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GUEST COMMENTARY

Cellular Immunity in Osteoarthritis: Novel Concepts for an Old Disease

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Osteoarthritis (OA) is the most common chronic joint disease. A vast majority of the elderly have radiographic signs of OA, and the majority of those experience clinical manifestations such as pain, joint destruction, and long-term disability. There is little disagreement that OA is a heterogeneous disease. In some cases, joint trauma can lead to accelerated or premature secondary OA, which may represent a common degenerative pathway. Nevertheless, in other cases, an initiating factor cannot be pinpointed. OA is believed to be a disease of the articular cartilage but the agent(s) or event(s) that triggers and perpetuates the relentless cartilage destruction remains unknown. It is clear now that this constellation of events is not associated with aging, and traumatic, hormonal, environmental, and genetic factors are the obvious culprits in the pathogenesis of OA.

The participation of the immune system and of inflammatory mediators in the pathogenesis of OA has been a subject of debate, which has led even to different names for the disease, like "osteoarthrosis" or "degenerative joint disease." It is known that periods of profound inflammation appear during the course of the disease in many patients and that inflammatory infiltrates can be found in the synovial membrane in OA joints. It is of importance to find out the exact contribution of immune system-mediated damage since this not only would improve our understanding of the disease but might also alter our therapeutic approaches. Current treatment of OA is symptomatic, empiric, unsatisfactory, and totally unable to either halt, delay, or modify the progressively relentless articular destruction that characterizes the course of OA (reviewed in reference 4).

T cells in Ag (or autoAg)-mediated inflammatory disease. T cells recognize antigen (Ag) using variable domains of the clonotypic α/β (or γ/δ) chains, which are part of the specific cell surface Ag receptor (T-cell receptor [TCR]). This recognition leads to activation, proliferation, and secretion of soluble products (e.g., cytokines); expression of novel cell surface markers; acquisition of effector functions; or anergy, tolerance, and apoptosis (32). The presence of specific Ag(s) leads to preferential (clonal) expansion of T cells bearing the relevant clonotypic TCRs. Polyclonal T-cell expansion should indicate either nonspecific or superantigen-mediated processes. On the other hand, while monoclonality is a marker of neoplasia, oligoclonal T-cell expansion is considered to be an indirect indicator of the presence and persistence of specific Ag(s).

The presence of T cells in inflammatory infiltrates raises questions regarding their composition (polyclonal, oligoclonal, or monoclonal) and about the nature of the antigenic stimuli that elicit their expansion and accumulation. The search for specific Ag(s) initiating the inflammatory response is always laborious and frequently frustrating. Therefore, investigators have pursued the characterization of the nature of the accumulated T cells and the molecular identification of the variable TCR domains that recognize and bind the presumptive Ag(s). Furthermore, specific Ags may correlate with discrete patterns of T-helper (TH) cell-derived cytokine responses. The pattern of secreted cytokines determines to an extent the outcome of the immune response. Intracellular pathogens, delayed-type hypersensitivity responses, and effective cell-mediated cytotoxicity are related to the release of interleukin 2 (IL-2) and gamma interferon (IFN-γ) (TH1 pattern). In contrast to these cellular immune responses, the TH2 cytokine pattern is associated with the release of IL-4 and IL-5 encountered in allergic diseases and parasitic infections (22).

Restricted clonal T-cell expansion and an unbalanced TH1/TH2 pattern are being noted in an increasing number of diseases. With the help of modern molecular biology techniques the study of classic inflammatory diseases is now possible. Well-studied examples include the analysis of T-cell repertories in multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and giant cell arteritis (GCA), among others.

Potentially pathogenic T-cell clones have been identified in MS. Different groups have identified oligoclonal T-cell expansion in central nervous system lesions, in peripheral blood, and in the cerebrospinal fluid of MS patients. These T cells bear either α/β or the nonconventional γ/δ clonotypic TCR chains. Different dominant epitopes of the suspected autoAg (myelin basic protein) in MS are identified by T-cell clones in different patients. These antigenic epitopes give rise to a few dominant clones, which persist for a long time in the same patient (1, 33, 34). Human MS and experimental allergic encephalomyelitis, the animal model counterpart of human MS, are characterized by cellular immune abnormalities and TH1 type cytokine production (12).

Restricted repertoires in the use of genes encoding the TCR variable regions have also been reported for patients with SLE. Clonal expansion of the T cells has been found in the peripheral blood of lupus patients, and the TCR δ-chain repertoire is biased (20). T cells bearing either α/β or γ/δ TCRs have been clonally expanded in vitro and have been shown to react preferentially with histone epitopes (24). The properties of these histone-reactive lupus T-cell clones have been well characterized. They represent clones with helper activity despite their phenotype, which commonly does not belong to the classic $CD4^+$ subtype. Moreover, recent studies revealed other inter-

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esting properties of these autoAg-specific clones from patients with SLE. First, the clones recognize their respective histone epitopes in a major histocompatibility complex-unrestricted fashion, and second, they become readily activated without the need for CD4 co-cross-linking (26).

Recent studies on the nature and properties of the infiltrating cells in GCA also yielded valuable information. T cells found in the inflammatory granulomatous lesions of GCA have undergone clonal expansion and secrete a restricted pattern of cytokines consistent with a TH1 profile. Only a few T-cell clones were identified in the lesions, and the T cells that are responsible for the production of cytokines like IFN-γ were even fewer. These studies indicate that a small number of specifically activated T cells represent the pathogenetically relevant cells (16, 17, 31).

