Editorial

A Tale of Two Diseases
Atherosclerosis and Rheumatoid Arthritis

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Acute coronary syndromes are responsible for most of the morbidity and mortality caused by coronary atherosclerosis. Both unstable angina and acute myocardial infarction are characterized by coronary thrombosis, usually caused by rupture or fissuring of a coronary plaque. Yet the occurrence of plaque rupture and coronary thrombosis is not related to severity of coronary plaques, and functional factors other than the mere presence of atherosclerotic lesions play an important role.1–2 Recent studies have focused on the inflammatory component of atherosclerosis, trying to highlight the differences between stable and unstable coronary plaques. An increasing body of evidence supports the hypothesis that atherosclerosis shares many similarities with other inflammatory/autoimmune diseases. Indeed, there are surprising similarities in the inflammatory/immunologic response observed in atherosclerosis, in unstable angina, and in rheumatoid arthritis, the prototype of autoimmune disease (Table). However, although our understanding of the molecular and immunological mechanisms of rheumatoid arthritis has greatly progressed, due to the relatively easy access to the diseased tissue (synovium) and to the availability of animal models, the study of the inflammatory and immunological components of atherosclerosis is still in its initial stages. Unfortunately, it is more difficult for cardiologists to follow the evolution of inflammatory response in plaques or make correlations with the clinical course. Furthermore, although mice models of atherosclerosis have been developed in the last few years, there are still no animal models able to reproduce the events occurring in acute coronary syndromes. Thus, the study of the molecular mechanisms of rheumatoid arthritis may give valuable hints for research on the inflammatory/immunological mechanisms of atherosclerosis and acute coronary syndromes.

See p 2135

Activation of inflammatory cells (in particular macrophages and mast cells), releasing many collagen-breaking enzymes within atherosclerotic plaques is likely to play an important role in destabilization of plaques.3 Collagen degeneration is also an essential element in the pathogenesis of rheumatoid arthritis. Local expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin) and of endothelin have been described in both diseases.4–5 Similarly, recent studies found that neoangiogenesis, known to be an important factor in the pathogenesis of rheumatoid arthritis,6 can also contribute to development of atherosclerosis.7 Activated T cells are also present in atherosclerotic plaques, as well as in rheumatoid synovium, and unstable plaques have an increased percentage of activated T cells expressing the IL2 receptor.8 It can be argued that these similarities are merely a consequence of chronic persistent inflammation. In this issue of Circulation, however, Liuzzo et al reported another important analogy, suggesting that the similarities between these 2 diseases may be more than a scientific curiosity.9

In this study, Liuzzo et al found increased levels of an unusual subset of T cells, CD4+CD28−, in 65% of patients with unstable angina, but not in patients with stable angina. This lymphocyte subpopulation was originally described in patients with rheumatoid arthritis and has been associated with presence of extra-articular disease and, in particular, vasculitis. Increased levels of T cells (both CD4+ and CD8+) producing IFN-γ and lower levels of T cells producing IL2 and IL4, suggesting an imbalance between Th1 and Th2 response, were also found in patients with unstable angina compared with patients with stable angina.9

The identification in the mouse of 2 populations of T helper (CD4+) cells (namely Th1 and Th2 cells) producing different pattern of cytokines has allowed a better understanding of the mechanisms of immune response in vivo.10 Th1 cells produce IFN-γ and activate monocyte/macrophage cells, whereas Th2 cells release cytokines (IL4, IL5, and IL10) which stimulate immunoglobulin production and eosinophil and mast-cell proliferation. Although in humans the distinction of Th1 and Th2 clones is more ambiguous, the distinction between Th1-like cells (IFN-γ+) and Th2-like cells (IL4+) can be useful for practical purposes. Th1 and Th2 responses are often mutually antagonistic, and the Th1/Th2 balance may be involved in the pathogenesis of several autoimmune diseases, including rheumatoid arthritis. The CD28 receptor is an important component of the T-cell activation. T-cell activation usually requires 2 signals: the first results from the interaction of the antigen-specific T-cell receptor with the antigenic peptide bound to major histocompatibility complex molecules on the antigen presenting cells; the second costimulatory signal is provided by the interaction of costimulatory receptors on the T cell with surface molecules expressed by the antigen presenting cell. The interaction of the CD28 receptor on the lymphocyte with receptors of the B7 family on the antigen presenting cell is one of the most
important of these costimulatory pathways. This signal induces T-cell activation, clonal expansion, and inhibits T-cell apoptosis. Activation of the T-cell receptor without costimulation of the CD28 receptor does not induce activation but anergy or cell death.11 Inhibition of the CD28 pathway by blocking the B7 receptor is a possible treatment for autoimmune diseases. However, presence of CD4+ T-cell clones is not associated with a reduced immune response. CD4+ CD28+ cells are rare in normal individuals (usually ~1%), although they tend to increase with advanced age. Higher levels of CD4+CD28+ cells are present in a subset of patients with rheumatoid arthritis,12 in particular in those patients with extra-articular disease or with vasculitis, but not in those with rheumatoid arthritis restricted only to joints.13 CD4+CD28− cells have several peculiar features differentiating them from the classic T helper cells: they do not depend on the B7/CD28 pathway for activation, do not express the CD40 receptor, are incapable of activating B cells, have significant cytolytic activity, and express high levels of IFN-γ (which induces monocyte activation). Thus, presence of a significant amount of CD4+CD28− cells could shift immune response from B-cell activation and production of immunoglobulins toward Th1-cell activation, with production of IFN-γ (which inhibits collagen synthesis by smooth muscle cells) and activate macrophage to release several matrix-degrading proteases.2 The importance of this pathway in the evolution of atherosclerosis is supported by the marked inhibition of atherosclerosis in Apo-E-deficient mice lacking the IFN-γ receptor.14 Interestingly, selective recruitment of Th1 cells into tissues depends on the expression of adhesion molecules, in particular E- and P-selectin15 and, possibly, ICAM-1 and VCAM-1,16 which are also highly expressed in atherosclerotic plaques. Although no study has specifically assessed the presence of CD4+CD28− T cells in atherosclerotic plaques, an immunohistochemical study found that only a very low percentage (~10%) of T cells in human plaques express the CD28 antigen,16 suggesting that many of the CD4+ cells would result in CD28−.

