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Digging in the "Soil" of the Aorta to Understand the Growth of Abdominal Aortic Aneurysms

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The central function of the aorta and all muscular arteries is to act as an efficient and durable conduit for pulsatile blood flow. As such, these vessels must preserve a nonthrombogenic lumen free of obstruction and maintain their structural integrity over a lifetime of cyclic hemodynamic stresses. The loss of structural integrity is the fundamental cause of aneurysm formation and ultimate rupture. Histologically, the complete or near-complete loss of intact medial elastic fibers has long been recognized as a distinguishing feature of aneurysms, particularly the relatively common infrarenal abdominal aortic aneurysm (AAA) (Figure 1). Mechanical studies of human tissues have confirmed the critical structural role of the elastic fiber in maintenance of arterial wall integrity.[1,2] Further, animal models of aneurysms have consistently been reproduced with the initiation of inflammatory and enzymatic cascades that result in medial elastic fiber degeneration.[3]

The elastolytic process in aneurysms is associated with several reflexively related features in humans: (1) an increase in expression and/or activity of elastin-degrading matrix metalloproteinases (MMPs): MMP-2,[4] MMP-3,[5,6] MMP-9,[7–9] MMP-7,[10] and MMP-12[11,12]; (2) an increase in tissue macrophages and other inflammatory cells[12,13]; and (3) a decrease in medial vascular smooth muscle cell (SMC) density (Figure 2).[14–16] The prevailing conception of this disease considers that the inflammatory cell infiltrate results directly or indirectly in the elaboration of the metalloproteinases[17] and that these proteases directly degrade elastin. Ultimately, pulsatile stresses are then brought to bear primarily on matrix constituents not designed to withstand this repetitive stress. Furthermore, as the aorta dilates, the distribution of force is altered, localized areas of supraphysiologic levels of wall stress develop,[18,19] and rupture occurs as the result of mechanical disruption of the remaining matrix components.

The vascular SMC must play a critical role in aneurysm pathobiology since it is capable of (1) matrix synthesis, (2) proteinase (and inhibitor) elaboration, and (3) inflammatory cell recruitment. As seen in the simplified schematic of Figure 3, the SMC plays a central role in its interactions (both positive and negative) with matrix-degrading enzymes and medial inflammation. Furthermore, SMCs are the principal cell type involved in the production of the extracellular matrix (ECM) components of the media, particularly elastin and collagen. Given that the most likely therapeutic window for medical therapy of aneurysm disease is after dilatation has been detected, stabilization of the aortic wall is likely to require both enzymatic inhibition and the synthetic, reparative activities of the SMCs producing ECM.

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Differentiation of SMCs in AAA

Diverse Phenotypes of the Vascular SMC

The term *smooth muscle cell* encompasses a rather diverse population of cells that perform a variety of functions within each tissue, including mechanical responses (eg, contraction, migration, and proliferation) and maintenance of the ECM (eg, synthesis of matrix proteins, growth factors, and cytokines). These cells tend to have unique tissue-specific functional phenotypes, such as found in the bladder, the gastrointestinal tract, the small airways of the lung, and vascular tissue. It is also now recognized that even among the vascular SMC population, there is no homogeneous phenotype.[20–30] These cells appear to undergo differentiation relative to their location in the vascular tree and their embryologic origin.

The relative differentiation of vascular SMCs may be critical to the health and stability of the matrix of a blood vessel for several reasons. First, the cells are, by far, the majority cell type present within the normal vessel wall, and they perform important mechanical functions integrated with the matrix. Second, these cells are responsible for the production of the structural proteins of the ECM. Third, these cells are capable of releasing cytokines and chemokines, which can result in the recruitment of the other cell types to the vascular wall. Fourth, these cells are capable of migration and the expression of matrix-degrading enzymes. Each of these functions will require the regulation of expression of a distinct set of genes unique to each process.

