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Autoimmune Diseases: Genes, Inflammation And Environment

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One of the important roles of the immune system is the distinction between 'self' and 'non self'. This complex system recognizes and eliminates agents there by protecting the organism against infection. T lymphocytes specifically recognize the extrinsic antigenic peptides found on the cell surface of antigen presenting cells (APC). Shortcomings in this specific recognition of non self and self antigens may occur due to the effect of incomplete clonal deletion in the thymus or elimination of the anergy of autoreactive T cells, to superantigens which can ambiguously activate T cells, or due to the modification of autoantigen by infected micro organisms, thus resulting in autoimmune diseases (AIDs) [1,2]. A major common feature of all AIDs is the presence of autoantibodies and inflammation, including mononuclear phagocytes, autoreactive T lymphocytes and plasma cells. Two major entities of AIDs were described: the first entity is the organ specific AIDs, which the expression of the disease is restricted to specific organs. The majority of cases target tissues are of neuroendocrine character. The most studied and well characterized organ specific AIDs was autoimmune thyroid diseases (AITD), type 1 diabetes, Addison disease and Sjogren syndrome. The second entity is the systemic AIDs which many tissues of the organism are affected. Target tissues and molecules are widespread in the body. The hallmarks of the systemic AIDs are vasculitis and arthritis. Prototypes are systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). The development, progression and evolution of AIDs depends on a combination of genetic and environmental factor.

The involvement of several genes in the genesis of AIDs has been proven for a long time. Multiple polymorphisms in each gene contribute to disease development. Most of important polymorphisms are located in regulatory regions of genes encode proteins are believed to play roles in immune system function. However, it has proved difficult to define the role of most of these genes

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polymorphisms in the failure of self tolerance to autoantigens and the development of autoimmunity. Among several genes associated with AIDs, the strongest associations are with particular HLA alleles, or the major histocompatibility complex (MHC) located in chromosome 6 [3,4]. MHC expression is essential for antigen presentation and immune responses. Both class I and II molecules bind processed antigenic peptides and present them to T lymphocytes [5]. It has been demonstrated that the HLA related gene region provides an important contribution to the genetic susceptibility of many but not all of the AIDs. Nevertheless, it is still not definitively known how different HLA alleles contribute to the disease. The problem of using knowledge of the genes involved to elucidate the pathogenesis of AIDs is much more daunting for other polymorphisms with odds ratios far lower than those for HLA alleles.

Genes out side of the MHC also contributed to predispose for developing AIDs [6]. A major large studies of RA, type I diabetes and lupus or their animal models, have revealed a number of non MHC genes that contribute to susceptibility [7,8,9]. Common susceptibility loci have been found for a number of different AIDs, including diabetes and myocarditis, suggesting that shared genes are involved in the progression and developement of AIDs [10]. Current evidence suggests that many of the genes conferring susceptibility control immunoregulatory mechanisms [11].

The development of AIDs depends on a complex interplay between APC like macrophages and dendritic cells, the helper T lymphocytes, T effector lymphocytes, cytotoxic T lymphocytes, B lymphocytes, antibodies and proinflammatory cytokines such tumor necrosis factor (TNF) and interleukin family (IL2, IL12 and IL17) [12,13,14]. These proinflammatory cytokines are produced in the innate and adaptive immune reaction and actin along range endocrine manner, affecting immune cells far removed from the site of infection or inoculation. Cytokine and cytokine receptor genetic polymorphisms have been linked to many different AIDs (15). Genetic polymorphisms in interleukin 23 (IL23) and Th17 lymphocytes have been implicated in chronic inflammatory and autoimmune mediated diseases such Crohn's disease ankylosing spondylitis and Behcet's disease [15,16]. Accordingly, inflammatory Th17 lymphocytes have been associated with tissue damage in all of AIDs, and treatment with monoclonal antibodies specific has shown efficacy in cellular infiltration, synovial hyperplasia and bone erosion [17]. Therefore, IL 23/Th17 is considered as an attractive therapeutic target in AIDs.

Environmental factors also play a role in the pathogenesis of AIDs. Their identification has critical importance for understanding individual susceptibility, but there are very few agents that clearly have a role and identification of generic risk factors remains elusive. The most important of these external factors are infectious agents, dietary intake, toxic agents and stress [18,19]. Infectious agents have long been the most well studied environmental factors. The best example of a relation between infection and immunity is acute rheumatic fever, which occurs following exposure in genetically susceptible hosts to Streptococcus pyogenes [20]. However, numerous other infectious agents have been suggested but not proved to have a role, including bacteria, other viruses such as herpes simplex virus and cytomegalovirus, parasites and fungi [21]. Many theories have been initiated to explain this association as well as epitope spreading, antigenic complementarity, and immoderate innate recognition receptor activation.

Another source of exogenous causes contributing to autoimmune pathogenesis is constituted of specific food elements. Disturbance of iodine metabolism are capable of perturbing the tolerance for thyroid autoantigens and leads to AITD. Chemical toxins or drugs constitute an important source of pathogenic factors in the development of autoimmunity. Tobacco smoke have appeared to be most important in the development of Graves disease and autoimmune thyroiditis [22]. Concerning type1 diabetes induction, several agents and drugs are toxic to b cells and able to induce insulitis and diabetes in rats and mice [23,24]. These drugs may directly influence cells of the immune system, leading to the disturbance of the delicate balance between responsiveness and tolerance.

A few characters are identical between all AIDs suggesting that common pathogenic mechanisms lead to the development and evolution of AIDs in genetically susceptible individuals. The autoimmune reaction is initiated, it is usually self sustained, leading to the

chronic or definitive impairment of the target tissue. The mechanisms underlying the perpetuation of an autoimmune reaction are still obscure, and this makes the treatment of AIDs even more complicated.

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