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A systems biology approach to the effect of aging, immunosenescence and vaccine response

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Abstract

Aging can lead to immunosenescence, which dramatically impairs the hosts' ability to develop protective immune responses to vaccine antigens. Reasons for this are not well understood. This topic's importance is reflected in the increases in morbidity and mortality due to infectious diseases among elderly persons, a population growing in size globally, and the significantly lower adaptive immune responses generated to vaccines in this population. Here, we endeavor to summarize the existing data on the genetic and immunologic correlates of immunosenescence with respect to vaccine response. We cover how the application of systems biology can advance our understanding of vaccine immunosenescence, with a view toward how such information could lead to strategies to overcome the lower immunogenicity of vaccines in the elderly.

Introduction

The cellular, genetic, and other aspects of aging result in a phenomenon known as "immunosenescence." While immunosenescence has protean effects on the health of the organism, it can particularly impair the host's ability to defend itself against microbial invasion by pathogens such as bacteria and viruses. This results from defects in innate and adaptive humoral and cellular immunity (see Figure 1). Such defects in immune response are readily apparent in humoral and cellular responses to vaccine antigens. Here, we will

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Competing Interests

Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland offers consultative advice on vaccine development to Merck & Co. Inc., CSL Biotherapies, Avianax, Sanofi Pasteur, Dynavax, Novartis Vaccines and Therapeutics, PAXVAX Inc, and Emergent Biosolutions. Drs. Poland and Ovsyannikova hold two patents related to vaccinia peptide research. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with Mayo Clinic Conflict of Interest policies.

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provide an overview of genetic variation in aging and evidence for impaired immune responses to common vaccines. We highlight how researchers are approaching a deeper understanding of immunosenescence and vaccine response from a systems biology point of view.

Systems biology and immunological response

Complex biological processes such as the immune response, or aging, are not the result of isolated events, single proteins, chemicals, enzymes, or even individual cell types; rather, they are the coordinated result of interacting cell types, tissues, alterations in gene regulation and expression, signaling pathways, and biological networks. It is the combined, synergistic effect of the individual parts that leads to immunity, aging, and immunosenescence. Although reductionist approaches have delivered valuable information regarding individual components (proteins, genes, single pathways, metabolites), a fundamental understanding of the whole picture will require a comprehensive examination of all the respective pieces of the puzzle.

Systems biology seeks to characterize, in a comprehensive or high-throughput manner, the behavior of each part of a biological system. It applies computational models to the data to predict and/or influence the system's behavior. As applied to immunology and vaccine response, it aims to define the mechanisms leading to immunity, and predict the resulting immune response after vaccination [1,2]. This can also be applied to immune alterations in the elderly (see Figure 2). Multiple groups have applied elements of systems biology, advanced bioinformatics, computer algorithms, and high dimensional assays to probe immune function and labeled their approaches as vaccinomics [3], systems vaccinology [2], systems immunogenetics [4], vaccine informatics/computational immunology [5,6], and reverse vaccinology [7,8]. Common to each approach is the application of appropriate tools (biological and computational) toward the understanding of immune function at a systems level. These studies revealed unexpected insights into the development of immune responses to vaccines. Querec *et al.* used a systems biology approach to discover that expression of the complement C1qB protein and the eukaryotic translation initiation factor 2 alpha were highly predictive of CD8+ T cell responses to yellow fever vaccine [9]. The same study identified a different signature, involving TNFRSF17, which predicted neutralizing antibody responses to the same vaccine. Another group applied a gene-set enrichment analysis to influenza vaccine recipients and identified a set of genes involved in B cell proliferation and immunoglobulin production, which predicted influenza vaccine responses with 88% accuracy. One group integrated genome-wide polymorphism analysis and eQTL to identify genes involved in antigen expression and intracellular trafficking as important determinants of influenza vaccine immunogenicity [10,11]. Other groups have used blood transcriptome analysis to identify an IFN-inducing gene signature associated with tuberculosis disease susceptibility [12]. This neutrophil-driven IFN signature correlated with pulmonary disease and vanished with successful treatment. Systems biology approaches have greatly enhanced our understanding of tuberculosis infection and immunity, and may provide biomarkers for diagnosis and treatment of tuberculosis infections as well as the development of new vaccines [12,13]. Systems immunology approaches have allowed us to identify important differences in innate and adaptive immune responses to different vaccines. For example,

innate responses after pneumococcal vaccine administration are dominated by an inflammatory response detectable ~7 hours after vaccination, while influenza vaccine induces a delayed (15-hour) IFN response [14]. Both vaccines elicit a Day 7 plasmablast response (defined by: gene expression [CD38, TNFRSF17]; elevated pathogen-specific serum Ab; and increases in circulating plasmablasts). Elements of this plasmablast signature have also been seen with yellow fever vaccine, perhaps indicating a key pathway activated by multiple viral vaccines. Many of these approaches are being employed with malaria and HIV vaccines in the early stages of research and development [15–18]. Variations of these approaches can be applied toward understanding, predicting, and eventually overcoming immunosenescence.

