Letter to the Editors

Subepicardial adipose tissue in human coronary atherosclerosis: another neglected phenomenon

In a recent paper in *Atherosclerosis*, Scher [1] presented an intriguing viewpoint about one neglected phenomenon: absence of atherosclerosis in intramyocardial coronary arteries. Scher discussed the difference in susceptibility to atherosclerosis between proximal and intramyocardial segments, focusing on myocardial contraction protection against the transfer of circulating LDL and monocytes into the intima. Anatomically, one may speculate that both intramyocardial arteries and tunneled (overbridged by myocardial fibers) epicardial arteries possess, in addition to tunica intima, media, and adventitia, tunica cardiomuscularis. If Scher’s viewpoint is a ‘likely’ hypothesis ([1], his Discussion, p. 3), could transplantation of tunica cardiomuscularis protect epicardial coronaries from atherosclerosis? Whatever the mechanism of atherosclerosis resistance of intramyocardial and overbridged coronary arteries, Scher neglected another phenomenon: the potential role of subepicardial adipose tissue (SEAT) in coronary atherosclerosis. This issue is discussed rarely, also by other authors. Another neglected phenomenon? Here we focus on it. The adipose tissue surrounding the most atherosclerosis-prone segment of the coronary artery, that is, the most proximal part of its left anterior descending (LAD) branch, is, in fact, the SEAT. In 1933, Smith and Willius [2] 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 past 5 years have seen an exponential growth in the understanding of endocrine and paracrine secretory function of adipose tissue [3–5], in addition to its role in lipid and energy homeostasis. The principle difference between SEAT and adipose tissue elsewhere in the body is its greater capacity for free fatty acid (FFA) release and uptake, thus acting as a local energy supply for the heart and/or as a buffer against toxic levels of FFA [2]. Neglected for nearly 60 years, the possible involvement of SEAT in atherosclerosis has been, at long last, currently addressed (reviewed in [5]). These findings taken together demonstrate an increase number of both lymphocytes and mast cells, and neovascularization. That is, an inflammatory response-to-injury, originally described by Russell Ross in the intima, may also occur in the ‘atherosclerotic’ SEAT. Probably, SEAT should not be considered an innocent bystander, but a paracrine, SEAT-to-adventitia player in coronary atherosclerosis. One thing appears to be certain: to further elucidate the role of SEAT in atherogenesis, we should no longer, as hitherto, ‘carefully’ cut it from the artery wall, but keep it attached and in place, and subject to thorough examination. One could also see small bundles of cardiomyocytes scattered in SEAT, in human coronary atherosclerosis (our unpublished observations). Could that be, in sense of Scher’s viewpoint, a natural compensatory reaction, an attempt of myocardial fibers to overbridge the coronary artery? Another important reason for SEAT to be studied in atherosclerosis is the close association of the coronary vasculogenesis with epicardial development [6,7], showing that coronary smooth muscle cells (SMC) distinguish themselves ontologically, structurally and functionally as compared with SMC in other great blood vessels. This is implicated in an increased susceptibility of the coronary artery to atherosclerosis [7]. However, the question arises as to whether SEAT may also contribute to that? Because macrophage colony-stimulating factor (MCSF) is a potent adipogenic factor [8], it is possible for the decreased atherosclerosis found in mice deficient in both MCSF and apolipoprotein E [9] to be mediated, at least in part, via a decreased growth of adipose tissue and/or a loss of passage of MCSF’s atherogenic signals from the artery-associated adipose tissue into the artery wall. It is also noteworthy that (i) leptin [10] and other adipose tissue-secreted molecules (adipocytokines, adipokines) [3,5], such as plasminogen activator inhibitor-1 [3,4], adiponectin [3], tissue factor [4], transforming growth factor-β [4], and nerve growth factor ([11]; also the manuscript submitted to *Atherosclerosis*), are implicated in atherogenesis, and (ii) lipidsoluble substances may accumulate in SEAT, and hence related to ischemic myocardial events [12]. We propose a comprehensive evaluation of SEAT-derived adipokines. Besides various adipokines with atherogenic potentials [3–5] adipose tissue secretes estrogens [13] and adiponectin [3], and accumulates carotenoids and tocopherols [14]; all these molecules...
may exert an antiatherogenic action. Learning more about the balance between such pro- and antiatherogenic molecules, SEAT may appear to be an important therapeutic target in coronary atherosclerosis.

Because advanced intimal lesions lead to luminal narrowing, resulting in infarction, the intima is prevailingly considered the most important vascular area involved in atherosclerosis. However, it may be much more than that. The involvement of adventitia has received recently an increasing attention (reviewed in [5]). If signals [15] and cells [16] can be translocated from the adventitia into the intima, and hence lead to intimal lesions, then why not look for similar reactions from the SEAT? Supportively, coronary artery-associated pericardium also reveals an inflammatory reaction in advanced atherosclerotic lesions (our unpublished observation). And pericardial fluid contains various biologically active molecules which can influence coronary artery biology [17]. In sum, it is better to appreciate the coronary artery neighbours, both myocardium and SEAT, than neglect them.

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References


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