QUO VADIS, ATHEROGENESIS?

PART 2. TUNICA ADIPOSA – THE NEW PLAYER IN THE PROCESS OF ATHEROGENESIS

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Abstract

Today, atherosclerosis is considered an immune-mediated inflammatory disease featured by endothelial dysfunction (intimal thickening), medial atrophy, and adventitial lesions associated with adipose dysfunction. Since Rudolf Virchow's time when the intima has been considered the most important vascular area involved in atherogenesis, our views on this multiplex phenomenon are indeed changing. Here we *Dance round* an emerging role played by perivascular adipose tissue (*tunica adiposa*) in the process of atherogenesis. We intend to integrate the traditional "inside-out" (intimal and medial) to an "outside-in" (adventitial and adipose) pathway of atherogenesis.

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Introduction

Recently, Part I of *Quo vadis, atherogenesis?*, focusing on vascular smooth muscle cell secretion, was published (1).

The secretion is a fundamental process in all cells, from the simple yeast to cells in human brain. On April 1898 Camillo Golgi communicated to the Medical-Surgical Society of Pavia, Italy, the discovery of the *internal reticular apparatus*, a novel intracellular organelle which he observed in nerve cells with the silver impregnation (*la reazione nera*) he had introduced for the staining of the nerve cells (1). However, the real existence of this organelle (apparatus or complex) was seriously questioned until it was finally identified by electron microscopy in the mid-1950s, mainly due to the excellent work of George Palade (2). According to Palade's classical concept (3) and Gunter Blobel's signal hypothesis (4), the protein secretory pathway constitutes of several intracellular processes: synthesis, targeting, sorting, storage (in case of regulated *versus* constitutive secretion), translocation and, finally, exocytosis including porocytosis (5) mediated by porosomes (6).

The secretory proteins are four major subtypes: lysosomal, plasmalemmal, recycled, and exported, these latter type of proteins as secreted by adipose cells being the focus of the present *Dance round*.

Adipose tissue cell secretion

In 1983 in Chicago, IL one of us (GNC) presented a lecture about the ultrastructure of secretory process in vascular smooth muscle cells. During the discussion, a question whether adventitial fibroblasts may migrate into the intima was raised. The answer of the lecturer was “I do not know. It seems impossible.” However, what seemed “impossible” in 1983 was proven possible in the 1990’s by other authors.

In 2000 we have wondered (7, 8): if signals and cells can be translocated from the adventitia into the intima, and hence lead to intimal lesions, then why not look for similar reactions from the perivascular adipose tissue? - hereinafter *tunica adiposa* or *adiposa* (9; Fig. 1). Understanding the precise interaction between the four vascular coats (intima, media, adventitia and adiposa) might be a novel, *quadripartite approach* in atherogenesis research (7-9).

In 1994 leptin, an adipocyte-secreted cytokine, was discovered and thus Fat’s Big Bang has exploded. Today, it is known that about 30 % of genes in adipose tissue cells (adipocytes, stromal-vascular cells, and associated immune cells) encoded for export more than 600 secretory proteins (21) collectively termed adipokines (11, 12). Altogether, recent studies have shifted the paradigm of adipose tissue, including that of *tunica adiposa*, from simple energy storage to the body’s major endocrine and paracrine organ (10-22; Fig. 2). Noteworthy, the phenotypic plasticity of *adiposa* from brown (atheroprotective) to white (atherogenic) adipose tissue (adipose whitening) is considered pivotal in the pathogenesis of cardiometabolic diseases (17).

One aspect of the role of *tunica adiposa*, also epicardial adipose tissue (EAT), is whether they facilitate or inhibit the process of atherogenesis. It is known that the proximal segments of coronary arteries are surrounded by subEAT, and these are atherosclerosis-prone as compared to the distal, intramyocardial, adipose-free, and atherosclerosis-resistant coronaries (10). However, when EAT is totally absent, as in congenital generalized lipodystrophy, coronary atherosclerosis can still occur, suggesting that a homeostatic presence of adipose tissue is required for coronary artery health, reminding the maxim “A little fat is good” or “Fatter is better?”. Yet (i) the removal of *tunica adiposa* enhances neointima formation after injury, which is attenuated by transplantation of subcutaneous adipose tissue, whereas (ii) the excision of coronary EAT (adipectomy) decreases the progression of atherosclerosis (13-16 and references therein).

Again, given the key role of inflammation in the development of atherosclerotic lesions, what role might then *tunica adiposa* play in the process of atherogenesis? Today, adipocrinology (both para- and endocrine) is increasingly implicated in the

Figure 1. Schematic presentation of vascular wall composed of four tissue coats (*tunicae*): intima, media, adventitia, and adiposa. Arrows show that tunica media is a target for at least two vasorelaxing factors, endothelium-derived relaxing factor (EDRF) and adipocyte-derived relaxing factor (ADRF), respectively. Discontinuous black line positioned at the adventitia–media border illustrates perivascular nerves. Small-sized discontinuous black lines located in tunica adiposa indicate adipose nerves. Black granules (except those linked to arrows) illustrate immune cells – their association with nerves and adipocytes is also depicted. From (16)

pathogenesis of cardiometabolic diseases including atherosclerosis (15-20, 22, 24). In basic research therefore we should no longer disregard adventitia and adiposa, but preserve them in place and subject to a thorough examination. In other words, we need to keep open our minds on all four vascular coats. Second, echocardiography, computer tomography, MRI, and other non-invasive imaging of heart- and artery-associated adipose tissue may identify high-risk population susceptible to atherosclerosis. Third, “non-touch harvesting technique” is an example of appreciation of adipoparacrinology in coronary artery bypass surgery. Fourth, adiposa like adventitia may represent a new target for *in situ* therapeutic applications.

The present challenge is therefore to cultivate integrative thinking about how we can make both vascular smooth muscle (1) and adipose paracrine secretion work for the benefit of human’s cardiovascular health. This may indeed be a step forward

Figure 2. Nerve growth factor, mast cell, and vasa vasorum changes in selected human atherosclerotic cardiac tissues expressed as percentage of controls. Note the alterations in presence of NGF and mast cells in subepicardial adipose tissue. From (24).

but not the whole route in the cell biology of atherosclerosis. Who knows, there may be other mechanism of atherogenesis waiting to be discovered. As Denys Wheatley wrote in his *Eureka review*, we “do need to think outside the box” (23).

Conflict of interest statement

The authors certify that they have no affiliations with or involvement in any organization with any financial interest in the subject matter discussed in the present *Dance Round*.

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