PVAT AND ATHEROGENESIS: A CROSSROAD OF WHITE AND BROWN ADIPOBIOLOGY

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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.*

Robert Frost, *The Road Not Taken*

In 1999, the prevailing response-to-injury hypothesis of Russell Ross stated that atherosclerosis is an inflammatory disease, leading - through *an inside-out road* - to endothelial and smooth muscle dysfunction resulting in the formation of atherosclerotic plaques (reviewed in 1). Accordingly, intima-media thickness became an accepted measure of structural vascular remodeling and a strong predictor of atherosclerosis. However, it is unlikely that such a road may solely travel the whole multiplex network like that of atherogenesis. Recently things changed dramatically and the attention was moved from *inside-out* to *outside-in road* emphasizing the role for adventitial and adipose dysfunction in the processes of atherogenesis (2, 3).

There are two major types of adipose tissues, white adipose tissue (WAT) and brown adipose tissue (BAT). Anatomically, WAT comprises two major depots, subcutaneous and visceral, and multiple small depots around internal organs (Fig. 1). On the other hand BAT is localized around kidney, adrenal, pancreas, liver and neck, as well as the thoracic aorta (perivascular adipose tissue, PVAT) and the epicardium (epicardial adipose tissue, EAT) (4, 5).

Figure 1. Schematic illustration of a large adipose depot (visceral and subcutaneous adipose tissue shown as one big circle in the middle) and small adipose depots (organ-associated adipose tissue shown as small circles at the periphery). Endocrine action (long arrows) and paracrine action (short arrows) of adipokines, lipokines and other adipose-derived signals on various organs. Organ parenchyma (grey) is surrounded by adipose tissue (white). From (20).

Received 4 December 2016, revised 15 December 2016, accepted 16 December 2016.

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Adipose tissue remodeling (phenotypic modulation) is a complex process that allow adaptation to external changes (reviewed in 5). A deeper understanding of this phenomenon may give better insights in the pathogenesis of obesity and related cardiometabolic diseases. And may facilitate the development of therapeutic modalities for them.

The modulation of PVAT from brown/thermogenic to white/proinflammatory phenotype is highlighted at an epigenetic level by Karl Blirando in his state-of-the-science (SOS) review published in this volume of *Adipobiology* (6). Regarding PVAT we prefer the term *tunica adiposa* (7, 8; Fig. 2) or periadventitial adipose tissue (PAAT) as a path to atherogenesis (9).

Figure 2. Schematic presentation of a cross-sectioned arterial wall consisted of *tunica intima*, *tunica media*, *tunica adventitia* and *tunica adiposa*. Adipose dysfunction is mediated by an unbalanced secretion of pro- and anti-inflammatory adipokines and lipokines, also an inhibition of the release of adipose-derived relaxing factors (ADRF), such as NO (10) and H₂S (11). EDRF, endothelium-derived relaxing factor. From (8).

We learn from Blirando's SOS that many factors associated with epigenetic signals are pivotal for a brown-to-white transition and, in turn, the metabolic syndrome and atherosclerosis. A large number of regulators at critical genes set up specific patterns of DNA methylation and histone phosphorylation, acetylation and/or methylation, which act as an epigenetic code to modulate the correct progress of adipocyte transition from BAT to WAT, a process termed *PVAT whitening*. The latter is a sort of outward remodeling, a pathological process triggered by a high fat

diet and/or inflammation. Blirando's SOS highlights the epigenetic regulation of PVAT's expression of key biomolecules involved in the control of metabolism and inflammation such as AMP-activated protein kinase (AMPK), sirtuin 1 (SIRT1), adiponectin, leptin and nerve growth factor (NGF); see Fig. 2 of (6).

According to most reports PVAT is found around vessels of large and medium size. In 1991, Soltis and Cassis reported for the first time that PVAT has an anti-contractile effect (12). Healthy PVAT is generally characterised by the degree of its thermogenic, anti-contractile and anti-inflammatory function. The loss of these properties is regarded as a dysfunction of PVAT. Whereas ontogeny defines PVAT localization around blood vessels, the main determinant of PVAT phenotype in adulthood seems to be the local environmental factors as illustrated in Blirando's figure 1A, B (6).

