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Role of Viruses and Bacteria-Virus Interactions In Autoimmunity

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Abstract

A potential role for viral and bacterial-viral interactions in the pathogenesis of autoimmune disease has been long recognized. Recently, intensive investigation has begun to decipher interactions between specific microbes with the host that contribute toward autoimmunity. This work has primarily focused on known viral and bacterial pathogens. A major challenge is to determine the role of bacteria that are typically considered as commensals as well as chronic viruses. Furthermore, equally challenging is to prove causality given the potential complexity of microbe-microbe interactions. Important initial contributions to this field have shown that specific interactions of microbes with hosts that contain a background of genetic susceptibility can play a role in autoimmune pathogenesis. In this review, we describe principles of immune tolerance with a focus on its breakdown during pathogenic as well as commensal relationships between the host and the microbial world.

Introduction

Autoimmunity simply stated is one's immune system responding to self. Self-recognition is an important physiological process contributing to the maintenance of homeostasis and is essential for tissue repair and regeneration. In contrast, autoimmune diseases are those in which the immune system inappropriately responds to self in a manner leading to tissue destruction or dysfunction. Autoimmune diseases encompass a diverse set of entities with more than 80 recognized autoimmune conditions afflicting an estimated 100 million people around the globe [1]. Increasing evidence has linked genetic polymorphisms in key immune system pathways to specific autoimmune disease development. A strong association for the development of certain autoimmune diseases has been tied to polymorphisms at the major histocompatibility complex [2], and genome wide association studies (GWAS) have further demonstrated links to critical of components of innate and adaptive immunity [3]. These links are explored in depth in this issue of *Current Opinions in Immunology* (Diamond/Gregersen; Sollid/Wucherpfennig; Wijmenga/Xavier).

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Despite insights from genetic studies and subsequent investigation, our understanding of autoimmune disease pathogenesis is far from complete. It is increasingly evident that inheritable factors do not fully explain the etiology of autoimmune conditions. Discordance in twin studies has spurred the search for environmental factors contributing to autoimmune disease pathogenesis [4,5]. Microbes, particularly pathogens, have long been investigated as a missing link between genetic predisposition and autoimmune disease pathogenesis. This hypothesis is supported by human epidemiological studies linking specific pathogens to a range of autoimmune diseases, phenomena that have been modeled and dissected in animal models [6]. Recently, attention has been focused on the role of commensal microbes in the development of autoimmune conditions. Here, we review principles of immune tolerance related to proposed mechanisms of autoimmune disease pathogenesis with a focus on the relationship between pathogens, commensal microbes, and the genetically susceptible host.

Immune Tolerance

To understand the pathogenesis of autoimmune disease, an understanding of the mechanisms in place to prevent its development is essential. The immune system is faced with a formidable task: to recognize and defend against foreign attack without inducing significant harm to the host. In addition to avoiding host antigens, the immune system is faced with the added complexity of distinguishing typically nonpathogenic commensal microbes from pathogens, an important function that is essential to preserve the mutually beneficial relationship between the host and microbiome.

Decades of investigation have focused on identifying the key mechanisms by which tolerance of the adaptive immune system is achieved. T-cell tolerance has been divided into central and peripheral mechanisms; detailed examination of which has been extensively reviewed elsewhere [7,8]. Briefly, central tolerance is achieved through the process by which T-cells are selected during thymic development. Lymphocytes that exhibit host MHC restriction (capable of recognizing host MHC) undergo positive selection, while lymphocytes that robustly respond to host MHC displayed self-antigens undergo negative selection. The fidelity of T-cell receptor (TCR) signaling is critical to the development of central tolerance. Accordingly, mutations in a downstream kinase (ZAP70) abrogate central tolerance and contribute to the development of autoimmune arthritis in a mouse model [9]. The importance of central tolerance is further illustrated by studies investigating AIRE, a transcription factor that is essential for T-cell negative selection via its ability to induce ectopic expression of host peripheral (non-thymic) proteins during T-cell development [10,11]. In the absence of AIRE, negative selection does not occur resulting in the development of multiple autoreactive T-cell clones, autoantibodies, and a wide range of autoimmune phenomena [12-14]. The role of AIRE in autoimmune pathogenesis is further strengthened by the discovery of multiple mutations in AIRE that are associated with autoimmune disease in humans [15].

