Immune Network and Autoimmunity

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The concept of autoimmunity is regarded as the inability of the immune system to distinguish between self and non-self. This oversimplification of the concept is far from explaining the complex and perplexing mechanisms that are postulated to lead to its development. The transition from autoimmune state, in which no corresponding clinical manifestation exist, to an autoimmune disease, is further complicated by the evidence of multiple factors that participate in the evolution of the disease state. This article is written in a stepwise manner, initially reviewing the basic elements of the immune system, which are essential to understanding the fundamental processes underlying the occurrence of autoimmunity. Subsequently, a description of the factors involved in the etiopathogenesis and the presumed triggering events leading to the emergence of autoimmune diseases are described, with special emphasis on the important role of the idiotypic network, either in the maintenance of the normal immune response, or in the breakdown of self-tolerance eventuating in the autoimmune disease.

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Introduction

The concept of autoimmunity is applied to refers to the response of the organism against its inherent constituents. Autoimmune disease represents the emergence of damage to the organism's tissues, associated with the presence of auto-antibodies, autoreactive cells or both (1). Since autoantibodies can be directed against any cellular structure (although it might be highly conserved throughout evolution), the corresponding clinical pictures of autoimmune diseases can be diverse and are significant in terms of morbidity and mortality. The evolution of autoimmune diseases is presumed to entail an interplay between several factors, constituting a distinct 'atmosphere' which enable a triggering event to evoke the disease (1, 2). These factors probably include genetic environmental and hormonal components which collectively form a 'mosaic'.

The immune system will be concisely reviewed to clarify its participation in the autoimmune response against self structures.

The Targeted Immune Response

The principal role of the immune system is to confer protection of the organism against foreign invading pathogens, which can gain access to the body by different routes. The targeted (specific) immune response is generated by the combined

interaction of the cellular and humoral response, both coordinated by the production of cytokines. Cellular immunity refers to the immune mechanisms mediated by T lymphocytes, regardless of immunoglobulin molecules, whereas humoral immunity denotes secretion of antibodies by B lymphocytes. The humoral and cellular arms of the immune system should be viewed, not as two independent mechanisms of self defense, but rather as acting in an orchestrated and synergistic manner to accomplish protection (3).

A. Cellular immune response

T-cell cycle is initiated in hematopoietic stem cells, differentiating in the thymus and subsequently wandering to the lymphoid tissue in the periphery (4, 5). T-cells are heterogeneous by virtue of their different functions (lysis of foreign cells, modulation of the interaction between B and T-cells, regulation of monocyte functions). The peripheral T-cells are discerned by their expression of antigenic markers. As such, T-cells carrying CD4 molecules (T-helpers) interact with antigen associated with MHC class II on the surface of the antigen presenting cell, and T-cells expressing CD8 molecules (cytotoxic T-cells) engage in suppression of the immune response (5, 6). The T-cell receptor is a molecule present on the surface of the T-cell, responsible for recognition of the complex antigen-major histocompatibility complex (MHC) I molecule (7–9). The variety of T-cell receptors is immense, thus accounting for its

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Table 1. Major Cytokines and their Biologic Activities

Cytokine	Activities
IL- α , IL- β	Lymphocyte activation; bone resorption, induction of fibroblasts synovial cells and endothelial cells; prostaglandin liberation
IL-2	T and B growth factor; increased secretion of several cytokines; activation of cytotoxic cells
IL-3	Proliferation of marrow stem cells; growth factor for: macrophages, eosinophils, mast cells
IL-4	Activation of B-cells and macrophages; stimulated proliferation of T-cells and mast cells; induce secretion of IgE by B-cells
IL-6	Induce antibody production and acute phase protein production by the hepatocytes
IL-10	Inhibit production of several cytokines
IFN- α	Decrease cell replication; increases MHC class I replication; disrupts viral replication
IFN- γ	Activate NK cells, cytotoxic T cells, endothelial cells and macrophages; anti-tumoral effects; increase expression of MHC class I and II
TNF- α	Acute phase reactant; anti-tumoral; activate macrophages; increase expression of MHC class I; bone resorption
TGF- β	Inhibit IL-1; improve tissue repair; suppress lymphocyte proliferation

IL: interleukin, IF: interferon, TNF: tumor necrosis factor, TGF: transforming growth factor.

abilities to recognize diverse antigens.

