Remodeling of the extracellular matrix is involved in the initiation and progression of a variety of diseases, including cancer and vascular pathology. However, our knowledge of the precise mechanisms that are involved in remodeling processes is still in its infancy. In this issue of Circulation Research, two studies, one by Bunton et al and one by Travis et al, provide important examples of the multiplicity and diversity of mechanisms for remodeling that give rise to vascular disease.

Marfan syndrome is a genetic disorder that results in thin vessel walls. The origin of this disease has been traced to mutations in fibrillin-1, a gene that encodes an extracellular matrix protein that forms microfibrils linking smooth muscle cells to elastin fibrils. Mice homozygous for a targeted hypomorphic allele of fibrillin-1 develop vessel walls with excessive deposition of extracellular matrix elements. Vessels also exhibit elastolysis and intimal hyperplasia. Bunton et al describe a similar sequence of events in patients with Marfan syndrome and, importantly, note that the vessel smooth muscle cells exhibit an abnormal synthetic repertoire, as detected by in situ hybridization and immunocytochemistry. This includes excessive elastin and matrix metalloproteinase-9 production. This latter collagenase is involved in remodeling processes. For instance, both disease processes are associated with enhanced expression of metalloproteinases, collagen, and glycosaminoglycans, such as hyaluronan.

Normally, vessel smooth muscle cells express a contractile, differentiated phenotype, but on injury they modulate to a synthetic phenotype that is characterized by enhanced expression of genes involved in producing new extracellular matrices. Examples of these gene products include collagenases, glycosaminoglycans, and matrix glycoproteins such as fibronectin. The remodeling smooth muscle cell is also highly motile and proliferative. This alteration from a differentiated to synthetic state seems to be regulated by growth factor receptors, such as platelet-derived growth factor, and by extracellular matrix receptors, such as integrins and hyaladherins. The growth factor and extracellular matrix receptors interact with each other to coordinate activation of signaling cascades, in particular those acting through heterotrimeric G proteins, tyrosine kinases, and mitogen-activated protein kinases. These collectively regulate expression of a broad spectrum of genes that control extracellular matrix remodeling as well as smooth muscle cell motility and proliferation. This knowledge has already led to the development of new therapeutic approaches that have been effective in reducing restenosis in animal models. For instance, inhibition of tyrosine kinases blocks neointimal formation by 50% in pig models. Although our understanding of the remodeling smooth muscle cell phenotype is rapidly expanding, a great deal remains to be done, particularly in understanding the role that extracellular matrix receptors play in controlling the above signaling pathways.

Several years ago, Geary et al noted that an injured artery wall resembles a healing wound in its sequence of remodeling events. This group proposed that remodeling processes in injured vessels contribute to contraction, as they do in wound healing, and this leads to vessel lumen narrowing. Interestingly, fibrosis and contraction of fetal skin wounds in several animal species are reduced compared with neonatal or adult skin. This anomaly has been attributed, in part, to the sustained accumulation of hyaluronan in fetal skin relative to adult skin. Subsequent studies have also shown that the addition of hyaluronan prevents collagen gel contraction by fibroblasts in vitro. Because hyaluronan accumulation is enhanced in injured vessels, Geary et al predicted that this glycosaminoglycan regulates contraction of injured vessels. They therefore assessed the effect of hyaluronan on the ability of primate smooth muscle cells to contract collagen gels in vitro, expecting to observe inhibition of gel contraction. Instead, they observed that hyaluronan promotes collagen gel contraction and that this process is associated with an enhanced pericellular accumulation of collagen that is not seen in the absence of hyaluronan. Both contraction and

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From the Department of Biochemistry/Oncology, University of Western Ontario, London Regional Cancer Centre, London, Ontario, Canada.

Correspondence to E.A. Turley, Department of Biochemistry/Oncology, University of Western Ontario, London Regional Cancer Centre, London, Ontario, Canada. E-mail eva.turley@lrcc.on.ca


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Extracellular Matrix Remodeling
Multiple Paradigms in Vascular Disease

E.A. Turley
collagen-gel alignment require β integrins and the hyaluronan receptor CD44. This process does not involve the hyaluronan receptor RHAMM, which, like CD44, is upregulated after smooth muscle cell injury and mediates motility of smooth muscle cells responding to injury. Interestingly, this mode of remodeling also does not involve collagenase activity.

CD44-hyaluronan interactions have previously been noted to result in the organization of complex coats that smooth muscle cells form in response to injury in vitro and are involved in cell motility and rounding during mitosis. However, an enhanced collagen fibril organization promoted by hyaluronan and CD44 has not previously been described. The collagen fibrils clearly originate from and organize around the smooth muscle cells bathed in hyaluronan and are reminiscent of the fibulin-1 fibrils that connect smooth muscle cells to elastic fibrils.

The studies by Bunton et al and Travis et al emphasize the importance of smooth muscle cell–extracellular matrix interactions in normal and aberrant vessel function. Of course, these studies also raise many additional questions. For instance, why does hyaluronan promote collagen gel contraction by smooth muscle cells but inhibit gel contraction by fibroblasts? Is this a cell-specific difference? Or are there differences in the experimental protocols of divergent studies that may seem minor now but could have major consequences on receptor display and hence cell response to its matrix? What are the precise conditions that permit hyaluronan-mediated contraction compared with those that promote coat formation or signaling of cell motility? CD44 has been shown to bind to metalloproteinase-9. Is this involved in the role of this collagenase in Marfan syndrome, and, importantly, why is it not involved in CD44-mediated collagen-fibril formation? Future experimentation will address these important issues. Both Travis et al and Bunton et al have identified key cell-extracellular matrix interactions that could point the way to novel therapeutic interventions and could not have been predicted from previous studies.

References


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E. A. Turley

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