Despite thymic selection mechanisms, some autoreactive T-cells escape central tolerance [16]. Such cells have been demonstrated in both healthy people and those with type 1 diabetes and multiple sclerosis [17-19]. Under physiologic conditions these autoreactive T-cells do not typically produce disease as they are controlled through peripheral tolerance, a

mechanism that prevents activation of these T-cells against self. Peripheral tolerance is achieved by limited lymphocyte trafficking, promotion of anergy through lack of co-stimulation, apoptotic deletion, and T-regulatory cell mediated suppression. The importance of peripheral tolerance has been established in animal models as well as human studies; GWAS analyses have linked several autoimmune diseases with loci associated with co-stimulatory molecules [20]. Moreover, patients with mutations in the key T-regulatory cell transcription factor FOXP3 develop significant life-threatening autoimmunity [21]. Significant work has demonstrated that dysregulation of certain T-cell subsets, including these T-regulatory cells and Th17 lineage cells, are important for the development of autoimmunity [22,23].

The innate immune system also plays essential roles in immune tolerance by governing the initial host response to damaged tissue and pathogens and as well as triggering appropriate adaptive immune responses. For example, the role of dendritic cells in both central and peripheral tolerance is well documented [24]. NK cells participate in immune tolerance through inhibitory cell surface receptors. Mutations in the killer immunoglobulin-like inhibitory receptors have been associated with autoimmune conditions such as alopecia areata, rheumatoid arthritis, and systemic lupus erythematosus [25-27]). Additionally, NK cells shape T-cell responses directly by deleting autoreactive T-cells and indirectly via secretion of cytokines known to regulate T-cell tolerance [28,29].

Infection and Autoimmunity

The role of microbes in development of autoimmune disease can best be appreciated by highlighting many of the proposed pathologic mechanisms at play. Microbe-driven or associated autoimmune diseases have been hypothesized to occur through a variety of classic processes including molecular or epitope mimicry of self-antigens, immune recognition of previously unexposed self-antigen, bystander activation of autoreactive lymphocytes, and superantigen mediated polyclonal T-cell activation with exaggerated cytokine release. Importantly, the role of bacteria and viruses in shaping the repertoire of T-cells subsets implicated in autoimmunity is also an ongoing area of interest [30,31]. Key examples of autoimmunity stemmed from the bacterial and viral pathogens are provided below.

The link between certain bacterial infections and autoimmunity is particularly compelling, and molecular mimicry is often implicated in autoimmune disease pathogenesis. One of the best studied examples is the occurrence of rheumatic fever that occurs after pharyngeal infection with the gram-positive bacteria *Streptococcus pyogenes*. The host antibody response is targeted against the bacterium's dominant carbohydrate epitope (N-acetyl-β -D-glucosamine) and a virulence factor (M-protein). These antibodies cross-react with cardiac myosin as well as laminin and vimentin, antigens that are found on both semilunar and atrioventricular valves of the host. Consequently, this host antibody response directly causes serious pathological sequela of rheumatic fever, carditis and cardiac valve dysfunction [32]. Post-infectious glomerulonephritis is another example of an autoimmune condition associated with prior infection. Here, nephritogenic strains of *Streptococcus* and *Staphylococcus* encode particular exotoxins [33,34]). Glomeruli are not acutely damaged by

these infections or toxins, and they are not a site of active bacterial infection. Instead, the process of molecular mimicry damages glomeruli through the process of cross reactive antibodies.

Medical treatment of the above autoimmune conditions has been shaped by these discoveries and the role of bacteria in autoimmune disease pathogenesis. For example, a patient diagnosed with rheumatic fever or post-infectious glomerulonephritis is typically given a course of antibiotics aimed at bacterial source control for the population at large even if the patient's initial pharyngitis has abated clinically or by microbial detection. This overall approach has been successful in the developed world with a decreasing incidence of both these diseases, coincident with an increased use of empiric antibiotics for pharyngitis [35].

However, similar successes have not yet been realized in autoimmune conditions linked to viruses, partly due to an incomplete understanding of their role in driving autoimmunity as well as inherent difficulty in viral diagnosis and effective antiviral treatments. The complex link between viruses and autoimmune conditions is exemplified by some of the first work demonstrating an association between viral infection and autoimmune disease pathogenesis. Work in the 1970s and 1980s showed an association between neonatal lymphocytic choriomeningitis (LCMV) and polyoma virus infection with immune complex glomerulonephritis and associated mortality [36]. Interestingly, further work showed that infection with LCMV inhibits development of two rodent models of autoimmune diabetes [37,38], a condition characterized by autoantibodies and reactive T-cell mediated destruction of pancreatic β-cells [39]. The finding that a specific viral infection carries divergent risks for the development of glomerulonephritis and type 1 diabetes highlights the complex relationship between virus infection and autoimmunity.

