

REVIEW ARTICLE

AUTOIMMUNITY - A BRIEF INSIGHT

ABSTRACT

Autoimmunity is characterized by the reaction of cells (auto reactive T-lymphocytes) or products (autoantibodies) of the immune system against the organism's own antigens (autoantigen). It may be part of the physiological immune response (natural autoimmunity) or pathologically induced, which may eventually lead to development of clinical abnormalities (autoimmune disease). Different mechanisms are involved in the induction and progression of autoimmunity. These include genetic or acquired defects in immune tolerance or immune regulatory pathways, molecular mimicry to viral or bacterial protein, an impaired clearance of apoptotic cell material.

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INTRODUCTION

Immunology is the science that deals with body's response to antigenic challenge (Latin Immunitas, freedom from). Immunity is of different types it can be innate (native) or acquired (adaptive) immunity. Immunity is a very broad scientific discipline involving concept of recognition, specificity and memory. Immunological mechanism are involved in the protection of the body against infectious agent but they can also damage host organism called as autoimmunity.¹ Autoimmunity is the mechanism where an organism fails to recognize its own constituent parts (down to the sub-molecular levels) as "self", which results in an immune response against its own cells and tissues.²

Autoimmunity is characterized by the reaction of cells (auto reactive T-lymphocytes) or products (autoantibodies) of the immune system against the organism's own antigens (autoantigen). It may be part of the physiological immune response (natural autoimmunity) or pathologically induced, which may eventually lead to development of clinical abnormalities (autoimmune disease).³ Different mechanisms, which are not mutually exclusive, may be involved in the induction and progression of pathologically autoimmunity these include genetic or acquired defects in immune tolerance or immune regulatory pathways, molecular mimicry to viral or bacterial protein, an impaired clearance of apoptotic cell material.⁴

Association of autoimmunity with disease

Disease of autoimmune origin usually exhibit the following features:¹

- An elevated level of Immunoglobulins
- Demonstrable autoantibodies
- Accumulation of lymphocytes and plasma cells at the sites of lesion.
- The occurrence of more than one type of autoimmune lesion in an individual.
- A genetic predisposition towards autoimmunity
- Higher incidence among females
- Chronicity, usually non reversible.

Classification of autoimmune diseases:

The Autoimmune diseases are classified based on site of involvement and nature of lesion as localized (or organ specific) and systemic (or non-organ specific)⁵

Localized (Organ specific) autoimmune diseases:

- Autoimmune diseases of the thyroid gland
- Hashimoto's disease (Lymphadenoid goiter)
- Thyrotoxicosis (Grave's disease)
- Addison's disease
- Autoimmune orchitis
- Myasthenia gravis
- Autoimmune diseases of the eye
- Pernicious anaemia
- Autoimmune disease of nervous the system
- Autoimmune disease of the skin

Systemic (non-organ specific) autoimmune diseases:

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Polyarteritis nodosa
- Sjogren's syndrome

The Autoimmune diseases is classified based on the various organ systems as follows:⁶

- | | |
|-----------------------|-------------------------------------------------------------------------------------------|
| A) Blood: | Hemolytic anaemia,
Leucocytopenia,
Thrombocytopenia. |
| B) GIT: | Pernicious anaemia,
Crohn's disease |
| C) Endocrine: | Thyroid- Hashimoto's
thyroiditis
Pancreas- IDDM Type 1 |
| D) Connective tissue: | Lupus erythematosus,
Systemic scleroderma,
Dermatomycositis,
Erythema multiforme |
| E) CVS: | Polyarthritis nodosa,
Wegner's granulomatousis, |

- Temporal arteritis
Endocarditis and
Myocarditis
- F) Locomotion: Rheumatoid arthritis,
Psoriatic arthritis,
Mysthena gravis
- G) Skin and Mucosa: Pphemphigoid-Bullous,
Benign cicatrical; Behcet's
syndrome, Desquamative
gingivitis, Recurrent
apthae, Lichen planus
- F) Salivary: Sjogren's syndrome
- G) Nervous: Polyneuritis and Multiple
sclerosis

Mechanisms of autoimmune diseases :

Cells or tissues may undergo antigenic alteration as a result of physical, chemical, or biological influences, such altered or neoantigens may elicit an immune response. Neoantigens can arise in a variety of ways. Physical agents such as irradiation may cause antigenic alteration. Several chemicals, including drugs may combine with cells and tissues and alter their antigenic nature. The various mechanisms of autoimmune diseases is listed are as follows

1. By pass of helper T-cell tolerance

Tolerance of CD4+ helper T cell is critical to the prevention of autoimmunity.

