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Dance Round

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

STATE-OF-THE-ARTERY: PERIADVENTITIAL ADIPOSE TISSUE *(TUNICA ADIPOSA)*

George N. Chaldakov[1], Marco Fiore[2], Peter I. Ghenev[3], Neşe Tunçel[4], Gorana Rančić[5], Pepa Atanassova[6], and Luigi Aloe[2]

[1]Division of Cell Biology, Medical University, Varna, Bulgaria, [2]Institute of Neurobiology and Molecular Medicine, CNR-European Brain Research Institute, Rome, Italy, [3]Department of General and Clinical Pathology, Medical University, Varna, Bulgaria, [4]Department of Physiology, Eskişehir Osmangazi University, Eskişehir, Turkey, [5]Department of Histology and Embryology, Medical Faculty, Niš, Serbia, and [6]Department of Anatomy and Histology, Medical University, Plovdiv, Bulgaria

Traditional view considers that the arterial wall is composed of three concentric tissue coats (tunicae)*: intima, media, and adventitia. However, large- and medium-sized arteries, where usually atherosclerosis develops, are consistently surrounded by periadventitial adipose tissue (PAAT). Here we update growing information about PAAT, and conceptualize it as the fourth coat of arterial wall, that is, tunica adiposa (in brief, adiposa, like intima, media, adventitia). Recent evidence has revealed that adipose tissue expresses not only metabolic, but also secretory (endo- and paracrine) phenotype, producing/releasing a large number of signaling proteins collectively termed adipokines. Through paracrine ("vasocrine") way, adiposa-derived mediators may contribute to various arterial functions such as contraction-relaxation, smooth muscle cell growth, inflammation, hemostasis, and innervation, hence to "outside-in" signaling pathway of atherogenesis.* ***Biomed Rev 2009; 20: 41–44.***

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Correspondence and reprints request to Dr George N. Chaldakov, Division of Cell Biology, Medical University, BG-9002 Varna, Bulgaria. Tel.: +359 52 754 394; E-mail: chaldakov@yahoo.com

INTRODUCTION

In 1983 at Department of Anatomy, University of Chicago Medical School, Chicago, IL, USA, one of us (GNC) delivered a lecture about fibroblast-like secretion by vascular smooth muscle cells, a key cell type in atherogenesis. 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 1996 by Shi et al (1).

The road less traveled (2)

The prevailing response-to-injury hypothesis of Russell Ross states that atherosclerosis is an inflammatory disease, leading to intimal lesions and luminal loss in large- and medium-sized arteries (3). Accordingly, intima-media thickness became an accepted measure of structural arterial remodeling and a strong predictor of atherosclerosis. However, it is unlikely that such one-direction road may solely travel the whole multiplex network like that of atherogenesis. Almost a decade ago, we have proposed an "interactive hypothesis" of atherogenesis, which appreciated the role of all structural components of the artery wall including periadventitial adipose tissue (PAAT) (4-6).

A long standing paradigm holds that the artery wall consists of three concentric tissue coats (*tunicae*): intima, media, and adventitia. However, large- and medium-sized blood vessels (where usually atherosclerosis develops) are consistently enveloped by PAAT, herein referred to as tunica adiposa (Fig. 1). Recent evidence has revealed that the adipose tissue is a dynamic endocrine and paracrine organ producing more than 100 signaling proteins, collectively termed adipokines (4,7-16), abundantly secreted by inflamed and hypoxic adipose tissue (12,13,15). Adiposa-derived mediators may contribute to vascular tone (17-19), inflammation (12,13,15,16) smooth muscle cell growth (14), hemostasis and vascular wound healing (reviewed in 20,21).

Given the key role of inflammation in the development of atherosclerotic lesions, what role might *tunica adiposa* play in the process of atherogenesis? For instance, it is

