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A Reviewon Cellular and Molecular Immunology: Autoimmunityand Autoimmune Diseases

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Abstract: The immune system walks a fine line to distinguish self from non- self in preserving the integrity of the host. The etiology and pathogenesis of many autoimmune diseases remain unknown. It is the failure of an organism in recognizing its own constituent parts as self, which allows an immune response against its own cells and tissues. Autoimmune disorders result from a breakdown of immunologic tolerance leading to an immune response against self-molecules. Approximately 3% of the populations in Europe and North America currently suffer from autoimmune diseases, many with symptoms of multiple disorders. Female have a significantly higher risk of developing an autoimmune disease than men, as >75% of those suffering from autoimmune diseases are female. The reasons for the sex role in autoimmunity are unclear. Women appear to generally mount larger inflammatory responses than men when their immune systems are triggered, increasing the risk of autoimmunity. A major barrier to understanding mechanisms of autoimmunity comes from difficulty in defining early events in these diseases. Genetic predisposition, environmental triggers, hormonal influences and toxicants are some determinants of Autoimmune Diseases (AD).High levels of dietary sodium are associated with raised blood pressure and adverse cardiovascular health and have been shown to affect the immune system. In relation to dietary proteins, it has been well established that different proteins and peptides in milk and wheat are involved in autoimmune diseases. The development of autoimmune disorder is a complex process. The main molecular and cellular mechanisms of autoimmune responses and their origins are numerous and diverse. To optimize the chances of therapeutic success it is essential to identify the environmental triggers first and then attempt to remove them from the patient's environment (e.g., toxic chemicals and food associated with autoimmunities). It is concluded that the advances made by the application of novel and high-throughput technologies to the analysis of diseased tissues, including miRNA and the autoantibody repertoire and the development of novel effective miRNA-based gene therapies will make the future of this field very bright.

Key words: Autoimmunity · Autoimmune Diseases · Immune System · Proteins · T Cells

INTRODUCTION

The immune system walks a fine line to distinguish self from non self in preserving the integrity of the host [1]. Interference with this fine line can result in over activity to self-antigens, leading to autoimmunity. During the past 20 years a significant increase has been observed in the incidence of autoimmune disease worldwide. The etiology and pathogenesis of many autoimmune diseases remain unknown. It does appear that a close interplay between environmental triggers and genetic factors is responsible for the loss of immunological tolerance and autoimmunities [2].

Autoimmunity is the failure of an organism in recognizing its own constituent parts as *self*, which allows an immune response against its own cells and tissues. Any disease that results from such an aberrant immune response is termed an autoimmune disease. Prominent examples include Celiac disease, diabetes mellitus type 1 (IDDM), Sarcoidosis, systemic lupus erythematosus

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(SLE), Sjögren's syndrome, Churg-Strauss Syndrome, Hashimoto's thyroiditis, Graves' disease, idiopathic thrombocytopenic purpura, Addison's Disease, rheumatoid arthritis (RA) and allergies. Autoimmune diseases are very often treated with steroids [1].

In relation to the role of heritability in autoimmunity, genome-wide association studies reported that genetics only accounted for a minority of autoimmunity cases and in many cases disease discordance exists in monozygotic twins [3]. For this reason, research and publications dedicated to environmental factors in autoimmunity have grown by an average of 7% every year since 1997 [2]. This includes toxic chemicals, infections and dietary components. Indeed, detection of reactive antibodies to various citrullinated peptides and proteins in autoimmune disease is the best indication for gene-environment interactions [4]. Autoimmune disorders result from a breakdown of immunologic tolerance leading to an immune response against self-molecules. In most instances the events that initiate the immune response to self-molecules are unknown, but a number of studies suggest associations with environmental and genetic factors and certain types of infections. Approximately 3% of the populations in Europe and North America currently suffer from autoimmune diseases, many with symptoms of multiple disorders [5].

This may be an underestimate, as epidemiologic studies are not available for some of the less common diseases. In addition, there are suggestions that a number of common health problems such as atherosclerosis and inflammatory bowel disease may have an autoimmune component [6]. Female have a significantly higher risk of developing an autoimmune disease than men, as > 75% of those suffering from autoimmune diseases are female [5].