Intriguingly, different viral infections are associated with opposing risks of type 1 diabetes development. While LCMV has been implicated in diabetes protection, current evidence points to a pathogenic role for enteroviral infection; a hypothesis fueled by epidemiological data and further supported by experimental animal models and isolation of virus from the pancreatic islets of Langerhans [40-42]. Interestingly, the enterovirus, Coxsackie B4, was shown to infect thymocytes both in cell culture and mice resulting in aberrant T-cell maturation potentially impacting the development of central tolerance [43,44]. Further evidence for the role of Coxsackie infection in development of type I diabetes stems from GWAS studies that identified the interferon-induced helicase (IFIH1) locus, a key innate immune sensor of Coxsackie infection, as a risk susceptibility region [45]. In addition, there is molecular similarity between the islet enzyme tyrosine phosphatase IA-2 and a conserved and highly immunogenic enterovirus capsid protein that may result in molecular mimicry [46].

When considering potential mechanisms of disease pathogenesis, viral association with autoimmune disease must be considered within the context of the dynamic relationship between the virus and host. After initial or acute infection, some viruses are capable of establishing persistence or latent infection. In fact, healthy humans harbor multiple lifelong viruses [47,48]. The establishment of persistent infection and latency is associated with

distinct viral gene expression from that during acute infection. These findings underscore the need to precisely understand which components of the viral life cycle contribute to autoimmunity.

Ebstein-Barr Virus (EBV) is one of the most well-studied viruses capable of latency and has been implicated in systemic lupus erythematosus, Sjogren's syndrome, and rheumatoid arthritis [49]. After initial early infection, EBV typically persists in the majority of the population in a latent form with a restricted gene expression pattern [50]. However, in patients with systemic autoimmune conditions, EBV is associated with increased viral loads, increased antibody titers, and altered cell-mediated immunity [49]. Whether these findings represent inability of genetically susceptible hosts to control acute infection, establish or maintain latency is unclear.

The development of chronic viral infections, such as hepatitis B and C, in certain individuals further calls attention to the importance of our understanding of the role of long-standing viral infection in autoimmune disease. Hepatitis infection can progress over years to liver failure and cancer development. Additionally, autoantibodies are frequently observed in patients, both children and adults, with chronic hepatitis virus [51]. However, the role of an autoimmune process in the disease evolution is unclear. Defining disease pathogenesis becomes difficult in chronic viral infections with ongoing inflammation and host cellular damage. Where does persistent infection end and autoimmunity begin? Does the immune response to persistent infection or to subsequent infections drive the evolution of autoimmune pathology? These questions showcase how much there remains to understand in the host-pathogen interaction.

Moreover, host genetics may contribute to whether a viral infection results in autoimmunity. This intricacy is exemplified by the role of a murine enteric infection in an experimental model of inflammatory bowel disease (IBD). Cadwell *et. al* showed that abnormalities associated with IBD including abnormal Paneth cell granule packaging in mice with a hypomorphic allele of ATG16L1 (a risk factor for Crohn's disease in humans) is dependent on persistent infection with murine norovirus [52]. This work underscores the potential role of viral infection in autoimmunity in a genetically susceptible host and may shed light on the vast heterogeneity of autoimmune disease development in the human population.

Commensal Bacteria and Autoimmunity

Our understanding of the importance of our microbiota is continuously evolving and is paramount in our understanding of autoimmune disease pathogenesis. The contribution of the gut bacterial microbiota increases cell number an estimated ten-fold and genes a hundred-fold to the overall superorganism. What role do these relationships and associated gene expression play in the induction and propagation of autoimmunity?

Although still mechanistically unclear, the role of the gut microbiome in the development of IBD is under intense investigation [53-55]. Differences in bacterial species isolated from fecal samples between healthy people and those with IBD have been demonstrated [56], and studies from monozygotic twins discordant for IBD has shown differences in gut microbial composition [57]. Consistent with a role of commensals in disease pathogenesis, IBD

patients treated with probiotics or antibiotics have a transient decrease in disease-associated symptoms [58]. However, little is known about which species is driving pathology. Recent investigation has illuminated the dysbiosis of the gut microbiota in pediatric patients with Crohn's Disease prior to antibiotic treatment, and strikingly antibiotic exposure further amplified the observed dysbiosis [59].

