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Autoimmunity: homeostasis of innate immunity gone awry

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Introduction

Autoimmunity is generally considered to represent an attack on self-tissues mediated by autoantibodies or self-reactive T cells. However, the recent identification of genetic variants in inflammatory diseases provides unequivocal examples of defects in innate immunity leading to autoimmunity. The complement system and DNases will be used as telling examples of how genetic variants in innate immune pathways produce injury directly or by triggering the adaptive immune system. The principles illustrated are likely representative of how other innate immune pathways mediate damage to self.

Direct tissue damage by dysregulated innate immunity

Atypical hemolytic uremic syndrome (aHUS): Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy (TMA) characterized by a triad of hemolytic anemia, thrombocytopenia and acute renal failure and is classified as enteropathic (diarrhea-associated) or non-enteropathic (atypical). Rare heterozygous mutations in a negative regulator (factor I, factor H or MCP) of the complement system's ancient alternative pathway (AP) as well as gain of function mutations in an AP component (C3 or factor B) have been identified in over 50% of aHUS cases (Atkinson *et al.*, 2005; Loirat & Fremeaux-Bacchi, 2011; Noris & Remuzzi, 2009; Richards *et al.*, 2007; Rodriguez de Cordoba, 2010). AP features a feedback loop that can amplify complement responses initiated by classical or lectin pathway activation or if the AP "tickover" exceeds regulatory activity. Thus, individuals carrying a mutation are predisposed to developing a rapid and inappropriately regulated storm of AP mediated complement activity on damaged endothelial cells and exposed basement membranes culminating in a TMA that most severely affects the kidney.

aHUS exemplifies how targeted gene sequencing in a rare disease identified deleterious, unique variants in multiple components of an innate immune pathway. This newly acquired understanding of aHUS pathogenesis has led to the use of targeted therapy. Eculizumab, a monoclonal antibody to C5, is FDA-approved for aHUS albeit based on as yet unpublished data (FDA, 2011). A recent review discusses its use and efficacy (Westra *et al.*, 2012). The concept of excessive AP response and the utility of eculizumab are currently being investigated in more common TMAs like enteropathic HUS (Menne *et al.*, 2012) and preeclampsia (Salmon *et al.*, 2011) as well as in a severe subset of preeclampsia known as hemolysis elevated liver enzymes low platelets (HELLP) syndrome (Fakhouri *et al.*, 2008; Fang *et al.*, 2008).

Age-related macular degeneration (AMD): AMD is a common, chronic organ specific example of AP driven tissue damage and is the leading cause of blindness in the industrialized world (Resnikoff *et al.*, 2004). AMD causes progressive central vision loss and, at an early stage, is characterized by drusen, which are focal depositions of extracellular debris between the retinal pigment epithelium (RPE) and Bruch's membrane. Drusen is a complex mixture of oxidized lipids, modified proteins, peptidoglycans and other cellular debris that stain positive for activation fragments and regulators of the AP (Johnson *et al.*, 2001).

In 2005, four groups reported that a single nucleotide polymorphism (SNP) in factor H, the major regulator of the AP in blood, confers significant susceptibility to AMD. Y402H increases the risk of AMD two- to four-fold in heterozygotes (402_{YH}) and five- to seven-fold in homozygotes (402_{HH}) (Edwards *et al.*, 2005; Hageman *et al.*, 2005; Haines *et al.*, 2005; Klein *et al.*, 2005). Studies of purified factor H from genotyped individuals show that the wild type (402_{YY}) binds more efficiently to RPE, C-reactive protein (Anderson *et al.*, 2010), and oxidized phospholipids than 402_{YH} or 402_{HH} (Shaw *et al.*, 2012). Interestingly, a group A streptococcus (GAS) virulence factor binds less efficiently to 402_{HH}, leading to greater complement driven GAS opsonization and phagocytosis (Haapasalo *et al.*, 2008) and therefore, providing an evolutionary reason for the high prevalence of this AMD risk allele.