It is well recognized that SMCs retain significant plasticity with regard to their expression profiles, which may allow them to modulate gene expression to participate in this myriad of functions. In particular, the phenotype of these cells in vivo and in vitro appears to be significantly affected by local environmental conditions. In tissue culture, vascular SMCs have been found to alter their phenotype significantly based on culture conditions. Generically, there have been two in vitro phenotypes referred to as the “contractile” and “synthetic” phenotypes with different expression and activity profiles, and in certain circumstances, particular SMC clones can undergo reversible conversion between these two phenotypes.[31]

There are limits to phenotypic modulation for specific SMCs, however, which are dictated by the differentiation state of the cell. Thus, under identical culture conditions, SMCs from different vascular mural compartments are found to have unique phenotypes and can be distinguished in culture. Frid and colleagues established that there is heterogeneity of cultured SMC phenotype even within a single segment of bovine pulmonary arterial media.[30] This evidence for local heterogeneity of cultured SMCs was recently extended to the internal thoracic artery in humans.[32] This suggests an important level of specialization of the medial SMC for particular tasks of vascular maintenance.

The understanding of SMC differentiation and its role in vascular pathology has been advanced primarily through the study of atherosclerosis. Atherosclerotic plaque has long been recognized to be a pathologic process that involves SMCs that populate the lesion and produce ECM and metalloproteinases. In atherosclerosis research, it has become clear that the SMCs that populate an intimal plaque consist primarily of a monoclonal or oligoclonal population of cells.[33–36] Moreover, these cells derived from atherosclerotic plaque are now known to have a unique phenotype compared with SMCs obtained from arterial media.[37,38] It is believed that the unique phenotype of these cells is critical for the development of atherosclerotic disease in humans.[35]

Unresolved Pathobiology: Role of the SMC in AAA

The predominant paradigm of aneurysm pathobiology describes the medial degeneration as developing secondary to an imbalance between proteolytic and matrix synthetic activities.

Obviously, the imbalance is weighted in favor of the proteolytic activity, with metalloproteinases appearing to be the most significant participating enzyme family. Within this context, SMCs, as a class, could participate on either side of the balance, either accentuating the matrix-degrading or the matrix-synthesizing/antiprotease roles. Therefore, the SMCs in AAA must be participating in the process of matrix degradation either through enhancement of the matrix proteolysis or through insufficient matrix repair or protection.

Despite their central role, study of the activity of the SMC in human aortic aneurysm tissue has been relatively superficial. Most of the human studies of SMC in aneurysm disease describe a decrease in the concentration of the cells within the media, evidence of SMC apoptosis, and poor in vitro propagation of SMC lines derived from aneurysmal tissue.[16,39–41] It has therefore been hypothesized that the matrix destruction seen in AAA in part results from a reduction in the quantity or activity of SMCs.[14–16,39,40] The implication here is that given adequate numbers or activity levels, the medial SMCs of the aorta are capable of mitigating the proteolytic injury either through the matrix-synthesizing capabilities of the SMC or enzymatic inhibition. Supporting this concept is evidence that SMC seeding can prevent AAA in a decellularized xenograft transplantation model of aneurysms.[42–44]

Alternatively, there is a body of evidence that directly implicates the SMC in the matrix destructive process of aneurysms. The ability of SMCs to degrade medial matrix has been well described in relation to migration of SMCs.[45,46] Furthermore, there is important evidence that protease expression by SMCs is critical to aneurysm development in humans and in certain models of aneurysmal degeneration.[47–51]

Thus, there is contradictory information on the function of these cells in the complex environment of the aneurysmal aortic wall. Ultimately, the true role of the medial SMC in human aneurysm development remains unknown. Deciphering the activities of these cells with respect to the medial ECM changes seen in aneurysms has great potential for assisting in devising therapies and improving our animal models of aneurysm disease. Fortunately, extensive studies of SMCs in the pathobiology of atherosclerotic disease can offer some important insights and techniques to understand the role of these cells in AAA.

SMC Differentiation in AAA

As shown in Figure 4, the prevalence of a differentiated phenotype of SMCs that predominantly express proteins associated with matrix degradation could result in a medial environment that results in elastin fiber degradation typical of aneurysms. Given the central role of the SMC in maintenance of the medial ECM of the aorta, understanding the phenotype of the resident SMC may be a critical link in our understanding of aneurysm pathobiology. There is evidence that SMCs derived from the wall of an AAA may be unique compared with cells from a nonaneurysmal artery, as suggested by the in vitro growth characteristics[16,39–41] and tissue studies of SMCs in aneurysms.[48] In studies performed over 10 years ago, SMCs explanted from aneurysms and normal aortas were compared under interleukin-1β (IL-1β) stimulation.[52] These studies examined a limited set of metalloproteinases and inhibitors with Western blotting but did identify unique responses of the aneurysm cells to cytokine stimulation.[52] However, there has been no ongoing systematic attempt to define this population of SMCs.