In systemic sclerosis the skin-infiltrating γ/δ-bearing T cells display oligoclonal expansion. It is interesting that the same clones have been identified in the peripheral blood and in other organ lesions. The same clones persist in the same patient over long periods of time, but different patients display different T-cell clones, suggesting that even if the suspected autoAg is a single macromolecule, different epitopes are involved in different patients (36).

For patients with RA several studies have shown the presence of oligoclonal T cells in the peripheral blood, rheumatoid nodules, and the synovial membrane in affected joints. These T-cell clones bear either α/β or γ/δ TCRs, and interestingly, the same clones have been identified in the synovial membranes of different affected joints and the peripheral blood of the same patient (9, 11, 14, 19, 21).

Oligoclonal T cells have been found in psoriatic skin lesions (2), in the pancreas in insulin-dependent diabetes patients (35), in the jejunum in celiac disease patients (23), in the peripheral blood of patients with Behcet's disease (3), in labial lacrimal lesions of patients with Sjögren's syndrome (29), and in cells obtained by bronchoalveolar lavage from patients with sarcoidosis (8). Different T-cell clones have been identified in patients with different subtypes of juvenile rheumatoid arthritis (7). Oligoclonality is not a feature of autoimmune diseases only, since it has also been reported for T cells of the peripheral lymphoid organs of patients with human immunodeficiency virus infection (18) as well as in the tumor-infiltrating lymphocytes of patients with bladder, renal-cell, and other malignancies (5, 15, 30).

In the final stages of the so-called collagen diseases nonspecific inflammation is the prevalent feature. Thus, the presence of T cells in such inflammatory infiltrates is no surprise. It is of interest to determine whether these infiltrating T cells are activated and furthermore if they are activated in a specific manner by an identifiable Ag. Specific activation of T cells means TCR-mediated activation and the production of IL-2.

Specifically activated T cells in the synovium in OA. In this issue Sakkas et al. report the presence of specifically activated T cells in the inflammatory infiltrates of synovial membranes obtained from patients with OA (25). The presence of inflammation in some patients with OA is well known, even though it is not generally considered a characteristic feature of the disease. Since this is a chronic form of inflammation, the presence of T cells in such infiltrates is not surprising. Indeed, T-cell aggregates were found in 65% of patients with OA. Other groups have previously reported accumulation of inflammatory cells in synovial tissue derived from patients with OA (6, 10).

Do the OA synovial-tissue-infiltrating cells represent oligoclonally expanded T lymphocytes? It has been reported that a limited number of activated T-cell clones, as detected by Southern blotting, predominate at the site of tissue injury in rheumatoid synovial membranes as well as in synovial tissue form patients with OA (28), suggesting that these disorders may represent two clinical syndromes that share a pathogenic process. It may also be stated that additional genetic or environmental factors may modify this process and direct it towards the OA or RA clinical picture.

Do T cells become activated following their homing at the OA synovial membranes, or do they represent activated cells recruited from the peripheral blood? Sakkas et al. report that the T cells that belong to the aggregates encountered in the synovial membrane in OA patients bear early (CD69), intermediate (CD25 and CD38), and late (CD45RO and HLA class II molecules) cell surface activation markers. The detection of early and late activation molecules on the surface of synovial-membrane T cells indicates that these cells homed inappropriately in the synovial membrane, where they were exposed to locally available and underwent activation. It should be noted that these Ags may represent autoAgs or environmental Ags that are deposited in the synovial tissue.

Are the activated T cells Ag specific or nonspecific? The authors show that in approximately 50% of OA patients synovial-membrane T cells produce IL-2 and IFN-γ but not IL-4, i.e., they show a TH1 pattern. T cells that infiltrate the synovial membranes of patients with RA also produce IL-2 and IFN-γ but not IL-4. It should be noted that other groups have found a mixed, TH1/TH2 pattern (13). While the presence of IL-2 transcripts denotes specific (TCR-mediated) T-cell activation, the presence of IFN-γ may have different implications that are of importance in the pathogenesis of OA. Recently, it was claimed that macrophage activation products (IL-1, tumor necrosis factor alpha), expression of HLA class II molecules on the surface of chondrocytes, and decreased collagen synthesis are factors that contribute to the pathogenesis of OA (4). All these may be attributed to the action of IFN-γ.

This study utilized synovial specimens from patients undergoing joint replacement surgery. Therefore, the specimens did not originate from patients with early joint disease, and the study did not examine synovial T-cell biology at the onset of the disease. At this final stage it is thought that the inflammation encountered in RA patients is not characteristic as in earlier phases of the disease and that at this point the classic inflammatory nature of the disease reverts to a more degenerative pattern. This may be responsible for the surprising similarity of finding for RA and OA infiltrates described in this study. The advanced stage of the disease at the point of study precludes the drawing of conclusions on early pathogenetic events. The nature of the initial insult in OA remains elusive. Nevertheless, the present study offers a new insight into the nature of more advanced disease, which is the problem every rheumatologist faces in everyday clinical practice.

Based on the evidence presented in the above study, in a good proportion of patients with OA a new player is revealed. The presence of T-cell aggregates undergoing in situ activation in a rather specific manner and the preferential production of TH1 cytokines which mediate macrophage activation among other functions support the hypothesis that a cell-mediated specific immune response is occurring in the OA synovium. The potentially antigenic or autoantigenic driving force(s) for this response is totally unknown.

Whatever the responsible Ag may be, therapeutic approaches such as TCR targeting with specific vaccines or anergy-inducing peptides may be at reach for patients with inflammatory OA. The observed TH1/TH2 imbalance should ignite considerations regarding therapeutic cytokine manipulation. Finally, the interesting data of this study put into question the rather dogmatic view that OA is a noninflammatory

disease. As many as 50%, at least, of advanced-OA patients clearly do not conform to this rule.

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