The immune response is mounted following presentation of the antigen to the lymphocytes by antigen presenting cells, examples of which are: macrophages, Langerhans cells and dendritic cells. The process of presentation requires the participation of MHC class I molecules on the surface of the antigen presenting cell. The antigen, prior to its presentation to the T-cell is processed and degraded and later associated with the MHC class I molecule to form a complex reacting with the T-cell receptor (8, 9). It should be outlined that the antigen presenting cell (APC) are capable of secreting cytokines (Table 1) that act to facilitate the interaction described above.

B. Humoral immune response

B-cells stem from bone marrow precursors and later localized in the circulation as well as in follicles of peripheral lymphoid tissues. They are responsible for the production of antibodies, only following their final differentiation into plasma cells (10). B-lymphocytes are also involved in antigen presentation to T-cells, secretion of immunoregulating cytokines and establishment of 'memory' towards antigenic determinants (10, 11).

Direct activation of B-cells by distinct antigens is facilitated by binding to antigen receptors located within the membrane of the B-lymphocytes and under the influence of cytokines. This complex interaction render B-cell activated after which they proliferate and produce the appropriate antibody (11).

The final function of the B-cell (i.e. memory cell, plasma cell

or cytokine secreting cell) is determined by the profile of cytokines present, and the mechanisms of activation (through B-cell receptors for Fc region of IgG, or for complement components) (10, 11). The end product following antigenic stimulation is a population of B-cells producing and secreting one specific antibody towards the introduced antigen.

Immunoglobulins are glycoproteins forming 9 classes of isotypes: IgG, divided to 4 subclasses (IgG1–4), IgM, IgA comprising 2 subclasses (IgA1–2), IgD and IgE (12). The basic structure of immunoglobulins (similar in all five isotypes) consists of two identical heavy chains (MW 50,000–75,000) combined with two identical light chains (MW 25,000). Antigen specificity is determined by variable areas containing the antigen binding site, whereas the constant region (as can be inferred from its name), is common to all immunoglobulins of certain class. The hypervariable region is located in the variable region, representing the closest relationship with the epitope. The idiotypes, located in the variable region are the antigenic determinants of the immunoglobulins.

The diversity of antibody response is formulated due to encoding of the heavy and light chains by multiple genetic elements. As such, light chains are generated following pairing of VK and JK genes, whereas heavy chains exhibit greater diversity since they are created following assembly of three germline genes (VH, DH, JH) (4).

C. Orchestration of the immune response

Several intrinsic factors belonging to the immune system

itself are responsible for the modulation and regulation of the immune response. These factors deserve distinct consideration although they have been mentioned previously.

Cytokines are small proteins (MW 8,000–30,000) produced and secreted by a diverse population of cells (i.e. macrophages, monocytes, T and B cells, as well as non-lymphoid cells) (13–15). Cytokines elicit different actions including proinflammatory (TNF, IL-1, IL-2) and anti-inflammatory (TGF, IL-4, IL-6, IL-10) functions, stimulation of lymphocyte proliferation (IL-2, IL-7) etc. Signals influencing the secretion of cytokines include production of other cytokines. The regulation of cytokines is under the supervision of genetic factors (capable of generating corresponding inhibitors) and by the liberation of soluble forms of cytokine receptors.

The complement system consists of circulating glycoprotein constituents that can be triggered and activated in two major patterns to initiate a cascading chain of events, the consequence of which leads to diverse influences on the progression and perpetuation of the immune response (16). This cascade can, therefore, be activated by the *classical* pathway (immune complexes comprising IgM and IgG) or by the *alternative* pathway – independent of antibodies (by bacterial LPS; lipopolysaccharide).

The idiotypic system – will later be reviewed in detail.

Natural autoimmunity. The detection of natural autoantibodies which exhibit distinct properties, entailing poly-reactivity and polyspecificity in normal subject was followed by numerous reports attributing protective and regulatory virtues to this specific subpopulation of autoantibodies (mainly consisting of IgM autoantibodies secreted by CD5 positive B-cells) (17). As such, natural autoantibodies were proposed as conferring protection by inhibition of IgG binding to self antigens and by enhancing resistance against viral and parasitic infections.

Suppressor T-cells. As can be recalled, suppressor T-cells constitute a distinct subset of T-cells in charge of down-regulating the expression of either T-cells and immunoglobulin secreting cells (18).

Autoimmune State and Autoimmune Disease

A. Historical aspects and basic concepts

The concept of tolerance, designating the ability of the immune system to recognize self from non-self, had initially been attributed to the *absence* of antibodies targeted against self structures (autoantibodies) or autoreactive cells (lymphocytes). This notion was coined by Ehrlich (19) in 1904, using the expression ‘horror autotoxicus’ to refer to the deleterious effects resulting from the mere existence in the circulation of autoantibodies. Following this line of thought, Burnet (20) has gone further to suggest that the elimination of the ‘*forbidden culprits*’ of autoimmune disease (namely the autoreactive lymphocyte clones) was achieved during fetal development and the progeny of these ‘*forbidden clones*’ would necessarily imply that autoantibodies will be generated with evolvement of an autoimmune disease.

