Integrin α7β1 COMPels Smooth Muscle Cells to Maintain Their Quiescence

Elaine W. Raines, Karin E. Bornfeldt

Arterial smooth muscle cells (SMCs) normally reside in the arterial wall in a differentiated contractile state. Following injury, such as that caused by angioplasty or stenting, or in more chronic conditions, such as atherosclerosis, some SMCs in the arterial wall convert to a less differentiated state, often termed dedifferentiated, synthetic, or proliferative state.1 These dedifferentiated or synthetic SMCs gain the ability to respond to growth factors, and to migrate and proliferate. At the same time, they lose several cytoskeletal markers of differentiation and most likely their ability to respond to contractile stimuli and to contribute to vessel contraction. It has long been known that there is an inverse correlation between SMC proliferation and their expression of cytoskeletal markers of differentiation.2 Understanding of the factors regulating SMC differentiation is important, because maintaining SMC differentiation in conditions normally associated with increased SMC dedifferentiation would presumably prevent restenosis following angioplasty and development of irreversible atherosclerotic lesions characterized by SMC proliferation and migration.

What are the extracellular cues that determine the differentiation state of SMCs? It has been known for decades that the extracellular matrix (ECM) surrounding SMCs is an important factor, and perhaps the principal factor, for maintaining SMCs in a differentiated state. Thus, SMCs isolated from the arterial wall and plated onto laminin or type IV collagen retain their differentiated phenotype to a greater extent than do SMCs plated onto fibronectin or monomeric type I collagen.3–4 Interestingly, the ECM surrounding the SMC not only regulates the differentiation state of the SMC but also determines whether the cell is able to respond to the action of growth factors, such as platelet-derived growth factor (PDGF). In addition, the 3D structure of the ECM is known to be of major importance in regulating SMC responsiveness to growth factors and their proliferative capacity. For example, monomeric type I collagen supports SMC proliferation and PDGF mitogenic signaling, whereas the same collagen in a fibrillar state efficiently prevents PDGF signaling and subsequent proliferation.5 The ECM of the arterial wall is dramatically altered following angioplasty and in atherosclerosis, and it has been hypothesized that changes in ECM precede dedifferentiation and proliferation and migration of SMCs.6

The study by Wang et al, published in this issue of Circulation Research, now adds another ECM protein, cartilage oligomeric matrix protein (COMP) (also known as thrombospondin 5) to the group of ECM components that regulates SMC differentiation state.7 COMP is a pentameric glycoprotein expressed at high levels in cartilage but also in other tissues. Wang et al demonstrate that COMP levels are reduced following balloon injury of rat carotid arteries and by PDGF stimulation of SMCs in culture, concomitant with decreased expression of the SMC differentiation markers smooth muscle α-actin, SM22α, and calponin.7 Furthermore, reduction in endogenous COMP expression by small interfering RNA resulted in reduced expression of the above SMC differentiation markers, suggesting that SMC binding to COMP favors maintenance of a differentiated phenotype. Reciprocally, overexpression of COMP promoted a differentiated and contractile phenotype of isolated SMCs and inhibited PDGF-induced signaling. This group showed last year that forced overexpression of COMP suppressed neointima formation after arterial injury.8 In the present study,7 this observation has been extended to demonstrate that overexpression of COMP prevents downregulation of calponin and SM22α in the rat carotid balloon injury model and that it also increases arterial contraction in response to phenylephrine.

The ECM controls SMC phenotype through a large number of integrins and other adhesion molecules. ECM proteins that help maintain SMCs in a differentiated phenotype, such as fibrillar type I collagen and type IV collagen, are expressed in normal uninjured blood vessels, as are their integrins/receptors (Figure). Integrin αβ1 also appears to belong to the group of integrins that maintains SMC differentiation,8 but the ligand responsible for mediating this effect has not yet been identified. In the study by Wang et al.,7 integrin αβ1, but not αβ2, was shown to mediate the SMC differentiating effect of COMP. The αβ1 integrin is a laminin receptor, and an αβ1 integrin–deficient mouse10 mimics the effects of COMP deficiency on neointimal formation, suggesting that this integrin is particularly important in maintaining the SMC in a differentiated state.

