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Complexities in the Relationship Between Infection and Autoimmunity

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Abstract

The possible role of infections in driving autoimmune disease (AD) has long been debated. Many theories have emerged including release of hidden antigens, epitope spread, anti-idiotypes, molecular mimicry, the adjuvant effect, antigenic complementarity, or simply that AD could be a direct consequence of activation or subversion of the immune response by microbes. A number of issues are not adequately addressed by current theories, including why animal models of AD require adjuvants containing microbial peptides in addition to self tissue to induce disease, and why ADs occur more often in one sex than the other. Reviews published in the past 3 years have focused on the role of the innate immune response in driving AD and the possible role of persistent infections in altering immune responses. Overall, recent evidence suggests that microbes activating specific innate immune responses are critical, while antigenic cross-reactivity may perpetuate immune responses leading to chronic autoinflammatory disease.

Keywords

Autoimmunity; Autoimmune disease; Theories; Infection; Innate immunity; Molecular mimicry; Epitope spread; Inflammasome; Toll-like receptors; Antigenic complementarity; Bystander effect; Adjuvant effect; Anti-idiotypes; Autoantibodies; Immune dysregulation

Introduction

A number of theories have been proposed to explain how infections could cause autoimmune diseases (ADs). Although not exhaustive, the list includes hidden/cryptic antigens, epitope spread, anti-idiotypes, molecular mimicry, the adjuvant or bystander effect, antigenic complementarity, or, simply, that AD is one possible consequence of an infection

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Compliance with Ethics Guidelines
Conflict of Interest
DeLisa Fairweather is a board member of the Myocarditis Foundation.
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Human and Animal Rights and Informed Consent
This article does not contain any studies with animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

(Table 1) [1–5]. An underlying assumption of many of these theories is that AD results because of a "defect" in the immune response [6–8]. AD was originally defined in this way because, in the 1950s when theories were first being proposed, it was believed that the immune response would not attack "self" [9]. However, we now realize that self-reactivity is part of normal regeneration and healing processes [10]. Cellular debris must be removed when cells are damaged or die of natural causes, and the immune system plays a central maintenance and healing role. It is now clear that autoantibodies (autoAb) frequently arise following infections, particularly viral infections, and these are often associated with the onset of AD. Recent reports on the role of infections in AD highlight the importance of the innate immune response in its induction, an arm of the immune response that was not realized to be important in the 1950s when AD theories were first being proposed. These and other more recent findings indicate the need to reexamine the role of infection in the induction of AD. This review will describe theories published in the past 3 years on the role of infections as a primary cause of AD, with special emphasis on autoimmune myocarditis (AM).

Current Theories

Hidden/ Cryptic Antigens

One of the oldest theories regarding the origins of AD is the hidden antigen theory. It is based on the idea that self antigens (Ags) are usually not "seen" by the immune system during thymic education and are thus "hidden" or "cryptic". For this reason, potentially autoreactive T and B cell clones against autoAgs are not deleted or tolerized. Tissue damage that results in the release of hidden antigens can activate preexisting autoreactive immune cell clones resulting in autoimmune disease. This theory does not directly suggest a role for infections, but it is commonly assumed that infections, and lytic viruses in particular, contribute to AD by releasing "hidden" self antigens. However, a problem with this idea is one of "timing". Autoreactive T and B cells generally appear 7–14 days after antigen presentation (day 0) with a novel antigen in animal models of AD. In AM, self-reactive T and B cells arise in tandem with viral replication in the heart rather than following the tissue damage, arguing for direct activation of autoimmunity by infection rather than indirect activation by release of cryptic self antigens. Furthermore, cryptic antigens would most likely derive from immunologically privileged tissues such as the testes, eyes, and brain, while in reality ADs affect many unprivileged sites like the heart, intestine, and joints [11]. Additionally, if release of self antigen was sufficient to induce AD on its own, as the theory suggests, then administration of damaged self tissue should be able to cause AD in animal models. However, this is not the case [9]. Administration of damaged self tissue, antigens, and/or peptides always requires adjuvants that contain microbes to initiate disease (Table 1) [9, 12]. Incomplete Freund's adjuvant, minus inactivated *Mycobacterium*, is not capable of inducing AD when paired with self antigens. These findings suggest that microbes plus tissue damage are needed to cause AD. A clinical correlate is that cardiac infarction, heart surgery, and cardiac transplantation all result in the production of autoAbs against heart antigens [13], but the individuals are not reported to develop myocarditis, an autoimmune cardioinflammatory disease. Overall, these data suggest that, while tissue damage and release of cryptic self antigens may be necessary, it is not sufficient in itself to generate an AD on its own, at least not as a single event.