The immunogenetics of aging and vaccine response offer insight into the effect of aging on the immune system, and offer possibilities for identifying and repairing or overcoming such defects through systems biology approaches in an attempt to induce protective immune responses to pathogens that threaten health and well-being of a large segment of the population.

Genetic Variation and Aging

Immunosenescence is generally defined as age-related changes to the immune system that result in increased susceptibility to infectious diseases and a decreased response to vaccination [19]. The identification of genetic determinants of immunosenescence could transform aging research, including vaccine and adjuvant development in the elderly, and development of novel approaches to overcoming aging defects [20]. Although immunosenescence can be attributed to many factors, recent data have demonstrated that there is host genetic variation related to aging. In a study of 423 healthy Icelandic individuals (17 to 89 years of age), an age-associated decrease in the frequency of the C4B*Q0 allele of the complement C4B gene was found to be associated with a negative effect on health or survival in subjects with coronary artery disease [21]. Several studies reported the relationship between polymorphisms of adipokine genes and age-associated diseases [22,23]. In a study of 110 elderly subjects (>85 years old), genetic variation in the adiponectin (SNP rs1501299) and leptin (SNP rs7799039) genes is linked to the gender-specific longevity phenotype [24]. A protective role of the longevity-associated D2S1338-18 allele established in a comparison between deceased and living populations is also suggested [25], which indicates genetic polymorphisms may play a role in immunosenescence-related phenotypes.

Antiviral immunity against pathogens, including influenza virus, is greatly reduced in the elderly. A heritable contribution to predisposition to a fatal outcome from influenza infection has been proposed [26,27]. One important gene for the anti-inflammatory response to influenza virus infection is the heme oxygenase-1 gene (HO-1) [28]. A decline in antibody production after influenza vaccination has been linked to the HO-1 and HO-2 gene polymorphisms [29]. Decreased antibody production in response to influenza vaccine was observed in an aged HO-1-deficient mouse model, suggesting that HO gene expression is an important element of the impaired age-related response to influenza vaccine [29].

There is evidence that age-related modifications in gene expression may play a role in the physiological changes detected with aging. To understand how transcriptomic changes may contribute to the aging process, total RNA transcripts in peripheral blood mononuclear cells were compared between healthy young (25 to 48 years of age) and old (75 to 103 years of age) individuals [30]. Of the 148 transcripts proposed to be involved in immunosenescence and stress reaction, 16 transcripts mainly related to modification of immune function (e.g., CD28, CD69, LCK, CD86, cathepsins, etc.) were differentially expressed in old subjects, suggesting that these transcriptomic biomarkers may be biomarkers of aging [30]. A recent report by Harries *et al.* suggested that human aging is associated with a few changes in individual gene expression (i.e., deregulation of mRNA processing pathways) [31]. Many studies have used epigenome-wide DNA methylation analysis for measurement of the methylation status at CpG sites (dinucleotides) and found multiple CpG sites associated with DNA methylation and aging [32,33]. Understanding the effect of age on DNA methylation (histone modifications and changes to chromatin structure) could improve our knowledge of the role of epigenetic variations in the process of human aging.

Preliminary data from peripheral blood mononuclear cell (PBMC) miRNAs indicate down-regulation of miR-590-5p expression three days after influenza vaccination in subjects 50–74 years old ($p < 0.0006$) (Kennedy RB, unpublished data). In humans, miR-590-5p was found to target the expression of mRNAs involved in the transforming growth factor, beta receptor II (TGFBR2) pathway, and is predicted to affect both MED21 and SATB1 genes (which are, respectively: a transcription activator regulating expression of RNA polymerase II genes; and a transcriptional repressor, which controls gene expression through chromatin remodeling and affects IL-2, IL2RA, and Ig genes in T and B cells) (Kennedy RB, unpublished data). In addition to the findings associated with miRNAs, it has been shown that mitochondrial DNA damage, such as mtDNA deletions and point mutations, may also accumulate in human CD4+ T lymphocytes with age and may play a role in T cell aging and immunosenescence [34]. Such studies are beginning to elucidate molecular mechanisms behind immunosenescence in the elderly.

Immunosenescence and vaccine response

The complex nature of immunosenescence makes it a difficult measure to quantify. Vaccination of older adults against influenza, hepatitis, or pneumococcal disease does not induce the same level of protective immunity as that observed in a comparable, but younger, population [35–40]. To our knowledge, a definitive explanation for this has not been reported. Most studies have focused on single forms of immunosenescent-related deficiencies in vaccine response. We provide a brief summary of results from studies on age-related changes to immunity after vaccination (see Table 1). These examples highlight very specific perturbations. It is important to acknowledge that all of these—as well as yet-to-be discovered—immunosenescent factors influence immune responses in older adults.

