia and immune reconstitution assessment. *Proceedings of the National Academy of Sciences of the United States of America*. 108:21194–21199. [PubMed: 22160699]
197. Robins HS, et al. Digital genomic quantification of tumor-infiltrating lymphocytes. *Science translational medicine*. 5:214ra169.
198. Maldonado L, et al. Intramuscular therapeutic vaccination targeting HPV16 induces T cell responses that localize in mucosal lesions. *Science translational medicine*. 6:221ra213.
199. Venet F, et al. Decreased T-cell repertoire diversity in sepsis: a preliminary study. *Critical care medicine*. 41:111–119. [PubMed: 23222261]
200. Lavinder JJ, et al. Identification and characterization of the constituent human serum antibodies elicited by vaccination. *Proceedings of the National Academy of Sciences of the United States of America*. 111:2259–2264. [PubMed: 24469811]
201. Ademokun A, et al. Vaccination-induced changes in human B-cell repertoire and pneumococcal IgM and IgA antibody at different ages. *Aging cell*. 10:922–930. [PubMed: 21726404]
202. Jiang N, et al. Lineage structure of the human antibody repertoire in response to influenza vaccination. *Science translational medicine*. 5:171ra119.
203. Wiley SR, et al. Targeting TLRs expands the antibody repertoire in response to a malaria vaccine. *Science translational medicine*. 3:93ra69.
204. De Jager PL, et al. ImmVar project: Insights and design considerations for future studies of “healthy” immune variation. *Seminars in immunology*. 2015; 27:51–57. doi:10.1016/j.smim.2015.03.003. [PubMed: 25819567]
205. Lee MN, et al. Common genetic variants modulate pathogen-sensing responses in human dendritic cells. *Science*. 2014; 343:1246980. doi:10.1126/science.1246980. [PubMed: 24604203]
206. Doria-Rose NA, et al. Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies. *Nature*.

207. Liao HX, et al. Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus. *Nature*. 496:469–476. [PubMed: 23552890]
208. Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. *Science*. 1996; 271:1582–1586. [PubMed: 8599114]
209. De Boer RJ, et al. Recruitment times, proliferation, and apoptosis rates during the CD8(+) T-cell response to lymphocytic choriomeningitis virus. *Journal of virology*. 2001; 75:10663–10669. doi: 10.1128/JVI.75.22.10663-10669.2001. [PubMed: 11602708]
210. Nowak, M.; May, RM. *Virus dynamics: mathematical principles of immunology and virology: mathematical principles of immunology and virology*. Oxford University Press; UK: 2000.
211. Forst CV. Network genomics—a novel approach for the analysis of biological systems in the post-genomic era. *Molecular biology reports*. 2002; 29:265–280. [PubMed: 12463419]
212. Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. *Nucleic acids research*. 2000; 28:27–30. [PubMed: 10592173]
213. Karp PD, et al. The EcoCyc and MetaCyc databases. *Nucleic acids research*. 2000; 28:56–59. [PubMed: 10592180]
214. Overbeek R, et al. WIT: integrated system for high-throughput genome sequence analysis and metabolic reconstruction. *Nucleic acids research*. 2000; 28:123–125. [PubMed: 10592199]
215. Forst CV, Schulten K. Phylogenetic analysis of metabolic pathways. *J Mol Evol*. 2001; 52:471–489. doi:10.1007/s002390010178. [PubMed: 11443351]
216. Stokes CL. Biological systems modeling: Powerful discipline for biomedical e-R&D. *AICHe journal*. 2000; 46:430–433.
217. Calvano SE, et al. A network-based analysis of systemic inflammation in humans. *Nature*. 2005; 437:1032–1037. doi:10.1038/nature03985. [PubMed: 16136080]
218. Zhang B, Horvath S. A general framework for weighted gene co-expression network analysis. *Statistical applications in genetics and molecular biology*. 2005; 4:Article17. doi: 10.2202/1544-6115.1128. [PubMed: 16646834]
219. Di Narzo AF, et al. Decrease of mRNA Editing after Spinal Cord Injury is Caused by Down-regulation of ADAR2 that is Triggered by Inflammatory Response. *Scientific reports*. 2015; 5:12615. doi:10.1038/srep12615. [PubMed: 26223940]
220. Song WM, Zhang B. Multiscale Embedded Gene Co-expression Network Analysis. *PLoS Comput Biol*. 2015; 11:e1004574. doi:10.1371/journal.pcbi.1004574. [PubMed: 26618778]
221. Song WM, Di Matteo T, Aste T. Building complex networks with Platonic solids. *Phys Rev E Stat Nonlin Soft Matter Phys*. 2012; 85:046115. [PubMed: 22680546]
222. Song WM, Di Matteo T, Aste T. Hierarchical information clustering by means of topologically embedded graphs. *PLoS One*. 2012; 7:e31929. doi:10.1371/journal.pone.0031929. [PubMed: 22427814]
223. Reiss DJ, Baliga NS, Bonneau R. Integrated biclustering of heterogeneous genome-wide datasets for the inference of global regulatory networks. *BMC bioinformatics*. 2006; 7:280. doi: 10.1186/1471-2105-7-280. [PubMed: 16749936]
224. Zak DE, Aderem A. Systems biology of innate immunity. *Immunological reviews*. 2009; 227:264–282. doi:10.1111/j.1600-065X.2008.00721.x. [PubMed: 19120490]
225. Yang X, et al. Validation of candidate causal genes for obesity that affect shared metabolic pathways and networks. *Nat Genet*. 2009; 41:415–423. [PubMed: 19270708]
226. Zhang B, et al. Integrated Systems Approach Identifies Genetic Nodes and Networks in Late-Onset Alzheimer's Disease. *Cell*. 2013; 153:707–720. [PubMed: 23622250]
227. Zhang B, Tran L, Emilsson V, Zhu J. Characterization of Genetic Networks Associated with Alzheimer's Disease. *Methods Mol Biol*. 2016; 1303:459–477. doi: 10.1007/978-1-4939-2627-5_28. [PubMed: 26235085]
228. Brown GR, et al. Gene: a gene-centered information resource at NCBI. *Nucleic acids research*. 2015; 43:D36–42. doi:10.1093/nar/gku1055. [PubMed: 25355515]

