The Smooth Muscle Cell: Sinner or Saint in Restenosis and the Acute Coronary Syndromes?

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Proliferation of arterial smooth muscle cells has held center stage as the culprit in restenosis for almost two decades. Many strategies for combating restenosis target smooth muscle replication. However, none have proven beneficial in clinical trials. Indeed, inhibition of smooth muscle proliferation in human patients might produce the undesired effect of destabilizing vulnerable atherosclerotic plaques because these cells furnish the collagen responsible for the biomechanical strength of the plaque. Actually, in some cases the benefit of angioplasty may depend on stimulating smooth muscle replication and collagen elaboration, converting an “unstable” to a more stable plaque. Moreover, recent clinical and experimental evidence suggests that restenosis depends less on neointimal hyperplasia than on constrictive remodeling (i.e., advential scarring, producing a smaller lumen), a process independent of smooth muscle replication. The recognition that plaques vulnerable to disruption often do not produce flow-limiting stenoses highlights a need for reassessment of the strategies to treat or prevent the acute coronary syndromes. We should strive to treat aggressively risk factors such as hyperlipidemia whose control appears to stabilize plaques. Trials are even underway comparing such risk factor management with coronary artery intervention. If we could identify potentially unstable atheroma before they are evident, clinically, we might even contemplate angioplasty of nonsignificant stenoses to induce smooth muscle cell proliferation and reinforce the plaque’s fibrous cap. This proposal may seem preposterous, yet we perform “primary” angioplasty every day in patients with an acute myocardial infarction whose “culprit” lesions underlying the thrombus are often not critical. Our knowledge of the biology of restenosis has lagged behind our practice of coronary intervention. Advances in understanding the biology of the complications of interventional therapy, hand in hand with technical advances, should help us to devise more rational and enduring approaches to benefiting our patients.

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Since the introduction of percutaneous balloon angioplasty as a treatment of human coronary artery stenosis some two decades ago, proliferation of arterial smooth muscle cells has held center stage as the protagonist in restenosis, a complication that has dogged the long-term success of this modality in many patients (1,2). A number of gene transfer–related strategies currently aimed at combating restenosis after angioplasty target smooth muscle replication. However, we speculated in 1995 that “Inhibition of smooth muscle proliferation in human patients might produce the undesired effect of destabilizing vulnerable regions of atherosclerotic plaques...” (3). Smooth muscle cell proliferation was subsequently proposed as a therapy for plaque stabilization (4). Indeed, in certain cases the major mechanism of benefit of angioplasty may depend on smooth muscle replication and elaboration of a collagenous extracellular matrix. Overstretching a stenosed artery wall to render the inner lumen equal to the upstream normal lumen with a balloon induces an injury that not only macroscopically destroys the artery’s structure, but can modulate smooth muscle cell function from quiescence to a proliferative, migratory and extracellular matrix-producing phenotype (5,6). In this respect, angioplasty constitutes a kind of gene therapy itself, not requiring transfer of exogenous genetic material, but eliciting a new program of endogenous gene expression. Functions of smooth muscle cells so altered by angioplasty can dramatically alter the structure of the dilated artery for several months.

Curiously, we have used coronary angioplasty for two decades without understanding how it works. Initially, Gruentzig et al. (7) intended to remodel the artery wall by compressing the plaque underlying the stenosis without deep arterial injury. Pathologic studies (8) later demonstrated that balloon angioplasty actually fractures plaques and dissects the artery wall, often expanding the portion with less plaque in eccentric lesions. In response to this injury, smooth muscle cell proliferation, migration and matrix synthesis may contribute to the formation of a thickened intima in experimental animal models. Thus, in humans, neointimal hyperplasia was presumed responsible for restenosis, which plagued up to 30% to 50% of angioplastied vessels (9). We and others (10–15) have recently
shown that restenosis does not necessarily depend on neointimal hyperplasia after experimental angioplasty, a concept now verified in patients by intravascular ultrasound observations revealing that intima–media thicknesses are similar in arteries with or without angiographically determined restenosis after angioplasty.