Epitope Spread

An alternative to the cryptic antigen theory is that AD results from epitope spreading. An epitope is a single antigenic site targeted by one, specific antibody, or T cell. The epitope spread theory was proposed in 1992 by Lehmann et al. to explain a common observation that the dominant autoAg/ epitope targeted during AD is not usually the autoAg present

during the early stages of disease pathogenesis (in animal models) [14]. Epitope spread occurs as part of the normal immune response to control infections. Initially, the immune response recognizes a dominant antigen and produces a T cell- and B cell-specific response against it. When it later reencounters the same pathogen, it produces an immune response against a second dominant antigen of the pathogen so that the adaptive immune response becomes better able to prevent infection with each future event, recognizing increasing numbers of epitopes for each microbial agent. This is the main reason why influenza vaccines must be changed each year because the virus evades the immune response by changing the "dominant" antigens on its surface membrane. It is well known, and often part of an AD diagnosis, that ADs usually only present clinically after several autoAbs directed against the target organ are present [11]. These observations suggest that infections or other agents that can cause release of and/or induce the immune system to target self antigens must be reoccurring so that the immune response spreads sufficiently.

Reoccurring physical, infectious, and/or chemical agents that can cause damage to a particular organ [15, 16] or persistent viral infections [17] may eventually result in epitope spread targeting self antigens. Although this theory does not propose a specific role for infections in causing AD, it is often assumed or proposed that infections are the agents causing damage to tissues, as in the animal model of multiple sclerosis induced using Theiler's virus [18, 19]. Inherent in this theory is the concept that multiple infections or reoccurring damage to the target organ results in multiple autoAbs some of which can induce AD. Thus, the epitope spread theory predicts that AD only occurs long after the initial (or repeated) infection or damage, so that the simultaneous induction of atuoAbs with infection should not occur with epitope spread. Although this may not be the case with all experimental models of AD, we have found that infection with coxsackievirus B3 (CVB3) or murine cytomegalovirus (MCMV) produces autoAbs against cardiac myosin during acute myocarditis simultaneous with viral replication in the heart [20].

Anti-idiotype Theory

Based on the observation that infectious agents often use cellular receptors to infect particular tissues or cell types, Plotz proposed in 1983 that this could generate anti-idiotype autoAbs that cause AD [21]. Thus, an Ab aimed at the viral antigen used by the virus to bind to a host cell receptor would also bind the host cell, potentially resulting in AD. A number of problems exist with this theory. Although some candidate receptors exist [22, 23], for most Ads, it is not clear what cellular receptors are being targeted by anti-idiotype Abs. It is also unclear how this theory would generate multiple autoAbs over time, unless the infectious agent targets multiple cellular receptors (see previous section). Anti-idiotype or cross-reactive autoAbs between viruses, bacteria, and self antigens have been detected both clinically and in animal models of AD, including AM [24–27]. We (Root-Bernstein et al. 2009) have shown that Abs directed against CVB3, a virus that induces AM, also behave as idiotype Abs against actin and recognize antibodies against cardiac myosin as "anti-idiotypes" [28, 29]. Since myosin is believed to be the primary autoAg in CVB3-induced AM, perhaps the anti-myosin antibody is actually an anti-idiotype against the CVB3-actin antibody. A further complication is that anti-idiotype Abs can inhibit inflammation in animal models of CVB3-induced myocarditis [24, 30, 31], suggesting that they may perform a "regulatory" rather than pathogenic role. Moreover, some ADs like myocarditis have a primarily cell-mediated rather than autoAb-mediated pathology. On the other hand, we have suggested that T cell "idiotypes" can activate "anti-idiotypic T cells" along the same model as idiotype-anti-idiotype Abs. In type 1 diabetes mellitus, for example, T cell receptors (TCR) activated within individual patients recognize other activated TCR as "antigens" [32, 33]. Whether such complementary TCR are indeed "anti-idiotypic", and whether they play pathogenic or regulatory roles, remain to be determined.