Therefore, tolerance may be broken if the helper T cells is bypassed or substituted.⁷

2. Emergance of sequestered antigen

The induction of tolerance requires interaction between the antigen and the immune system. Thus any self-antigen that is completely sequestered during development is likely to he viewed as foreign if introduced into circulation, and an immune response will develop.⁸

3. Imbalance of suppressor helper T-cell function

A loss of suppressor T cell function will contribute to autoimmunity and conversely, excessive T-cell help may drive B cells to extremely high levels of autoantibody production.⁷

4. Microbial agents in autoimmunity

A variety of microbes, including bacteria, mycoplasmas and viruses have been implicated in triggering autoimmunity. Microbes may trigger autoimmune reactions in several ways. First, viral antigens and autoantigens may become associated to form immunogenic units and bypass T-cell tolerance. Second, some viruses (EBV) are nonspecific, polyclonal B-cell mitogens and may thus induce formation of autoantibodies. Third, viral infection may result in loss of suppressor T-cell function.⁸

5. Molecular mimicry

Several infectious agents cross react with human tissues and their haptenic determinants. The infecting microorganisms may trigger an antibody response by presenting the cross reacting haptenic determinants in association with their own carrier to which helper T cell are not tolerant. The antibody so formed may then damage the tissue that shares cross reacting determinants.⁷

6. Polyclonal lymphocyte activation

Several microorganisms and their products are capable of causing polyclonal (i.e antigen nonspecific) activation of B cells.⁸

Environmental triggers in autoimmunity

Autoimmune disorders may result from multiple interactions of genes and environmental factors. Even if one inherit a genetic predisposition, the autoimmune disease will not occur unless there is an environmental trigger. There are several suspects in the search for triggers such as viruses, bacteria, diet, toxins, radiation, metal, estrogen, chronic infections etc. 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 can act to initiate an autoimmune process.⁹



Genetic factors in autoimmunity

The different genes can increase susceptibility to autoimmune diseases. Established genetic risk factors include genes encoding histocompatibility molecules, complement proteins, immunoglobulins, peptide transporter proteins, and genes controlling the production of sex hormones. Each factor may independently enhance the immunogenicity of autoantigens, either by increasing their processing and presentation of B lymphocytes and macrophages or by increasing the chance for recognition by autoreactive T and B lymphocytes.¹⁰

Nutrition and autoimmunity:

Nutritional deficiencies can alter the immune response. Example, protein–energy malnutrition is widespread in developing countries and results in the functional impairment of T-cells, phagocytic cells and secretory immunoglobulinA antibody response, as well as reduced levels of several complement components. Other impairments of immune function have been reported for moderate deficiencies of trace minerals (such as zinc) and vitamins (particularly A and D).¹¹

Apoptosis and autoimmunity

Apoptosis Greek word means “falling of leaves from trees and defined scientifically as programmed cell death. Apoptosis is essential to regulate and maintain tissue growth and maintain homeostasis. Dying cells undergo morphological modifications including chromatin condensation, nuclear fragmentation and generation of apoptotic bodies. Furthermore, they express so called “eat-me” signals on the cell surface that allow macrophage recognition and phagocytosis. Clearance of apoptotic cells is fundamentally important, since otherwise apoptotic cells tend to become secondary necrotic, release intracellular contents, and provoke inflammation and autoimmunity. Within the immune system alone, it has been estimated that more than 109 cells undergo apoptosis daily and these are cleared rapidly by neighboring tissue cells or professional phagocytes, normally without inciting an inflammatory reaction. Indeed, the most significant difference between phagocytosis of pathogens and the uptake of apoptotic cells has been traditionally considered

the immune response. A pro-inflammatory reaction is often induced after phagocytosis whereas the secretion of anti-inflammatory cytokines follows the engulfment of apoptotic cells.¹²

It is found that autoantigens are found within apoptotic bodies and that apoptotic cells are critical in the presentation of antigens, activation of innate immunity and regulation of macrophage cytokine secretion.

