

The Mosaic of Autoimmunity: The Novel Factors of Autoimmune Diseases

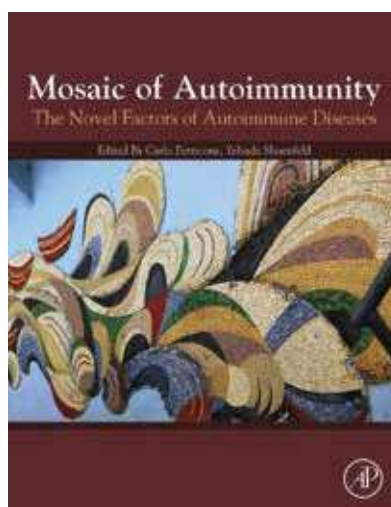
Edited by Carlo Perricone and Yehuda Shoenfeld

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The complexity of autoimmunity was never so big and puzzling as it is today. The new edition of *Mosaic of Autoimmunity: The Novel Factors of Autoimmune Diseases*, edited by Carlo Perricone and Yehuda Shoenfeld [1] reflects this complexity and covers a spectrum of important issues, such as the relevance of T cells in autoimmunity. These cells include T helper (Th) 17 cells, double-negative T cells, T follicular helper cells, and T regulatory cells. The book covers aspects of pro-inflammatory pathways or regulatory/suppressive functions of natural killer (NK) cells and dendritic cells in immune-mediated diseases. It contains updates on the role of genetics, environmental factors, hormones, and infections in autoimmunity. This informative and comprehensive book should be on the desk of all researchers and physicians with an interest in autoimmunity.

T CELL SUBSETS AND AUTOIMMUNITY

The positive selection of T cells in the thymus enables the generation of different subsets that are defined by their T-cell receptor composition ($\alpha\beta$ chains or $\gamma\delta$ chains) and the expression of co-receptors, namely CD4 T helper cells and CD8 cytotoxic cells. In parallel to this process, some autoreactive T cells leak into the periphery when negative T cell selection in the thymus fails. When T cells recognize self-antigens with low affinity they may develop into T regulatory cells, which will later control autoreactive T cells in attempt to prevent autoimmunity [2,3]. Eventually, most T cell subsets have a role in the pathogenesis of autoimmune diseases, either because of the overexpression and production of pro-inflammatory cytokines or because of the failure of T regulatory cells to prevent autoimmunity [4].



Th1 cells: Th1 cells express interferon gamma (IFN γ) as their signature cytokine. They are pathogenic and mediate immune responses against non-self-pathogens. They also impact the development of immune-mediated diseases.

Th2 cells: Th2 cells express and produce interleukin (IL)-4, IL-13, and IL-5. They contribute to the development of allergies but also support other humoral responses by secreting IL-6, IL-9, and other cytokines [5].

T follicular helper cells (Tfh): Tfh are CD4+ T cells that express the transcription factor Bcl6 and the chemokine receptor CXCR5, which enable them to migrate into germinal centers. T follicular helper cells assist and activate B cells leading them to differentiate into long-lived plasma cells and to produce high affinity autoantibodies. Obviously, Tfh cells are increased in autoimmune diseases, such as systemic lupus erythematosus (SLE), and correlate with disease severity and with the titers of anti-

dsDNA antibodies. Tfh cells in SLE patients may secrete IL-17 and promote B cell activity in the kidney, which may contribute to the development of nephritis [6-8].

Th17 cells: Th17 cells express the transcription factor ROR- γ t, and when stimulated they produce the pro-inflammatory cytokines IL-17, IL-21, IL-22, and IFN- γ , all of which play role in the development of autoimmune diseases. In inflamed organs, they induce lymphoid follicles where B cells are activated and become autoreactive. IL-17 and related cytokines are increased in autoimmune diseases such as rheumatoid arthritis (RA), SLE, and Sjögren's syndrome. Research has shown that IL-17 knockout mice are less prone to develop autoimmune diseases such as collagen-induced arthritis or experimental autoimmune encephalitis. These findings provided the rational of targeting IL-17 in these diseases [9,10].

CD8+ T cells: CD8+ T cells are the main cytotoxic cells against intracellular pathogens and tumors but are also known for their ability to regulate autoimmune and allergic diseases. In CD8 knockout mice, experimental autoimmune encephalomyelitis symptoms improved following the adoptive transfer of CD8+CD28^{low} T cells. In addition, CD8+ Treg cells were found to be essential for the optimal function of CD4+Tregs [11].