Molecular Mimicry

The concept of molecular mimicry was first posited by Damian in the early 1960s to explain how parasites evolved proteins that mimic host proteins in order to camouflage themselves from the immune system [34–36]. The concept was broadened substantially by Lane and Koprowski in 1982 because of increasingly frequent reports of Abs against infectious agents that cross-reacted with host cellular proteins [37]. The idea that molecular mimicry could drive AD was proposed a year later by Koprowski and Fujinami and Oldstone [38, 39]. Abundant evidence now exists for cross-reactivity between pathogens and self antigens [26, 27, 40–44], but the requirement for molecular mimicry in the induction of AD has recently been challenged [45]. One limitation is that most studies of molecular mimicry have relied on linear rather than conformational epitopes because simple software tools for comparing protein conformations are generally lacking. And so whether the immune system sees these linear epitopes as “cross-reactive” to host Ags remains unclear. Another issue is that mimicry is extremely common, but most ADs are not. Additionally, most ADs display a marked sex difference in incidence and severity, and it has not been explained why cross-reactivity against common self antigens produces disease in mainly one sex (although most ADs occur more frequently in women, many like myocarditis occur mainly in men) [11, 46, 47]. Interestingly, purified autoAgs that are cross-reactive with pathogens only induce AD in animal models when paired with an adjuvant that contains an inactivated pathogen (i.e. complete Freund’s adjuvant) or pathogen-derived toxin (i.e. Pertussis toxin) [12, 42]. These data suggest that cross-reactivity between microbes and self is just part of the requirement for disease induction. Interestingly, in a recent review by Fujinami, one of the originators of the theory, he states that molecular mimicry does not account for T cell activation in a number of Ads, and proposes that dual TCRs (a single T cell with TCRs for both foreign and self antigens) may account for the apparent cross-reactivity [8].

The Adjuvant or Bystander Effect

Another popular theory is that infections stimulate the immune response by activating receptors on innate immune cells and releasing proinflammatory cytokines that can then activate preexisting autoreactive T and B cells (that escaped thymic deletion) to drive AD [4, 20, 48]. It has been proposed that this second signal or innate stimulation is needed in order for self antigen to induce AD. This would explain the need for adjuvants in animal models of AD. One question that is not yet resolved is whether this method is “non-specific” (i.e. any innate activation) or “innate immune-specific” (i.e. directed against a specific Toll-like receptor/TLR or the inflammasome, for example). Gorton et al. (2010) found that well-characterized non-microbial adjuvants could not replace complete Freund’s adjuvant (CFA) in the induction of Streptococcal M protein-induced AM [49], suggesting specificity of the innate response. Interestingly, certain self peptides like cardiac myosin have been found to activate TLRs, like TLR2 and TLR4 [50]. Perhaps self peptide activation of the innate immune response acts synergistically with microbes to cross a threshold that leads to induction of AD. Persistent viruses, like Epstein–Barr virus (EBV) which remains latently in memory B cells throughout life, are top candidates for providing a strong bystander effect over long periods of time [48]. Perhaps the strongest evidence for the importance of the innate immune “adjuvant or bystander” effect is the significant impact on AD that is found in knockout mice when a particular cytokine or TLR is globally knocked out, thereby altering the innate immune response [20, 51, 52].