Postulating a unique phenotype for SMCs populating aneurysmal segments of the arterial tree begs the question of the origins of the diversity of these cells. Unlike the endothelial cells that appear to derive from primary endothelial or endodermal tubes, in the embryo, SMCs seem to arise locally from the surrounding mesenchyme[53,54] or from the neural crest.[55] It has also been reported that certain situations can result in endothelial cells delaminating, migrating, and transdifferentiating into SMCs.[56] Finally, SMCs populating intimal plaque can derive from circulating bone marrow–derived stem cells,[57–59] although this has been specifically disputed.

[60] Any or all of these may have an impact on the development of unique populations of SMCs in aneurysms.

The embryologic origins of the SMC during development may be particularly useful in explaining localized differences in arterial pathology. For example, mesenchyme of the head and neck derives from ectoderm, whereas mesenchyme of the lower body derives from mesoderm.[61] Differences in aortic SMCs persist and can be identified topographically even in young adults without significant aortic disease.[62]

In the context of aneurysm disease, it is remarkable that the vast majority of arterial aneurysms occur in an anatomically defined segment, including the distal aorta, common iliac, and internal iliac arteries. The predisposition of aneurysms for this portion of the aorta has been explained in many different ways, including blood flow and wall stress dynamics, as well as differences in medial structure.[63–66] However, these explanations do not generally allow for an understanding of the development of aneurysms in the adjacent iliac system. On the other hand, differential SMC ontogeny related to the local properties of the mesenchyme could result in a regional predominance of cells with a differentiation bias toward matrix degradation. Given the anatomic continuity of the most affected segments of the vascular tree, this might reasonably account for the localized anatomic distribution of aneurysm disease. The localized differences in matrix of the infrarenal aorta could be accounted for by uniquely differentiated SMCs as well.[64] Furthermore, clonal expansion of pathologic SMCs has not been demonstrated in animals,[36,53,67] which may relate to the absence of spontaneous aneurysmal disease in animals.

Elastolysis and SMCs in AAA

As noted above, an SMC population within the media of the wall of an aneurysm may have a phenotype that promotes matrix degeneration. One means by which a unique population of SMCs in AAA may impact the course of the disease is through production of active metalloelastases. Alternatively, SMCs may participate in matrix degeneration through an inability to produce appropriate antiproteases. Several lines of evidence suggest that SMCs may play an integral role in the MMP-mediated characteristic degradation of elastin in AAA.

Metalloelastases in AAA

Although a complete review of MMP activities in AAA is beyond the scope of this monograph, briefly, both constitutive and inducible production of elastolytic enzymes MMP-2, MMP-9, MMP-7, and MMP-12 can be identified within human AAA tissues. Davis and colleagues showed that large amounts of MMP-2 are bound to the ECM.[68] A large portion of this matrix-bound MMP-2 is found in the activated form, suggesting that MMP-2 is activated in AAAs and tightly sequestered within the extracellular space. MMP-9 has attracted particular interest because it is abundantly produced by human AAA tissues in vitro.[69] Elevated amounts of enzymatically active MMP-12 are also produced in human AAA tissue.[12] Importantly, MMP-12 is prominently localized to residual elastin fiber fragments within aneurysm tissue by immunohistochemistry, a pattern distinct from other elastolytic MMPs. Stromelysin has been detected in human AAAs by immunoblotting and messenger ribonucleic acid analysis,[9,70–72] but its role in aneurysm development remains unclear. Stromelysin may play a significant role, however, by activating the proenzyme form of other MMPs, particularly MMP-9.[73]