Young, post pubescent women have been shown to be approximately 10 times more susceptible than men to developing autoimmune disease [7] Although the underlying mechanisms for this predisposition are currently being investigated, it is known that females and castrated males produce much higher levels of estrogen and reduced levels of testosterone and it is well documented that estrogen and estrogen like chemicals may alter the immune response [8]. Much of the evidence supporting a role for estrogen in the development of autoimmune diseases comes from animal models rather than human studies. In autoimmune prone mice, estrogen administration greatly enhances mortality in both males and females [9].

The reasons for the sex role in autoimmunity are unclear. Women appear to generally mount larger inflammatory responses than men when their immune systems are triggered, increasing the risk of autoimmunity. Involvement of sex steroids is indicated by that many autoimmune diseases tend to fluctuate in accordance with hormonal changes, for example, during pregnancy, in the menstrual cycle or when using oral contraception. A history of pregnancy also appears to leave a persistent increased risk for autoimmune disease. It has been suggested that the slight exchange of cells between mothers and their children during pregnancy may induce. Autoimmune diseases are defined as diseases in which immune responses to specific self-antigens contribute to the ongoing tissue damage that occurs in that disease. ADs may be either tissue-specific (e.g., thyroid, β-cells of the pancreas), where unique tissue-specific antigens are targeted, or may be more systemic, in which multiple tissues are affected and a variety of apparently ubiquitously expressed auto antigens are targeted [10]. Genetic risk factors play an important role in autoimmune disease susceptibility. Recent advances genotyping techniques, statistical methods and the organization of large patient cohorts have facilitated explosive progress in this field and our understanding of the genetic architecture of human autoimmunity is rapidly expanding [11].

Autoimmunity is not set off by a single cause and is triggered by a variety of agents and molecular and cellular pathways and events. Several elements and mechanisms underlying autoimmune responses have been identified. However, even if a given autoimmune disease were to be initiated primarily by a single trigger, other events and regulating mechanisms come into play, thereby adding complexity to the process. This review focuses on the current understanding of the mechanistic principles that underlie autoimmune diseases. We provide an outlook on novel class of immune regulators that play an essential role in multiple patho-physiological processes of multiple autoimmune diseases.

Overview of development of autoimmunity:A major barrier to understanding mechanisms of autoimmunity comes from difficulty in defining early events in these diseases. Since, diseases are only recognizable after development of the diagnostic phenotype, there has been the tendency to interpret findings made at diagnosis with findings present at initiation. According to Arbuckle *et al*. [12], the development of ADs can be

divided into four phases: i. Susceptibility phase, ii. Initiation phase, iii. Propagation phase and iv.Regulation phase.

The full collaboration of both the innate and adaptive arms of the immune system plays a crucial role in the promotion or inhibition of autoimmune disease. Generally, to clear infections the innate immune cells can up regulate co stimulatory molecules and produce a mixture of pro and anti-inflammatory cytokines such as interleukin-1-beta (IL-1), IL-12, transforming growth factor-beta (TGF-), IL-23, tumor necrosis factor-alpha (TNF-) and IL-6 that regulate the adaptive arm of the immune system [13].

Determinants of Autoimmune Disease

Genetic Predisposition: There have been important advances in the genetics of autoimmunity in several mouse models. These studies highlight a critical role for pathways of tolerance induction, immunoregulation and setpoints/thresholds for histocompatibility complex (MHC) cannot present an antigen, that antigen cannot elicit a response and would not be an auto antigen in that host. The presence or absence of the appropriate MHC would determine whether the potential auto antigen is presented andthe occurrence or otherwise of a response to the antigen.

Environmental Triggers: Environmental stimuli, including chemical agents and pathogens, show significant links to AD onset or flare-ups in both humans and animal models [15]. Certain chemical and pharmaceutical agents have been linked to the onset of particular systemic AD symptoms. For example, toxins such as the heavy metal mercuric-chloride or polyvinyl-chloride can precipitate immune complex nephritis, systemic sclerosis, or the development of auto antibodies.The mechanism by which these environmental factors induce autoimmunity includes epigenetic changes (DNA methylation and histone modification), reaction with the self-component to generate novel antigens, aberrant cell death releasing cellular material that can lead to inflammasome activation and production of pro-inflammatory cytokines and molecular mimicry [16].

Infections with certain viruses, bacteria and mycoplasma appear to provoke the initiation of systemic AD in genetically predisposed individuals. Moreover, a severe bacterial or viral infection may trigger an increase in autoreactive antibodies or conventional T cells that leads to a flare-up of quiescent AD or an exacerbation of existing symptoms[17].

