

Key outcomes of the meeting

- Autoimmune phenomena might result from unresolved inflammation.
- Unresolved inflammation might result from tissue-specific autoimmunity.
- Autoimmunity might result from neoepitope formation by post-translational modification of self proteins.
- Endogenous retroviruses might trigger pro-inflammatory and tissue destructive pathways.
- Exogenous microbial antigens might trigger autoimmunity.

well defined, thus facilitating the delineation of T-cell specificities (J. Sieper, Benjamin-Franklin Free University, Berlin, Germany) that might contribute to the conversion of immunity into joint pathology. B.T. Huber (Tufts University School of Medicine, Boston, MA, USA) demonstrated that the *Borrelia burgdorferi* outer surface protein A (OspA) plays a major role in the induction of crossreactive T-cell responses to the 'self' determinant leukocyte integrin LFA-1 (Ref. 5). OspA-specific T-cell clones could be cultured from the synovial fluid of patients with treatment-resistant Lyme

arthritis. Upon stimulation with an LFA-1 peptide, 7–10% of these T cells proliferated and produced Th2 cytokines, in particular IL-13. Interestingly, these dual specificity T-cell clones were predominantly restricted to the 'shared epitope' (HLA-DRB1*01 or HLA-DRB1*04) that is also associated with aggressive forms of RA. Thus, the data indicate that the potential pathogenic role of a molecular mimicry between OspA and LFA-1 is to drive antibody-mediated immunity.

Concluding remarks

Two opposing mechanisms for the development of inflammatory erosive arthritis were presented. An unbalanced cytokine profile with a dominance of pro-inflammatory mediators (TNF and IFN- γ) might cause tissue destruction, following which autoimmune phenomena might be generated. By contrast, autoimmunity itself might trigger and/or sustain an inflammatory attack on joint integrity. Further study is required to delineate whether these mechanisms are mutually exclusive or coexist in a self-perpetuating manner, as suggested in Fig. 1. Novel therapeutic strategies will also have to address these issues, as pointed out by F.C. Breedveld (University Medical Centre, Leiden, The Netherlands), A.F. Kavanaugh (University of California at San Diego, CA,

USA) and A. Radbruch (Deutsches Rheuma Forschungszentrum, Berlin, Germany).

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Atherosclerosis as an infectious, inflammatory and autoimmune disease

Yehuda Shoenfeld, Yaniv Sherer and Dror Harats

The European Atherosclerosis Society Workshop on the Immune System in Atherosclerosis was held at the Hotel Intercontinental, Geneva, Switzerland, from 8–11 March 2001.

Atherosclerosis (AS) is a multi-factorial process and its outcome, coronary heart disease, is considered to be responsible for the greatest number of deaths worldwide. This meeting focused on AS as an immune-mediated disease, with special emphasis on its association with infectious and autoimmune conditions. These new aspects of AS research will encourage the search for novel immunomodulatory therapies for AS.

At the European Atherosclerosis Society Workshop, 200 researchers and

physicians gathered in Geneva to summarize the current data indicating that AS is indeed an immune-mediated disease¹, without disregarding the traditional risk factors (e.g. smoking and diabetes). These experts concluded that it is time to consider novel immunomodulatory therapies to prevent and/or treat AS. Approximately 40% of subjects having myocardial infarction (MI) or cerebrovascular accident (CVA) are not exposed to any of the traditional risk factors for AS. Furthermore, in some classical autoimmune rheumatic diseases, such as systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), rheumatoid arthritis and vasculitis,

one can also find accelerated progression of AS, thus suggesting that inflammatory and immune mechanisms are involved in the rapid process of plaque formation.

Atherosclerosis as an infectious disease

Many viruses, bacteria and even parasites are claimed to affect AS plaque deposition. Among them, *Chlamydia pneumoniae* probably has the strongest association with AS (S. Gupta, London, UK). There is a close relationship between *C. pneumoniae* infection, IgG and IgM titers, and increased evidence of MI, CVA and peripheral vascular disease (PVD). *C. pneumoniae* antigens are found in AS plaques, and T-cell reaction to these

Box 1. The Witebsky and Rose criteria for autoimmunity are fulfilled in atherosclerosis

- Defined autoantigens: HSP-60, oxLDL and β 2GPI.
- Active immunization of naive animals with HSP-60 or β 2GPI induces the respective autoantibodies and accelerates the formation of atherosclerosis (AS). Immunization with oxLDL leads to the formation of protective autoantibodies.
- Autoantibodies: the pathogenic role of anti-HSP-60, anti-oxLDL and anti- β 2GPI has been delineated in clinical studies and experimental models.
- The passive transfer of T cells (non-specific or specific: anti- β 2GPI) leads to AS development in naive mice.
- Immunomodulation of mice with AS ameliorates the disease symptoms.

antigens has been demonstrated. Experimental models illustrate the pathogenic role of *C. pneumoniae* and the unique heat-shock protein (HSP)-60. Yet, recent studies do not support this notion. Other major AS-associated pathogens are *Helicobacter pylori*, Epstein-Barr virus and cytomegalovirus. For some pathogens, interfering pathogenic mechanisms have been described, such as cytomegalovirus gene-induced proliferation of smooth-muscle cells. From data showing a correlation between increased AS incidence and chronic bronchitis, as well as periodontitis, it has been suggested that any infectious agent, and especially multiple chronic infections, could result in accelerated AS formation. This multiplicity was confirmed recently in experimental animal models. There is no doubt therefore, that chronic infections with specific or nonspecific infectious agents can contribute to the acceleration of AS development, either by nonspecific mechanisms [hypercoagulability, and increased adhesion molecule and elevated C-reactive protein (CRP) levels] or by more specific mechanisms such as

induction of HSP-60 expression and eventually pathogenic anti-HSP-60 antibody production (S.E. Epstein, Washington, WA, USA).