A highly penetrant rare variant (R1210C), known to alter factor H binding to C3b and endothelial cells (Manuelian *et al.*, 2003), was recently reported in AMD patients (Raychaudhuri *et al.*, 2011). Other protective and risk associated SNPs have been identified in factor H (Hageman, 2008) and in other participants of AP (factor I, factor B and C3). The combined analyses of risk variants in members of the AP can account for nearly 75% of AMD cases (Gold *et al.*, 2006; Seddon *et al.*, 2009).

These two examples illustrate a concept of “innate autoimmunity”: an overactive AP in a genetically susceptible host mediating damage to self (figure 1). In aHUS, the injury is an acute event focused on the endothelium and the kidney basement membrane, while in AMD tissue damage accumulates over years and even decades in the retina. Both diseases evince how a variant in a regulatory protein or a gain of function mutation in an activator of a simple proinflammatory pathway of innate immunity can lead to autoimmunity.

Deficiencies in innate immunity generating an adaptive immune response

Systemic lupus erythematosus (SLE): Lupus has served as a paradigm for autoimmunity since antinuclear antibodies were first detected in these patients' sera over 70 years ago. In the 1960s, immune complexes with complement fragments were noted in SLE renal lesions (Koffler *et al.*, 1969b) and anti-dsDNA antibodies were shown to be a risk factor for lupus nephritis (Koffler *et al.*, 1969a). These observations led to a SLE pathogenesis model in which autoantibodies bind nuclear antigens, fix the classical pathway of complement activation and deposit in tissues (Koffler *et al.*, 1971).

Surprisingly, a deficiency in any of the early complement components of the classical pathway (C1q, C1r, C1s, C4 or C2) was identified a few years later to be a major risk factor for developing SLE. Approximately 90% of C1q and 80% of C4 deficient individuals develop SLE (Pickering *et al.*, 2000; Walport, 2001). The “lupus paradox” arose because, if SLE is mediated by autoantibodies activating the classical pathway, should not C1q or C4 deficiency be protective (Carroll, 1998)?

Since the 1980s, the concept of defective clearance of immune complexes containing nuclear antigens has been a centerpiece of lupus pathophysiology (Atkinson, 1989; Lachmann, 1984). Initially, it was thought to be the defective removal of foreign nuclear

material derived from retroviruses that led to “autoantigen” development. Subsequently, studies in complement deficient mice have turned the focus to self-nuclear antigens as the immunogen. C1q deficient (C1q^{-/-}) mice develop high titer antinuclear antibodies and 25% develop glomerulonephritis (Botto *et al.*, 1998). C1q^{-/-} mice accumulate apoptotic bodies in their glomeruli that correlated with disease severity. This observation and other similar data led to the hypothesis that C1q and early classical pathway partners are critical for the proper clearance of nuclear debris derived from apoptotic and necrotic cells (Carroll, 1998; Walport, 2001).

Deoxyribonuclease1 (DNase1): The initial report of SLE patients having decreased levels of DNase1, the major extracellular endonuclease that cleaves both single and double-stranded DNA was in 1981 (Chitrabamrung *et al.*, 1981). Lupus prone mice were also reported to have reduced levels of “DNase” in both sera and urine (Macanovic & Lachmann, 1997). Mice deficient in DNase1 developed both antinuclear and anti-dsDNA antibodies and glomerulonephritis (Napirei *et al.*, 2000).

Subsequently, two SLE patients were reported to have heterozygous DNase1 mutations and decreased DNase enzymatic activity (Yasutomo *et al.*, 2001). In 2011, Al-Mayouf *et al.* sequenced DNASE1L3, one of three human homologs of DNase1, in 6 Saudi Arabian families affected with predominately early onset, severe, anti-dsDNA positive SLE in an autosomal recessive pattern. A fully penetrant homozygous 1 base pair deletion in DNASE1L3 segregated perfectly with SLE. The protein encoded by the mutant DNASE1L3 lacked enzymatic activity (Al-Mayouf *et al.*, 2011). These studies have shifted the SLE pathogenesis model toward a self-antigen driven disease caused by an inadequate clearance of “altered self” nuclear material (Walport, 2000).