Hormonal Influences: A striking common feature of many ADs in both humans and experimental animal models is that females are more susceptible to autoimmune conditions than males [18]. More than 85 percent of patients with thyroiditis, scleroderma, lupus and SS are females [19]. In addition to genetic factors such as X-chromosome abnormalities, sex hormones such as estrogens and androgens are believed to play a significant role in the sex-based susceptibility to many ADs. Researchers hypothesize that the expression of hormones or factors associated with the development of sex-specific organs can activate previously tolerant or ignorant lymphocytes. Indeed, in a mouse model of SLE, the administration of estrogen unregulated Bcl-2 in B cells and blocked B cell toleration [20].

Toxicants and Autoimmunity: The mechanism of toxicant-induced autoimmunity is described by either toxicant induction of aberrant cell death making the hidden cellular material available to anti-gen presenting cells [21] or by immune reactions to xenobiotics through covalent binding of chemicals or haptens to human tissue proteins and formation of neo antigens [22]. This is due to the fact that reactive organic compounds most often bind covalently; that is, their electrophilic properties enable them to react with protein nucleophilic groups such as thiol, amino and hydroxyl groups. Examples of such reactive, haptenic compounds that frequently lead to sensitization after dermal contact or inhalation are toluene diisocyanate, trimellitic anhydride, phthalic anhydride, benzoquinone, formaldehyde, ethylene oxide, dinitrochloro benzene, picrylchloride, penicillins and D-penicillinamine.

Mechanisms Underlying Autoimmune Disorders

Pathogen-Related Mechanisms

Molecular Mimicry: Thefirst pathogen-related hypothesis, called molecular mimicry (or antigenic mimicry), holds that auto reactive lymphocytes in the periphery are sometimes activated by cross-reacting pathogen antigens [23]. In the most likely mechanism by which infection induces autoimmunity, foreign antigens very often may bear sufficient structural similarity to self-antigens. This is called antigenic mimicry or molecular mimicry. Immune response to microbial antigens could result inactivation of T cells that are cross-reactive with self-antigens. This is due to the fact that a single T cell can respond to various peptides with similar charge distribution and over all shape [24].

Induction of Inflammation and Dendritic Cell Maturation: Infectionby a pathogen induces inflammation, supplying "danger signals" and a cytokine milieu that favors dendritic cell (DC) maturation and activation. Many investigators [25] have now provided evidence that this inflammation-induced maturation of DCs that may be the key link between pathogen infection and autoimmunity, the so called "adjuvant effect." The hypothesis is that bacterial DNA, bacterial components and endogenous nucleic acids released upon pathogen-induced cell death are particularly potent adjuvants because they engage the Toll-like receptors (TLRs) of immature DCs. Following TLR engagement, DCs are induced to mature and up regulate their expression of co stimulatory molecules. When such mature DCs encounter auto reactive T cells in the lymph node, activation leading to an autoimmune response may result if the pMHC derived from a pathogen or self-antigen is recognized by the T cell. Thus, auto reactive T cells that might have been held quiescent due to a lack of co stimulation and/or the effector actions of Treg cells regain their capacity for activation.

Microbial Super Antigen; Another theory to account for at least some episodes of pathogen-linked AD involvesmicrobial super antigens. These molecules can non-specifically activate a large number of different T cell clones by binding directly to particular T-cell receptor (TCR) Vβ sequences [26]. Super antigens are believed to play role in relapses of AD or the exacerbation of existing AD, but they do not appear to be able to initiate AD.

Altered Proteins

Protein Mutation And Altered Expression: Mutations and altered expression of proteins provide important sources of self-antigens that trigger autoimmune responses. Novel forms of auto antigens generated by mutation, truncation, or splicing. Since the final epitopes generated and loaded on to MHC class II can be profoundly influenced by single early cleavage events during antigen processing, relatively minor but critically placed changes in the primary structure of auto antigens may have the capacity to influence peptide selection. Mutations in the autoimmune regulator gene are responsible for the development of autoimmune polyendocrinopathy candidiasis ectodermal dystrophy [27]. Mutations in the coding part of human mannose-binding lectin increase the risk of infection and autoimmunity [28].

