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Mini-Review

Immunopathogenesis of Autoimmune Diseases

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Abstract

Autoimmunity is arisen by numerous coextensive mechanisms that are in connection with the existence of auto-reactive immune cell subsets and defeat of immunological tolerance. Autoimmune diseases affect more than 3% of the world population, amongst which 80% are women. Autoimmune diseases are categorized by abnormal immune responses against healthy cells and tissues. Nevertheless, the particular pathogenesis of autoimmune disease remains vague. In this study, I review pathogenesis of autoimmune diseases, such as SLE, RA, MS and T1DM, which are categorized by the existence of autoreactive immune cells or the progress of particular autoantibodies.

Abbreviations (if used)

ACPAs - Anticyclic Citrullinated Peptide Antibodies
CNS- Central Nervous System
IC- Immune Complex
IFN-α- Interferon alpha
MSG- Minor Salivary Gland
MS- Multiple Sclerosis

pSS- Primary Sjögren's syndrome
RA- Rheumatoid Arthritis
RF- Rheumatoid Factor
RANKL - Receptor Activator of Nuclear Factor Kappa-B Ligand
SLE- Systemic Lupus Erythematosus
TLR- Toll-Like Receptor
T1DM- Type 1 diabetes

Introduction

Autoimmune diseases contain a wide-ranging group of human disorders that are categorized by the defeat of immunological tolerance to self-antigens and the existence of autoreactive immune cells and (or) autoantibodies aiming healthy cells and normal tissues [1]. Numerous disorders such as Multiple Sclerosis (MS) is characterized as organ-specific autoimmune diseases, whereas, Systemic Lupus Erythematosus (SLE), and Rheumatoid Arthritis (RA) are typical examples of systemic autoimmune diseases [1]. Defeat of tolerance throughout central and peripheral differentiation of the adaptive immune response may cause to unrestrained activation of self-reactive B and T cells which prompt autoimmunity supported by the cells of the innate immunity [2]. Environmental factors are outside causes for autoimmune diseases and they use their effects in genetically predisposed individuals. Comparable to genetic factors, each autoimmune disease has its own set of recognized prompting aspects [3]. In the meantime, the detection of common features of disease pathogenesis could suggestion the chance to use identified drugs or therapeutic approaches crossways numerous disorders [4]. In this mini-review pathogenesis of autoimmune diseases are discussed.

Systemic lupus erythematosus

Systemic lupus erythematous (SLE) is a chronic multisystem autoimmune disease and categorized with the production of various autoantibodies, Immune Complex (IC) deposition and end organ injury[5]. SLE is predominantly affects women compared to males (20–40 years) (9:1 ratio) [6]. The clinical appearances of SLE are multifaceted ranging from arthralgias and oral ulcerations to severe and deadly neurological, renal, and haematological disease and almost all organs and tissues counting lung, kidney, skin, vasculature and even brain are contributed [5]. B cells play a key role in pathogenesis of SLE through secretion of wide-range of different autoantibodies. Cytokine network imbalance, particularly dysregulation of IL-10–IL-12 axis and excess production of IFN-α play a critical role in the damaged cellular immune responses in patients with SLE [7]. Increased proportions of IL-17 and Th17 cells enhance the expansion of peripheral memory B-cell repertoire and decrease the frequency of Treg cells in SLE [8]. Environmental factors, such as ultraviolet light, infection, dietary elements, demethylating mediators, drugs and environmental oestrogen may be complicated in etiology of the disease [9]. In patients with SLE, auto-reactive cells are creating enormous amounts of autoantibodies against self-nuclear antigens which make immune complexes with self-nucleic acids and present in SLE serum. Meanwhile self-RNA and self-DNA in the form of protein complexes can act as TLR7 and TLR9 ligands; motivation of TLRs is recommended as an extra signal causal to activate and/or modulation of the abnormal adaptive immune response [10]. A new study revealed that non-inflammatory phagocytosis of apoptotic cells is reduced in SLE patients. Persistently circulating apoptotic waste may encounter inflammatory elimination pathways and serve as immunogen for the initiation of autoreactive lymphocytes and as antigen for IC creation [5].

Rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disease and chronic systemic inflammatory disease which is considered by chronic synovitis that causes to tissue dysfunction such as restricted injury to articular cartilage, bone, tendon and ligament, followed by loss of function [11]. Circulating Anticyclic Citrullinated Peptide Antibodies (ACPAs) and Rheumatoid Factor (RF) are particular biomarkers for RA, and are characteristically accompanying with worse consequences [12]. Numerous investigators have described a decreased proportion and damaged suppressive function of $CD4^{+}CD25^{+}$ Tregs in the peripheral blood of RA patients. The percentage of Th17 cells and the levels of related cytokines IL-17, IL-23, IL-6, and TNF-α were considerably greater in the peripheral blood of RA patients [13]. Osteoclasts are the only cells that break the bone, and they are a specifically discriminated type of macrophage[14]. Osteoclasts differentiate from monocytes, and Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) stimulates this process. Th17 cells have been found in the synovial tissue of patients with RA. IL-17 motivates the osteoblasts in the joints, prompting RANKL expression [14]. Now, through the interaction with osteoblasts, monocytes react to RANKL and mature into osteoclasts. IL-22 produced by Th17 cells definitely regulates chronic inflammation [15]. IL-22 motivates synovial fibroblasts to prompt cell proliferation and the production of inflammatory chemokines. Furthermore, IL-6 produced by fibroblasts responding to IL-17 derived from Th17 cells increases inflammation. IL-6 motivates synovial tissue in an autocrine manner, deteriorating the circumstance by strengthening cycle that releases inflammatory mediators [16].

Primary Sjögren's syndrome

Primary Sjögren's syndrome (pSS) is a heterogeneous disease at a crossroad of systemic autoimmune disorders and lymphoprolipherative conditions [17]. It is commonly renowned that environmental triggers such as viruses may start the cascade of procedures causing to the inflammation and disturbance of the exocrine glands as well as to the systemic pSS appearances [18]. Not remarkably consequently, Toll-like receptors (TLRs), type 1 IFN pathway, IL-1 family cytokines, and NK cells have been broadly involved in pSS[18]. IL-6 be capable to stimulate Th17, therefore in order relating innate to adaptive immunity [18]. Th1 cells are well-thought-out to be the main CD4+ T cell subset infiltrating minor salivary gland biopsies while the existence of B cells shows a main complexity in the infiltrates. Indeed, it is now supposed that B cells play an essential role in pSS through the production of autoantibodies, including anti-Ro/SSA, anti-La/SSB, cryoglobulins, RF, and through glandular infiltration causing to the progress of ectopic germinal centres and, possibly, lymphoproliferative disease [19]. IL17+ inflammatory cells were specially detected around lymphatic vessels in pSS Minor Salivary Gland (MSG) epithelial cells, thus proposing a pro-lymphangiogenic function of IL-17 in pSS [20]. High local production of soluble form of IL-7 receptor (sIL7R) was associated with increased B cell activity, autoimmunity, and risk for lymphoid neogenesis [21].

Psoriasis

Psoriasis is a chronic inflammatory skin disease described by hyperproliferation and abnormal differentiation of epidermal cells. Pronounced acanthosis and inflammatory infiltration such as of neutrophils and lymphocytes are distinguished in injuries [14]. Psoriasis is triggered by a complex interaction between the immune system, psoriasis-associated predisposition loci, autoantigens, and multiple environmental factors

[22]. Plaque psoriasis, the most common disease variant, generally displays as erythematous plaques with thick scaling on the extensor surfaces, scalp, and trunk [23,24]. Almost one third of patients with chronic disease go on to progress psoriatic arthritis, an inflammatory arthritis considered by nail disease, asymmetric oligoarthritis, enthesitis, and/or dactylitis [24]. The disadvantageous inflammatory events associated with psoriatic disease are not restricted to the skin and account for an increasing number of comorbid conditions, counting chronic kidney disease, cardiometabolic disease, metabolic syndrome, stroke, gastrointestinal disease, and malignancy [25]. Current studies explained that Th17 cells contribute to the onset of psoriasis [26]. Th17 cells that have infiltrated the skin create IL-17 and IL-22. IL-22 stimulates keratocytes in the skin, causing to the activation of STAT3, followed by the proliferation of keratinocytes and acanthosis [27]. IL-17 and IL-22 prompt keratinocytes to express CXCL1 and CXCL8, persuading further cell infiltration [28]. IL-36 is created by keratinocytes and motivates resident DCs that are usually current in the skin. In response to IL-36, DCs express IL-23, which seems to increase the pathogenicity of Th17 cells [29].

Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic inflammatory autoimmune disease that injuries the Central Nervous System (CNS) [30]. MS has been described by demyelinated regions in the white and grey matters of brain and spinal cord and defined by the loss of myelin sheaths and oligodendrocytes [31]. The white matter lesions involve myelin breakdown go together with infiltrates of mononuclear phagocytes, B lymphocytes, plasma cells, dendritic cells and T lymphocytes. Macrophages are high proportion cells in the infiltrate that is followed by CD8+ T cells [32]. Th1 and Th17 are known to be the major cells contributed in MS pathogenesis [33]. The Th1 cytokines, IFN–γ, and TNF-α were higher in MS patients, however only the TNF-α levels were statistically considerable [34]. Studies showed the expression of IL-6, IL-1β, IFN-γ, and TNF-α in monocytes, microglial cells, and astrocytes were increased and are associated with active MS [35]. Demyelination of neuron sheath increases inflammatory processes to be activated, which is related to enhances of cytokines release and antibody production causing to injury of BBB and motivation of macrophage activation and oxidative stress pathways [36]. The role of the B cells in the immunopathogenesis of MS was identified following the discovery of intrathecal IgG, mainly consisting of IgG1 and IgG3 isotypes, in MS patients [37].

Type 1 Diabetes

Type 1 diabetes mellitus is a chronic autoimmune disease wherein endogenous insulin creation is strictly compromised as a consequence of an immune-mediated damage of pancreatic β-cells get up over a multifaceted interface of both genetic and immunologic factors [38]. The immunological identification of autoimmune diseases relies primarily on the recognition of autoantibodies in the serum of T1DM patients [38]. Type 1 diabetes is a polygenic disease. Risk of T1DM progression is discussed by specific HLA DR/DQ alleles [e.g., DRB1*03-DQB1*0201 (DR3) or DRB1*04-DQB1*0302 (DR4)] [39]. Viral antigens can also play a role in the generation of beta cell autoimmunity. Enteroviruses may be involved in the autoimmune pathogenesis of T1DM [40]. Type 1 diabetes was not constantly deliberated as the classical organ-specific disease it is currently renowned to be. Insulin dependent diabetes was recognized to irregularly arise in the Autoimmune Polyendocrine Syndrome I (APS I), a classic autoimmune syndrome with T-cell and B-cell antibody defects attentive at adrenal, parathyroid, gonadal, thyroid and other tissues [41]. This condition is

now known to be caused by mutations in the autoimmune regulator gene (AIRE) [42]. Moreover, the presence of insulin autoantibodies and other autoantibodies against frequent islet proteins was not exposed until years later [43]. A key differentiating feature between type 1 and type 2 diabetes is the presence of autoantibodies against β-cell autoantigens. More than 90% of individuals with newly identified type 1 diabetes have one or more of the subsequent autoantibodies at disease start; those reactive to Insulin (IAA), Glutamic Acid Decarboxylase (GADA), Insulinoma-Associated Autoantigen 2 (IA2A), And Zinc Transporter 8 (ZnT8A) [43].

Conclusions

Our immune system established to protect us contrary to attacking pathogens and to support tissue healing after damage. In autoimmune diseases, mechanisms that control the stability between recognition of pathogens and evading of self-attack are damaged. Moreover, regulate of inflammation is missing, causing to constant immune activation deprived of any overt infection, with diverse amplitudes throughout flares and inactive disease. Autoimmune diseases are definite by an immune response against self-tissues. Immune cells injury tissues over killing cells or releasing cytotoxic cytokines, prostaglandins, reactive nitrogen or oxygen intermediates. $CD25^{+}$ $CD4^{+}$ Treg cells play a key role in the protection of immunologic self-tolerance and modulation of self-reactive physiological and pathological immune responses. Dysfunction of Treg cells leads to loss of self-tolerance and entrance of autoimmune diseases.

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