

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Why Does Rheumatoid Arthritis Involve the Joints?

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A long-standing question in rheumatology is why inflammatory arthritides such as rheumatoid arthritis involve the joints. Many studies have addressed this question; a recent article by Lee et al.¹ provides a new answer that is both obvious and intriguing. Rheumatoid arthritis affects the joints because of the essential role of the synovium in regulating inflammation.

The normal synovial membrane is a thin, glistening tissue that lines the diarthrodial joints. Its name (which contains the root “ovum”) derives from its visual similarity to the thin lining under the shell of a chicken egg. The membrane normally consists of a lining layer that is only a few cells thick and a sublining layer that consists of loose connective tissue. The lining layer contains fibroblast-like synoviocytes and macrophages, and it produces extracellular-matrix molecules and synovial fluid.

In rheumatoid arthritis, there is a dramatic increase in the number of cells in the lining layer, and the sublining layer becomes infiltrated with inflammatory cells, including lymphocytes, macrophages, and mast cells.² These cells produce cytokines that, together with locally produced autoantibodies, are thought to drive the chronic inflammatory process. Fibroblast-like synoviocytes contribute to the inflammatory milieu by producing cytokines and other inflammatory mediators, but the relative contributions of the resident synovial cells and the infiltrating inflammatory cells have been controversial. Moreover, the potential role of the synovium in orchestrating the behavior of the inflammatory cells has not been delineated in great detail.

Lee et al. showed that fibroblast-like synoviocytes organize themselves into synovial tissue by means of cell–cell interactions mediated by cadherin-11. In the absence of cadherin-11, the synovium is disorganized and there is muted production of extracellular-matrix molecules (Fig. 1).

Previous studies³ have shown that fibroblast-like synoviocytes can contribute to synovial in-

flammation. For example, mice that are partly deficient in a molecule uniquely expressed in the synovium by fibroblast-like synoviocytes are resistant to collagen-induced arthritis.⁴ Similarly, Lee et al. observed that mice that are deficient in cadherin-11 are resistant to a form of inflammatory arthritis. The model they used involved the transfer of pathogenic antibodies, indicating that an intact synovial-lining layer with functional fibroblast-like synoviocytes is necessary for the effector phase of inflammatory arthritis after immune reactivity has been generated. Although the detailed molecular events that are attenuated by cadherin-11 deficiency in acute and chronic arthritis have yet to be delineated, it is clear that the synovial lining and functional fibroblast-like synoviocytes have a critical role in the course of inflammatory arthritis. Moreover, cadherin-11, which is a cell-surface molecule and therefore relatively accessible to exogenous agents, represents a potential therapeutic target for controlling inflammatory arthritis.

Rheumatoid inflammation causes damage to both articular cartilage and periarticular bone. This damage was previously thought to result, nonspecifically, from chronic inflammation, and it can be ameliorated by some antiinflammatory therapies.⁵ There is, however, a clear indication that damage to bone and cartilage is mediated by distinct physiological pathways. For example, the abundant osteoclasts that are characteristic of rheumatoid inflammation directly damage bone, although they do not appear to affect cartilage.² Several studies³ have suggested that fibroblast-like synoviocytes mediate cartilage damage. The study reported by Lee and colleagues provides support for this hypothesis; cadherin-11 deficiency protected mice from cartilage damage but not from bone erosion, probably because cadherin-11 seems to mediate the migration of fibroblast-like synoviocytes over the articular cartilage and its subsequent damage.

