

DANCE ROUND



WE DANCE ROUND IN A RING AND SUPPOSE,
BUT THE SECRET SITS IN THE MIDDLE AND KNOWS.
ROBERT FROST

CONCEPTUAL NOVELTIES IN ATHEROGENESIS: SMOOTH MUSCLE CELLS, ADVENTITIA, AND ADIPOSE TISSUE

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Here the questions we are dancing round include conceptually new findings about the role of arterial smooth muscle cells (SMC), adventitia, and adipose tissue, particularly, artery-associated adipose tissue (AAAT) in the formation and dynamics of atherosclerotic lesions.

THE SMOOTH MUSCLE CELL: OCCLUSION VERSUS RUPTURE

The arterial SMC is a pleiotropic cell capable of phenotypic modulation associated with secretion of multiple matrix molecules as well as mediators of cell growth, migration, inflammation, and healing (1-4). Today, Russell Ross' response-to-injury paradigm (1), established by 1973, is still the prevailing understanding of atherogenesis. It states that "the lesions of atherosclerosis represent a protective, inflammatory-fibroproliferative response" that involves several aspects of vascular wound healing. Proliferation, migration, and secretory activities of SMC are determinantly implicated in this intimal phenomenon (1-4). Consequently, modulation of arterial SMC from contractile to secretory phenotype resulting in cell proliferation and matrix molecule oversecretion has, for

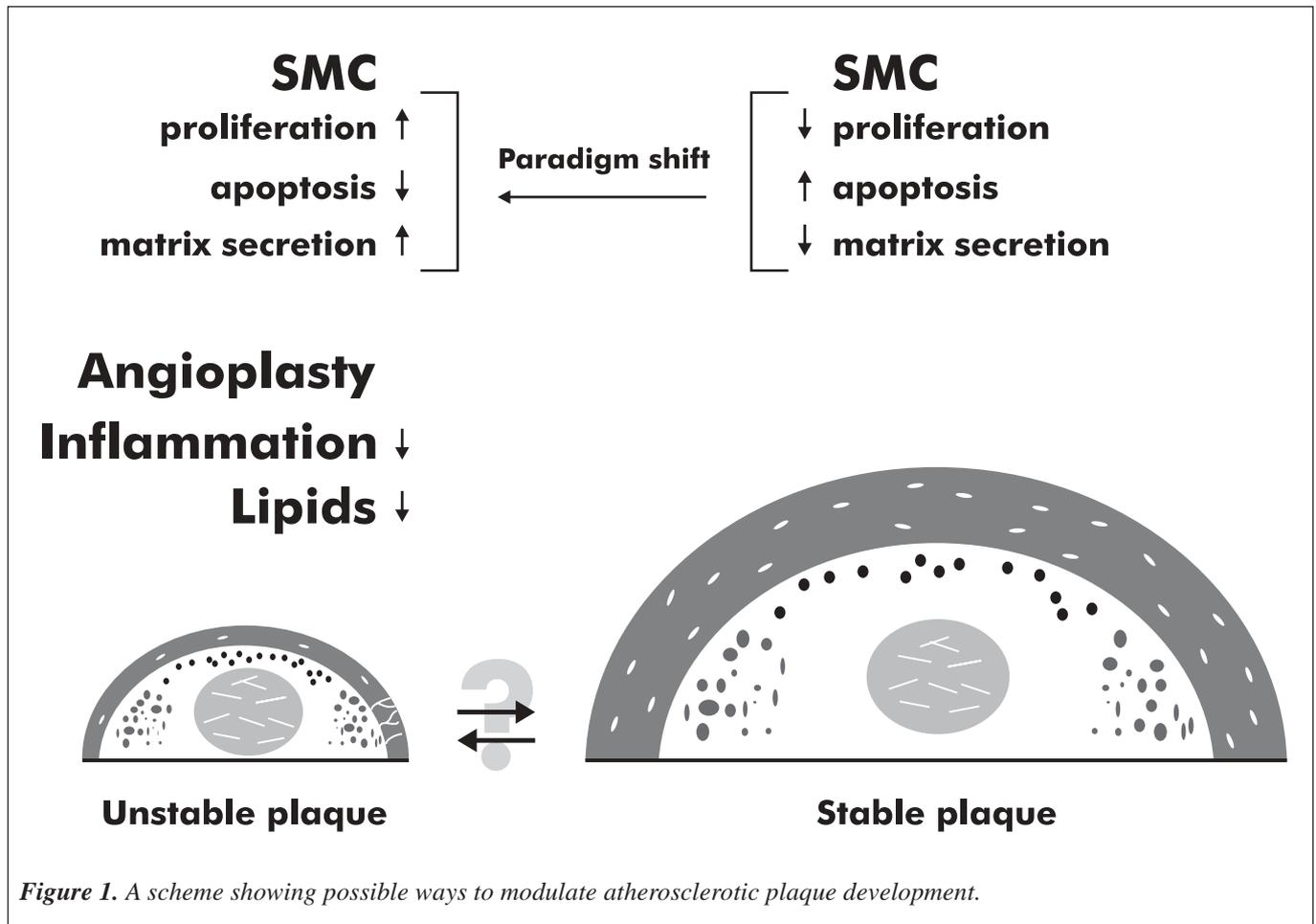
almost three decades, held center stage as the protagonist in plaque formation as well as angioplasty-associated neointimal hyperplasia. Indeed, scientific communities can be surprisingly resistant to new findings or ideas that do not fit the accepted paradigm. Hence the increased SMC proliferation/matrix production was shaped as the major enemy to be pursued, as it causes high grade arterial occlusion. However, things changed dramatically in the mid-1990's. The historian Thomas Kuhn refers to such changes as a "paradigm shift". Thus the attention was moved from the plaque-associated occlusion toward the integrity of plaque's fibrous cap as a critical factor for the plaque stability (4-7). And, respectively, from decreasing SMC proliferation/matrix production aimed at vascular occlusion decrease toward increasing SMC proliferation/matrix production aimed at plaque rupture prevention.