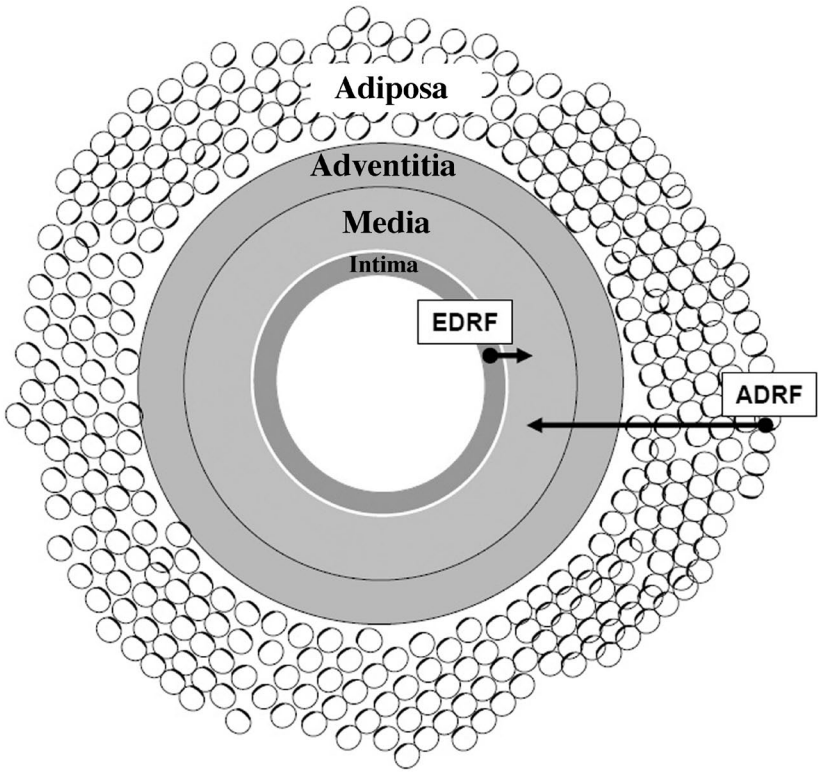

Figure 1. *Schematic presentation of vascular wall composed of four tissue coats* (tunicae)*: intima, media, adventitia, and adiposa. Arrows show that* tunica media *is a target for at least two vasorelaxing factors, endothelium-derived relaxing factor (EDRF) and adipocyte-derived relaxing factor (ADRF), respectively. Modified from reference 20.*

know that the proximal segments of coronary arteries are surrounded by subepicardial adipose tissue, and these segments are atherosclerosis-prone as compared to the distal, intramyocardial, *tunica adiposa*-free segments, which are atherosclerosis-resistant (4-6). Moreover, the evidence that the growth of adipose tissue mass is associated with tissue hypoxia (16) and, consequently, an accumulation of macrophages and T-lymphocytes, has raised the hypothesis that the inflamed adipose tissue is a primary event involved in the genesis of systemic and local (also vascular) disorders (15). Note that both external and internal fat accumulation (22) is associated with an imbalanced secretion represented by a decreased release of antiinflammatory adipokines (13) and an enhanced release of proinflammatory adipokines (12,15) (Table 1). Such an friend-or-enemy (good cop-or-bad cop, as Americans used to say) secretory capacity of *tunica adiposa* requires specific pharmacological manipulation, aiming at boosting the production and/or receptor sensitivity of antiinflammatory adipokines (13,20), also vasorelaxing factors (17,18).

Cumulatively, adipobiology might be a new filed in vascular medicine. Hence (*i*) in basic research, we should no longer cut *tunica adiposa*, but keep it attached and in place, and subject to thorough examination, (*ii*) not only intima-media and epicardial adipose tissue thickness, but also adiposa thickness should be imaged, for example, in identifying high-risk population susceptible to atherosclerosis and monitor vascular wall changes during follow-up studies and therapeutic trials, (*iii*) adiposa may represent a new therapeutic target for vascular diseases, and (iv) structure-based mathematical models for arterial remodeling should also consider the forth arterial coat.

CONCLUSION

Here we have spotlighted an adipose road of atherogenesis, focusing on the possible paracrine role of *tunica adiposa* in an "outside-in" signaling pathway.

"And that has made *some* difference", paraphrasing Robert Frost's *The road not taken* (2).

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Table 1. *A selected list of adipose tissue-derived mediators, as related to atherosclerosis and hypertension*

Antiinflammatory adipokines
Adiponectin, IL-1 receptor antagonist, IL-10, metallothioneins, adrenomedullin
Metabotrophic adipokines*
NGF, BDNF, CNTF
Proinflammatory adipokines
Leptin, IL-1, IL-6, IL-17, IL-18, IL-33, TNF-α, CRP, resistin, visfatin, vaspin, MIP-1 (CCL2), IL-8 (CXCL8), fractalkine (CX3CL1), RANTES, hepcidin, substance P, homocysteine**
Vasodilators
Adipocyte-derived relaxing factor, nitric oxide (NO), hydrogen sulfide (H_2S), adiponectin, cardiac natriuretic peptide, adrenomedullin
Vasoconstrictors
Superoxide anion, angiotensin II, endothelin-1
Hemostasis-related factors
Plasminogen activator inhibitor-1, tissue factor

Abbreviations: IL, interleukin; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factors; TNF-α, tumor necrosis factor-alpha; CRP, C-reactive protein; MIP-1 (CCL2), monocyte chemoattractant protein MIP-1 (Cysteine-Cysteine modif chemokine Ligand 2); RANTES, regulated on activated normal T-cell expressed and secreted. Note, all components of renin-angiotensin system are also expressed in PAAT (7,19), suggesting a role in the development of hypertension.

* NGF, BDNF and CNTF are not only for nerves, but they also improve glucose, lipid and energy homeostasis (20,21).

** Hyperhomocysteinemia is in the list of global cardiometabolic risks. This sulfur-containing aminoacid deriving from the methionine metabolism may also be consider "adipokine" - all enzymes involved in the synthesis and metabolism of homocyteine are expressed in adipose tissue (23).

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   …two roads diverged in a wood, and I -
   I took the one less traveled by,
   And that has made all the difference.
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