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 fibers. 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.

Vessel restenosis remains a major factor limiting the success of balloon angioplasty of coronary and carotid arteries. The assumption that intimal hyperplasia is solely responsible for vessel narrowing after balloon injury is being challenged, and evidence is mounting that arterial wall remodeling also contributes to vessel narrowing. Balloon angioplasty reprograms smooth muscle cells to a synthetic phenotype that resembles the remodeling phenotype of vessel smooth muscle cells from patients with Marfan syndrome.

Extracellular Matrix Remodeling
Multiple Paradigms in Vascular Disease

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The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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collagen-gel alignment require β3 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.7 and Travis et al.8 both 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, and this is 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.8 and Bunton et al.7 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.7,8

References


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