The fibrous cap is made up by SMC and SMC-secreted matrix molecules such as (pro)collagen, a major contributor to the mechanical integrity of the fibrous cap. Basic and clinical studies recognized that human atherosclerotic plaques prone to alterations involving fissuring, erosion, ulceration and rupture of the plaque surface (unstable plaques, "ulcerative

Biomed Rev 2000; 11: 63-67.

Received 15 September 2000 and accepted 17 November 2000.

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intimitis”) usually have fewer SMC, less collagen fibers, numerous inflammatory cells, and a large, lipid-rich core. This insufficiency in SMC/matrix forms a thin, vulnerable fibrous cap, while SMC/matrix excess improves the biomechanical strength of the fibrous cap, thus stabilizing the plaque surface (stable plaques, “fibrous intimitis”). In effect, the decreased SMC proliferation/matrix production, rather than their increase, directly accounts for plaque complications, such as unstable angina and myocardial infarction. Hence, until things change again, the SMC/matrix appear to be a good friend rather than a potential enemy, since it stabilizes/heals plaques, although increasing the occlusion grade (5-7). However, from therapy standpoint, where stands the balance of having either too much (excessive occlusion) or too little (excessive vulnerability) of “the good SMC” (Fig. 1)? Further work on molecular and cellular mechanisms of wound-healing phenotypes, including scarring, keloid and ulceration, is required for the better understanding of intima-based vascular occlusion and rupture in atherosclerosis. Intriguingly, the antiatherosclerotic factors es-

trogen and transforming growth factor- β (8) accelerate skin wound healing (9), and a potential atheroprotective factor, nerve growth factor (10), also exerts healing effect in both skin wounds (11,12) and corneal ulcers (13).

ADVENTITIA: INTIMAL HYPERPLASIA AND FIBROCONTRACTIVE REMODELING

The involvement of adventitia in intimal lesion formation seems to be another conceptual novelty in atherogenesis. There is at present growing evidence that adventitial and/or periadventitial manipulations of the artery can lead to intimal lesions. For example, positioning of a silastic collar around the artery (Moncada model of atherosclerosis) (14-16), removal of the adventitia (17), chronic application of interleukin-1 β (18) or platelet activating factor (19) result in atherosclerotic-like intimal lesions. These findings are consistent with the possibility that intimal lesions may be initiated by hypoperfusion or thrombotic occlusion of the adventitial vasa vasorum and by adventitial inflammation, and hence “in some cases athero-

sclerosis is a disease of the outer layers of the arterial wall" (16). Also, a large proportion of the intimal macrophage foam cells may derive from adventitial foam cells rather than from blood monocytes (14).

Further, emerging evidence demonstrates that lumen narrowing is caused in large part by fibrocontractive adventitial scarring (5,20-22) and by adventitial inflammation (23) rather than intimal hyperplasia.

ADIPOSE TISSUE: A SOURCE OF ATHEROGENESIS-RELATED MOLECULES

Recent publications provide increasing evidence of secretory functions of adipose tissue. Since the end of 1994 when leptin, a secretory product of the obese (*ob*) gene, had been discovered, the endocrine function of adipose tissue has additionally received intense scientific coverage, showing that elevated plasma levels of adipocyte-secreted molecules may have important roles in the development of atherosclerosis (24,25). However, the AAAT secretion of molecules with atherogenesis-related potential has thus far received little attention (26). Respectively, subepicardial adipose tissue (SEAT) may represent an excellent example of AAAT in atherosclerosis (10).