In rheumatoid arthritis, levels of CD4+CD28− are usually stable for years and are not related to waxing and waning of symptoms. Indeed, Liuzzo et al found persistently increased levels of CD4+CD28− and IFN-γ+ T cells even at 2 to 6 months after the end of the unstable phase. It is probable to speculate that increased levels of CD4+CD28− and the long-term shift of immune activation toward a Th1-like response could be present before the onset of unstable angina. This could identify a subgroup of patients with an inflammatory/immunologic response facilitating plaque instability because Th1-like cytokines (IFN-γ) can induce macrophage activation and cytolyis and inhibit collagen synthesis. However, it should be underscored that about one third of the patients with unstable angina had levels of CD28− similar to that of stable patients, and only 9% of all CD4+ lymphocytes were CD28−, a percentage lower than that found in patients with rheumatoid vasculitis. Furthermore, it is not clear whether the long-term increase in CD4+CD28− population is related to the presence of lymphocyte activation during the acute phase of unstable angina.

The presence of systemic immune activation in unstable angina has been assessed by previous clinical studies17–20 that
have focused mainly on markers of T-cell activation, such as soluble IL2 receptor (sIL2R) and presence of activated T cells, expressing both the T-cell–specific surface molecule CD3 and the activation marker HLA-DR (CD3^+DR^+ cells). Although 2 studies found evidence of T-cell activation in patients with unstable angina,18,19 other studies reported negative results.17,20 These contradictory findings may be explained in part by the differences in the inclusion criteria. However, immunologic response is a time-dependent phenomenon not easily assessed by an analysis limited to a single time point. The 2 studies that assessed markers of T-cell activation in a time period compatible with the physiological immunologic response found significant signs of T-cell activation in unstable angina compared with stable angina.18,19

Liuazzo et al found a marked increase of both CD4^+ and CD8^+ lymphocytes producing IFN-γ in the early phase of unstable angina, whereas the percentage of lymphocytes releasing IL2 or IL4 was reduced. During waning of symptoms 2 weeks after discharge, there was a significant shift in the T-cell response, with increased levels of IL4^+ lymphocytes. These findings suggest that resolution of unstable angina may be associated with a shift of immune response from a Th1-like cytolytic response to a Th2 response associated with immunoglobulin production and inhibition of macrophage activation. Indeed, in a previous study an increase of activated T cells (CD3^+DR^+) and IgM in the 2 weeks after discharge was associated with lower levels of C-reactive protein at admission and with an uncomplicated clinical outcome.19 These findings suggest the presence of specific antigenic stimuli in unstable angina. However, these intriguing findings come from 2 very small groups of patients and may be explained in part by several confounding factors. In particular, myocardial revascularization, which presumably was performed in most of these patients, was found to decrease levels of sIL2R in patients with stable angina,21 and it might have similar effects in patients with unstable angina. Lymphocyte activation may be due in part to the release of myocardial antigens during episodes of small myocardial necrosis, common in severe unstable angina.22 Thus, the significance of the transient change of immune markers observed in the subacute phase of unstable angina is unclear; further studies, including a larger number of patients, should address this issue.

The increasing knowledge of the inflammatory and immunological mechanisms of rheumatoid arthritis is leading to the development of new and effective strategies for the treatment of this disease, in particular anti-cytokine strategies, immunological interventions, and modulation of the Th1/Th2 response. The knowledge of the inflammatory and immunological mechanisms of coronary heart disease is still at its beginning and is raising more questions than answers. However, this innovative approach may lead to new discoveries that could improve our understanding of the basic mechanisms of this disease and, possibly, lead to innovative, fascinating strategies for prevention and treatment of atherosclerosis and its complications.

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