

Autoimmun Reactions in AIDS and positive HIV-test results:

Reactivity of Sera from Systemic Lupus Erythematosus and Sjögren's Syndrome Patients with Peptides Derived from Human Immunodeficiency Virus p24 Capsid Antigen

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<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=121355&blobtype=pdf>

Polyspecific Self-Reactive Antibodies in Individuals Infected with Human Immunodeficiency Virus Facilitate T Cell Deletion and Inhibit Costimulatory Accessory Cell Function

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<http://www.journals.uchicago.edu/JID/journal/issues/v180n4/981172/981172.web.pdf>

Neuroimmune mechanisms in health and disease: 2. Disease.

H Anisman, M G Baines, I Berczi, C N Bernstein, M G Blennerhassett, R M Gorczynski, A H Greenberg, F T Kisil, R D Mathison, E Nagy, D M Nance, M H Perdue, D K Pomerantz, E R Sabbadini, A Stanisz, and R J Warrington

<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1335357&blobtype=pdf>

Polymerase chain reaction fails to incriminate exogenous retroviruses HTLV-I and HIV-1 in rheumatological diseases although a minority of sera cross react with retroviral antigens.

P N Nelson, A M Lever, F E Bruckner, D A Isenberg, N Kessar, and F C Hay

<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1005456&blobtype=pdf>

Anti-human immunodeficiency virus type 1 antibodies of noninfected subjects are not related to autoantibodies occurring in systemic diseases.

R Kämmerer, P Bürgisser, and P C Frei

<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=170179&blobtype=pdf>

Preliminary evidence for idiotype-antiidiotype immune complexes cross-reactive with lymphocyte antigens in AIDS and lupus.

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Several investigators have proposed that autoimmunity may be induced by idiotype-antiidiotype antibody networks. It is generally assumed that the antiidiotype is produced in response to the idiotype, and therefore that autoimmune diseases have single antigenic initiators. The theory of multiple-antigen-mediated autoimmunity (MAMA) proposes, on the other hand, that idiotype and antiidiotype result from two primary immune responses to two chemically complementary antigens. Because of the complementarity of the antigens, and the complementarity of the antibodies for the antigens, the antibodies will themselves be complementary. They will thus form circulating immune complexes, the self-nonsel self distinction diffusion (DAD) experiments (a modification of Ouchterlony immunodiffusion), in which 1800 pairs of antibodies were screened for their ability to form precipitating complexes. Four sets of antibodies associated with AIDS (HIV + Staphylococcus; HIV + Mycoplasma; CMV + Mycoplasma; and HBV + Mycoplasma) specifically precipitated each other, and one of the antibodies in each set also precipitated monoclonal antibodies against one or more lymphocyte protein markers. These results therefore demonstrate that idiotype-antiidiotype antibodies can be elicited by independent antigens and may induce AIDS-related forms of autoimmunity directed at lymphocytes.

Hepatitis C-associated autoimmunity in patients coinfectd with HIV.

[Woitas RP](#), [Stoschus B](#), [Terjung B](#), [Vogel M](#), [Kupfer B](#), [Brackmann HH](#), [Rockstroh JK](#), [Sauerbruch T](#), [Spengler U](#).

Background: Hepatitis C virus (HCV) infection is associated with multiple extrahepatic manifestations. It is unclear to what extent extrahepatic manifestations occur in HIV/HCV coinfection. Methods: We prospectively assessed cross-sectional frequencies of autoimmune manifestations in HIV/HCV-coinfectd patients (n=98), HIV-mono-infected (n=45) and HCV-mono-infected patients (n=78). Diagnostic vasculitis scores, HCV and HIV loads, CD4 cell counts, thyroid-, cardiolipln-, non-organ-specific tissue antibodies (nuclear, smooth muscle, anti-liver-kidney-microsome, neutrophil-cytoplasmic) and cryoglobulins were determined. Results: Synergistic effects of HCV and HIV infection were observed with respect to the prevalence of antibodies against thyroglobulin (HCV infection 15.4%, HIV infection 8.8%, HIV/HCV coinfection 30.6%; P<0.001) and cardiolipln antibodies (HCV infection 9.0%, HIV infection 31%, HIV/HCV coinfection 46%; P<0.001). Cryoglobulinemia type III, was significantly associated with HCV infection (HCV, 25.6%; HIV/HCV, 20.4%) but not with HIV infection (4.4%, P<0.05). Rheumatoid factor was commonly detected in patients with HCV infection (48%), but occurred considerably less frequently in patients with HIV infection (4.4%) or HIV/HCV coinfection (9.5%, P<0.01). Conclusion: HIV coinfection appears to differentially modulate the frequency of HCV-related autoimmunity. However, autoimmunity is rarely accompanied by clinical manifestations.

