Editorial

Protease cascades provide an efficient means of rapidly generating large numbers of active effector molecules, which in turn serve a variety of diverse biological functions. The selective advantages of this strategy for extracellular host defense mechanisms is reflected in the successful evolution of the complement and coagulation protease cascades. The latter protease cascade is of ancient origin with primitive elements in lower invertebrates, is an established cascade in higher invertebrates (1), and is found in its fully developed form in vertebrates (2).

In this issue of the *Journal,* Cirino and colleagues (3) provide direct evidence for a new inflammatory effector pathway that could follow from initiation of the coagulation protease cascade on cells in a local tissue site. They demonstrate quite clearly that, upon proteolytic conversion of Factor X from inactive zymogen to the active protease Factor Xa, a distinct inflammatory response is elicited in vivo. This cascade follows from binding of Factor Xa to its cognate receptor, effector protease receptor-1 (EPR-1). Not only is there simple and direct evidence that Factor Xa injected into the footpad of rats rapidly elicits a transient edema, but also that the response can be recapitulated by use of the ligand sequence from Factor Xa, which corresponds to the linker sequence between EGF-1 and EGF-2 domains of the protein, and a sequence that has no perceived propensity to fold into a defined structure that might serve as a ligand structure. The evidence becomes more compelling when supported by neutralization of the inflammatory effect of Factor Xa injection by local administration of a linear peptide constituting at least in part a Factor Xa–binding sequence from the Factor Xa receptor EPR-1. It is difficult to argue with this evidence, that engagement of EPR-1 on some cell in the rat footpad is responsible for direct or indirect elicitation of the local edematous reaction.

The specificity of this particular pathway was evident when it was found that Factor IXa, the homologous protease product of the alternative zymogen substrate for the tissue factor (TF) complex with factor VIIa (TF:VIIa), was without such inflammatory effects. Notably, Factor IXa does not bind to EPR-1. Thus, even though the TF:VIIa complex on a cell surface can generate both Factors Xa and IXa (2), only the former, through binding to the transmembrane cell surface receptor EPR-1, is able to elicit the inflammatory response.

This is but one more example of the induction by extracellular proteases of intracellular signals after occupancy of a specific cellular receptor with or without proteolytic activation of the receptor. The thrombin receptor (4) is a well characterized example of a protease receptor that is activated by the proteolysis of a peptide bond in the receptor with resultant cellular signaling. In contrast, occupancy of the urokinase receptor results in cellular signaling without the requirement of proteolysis by the bound protease ligand (5). A further variation on this theme is found with Factor Xa and EPR-1. Whereas occupancy of EPR-1 is a requisite step, the docked Factor Xa must be proteolytically active to elicit a proliferative response by endothelial and vascular smooth muscle cells (6). The present study supports the notion that occupancy alone can also elicit cellular responses without proteolytic function, since the peptide analogue alone was able to recapitulate the inflammatory response. This explanation would also appear to be the case for anti–EPR-1 signaling of antigen-selective immunosuppression elicited in vivo by administration of a specific monoclonal antibody to EPR-1 (7).

But where does this lead us in understanding the observed edema response? What was the target cell, and how was the response produced in vivo? One is led by preliminary data with pharmacologic inhibitors to implicate the local mast cell. Inhibition of serotonin either by methysergide or by cyprohepadine (which also inhibits histamine), blocks the edema response. Is EPR-1, however, expressed on the mast cell? This and other questions regarding various forms of tissue pathobiology remain to be elucidated. With the current tools, nonetheless, we can anticipate exposition of both the general paradigm and the details upon which ultimate understanding rests.

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