Three prime repair exonuclease 1 (TREX1 or DNase3): Aicardi-Goutières syndrome (AGS) is a rare autosomal recessive disease of infancy featuring a severe encephalitis with prominent lymphocytic infiltration and elevated CSF type 1 IFN. Loss of function homozygous mutations in TREX1, the major human intracellular 3' to 5' exonuclease, cause AGS (Crow *et al.*, 2006; Rice *et al.*, 2007). However, unlike AGS patients, the TREX1 knockout mouse died of a noninfectious autoimmune inflammatory myocarditis (Morita *et al.*, 2004) but also featured a type 1 IFN dependent production of anti-nuclear antibodies and glomerulonephritis with immune complex deposition (Stetson *et al.*, 2008).

Due to several autoimmune characteristics exhibited by TREX1 knockout mice and AGS patients, Lee-Kirsch and colleagues sequenced the TREX1 gene in lupus patients. In German and United Kingdom cohorts, they identified TREX1 mutations in 2% (9/417) of SLE patients (Lee-Kirsch *et al.*, 2007). No functional analyses were performed on the missense mutations but one of the 9 mutations described, R114H, had been previously reported in AGS as having decreased enzymatic activity (Orebaugh *et al.*, 2011). In a subsequent large GWAS, Namjou *et al.*, reported multiple TREX1 SNPs associated with SLE that were unique to a particular ethnic population (Namjou *et al.*, 2011). Through GWAS, approximately 20 distinct lupus susceptibility loci (OR 1.1 to 2.0) have been described, but none has as strong of an effect as TREX1 (OR 25) (Harley *et al.*, 2009).

Gall and colleagues recently elucidated how TREX1 mutations could lead to autoimmunity. The Interferon Stimulatory DNA pathway (ISD) is one of two recognized Toll-like Receptor (TLR) independent intracellular DNA recognition pathways (Karayel *et al.*, 2009). Upon activation by primarily ssDNA, ISD induces the expression of TREX1 and a lymphocyte-independent type I IFN response. In turn, TREX1 metabolizes ISD activators to limit the IFN response (Stetson *et al.*, 2008). TREX1^{-/-} mice manifest a dysregulated type 1 IFN response that requires an intact adaptive immune system to manifest an autoimmune

phenotype (Gall *et al.*, 2012). In the case of TREX1^{-/-} mouse, the IFN response drives the development of autoreactive T cells while in DNase1^{-/-} mouse an inability to properly clear extracellular DNA leads to TLR activation. Activation of TLRs on antigen presenting cells then result in autoreactive T and B cells and a type 1 IFN response (Elkon & Wiedeman, 2012; Liu & Davidson, 2012).

In sum, a deficiency in innate immunity such as an early component of the classical complement pathway or a nuclease can lead to inadequate clearance of DNA debris. By one of several mechanisms, accumulated nuclear materials trigger the adaptive immune response to form autoreactive T cells and anti-nuclear antibodies.

Conclusion

In most paradigms of autoimmunity, innate immunity was traditionally viewed as playing a modest role in etiopathogenesis. However, the examples described herein demonstrate how disruptions in homeostasis of the innate immune pathways mediate self-tissue injury via an excessive inflammatory response or by triggering adaptive immunity. Too little regulation may produce an acute thrombomicroangiopathic state like aHUS or a chronic, localized inflammatory condition of the retina like AMD. On the other hand, a defect in innate immunity (i.e. complement or nucleases) may impair nuclear debris clearance. Such “garbage” is modified and can serve as a self-antigen as well as creating a cytokine milieu that drives the adaptive immune system to break T-cell tolerance and stimulate B cells to produce autoantibodies.

List of abbreviations defined in text

aHUS	atypical hemolytic uremic syndrome
TMA	thrombotic microangiopathy
AP	alternative pathway
HUS	hemolytic uremic syndrome
HELLP syndrome	hemolysis elevated liver enzymes low platelets
AMD	age-related macular degeneration
RPE	retinal pigment epithelium
SNP	single nucleotide polymorphism
GAS	group A streptococcus
SLE	systemic lupus erythematosus
DNase1	deoxyribonuclease 1
TREX1	three prime repair exonuclease 1
AGS	Aicardi-Goutières syndrome
ISD	Interferon Stimulatory DNA pathway
TLR	Toll-like Receptor
GWAS	genome wide association study

Not defined

CSF	cerebrospinal fluid
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IFN interferon