Animals models have consistently borne out the importance of the gut microbiota in IBD with disease phenotypes ameliorated or absent in animals housed in germ-free or specific pathogen free facilities [60]. In the hypomorphic Atg16l1 mouse model, dextran sodium sulfate induced colitis that produces features of human IBD is abrogated in antibiotic treated animals [52], further supporting the importance of the microbiota in genetic susceptibility models. This study also highlights the complex interaction of commensal bacteria and chronic viral infection [61]. Spontaneous colitis development in the *IL-10-/-* mouse model is dependent on commensal relationships and the ability to signal through MyD88, a key adaptor protein in Toll-like receptor signaling and innate immune recognition of bacteria [62]. Prior work in our laboratory has demonstrated that in the antibiotic responsive mouse model of IBD (*IL10-/-* and T-cell dominant negative TNF-β), a subset of commensal Bacteriodes species can induce disease pathology [63]. Further underscoring the complex interactions between viruses, bacterial commensals and genetic susceptibility in disease pathogenesis, a recent study demonstrated that the gut microbiota is required for murine norovirus to induce disease in the *IL-10-/-* model of IBD [64].

Intriguingly, the effect of gut commensal relationships on autoimmune disease development is not simply local, but has systemic effects. In a mouse model of rheumatoid arthritis, germ-free animals are protected from arthritis [65], and differences in the gut microbiota composition have also been demonstrated in patients with early rheumatoid arthritis compared to those with fibromyalgia [66]. These findings imply that further study of microbiota and autoimmune pathogenesis may reveal far reaching, and potentially surprising, effects.

To further add to this complexity, our bacterial microbiota hosts its own virobiota, existing as bacteriophages. These viruses are capable of regulating the gut microbiota composition; production of a specific bacteriophage confers a selective growth advantage to *Enterococcus faecalis* over related *Enterococcus* strains in its intestinal niche [67]. An additional layer of intricacy appears when one considers the presence of retroviral elements inserted into our genome. In fact, patients with multiple sclerosis have increased DNA copies of and transcription from a particular retroelement compared to controls with corresponding protein expression confirmed by brain immunohistology [68]. The above examples emphasize how systematic characterization of microbiota and virobiota in currently established animal models is critical for understanding their applicable toward studying human disease. Conversely, detailed analysis of the microbiota and virobiota in human disease will be paramount to aid the generation of more precise animal models.

Conclusion/Future Areas of Investigation

The role of our microbiota in autoimmune disease development is supported by numerous human studies and experimental animal models. While we have learned a great deal about host and pathogen immunity, true causality has remained elusive and difficult to prove in humans. Much work has focused on pathogenic relationships between the microbiota and host organism in disease development with loss of immune tolerance through molecular mimicry as a major pathogenic mechanism. Undoubtedly, the role of microbes in the dysregulation of key T-cell subsets implicated in autoimmunity will be particularly informative in future studies. Furthermore, we have only become to scratch the surface of the role of chronic infections and commensal relationships in autoimmune conditions, and future studies will undoubtedly seek to delineate their effects. Such work will undoubtedly be aided by significant advances in sequencing technology and expansion of our understanding of the composition and relationship between the microbiota and host.

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References

1. Selgrade MK, Cooper GS, Germolec DR, Heindel JJ. Linking environmental agents and autoimmune disease: an agenda for future research. Environ Health Perspect. 1999; 107 Suppl 5:811–813. [PubMed: 10502548]
2. Fernando MM, Stevens CR, Walsh EC, De Jager PL, Goyette P, Plenge RM, Vyse TJ, Rioux JD. Defining the role of the MHC in autoimmunity: a review and pooled analysis. PLoS Genet. 2008; 4:e1000024. [PubMed: 18437207]
3. Cho JH, Gregersen PK. Genomics and the multifactorial nature of human autoimmune disease. N Engl J Med. 2011; 365:1612–1623. [PubMed: 22029983]
4. Bogdanos DP, Smyk DS, Rigopoulou EI, Mytilinaiou MG, Heneghan MA, Selmi C, Gershwin ME. Twin studies in autoimmune disease: genetics, gender and environment. J Autoimmun. 2012; 38:J156–169. [PubMed: 22177232]
5. Javierre BM, Hernando H, Ballestar E. Environmental triggers and epigenetic deregulation in autoimmune disease. Discov Med. 2011; 12:535–545. [PubMed: 22204770]
6. Munz C, Lunemann JD, Getts MT, Miller SD. Antiviral immune responses: triggers of or triggered by autoimmunity? Nat Rev Immunol. 2009; 9:246–258. [PubMed: 19319143]
7. Starr TK, Jameson SC, Hogquist KA. Positive and negative selection of T cells. Annu Rev Immunol. 2003; 21:139–176. [PubMed: 12414722]
8. Klein L, Kyewski B, Allen PM, Hogquist KA. Positive and negative selection of the T cell repertoire: what thymocytes see (and don't see). Nat Rev Immunol. 2014; 14:377–391. [PubMed: 24830344]
9. Sakaguchi N, Takahashi T, Hata H, Nomura T, Tagami T, Yamazaki S, Sakihama T, Matsutani T, Negishi I, Nakatsuru S, et al. Altered thymic T-cell selection due to a mutation of the ZAP-70 gene causes autoimmune arthritis in mice. Nature. 2003; 426:454–460. [PubMed: 14647385]
10. Akirav EM, Ruddle NH, Herold KC. The role of AIRE in human autoimmune disease. Nat Rev Endocrinol. 2011; 7:25–33. [PubMed: 21102544]
11. Giraud M, Yoshida H, Abramson J, Rahl PB, Young RA, Mathis D, Benoist C. Aire unleashes stalled RNA polymerase to induce ectopic gene expression in thymic epithelial cells. Proc Natl Acad Sci U S A. 2012; 109:535–540. [PubMed: 22203960]