229. Smyth MJ, Ngio SF, Ribas A, Teng MW. Combination cancer immunotherapies tailored to the tumour microenvironment. *Nature reviews. Clinical oncology*. 2016; 13:143–158. doi:10.1038/nrclinonc.2015.209.
230. Wagner AH, et al. DGIdb 2.0: mining clinically relevant drug-gene interactions. *Nucleic acids research*. 2016; 44:D1036–1044. doi:10.1093/nar/gkv1165. [PubMed: 26531824]
231. Medzhitov R. Origin and physiological roles of inflammation. *Nature*. 2008; 454:428–435. doi: 10.1038/nature07201. [PubMed: 18650913]
232. Csermely P, Korcsmaros T, Kiss HJ, London G, Nussinov R. Structure and dynamics of molecular networks: a novel paradigm of drug discovery: a comprehensive review. *Pharmacology & therapeutics*. 138:333–408. [PubMed: 23384594]
233. Wang IM, et al. Systems analysis of eleven rodent disease models reveals an inflammatome signature and key drivers. *Molecular systems biology*. 8:594. [PubMed: 22806142]
234. Kidd BA, Peters LA, Schadt EE, Dudley JT. Unifying immunology with informatics and multiscale biology. *Nature immunology*. 15:118–127. [PubMed: 24448569]
235. Chen R, et al. Personal omics profiling reveals dynamic molecular and medical phenotypes. *Cell*. 148:1293–1307. [PubMed: 22424236]
236. Gibbs WW. Medicine gets up close and personal. *Nature*. 506:144–145. [PubMed: 24522582]
237. Hood L, Friend SH. Predictive, personalized, preventive, participatory (P4) cancer medicine. *Nature reviews*. 8:184–187.
238. Bohnhorst JO, Thoen JE, Natvig JB, Thompson KM. Significantly depressed percentage of CD27+ (memory) B cells among peripheral blood B cells in patients with primary Sjogren's syndrome. *Scand J Immunol*. 2001; 54:421–427. [PubMed: 11555410]

Figure 1. Example immune response networks

A) A pharmacologically addressable response network is shown. By inhibiting CHEK1, viral protein production is severely limited. Node colors (cell viability) and node border colors (viral replication) refer to negative (blue) and positive (red) Z-scores after RNAi analysis indicating low and high viral replication/cell viability, respectively²³⁸. **B)**

Regulation of the mTOR pathway by a naphthalimide compound. REDD1 (DDIT4) is activated by the compound. Node colors indicate up- (red) and down- (blue) regulated genes between compound and DMSO (control) treated A549 cells. Edge colors denote edge scores (yellow edges have high score).

Figure 2.
The relationship between immune, inflammasome, and inflammation gene signatures.

Figure 4.
A core causal network in inflammation. The predicted key drivers are highlighted in larger size and red color.