Antigenic Complementarity

One attempt to pull together some of the apparently contradictory observations summarized above is the antigenic complementarity theory [53, 54]. This theory states that ADs are caused by specific combinations of microbial antigens (i.e. more than one microbe is needed), at least one of which mimics self [1, 55, 56]. The Ags must be molecularly

complementary to each other (i.e. the antibodies or T cells induced by a pair of antigens must also recognize each other as antigens). As a result, the pair of T and B cells that are activated are also complementary to each other and drive an anti-idiotypic type of response. Because of the necessity for complementarity, only specific self peptides and specific microbes would be cross-reactive and generate AD. For example, *Mycobacterium tuberculosis* antigens in CFA and cardiac myosin would need to be complementary mimics. Xie et al. report that formalin-inactivated group A streptococci, which mimic cardiac myosin, could induce autoimmune valvulitis in rats if injected with complete Freund's adjuvant but not in the absence of CFA [57]. CVB3 will induce myocarditis in rodents that is similar to myocarditis in patients (i.e. no deaths and low-level viral replication in the heart) if cardiac proteins/damaged heart tissue are injected with virus at day 0 [58], suggesting that CVB3 could be complementary to cardiac proteins (see Root-Bernstein et al. 2009 showing similarity of CVB3 with actin that complements cardiac myosin [28]). The presence of actinomyosin complexes in the salivary gland may also explain why MCMV injected with salivary gland tissue at day 0 causes a similar, although less severe, form of myocarditis [20]. Effectively, the pair of microbes or microbe plus selfAg is acting as an adjuvant because of the antigenic complementarity. This theory explains in part the low incidence of AD initiated by common infections such as group A streptococci and Coxsackie viruses, since uncomplicated, individual infections should not be able to induce AD. It does not, however, address why mainly males develop myocarditis and DCM. However, it encompasses the importance of innate recognition of damaged self and microbes, with the ability of antigenic complementarity between T and B cells to further expand the autoreactive adaptive response.

A direct role for infections?

Innate Immunity: Damaged Self, TLR, and the Inflammasome

Many of the theories discussed so far focus on the role of the Ag-specific adaptive immune response in the development of AD. However, these theories were devised before the realization of the critical role the innate immune response plays in the development of adaptive immunity, which began around 2000 [20, 59]. Now we know that the innate response "specifically" directs the adaptive immune response. Recent examination of initiation of immune responses in AD animal models reveals that innate mechanisms like danger-associated molecular patterns (DAMPs) and TLRs strongly drive reactivity to self and determines the type of adaptive immune response (i.e. Th1, Th2). Most reviews discussing possible mechanisms of microbially-induced autoimmunity have not reinterpreted past and current theories in light of our new understanding of the role of innate immunity in the process. This is critically needed (Table 2). The focus of many investigators (and review articles) continues to be on either innate or adaptive immunity, rather than on both.

A consistent theme in recent reviews is the role of pathogen initiated activation of TLRs and the inflammasome on the development of AD [6, 60–64]. Increasing evidence indicates that many adjuvants, such as alum and *Pertussis* toxin, used to induce AD in animal models stimulate TLRs and specifically TLR4 and the inflammasome [62, 65, 66]. So, one important question is whether adjuvants that do not induce AD also fail to activate TLR4 and/or the inflammasome (e.g., Gorton, et al. 2010 [49]). Another is whether co-infections (cf. antigenic complementarity) hyper-stimulate TLR4 and the inflammasome, or induce complementary innate responses. An important recent finding is that innate TLR4/inflammasome activation can increase Th1- and Th17-type immune responses, which are frequently associated with AD in animal models [67, 68]. It is now realized that damaged and dying host cells release nuclear particles that activate TLRs, providing a receptor-specific mechanism for the adjuvant effect [69–72].