12. Anderson MS, Venanzi ES, Klein L, Chen ZB, Berzins SP, Turley SJ, von Boehmer H, Bronson R, Dierich A, Benoist C, et al. Projection of an immunological self shadow within the thymus by the aire protein. Science. 2002; 298:1395–1401. [PubMed: 12376594]

13. Ramsey C, Winqvist O, Puhakka L, Halonen M, Moro A, Kampe O, Eskelin P, Pelto- Huikko M, Peltonen L. Aire deficient mice develop multiple features of APECED phenotype and show altered immune response. Hum Mol Genet. 2002; 11:397–409. [PubMed: 11854172]

14. Kuroda N, Mitani T, Takeda N, Ishimaru N, Arakaki R, Hayashi Y, Bando Y, Izumi K, Takahashi T, Nomura T, et al. Development of autoimmunity against transcriptionally unrepressed target antigen in the thymus of Aire-deficient mice. J Immunol. 2005; 174:1862–1870. [PubMed: 15699112]

15. Capalbo D, Giardino G, Martino LD, Palamaro L, Romano R, Gallo V, Cirillo E, Salerno M, Pignata C. Genetic basis of altered central tolerance and autoimmune diseases: a lesson from AIRE mutations. Int Rev Immunol. 2012; 31:344–362. [PubMed: 23083345]

16. Bouneaud C, Kourilsky P, Bousso P. Impact of negative selection on the T cell repertoire reactive to a self-peptide: a large fraction of T cell clones escapes clonal deletion. Immunity. 2000; 13:829–840. [PubMed: 11163198]

17. Danke NA, Koelle DM, Yee C, Beheray S, Kwok WW. Autoreactive T cells in healthy individuals. J Immunol. 2004; 172:5967–5972. [PubMed: 15128778]

18. Raddassi K, Kent SC, Yang J, Bourcier K, Bradshaw EM, Seyfert-Margolis V, Nepom GT, Kwok WW, Hafler DA. Increased frequencies of myelin oligodendrocyte glycoprotein/MHC class II-binding CD4 cells in patients with multiple sclerosis. J Immunol. 2011; 187:1039–1046. [PubMed: 21653833]

19. Yang J, Danke N, Roti M, Huston L, Greenbaum C, Pihoker C, James E, Kwok WW. CD4+ T cells from type 1 diabetic and healthy subjects exhibit different thresholds of activation to a naturally processed proinsulin epitope. J Autoimmun. 2008; 31:30–41. [PubMed: 18385016]

20. Maier LM, Hafler DA. Autoimmunity risk alleles in costimulation pathways. Immunol Rev. 2009; 229:322–336. [PubMed: 19426231]

21. Katoh H, Zheng P, Liu Y. FOXP3: Genetic and epigenetic implications for autoimmunity. Journal of Autoimmunity. 2013; 41:72–78. [PubMed: 23313429]

22. Bedoya SK, Lam B, Lau K, Larkin J 3rd. Th17 cells in immunity and autoimmunity. Clin Dev Immunol. 2013; 2013:986789. [PubMed: 24454481]

23. Liston A, Gray DH. Homeostatic control of regulatory T cell diversity. Nat Rev Immunol. 2014; 14:154–165. [PubMed: 24481337]

24. Ganguly D, Haak S, Sisirak V, Reizis B. The role of dendritic cells in autoimmunity. Nat Rev Immunol. 2013; 13:566–577. [PubMed: 23827956]

