Osteopontin: a bridge between bone and the immune system

Ellen M. Gravallese

Beth Israel Deaconess Medical Center, Harvard Institutes of Medicine, Boston, Massachusetts, USA

The molecular mechanisms underlying the putative role of osteopontin in the chronic inflammatory disease rheumatoid arthritis are unclear. A study in a murine model of arthritis now demonstrates that a specific antibody directed against the exposed osteopontin epitope SLAYGLR (see the related article beginning on page 181) is capable of preventing inflammatory cell infiltration in arthritic joints.


In recent years a number of studies have linked factors involved in inflammation to those critical for bone physiology and remodeling. One well described story is that of the receptor-activator of NF-κB ligand (RANKL)/osteoprotegerin (OPG) system, which plays a role in the interaction between dendritic cells and T cells in the immune system and is the critical regulatory system for bone remodeling under physiologic conditions (1, 2). The RANKL/OPG system is also likely to play an important role in several forms of pathologic bone loss, including that seen in osteoporosis, certain forms of cancer, and inflammatory arthritis (3). There is mounting evidence for the role of another cytokine, osteopontin (OPN, “bone-bridging” protein), also known as early T cell activation gene-1 (Eta-1), in providing a link between the immune system and bone. In this issue of the JCI, Yamamoto et al. (4) provide important new evidence indicating a role for OPN in the pathogenesis of inflammatory arthritis and associated joint destruction.

Osteopontin is a phosphorylated glycoprotein secreted by activated macrophages, leukocytes, and activated T lymphocytes, and present in extracellular fluids, at sites of inflammation, and in the ECM of mineralized tissues (5, 6). This cytokine mediates important cell-matrix and cell-cell interactions. OPN is abundant in bone, where it facilitates the attachment of osteoclasts to the bone matrix via an interaction with cell surface αvβ3 integrin and CD44, the hyaluronic acid receptor (7). OPN−/− mice have a subtle bone phenotype, with delayed and impaired bone resorption (7). In the immune system, OPN plays a role in chemotaxis, leading to the migration of macrophages and dendritic cells to sites of inflammation. Activation of T lymphocytes results in an increase in OPN transcription, hence its alternative designation as Eta-1. Weber et al. have demonstrated that OPN is a T lymphocyte suppressor factor and that it enhances B lymphocyte Ig production and proliferation (8). In addition, OPN is an important cytokine mediates Th1 immunity (9).

OPN interacts with a variety of cell surface receptors, including the αvβ3, αvβ5, αvβ1, αvβ1, αvβ1, and αvβ1 integrins, as well as CD44. Binding of OPN to these cell surface receptors stimulates cell adhesion, migration, and specific signaling functions. The major integrin-binding site in OPN is the arginine-glycine-aspartate (RGD) integrin-binding motif, which is required for the


The Journal of Clinical Investigation | July 2003 | Volume 112 | Number 2

147
adherence of many cell types to OPN. However, other sequences within OPN have also been shown to mediate cell adherence. For example, cleavage of human OPN by thrombin exposes the SVVYGLR sequence (SLAYGLR in the mouse), promoting the adherence of cells expressing α9 and α4 integrins.

**Potential role for OPN in the pathogenesis of inflammatory arthritis**

Several prior studies have suggested an important role for OPN in the pathogenesis of inflammatory arthritis. OPN mRNA and protein have been demonstrated to be expressed in synovial tissues from patients with rheumatoid arthritis (RA), predominately by fibroblastic cells, and at sites of pannus invasion into cartilage (10). In murine collagen-induced arthritis (CIA), OPN was detected in synovial tissues and at sites of osteoclast-mediated bone resorption, where its expression colocalized to sites of αβ3 integrin expression (11). OPN has thus been implicated in the process of joint destruction in arthritis.

In their report in this issue of JCI, Yamamoto et al. (4) studied CIA and an animal model of RA known as collagen antibody–induced arthritis (CAIA). Arthritis was induced by the transfer of anti–type II collagen antibodies in C57BL/6 mice boosted with an intraperitoneal injection of LPS. These authors report that splenic monocytes from arthritic mice expressing α4 and α9 integrins demonstrated enhanced migration toward thrombin-cleaved OPN compared with splenic monocytes from nonarthritic mice. Of note is the fact that the ratio of the thrombin-cleaved form of OPN to noncleaved OPN was previously shown to be significantly increased in the plasma and synovial fluid of patients with RA compared with plasma from healthy controls and from patients with osteoarthritis (11). Furthermore, treatment of mice with an antibody (M5 Ab) directed against the sequence SLAYGLR, exposed by thrombin cleavage of murine OPN, inhibited synovitis and inflammatory cell infiltration into the joints of treated mice compared with those of arthritic control mice (4). M5 Ab treatment also resulted in protection from cartilage destruction in this murine model of RA.

