AUTOIMMUNITY

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Summary

Subject of autoimmunity is reviewed. Mechanism of production and damage by autoantibodies and autoimmunity is discussed in detail. Criteria of labelling a disease autoimmune and steps in diagnosing them are enumerated.

Autoimmunity is regarded as a failure of the organism's normal capacity to distinguish between self and nonself, where the mechanism which normally suppresses the production of antibodies to the patient's own tissues breaks down[1].

It is known that antibody formation can be provoked by antigenic components of micro-organisms which may neither be toxic nor harmful in any way and also by foreign proteins which are essentially bland. This means that the body cannot distinguish harmful from a bland antigen[2]. This is the case with a substance of foreign origin and it used to be taken for granted that the body would never respond immunologically to its own antigens by antibody formation. Ehrlich[3] coined the term horror autotoxicus to such a process of autoimmunity. But as early as 1900, Metalin-Koff[4] showed that guineapigs could produce antibodies active against their own spermatozoa i. e. autoantibodies. Subsequently autoantibodies against other tissues like lens proteins, brain, thyroid, adrenal, kidney, skin and cardiac tissues have also been detected. Burnet[5] formulated a concept which he called "self maker hypothesis" stating that antigens originating in the body itself are recognised and therefore ignored by the antibody forming cells, wherein the molecular pattern of body protein seems to be marked self and organic matter from outside is marked nonself, and antibodies are formed against it. Similarly those cells of the body which are of a very short life such as RBCs and lymphocytes, the so called expendable cells also behave not as self but as nonself as reticuloendothelial cells not only dispose of the expendable cells but also initiate the mechanism for the formation of antibodies. Thus according to Burnet[6] each cell of the body contains a warning "self maker component" and this is established during embryonic life which prevents the body from producing an immunologic response to constituents of one of its own cells. It might be predicted that under special circumstances the working of this mechanism which maintains immunological tolerance to the individual's own antigens fails and allows the production of antibodies against or sensitization by products of animal's own tissues. This process is called autoimmunization or autosensitization. The result may be the production of antibodies or cell mediated hypersensitivity which can result in tissue damage and so called

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autoallergic or auto-immune disease. Mackay and Burnet[7] believe that the immunologic tolerance to the organism's own antigens which normally develops, is destroyed, probably by the development, presumably by mutation of a new clone of immunologically competent cells which are uninstructed not to respond to the organism's own antigens and therefore begin to elaborate antibodies to these antigens. Another and perhaps more acceptable explanation is that of immunological paralysis where antigenic constituents of the body reach antibody forming cells in such large amounts that these cells are kept saturated and unable to respond[1].

Autoantibodies

These are the antibodies produced against the antigens of an organism's own tissue and have to be differentiated from isoantibodies produced against the antigens of another animal of the same species and heteroantibodies, produced against the antigens of different species.

Antibodies are of two types:

(a) Cellular antibody: This is mediated by the immunologically competent lymphoid cells (immunocytes) and is responsible for delayed sensitivity reaction e.g. tuberculin reaction. Cellular antibody production may occur without humoral antibody production as in patients with hypogammaglobulinemia. This antibody can be conveyed by transfer of sensitized lymphoid cells only.

(b) Humoral antibody: This is usually a gammaglobulin, synthesized by plasma cells and may react with antigens to cause cell destruction directly or render the antigen more susceptible to phagocytosis. They are responsible for immediate sensitivity reactions like anaphylaxis and urticaria. It is present in serum and may be transferred by infusion of serum alone.

Autoantibodies might be expected to occur in two circumstances, one in which they play a major role in causing disease, the other in which they develop as a purely secondary phenomenon after a tissue has been injured. At present, it is not known whether the autoantibodies that have been reported in human diseases fall into the first or second category.

Production of autoantibodies

The immune apparatus which is responsible for the production of antibodies is the lymphoreticular system (lymphocytes, reticular cells, plasma cells and macrophages found in spleen, lymphnodes, thymus and peyers patches of G.I. Tract) which produces both humoral and cellular antibodies.

There seems to be 3 ways in which autoantibodies can be produced.