25. Petukhova L, Duvic M, Hordinsky M, Norris D, Price V, Shimomura Y, Kim H, Singh P, Lee A, Chen WV, et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. Nature. 2010; 466:113–117. [PubMed: 20596022]

26. Bai Y, Zhang Y, Yang Q, Hou Y, Hu N, Wang D, Sun H. The aberrant expression of stimulatory and inhibitory killer immunoglobulin-like receptors in NK- and NKT-cells contributes to lupus. Clin Lab. 2014; 60:717–727. [PubMed: 24839813]

27. Prakash S, Alam S, Bharadwaj U, Aggarwal A, Mishra RN, Agrawal S. Associations of killer cell immunoglobulin like receptors with rheumatoid arthritis among North Indian population. Hum Immunol. 2014; 75:802–807. [PubMed: 24912006]

28. Lu L, Kim HJ, Werneck MB, Cantor H. Regulation of CD8+ regulatory T cells: Interruption of the NKG2A-Qa-1 interaction allows robust suppressive activity and resolution of autoimmune disease. Proc Natl Acad Sci U S A. 2008; 105:19420–19425. [PubMed: 19047627]

29. Tian Z, Gershwin ME, Zhang C. Regulatory NK cells in autoimmune disease. J Autoimmun. 2012; 39:206–215. [PubMed: 22704425]

**30. Brindley SM, Lanham AM, Karrer FM, Tucker RM, Fontenot AP, Mack CL. Cytomegalovirus-specific T-cell reactivity in biliary atresia at the time of diagnosis is associated with deficits in regulatory T cells. Hepatology. 2012; 55:1130–1138. This study identified an increased T-cell response to CMV in the majority of patients at the time of biliary atresia diagnosis as well as decreased regulatory T-cell frequencies, particularly in CMV+ patients. The work supports a

biliary atresia model of virus induced injury and subsequent autoimmune response. [PubMed: 22105891]

**31. Wang Y, Begum-Haque S, Telesford KM, Ochoa-Reparaz J, Christy M, Kasper EJ, Kasper DL, Robson SC, Kasper LH. A commensal bacterial product elicits and modulates migratory capacity of CD39 CD4 T regulatory subsets in the suppression of neuroinflammation. Gut Microbes. 2014; 5:552–561. The authors show that a bacterial capsular polysaccharide from a gut commensal modulates regulatory T-cell migration via an ectonucleotidase, CD39, in an experimental autoimmune encephalomyelitis model. This study furthers the field in understanding how commensal relationships impact distal host autoimmunity. [PubMed: 25006655]

32. Cunningham MW. Streptococcus and rheumatic fever. Curr Opin Rheumatol. 2012; 24:408–416. [PubMed: 22617826]

33. Kambham N. Postinfectious glomerulonephritis. Adv Anat Pathol. 2012; 19:338–347. [PubMed: 22885383]

34. Nast CC. Infection-related glomerulonephritis: changing demographics and outcomes. Adv Chronic Kidney Dis. 2012; 19:68–75. [PubMed: 22449343]

35. Jackson SJ, Steer AC, Campbell H. Systematic Review: Estimation of global burden of non-suppurative sequelae of upper respiratory tract infection: rheumatic fever and post-streptococcal glomerulonephritis. Trop Med Int Health. 2011; 16:2–11. [PubMed: 21371205]

36. Tonietti G, Oldstone MB, Dixon FJ. The effect of induced chronic viral infections on the immunologic diseases of New Zealand mice. J Exp Med. 1970; 132:89–109. [PubMed: 4323748]

37. Dyrberg T, Schwimmbeck P, Oldstone M. The incidence of diabetes in BB rats is decreased following acute LCMV infection. Adv Exp Med Biol. 1988; 246:397–402. [PubMed: 3250261]

38. Oldstone MB. Prevention of type I diabetes in nonobese diabetic mice by virus infection. Science. 1988; 239:500–502. [PubMed: 3277269]

39. Wallberg M, Cooke A. Immune mechanisms in type 1 diabetes. Trends Immunol. 2013; 34:583–591. [PubMed: 24054837]

40. Hyoty H, Hiltunen M, Knip M, Laakkonen M, Vahasalo P, Karjalainen J, Koskela P, Roivainen M, Leinikki P, Hovi T, et al. A prospective study of the role of coxsackie B and other enterovirus infections in the pathogenesis of IDDM. Childhood Diabetes in Finland (DiMe) Study Group. Diabetes. 1995; 44:652–657. [PubMed: 7789630]