The report by Lee et al. provides a new take on

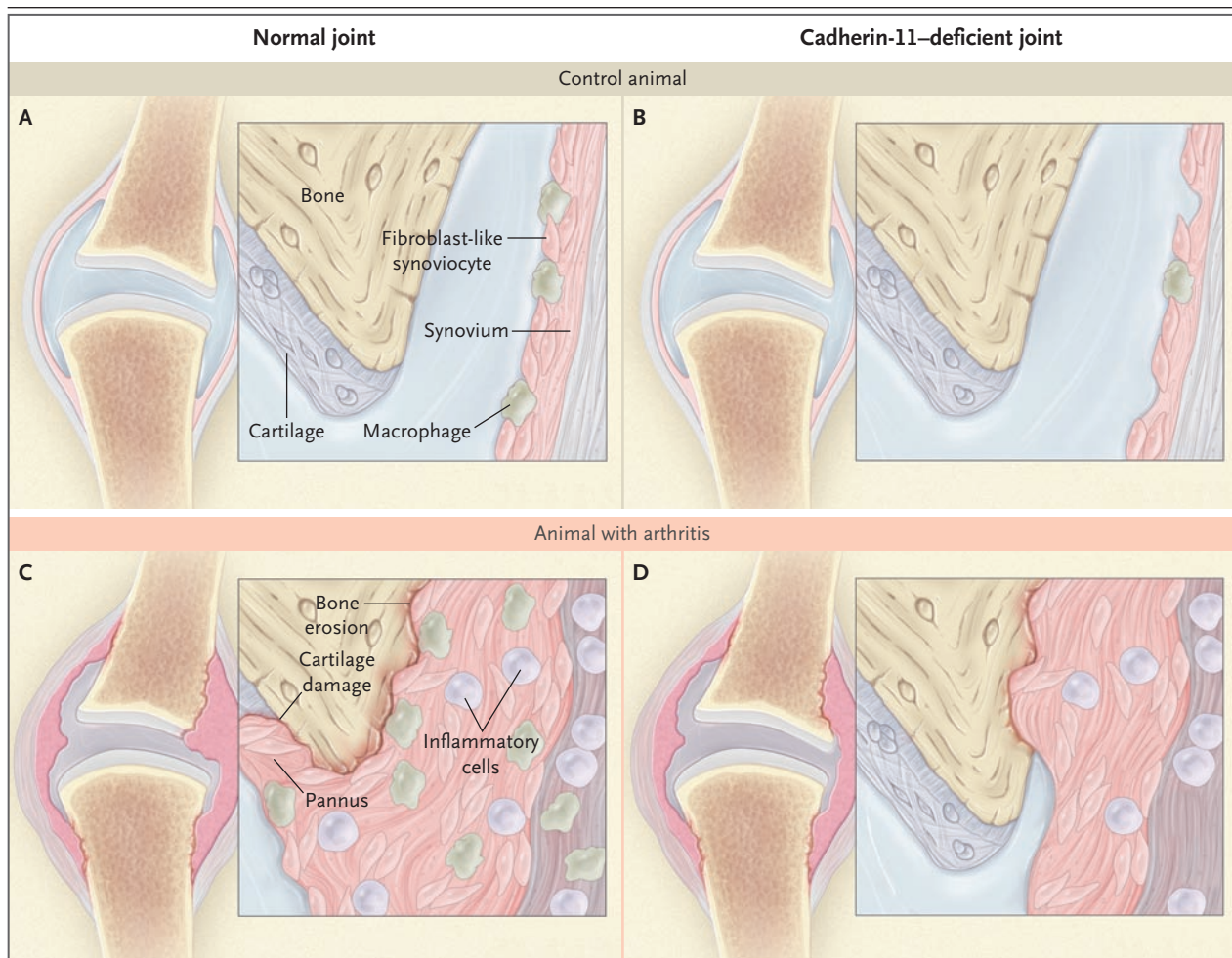


Figure 1. Cadherin-11 and Inflammation.

The normal synovium contains a lining layer that consists of macrophages and fibroblast-like synoviocytes (Panel A). In the absence of cadherin-11, the lining layer is disorganized, and the extracellular matrix is scant and ill-formed (Panel B). Arthritogenic antibodies induce a number of changes in the normal joint, including an increase in the number of cells in the synovial-lining layer, infiltration of the synovium with inflammatory cells, the development of bone erosions, and the establishment of pannus (granulation) tissue that grows over the cartilage and damages it (Panel C). In the absence of cadherin-11, the synovium remains disorganized, pannus tissue does not form, and cartilage damage is prevented, although bone erosions still develop (Panel D).

the synovium. It shows that fibroblast-like synoviocytes mediate both cartilage damage and acute and chronic inflammation. The synovium, therefore, is not an innocent victim of infiltrating inflammatory cells. Rather it is an innkeeper that regulates the entry and behavior of itinerant, potentially troublemaking inflammatory cells as well as its own capacity to damage specific parts of its environment.

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