However, the recent 30 years have brought about considerable change in the understanding of autoimmune processes with the realization that appropriate stimulation by selecting the immunogen and the immunizing method could lead to the elaboration of antibodies to either environmental insults or to highly conserved innate structures of the organism (i.e. actin, histones, ribonucleic acids etc.). It also became apparent that distinction should be done between the *autoimmunity state*, signifying the potential of the immune system to generate antibodies that identify self constituents and *autoimmune diseases*, collectively accounting for a wide spectrum of clinical manifestations associated with the existence of autoantibodies or autoreactive cell lines.

It should be emphasized that the presence of autoantibodies, even in huge amounts does not necessarily result in emergence of an autoimmune disease. This can be learnt from screening of healthy family relatives of patients with autoimmune diseases (21), found to possess high titers of autoantibodies as well as patients with monoclonal gammopathies (22).

The transition from *autoimmunity state* to *autoimmune disorder* probably results from a trigger mechanism in a prone subject. This setting, facilitating the evolution towards a clinically overt disease will later be addressed.

B. Definitions and classifications of autoimmune diseases

A standardization with regard to the definition and diagnosis of autoimmune diseases has not yet been conclusively accomplished. The detection of autoimmune diseases still rely largely on the classical criteria set by Witebski in 1962, demanding:

- 1) A defined circulating antibody or cell mediated immunity to autoantigens.
- 2) Definition of the specific autoantigen.
- 3) The ability to produce the diseases in experimental animal by passive transfer of the antibody or the self-reacting cells.
- 4) The ability to produce the disease in an experimental animal by immunization with the self-antigen (with complete Freund's adjuvant).
- 5) The ability to generate the antibody or self reacting cell following the immunization in 4).

The limitation of these criteria are obviated by attempting to apply them to disease that are thought to represent seemingly classic autoimmune diseases such as systemic lupus erythematosus (SLE), which do not fulfill all the criteria (SLE could not be induced in naive murine models by immunization with DNA or Sm). The shortcomings of the initial set of criteria have led to their subsequent revision by Rose & Bona in 1993 (23).

Different methods of classification have been proposed for autoimmune diseases. An accepted method is based upon the organs afflicted. Accordingly, diseases involving multiple organs include: SLE, rheumatoid arthritis, Sjögren's syndrome and scleroderma, whereas organ-specific diseases encompass: Graves' disease, Hashimoto's thyroiditis, Myasthenia gravis, Polymyositis, Pernicious anemia, Addison's disease, Insulin dependent diabetes mellitus (IDDM), primary biliary cirrhosis, autoimmune hemolytic anemia, Idiopathic thrombocytopenic purpura, Goodpasture's syndrome and pemphigus.

Another classification for autoimmune diseases refers to the mechanism of damage by which disease is evoked. As such, humoral afflicted diseases include for example, myasthenia gravis and immune thrombocytopenic purpura, while cell-mediated mechanisms are evident in IDDM, Hashimoto's thyroiditis and rheumatoid arthritis.

C. Factors involved in the emergence of autoimmune diseases

Genetic background – Genetic predisposition is considered a principal factor involved in the evolution towards an autoimmune disorder. The classic proof resides in the MHC class II genes, which are known to be associated with a higher risk of contracting autoimmune disorders. Examples for this recognized relation is conveyed in studies showing the occurrence of lupus nephritis in as being related to the I-Aq β chain locus of SWR mice (24).

Additionally, it has been observed that application of antibodies directed against class II molecules ameliorated the disease in (NZB×NZB) F₁ mice, possibly pointing towards the H-2 linked genes, as responsible for this influence (24).

It has been repeatedly demonstrated that aberrant expression of MHC class II molecules in different cells or alternatively, their normal expression in cells that should not normally harbor them, may prevent the development of T-cell tolerance, resulting in autoimmune disorders (25). However, it should be mentioned that the aberrant expression could equally represent an epiphenomena of an already triggered autoimmune response.

Studies in human provide additional proof to the contribution of genetic factors to the setting, following which autoimmune states evolve. These are exemplified by works attesting for an increased concordance rates for IDDM (26) amongst identical twins (70%) provided they were DR3/DR4 positive as compared to 40% if they were not. A strong association of HLA DR5 with the emergence of scleroderma have been reported, either among the subjects or their relatives (27). Similar studies exist and are beyond the scope of this paper. Yet, it should be stressed that the mere existence of a distinct genetic predisposition can not eventuate in an autoimmune disorder.