41. Yeung WC, Rawlinson WD, Craig ME. Enterovirus infection and type 1 diabetes mellitus: systematic review and meta-analysis of observational molecular studies. BMJ. 2011; 342:d35. [PubMed: 21292721]

42. Ylipaasto P, Klingel K, Lindberg AM, Otonkoski T, Kandolf R, Hovi T, Roivainen M. Enterovirus infection in human pancreatic islet cells, islet tropism in vivo and receptor involvement in cultured islet beta cells. Diabetologia. 2004; 47:225–239. [PubMed: 14727023]

43. Chatterjee NK, Hou J, Dockstader P, Charbonneau T. Coxsackievirus B4 infection alters thymic, splenic, and peripheral lymphocyte repertoire preceding onset of hyperglycemia in mice. J Med Virol. 1992; 38:124–131. [PubMed: 1334127]

44. Brilot F, Geenen V, Hober D, Stoddart CA. Coxsackievirus B4 infection of human fetal thymus cells. J Virol. 2004; 78:9854–9861. [PubMed: 15331720]

45. Smyth DJ, Cooper JD, Bailey R, Field S, Burren O, Smink LJ, Guja C, Ionescu-Tirgoviste C, Widmer B, Dunger DB, et al. A genome-wide association study of nonsynonymous SNPs identifies a type 1 diabetes locus in the interferon-induced helicase (IFIH1) region. Nat Genet. 2006; 38:617–619. [PubMed: 16699517]

46. Harkonen T, Lankinen H, Davydova B, Hovi T, Roivainen M. Enterovirus infection can induce immune responses that cross-react with beta-cell autoantigen tyrosine phosphatase IA-2/IAR. J Med Virol. 2002; 66:340–350. [PubMed: 11793386]

**47. Wylie KM, Mihindukulasuriya KA, Zhou Y, Sodergren E, Storch GA, Weinstock GM. Metagenomic analysis of double-stranded DNA viruses in healthy adults. BMC Biol. 2014; 12:71. This study analyzed data from the Human Microbiome Project generated from sampling healthy subjects and found an average of 5.5 double stranded DNA viruses per subject and a distinct virome between subjects. This information highlights the significance of the virome in

healthy people and its importance in understanding human health and host immunity. [PubMed: 25212266]