Serum non-organ specific autoantibodies in human immunodeficiency virus 1 infection.

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Serum samples from 66 seropositive subjects (56 with a history of intravenous drug abuse), including asymptomatic carriers and patients with persistent generalised lymphadenopathy (PGL), AIDS related complex (ARC), and AIDS, were tested by indirect immunofluorescence on rat tissue sections and HEp-2 cells for the presence of antibodies to nuclei, smooth muscle, intermediate filaments (anti-IMF) and microfilaments (anti-MF).

Counterimmunoelectrophoresis was also used to detect antibodies to extractable nuclear antigens. Smooth muscle antibodies with the V pattern or antinuclear antibodies, mainly of the speckled type, or anti-IMF, occurred in 35 cases, being widely distributed in all groups. Such an autoantibody response resembles the "viral" autoimmunity described in various infectious diseases and in particular that of non-A, non-B post-transfusion hepatitis. Autoantibodies may be of some prognostic relevance, as the prevalence of smooth muscle antibodies V increased as the disease progressed (asymptomatic carriers 20%, those with PGL 29%, those with ARC 47%, and those with AIDS 63%). In the PGL group autoantibody positivity correlated with the presence of skin anergy. The fact that autoantibodies were more frequently detected in patients with circulating immune complexes suggests that these can contain autoantibodies and the corresponding autoantigens.

Distribution of antibodies against denatured collagen in AIDS risk groups and homosexual AIDS patients suggests a link between autoimmunity and the immunopathogenesis of AIDS.

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Autoimmunity often precedes the onset of AIDS-related complex or AIDS, and a number of autoantibodies have been described in AIDS patients and persons at risk for AIDS. The presence of such antibodies provokes speculation that autoimmunity is a component of AIDS pathogenesis. We report evidence of an autoantibody (anticollagen) common to all homosexual AIDS patients studied. High titer serum reactivity against collagen was detected in all homosexual AIDS patients, and in HIV+ homosexuals (66%), HIV+ i.v. drug users (38%) HIV- homosexuals (32%), HIV+ transfusion recipients (22%), and HIV+ hemophiliacs (13%), but not in HIV- i.v. drug users, HIV- transfusion recipients, HIV- hemophiliacs, rheumatoid arthritis patients, or controls. Anticollagen reactivity does not correlate with serum IgG levels, so it is not merely a reflection of polyclonal B-cell activation. Titration of anticollagen positive sera typically revealed anticollagen antibody titers 100 times those of normal sera. Affinity purification and immunoblot analysis confirmed the antibody nature of the anticollagen reactivity. The anticollagen antibodies react preferentially with primary determinants of types I and III collagen revealed after heat denaturation. Similar antibodies occur infrequently in rheumatoid arthritis patients, more often on SLE, and frequently in graft vs host disease and lepromatous leprosy. Levels of anticollagen activity in HIV+ i.v. drug users and transfusion recipients correlate with serum beta 2-microglobulin levels, suggesting that those persons with anticollagen antibodies are at greater risk of developing AIDS. This correlation, the fact that anticollagen antibodies occurred in all homosexual AIDS patients tested, and the occurrence of antibodies against denatured collagen in immune disorders with features similar to AIDS suggest these antibodies may be related to disease progression. The association of anticollagen autoantibodies with AIDS and certain other infections and immune disorders may reflect common immunopathogenic features in the etiology of these disorders.

