Open questions concerning the specificity of anti-HIV antibodies. Do they belong to the group of antibodies against cellular structures?

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Two years ago the working-group of G.M. Shearer demonstrated that autoantibodies in the serum of patients with lupus erythematosus and in the serum of mice with experimentally induced lupus erythematosus are capable of reacting specifically with glycoprotein (gp) 120 and peptides of the HIV-1 envelope (1). The formation of antibodies with anti-HIV specificity against gp 120 and the associated peptides in lupus erythematosus disseminatus is an indication that anti-HIV antibodies can be formed within the framework of polyclonal B-cell activations in systemic autoimmune diseases. Thus the question arises whether anti-HIV antibodies should generally be classified in the large group of autoimmune antibodies against cellular structures. These are described as antinuclear auto- antibodies (2,3).

Lupus erythematosus disseminatus is the prototype of a systemic autoimmune disease with widespread involvement of the different organ systems. This group of diseases also includes rheumatoid arthritis, Sjögren's syndrome, scleroderma and mixed forms of inflammatory diseases of the connective tissue. In these diseases, as a result of an activation of polyclonal B cells, one finds a large number of humoral autoantibodies against cellular and extracellular structures.

Humoral autoantibodies in AIDS

In their review of chronic infections and autoimmunity, M. Abu-Shakra and Y. Shoenfeld mention that the following autoantibodies have been found in AIDS patients: antinuclear autoantibodies, rheumatoid factors, antibodies against erythrocytes, platelets, granulocytes and lymphocytes, as well as antibodies against sperms (4). In fact, there is extensive literature available on humoral antibodies in AIDS patients, in which autoantibodies against actin, myosin, trinitrophenol and thymosin have also been described (5-7). In addition, in many works attention is drawn to the close connection between the retroviruses and autoimmune diseases, without it being possible to explain the pathogentic mechanisms of these relationships (8).

Horizontal transmission of HIV structures as triggering factors for autoimmune reactions

RNA viruses which are localised by reverse transcriptase into the DNA of the host genome, where they are integrated as endogenous self-structures, are known as retroviruses (9). For this reason the horizontal transmission of retroviruses may be considered as the transmission of genetic structures between individuals of the same species. The immunological reactions occurring in retroviral infections are therefore to be considered as alloimmune reactions and thus have to be classified as regularities of transplantation immunology. In this respect it is seen that immune-competent recipients of transplants react with an effective cellular immune response and thereby reject the transplant. Moderately immunosuppressed recipients of transplants, such as those under long- term treatment with cyclosporins for example, are able to live with their transplant for long periods without

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problems. In contrast, transplant recipients with pronounced suppression of their cellular immune reactions are as a rule adversely affected by the activated immune system of the transplant, within the framework of a "graft versus host" reaction, which at worst can lead to the death of the patient (10). In blood transfusions, the elimination of alloreactive genetic structures of the donor through cellular immune reactions of the recipient is the norm. "Graft versus host" reactions are extremely rare.

Acute and chronic "graft versus host" reactions (GVHR)

The study of GVHRs in mice that were injected with lymphocytes from the parent animals has provided important insights into the mechanisms involved in acute and chronic GVHRs. With the injection of donor lymphocytes which show differences in MHC loci of Classes I and II, from the recipient animals, an acute lethal immunosuppressive GVHR occurs in the receiver animals, characterised by anaemia and hypogammaglobulinaemia, with increased mortality due to increased susceptibility to infections. If the difference between the donor lymphocytes and the recipient lymphocytes is limited to MHC loci of Class II a chronic GVHR develops, with stimulation of the polyclonal B cells and the formation of humoral autoantibodies within the framework of a lupus-like syndrome. The stimulation of the formation of autoantibodies is due to the long-term persistence of alloreactive T-4 cells (11).

The significance of the shift in the Th-1/Th-2 equilibrium in systemic autoimmunisation

As we have shown in our previous studies, an acquired weakening of the cellular immune reactions is the leading factor in the pathogenesis of AIDS (12). In this, the opposing behaviour of the humoral and the cellular immune reactions plays a decisive role. Characteristic for this is the behaviour of the cytokine profile of the Th-1 and the Th-2 cell-groups of the $CD4^+$ helper cells. The Th-1 cells produce primarily IL-2, IL-12 and IFNγ and through them stimulate the cellular immune reactions. The Th-2 cells produce mainly IL-4, IL-6 and IL-10, and through them stimulate the humoral immune reactions. The Th-1/Th-2 equilibrium of the cytokine production of $CD4^+$ lymphocytes is subject to the stress-induced neuroendocrine control of the immune system. Here, the relationship between cortisol and dehydro- epiandosterone (DHEA) plays the decisive role.