(a) Autoantibodies to red cells may be of heterogenic origin formed in response to infection, possibly inapparent, by micro-organisms which possess antigens related chemically to antigens present in human red cells. These antibodies do not represent the result of a true autoimmunization and Wiener[9] compared their reaction with human red cells to the opening of a lock by a skeleton key.

(b) Wiener[9,10] suggested that individuals exist who have a remarkable capacity to form antibodies. Some of these individuals produce antibodies against antigens which are generally found to be extremely weak. Such individuals may form true autoantibodies.

(c) Wiener[9] mentioned the hypothesis that bacteria or viruses, toxins and other hemagglutinating or hemolytic agents may alter red cells and thus render them autoantigenic.

Mechanism of damage by autoantibodies[11]

According to Raffel[12] there seem to be four conceivable mechanisms by

which tissue damage could be brought about by autoantibodies and Wiener[9] has suggested a fifth mechanism also.

(a) Cytotoxicity : The antibodies bring about the destruction of cells against which they are directed. e.g. acquired hemolytic anaemia.

(b) Arthus reaction : Intravascular antigen antibody reaction takes place which in turn causes damage to the organ in which this takes place. In experimental encephalomyelitis small lesions occurring in blood vessels have been described. Skin transplants from one person to another fail as a rule and there is no doubt that an immunological mechanism is involved, although circulating antibodies have not usually been found. The fact that transplants will grow in the (avascular) anterior chamber supports this view.

(c) Delayed sensitivity: Development of delayed type of hypersensitivity to a tissue antigen leads to injury or death of cells exposed to it.

(d) Toxicity of injected material: There seems to be no positive evidence for a direct toxic action of homologous tissue material and the available evidence suggests more strongly an immunological mechanism.

(e) Intravascular 'Conglutination' by red cell autoantibodies resulting in disseminated vascular damage due to obstruction of circulation to tissues and organs.

It is possible that two or more mechanisms operate simultaneously in certain cases.

Mechanism of development of autoimmunity

The following hypothetical processes might conceivably give rise to autoimmunization.

1. Primary fault of the antigen[2].

(a) Normally the body is capable of recognizing its own tissues and the immune apparatus does not react against the body's own antigens to produce antibodies. This is known as immunological tolerance. This tolerance is an actively induced state created and maintained by interaction between antigenic body components and immunologically competent cells and is not a genetically determined lack of reactivity to self components. This hypothesis is justified by the following experiment in a frog. Removal of posterior pituitary in embryonic development permanently impaired pigmentation, so that an albino resulted. Attempts of replacement grafting in adult life of an autologous posterior pituitary (meanwhile maintained as a graft in another tadpole) failed i.e., the graft was rejected and the albino state was not changed, presumably since the normal state of tolerance of frog to its own posterior pituitary depends upon continued physical contact with the developing immunological system.

Thus a particular antigenic component or type of cell might not be formed until the critical period of immunological immaturity is past. Spermatozoa came into this category, appearing only after embryonic life and being sufficiently distinct from other cells to act as antigen even in the animals which made them. Normally they do not act this way because of their anatomical segregation as they are stored and secreted away from the immunologically competent cells. Sometimes the barrier can be broken down as in the case of an infection of testis (mumps) and then immunization of the person can apparently develop with his own spermatozoa (granulomatous orchitis). Similar is the case with lens protein.

(b) Another mechanism by which the body might become immunized

against its own tissue components would be when cells which formed distinctive proteins or other potential antigens even during embryonic life are always segregated from normal contact with the immune apparatus thus preventing develpoment of any tolerance. Some constituents of brain possibly on account of the lack of draining system of lymphatics is thus often able to accept a homograft. Experimentally it has been found that an animal's own brain suspension injected into its own subcutaneous tissue induces antibodies to it and an allergic reaction causes brain inflammation (experimental allergic encephalitis). An analogous process in man seen clinically is the encephalitis which follows the use of rabies vaccine containing animal brain or spinal cord. Thus an escape into the circulation of a tissue antigen to which tolerance has not been acquired, due to their isolation from the immune apparatus during the stage of immunological immaturity, results in autoantibody production and an autoimmune disease. Such tissues are brain (no lymphatic drainage), thyroid (cell membrane barrier of thyroid acini) uveal tract (blood aqueous barrier), gastric mucosa (cell membrane barrier) and adrenals (cell membrane barrier)[13]. The antibodies thus formed are usually organ specific and the resultant disease is usually localized to a particular organ. Examples of such "segregation antigen disease" may be Hashimoto's disease and forms of sporadic myxedema, addison's disease, atrophic gastritis or pernicious anaemia, phaco-anaphylactic endophthalmitis, some cases of polyneuritis and acute encephalitis[14].