Atherosclerosis as an inflammatory disease

The relationship between high CRP levels and an increased risk of AS is no longer in doubt (P. Libby, Boston, MA, USA). High serum CRP levels correlate with an increased incidence of MI, CVA and PVD, as well as with mortality. CRP might play a pathogenic role in atherogenesis through the induction of expression of adhesion molecules, as well as chemokines, such as macrophage chemoattractant protein-1. This results in an attractive milieu for recruiting circulating monocytes to the arterial wall (E.T.H. Yeh, Houston, TX, USA). Thus, pharmaceutical companies are directing their efforts to discovering compounds that lower CRP levels. In addition to CRP, serum amyloid protein, fibrinogen, troponin, soluble adhesion molecules and other acute-phase proteins play a part in the acceleration of AS plaque formation.

Atherosclerosis as an autoimmune condition

AS fulfills the four criteria delineated by Witebsky and Rose to define a condition as autoimmune in nature (Box 1). Several autoantigens and their respective autoantibodies are considered to be associated with AS (D. Harats, Tel-Hashomer, Israel)².

HSP-60

G. Wick (Innsbruck, Austria) first claimed that HSP-60 is involved in AS (Ref. 3). Anti-HSP-60 antibody titers correlate with the degree of AS in carotid ultrasound studies. The increase in anti-HSP-60 antibody levels could result from direct turbulence damage to bifurcated arteries or could be caused by infectious agents (e.g. *C. pneumoniae*) releasing HSP-60, which becomes immunogenic. T-cell lines cultured from the AS plaque proliferate when exposed to HSP-60 and both the autoantibodies as well as the autoantigen can be found in the plaque. Finally, active immunization of rabbits and apolipoprotein-E or low-density lipoprotein (LDL)-receptor knockout mice with HSP-60 leads to accelerated formation of AS plaques.

Oxidized LDL

Oxidized LDL (oxLDL) is the prime candidate for an autoantigen. It is incriminated in foam cell generation through uptake by the unregulated scavenger receptors on macrophages, and anti-oxLDL antibodies correlate not only with MI, CVA and predictions of progression of coronary AS, but also with the restenosis of angioplastic vessels (T. Koike, Hokkaido, Japan). Anti-oxLDL antibodies also enhance oxLDL uptake by monocytes. Yet, repeated immunizations of rabbits and mice with oxLDL resulted in the generation of anti-oxLDL antibodies but a reduction in AS. The differences between the protective and pathogenic anti-oxLDL antibodies have yet to be elucidated (J.L. Witztum, San Diego, CA, USA).

 β -2-glycoprotein-I

β -2-glycoprotein-I (β 2GPI) is a normal glycoprotein synthesized by the liver that behaves as an anti-coagulant and is also an anti-atherogenic agent. Binding of β 2GPI to oxLDL reduces the uptake of

Key outcomes of the workshop

- AS is an inflammatory process in which C-reactive protein is involved by inducing the expression of adhesion molecules and chemokines in arterial endothelial cells, with the subsequent recruitment of monocytes to the arterial wall.
- *C. pneumoniae* and other infectious agents are candidate inflammatory triggers of AS.
- Autoimmune factors, including autoantigens, autoantibodies and reactive lymphocytes, play a role in determining the extent and nature of the AS plaque.
- oxLDL plays an important role in the pathogenesis of AS; elevated anti-oxLDL antibody levels are associated with AS and other vascular diseases.
- AS progression is accelerated in several autoimmune conditions, including SLE and APS.
- Animal models suggest that AS can be immunologically manipulated; this type of therapy might be used in the future in humans.

oxLDL by scavenger receptors on macrophages. β 2GPI is found in the AS plaque (J. George, Tel-Aviv, Israel), and it is the target antigen in APS, another condition intimately involved with AS (M. Khamashta, London, UK). Antibodies to β 2GPI can be found in SLE and APS, and post-infection (O. Vaarala, Helsinki, Finland). Antibody titers correlate with AS and in *in vitro* studies they enhance oxLDL uptake by macrophages. Recently, in a classical study⁴, accelerated AS plaque formation was induced in LDL-receptor-deficient mice by the passive transfer of lymphocytes from the lymph nodes and spleens of mice actively immunized with β 2GPI.

Treatment strategies

Therefore, it seems that autoimmune accelerated AS is caused by multiple autoantigenic stimuli and is the result of multiple humoral and cellular infections. Having concluded that AS has an autoimmune nature, it is not surprising that this process can be manipulated very effectively by immune modulation (Y. Shoenfeld, Tel-Hashomer, Israel). In many patients the disease can be treated

either by chronic antibiotic intake (i.e. azithromycin) or statin therapy. The latter has been found to affect AS beyond the ability of statins to reduce cholesterol levels (F. Mach, Geneva, Switzerland). Statins have been found to decrease MHC class II as well as adhesion molecule expression on the vascular wall. AS is also reduced upon CD3⁺ lymphocyte depletion and anti-CD40 antibody therapy. Similarly, intravenous immunoglobulin (IVIg) therapy leads to a 40% reduction in the extent of plaque formation. It is likely that IVIg acts in part through anti-idiotypic antibodies against oxLDL, nonspecific blockade of macrophages and infusion of natural, protective anti-oxLDL antibodies.

Concluding remarks

AS is an infectious and inflammatory condition. Both humoral and cellular autoimmune mechanisms are involved in acceleration of formation of the AS plaque. In the near future, various vaccines, tolerance-induction protocols and immunomodulators should be routinely incorporated into the scheme of

prevention and therapy of cardiovascular diseases.

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