The regulation of MMP activities is critical to prevent widespread tissue destruction, both in normal tissues undergoing remodeling and in disease.[74–76] MMPs are thereby controlled at several levels, including the induction and suppression of MMP gene transcription, extracellular activation, and interaction with natural inhibitors. MMPs are secreted as

zymogens (pro-MMPs) and are maintained in an inactive state by the presence of the amino-terminal propeptide domain. Enzymatic cleavage of the propeptide is the most likely mechanism of MMP activation in vivo, indicating that extracellular processing of pro-MMPs is required, with few exceptions, to achieve full catalytic activity.[77] Proteases known to be effective activators of one or more elastolytic MMPs include plasmin,[78,79] trypsin,[80,81] chymase,[82] active MMPs,[48] and others. Several lines of evidence suggest that these MMP activators are present in significantly elevated quantities in aneurysm tissue, particularly the plasminogen activators urokinase (uPA) and tissue plasminogen activator (tPA).[83,84] Evidence exists to suggest that increases in expression of the fibrinolytic proteins are important for the progression of small aortic aneurysms.[85,86] Furthermore, in multiple models, plasminogen activators appear to play a crucial role in the development of experimental aneurysms.[87–89]

SMC and MMP Expression

Proteolytic enzyme secretion in SMCs is a well-recognized capability. Unstimulated SMCs produce MMP-2 both in vivo and in vitro,[90,91] whereas MMP-3, MMP-7, MMP-9, and MMP-12 are expressed in vivo in vessel walls associated with inflammation, shear stress, or injury.[92–96] In cell culture, SMCs can be induced to express the elastolytic MMPs 3, 9, and 12, under specific cytokine or other receptor stimulation.[90,91,97–100] Expression of MMP-7, however, has not been demonstrated from human vascular SMCs in culture. As noted, MMP-2 is expressed constitutively by SMCs, although augmented expression can be stimulated by platelet-derived growth factor (PDGF).[101] Although MMP-12 is not expressed constitutively by SMCs, its expression can also be stimulated by PDGF through an AP-1-dependent mechanism.[98] Expression and synthesis of both MMP-9 and MMP-3 in SMCs are induced by IL-1β and tumor necrosis factor α[90] through nuclear factor (NF)-κB.[102,103] All of these cytokines have been found to be upregulated in human aneurysm tissue and thus may have a role in stimulating SMCs in vivo.[104,105]

In addition to producing these potentially elastolytic metalloproteases, SMCs are also capable of producing the enzymes that can activate them as well. Vascular SMCs may effect activation of MMPs produced through the expression and activity of plasminogen activators, uPA and tPA, or a membrane-bound metalloproteinase, MT1-MMP.[11,47,106–108]

Protease Expression in Aneurysm-Derived SMCs

As noted above, the role of the SMC as it relates to the degradation of medial elastin in aneurysms is vaguely understood, and contrary hypotheses exist in regard to their participation in aneurysm genesis. Yet there are data to suggest that SMCs in patients with aneurysms are unique and, moreover, are associated with alterations in protease or inhibitor expression. In an early study by Keen and colleagues, SMCs grown in explant culture from the aortas of patients with aneurysms and from the aortas of elderly individuals donating organs demonstrated differential expression of tissue inhibitor of metalloproteinase 1 (TIMP-1) in response to IL-1β stimulation.[52] In fact, it was found that SMCs from AAA had a significant increase in TIMP-1 production, whereas no effect was seen in cells from normal aortas, which has been confirmed by others.[90] Although this may suggest an antiproteolytic bias of these cells, expression of TIMP-1 and certain MMPs are known to be coordinately regulated through NF-κB and AP-1 transcription factors, thus suggesting that there may have been significant increases in elastolytic MMPs that were not recognized.[109,110]

In a study by the same group the following year, evidence supporting this later interpretation was presented.[111] It was found that unstimulated SMCs derived from AAA were found to produce detectable amounts of uPA, whereas control SMCs did not express uPA. There was also significantly more tPA produced by the aneurysm-derived SMCs than the SMCs from normal aortic tissue.[111] Although not evaluated in this study, this may have increased the

activity of the MMPs secreted from these same cells. This suggests that SMCs from aneurysms may actively participate in the production of a proproteolytic environment in the aortic media.