HIV and autoimmunity

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The association of immune dysfunction in patients with human immunodeficiency virus (HIV) infection and AIDS and the development of autoimmune diseases is intriguing. Yet, the spectrum of reported autoimmune phenomena in these patients is increasing. An infectious trigger for immune activation is one of the postulated mechanisms and derives from molecular mimicry. During frank loss of immunocompetence, autoimmune diseases that are predominantly T cell subtype CD8 driven predominate. There is evidence for B cell stimulation and many autoantibodies are reported in HIV patients. We propose a staging of autoimmune manifestations related to HIV/AIDS manifestations and the total CD4 count and viral load that may be beneficial in identifying the type of autoimmune disease and establishing the proper therapy. In stage I there is the acute HIV infection, and the immune system is intact. In this stage, autoimmune diseases may develop. Stage II describes the quiescent period without overt manifestations of AIDS. However, there is a declining CD4 count indicative of some immunosuppression. Autoimmune diseases are not found. During stage III there is immunosuppression with a low CD4 count and the development of AIDS. CD8 T cells predominant and diseases such as psoriasis and diffuse immune lymphocytic syndrome (similar to Sjogren's syndrome) may present or even be the initial manifestation of AIDS. Also during this stage no autoimmune diseases are found. In stage IV there is restoration of immune competence following highly active anti-retroviral therapy (HAART). In this setting, there is a resurgence of autoimmune diseases. The frequency of reported rheumatological syndromes in HIV-infected patients ranges from 1 to 60%. The list of reported autoimmune diseases in HIV/AIDS include systemic lupus erythematosus, anti-phospholipid syndrome, vasculitis, primary biliary cirrhosis, polymyositis, Graves' disease, and idiopathic thrombocytopenic purpura. Also, there is an array of autoantibodies reported in HIV/AIDS patients which include anti-cardiolipin, anti-beta2 GPI, anti-DNA, anti-small nuclear ribonucleoproteins (snRNP), anti-thyroglobulin, anti-thyroid peroxidase, anti-myosin, and anti-erythropoietin antibodies. The association of autoantibodies in HIV-infected patients to clinical autoimmune disease is yet to be established. With the upsurge of HAART, the incidence of autoimmune diseases in HIV-infected patients is increasing. In this review, we describe the various autoimmune diseases that develop in HIV/AIDS patients through possible mechanisms related to immune activation.

Cytokines and the immune response.

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Cytokines participate in many physiological processes including the regulation of immune and inflammatory responses. These effector molecules are produced transiently and locally controlling the amplitude and duration of the response. A variety of experiments has shown that excessive or insufficient production may significantly contribute to the pathophysiology of a range of diseases. Particularly cytokines released by CD4⁺ T cells at the onset of an immune response are thought to be decisive for pathological or physiological consequences. The meeting in Budapest was focussed on cytokines known to contribute to the pathophysiology of autoimmune diseases, infectious diseases and allograft rejection (e.g., IL-1, IL-4, IL-6, IL-10, IL-12, TNF-alpha and IFN-alpha, -beta, -gamma). A central role for IFN-gamma in autoimmunity was suggested by blocking experiments in vivo using monoclonal antibodies and soluble forms of the IFN-gamma receptor (IFN-gamma SR). These agents ameliorated disease development in a variety of experimental autoimmune diseases in rodents. In a mouse model for the human disease Myasthenia gravis, IFN-alpha was found to reduce both the incidence and progression of the disease. Treatment of *R. aurantiacus*-infected

mice with anti-IL-4 monoclonal antibodies (mAbs) was reported to interfere with the regression of granulomas in spleen and liver, most likely through inadequate IL-4-mediated suppression of IFN-gamma production. In addition, it was shown that mice with disrupted IFN-gamma R genes died rapidly after infection with the BCG strain of *M. bovis*, whereas normal mice survived the infection. IL-12 was found to be the main inducer of IFN-gamma during the lethal Shwartzman reaction. TNF-alpha was identified as the principal cause of mortality after the second injection with LPS. In a variety of studies examining the role of cytokines in the pathogenesis of AIDS, much attention was given to the in vitro effects of HIV-1 and/or the HIV-1 viral membrane protein gp120 on triggering cytokine production by peripheral blood leukocytes (PBLs) and purified monocytes/macrophages (Mø) originating from healthy donors. Gp120 as a sole agent significantly suppressed IFN-gamma production by mitogen-stimulated PBLs and induced the production of IFN-alpha in cultures of normal human peripheral blood mononuclear cells (PBMCs). In a human macrophage cell line, TNF-alpha exerted a stimulatory effect on viral replication and programmed cell death induced by HIV-1 which was potentiated by the simultaneous incubation with IFN-gamma. Upon transfection of human PBLs and CD4+ T cells with a retroviral vector encoding human IFN-beta, a notable reduction in reverse transcriptase activity after HIV-1 challenge was observed. Gp120 was also found to induce both IL-6 and TNF-alpha expression and to induce morphological changes reminiscent for apoptosis in primary astrocytes and in a re-aggregated human brain cell model, suggesting a role for these cytokines in the neuropathology of AIDS dementia. Moreover, data were presented indicating that cytokine-induced expression of cell adhesion molecules (e.g., ICAM-1) in HIV-1 infected U 937 cells leads to high level incorporation of this molecule in the membrane of the viral progeny which may play a role in the attachment of such virions to CD4-negative cells.