References

- Al-Mayouf SM, Sunker A, Abdwani R, Arawi SA, Almurshedi F, Alhashmi N, Al Sonbul A, Sewairi W, Qari A, Abdallah E, Al-Owain M, Al Motywee S, Al-Rayes H, Hashem M, Khalak H, Al-Jebali L, Alkuraya FS. Loss-of-function variant in DNASE1L3 causes a familial form of systemic lupus erythematosus. *Nat Genet.* 2011; 43(12):1186–1188. [PubMed: 22019780]
- Anderson DH, Radeke MJ, Gallo NB, Chapin EA, Johnson PT, Curletti CR, Hancox LS, Hu J, Ebright JN, Malek G, Hauser MA, Rickman CB, Bok D, Hageman GS, Johnson LV. The pivotal role of the complement system in aging and age-related macular degeneration: hypothesis re-visited. *Prog Retin Eye Res.* 2010; 29(2):95–112. [PubMed: 19961953]
- Atkinson JP. Complement deficiency: predisposing factor to autoimmune syndromes. *Clin Exp Rheumatol.* 1989; 7 (Suppl 3):S95–101. [PubMed: 2691164]
- Atkinson JP, Liszewski MK, Richards A, Kavanagh D, Moulton EA. Hemolytic uremic syndrome: an example of insufficient complement regulation on self-tissue. *Ann N Y Acad Sci.* 2005; 1056:144–152. [PubMed: 16387683]
- Botto M, Dell'agnola C, Bygrave AE, Thompson EM, Cook HT, Petry F, Loos M, Pandolfi PP, Walport MJ. Homozygous C1q deficiency causes glomerulonephritis associated with multiple apoptotic bodies. *Nat Genet.* 1998; 19(1):56–59. [PubMed: 9590289]
- Carroll MC. The lupus paradox. *Nat Genet.* 1998; 19(1):3–4. [PubMed: 9590274]
- Chitramamrung S, Rubin RL, Tan EM. Serum deoxyribonuclease I and clinical activity in systemic lupus erythematosus. *Rheumatol Int.* 1981; 1(2):55–60. [PubMed: 6287560]
- Crow YJ, Hayward BE, Parmar R, Robins P, Leitch A, Ali M, Black DN, Van Bokhoven H, Brunner HG, Hamel BC, Corry PC, Cowan FM, Frints SG, Klepper J, Livingston JH, Lynch SA, Massey RF, Meritet JF, Michaud JL, Ponsot G, et al. Mutations in the gene encoding the 3'–5' DNA exonuclease TREX1 cause Aicardi-Goutieres syndrome at the AGS1 locus. *Nat Genet.* 2006; 38(8): 917–920. [PubMed: 16845398]
- Edwards AO, Ritter R 3rd, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. *Science.* 2005; 308(5720):421–424. [PubMed: 15761121]
- Elkon KB, Wiedeman A. Type I IFN system in the development and manifestations of SLE. *Curr Opin Rheumatol.* 2012; 24(5):499–505. [PubMed: 22832823]
- Fakhouri F, Jablonski M, Lepercq J, Blouin J, Benachi A, Hourmant M, Pirson Y, Durrbach A, Grunfeld JP, Knebelmann B, Fremeaux-Bacchi V. Factor H, membrane cofactor protein, and factor I mutations in patients with hemolysis, elevated liver enzymes, and low platelet count syndrome. *Blood.* 2008; 112(12):4542–4545. [PubMed: 18658028]
- Fang CJ, Fremeaux-Bacchi V, Liszewski MK, Pianetti G, Noris M, Goodship TH, Atkinson JP. Membrane cofactor protein mutations in atypical hemolytic uremic syndrome (aHUS), fatal Stx-HUS, C3 glomerulonephritis, and the HELLP syndrome. *Blood.* 2008; 111(2):624–632. [PubMed: 17914026]
- Fda. Eculizumab. 2011. Available online at: <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm273089.htm>
- Gall A, Treuting P, Elkon KB, Loo YM, Gale M Jr, Barber GN, Stetson DB. Autoimmunity initiates in nonhematopoietic cells and progresses via lymphocytes in an interferon-dependent autoimmune disease. *Immunity.* 2012; 36(1):120–131. [PubMed: 22284419]
- Gold B, Merriam JE, Zernant J, Hancox LS, Taiber AJ, Gehrs K, Cramer K, Neel J, Bergeron J, Barile GR, Smith RT, Hageman GS, Dean M, Allikmets R. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. *Nat Genet.* 2006; 38(4):458–462. [PubMed: 16518403]
- Haapasalo K, Jarva H, Siljander T, Tewodros W, Vuopio-Varkila J, Jokiranta TS. Complement factor H allotype 402H is associated with increased C3b opsonization and phagocytosis of *Streptococcus pyogenes*. *Mol Microbiol.* 2008; 70(3):583–594. [PubMed: 18627465]

