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Cytokines pre-determined by genetic factors are involved in pathogenesis of Rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is associated with the presence of autoreactive CD4 T cells that produce pro-inflammatory cytokines. The role of genetic factors in the predilection to develop RA is strongly supported by the increased presence of certain HLA class II molecules in patients. The HLA class II genes are highly polymorphic and are critical for generating an immune response to clear infections. Production of Th1 and Th17 response by the CD4 T cells helps to clear infections. HLA-DQ8 is a promiscuous binder and presents many peptides generating immune response and producing a Th17 response. DRB1*0401 is associated with the production of both IL-17 and IFN-γ. Thus both DR4 and DQ8 can clear infections by producing TH1/Th17 cytokines, but their presence increases the risk of developing RA. Using transgenic mice expressing human HLA genes, we have shown that HLA polymorphism determines the cytokine profile. DRB1*04 molecules modulate the DQ8-restricted response and determine the outcome of arthritis in mice carrying DR4/DQ8 haplotype. Thus, interaction between DQ and DR molecules determines the cytokine milieu and propensity of the HLA haplotype to predispose to autoimmunity.

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1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease caused by the inflammatory changes in the immune system. While the causative antigen of RA is unknown, an infectious etiology has been suggested based on an improvement in patients treated with antibiotics [1]. Many infectious agents like EBV and parvovirus, among others, have been implicated in the pathogenesis of RA although the mechanism by which pathogens cause pathology is unknown. One proposed mechanism by which infectious agents and other environmental factors are involved in causing autoreactivity is called "molecular mimicry". During infection the body generates a response to clear infection but a cross reactive response to epitopes of the infectious agents that are similar to self-protein can cause autoreactive T cells to expand. Even after clearance of infection, this autoreactive response may continue, due in part, to the availability of the self-protein. Modification of proteins occurs in normal healthy state to generate immune response. However during the process of post translational modifications, cryptic epitopes sharing sequences with viral or bacterial proteins may become available. There is some evidence that suggests that certain modified peptides bind the HLA-DR molecules better than naïve peptides [2].

The HLA molecules are encoded on chromosome 6 and are crucial in clearing infections by generating an immune response to pathogens. The class I and class II genes are the two major classes of the HLA loci that are involved in fighting infections. HLA genes encoded in the class I- B loci and class II –DRB1 loci are the most polymorphic. The polymorphism of HLA genes is attributed to the selective pressures of pathogens. Thus the HLA alleles that generate a response against most pathogens by activating CD4 + T cells and producing cytokines, resulting in clearance of infections, have been preserved. This is supported by a recent meta-analysis showing association of certain HLA alleles with an effective clearance of infections [3].

According to the paradigm, presentation of a peptide via class I molecules activate CD8 T cells while class II molecules activate CD4 T cells. Activated T cells produce cytokines to clear infections. While both class I and class II alleles generate responses to infectious agents, only class II molecules have been associated with a predisposition to autoimmunity. Several hypotheses have been put forth to explain the HLA association with autoreactivity, however, the mechanism by which class II molecules predispose to autoimmunity still remains an enigma. Positive and negative T cell selection in the thymus by the HLA molecules provides one mechanism. The other is the HLA-mediated antigen presentation to CD4 T cells and subsequent cytokine production. However, the immune response generated via class II molecules may also lead to bystander damage which, in certain conditions, causes pathology.

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2. Cytokines and class II genes in infections

The major function of class II molecules is to clear infections through the adaptive immune response. Presentation of the MHC-peptide complex by antigen presenting cells to CD4 T cells leads to production of cytokines, Th1, Th2, Th9 and Th17. For clearing intracellular bacterial and viral infections, IFN-γ production by Th1 cells leads to a cellular response, differentiation of CD4 T cells into Th1 cells and the activation of macrophages which produce Th1 cytokines. IFN-γ also increases expression of MHC class II molecules, thereby increasing MHC-restricted antigen presentation and adaptive immune response. Production of IFN-γ suppresses the Th2 and Th17 response, skewing the response to be Th1.

Clearance of extracellular bacterial and fungal infections requires Th17 cells. Among Th17 cytokines, IL-17 is one of the most studied. IL-17 is a pleiotropic cytokine that acts on many immune and epithelial cells [4]. Binding of IL-17 to its receptor activates production of other pro-inflammatory cytokines, IL-1β, IL-6, and TNF-α as well as various chemokines resulting in the recruitment of neutrophils, macrophages and lymphocytes. IL-6 in conjunction with TGFβ amplifies differentiation of Th17 cells in a positive feedback loop. IL-17 also promotes a humoral response that is essential for clearing extracellular pathogens. Recently, an important role of Th17 cells has been shown in mucosal associated infections in lungs and guts [5]. However, in some individuals, an amplified immune response to clear infectious agents leads to tissue damage ensuing inflammatory autoimmune diseases. Inflammatory diseases including RA have increased numbers of IL-17 producing cells [6,7].

