Proteolysis of Pericellular Matrix
A Process Linking Inflammation to Plaque Destabilization and Rupture

Ken A. Lindstedt, Petri T. Kovanen

The two major general cellular concepts in atherogenesis, foam cell formation and growth of smooth muscle cells (SMCs) in the arterial intima, have not been able to satisfactorily explain the evolution of advanced complex atherosclerotic lesions behind acute atherothrombotic events leading to acute coronary syndromes. Rather, in terms of intimal pathophysiology, the two above cellular processes can be considered beneficial and homeostatic, the formation of foam cells resulting in clearance of toxic substances from the tissue, and growth of SMCs strengthening it. The basic pathology behind the acute coronary syndromes, again, relates to rupture of unstable coronary plaques consisting of a large extracellular necrotic lipid and a thin fibrous cap covering it. At the cellular level, a switch from cell growth to cell death, notably to apoptosis, may be involved in transforming a stable plaque into an unstable one. Thus, death of foam cells likely contributes to the formation of the necrotic lipid core, and death of SMCs to cap remodeling with ensuing formation of a thin and vulnerable cap. Stromal cells, such as the intimal SMCs, need an intact matrix environment for normal function and survival. Hence, also the vulnerability of an atherosclerotic plaque may critically depend on the integrity of the peri- and extracellular matrices of the plaque SMCs.1,2 In vitro studies have revealed that plaque-infiltrating inflammatory cells, such as macrophages and mast cells, are capable of secreting a variety of proteolytic enzymes. Some of them can degrade peri- and extracellular matrix components either directly or indirectly by activating local matrix metalloproteinases, and so induce SMC apoptosis.3,4

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Several recent reports have shown that cytolytic T cells, by secreting granule-associated serine proteases, ie, granzymes, can induce apoptosis in target cells, such as the vascular SMCs.5 Among several different granzymes secreted by activated T cells, granzyme B has been the best candidate for the induction of apoptosis.6 The general idea has been that granzyme B can induce apoptosis of cultured SMCs independently of perforin, ie, without entering the target cell. This unexpected observation prompted the authors to search for potential target molecules outside the cell, ie, on the cell surface. Interestingly, they found that, in addition to its previously known intracellular actions, granzyme B can also act extracellularly by directly degrading pericellular components of the target cells, such as fibronectin. By doing so, granzyme B interferes with the formation of focal adhesions necessary for outside-in-mediated cell-survival signaling. Similarly, apoptosis of cultured vascular SMCs due to degradation of pericellular fibronectin and interruption of focal adhesion kinase–mediated outside-in survival signaling was recently observed when the mast cell–derived neutral serine protease chymase was added to the cells.4,8 Physiologically, chymase is exocytosed from activated mast cells as a granular macrocomplex, in which it is bound to heparin proteoglycans. Thus, a strong similarity exists between the exocytotic mechanism by which either activated mast cells or cytotoxic T cells induce fibronectin degradation and SMC apoptosis. Indeed, both mechanisms have been called “granule-mediated pathways.”9,10 However, differences also exist between the two systems. Thus, in contrast to the chymase-generated fibronectin degradation products, which are able to act as disintegrins, the fibronectin fragments produced by granzyme B do not induce SMC apoptosis. Thus, depending on their cleavage specificity, the extent of SMC apoptosis induced by different proteases may vary. Interestingly, granzyme H, another member of the granzyme family secreted by cytotoxic T cells and NK cells,11 has chymase-like proteolytic activities. Thus, this enzyme may generate fibronectin fragments capable of inducing SMC apoptosis by a disintegrin-type mechanism.12 Whether other proteins also necessary for cell adhesion and survival, such as vitronectin and laminin, are potential targets for proteolysis-mediated cell death remains to be shown. The use of protease proteomics may aid in the discovery of protease-sensitive new native substrates present in atherosclerotic plaques. Discoveries of such targets would extend the field of the disintegrin-type mediated SMC apoptosis to include, in addition to the immediate pericellular microenvironment, also the more distant regions in the plaque.

From the Wihuri Research Institute, Helsinki, Finland.

Correspondence to Petri T. Kovanen, Wihuri Research Institute, Kalliolinnantie 4 FI-00140, Helsinki, Finland. E-mail petri.kovanen@wri.fi

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The present and previous work describing protease-induced degradation of a peri- and extracellular matrix component, the fibronectin, followed by target cell apoptosis, offers a novel mechanistic explanation to the pathogenesis of acute coronary syndromes, as well as to other vascular diseases where matrix remodeling is a critical determinant (Figure). Thus, proteolytic degradation of matrix components followed by cell death and plaque rupture forms a new link between inflammation and acute coronary syndromes. However, for a more explicit understanding of the role of neutral proteases released by infiltrating inflammatory cells in the conversion of a clinically silent plaque into a dangerous and potentially killing plaque, animal models of plaque rupture need to be established. It may well be that transient overexpression of a protease, such as granzyme B or chymase, in a senescent atherosclerotic mouse model, such as the LDLR−/− or apoE−/− mouse, would be sufficient to trigger plaque rupture.

References
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