Post Translational Modification: Posttranslational modification of self-proteins has an effect on intracellular signaling and protein recognition by the immune system and creates auto-antigens that are not subjected to immune tolerance [29]. There is a range of possible post-translational modifications (PTMs) of auto antigens that can allow immune recognition of neo-self epitopes, including phosphorylation, proteolytic cleavage, ubiquitination, transglutamination, citrullination and isoaspartyl modification [30]. An example of a posttranslational modification is the non-enzymatic modification of the carboxyl side groups of aspartate residues to isoaspartyl side chains that causes altered T cell function and autoimmune responses [31]. Citrullination of the guanidinium side chains of arginine in proteins by peptidyl arginine deaminase has been implicated in rheumatoid arthritis pathogenesis [32].

Disordered Proteins: Denatured proteins [33], natively disordered or misfolded proteins can trigger immune responses against self-proteins. Misfolding produces molecular species that have incorrectly-formed three-dimensional structures. Heat-shock proteins and other molecular chaperones assist the correct folding, stabilization and translocation of proteins. Defects in the function or expression of heat-shock proteins and other molecular chaperones might play a causative role in the stimulation of autoimmunity [34]. Antibodies against heat-shock proteins have been found to recur in ADs [35]. Such auto antibodies can interfere with the ability of heat-shock proteins to affect their function in protein refolding.

Sequestered Proteins: Sequestered proteins are normally sheltered from immune recognition. However, they can become immunogenic once exposed to recognition by immune cells and induce efficient immune responses. Several autoimmune disorders have been linked to apoptosis [36]. Apoptosis, a process of programmed cell death and removal of damaged cells, results in the release of cell components that are then made accessible to immune recognition.

Epitope Spreading: Epitope spreading is a phenomenon in which the immune system expands its response beyond the original epitope recognized by T or B cells to induce the release of non-cross-reactive epitopes that are recognized by the immune system later [37]. Epitope spreading can result from a change in protein structure. One such example is protein citrullination, the changing of an amino acid from arginine to citrulline. This can result not only in immune reaction against the original protein or its citrullinated form, but also against other citrullinated proteins. Epitope spreading is demonstrated in rheumatic

fever, in which a chronic autoimmune response against streptococcal M protein and heart valve tissue can result in immune response against collagen or laminin. This immune response against collagen or laminin is no longer specific to the bacterial M protein or its cross-reactive tissue protein. In pemphigus, blistering of the mouth precedes blistering of the skin and blisters in the mouth are associated with the presence of antibodies against desmoglein-3 protein, which is specific to the mouth epithelial cell antigens. It is only later on when T cells attack skin desmoglein-1 that auto antibodies are produced against skin-specific antigens and skin blistering develops [38].

Bystander Activation and Stimulation of Pattern Recognition Receptors: By stander activation occurs when viral antigens stimulate toll-like receptors and other pattern recognition receptors become activated in the inflammatory environment [39]. This activation of receptors on an antigen presenting cell (APC) causes the release of pro inflammatory cytokines which can induce tissue damage and the release of hidden antigens. The release of tissue antigens can activate auto reactive T cells that initially were not involved in the immune reactivity against the original infection [24]. Additionally, virally infected APCs and the concomitantly released mediators are able to activate auto reactive Th1or Th17 cells in a bystander manner. Upon recognition of virally infected tissue cells, viral-specific T cells then release cytotoxic granules such as granzymes and cytokines such as TNF-, IL-17, lymphotoxin and nitric oxide. This inflammatory environment can lead to the bystander killing of uninfected neighboring cells. Microbial super antigens can induce a broader form of bystander activation by cross linking MHC class II molecules to TCRs on APCs and Tcell activation. T cells that are stimulated in this manner may contain a subset recognizing specific tissue antigen [40].

Cellular Mechanisms of Autoimmune Disease

Role of T Cells in Initiating and Regulating Autoimmunity: There is abundant evidence that potentially auto reactive T cells can mature and reach the periphery in most individuals. Numerous “loopholes” in self-tolerance may allow this. Some organ-sequestered antigens are never presented adequately in the thymus. In addition, some self-peptides may not be processed and presented efficiently in the thymus. T cells that escape negative selection against these peptides may be activated in the periphery when these peptides are created by altered proteolysis during inflammation and by post-translational modifications of peptides, such as glycosylation or citrullination [41].