Most individuals have viral and bacterial infections at some point of their life but not all individuals who are infected develop autoreactivity. Most of the autoimmune diseases are strongly associated with certain class II alleles. Even though the HLA-DR and DQ genes are highly polymorphic, the 3 most common haplotypes present in various autoimmune diseases are DR2/DQ6, DR3/DQ2, and DR4/ DQ8. These haplotypes are also present with high frequency in the healthy population. One can speculate that these class II haplotypes are promiscuous binders and are good for clearing infection. However, variability in the outcome of infectious diseases suggests a role for genetic factors. This is supported by the observations that the outcome of hepatitis C virus infection is influenced by the MHC class II genotype, both DRB1∗0401 and DRB1∗1501 are linked with increased clearance of hepatitis C [8]. Similarly, clearance of hepatitis B is also associated with certain HLA genotypes [3].

This led us to hypothesize that the HLA alleles that can generate a strong immune response and produce IFN-γ or IL-17 to infectious agents may have been selected and preserved over generations. However, some infectious agents may harbor epitopes that share similarities with human proteins. While these epitopes may not be available easily in normal healthy state, they may become available due to post translational modifications. Post-translational modifications like citrullination are known to open the folded structure of the protein exposing some of the cryptic epitopes. If these cryptic epitopes are available to the activated immune cells for presentation, a self-reactive response may be generated. One such example is alpha-enolase, which is a conserved molecule throughout eukaryotes and prokaryotes. Antibodies to citrullinated alpha enolase are expressed in the joints of RA patients. A recent study showed that a cross-reactive response to a bacterial enolase may prime autoimmunity in a subset of patients [9]. Citrullination is a process where the amino acid arginine in a protein is replaced with citrulline. This process has physiologic relevance as it is required for the generation of skin, hair follicles, and myelin sheaths of nerve fibers as well as for transcriptional and chromatin compaction regulation [10]. Antibodies to citrullinated proteins have been described not only in RA but in many other inflammatory diseases including multiple sclerosis and myositis [11–13]. Thus while citrullinated proteins are a part of healthy state , in individuals with certain class II alleles, a loss of tolerance to citrullinated proteins or an autoreactive response generated after clearance of an infectious agent may cause onset of disease. This could be due, in part, to a storm of cytokines produced to clear infections. This is supported by the association of HLA class II alleles like DRB1∗0401 with the presence of anti-citrullinated antibodies.

3. Cytokine and rheumatoid arthritis

Cytokines have a fundamental role in causing inflammation and now it has become clear that cytokines are the prime suspects in articular destruction [14]. The role of cytokines in the pathogenesis of RA is underscored by the success of treatment with anti-TNF antibodies in RA patients. The success of TNF-inhibitor has set the stage for using inhibitors of other pro-inflammatory cytokines in RA. The rheumatoid joints have infiltrating macrophages that can secrete chemokines and cytokines of the innate and adaptive immune system. The recruitment of activated T and B cells involves secretion of chemokines by antigen presenting cells and synovial endothelium. Activated T cells produce cytokines in the joints further amplifying the inflammatory cascade. A recent study showed an increased numbers of pro-inflammatory cytokines producing T cells reactive to citrullinated Vimentin [15]. There is a preponderance of Th1 cells in rheumatoid joints with the majority of cells producing IFN-γ [16]. IFN-γ can enhance the production of other Th1 cytokines like IL-1, IL-6 and TNF-α. IL-6 is a potent pro-inflammatory Th1 cytokine that regulates hematopoiesis and is associated with differentiation of T and B cells [17]. Blocking IL-6R with an antibody has been shown to be effective in some patients [18]. Presentation of cartilage antigens in the joints can further cause perpetuation of an ongoing inflammatory cascade in the joints. RA has been suggested to be a Th17 dependent disease, IL-17 producing cells have been observed in RA synovium [6] . IL-23, a member of IL-12 family, can cause differentiation of naïve cells into IL-17 producing cell. IL-17 is a pro-inflammatory cytokine which acts on various cells and also induces osteoclast differentiation via the RANKL pathway [19]. Activation of IL-17R induces production of other inflammatory cytokines and chemokines that initiate recruitment of neutrophils, macrophages and lymphocytes. Phase I trials of anti-IL-17 antibodies have shown some efficacy in RA patients. A role of Th17 in RA is further supported by animal models of arthritis [20–22]. While Th1 and Th17 cytokines are associated with pathogenesis in RA, Th2 cytokines are associated with protection from arthritis. However, higher levels of IL-13 are present in RA patients as compared to that of healthy individuals [23]. The other cytokines produced in the joints, which include IL-15 and IL-10, may be important for preventing T and B cells from undergoing apoptosis and for T cell function [16,24]. Chronic inflammation can lead to production of IL-10 and TGF-β that can diminish inflammatory cytokines. While both of these cytokines are immunomodulatory, TGF-β is also involved in pro-inflammatory pathways as it induces differentiation of pathogenic Th17 cells in the presence of IL-6 [25]. Thus it is not clear if these cytokines are inhibitory in joints. These studies demonstrate an unmet need to define other biologics that may be effective for subsets of patients who do not respond to the available drugs. A recent study identified a signature cytokine profile, produced by PBMCs to various stimuli, to define myocardial dysfunction in RA patients [26]. Using DR4 tetramers, it was shown that while both RA patients and healthy individuals harbor DR4 positive T cells although T regulatory cells are diminished in patients [27]. This may explain inability of RA patients to

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