Activation of the innate branch of the immune system is crucial for the production of a robust adaptive response [41]. This is, in part, accomplished through the production of inflammatory mediators (i.e., cytokines and chemokines) after activation of pattern recognition receptors (TLRs, NLRs, CLRs, RLRs) by pathogen-associated molecular

patterns (PAMPs). There is an age-related decline in TLR-induced expression of the CD80 costimulatory molecule that is associated with a decrease in humoral immunity to influenza vaccine [42]. There is also a diminished level of TLR-induced secretion of the inflammatory cytokines IL-12/p40, IL-6, TNF- α , and IFN- α in DCs from older subjects, which correlates with a reduced influenza-specific antibody response [43]. An age-associated decrease in antibody response to influenza vaccine also inversely correlates with elevated levels of the anti-inflammatory, cytokine IL-10 [44]. Overall, immunosenescent factors influencing innate immunity, and the subsequent adaptive response to influenza vaccine, appear to involve altered activation of effector cells and the dysregulated release of pro- and non-inflammatory mediators.

Immunosenescence and its effect on adaptive immunity have been extensively studied. In the context of vaccine response and cellular immunity, an increase in CD8⁺CD28^{null} T cells is associated with poor immunity to influenza vaccine [45,46]. The proliferative response of T-cells from older adults after vaccination against hepatitis B is diminished, which may be due to differences in expression of CD62L [47]. There is a decline in the frequency of influenza-specific CD4⁺ memory T-cells, and CD8⁺ effector and effector memory cells exhibit decreased cytolytic properties in response to influenza vaccine in older subjects [48,49]. Along with changes to cellular immunity, aging significantly impacts vaccine-induced humoral immunity. Sasaki *et al.* observed differences in the number of influenza vaccine-specific plasmablasts and plasmablast-derived polyclonal antibodies (PPAbs) from elderly, compared to young adults, but saw no observable difference in affinity or avidity [50]. This is not the case with pneumococcal vaccine, where older adults produce similar concentrations of antibodies as younger subjects, but with markedly lower potency and opsonic capacity [51]. These findings suggest there are differential age-associated effects that are specific to the vaccine administered. A successful vaccine candidate that elicits protective immunity against infectious diseases will incorporate factors that overcome the significant age-associated decline in the immune system over time.

Summary

Understanding mechanisms of immunosenescence and how they impact immune response to vaccines is critical to protecting aging individuals from infectious agents and other diseases. The elderly suffer disproportionate morbidity and mortality due to infectious diseases, and yet few vaccines have been developed to provide protective immunity specific to the elderly. Early research, as reviewed herein, identified age-related impacts on genes whose function is critical to innate and adaptive immune response to exogenous antigens. These early findings must be coupled with more sophisticated assays that can be utilized in a systems biology paradigm to holistically understand the simultaneous changes and interactions that together impair immune responses. Such understanding, informed by knowledge from other fields of endeavor, may allow us to identify and repair or overcome the obstacles to development of protective immune responses that aging imposes on the immune system. In turn, such understanding will lead to new vaccine approaches, new vaccine adjuvants, and perhaps new methods of vaccine administration or schedules that together may reverse the terrible burden of infectious disease threats in the aging human host.

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Highlights

- Immunosenescence leads to increased susceptibility to infection and decreased vaccine response
- HO gene expression may be an important element in age-related impairment of response to influenza vaccine
- A systems level approach is needed to define the complex biological processes of immunosenescence
- Systems biology has revealed vaccine-specific, age-related changes to apoptosis gene modules

Figure 1.
Immunologic Changes Due to Immunosenescence

Figure 2.

The Incorporation of Immunosenescence Markers into a Predictive Vaccine Response and Systems Biology Model. There is a diminished immune response to vaccines in the elderly. Specific factors that have been shown to be associated with this response (for example: chronological age, body mass index (BMI), CD28 expression on CD8 T-cells; telomerase reverse transcriptase (TERT); and T-cell receptor excisions circles (TREC)). Current systems biology approaches focus on incorporating these immunosenescence markers into a predictive vaccine response model in hopes of better understanding the complex intricacies of the aging immune system. [1] *Novel insights will be gained by new research approaches aimed at studying metabolomics, metagenomics, and the host microbiome.

Table 1

Examples of age-related factors influencing vaccine response

	Innate Immunity	Adaptive Immunity
Influenza Vaccine ↓ Antibody response	↓ CD80 expression ↓ TLR-induced secretion of the inflammatory cytokines in DCs ↑ IL-10 levels * Age-related changes to gene modules involved in apoptosis	↑ CD8+CD28 ^{null} cells ↓ Plasmablasts and PPAbs
↓ Cellular response		↓ Influenza-specific CD4+ memory T-cells ↓ CD8+ T-cell cytolytic properties
Hepatitis Vaccine ↓ Cellular response		↓ CD62L-associated decrease in CD4+ T-cell proliferation
Pneumococcal Vaccine ↓ Antibody response		↓ In antibody potency and opsonization properties

* Furman et al. deployed a systems biology approach to determine age-related changes to seasonal influenza vaccine response [52].