Persistent Viruses: Effects on B cells and Immune Subversion

Persistent viruses, like EBV and hepatitis C virus (HCV), that chronically infect B cells, not only provide an adjuvant effect to the immune system but are also likely to directly alter B cell function in a way that could cause unregulated production of autoAbs leading to mixed cryoglobulinemia and Ads, like systemic lupus erythematosus, rheumatoid arthritis (RA), Sjogren's syndrome, hepatitis, and thyroiditis [3, 48, 73–75]. Persistent viruses may also cause the activation of endogenous human retroviruses present in B cells, further dysregulating the immune and autoAb response and providing a link between chronic inflammation and the progression to cancer [76, 77]. Another possibility is that persistent infections lead to T and B cell follicles in target organs (found in multiple sclerosis, RA, systemic sclerosis, and thyroiditis) that promote AD [78]. The natural aging process is known to promote autoreactive memory B cell survival [79], and so, if viruses target autoreactive memory B cells, they may be able to persist longer in the host with a side effect being AD. Persistent infections have also been postulated to increase myasthenia gravis, where autoAbs are formed against the acetylcholine receptor [80]. Recent evidence suggests that EBV, poliovirus and other pathogens lead to myasthenia gravis by increasing TLR4, interferons, and complement/immune complexes while decreasing T regulatory cells (Treg) (Table 2) [80]. These observations are remarkably similar to the type of immune response induced by CVB3 infection that leads to myocarditis [46]. However, CVB3 is a lytic rather than a classically persistent virus, suggesting that a common activation pathway (i.e. TLR4, inflammasome), rather than viral persistence per se, may be needed to induce AD. We have evidence to suggest that the chronic stage of myocarditis/DCM develops due to the induction of cardiac remodeling genes during acute myocarditis rather than due to persistence of virus [68]. Importantly, most viruses and bacteria employ a vast array of mechanisms to circumvent the host immune response, like coding for cytokine mimics and dysregulation of immune regulatory mechanisms [81, 82]. Thus, it is possible that AD is simply a side effect of pathogen activation and/or subversion of the immune response. Or, according to Zinkernagel, "an autoimmune disease is a viral disease in which the virus is unknown" [83].

Conclusions

To some extent experimental and clinical evidence exists for all of the current theories of how infections could cause AD. However, several issues need to be addressed (Table 2). Few theories adequately explain why some ADs occur almost exclusively in women, like thyroiditis, while others occur primarily in men, like myocarditis. Additionally, theories need to provide an understanding of the mechanism that includes the progression of disease from its initiation during innate immunity through the development of an adaptive immune response. Currently, most reviews provide a perspective for only innate or adaptive immunity, rather than for both. There needs to be improved efforts to match animal models to clinical disease, and, as needed, to develop new animal models that better match the clinical picture. Our understanding would be improved by investigators designing experiments to test the predictions that differentiate between multiple theories rather than attempting to "prove" only their favorite theory. We have come a long way in our understanding of the potential for infections to cause AD, but identification of the mechanism(s) still needs refinement.

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Table 1

Theories of how infections could cause autoimmune diseases

Theory	Description	References
Hidden/cryptic antigen	Tissue damage releases hidden antigens	1, 2, 5
Epitope spread	Multiple epitopes against self needed before AD develops	14, 18, 19
Anti-idiotype	Cellular receptor targets induce cross-reactive autoAbs	21, 25, 28, 29
Molecular mimicry	Accidental cross-reactivity	8, 26, 27, 34–44
Adjuvant/bystander effect	Microbial activation of pre-existing autoreactive immune cells	4, 20, 48
Antigenic complementarity	Multiple infections by microbes that share antigenic complementarity/ cross-reactivity	1, 28, 53–56
Consequence of infection (and/ or chemical)	Damages and releases self tissue and danger signal (inflammasome activation)	3, 6, 60–66
• Viral persistence	Repeated activation drives epitope spread	3, 48, 73–77
• Cytokine dysregulation	Ex. Increased Th17 allows AD	7, 27, 58, 67
• Disrupt immune regulation	Ex. Increased Treg allow AD	81, 83

Table 2

Factors needed to cause autoimmune disease

Factors
• Damaged self-antigen + microbial antigen (active or inactivated) presented by antigen presenting cells at day 0
• Innate immune response directs adaptive response (i.e. autoreactive T and B cells)
• Cross-reactivity and/or antigenic complementarity
• Re-occurring damage
• Common mechanism: Ex. TLR2/TLR4 and inflammasome activation (activated by self and microbes)
• Sex difference in immune response
• Unregulated autoantibody production
• Decreased regulatory mechanisms