Hormonal factors – considerable evidence have been presented to support the influences of sex hormones on the development of autoimmune diseases (28). Estrogen introduction in murine models have resulted in shortened survival and increased production of various autoantibodies, while testosterone seemed to exert opposing impact. The effects of prolactin in inducing autoimmune diseases have also gained substantial support (29).

The conclusions regarding the importance of sex hormones in humans could be inferred from several observations, consisting of an increased prevalence of autoimmune diseases in woman, a clinical course of diseases that corresponds with changes in the hormonal profile (puberty, pregnancy, postpartum periods etc.) and the findings of higher prevalence of autoantibodies among women (30).

Immunodeficiency states – Several immunodeficiency states

are associated with autoimmune phenomena (31). Examples of such conditions include: Common variable immunodeficiency (associated with SLE and autoimmune hemolytic anemias) and X-linked agammaglobulinemia (associated with Dermatomyositis). However, IgA deficiency seems to be more frequently related to autoimmunity, either due to the abundant description of numerous autoantibodies associated with this condition (i.e. anti-nuclear antibodies, rheumatoid factor, anti dsDNA etc.) and the significantly higher incidence of various autoimmune diseases (e.g. SLE, rheumatoid arthritis, dermatomyositis, idiopathic thrombocytopenic purpura (ITP) etc.) described among these patients.

Additionally, complement deficiencies (31) have also been described in relation with autoimmune disorders. As such, deficiencies in C2, C4 and C1 have been linked primarily to SLE, but also to other autoimmune diseases.

Environmental factors – These are probably the most intriguing factors known to associate with autoimmune diseases. The largest group among the environmental factors consist of bacterial, viral and parasitic infections (32–34). The works pointing towards the temporal relation between a possible infectious pathogen and the development of an autoimmune conditions can not be summarized here, since they require distinct consideration. It should be mentioned however, that there are several lines of evidence suggesting their involvement. These include the observation of autoimmune phenomena following infections, detection of high titers of antibodies against various infectious agents in patients with autoimmune diseases etc. (34). The mechanisms by which an infectious insult results in the precipitation of autoimmune disease has not been conclusively elucidated, however, several attractive explanations were advocated, probably accounting for the existence of more than one triggering mechanism and include: 1) *Molecular mimicry*, a term initially introduced by George Snell. It has been explained on the basis of structural antigen similarities between the infectious agent and the host cell, resulting in the generation of autoantibodies that overwhelm tolerance and therefore may induce a state of autoimmunity (35). The concept of *molecular mimicry* has recently been extended due to the introduction of new animal models involving the immunogenicity of cytochrome C protein (reviewed in 36). It has been suggested that *cryptic self epitopes* (e.g. ones that are not normally produced by the antigen presenting cell in sufficient levels to allow for activation of T-cells) are being up-regulated through the generation of autoreactive B cells by the foreign immunogen (i.e. foreign cytochrome C). The *cryptic self epitopes* are thought to induce breakdown of tolerance by autoreactive T-cells, suggesting a possible mechanism by which *molecular mimicry* may trigger autoimmunity. Exposure to foreign antigens mimicking self epitopes may also act to exert the so-called "epitope spreading" (reviewed in 28). This term has been introduced to denote a widened immune response consisting of *intramolecular spreading* (a reaction towards epitopes other than the inciting ones, on the foreign pathogen) and subsequently to *intermolecular spreading* (i.e. a response to antigens other than the pathogenic one), present in the site of

tissue inflammation.

2) *Aberrant expression major histocompatibility complex class II* (discussed previously)

3) *Superantigens* are viral or bacterial antigens capable of provoking an elaborate immune response by interacting with an exceedingly high number of T-cells (37). The uniqueness of the superantigen also stems from its ability to bind directly to the surface of the MHC class II molecule with no prior processing as observed in conventional antigens.

4) *Polyclonal activation* refers to the amplification of a pre-existing autoimmune reaction by certain bacterial products, as well as cell wall components due to their adjuvant effect (38). The adjuvant evokes massive secretion of autoantibodies resulting from the polyclonal activation of B-cell lines.

Other environmental factors have been associated with the evolution of autoimmunity states and include:

*Ultraviolet light which has been shown to play detrimental role in the clinical course of SLE and discoid lupus erythematosus (DLE) by increasing the severity of the skin lesions in the areas exposed to the sunlight (39).