- Hageman, G.; Gehrs, K.; Johnson, LV; Anderson, D. Age-Related Macular Degeneration (AMD). In: Kolb, H.; Fernandez; Nelson, R., editors. *Webvision: The Organization of the Retina and Visual System*. University of Utah Health Sciences Center; Salt Lake City: 2008.
- Hageman GS, Anderson DH, Johnson LV, Hancox LS, Taiber AJ, Hardisty LI, Hageman JL, Stockman HA, Borchardt JD, Gehrs KM, Smith RJ, Silvestri G, Russell SR, Klaver CC, Barbazetto I, Chang S, Yannuzzi LA, Barile GR, Merriam JC, Smith RT, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. *Proc Natl Acad Sci U S A*. 2005; 102(20):7227–7232. [PubMed: 15870199]
- Haines JL, Hauser MA, Schmidt S, Scott WK, Olson LM, Gallins P, Spencer KL, Kwan SY, Nouredine M, Gilbert JR, Schnetz-Boutaud N, Agarwal A, Postel EA, Pericak-Vance MA. Complement factor H variant increases the risk of age-related macular degeneration. *Science*. 2005; 308(5720):419–421. [PubMed: 15761120]
- Harley IT, Kaufman KM, Langefeld CD, Harley JB, Kelly JA. Genetic susceptibility to SLE: new insights from fine mapping and genome-wide association studies. *Nat Rev Genet*. 2009; 10(5): 285–290. [PubMed: 19337289]
- Johnson LV, Leitner WP, Staples MK, Anderson DH. Complement activation and inflammatory processes in Drusen formation and age related macular degeneration. *Exp Eye Res*. 2001; 73(6): 887–896. [PubMed: 11846519]
- Karaye E, Burckstummer T, Bilban M, Durnberger G, Weitzer S, Martinez J, Superti-Furga G. The TLR-independent DNA recognition pathway in murine macrophages: Ligand features and molecular signature. *Eur J Immunol*. 2009; 39(7):1929–1936. [PubMed: 19551900]
- Klein RJ, Zeiss C, Chew EY, Tsai JY, Sackler RS, Haynes C, Henning AK, Sangiovanni JP, Mane SM, Mayne ST, Bracken MB, Ferris FL, Ott J, Barnstable C, Hoh J. Complement factor H polymorphism in age-related macular degeneration. *Science*. 2005; 308(5720):385–389. [PubMed: 15761122]
- Koffler D, Agnello V, Carr RI, Kunkel HG. Anti-DNA antibodies and renal lesions of patients with systemic lupus erythematosus. *Transplant Proc*. 1969a; 1(4):933–938. [PubMed: 4939688]
- Koffler D, Agnello V, Carr RI, Kunkel HG. Variable patterns of immunoglobulin and complement deposition in the kidneys of patients with systemic lupus erythematosus. *Am J Pathol*. 1969b; 56(3):305–316. [PubMed: 4186204]
- Koffler D, Agnello V, Thoburn R, Kunkel HG. Systemic lupus erythematosus: prototype of immune complex nephritis in man. *J Exp Med*. 1971; 134(3):169–179. [PubMed: 19867364]
- Lachmann PJ. Inherited complement deficiencies. *Philos Trans R Soc Lond B Biol Sci*. 1984; 306(1129):419–430. [PubMed: 6149584]
- Lee-Kirsch MA, Gong M, Chowdhury D, Senenko L, Engel K, Lee YA, De Silva U, Bailey SL, Witte T, Vyse TJ, Kere J, Pfeiffer C, Harvey S, Wong A, Koskenmies S, Hummel O, Rohde K, Schmidt RE, Dominiczak AF, Gahr M, et al. Mutations in the gene encoding the 3′-5′ DNA exonuclease TREX1 are associated with systemic lupus erythematosus. *Nat Genet*. 2007; 39(9):1065–1067. [PubMed: 17660818]
- Liu Z, Davidson A. Taming lupus-a new understanding of pathogenesis is leading to clinical advances. *Nat Med*. 2012; 18(6):871–882. [PubMed: 22674006]
- Loirat C, Fremeaux-Bacchi V. Atypical hemolytic uremic syndrome. *Orphanet J Rare Dis*. 2011; 6:60. [PubMed: 21902819]
- Macanovic M, Lachmann PJ. Measurement of deoxyribonuclease I (DNase) in the serum and urine of systemic lupus erythematosus (SLE)-prone NZB/NZW mice by a new radial enzyme diffusion assay. *Clin Exp Immunol*. 1997; 108(2):220–226. [PubMed: 9158089]
- Manuelian T, Hellwege J, Meri S, Caprioli J, Noris M, Heinen S, Jozsi M, Neumann HP, Remuzzi G, Zipfel PF. Mutations in factor H reduce binding affinity to C3b and heparin and surface attachment to endothelial cells in hemolytic uremic syndrome. *J Clin Invest*. 2003; 111(8):1181–1190. [PubMed: 12697737]
- Menne J, Nitschke M, Stingle R, Abu-Tair M, Beneke J, Bramstedt J, Bremer JP, Brunkhorst R, Busch V, Dengler R, Deuschl G, Fellermann K, Fickenscher H, Gerigk C, Goettsche A, Greeve J, Hafer C, Hagenmuller F, Haller H, Herget-Rosenthal S, et al. Validation of treatment strategies for

