AIF-1 in the Activated Smooth Muscle Cell
Spectator or Participant?

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In response to an environmental stimulus, a subset of smooth muscle cells (SMCs) within the vessel wall is induced to increase expression of multiple genes (SMC activation). Balloon injury, for example, initiates a cascade of repair mechanisms that result in migration and proliferation of SMCs, forming a neointima. SMC activation likely contributes to the vascular remodeling associated with hypertension, atherosclerosis, and restenosis after balloon angioplasty. Cytokines and growth factors are among the signals to activate induction of genes in otherwise-quiescent SMCs. Recent advances in vascular biology have identified the molecular signals that mediate these processes, the cytokine-responsive genes that characterize the activated SMCs, and the pathophysiological importance of their gene products.

One of the first genes expressed in response to vascular injury is the immediate-early gene (egr-1), which activates expression of multiple transcription factor genes. This cascade may be responsible for induction of the response to injury, including SMC proliferation.1 The expression of a substantial number of genes has been proposed to differentiate intimal SMCs from medial SMCs.2 In addition to activation of transcription and translation factors, there is increased expression of genes for receptors, growth factors, cytokines, adhesion molecules, extracellular matrix, and proapoptotic mediators3–10 in the activated SMCs.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Autieri and colleagues13 report that SMC expression of allograft inflammatory factor-1 (AIF-1) is also increased in response to vascular injury. AIF-1 was first identified by Utans et al13 as a novel myeloid factor in rats, selectively expressed by inflammatory cells, and inducible by interferon-γ. Translation of the open reading frame predicted a protein of 147 amino acids with a hydrophilicity plot consistent with membrane-spanning proteins and a single EF-hand domain suggesting potential involvement as a calcium-binding protein. However, the function of AIF-1 was not known.

The human isoform of AIF-1 was described by Autieri et al14 and compared with rat AIF-1; it is 4 amino acids shorter, with an 83% amino acid sequence homology. Similar to the situation in the rat, expression of AIF-1 was greatest in human lymphoid tissue; however, unlike rat AIF-1, human AIF-1 was also expressed in vascular SMCs. Expression of AIF-1 in human SMCs was also cytokine responsive, suggesting a potential role of this gene in SMC activation.

Autieri and coworkers12 describe AIF-1 expression in 2 distinct models of arterial injury: mechanical injury (balloon angioplasty) and immunological injury (cardiac allograft). Although AIF-1 is not found in normal swine coronary arteries, mRNA expression of AIF-1 is detectable within 24 hours after balloon injury. AIF-1 expression is transient, with protein levels peaking at 3 to 7 days and declining by 14 days postinjury. A similar transient increase in AIF-1 expression is found in SMCs of aortas isolated from rat cardiac allografts. Similarities in the kinetics of AIF-1 expression in these 2 models of vascular injury suggest conservation of the mechanism mediating the SMC response to injury.

Although the function of AIF-1 in vascular injury is not known, the authors have shown that transfection of cultured human SMCs with AIF-1 increased proliferation. Also, within 3 days of balloon angioplasty, there was evidence of SMC proliferation into the neointima. Although these observations support a role of AIF-1 in SMC mitogenesis, several observations argue against AIF-1 as an inducer of proliferation. First, after vascular injury, AIF-1 expression is increased in SMCs throughout the medial layer of the vascular wall and is not restricted to cells in the neointima. Second, although AIF-1 expression quickly returns to normal in the allograft model, it is not until days 30 to 75 that SMCs typically appear in the neointima.15 Third, as demonstrated by Autieri et al, nonproliferative cytokines are also capable of stimulating AIF-1 expression. These observations suggest that although expression of AIF-1 may be sufficient to induce SMC proliferation in vitro, its expression in vivo is likely a marker of SMC activation, rather than an inducer of proliferation. Because transduction of AIF-1 increased proliferation of cells maintained in media containing serum, AIF-1 function may involve modulation of growth factor effects.

In contrast to its expression in SMCs, in an earlier study of cardiac allografts, expression of AIF-1 was confined to inflammatory cells and did not peak until 28 days before...
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increased throughout medial SMCs before localizing to the luminal surface in the neointima. Like AIF-1, after vascular injury remained high in medial SMCs, it localized to the occurred in medial and neointimal SMCs, and although expres-

product. Early after balloon injury, AIF-1 expression oc-

ticed. The absence of expression in myocytes after cardiac allograft implies that AIF-1 is not ubiquitously upregulated in all cells as a response to inflammation.

Detecting differences in the expression of genes between activated and quiescent SMCs is easier than establishing their physiological role. Given the myriad substances whose expression is altered after vascular injury, can each be expected to have a direct physiological role in the response to injury? Or does the overexpression of some genes represent nonspecific upregulation of factors that have no role in the SMC response to injury? How are the functions of these molecules orchestrated to produce both the good and the bad consequences of the vascular response? It is likely that the induction of some genes in the SMCs reflects dysregulated activation, similar to neoplastic growth.

The pattern of expression of the gene products of activated SMCs may provide important clues to the function of the product. Early after balloon injury, AIF-1 expression occurred in medial and neointimal SMCs, and although expression remained high in medial SMCs, it localized to the luminal surface in the neointima. Like AIF-1, after vascular injury inducible nitric oxide synthase (iNOS) expression was increased throughout medial SMCs before localizing to the luminal neointimal cells. Because NO inhibits platelet function and induces vasorelaxation, these findings suggest a potential role of iNOS in the protection of the vessel from thrombosis and vasospasm. Future studies into the direct effects of AIF-1 on vascular function may help to define the role of this protein in vascular injury.

Another important clue as to the function of AIF-1 in vascular injury is to understand the stimulus for its induction. A number of soluble factors can induce activation of SMCs, including products of the renin-angiotensin19,20 and kallikrein-kinin systems,21 oxidized cholesterol,22 arachidonic acid,23 cytokines,24 and growth factors. It is not clear whether the genes overexpressed in response to these diverse stimuli represent a specific and differentiated response or generalized activation. The potential for stimulant-specific gene expression is supported by the observation that by Autieri and colleagues that expression of AIF-1 did not increase identically in response to different cytokines. These differences may be related to differences in the molecular mechanisms of activation, suggesting that the specific stimulus may determine the fate of the SMCs. For example, the balance in activation of the mitogen-activated protein kinase cascades, which relay extracellular stimuli to the transcriptional machinery in the nucleus by their ability to regulate the activity of transcription factors, will likely determine whether an activated SMC will undergo proliferation or apoptosis.25

Substances such as AIF-1, in addition to the myriad other recently described factors, may have an important functional role (good or bad) or have no functional role in the response of the blood vessel to injury. It can be difficult to satisfy Koch’s postulates in complex biological systems, especially if there is redundancy of mechanisms. It may also be difficult to make sense of a biological system that is responding to conditions of disease for which it has not had benefit of evolutionary adaptation. The challenge will be to identify critical molecules as potential therapeutic targets that can tame the activated SMCs.

References


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