As explained earlier, the study of alloimmune reactions in rodents has shown that systemic autoimmunisations are associated with a shift in the Th-1/Th-2 equilibrium of the $CD4^+$ lymphocytes. Chronic "graft versus host" reactions show an MHC-II-class-induced activation of the B cells with increased IL-4 and decreased IL-2 activity. The excess of T-2 cells triggers the formation of antinuclear autoantibodies within the framework of lupus-like inflammatory reactions (11).

Extensive literature is available on the activation of autoimmune reactions within the framework of infectious and toxic inflammations (4). We are grateful to A. Schaffner and B. Rager-Zisman for an excellent review on virus-induced autoimmunity (13). Of special interest for the pathogenesis of AIDS in haemophiliacs are recent works on the activation of autoimmune reactions in hepatitis C (14). The toxic induction of autoimmune reactions has for several years been the field of research of E. Gleichmann who, with his working-group, has shown that toxic-induced autoimmune reactions behave in the same way as alloimmune diseases, whereby in both cases a T-2 profile of the $CD4^+$ helper cells play the central role (+5).

The close connection between our knowledge of retroviruses and autoimmune rheumatic

diseases gave rise to discussions as to whether endogenous or exogenous retroviruses play a role in the aetiology of these diseases. However, no conclusive results were obtained in this respect (16). The contrary idea, that antiretroviral antibodies should be classified in the large group of the autoimmune antibodies has to our knowledge not been considered up till now.

Yin-Yang shifts of macrophage activity as triggering factors for autoimmune diseases

As already mentioned, during the last ten years it has been recognised that in immune reactions a state of equilibrium exists between B-cell-dependent humoral and T-cell-dependent cellular immune reactions, which in all stress reactions is shifted in favour of the humoral immune reactions and to the disadvantage of the cellular immune reactions. Immune competence is defined as a state of equilibrium between humoral and cellular immune reactions (17).

The processing of the cell fragments resulting from the continuous cell metabolism is a permanent physiological task of the immune system. The human organism consists of about 10^{14} cells (18). The around 10^{12} apoptotic cell fragments that are produced daily are recognised by the cytotoxic T cells originating from the thymus and by the natural killer cells, and are transmitted to the macrophages, which process them without any signs of inflammation. The macrophage activity corresponds to the Yin situation. It is trophotropic and anabolic.

In contrast, every stress-induced adjustment of the immune system to the elimination of exogenous "non-self" structures by humoral antibodies produced from B cells is a special, temporary task of the immune system. It is always associated with an inflammatory activation of the macrophages. In this process the stress-induced hypercorticolism causes a reduction of the Th-1 lymphokines IL-2, IL-12 and IFNγ. In the macrophages this causes an increased release of O_2 radicals and inflammation mediators such as IL-1 and TNFα. At the same time this neuroendocrine situation weakens the standstill capacity of the macrophages towards their intracellular microorganisms. In addition, their defence against opportunistic microorganisms is impaired. This macrophage activity corresponds to the Yang situation. It is ergotropic and catabolic and is generally described as an acute-phase reaction.

The Th-1 cytokine profile of the $CD4^+$ lymphocytes corresponds to the Yin situation of the macrophage activity, while the Th-2 profile corresponds to the Yang situation of this activity (19).

According to what has been said, autoimmune diseases are to be understood as being the pathological effects of a continuous inflammatory macrophage activity, in which the increased performance of the immune system is directed towards endogenous structures, in order to eliminate exogenous "non-self" structures. In systemic autoimmune diseases such as lupus erythematosus disseminatus the persistent hyperactivity of the B-cell functions is the principle factor responsible for these conditions.

From what has been said, it emerges that there is much that speaks for the fact that the close association between retroviral diseases and autoimmune diseases is due to the same mechanism of a continuous hyperactivity of the B-cell functions. It should therefore be worthwhile to seriously address the question whether the anti-HIV antibodies can retain the individual identity accorded them up until now, or whether they should be classified in the large group of humoral autoantibodies against cellular structures. In this respect,

clarification of the relationship of the retroviral proteins to the endogenous proteins plays a central role.