- enterohaemorrhagic *Escherichia coli* O104:H4 induced haemolytic uraemic syndrome: case-control study. *Bmj*. 2012; 345:e4565. [PubMed: 22815429]
- Morita M, Stamp G, Robins P, Dulic A, Rosewell I, Hrivnak G, Daly G, Lindahl T, Barnes DE. Gene-targeted mice lacking the Trex1 (DNase III) 3'→5' DNA exonuclease develop inflammatory myocarditis. *Mol Cell Biol*. 2004; 24(15):6719–6727. [PubMed: 15254239]
- Nanjou B, Kothari PH, Kelly JA, Glenn SB, Ojwang JO, Adler A, Alarcon-Riquelme ME, Gallant CJ, Boackle SA, Criswell LA, Kimberly RP, Brown E, Edberg J, Stevens AM, Jacob CO, Tsao BP, Gilkeson GS, Kamen DL, Merrill JT, Petri M, et al. Evaluation of the TREX1 gene in a large multi-ancestral lupus cohort. *Genes Immun*. 2011; 12(4):270–279. [PubMed: 21270825]
- Napirei M, Karsunky H, Zevnik B, Stephan H, Mannherz HG, Moroy T. Features of systemic lupus erythematosus in Dnase1-deficient mice. *Nat Genet*. 2000; 25(2):177–181. [PubMed: 10835632]
- Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. *N Engl J Med*. 2009; 361(17):1676–1687. [PubMed: 19846853]
- Orebaugh CD, Fye JM, Harvey S, Hollis T, Perrino FW. The TREX1 exonuclease R114H mutation in Aicardi-Goutieres syndrome and lupus reveals dimeric structure requirements for DNA degradation activity. *J Biol Chem*. 2011; 286(46):40246–40254. [PubMed: 21937424]
- Pickering MC, Botto M, Taylor PR, Lachmann PJ, Walport MJ. Systemic lupus erythematosus, complement deficiency, and apoptosis. *Adv Immunol*. 2000; 76:227–324. [PubMed: 11079100]
- Raychaudhuri S, Iartchouk O, Chin K, Tan PL, Tai AK, Ripke S, Gowrisankar S, Vemuri S, Montgomery K, Yu Y, Reynolds R, Zack DJ, Campochiaro B, Campochiaro P, Katsanis N, Daly MJ, Seddon JM. A rare penetrant mutation in CFH confers high risk of age-related macular degeneration. *Nat Genet*. 2011; 43(12):1232–1236. [PubMed: 22019782]
- Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP. Global data on visual impairment in the year 2002. *Bull World Health Organ*. 2004; 82(11):844–851. [PubMed: 15640920]
- Rice G, Patrick T, Parmar R, Taylor CF, Aeby A, Aicardi J, Artuch R, Montalto SA, Bacino CA, Barroso B, Baxter P, Benko WS, Bergmann C, Bertini E, Biancheri R, Blair EM, Blau N, Bonthron DT, Briggs T, Brueton LA, et al. Clinical and molecular phenotype of Aicardi-Goutieres syndrome. *Am J Hum Genet*. 2007; 81(4):713–725. [PubMed: 17846997]
- Richards A, Kavanagh D, Atkinson JP. Inherited complement regulatory protein deficiency predisposes to human disease in acute injury and chronic inflammatory states: the examples of vascular damage in atypical hemolytic uremic syndrome and debris accumulation in age-related macular degeneration. *Adv Immunol*. 2007; 96:141–177. [PubMed: 17981206]