Modern diets and diseases: NO-zinc balance. Under Th1, zinc and nitrogen monoxide (NO) collectively protect against viruses, AIDS, autoimmunity, diabetes, allergies, asthma, infectious diseases, atherosclerosis and cancer.

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Thanks to progress in zinc research, it is now possible to describe in more detail how zinc ions (Zn^{++}) and nitrogen monoxide (NO), together with glutathione (GSH) and its oxidized form, GSSG, help to regulate immune responses to antigens. NO appears to be able to liberate Zn^{++} from metallothionein (MT), an intracellular storage molecule for metal ions such as zinc (Zn^{++}) and copper (Cu^{++}). Both Zn^{++} and Cu^{++} show a concentration-dependent inactivation of a protease essential for the proliferation of the AIDS virus HIV-1, while zinc can help prevent diabetes complications through its intracellular activation of the enzyme sorbitol dehydrogenase (SDH). A Zn^{++} deficiency can lead to a premature transition from efficient Th1-dependent cellular antiviral immune functions to Th2-dependent humoral immune functions. Deficiencies of Zn^{++} , NO and/or GSH shift the Th1/Th2 balance towards Th2, as do deficiencies of any of the essential nutrients (ENs) - a group that includes methionine, cysteine, arginine, vitamins A, B, C and E, zinc and selenium (Se) - because these are necessary for the synthesis and maintenance of sufficient amounts of GSH, MT and NO. Via the Th1/Th2 balance, Zn^{++} , NO, MT and GSH collectively determine the progress and outcome of many diseases. Disregulation of the Th1/Th2 balance is responsible for autoimmune disorders such as diabetes mellitus. Under Th2, levels of interleukin-4 (II-4), II-6, II-10, leukotriene B4 (LTB4) and prostaglandin E2 (PGE2) are raised, while levels of II-2, Zn^{++} , NO and other substances are lowered. This makes things easier for viruses like HIV-1

which multiply in Th2 cells but rarely, if ever, in Th1 cells. AIDS viruses (HIVs) enter immune cells with the aid of the CD4 cell surface receptor in combination with a number of co-receptors which include CCR3, CCR5 and CXCR4. Remarkably, the cell surface receptor for LTB₄ (BLTR) also seems to act as a co-receptor for CD4, which helps HIVs to infect immune cells. The Th2 cytokine II-4 increases the number of CXCR4 and BLTR co-receptors, as a result of which, under Th2, the HIV strains that infect immune cells are precisely those that are best able to accelerate the AIDS disease process. The II-4 released under Th2 therefore not only promotes the production of more HIVs and the rate at which they infect immune cells, it also stimulates selection for the more virulent strains. Zn⁺⁺ inhibit LTB₄ production and numbers of LTB₄ receptors (BLTRs) in a concentration-dependent way. Zn⁺⁺ help cells to keep their LTB₄ 'doors' shut against the more virulent strains of HIV. Moreover, a sufficiency of Zn⁺⁺ and NO prevents a shift of the Th1/Th2 balance towards Th2 and thereby slows the proliferation of HIV, which it also does by inactivating the HIV protease. Research makes it look likely that deficiencies of ENs such as zinc promote the proliferation of Th2 cells at the expense of Th1 cells. Zinc deficiency also promotes cancer. Under the influence of Th1 cells, zinc inhibits the growth of tumours by activating the endogenous tumour-suppressor endostatin, which inhibits angiogenesis. The modern Western diet, with its excess of refined products such as sugar, alcohol and fats, often contains, per calorie, a deficiency of ENs such as zinc, selenium and vitamins A, B, C and E, which results in disturbed immune functions, a shifted Th1/Th2 balance, chronic (viral) infections, obesity, atherosclerosis, autoimmunity, allergies and cancer. In view of this, an optimization of dietary composition would seem to give the best chance of beating (viral) epidemics and common (chronic) diseases at a realistic price.