NATURAL KILLER CELLS AND AUTOIMMUNITY

NK cells are 10–15% of peripheral blood lymphocytes and 5% of all mononuclear cells in peripheral lymph nodes. NK cells may act protective or pathogenic in the pathogenesis of different autoimmune diseases, and in some cases even change roles during the

same disease. The number of circulating NK cells was reported by many to be altered in autoimmune diseases such as RA, SLE, Sjögren's syndrome, and multiple sclerosis (MS). These findings suggest that NK cells play a regulatory role in autoimmunity, and that they are a source of Th2 cytokines. Therefore, when these cells are reduced they allow an overabundance of Th1 cytokines resulting in increased autoimmunity [12]. However, the capacity of NK cells to kill immune cells and/or produce IFN- γ means that they may become a damaging and disease-promoting factor in autoimmunity rather than having a protective role.

The microenvironment in which NK cells mature under different triggers and effector responses excreted by pro-inflammatory cytokines such as IL-6, TNF- α , and factors such as progesterone and prolactin, dictate the direction of NK action. Specifically with RA, NK cells comprise a significant fraction of the lymphocytes in the synovial fluid during the early phases of disease. The majority of NK cells in the synovial fluid of RA patients is CD56high with increased expression of CD94 and altered expression of killer cell inhibitory receptors.

In contrast to the accumulation of activated CD56high NK cells in the synovium, circulating NK cells are lower in the peripheral blood of RA patients. CD56high NK cells produce high amounts of pro-inflammatory cytokines but have decreased cytotoxicity in peripheral blood in correlation with increased RA severity. This observation corresponds with the finding that NK cell depletion in patients with early onset of arthritis have increased disease severity as well as increased autoantibody and IL-17 production [13]. Thus, NK cells are important in RA, mainly in the synovial ground where they should be targeted. NK cells were shown by many to impact the pathogenesis of SLE. When assessed in peripheral blood they were found to be significantly reduced in association with SLE-disease severity. However, tissue NK cells mediate renal damage contributing to glomerular inflammation. This result is shown by the increased killing of tubular

epithelial cells. In nephritic lupus kidney, NK cells produce high levels of cytotoxic granules (perforin and granzyme B) and IFN- γ . They also express CD226 (the NK-activating receptor). The explanation for reduced NK cells in peripheral blood of SLE patients is not well defined. It is possible that NK cells are depleted as a result of increased death or emigrate to the kidney in SLE following their increased expression of CXCR3 [14].

HORMONES AND AUTOIMMUNITY

The involvement of hormones in the development of autoimmune diseases is shown by the female predominance of diseases such as RA and SLE, with ratios of 3:1 and 9:1, respectively. In fact, most immune cells express receptors for estrogen, progesterone, prolactin, and other hormones. As such, estrogen was shown to enhance the response to antigens of mononuclear cells taken from women, switching the immune response toward Th2 dominance and the activation of B cells, antibody production, and IFN response. SLE and MS appear to worsen in the premenstrual phase, whereas RA worsens during menstruation. The influence of sex hormones on the development of SLE comes from changes in disease severity during pregnancy or postpartum [14].

Estrogen and autoimmunity: Estrogen has two functionally receptors (ERs) – ER α and ER β – both of which are expressed on B and T cells, as well as dendritic cells, neutrophils, macrophages, and NK cells. Estrogen influences the maturation and activation of T and B cells and induces the production of pro-inflammatory cytokines and autoantibodies, respectively. Exposure to estrogen decreases the number of developing thymic CD4+/CD8+ T cells and promotes lymphogenesis in the liver, enabling cells to escape negative selection and leading to the accumulation of autoreactive cells. The cells also support the survival of autoreactive T cell clones by increasing Bcl2 expression and inducing Th2 responses and increased levels of IL-4 and IL-5 [15].

