Is there a pathophysiological role for perivascular adipocytes?

Stefan Engeli
Franz Volhard Clinical Research Center, Medical Faculty of the Charité, Humboldt University of Berlin, and Helios Klinikum, Berlin, Germany

In this issue of American Journal of Physiology-Heart and Circulatory Physiology, Barandier et al. (1) describe that conditioned medium of cultured murine adipocytes (3T3-L1 cells) or rat perivascular adipose tissue stimulates human vascular smooth muscle cell proliferation. The growth factor(s) responsible are secreted by mature adipocytes but not by preadipocytes, are hydrosoluble proteins with a molecular mass >100 kDa, and act independently of the p42/p44MAPK pathway.

Similar in vitro approaches in which coculture systems or conditioned media were used demonstrated in the past that human adipocytes inhibit in vitro adipogenesis of human preadipocytes (11), stimulate aldosterone secretion in human adrenocortical cells (NCI-H295R) (6), decrease insulin sensitivity in human primary skeletal muscle cells (5), and directly activate integrin expression on endothelial cells (4). In the present article, however, Barandier et al. (1) went further and also investigated several animal models. They found that aging and diet-induced obesity in Wistar-Kyoto rats enhanced the proliferative activity of conditioned medium of perivascular adipose tissue. In contrast, genetically determined obesity in leptin receptor-deficient obese Zucker rats had no additional effect on the proliferation of vascular smooth muscle cells. This article contributes importantly to the recent interest in the pathophysiological role of perivascular adipose tissue. Endocrine and paracrine actions of adipocytes, especially of those in the vicinity of cardiovascular organs, most likely link obesity and cardiovascular disease (16). This link has been well documented for several years in epidemiological studies (20).

The interest in perivascular adipose tissue developed only very recently; however, the issue itself has a much longer history. Whereas the introduction of the concept that the endothelium regulates vascular tone was originally based on local secretion of vasoactive and inflammatory molecules with or cleaned from the adventitial layer. The first important finding was that the mechanical properties of cleaned or intact aortic rings were not different. Second, they demonstrated that periaortic adipose tissue plays an important role for both norepinephrine clearance (when added exogenously) or nor-epinephrine release (when electric field stimulation was applied to the vascular rings), the latter being dependent on functional angiotensin receptors.

Following this path, Löhn et al. (12) described in 2002 the so-called “adventitium-derived relaxing factor” (ADRF), which was shown to be produced by isolated adipocytes and diminished the contractile response of intact aortic rings to serotonin, angiotensin II, or phenylephrine. They suggested that perivascular adventitial adipocytes release a transferable ADRF that acts by tyrosine kinase-dependent activation of potassium channels in vascular smooth muscle cells. The molecular nature of ADRF is still unknown; however, its presence has been confirmed in small mesenteric arteries (10). ADRF acts independently of leptin receptors; however, leptin itself was also able to diminish angiotensin II-induced vasoconstriction by leptin receptor-mediated inhibition of intracellular calcium increase in smooth muscle cells of the rat aorta (8).

Not only the regulation of vascular contraction appears to be influenced by perivascular adipose tissue. Inflammation after balloon injury was present not only in the intima and media but also in the adventitia (15). After an initial invasion of neutrophils, macrophages accumulated in the perivascular adipose tissue for several days. A somewhat similar situation has been described for adipose tissue of obese mice, where an increase of macrophages was observed (19, 21). A possible scenario is that the increase in adipocyte size during weight gain leads to increased secretion of monocyte chemoattractant protein 1 (MCP-1) from adipose tissue (18). MCP-1 stimulates the expression of adhesion molecules on monocytes, thus allowing the invasion of adipose and other tissues. Macrophage secretory products, such as interleukin-6, TNF-α, and radical oxygen species may then act on adipocytes and lead to impaired local glucose and fatty acid metabolism (2). With respect to obesity-associated vascular disease, one may speculate that perivascular inflammation may act additionally to and perhaps also independently of endothelial damage-associated vascular inflammation.

The possible contribution by perivascular adipocytes to the regulation of vascular tone and to vascular remodeling appears to be especially important because of the current obesity epidemic that has resulted in increased numbers of diabetic and hypertensive patients. If perivascular adipocytes react like adipocytes in other depots, a dysregulation of the secretion of vasoactive and proinflammatory molecules can then be expected. Many molecules that are secreted by adipocytes are secreted in a size-dependent manner, and secretion increases with obesity and increased adipocyte volume. Thus dysregulated local secretion of vasoactive and inflammatory molecules...
in obesity may play an important role for cardiovascular pathophysiology. This hypothesis, however, needs to be vigorously tested in different animal models of obesity, and other adipose tissue depots in contact with cardiovascular organs (e.g., pericardial and perirenal) must also be considered in these analyses (13, 14). Furthermore, advantage should be taken of the fact that longitudinal studies, including multiple time point samples, are possible in weight-gaining animals, so that early changes in the function of perivascular and other adipose tissue depots can be detected that may possibly precede profound obesity-related changes such as atherosclerosis, endothelial dysfunction, and hypertension.

REFERENCES