Today's paradigm says that atherosclerosis mainly occurs in arteries surrounded by white PVAT (Fig. 3). There is not a clear division of pure BAT or pure WAT in both PVAT and EAT. Plasticity and infiltration of brown adipocytes in WAT may lead to the formation of *brite adipose tissue* (brown in white). Accordingly, beige or brite adipocytes are newly identified type of brown adipocyte distinct from the classical brown adipocyte that makes up the interscapular thermogenic organ of other mammals (4, 6, 13 for PVAT; 4, 5, 14 for EAT).

Until recently, physicians have looked upon obesity and related diseases as an accumulation of external adipose tissue (subcutaneous and abdominal). This was routinely evaluated by anthropometric measurements including BMI and waist, hip and, recently, neck circumference. However, recent data using non-invasive imaging, such as echography, computed tomography, MRI and positron emission tomography, reveal a new picture of adipotopography. We should therefore focus our attention not only on anthropometric values of external adipose tissue, but - more importantly - the "weight" of internal, organ-associated adipose tissue, including PVAT/*tunica adiposa*. Thin outside, fat inside (TOFI) and other phenotypes of adipose distribution are based on imaging data (17) and illustrated in Table 1 herein.

Table 1. Adipotopography – variations+

TOFI**	thin outside, fat inside
TOTI*****	thin outside, thin inside
FOFI*	fat outside, fat inside
FOTI***	fat outside, thin inside

+ The number of asterisks indicates quality, here – the quality of cardiometabolic health, as related to adipose tissue distribution. TOTI represents a highest, whereas FOFI the lowest quality of cardiometabolic health.

Figure 3. Regional differences in periaortic perivascular adipose tissue (PVAT) are related to distinct functions and pathological complications. The differences in PVAT might also appear within different regions of the same vessel, as schematically illustrated herein. Aortic arch and thoracic aorta are surrounded by brown adipose tissue, whereas abdominal aorta by white adipose tissue. It may be brown PVAT which makes thoracic aorta resistance to high-fat feeding thus protecting the artery wall against atherosclerosis. Contrary, white PVAT is highly responsive to high-fat diet and thus being prone to the development of atherosclerosis. Modified from (13).

As we stated in 2000, it is imperative that “to further elucidate the vascular function, we should no longer, as hitherto, cut PAAT from the vascular wall, but keep it attached and in place, and subject to thorough examination” (2; updated in 4-6, 15, 16, 18, 19). And that has made *some* difference, paraphrasing Robert Frost.

Yet, at least one question remains unanswered: could the concept of PVAT/EAT whitening (4, 6, 14, 18, 19) also work in adipose tissue surrounding other internal organs (Table 2).

Table 2. Examples of adipoparacrinology of diseases. From (20).

(i)	Epicardial adipose tissue and cardiometabolic diseases
(ii)	Periadventitial adipose tissue (tunica adiposa) and atherosclerosis
(iii)	Mesenteric adipose tissue and Crohn's disease and ulcerative colitis
(iv)	Peripancreatic adipose tissue and type 2 diabetes mellitus
(v)	Mammary gland-associated adipose tissue and breast cancer
(vi)	Periprosthetic adipose tissue and prostate cancer
(vii)	Lymph node-associated (perinodal) adipose tissue and HIV-associated adipose redistribution syndrome (HARS)
(viii)	Infrapatellar fat pad (Hoffa's fat pad) and osteoarthritis
(ix)	Orbital adipose tissue and thyroid-associated (Graves') ophthalmopathy
(x)	Subcutaneous adipose tissue and skin diseases
(xi)	Parasellar region-associated adipose body and brain disorders (?)
(xii)	Periovarian adipose tissue and ovary disorders (?)
(xiii)	Epididymal adipose tissue and sexual disorders (?)
(xiv)	Retromalleolar adipose tissue and Achilles tendon disorders (?)
(xv)	Epidural adipose tissue and spinal cord disorders (?)

Acknowledgements

We thank the National Research Council, Rome, Italy for a continuing financial support. We apologize to the authors of many relevant articles that were not quoted here for reason of brevity.

Conflict of interest statement

The authors have no conflicts of interest.

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