In vitro studies were performed to demonstrate that the M5 Ab blocked the formation of osteoclast-like cells induced from bone marrow–derived precursors by treatment with RANKL and M-CSF. In addition, this antibody blocked the induction of calcium release from bone by parathyroid hormone (PTH) and IL-1α in vitro (4). It has been previously demonstrated that PTH-induced bone resorption is dependent on OPN (12). These results suggest that one role of the M5 Ab in joint protection could be the blockade of osteoclast differentiation and function in vivo. A limitation of this study is that bone destruction was not directly assessed in the in vivo animal studies presented, and tartrate-resistant acid phosphatase–positive osteoclast-like cells were not quantitated in mice with and without M5 Ab treatment. In addition, since M5 Ab treatment inhibits joint inflammation in this animal model, protection from joint destruction may be a secondary phenomenon related to the general decrease in inflammation. Therefore a direct role of OPN in bone erosion in this model could not be determined. Given the important role of OPN in bone remodeling, such studies would be of great interest. Nonetheless, the effects on the clinical and histologic parameters studied provide convincing additional evidence for a role of OPN in arthritic inflammation, and specifically for its role in the recruitment of inflammatory cells to arthritic joints.

**Arthritis in the setting of OPN deficiency**

Based on this information, one might expect that arthritis would be significantly attenuated in mice deficient in OPN. In fact this has been demonstrated in a CAIA model of RA (13) similar to that used in the study presented in this issue of JCI (4). OPN-deficient mice were found to have marked attenuation of joint swelling and articular cartilage destruction compared with arthritic wild-type mice and had no increase in urinary levels of deoxypyridinoline, a marker of bone destruction (13). These data support a role for OPN in both the inflammatory and the joint-destructive processes in arthritis. Interestingly, however, these results were called into question in a recent report in Science (14) in which OPN was deleted by homologous recombination of strain 129–derived cells, and backcrossed into a CIA- and CAIA-susceptible strain for 12 generations. These authors then induced CIA and CAIA in the OPN-deficient mice and in littermates and demonstrated no effect of OPN deficiency in either form of murine arthritis. They concluded that prior observations in OPN-deficient mice showing protection from arthritis may have resulted from the deletion of polymorphic genes linked to OPN from strain 129, rather than from the deletion of OPN itself. These authors provided a list of several other genes within the deleted locus that could be important for arthritis pathogenesis.

The study of Yamamoto et al. (4) certainly adds to our understanding of the mechanisms by which OPN contributes to the pathogenesis of inflammatory arthritis. Given the clear and important role of OPN in inflammatory processes and bone remodeling, it will be of considerable interest to resolve some of the remaining controversies regarding the role of OPN in this disease.

---

Salicylic acid: an old dog, new tricks, and staphylococcal disease

Mathias Herrmann

Department of Bacteriology and Hygiene, Institute of Medical Microbiology and Hygiene, University of Saarland, Homburg/Saar, Germany

Aspirin has been shown to cause a reduction in the virulence of *Staphylococcus aureus*–associated endocarditis. A new study (see the related article beginning on page 222) reveals that salicylic acid, the major metabolite of aspirin, acts at the level of transcription to downregulate the production of fibronectin, fibrinogen, and α-hemolysin — virulence factors necessary for bacterial replication in host tissues and, now, potential therapeutic targets.


While these observations pointed toward complex but, according to their adhesive function, rather propathogenic events at the bacteria-endocardium interface, the role of platelets had to be reevaluated after the discovery that they function as specialized inflammatory cells (21) in response to secretion of antimicrobial peptides. In fact, paradoxically, hyperexpression of α-toxin by *S. aureus* results in diminished virulence in experimental endocarditis, possibly because of the release of platelet microbicidal proteins (22).

The attributed role of platelets in the disease process that results in endovascular infection has prompted a number of researchers to interfere with platelet function for prevention or treatment of endocarditis. Acetylsalicylic acid (ASA, aspirin) has been used in vitro and in a number of experimental models to reduce vegetation sizes and to mitigate the course of disease (23–25). Similar effects have also been observed by Kupferwasser et al. (26). However, when they studied its metabolite, salicylic acid (SAL), in parallel to ASA, they made the interesting observation that pretreatment of bacteria with SAL reduced attachment to the valvular epithelium to an even greater extent than administration of ASA. This observation was accompanied by the in vitro finding that SAL-pretreated *S. aureus* cells bound to

---