On the other hand, integrins whose ECM ligands promote SMC dedifferentiation are often not expressed under normal conditions. For example, the fibronectin receptor, αβ1, is not expressed in quiescent vessels in vivo, nor are fibronectin fibrils detected. However, following injury, αβ1 is upregulated in less differentiated SMCs, and fibronectin fibril assembly is localized to these same cells.11 Similarly, colla-
Proteases capable of degrading the ECM, particularly the matrix metalloproteinases, have essential roles in structurally remodeling the vascular tissue. Following injury and in atherosclerosis, new ECM proteins are expressed in remodeling tissues and stimulates SMC migration and matrix metalloproteinase synthesis. Vitronectin is a component of plasma that infiltrates the vessel wall following injury or endothelial dysfunction, and in vitro induces loss of contractility through integrin $\alpha_\beta_1$. Thus, integrins through interactions with specific ECM components, some of which are dynamically altered following injury, can control the SMC differentiation phenotype.

In vivo transition of SMC to the dedifferentiated phenotype is associated with major remodeling of the vascular tissue. Proteases capable of degrading the ECM, particularly the matrix metalloproteinases, have essential roles in structurally digesting and altering matrix proteins, including their conversion to signaling molecules. It has been hypothesized that degraded matrix, such a type I collagen, may be required to release SMC from quiescence-sustaining matrices in which they are embedded. COMP is cleaved by proteases of the closely related ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family, ADAMTS-7 and ADAMTS-12. Thus, the reduced levels of COMP following vascular injury might be attributable to a combination of proteolysis and reduced transcription. In addition to increased proteolysis of quiescence-sustaining ECM components, SMCs and other cells in the vascular wall synthesize ECM components that support dedifferentiation.

Although the studies of Wang et al demonstrate a clear role for COMP-integrin $\alpha_\beta_1$ interactions in the maintenance of SMC differentiation in vivo in the rat carotid artery balloon injury model, what is the function of COMP in human vascular disease and other models of vascular injury, such as atherosclerosis? It is possible that regional differences in integrin $\alpha_\beta_1$ expression, such as those reported in humans for integrin $\alpha_\beta_1$, may restrict the contribution of COMP to maintenance of SMC quiescence to specific anatomic sites.

The study by Wang et al has increased our understanding of the ECM–integrin interactions that determine the SMC differentiation state, but a number of important questions remain to be answered. For example, is COMP responsible for the effects of other ECM proteins on SMC differentiation? It is possible that, for example, fibronectin promotes SMC dedifferentiation by altering the ability of SMCs to produce and secrete COMP, whereas laminin or type IV collagen might have the opposite effect. Alternatively, does COMP act, in part, through its catalysis of collagen fibrillogenesis? To what extent do cells other than SMCs promote dedifferentiation (e.g., macrophages as a source of proteases in atherosclerosis)? Do lipid mediators or other systemic factors help tip the balance? Furthermore, what strategies could be used to inhibit dedifferentiation of SMCs in animal models and in human subjects? Answers to these questions are likely to bring us closer to strategies for the treatment of several vascular diseases. We are following this field with interest as we enter a new decade of research.

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None.

References

Non-standard Abbreviations and Acronyms

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<thead>
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<th>Abbreviation</th>
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<tbody>
<tr>
<td>ADAMTS</td>
<td>a disintegrin and metalloproteinase with thrombospondin motifs</td>
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<tr>
<td>COMP</td>
<td>cartilage oligomeric matrix protein</td>
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<tr>
<td>ECM</td>
<td>extracellular matrix</td>
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<tr>
<td>PDGF</td>
<td>platelet-derived growth factor</td>
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<td>SMC</td>
<td>smooth muscle cell</td>
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