*Silicone implants have been suggested by some authors to induce the production of a wide spectrum of antibodies, and some described increased incidence of autoimmune phenomena (40). However, this issue remains debatable due to large studies failing to repeat these results (41).

*The induction of Scleroderma-like disease following the mistaken ingestion of rapeseed oil (42).

*Smoking has been recognized as a risk factor for the contraction of autoimmune diseases (Graves' disease and rheumatoid arthritis) and the exacerbation of others (precipitation of pulmonary hemorrhage in patients with Goodpasture's syndrome) (43).

Autoimmunity and the Idiotypic Network

The idea of an immune response regulated by unique antigenic determinants has initially been introduced by Jerne in 1974 (44). Accordingly, the idiotypic determinants of each antibody molecule are complemented by those of another, formulating the so-called 'idiotypic network', which is capable of regulating the expression of immunoglobulins. It has been speculated that the antigen stimulates the generation of an antibody (Ab1) bearing a distinct antigen binding site termed – idio- type, which is capable of activating the immune system to elaborate antibodies, recognizing the idio- type (Ab2 or anti-Id). The latter bears structural resemblance with the antigen. If indeed, the antigen was an antibody, then we would end with an Ab2 which is practically identical to the initial antibody. It follows from the above, that this cascading network have the potential of regulating the extent of the immune response by virtue of its complementary idiotypes which are capable of exerting seemingly opposing influences. Once an antibody is considered pathogenic, its introduction would follow production of anti-idiotypic antibodies (Ab2), which may actually oppose its actions. Yet, the latter would lead to the generation of anti-anti-idiotypes (Ab3), which then again resemble the initial pathogenic anti-

Figure 1. Idiotypic induction of autoimmune diseases. Introduction of an antibody (autoantibody, or anti-infective agent antibody carrying pathogenic idiotypes) leads to the generation of Ab2 (anti-autoantibody or anti-Id). After an incubation time, Ab3 is produced, which may have binding characteristics, similar to the original autoantibody or to specific autoantibodies associated with a disease.

body (Ab1) and therefore exert deleterious effects (Fig. 1).

The significance of the idiotypic network concept is obviated not only in terms of explaining regulatory mechanisms, but more important, in elucidating disease models (45). The practical application of the latter, which also lend additional proof to the validity of this theory is represented by a set of models by which active dysregulation of the idiotypic network has been accomplished with a resultant induction of the full blown autoimmune diseases (46–49). Accordingly, immunization of naive mice by several antibodies carrying pathogenic idiotypes (Ab1), led to evolution of autoimmune diseases (SLE, antiphospholipid syndrome). Thus, it is conceivable that infection, for instance, may trigger autoimmune diseases by inducing anti-bacterial antibodies harboring pathogenic potential. These antibodies may evoke dysregulation of the idiotypic network provided that a supplementary adjuvant (or superantigen) is present, in an individual who is initially predisposed to autoimmune diseases due to existence of the factors outlined previously. The accumulating data supporting the theory of idiotypic dysregulation led to a reevaluation of the revised criteria set by Rose & Bona in 1993 (23). An additional criteria has been proposed by Shoenfeld to extend the above ones, suggesting induction of an autoimmune disease in an experimental model by active immunization with the autoantibody (Id) itself (45).

Conclusions

It can be inferred from what is stated above, that autoimmune diseases are truly a diverse group of clinical disorders capable of involving any organ or system of the organism. Probably the most perplexing enigmas concerning this field of research relates to the mechanisms underlying the development of the autoimmune state and autoimmune disease.

Figure 2. The factors involved in the evolution of an autoimmune disease. Evolution of an autoimmune disease from a “state of autoimmunity” may require the participation of multiple elements consisting of environmental, hormonal, immunological and genetic ones. This factors may act collectively or each one a part, to render an individual prone to autoimmune disease following an inciting ‘triggering event’.

Although definite or even conclusive answers to these questions can not be provided, it is reasonable to state that the evolution of the autoimmune manifestations and diseases follows a triggering event (i.e. infection or other environmental insult) introduced to an individual, rendered prone to develop autoimmune disease by virtue of certain properties (e.g. distinct genetic background, stimulation by certain hormones etc.) (Fig. 2).

It is therefore of utmost importance to delineate the exact mechanisms participating in the development of autoimmune conditions, since it would provide means of tracing the population at risk of contracting these diseases and target the efforts at trying to prevent its occurrence. This will enable a much more effective method of reducing morbidity and mortality from autoimmune diseases as compared to treating these patients after the disease has already evolved.

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