Recent advances:

Proteomic approach to autoimmune disorders¹³

Proteomics is the study of structural and functional endowment of cells, tissues or organs. This science brings together powerful tools-physical separation techniques like 2-D electrophoresis and mass spectroscopy. It also includes various monoclonal antibodies and other probes coupled with which analysis is done by systems biology approach using modern software. Various statistical, probabilistic, humanistic and artificial neural network algorithms and at the same time incorporating elements of fractional theories are used to study the interactions of multitude of proteins in the cell. This allows separation of large background high concentration proteins inside the cell from pathobiologically and aetiologically relevant protein molecules present in nano, femto or even atto molar concentrations. Pattern recognition algorithm in modern proteomic techniques will help in understanding aetiopathogenesis of disease, discovering diagnostically and prognostically important biomarkers and molecular targets for future discovery. These techniques will have important applications in autoimmune disorders and other disorders which are difficult to manage.

Proteomic technologies hold the potential to revolutionize clinical care by providing tools for the discovery of biomarker for diagnosis, prediction of disease course, guiding therapeutic selection and monitoring response to therapy. Nevertheless tremendous work remains to develop refine validate and apply proteomics technologies to identify biomarker in autoimmune disease. To highlight several proteomics technologies and their application to autoimmune disease includes the following.¹⁴

1. 2-DE and MS for autoantigen and biomarker discovery
2. Autoantigen microarrays to characterize autoantibody response
3. Antibody array technologies to profile cytokines and other biomolecules
4. Reverse phase protein array (RPPA) studies to analyze phosphoproteins
5. Flow cytometric analysis of phosphoproteins

Induction of immune tolerance by dendritic cells: Implication for preventive and therapeutic immunotherapy of autoimmune disease¹⁵

Dendritic cells (DC) have a key role in controlling the immune response, by determining the outcome of antigen presentation to T cells. Through costimulatory molecules and other factors, DC is involved in the maintenance of peripheral tolerance through modulation of the immune response. This modulation occurs both consecutively, and in inflammation, in order to prevent autoimmunity and to control established immune responses. Dendritic cell control of immune responses may be mediated through cytokine or cell- contact dependent mechanisms. This understanding reaches a level at which DC- based therapies are helpful for the induction of immune regulation in autoimmunity.

Haemopoietic stem cell transplantation for autoimmune disease¹⁶

Transplantation of haematopoietic stem cells capable of self renewing and reconstituting all types of blood cell can treat numerous lethal diseases, including leukaemias and lymphomas. It may now be applicable for the treatment of autoimmune diseases and severe immune-mediated disorders, such as therapy-resistant rheumatoid arthritis and multiple sclerosis. Studies in animal models show that the transfer of haematopoietic stem cells can reverse autoimmunity, and several mechanistic pathways may explain this phenomenon. The outcome of ongoing clinical trials, as well as of studies in patients and animal models, will help to determine the role that stem-cell transplantation can play in the treatment of autoimmune diseases.

The Use of Microarrays to Study Autoimmunity¹⁷

Microarray technology provides an unprecedented and uniquely comprehensive probe into the coordinated workings of entire biological pathways and genomic-level processes. In general terms, microarrays refer to a variety of platforms in which high-density assays are performed in parallel on a solid support. The multiple sclerosis, systemic lupus erythematosus, and Sjogren's syndrome illustrate the potential for gaining new insights into the pathophysiology of these complex autoimmune disorders on a global, molecular scale. These new insights are likely to significantly improve our understanding of disease processes, diagnosis, identification of new therapeutic targets, and identification of patients most likely to benefit from specific and tailored therapies.

CONCLUSION:

Autoimmunity is the mechanism where an organism fails to recognize its own constituent parts (down to the sub-molecular levels) as "self", which results in an immune response against its own cells and tissues. Any disease that results from such an aberrant immune response is termed an autoimmune disease. Autoimmune diseases generally have varied systemic manifestations. The disease process may affect any organ system in the body and create physical, psychological, social and economical disability in the patient. This is an attempt to review the available literature on autoimmunity.

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