In this issue of *The Journal*, McKee et al. (1) present evidence that the binding of low molecular weight fragments of hyaluronan (HA) to alveolar macrophages via CD44 elicits the expression of a number of pro-inflammatory chemokines. These observations extend earlier findings reported by this group showing that HA fragments are capable of activating NF-κB (2) and induce the expression of insulin-like growth factor-I by murine macrophages (3). These studies bring together two disparate and previously unconnected observations regarding the expression and biological activity of HA fragments. The first observation is that HA fragments are present at abnormally high levels in the joints of patients with rheumatoid arthritis (RA) and in other inflammatory conditions (4, 5). These HA fragments are thought to arise primarily as a result of activated leukocyte driven extracellular matrix degradation at sites of inflammation and their presence has been proposed as a biological marker of disease. The second observation is that HA fragments but not HA polymers have angiogenic activity, a process which has been proposed to play a key role in the maintenance and progression of RA and other chronic inflammatory diseases (6). The findings by Nobel and his colleagues suggest that the high levels of HA fragments found in inflamed tissues bind to leukocytes and other CD44 expressing cells and trigger a cascade of signaling events which are involved in maintaining and/or amplifying the inflammatory response. It is of interest to note that the biological activities elicited by the HA fragments are distinct from those elicited by the HA polymers. While HA polymers are components of extracellular matrix and a substrate for CD44 mediated cell adhesion, HA fragments are signaling molecules which alert the immune system that significant tissue damage has occurred at a site of inflammation.

The role of CD44 as a hyaluronan receptor (7–9) has been known for many years and is consistent with the hypothesis that CD44 is a cell adhesion molecule (10). In recent years many studies designed to explore the role of CD44 as a cell adhesion receptor have given rise to a large body of data demonstrating that this is a major function of CD44. For example, the results of two recent studies provide evidence that CD44-HA interactions mediate the binding of lymphocytes to cultured endothelial cells (11) and tonsilar stromal cells (12). These findings indicate that CD44 significantly contributes to the recruitment of leukocytes to sites of inflammation and to their migration through lymphatic tissues. However, although it is clear that CD44 functions as a cell adhesion molecule, there is also substantial evidence that CD44 is a potent signaling receptor. Early studies using anti-CD44 mAb to trigger the receptor in lieu of a physiological ligand established that CD44 is a costimulatory molecule on T cells (13–17). It is now known that similar effects can be triggered through CD44 following HA binding (9, 18, 19). The findings reported in this issue of *The Journal* by McKee et al. (1) add to our understanding of CD44 as a signaling receptor and further support the notion that the function of CD44 as a signaling molecule is as important as its function as a cell adhesion receptor (14, 20).

Recently, three groups have reported that anti-CD44 mAb have potent anti-inflammatory activity in vivo. Administration of an anti-CD44 mAb (IM7) was found to prevent cutaneous delayed-type hypersensitivity (DTH) responses (21). This same anti-CD44 mAb was found to prevent the progression of ongoing collagen induced arthritis, blocking leukocyte infiltration and tissue swelling (22, 23). In these two studies the investigators reported that the anti-CD44 mAb mediated the rapid release of CD44 from the surface of CD44 positive leukocytes presumably preventing the CD44-HA mediated recruitment of leukocytes. The findings by McKee et al. (1) and those reported by others on the role of CD44 as a signaling molecule suggest that the potent anti-inflammatory effects resulting from the mAb mediated shedding of CD44 from leukocytes may prevent not only leukocyte recruitment but also prevent their activation. This dual effect might account for the potent anti-inflammatory activity of this anti-CD44 mAb in vivo.

It is not possible to review in this short format the full complexity of the CD44 antigen: its multiple isoforms, its multiple ligands, and its varied and complex biological activities. The report of McKee et al. raises new and interesting questions regarding the function of CD44. For example, are all CD44 isoforms capable of binding HA fragments? Does the interaction between CD44 and HA fragments in other cell types lead to a signaling event? In particular, are the previously reported angiogenic properties of HA fragment mediated by CD44 molecules expressed on vascular endothelial cells? Is the ability of CD44 to bind HA fragments regulated in the same way as the interaction between CD44 and the HA polymer? Clearly, the recent findings by Nobel and his colleagues remind us that much remains to be learned about the function of the CD44 antigen and one of its ligands, HA.

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References