Subepicardial adipose tissue, adipokines and coronary atherosclerosis

Given the key role of inflammation and fibrosis in the initiation and development of atherosclerotic lesions, what role might AAAT play in atherogenesis? The AAAT that is conjunctioned to the adventitia of the most atherosclerosis-prone portions of the coronary artery, that is, the most proximal part of its left anterior descending (LAD) branch, is, in fact, subepicardial adipose tissue (SEAT). In 1933, Smith and Willius (cited in 27) have pointed out a functional relationship between the SEAT and the LAD coronary artery, and stated that SEAT is "not a passive storehouse for fat". The principle difference between SEAT and adipose tissue elsewhere in the body is its greater capacity for free fatty acid release and uptake, thus acting as a local energy supply for epimyocardium and coronary arteries and/or as a buffer against toxic levels of free fatty acids (27). Another important reason for SEAT to serve as an excellent example of AAAT in atherogenesis is the close association of the coronary vasculogenesis with epicardial and subepicardial development, including epicardium derived mesenchymal cells which invade the subepicardial matrix and differentiate into coronary vascular SMC and endothelial cells, and perivascular fibroblasts (28). Thus coronary vascular SMC distinguish themselves ontologically, structurally and functionally as compared to SMC in other great blood vessels, such as the aorta. The heterogeneity between these cells may subsequently involve an increased susceptibility of

the coronary artery to atherosclerosis (29). Hence the question arises as to whether SEAT may also contribute to that?

Neglected for nearly 60 years, the possible involvement of SEAT in atherogenesis has been, at long last, currently addressed (10,30-32). Specifically, recent work provides the first evidence to suggest that the altered presence of nerve growth factor (NGF), p75NGF receptor, and mast cells in SEAT may be implicated in the pathobiology of human coronary atherosclerosis (10). Altogether, these findings suggest the possibility that an inflammatory response-to-injury (1) may also occur in the "atherosclerotic" SEAT. The adipose tissue-secreted molecules (adipokines) (26; see 25 for adipocytokines, adipocyte-secreted molecules), that may be implicated in the pathogenesis of atherosclerosis are presented in Table 1. Whatever changes occur in AAAT, little is known of whether they can be causally associated with atherosclerosis or if they are a paracrine response to the injuries developing within the artery wall, particularly in the adventitia. If the first possibility is considered valid, then differences in molecular composition of AAAT may help to explain the preponderance of atherosclerosis in certain arterial regions. Note that in cholesterol-fed rabbits, the portion of LAD coronary arteries running in the SEAT reveals atherosclerotic lesions, while the portion running in the myocardium is free of atherosclerotic lesions (31,32). Therefore, a comprehensive evaluation of AAAT-derived adipokines becomes mandatory, since identification of these molecules may yield clues to a possible transmission of proatherogenic and/or antiatherogenic stimuli, from AAAT toward artery wall (see Table 1). Hence, to further elucidate the potential role of

Table 1. *Adipokines as potentially related to atherogenesis**

Leptin
Tumor necrosis factor- α
Interleukin-1, -6, -8
Plasminogen activator inhibitor-1
Adiponectin
Transforming growth factor- β
Tissue factor
Lipoprotein lipase
Macrophage colony-stimulating factor
Nerve growth factor
Renin-angiotensin
Insulin-like growth factor
Estrogens
FIZZ1

* For references see the text.

AAAT in atherosclerosis, we should no longer, as hitherto, cut it from the artery wall, but keep it attached and in place, and subject to thorough examination. If signals (18,19,33) and cells (14,20) can be translocated from the adventitia into the intima, and hence lead to endothelial changes (33), atherosclerotic-like intimal lesions and coronary artery spasm (14,18,19), and also neointimal lesions after endoluminal coronary injury (20), then why not look for similar reactions from the AAAT?

CONCLUSION

Taken together, these new findings conceptually move the field forward by illuminating the fundamental importance of arterial SMC proliferation and matrix molecule secretion in the stability of the plaques. And, set up intimal hyperplasia, adventitial remodeling and AAAT secretion into an interactive context of atherogenesis (see 26). We may therefore argue that further evidence derived from vascular biology and vascular medicine of atherosclerosis will continue to provide conceptual novelties in the pathogenesis and therapy of this life-and quality of life-threatening disease.

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