Moreover, stenting, which is known to induce smooth muscle proliferation, represents the first interventional strategy able to maintain lumen caliber sufficiently to lessen the need for further therapy (although this results primarily from the more effective initial dilatation achieved) (16–18). In most cases of restenosis, constrictive remodeling, including adventitial scarring producing a smaller lumen, appears to be the principal mechanism of restenosis, exonerating intimal smooth muscle cell proliferation and calling into question strategies that target this process (19–21).

Rather than focus on the decrease in lumen caliber known as restenosis that occurs in a minority of patients after angioplasty, it is instructive to consider why the majority of plaques become clinically stable after this iatrogenic injury. Thrombosis (usually on disrupted plaque) causes most acute coronary syndromes. Indeed, atherectomy samples showed a clear relation between prevalence of thrombus and the clinical scoring system of the Braunwald classification (22). After angioplasty, the wounding by the balloon induces a healing response prominently featuring extracellular matrix elaboration by smooth muscle cells (23). This matrix can reinforce the fibrous skeleton of previously fragile atheromata, as shown by intravascular ultrasound (14). Angioscopy has revealed that healing after angioplasty results in a smooth, concentric, white plaque surface lacking the thrombi present in >70% of culprit lesions producing unstable angina (24). These observations demonstrate directly the healing process evoked by angioplasty.

Human atherosclerotic plaques prone to rupture appear to have friable fibrous caps weakened by relative lack of extracellular matrix. This impaired matrix skeleton may result from reduced synthesis of the macromolecules of the extracellular matrix or excessive activity of enzymes, such as matrix metalloproteinases, which digest the extracellular matrix (3). Indeed, sites where human coronary plaques rupture and produce thrombosis characteristically have few smooth muscle cells, and we have fostered the notion that such regions of atherosclerotic plaque may undergo attrition of smooth muscle cells by death, including apoptotic mechanisms, as a consequence of local inflammation (25). Thus, the lack of smooth muscle cells, rather than their excess, seems to correlate with the dreaded thrombotic complications of coronary artery disease, such as unstable angina and acute myocardial infarction.

The recognition that plaques vulnerable to disruption most often do not produce flow-limiting stenoses should occasion a reassessment of the strategies to treat or prevent the acute coronary syndromes (26). Should we, for example, perform angioplasty of nonsignificant stenoses to induce smooth muscle cell proliferation? This proposal seems preposterous, yet cardiologists perform “primary” angioplasty every day in patients in the throes of acute myocardial infarction, in whom we have learned that the “culprit” lesion underlying the occluding thrombus produces a fixed stenosis >70% in <15% of cases (27–29).

Of course, preventing plaque rupture by performing angioplasty in nonocclusive atheroma would require methods to identify a priori patients at risk and lesions prone to rupture. Cardiologists must now adopt the stance of geologists who attempt to predict which dormant volcano will erupt when, or which seismic fault will give way at what moment to produce a calamitous event. Perhaps plasma markers of inflammation (e.g., C-reactive protein, soluble adhesion molecules) will help us to identify the patients at risk. Noninvasive imaging modalities, such as magnetic resonance, may help pinpoint plaques susceptible to rupture in such patients. Such subsets of patients would be selected for intensive medical intervention aimed at stabilizing plaques, some proven (e.g., lipid lowering), others more speculative (e.g., anti-inflammatory agents, metalloproteinase inhibitors). In some cases, even “prophylactic” angioplasty may prove beneficial.

From the “classical” view of smooth muscle cell proliferation as the enemy after angioplasty, we have begun to accept the concept that intimal cell replication may not play a decisive role in the pathogenesis of restenosis. We should now consider that smooth muscle cell proliferation in some situations may even prove beneficial, furnishing a necessary part of both the healing process after clinical or iatrogenic plaque rupture (angioplasty). This heretical view will doubtless require time to become accepted, even though it is already being implemented in the clinic. This would not the first time that understanding of a biological mechanism followed empiric adoption of a treatment by practitioners.

References