(c) Alteration of tissue antigens: Normal tissue elements may alter antigenically by drugs, infection, irradiation and other means and thus rendered foreign to the immune apparatus.

Since the surface tertiary of macromolecules is all important in determining antigenic specificity, it is possible that body components especially proteins may undergo sufficient deformation in vivo to create new surface determinants. Even the combination of antigen antibody leads to considerable morphological change in the molecules of antibody depending on the combination ratio involved.

(i) Apronal or quinidine induced thrombocytopenic purpura. The drugs alter the platelets antigenically and antibodies formed against such platelets cause their agglutination leading to thrombocytopenia. Other examples are autoimmue hemolytic anaemia induced by methyl dopa and contact dermatitis.

(ii) Black water fever: Malaria infection of red cells may alter them antigenically and invoke antibody production giving rise to hemolysis. Quinine may catalyse the antigen antibody reaction.

(iii) Bacterial antigens may be helped by body tissues which act as haptens in the production of antibodies. The antibody thus formed not only reacts against the bacteria but also with the body tissues which acted as haptens. Thus in acute glomerulonephritis, streptococcus and glomerular tissue together act as antigen, antibody thus formed reacting with glomerulus. Similar mechanisms may be responsible for rheumatic fever, arthritis following bacillary dysentery, Reiters syndrome following non gonococcal urethritis due to mycoplasma and autoimmune hemolytic anaemia following viral infection.

(d) Cross reacting foreign antigens[16]:

A foreign antigen (bacteria, viruses etc.) may have similar antigenic property like that of host's tissue and the antibody produced against it may cross react with the host tissue. Antibodies against streptococcus may cross react with cardiac muscle giving rise to carditis

of rheumatic fever. Some intestinal bacteria notably a variety of Esch coli may produce antibodies which will cross react with the tissues of colon causing ulcerative colitis.

2. Primary fault of the antibody forming system

The immunocytes of the lymphoreticular system may be abnormally altered by different means. These altered cells may not recognise normal tissue components as 'self' and may produce antibodies against them.

(a) Malignant change: Autoimmune hemolytic anaemia, thrombocytopenia secondary to lymphosarcoma, Hodgkins disease, chronic lymphatic leukaemia etc. are examples.

(b) Development of forbidden clones[5]: Non-malignant clones of immunocytes having the ability to produce antibody against self antigens may appear in the lymphoreticular system and if they can not be eliminated, they lead to the production of autoantibodies against many tissue components of the body. The consequent pathological lesions are therefore generalised and widespread. SLE, systemic sclerosis, dermatomyositis, rheumatoid arthritis, polyarteritis nodosa are examples of such "disturbed tolerance diseases".

(c) Breakdown of tolerance: The state of tolerance is maintained by continued or repeated exposure of tissues to the immune mechanism. The tolerance could fail if the immunogenic markers were temporarily absent and later returned (e.g., embryonic antigens which are found in some tumours of GI tract).

(d) There are some diseases in which antibody production is non organ specific but the tissue infiltration is rather limited to one or more organs. These constitute a group, intermediate between organ specific and generalized disease group. e.g., sjogrens syndrome, myasthenia gravis, DLE, diffuse interstitial fibrosis of lungs.

In skin[18] keratin and distal epidermal cells undergoing keratinization, by virtue of their remote location and relative avascularity might be considered foreign by immune apparatus. These cells are very amenable to alteration by chemicals, physical trauma and radiation and thus can go antigenic if permitted to gain access to the immunological system. On the other hand for obvious reasons of rich blood and lymph vascularity and less amenability to external factors, tissue antigens of corium are poor autoantigens.

Further it is possible that cutaneous antigens might be the target of spontaneously developing autoantibodies in disease of abnormal antibody production. Thus like hemolytic anaemia, exfoliative dermatitis might also develop in malignant lymphomas on autoimmune basis.