48. Virgin HW, Wherry EJ, Ahmed R. Redefining chronic viral infection. Cell. 2009; 138:30–50. [PubMed: 19596234]
49. Draborg AH, Duus K, Houen G. Epstein-Barr virus in systemic autoimmune diseases. Clin Dev Immunol. 2013; 2013:535738. [PubMed: 24062777]
50. Babcock GJ, Hochberg D, Thorley-Lawson AD. The expression pattern of Epstein-Barr virus latent genes in vivo is dependent upon the differentiation stage of the infected B cell. Immunity. 2000; 13:497–506. [PubMed: 11070168]
51. Vergani D, Mieli-Vergani G. Autoimmune manifestations in viral hepatitis. Semin Immunopathol. 2013; 35:73–85. [PubMed: 23010889]
52. Cadwell K, Patel KK, Maloney NS, Liu TC, Ng AC, Storer CE, Head RD, Xavier R, Stappenbeck TS, Virgin HW. Virus-plus-susceptibility gene interaction determines Crohn's disease gene Atg16L1 phenotypes in intestine. Cell. 2010; 141:1135–1145. [PubMed: 20602997]
53. Chervonsky AV. Microbiota and autoimmunity. Cold Spring Harb Perspect Biol. 2013; 5:a007294. [PubMed: 23457255]
54. Blander JM, Torchinsky MB, Campisi L. Revisiting the old link between infection and autoimmune disease with commensals and T helper 17 cells. Immunol Res. 2012; 54:50–68. [PubMed: 22460741]
55. Kaur N, Chen CC, Luther J, Kao JY. Intestinal dysbiosis in inflammatory bowel disease. Gut Microbes. 2011; 2:211–216. [PubMed: 21983063]
56. Takaishi H, Matsuki T, Nakazawa A, Takada T, Kado S, Asahara T, Kamada N, Sakuraba A, Yajima T, Higuchi H, et al. Imbalance in intestinal microflora constitution could be involved in the pathogenesis of inflammatory bowel disease. Int J Med Microbiol. 2008; 298:463–472. [PubMed: 17897884]
57. Willing B, Halfvarson J, Dicksved J, Rosenquist M, Jarnerot G, Engstrand L, Tysk C, Jansson JK. Twin studies reveal specific imbalances in the mucosa- associated microbiota of patients with ileal Crohn's disease. Inflamm Bowel Dis. 2009; 15:653–660. [PubMed: 19023901]
58. Campieri M, Gionchetti P. Probiotics in inflammatory bowel disease: new insight to pathogenesis or a possible therapeutic alternative? Gastroenterology. 1999; 116:1246–1249. [PubMed: 10220518]
**59. Gevers D, Kugathasan S, Denson LA, Vazquez-Baeza Y, Van Treuren W, Ren B, Schwager E, Knights D, Song SJ, Yassour M, et al. The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe. 2014; 15:382–392. This study demonstrated that the gut microbiome of pediatric patients with inflammatory bowel disease prior to treatment is different than non-IBD patients, and this signature correlated with disease severity. Antibiotic treatment further amplified the observed dysbiosis. [PubMed: 24629344]
60. Strober W, Fuss IJ, Blumberg RS. The immunology of mucosal models of inflammation. Annu Rev Immunol. 2002; 20:495–549. [PubMed: 11861611]
61. Moon C, Stappenbeck TS. Viral interactions with the host and microbiota in the intestine. Curr Opin Immunol. 2012; 24:405–410. [PubMed: 22626624]
62. Rakoff-Nahoum S, Hao L, Medzhitov R. Role of toll-like receptors in spontaneous commensal-dependent colitis. Immunity. 2006; 25:319–329. [PubMed: 16879997]
63. Bloom SM, Bijanki VN, Nava GM, Sun L, Malvin NP, Donermeyer DL, Dunne WM Jr, Allen PM, Stappenbeck TS. Commensal Bacteroides species induce colitis in host-genotype-specific fashion in a mouse model of inflammatory bowel disease. Cell Host Microbe. 2011; 9:390–403. [PubMed: 21575910]
**64. Basic M, Keubler LM, Buettner M, Achard M, Breves G, Schroder B, Smoczek A, Jorns A, Wedekind D, Zschemisch NH, et al. Norovirus triggered microbiota-driven mucosal inflammation in interleukin 10-deficient mice. Inflamm Bowel Dis. 2014; 20:431–443. The authors show that murine norovirus infection causes gut permeability, decreased tight junction molecule expression, and increased epithelial apoptosis in the IL-10 mouse model of IBD. They further demonstrate that these findings are partly dependent on the gut bacterial microbiota, as

germ-free animals infected with MNV did not show barrier disruption or inflammatory changes. [PubMed: 24487272]

65. Abdollahi-Roodsaz S, Joosten LA, Koenders MI, Devesa I, Roelofs MF, Radstake TR, Heuvelmans-Jacobs M, Akira S, Nicklin MJ, Ribeiro-Dias F, et al. Stimulation of TLR2 and TLR4 differentially skews the balance of T cells in a mouse model of arthritis. J Clin Invest. 2008; 118:205–216. [PubMed: 18060042]

66. Vaahtovuo J, Munukka E, Korkeamaki M, Luukkainen R, Toivanen P. Fecal microbiota in early rheumatoid arthritis. J Rheumatol. 2008; 35:1500–1505. [PubMed: 18528968]

**67. Duerkop BA, Clements CV, Rollins D, Rodrigues JL, Hooper LV. A composite bacteriophage alters colonization by an intestinal commensal bacterium. Proc Natl Acad Sci U S A. 2012; 109:17621–17626. This study examined the bacteriophages of Enterococccus faecalis and found that one phage confers a selective advantage to E. faecalis *in vivo*. These findings highlight the role of bacteriophages in the determination of the gut microbiome composition. [PubMed: 23045666]

**68. Perron H, Germi R, Bernard C, Garcia-Montojo M, Deluen C, Farinelli L, Faucard R, Veas F, Stefas I, Fabriek BO, et al. Human endogenous retrovirus type W envelope expression in blood and brain cells provides new insights into multiple sclerosis disease. Mult Scler. 2012; 18:1721–1736. The authors evaluated the association between a retroviral element expression and multiple sclerosis and found a significant correlation with its presence in the serum and PBMCs compared to healthy controls. Furthermore, among those with MS, increased copy number was associated with chronic progressive disease state. [PubMed: 22457345]

Highlights

- Microbiota is implicated in the development of autoimmunity but causality in humans is elusive.
- Understanding of chronic infection and commensals are also needed to decipher pathogenesis.
- These relationships are further complicated by host genetic susceptibility.
- Generation of precise animal models will aid our understanding and advance human health.