Prolactin and autoimmunity: Prolactin acts by binding to prolactin receptors well-expressed on most immune cells namely, monocytes, macrophages, and NK, T and B cells. Prolactin decreases the apoptosis of transitional B cells mediated by anti-IgM, contributing to the breakdown of B cell tolerance to self and the development of autoimmunity. Prolactin stimulates antigen-presenting cells expressing major histocompatibility complex (MHC) class II and promotes co-stimulatory molecules expression and antibody secretion. Clinical evidence is controversial in showing that in some diseases, such as Graves' disease, dermatomyositis, and SLE, serum level of prolactin is increased. Whereas patients with recent diagnosis of untreated RA show no difference in prolactin serum levels after hypothalamic stimulation with the releasing hormone. A possible explanation for this discrepancy is that prolactin correlates with a paracrine/autocrine mechanism of action at a tissue level, which is not always measurable in the circulation.

In this chapter of the book, the authors cover other important issues such as contraception and autoimmunity, namely, the possible thrombotic effects of hormonal contraception. They also discuss the epigenetic influence on sex disparities in autoimmune diseases [16].

INFECTIONS (VIRUSES, BACTERIA), VACCINES, AND AUTOIMMUNITY

In the introduction to this chapter the authors state that environmental factors, including the widespread use of antibiotics, immunization, Western diet habits, and exposure to infections and pollution are contributing to an orchestrated attack of our immune system, which in genetically susceptible individuals with compromised defense mechanisms cannot tolerate the autoimmune attack and immunological breakdown, which leads to initiation of innate and adaptive immune responses against self-antigens, persistent inflammation, cell destruction, and establishment of autoimmune disorders.

Among the environmental factors initiating autoimmunity, inflammatory

processes and infectious agents have been considered the most likely triggers. The question is which are the ones to blame and by which mechanisms do they operate. Discussing the host-microbe interactions, the authors describe this as a war of worlds or a world war? Our immune system is programmed in such a way that it can deal with hundreds of foreign invaders at the same time. Thus, it is logical to state that an epidemic war is occurring rather than a single battle. Microbes do not only fight for their survival against our immune system but also compete for their existence with other neighboring microbes. When the balance is lost and the pathogens prevail against the symbionts, dysbiosis is established, inflammation persists and tissue injury is established.

AUTOIMMUNE RHEUMATIC DISEASES AS MODELS TO STUDY INTERACTIONS BETWEEN VIRAL PATHOGENS AND MICROBES

The best studied triggers of autoimmunity are the DNA viruses, in particular Epstein-Barr virus (EBV) and cytomegalovirus as these two diseases have been considered to be the most likely triggers for a plethora of autoimmune diseases. Molecular mimicry between herpes simplex virus I (HSV1) and human autoantigens related to rheumatic diseases has been reported. The immediately-early protein of HSV1 contains epitopes with a significant degree of amino acid similarity with centromere protein B (CENP-B) and Sm antigens, targeting antigens in SSc and SLE, respectively. Anti-citrullinated peptide antibodies (ACPAs) are the serological markers of RA, and infectious agents that can act as antigenic sources of citrullinated peptides can be considered likely triggers of RA [17]. EBV has been proven to be an inducer of citrullinated peptides and has reasonably been considered a trigger of ACPAs and potentially of the disease. Latent cytomegalovirus infection, as detected by cytomegalovirus seropositivity, was associated with more severe joint damage in RA. Cytotoxic CD4+CD28-T cells are closely associated with cytomegalovirus seropositivity and appear expanded in patients with

RA. Cytomegalovirus is also implicated in the pathogenesis of SLE. IgA and IgG antibodies to cytomegalovirus pp52 early lytic antigens were significantly higher in SLE compared with healthy controls and were positively associated with lymphocyte counts. There are similarities between cytomegalovirus vacuolopathy and vascular damage seen in SSc, which is considered an indirect proof that cytomegalovirus may cause SSc [19].

In addition, a whole section of the book is dedicated to the role of vaccines in triggering autoimmunity. It is clear that vaccines are safe and important in preventing infectious viral diseases. However, in genetically predisposed individuals, vaccines are molecular mimickers of autoantigens promoting the development of autoimmune diseases. In this respect, the book is full of data on the role of adjuvants in inducing autoimmunity [20]. The contribution of silicone implants to the development of immune-mediated disorders and lymphoproliferative diseases is emphasized pointing to the growing interest in this field. Finally, many chapters are dedicated to issues such as genetics and autoimmunity, smoking, cannabinoids, and diet in autoimmunity. Laboratory assays and methods are crucial in the diagnosis and follow-up of autoimmune diseases. The innovations in this field are enormous and therefore are given a special section in this book.

CONCLUSIONS

This book is the bible of modern autoimmunity, and as such it contains all a medical professional needs to know in this field.

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