Further support of the unique properties of SMCs from AAA comes from a more recent study by Goodall and colleagues.[49] In these experiments, migration through a Matrigel layer was compared between SMCs derived from patients with AAA and normal controls. The SMCs from aneurysm patients showed significantly increased invasiveness under PDGF stimulation. This effect was associated with increased MMP-2 production compared with the normal controls. These enhanced responses to inflammatory stimuli may be an important feature of the SMCs in AAA as even crude extracts of aneurysm tissue demonstrate high levels of chemotactic and proinflammatory molecules.[104,105,112]

Summary

As described by Schwartz and colleagues over 10 years ago, the unique properties of the "soil" (the cellular responses) of the intima provide for the development of intimal arterial diseases.[53] Now a significant amount of evidence points to the likelihood that the SMCs that populate the media of aneurysms are unique and that they directly or indirectly participate in the medial elastin degeneration characteristic of AAA. Because maintenance of a functional aortic matrix depends on the SMC, restoration of the normal activities of these cells may be essential to stabilize and potentially repair the damage that is associated with aneurysmal degeneration. Evidence for this effect can be seen in recent studies in murine models with both repopulation of the aorta with normal SMCs[113] and alteration of SMC activities by modifying intracellular inflammatory response pathways.[114] Finally, identification of SMC differentiation profiles associated with aneurysms may provide the unique ability to identify those individuals with an increased propensity for aneurysm development prior to the phenotypic expression of the disease.

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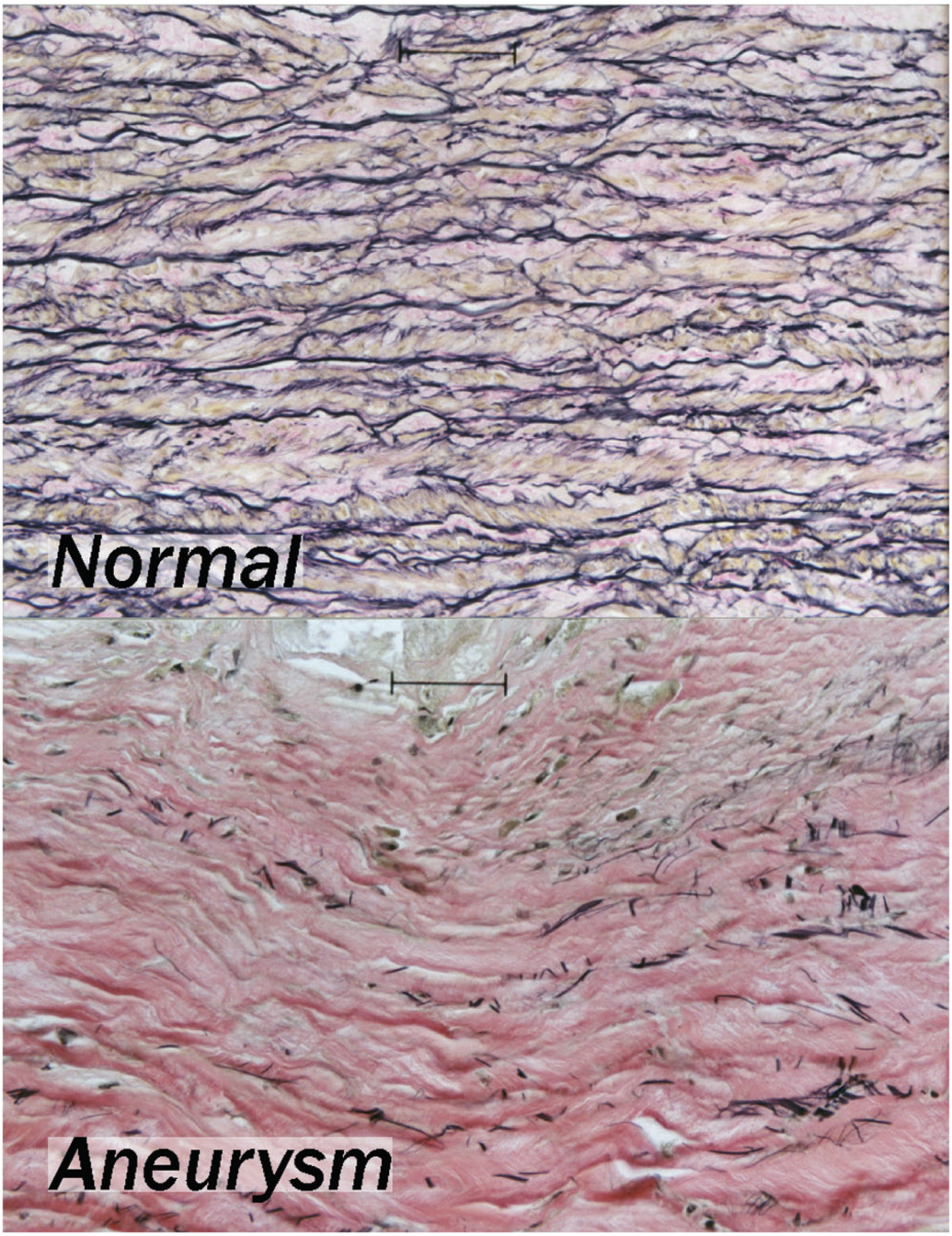

