Introduction

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An autoimmune disease is a result of the body's immune system attacking itself. When the immune system encounters non-self in its environment, it mounts an immune response against that foreign substance to protect itself from potential harm. In order to do this effectively, immune system must be able to recognize what is self in order to respond to non-self or foreign. In autoimmune diseases there is a failure to recognize some part of self. The resultant autoimmunity may be restricted to a single organ, a localized region or the whole individual. The consequences may vary from minimal to catastrophic, depending on the extent to which the body is affected. In an autoimmune disease pathologic signs are a consequence of the autoimmune response.

Autoimmune diseases are major causes of morbidity and mortality throughout the world. The physical, psychological and economic burden of these diseases is especially devastating because they often attack young adults. Many autoimmune diseases are more prevalent in women than in men and tend to appear during or shortly after puberty. However, autoimmune diseases that develop in men often are more severe. These diseases can affect virtually every site in the body including the endocrine system, connective tissue, gastrointestinal tract, heart, skin, and kidneys.

Autoimmune disorders like pemphigus, scleroderma, systemic lupus erythematosus, rheumatoid arthritis and dermatomyositis are diseases with little or extensive skin manifestation occurring as a result of dysfunction of the host immune system. There are various mechanisms involved in the pathogenesis of autoimmune skin diseases. The suppression of anti-self immune response can be either bypassed resulting in immune mediated destruction of tissue or there is a stimulation cross reaction by molecular mimicry or even by massive immune activation by microbial superantigens and other environmental agents. Defects in regulatory mechanisms responsible for self-tolerance too can result in autoimmunity.

Autoimmune diseases result from a combination of genetic, immunologic, hormonal, and environmental factors. Unfortunately, we do not know very many of the triggers. It must be emphasized, that these environmental triggers act only in individuals with a genetic

predisposition and not in the population at large. Although an autoimmune response occurs in most persons, clinically relevant autoimmune disease develops only in susceptible persons. Even with a genetic predisposition, most people do not develop an autoimmune disease unless something external acts on their body implying involvement of multiple factors. The disorders result from the synergistic action of a genetic predisposition (evidence based on familial and twin concordance studies) and exposure to novel environmental factors. It has long been recognized that environmental influences play an important role in the risk of developing autoimmune diseases. Time-latency considerations implicate stochastic factors or random probability in the etiopathogenesis of autoimmunity, whether they are somatic mutations or successive random gene-environment interactions.

Infectious agents are the most often cited environmental factors implicated as triggers of autoimmune diseases. Infectious agents may induce the breakdown of immunological tolerance and the appearance of autoreactivity. Chronic exposure to antigenic/ superantigenic stimulus or environmental toxins can lead to clonal anergy which will be reflected as decreased response to recall antigen stimulation. Molecular mimicry of common immunodeterminants or epitopes between invading microbe – viral, bacterial or parasitic and the host can produce the kind of immune response which recognizes both the microbial determinant and the shared host self-antigen. There is evidence that the development of certain autoimmune diseases may be associated with a bacterial or viral infection that stimulates production of antibodies and immune cells called T cells, which are targeted against bacterial proteins that closely resemble "self" proteins, leading to cross reactivity with healthy tissues. The concept of molecular mimicry is a viable hypothesis in the investigation of the etiology, pathogenesis, treatment, and prevention of autoimmune disorders. Other mechanisms involved may be pathogen induced modification of host proteins, especially, cytosolic proteins, major histocompatibility complex modification or shedding, tinkering with antigen presentation, virokines and the like microRNA role. The autoreactive T cells may play a useful role in promoting the immune response to infection. However, the specific relationship between infection and

autoimmunity is still unclear. The exact mechanisms by which infection induces a particular autoimmune disease are unknown.

Genetics accounts for about half of the risk of developing an autoimmune disease. The other half is the agent in the environment which triggers the process. In an individual with a susceptible genotype, exposure to environmental factors (such as infectious agents or environmental toxins) can act to initiate an autoimmune process. Autoimmune disease rates have been on the rise in developed countries during the last 50 years, compared to their developing counterparts, presumably because people in less developed countries are exposed to more pathogens. In India, rapid urbanization related increase in vehicular pollutants and indiscriminate use of pesticides on crops which subsequently enter the food chain may be contributing to the disease process and result in an increase in the number of such cases.

Microbial products can improve T-cell responses to self as well as foreign antigens. Whether or not infections, acting as adjuvants, induce autoimmune disease in the human population is not known. Paradoxical observations have been the strong association of certain microbial organisms with autoimmune diseases. A number of infecting microorganisms produce superantigens which are capable of polyclonal activation of T- and B-lymphocytes, and production of large amounts of antibodies of varying specificities, some of which may be self-reactive. Microbial infection can also cause polyclonal activation of autoreactive lymphocytes. There are very rare links between autoimmune disease and helminthic parasites.

Various autoimmune diseases have been associated with a number of bacterial and viral infections. In all of these diseases, the underlying problem is similar - the body's immune system becomes misdirected, attacking the very organs it should protect. Frequently, more than one autoimmune disease may be observed in the same animal, as well as an increased susceptibility to bacterial infection. Many autoimmune diseases tend to be difficult or impossible to cure, for the obvious reason that the focus of the immune response — self antigens — cannot be eliminated. The immunological tolerance of T cells induced by the intensity of antigen/ superantigen stimulus determines the course of

disease and it largely varies from individual to individual i.e. the level of anergic status. High burden of intestinal parasite(s) in rural as well as urban population, afflicted with apparent autoimmune disorder, may lead to persistent activation of immune system and an immunologically irrelevant hyporesponsive state.

There is a paucity of knowledge on the risk of various environmental and microbial stimulants which can modify the clinical expression of autoimmune diseases with extensive skin manifestation particularly pemphigus, scleroderma and systemic lupus erythematosus as well as the response to their treatment strategies. It, therefore, has been envisaged that an evaluation of immunologic potential of an individual suffering from autoimmune skin disease by means of estimating the cytokine profile after challenging the peripheral blood mononuclear cells with various stimuli and also detecting their anergic status will provide us with key indicators in monitoring the disease process and the therapy, thereby reducing the frequency of relapses and improving overall living quality.

The failure of conventional cellular immunological analysis to shed much light on the pathogenic mechanisms has also compounded the problem of autoimmune skin diseases. Recently developed therapies, such as tumor necrosis factor antagonists, have had remarkable successes, but the targets of such treatments do not remain unscathed; in fact, such interventions result in organ damage and not eliminate the (usually unknown) underlying causes. The realization that the development of autoimmunity is strongly influenced by inherited polymorphisms (or DNA sequence variations) brings hope that understanding the genetics of autoimmune diseases will provide insights into the causal derangements, and perhaps lead to new therapeutic strategies. The participation of cytokines in the induction and effector phases of the immune and inflammatory response shows that their polymorphism may be playing a critical role in the development of autoimmune diseases. The cytokine network is complex, with cytokines having both diverse and overlapping functions, including effects that are promoted or inhibited by other cytokines. Polymorphisms in genes encoding these crucial immunomodulatory

molecules may result in an altered level of expression and hence are considered important candidate genes for autoimmune disease susceptibility and severity.