Relationships of the glycoprotein gp 120 of the HIV envelope to actin

In their work on the occurrence of anti-HIV antibodies with specificity against gp 120 and the accompanying peptides in patients with lupus erythematosus disseminatus, the working-group of G.M. Shearer has shown that these antibodies differ from the anti-DNA autoantibodies of these patients (1). As a result of this the question of the specificity of this autoantibody population remained unanswered. The following arguments serve to indicate that these could be anti-actin autoantibodies. Glycoprotein 120 and protein 41 are generally considered to be fission products of protein 160, which is found in virally infected cells but not in the virus itself. Protein 120 is found only on the surface of protrusions occurring with the exocytosis of virus particles, but not in the released particles themselves (20). Thus the question arises whether these glycoproteins, which are described as envelope proteins of the retroviruses, are endogenous proteins. In the first description of the human immunodeficient viruses (HIVs) by the working-group of L. Montagnier, they mentioned the possibility that "the 45 k protein may be due to contamination of the virus by cellular actin, which was present in immunoprecipitates of all the cell extracts" (21). In fact, the oxidation of cellular sulphydryl groups leads to the polymerisation of actin, so that the binding of anti-actin autoantibodies has been suggested as a sensitive method for the indication of a lymphocyte activation (22-25).

Anti-actin antibodies are found in healthy individuals, but also especially in patients with autoimmune diseases. In the latter cases their antibody profile speaks against cross-reactivity with viral antigens. In all probability they are natural autoantibodies (26). They are particularly common in patients with chronic forms of hepatitis, where they play the same role as disease indicators as do the anticardiolipin antibodies in syphillis (14).

In order to explain the relationship of the demonstration of anti-HIV antibodies to viral or non-viral endogenous structures it seems to us to be essential to address, on a sound basis, the question of the anti-actin activity of anti-HIV antibodies against the envelope proteins of HIVs.

Based on these considerations, the sine qua non of an HIV infection in a case of AIDS is in our opinion invalid. Pathogenetically, stress-induced suppressions of the cellular immune reactions are to be placed at the beginning of the process. Besides the weakening of the defences against latent infections and opportunistic microorganisms, the impairment of the thymus-dependent immune functions causes an activation of the polyclonal B-cells, which in turn gives rise to autoimmune reactions with increased production of humoral autoantibodies. The increase in the anti-HIV-antibody content is to be understood as a marker of this activation of the polyclonal B cells. Therefore efforts aimed at the prevention of AIDS have to be directed primarily towards the correction of stress- induced suppressions of the cellular immune reactions, whereby suppression of the inflammatory activation of the macrophages is the most important objective (27).

Finally, we would like to draw attention to the fact that at the time when the working-groups of L. Montagnier and R.C. Gallo were developing the anti-HIV antibody test, it was widely believed that any synthesis and release of reverse transcriptase was an indication of the active production of retroviruses. Today, however, we know that RNA-controlled DNA polymerases fulfil certain physiological functions, for example as telomerases in the stabilisation of the extremities of chromosomes (28). It is therefore of interest to consider this particular viewpoint in a critical examination of the development of these tests at that time.

Summary

Two years ago the working-group of G.M. Shearer demonstrated that antibodies in the serum of patients with lupus erythematosus and in the serum of mice with experimentally induced lupus erythematosus are capable of reacting specifically with glycoprotein 120 and peptides from the HIV-I envelope. On the basis of these observations we put to ourselves the question whether this group of anti-HIV antibodies are to be considered as autoantibodies against cellular structures.

A literature search has shown that humoral autoantibodies occur frequently in patients with AIDS and display the same specificities as in patients with systemic auotimmune diseases. We would further point out that the horizontal transmission of HIV structures can act as the trigger for alloimmune reactions, whereby in recipients with severely suppressed cellular immune reactions "graft versus host" reactions can appear, with the development of humoral alloimmune reactions.

Furthermore, we have shown that autoimmune reactions have to be considered as pathological effects of a continuous inflammatory macrophage activity, whereby the increased performance of the immune system for the elimination of exogenous "non-self" structures is directed against endogenous structures. In this connection, in systemic autoimmune diseases such as lupus erythematosus the principal factor involved is the continuous hyperactivity of the B-cell functions.

Finally, we have shown that many observations point to the fact that anti-HIV antibodies with specificity against gp 120 and the associated peptides are autoantibodies against cellular actin.

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