Figure 1.
Elastin-specific stain in normal and aneurysmal aorta. Note elastic fiber destruction in the aneurysm despite minimal local inflammation.

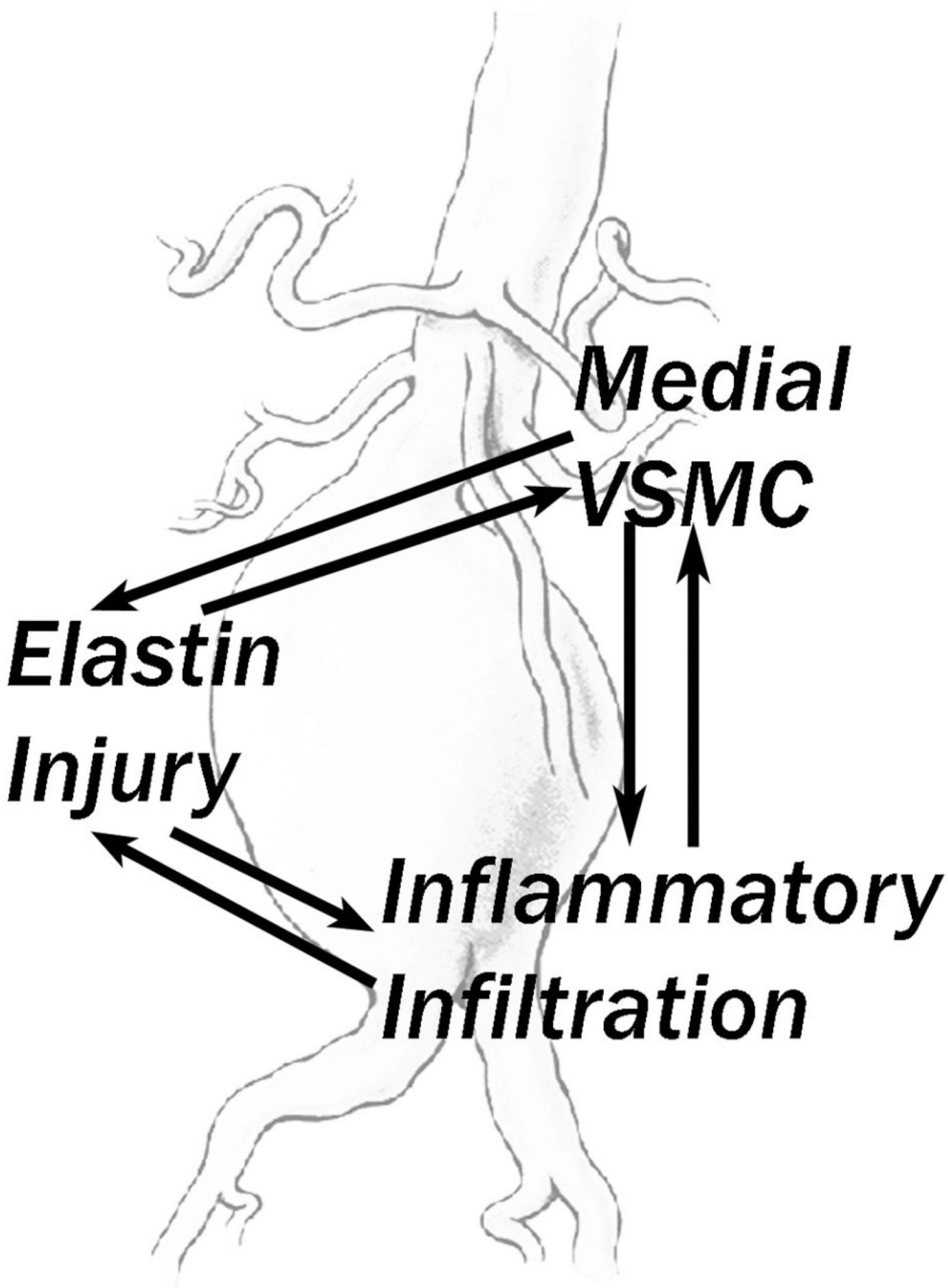

Figure 2.
Diagrammatic representation of the reflexive relationships that exist between the elastin matrix destruction (mediated by specific enzymes), loss of normal smooth muscle cell function and number, and inflammatory infiltration found in aortic aneurysmal disease. Each of those invariate findings of aneurysmal tissue can induce or increase the other findings, resulting in a destructive cycle leading to aortic wall failure. VSMC = vascular smooth muscle cell.