Finally the skin might serve as a battle ground of an entirely unrelated antigen-autoantibody system and suffer pathological alterations.

Production of autoimmune lesions

The demonstration of an autoantibody does not necessarily mean that the associated clinical state is autoimmune in its pathogenesis. An autoantibody should be shown to be destructive of its homologous antigen in order to be considered causative of the disease. Autoantibody might arise as a consequence of a disease as they presumably do in myocardial infarction in which antibodies directed towards cardiac tissue have been demonstrated[19]. They may also arise as an incidental consequence of pathogenic agents as in viral pneumonia, where the production of cold autohemagglutinin has little to do with the clinical symptoms of the illness.

It must be remembered that an autoimmune disease will not necessarily be produced even if there is presence of humoral or cellular antibodies in the system. Provocation of an autoimmune reaction and its intensity and the consequent tissue damage will depend upon :

(a) Genetic background of the individual i.e., the individual's immunological activity is probably genetically determined[20].

(b) Character and amount of antibody produced. Both humoral and cellular antibodies have a capacity to cause tissue damage. But humoral antibodies are less important than cellular in production of lesion. According to some authorities humoral antibodies might be a by-product of the disease rather than the cause and there is often little correlation between the titre of the circulating antibody and pathological changes in the tissues. Humoral antibodies can however cause damage to antigens which are easily accessible viz, formed elements of the blood and vascular endothelium[13]. The most prominent role in the production of pathological lesions is played by immunologically activated lymphoid cells, which aggregate about the target cells and destroy them. Within the target cells themselves certain 'Suicide granules' (lysosomes) accumulate at the apical membrane and release some autolytic hydrolases under specific immunological conditions and cause cell destruction[15].

Criteria for accepting a disease to be autoimmune[1, 19]

(a) There is a clear precipitating event, specific symptoms usually appear 2–3 weeks later, a period consistent with the production of an immunopathologic response. In addition such reactions are suppressed by corticosteroids.

(b) Pathologic lesions in these diseases show the typical picture of lymphoid granulomatous infiltration.

(c) Circulating antibodies should be demonstrated in the serum of patient or cell bound antibodies by indirect means.

(d) Antigen should be known.

(e) Specific antibodies should be produced against the same antigen in the experimental animal.

(f) The condition is often familial and the serum often gives a biological false positive reaction for syphilis.

(g) In at least one case the autoimmune disease could be passively transferred by infection of lymphoid cells from an animal suffering from the disease[21].

Diagnosis[14-17]

1. Detection of an autoantibody against some tissue constituents in patients with the disease. Various methods employed are :

(a) Precipitation reaction in fluid or gel medium.

(b) Tanned cell haemagglutination.

(c) Latex fixation.

(d) Bentonite flocculation. Protein antigens are attached to tannic acid treated red cells or adsorbed on agglutinable particles as latex or bentonite. These when treated with patient's serum containing antibody, agglutination occurs.

(e) Coomb's test (antiglobulin consumption) as done in autoimmune hemolytic anaemia. RBCs are coated with antibody globulin which causes their destruction. Detection of this coating of antibody globulin by antiglobulin constitutes coomb's test. Rabbit's antiserum to human globulin is used as antiglobulin to agglutinate the coated cells. Normal RBCs are

coated with globulin from patient with hemolytic anaemia and treated with antiglobulin, agglutination constitutes positive test, and is suggestive of autoimmune etiology.

(f) Complement fixation test.

(g) Immunofluorescence (Fluorescent antibody method).

(h) Immunoelectrophoresis.

(i) Intradermal skin testing.

(j) Passive cutaneous testing.

(k) Cytotoxicity[16]. Cytotoxic antibodies (found in some thyroid diseases) may be detected by treating viable human thyroid cells with patient's serum and a source of complement.

2. Histopathology. Allergic histopathology.

3. Animal pathogenicity[14],[16].

Some authors have suggested animal pathogenicity test in the manner done in infectious diseases. Two steps have been suggested. First the offending antigen which sometimes can be isolated in relatively pure form should be injected under defined conditions in an animal, and should thus be capable of reproducing both serological and pathological manifestations of the disease. Second the disease of experimental animal should be transferred to a normal animal by means of serum or suspension of lymphocytes.

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