Several well-studied animal models are generated by immunization of animals with peripheral organ antigens, such as type II collagen in collagen-induced arthritis and myelin-associated proteins in experimental allergic encephalomyelitis (EAE), which can engender robust T cell responses in the presence of appropriate adjuvants. In addition, immunization of normal mice with nuclear antigens or peptides derived from these antigens can result in lupus-like autoantibody production [42]. These experiments indicate that peripheral auto reactive T cells exist and are needed to be kept under control to prevent autoimmunity. Many cellular mechanisms prevent peripheral self-reactive T cells from mediating autoimmune responses.

The Roles of B Cells: Multiple checkpoints are involved in the prevention of activation of auto reactive B cells in the peripheral lymphoid tissues [43]. Auto reactive B cells are part of the normal peripheral B cell repertoire and defects in central B cell tolerance do not seem to be necessary to allow for pathogenic autoantibody production.

Influence of Antigen Presenting and Tissue Environment on Autoimmunity: It has been increasingly evident that the manner and environment in which T cells and B cells are activated can have profound effects on their subsequent differentiation and susceptibility to peripheral tolerance mechanisms [44]. Major differences between tissues in the responsiveness and cytokine secretion patterns of immune and non-immune cells also are important in the control of immunity and autoimmunity [45].

The Cytokine Network: In host defense, Th1 cells primarily enhance cell-mediated inflammatory immune responses, such as delayed-type hypersensitivity reactions, which frequently involve activation of macrophages and effector T cells. The ability to mediate an effective immune response against certain intracellular pathogens seems to depend strongly on the generation of a Th1 response. In contrast, Th2 cells mainly provide help for B cells by promoting class switching and enhancing the production of certain IgG isotypes and production of IgE, including in allergic diseases. T cells producing the cytokine IL-21 also may be important in promoting B cell functions [46]. The Th2 cytokines IL-4 and IL-10 also can function to limit macrophage activity [47] and Th2 cells may negatively regulate inflammation in AD.

Dietary Components and Autoimmunities: High levels of dietary sodium are associated with raised blood pressure and adverse cardiovascular health [46] and have been shown to affect the immune system. Lowlevels of vitamin D have been linked with MS, systemic lupus erythematosus (SLE), RA and other autoimmune disorders [49]. Lactose intolerance is no laughing matter for those afflicted with it or other milk-related disorders. The pleasures of a modern diet unfortunately come with cave at sand unexpected catches that urgently need investigation.

Sodium Chloride in Diet and Autoimmune Diseases: For the past five decades various studies have been conducted on Autoimmune Diseases the comparative sodium intake levels in different countries [46]. Animal experiments, epidemiological studies and clinical trials have provided convincing evidence for the detrimental effect of sodium intake on blood pressure (BP), coronary heart disease and stroke, as well as non-cardiovascular diseases [48].

The Role of Milk and Wheat Components in Autoimmune Diseases: In relation to dietary proteins it has been well-established that different proteins and peptides in milk and wheat are involved in autoimmune diseases [49].

CONCLUSION

From this review it can be concluded that the development of autoimmune disorder is a complex process. The main molecular and cellular mechanisms of autoimmune responses and their origins are numerous and diverse. Although knowledge regarding different aspects of the immunopathogenesis of these disorders, especially related to animal studies, has advanced dramatically in recent years, major gaps in knowledge of human AD pathogenesis persist.Putting all this information together, it appears that there are common mechanisms in the immune pathogenesis of multiple autoimmune reactivity's.

The cellular immunologic abnormalities involved in the initiation and perpetuation of disease also need much greater definition. Better understanding of these processes would also providenew molecular and cellular strategies for control and manipulation of autoimmune responses and diseases. The remarkable increase in information regarding the immune system and the genetic basis of complex traits, is likely to accelerate the pace of our understanding of human autoimmunity in the near future. To optimize the chances of therapeutic success it is essential to identify the environmental triggers first and then attempt to remove them from the patient's environment (e.g. Toxic chemicals and food associated with autoimmunity). In the case of infections, this also helps to guide the clinical use of various medications which are now often used for prophylaxis. Therefore, careful monitoring for the presence of infections in the patient's blood or tissue will be desirable for monitoring the effects of the drug therapy. The advances made by the application of novel and high-throughput technologies to the analysis of diseased tissues, including miRNA and the autoantibody repertoire and the development of novel effective miRNA-based genetherapies will make the future of this field very bright.

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