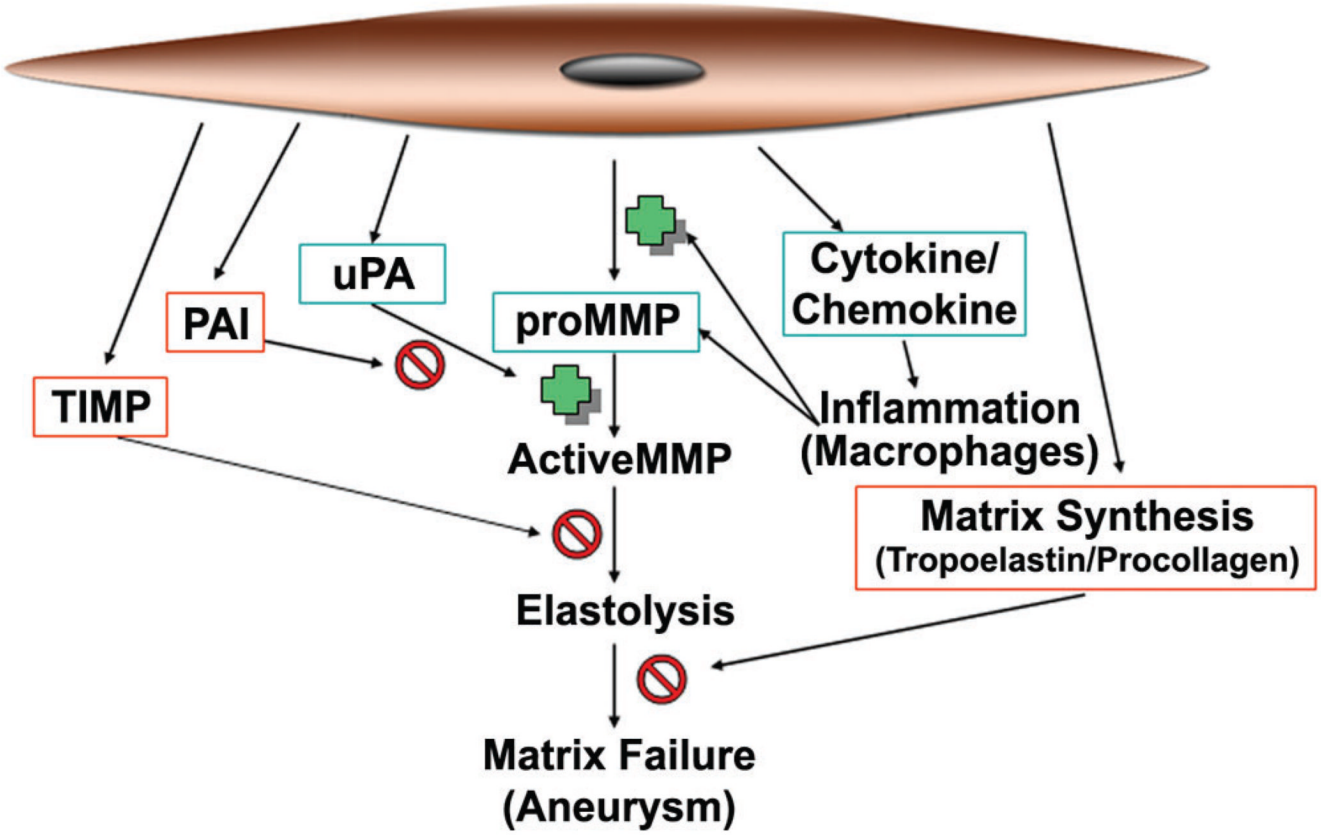

Figure 3.
Vascular smooth muscle cell products involved in matrix metalloproteinase (MMP)-mediated matrix injury in aneurysms. Products that may promote matrix injury are in *green*, and products that may reduce limit or repair matrix injury are in *red*. PAI = plasminogen activator inhibitor; TIMP = tissue inhibitor of metalloproteinase; uPA = urokinase.

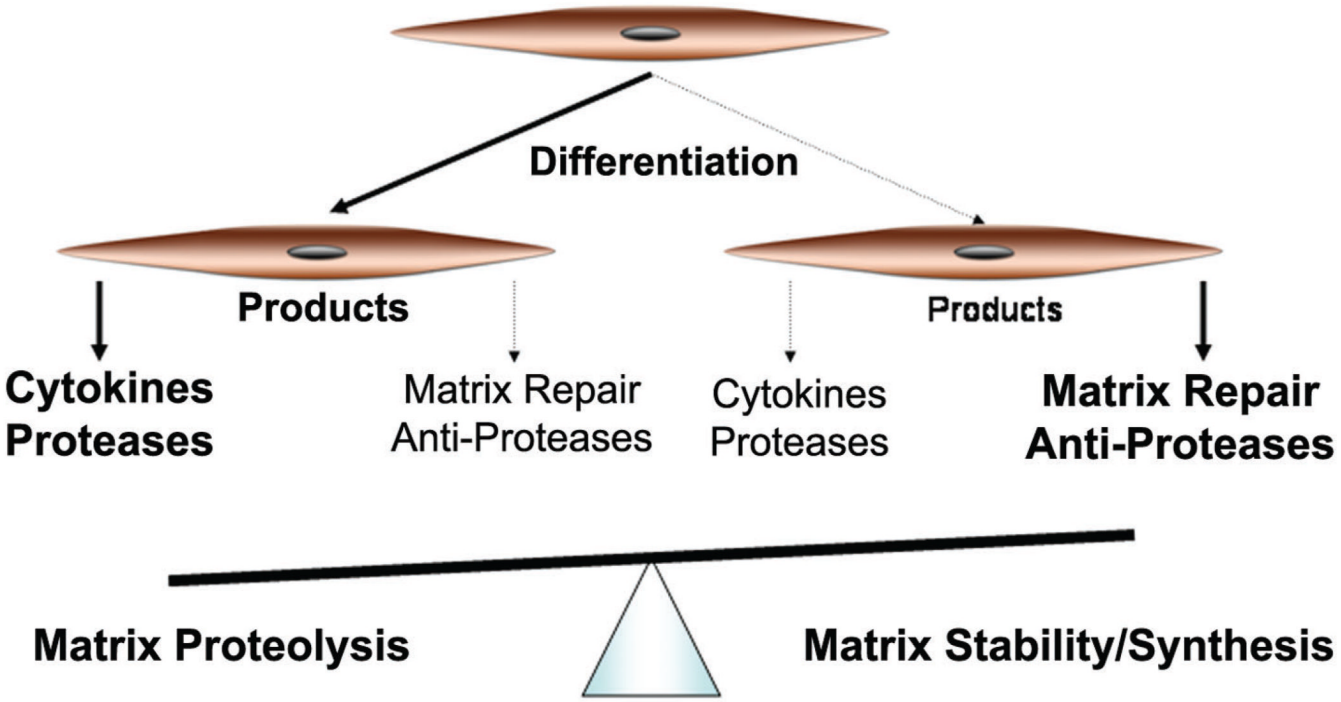

Figure 4.

In this simplified schematic, unbalanced differentiation of SMC could result in a predominance of cells that have a tendency to express proinflammatory and matrix-degrading products. These cells would feed into the cycle of aneurysmal degeneration once it is initiated by a secondary injury. A more balanced phenotype of SMC could express products that predominantly act to put a brake on the cycle and prevent inappropriate matrix damage.