- Rodriguez De Cordoba S. aHUS: a disorder with many risk factors. *Blood*. 2010; 115(2):158–160. [PubMed: 20075170]
- Salmon JE, Heuser C, Triebwasser M, Liszewski MK, Kavanagh D, Roumenina L, Branch DW, Goodship T, Fremeaux-Bacchi V, Atkinson JP. Mutations in complement regulatory proteins predispose to preeclampsia: a genetic analysis of the PROMISSE cohort. *PLoS Med*. 2011; 8(3):e1001013. [PubMed: 21445332]
- Seddon JM, Reynolds R, Maller J, Fagerness JA, Daly MJ, Rosner B. Prediction model for prevalence and incidence of advanced age-related macular degeneration based on genetic, demographic, and environmental variables. *Invest Ophthalmol Vis Sci*. 2009; 50(5):2044–2053. [PubMed: 19117936]
- Shaw PX, Zhang L, Zhang M, Du H, Zhao L, Lee C, Grob S, Lim SL, Hughes G, Lee J, Bedell M, Nelson MH, Lu F, Krupa M, Luo J, Ouyang H, Tu Z, Su Z, Zhu J, Wei X, et al. Complement factor H genotypes impact risk of age-related macular degeneration by interaction with oxidized phospholipids. *Proc Natl Acad Sci U S A*. 2012; 109(34):13757–13762. [PubMed: 22875704]
- Stetson DB, Ko JS, Heidmann T, Medzhitov R. Trex1 prevents cell-intrinsic initiation of autoimmunity. *Cell*. 2008; 134(4):587–598. [PubMed: 18724932]
- Walport MJ. Lupus, DNase and defective disposal of cellular debris. *Nat Genet*. 2000; 25(2):135–136. [PubMed: 10835621]
- Walport MJ. Complement. Second of two parts. *N Engl J Med*. 2001; 344(15):1140–1144. [PubMed: 11297706]

- Westra D, Wetzels JF, Volokhina EB, Van Den Heuvel LP, Van De Kar NC. A new era in the diagnosis and treatment of atypical haemolytic uraemic syndrome. *Neth J Med*. 2012; 70(3):121–129. [PubMed: 22516576]
- Yasutomo K, Horiuchi T, Kagami S, Tsukamoto H, Hashimura C, Urushihara M, Kuroda Y. Mutation of DNASE1 in people with systemic lupus erythematosus. *Nat Genet*. 2001; 28(4):313–314. [PubMed: 11479590]

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Figure 1.

Genetic variants in innate immune pathways mediate autoimmunity. Variants with a regulatory defect (bold arrow indicating too much innate immune activity) in the setting of a predisposing injury, lead to an excessive innate immune mediated inflammatory response. Variants with a clearance defect (dashed arrow indicating too little innate immune activity) lead to “garbage” accumulation. Modified “self” then triggers an adaptive immune response. Consequently, both overactivity and underactivity of an innate immune pathway could lead to autoimmunity.