# P-Selectin Glycoprotein Ligand-1: A Cellular Link Between Perivascular Adipose Inflammation and Endothelial Dysfunction

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In normal vascular physiology, nitric oxide (NO) plays a key role in maintaining the vascular wall in a quiescent state by inhibition of inflammation, cellular proliferation, and thrombosis (1). What is generally referred to as endothelial dysfunction should more appropriately be considered endothelial activation. Such activation may be beneficial to humans in certain instances, such as during infection, and harmful in others, such as during obesity.

During infection, a reduction in NO may allow for activation of endothelial expression of chemokines, cytokines, and adhesion molecules, designed to recruit and activate leukocytes and platelets. Endothelial activation (endothelial dysfunction) may be considered as a beneficial and physiological response to infection.

In the absence of an active infection, most cardiovascular risk factors (smoking, elevated lipids, hypertension, aging) reduce NO bioavailability—a maladaptive response that sets the stage for the development of atherosclerosis. The reduction in NO by cardiovascular risk factors removes an important anti-inflammatory mechanism in the vessel wall (2), which leads to greater recruitment and activation of vessel wall inflammation and thus to further reduction in NO bioavailability. In a sense, a vicious cycle is started.

The initial trigger for the reduction in vascular NO bioavailability during obesity may involve activation of vascular nuclear factor-κB by increased systemic levels of free fatty acid and/or increased local production of cytokines such as tumor necrosis factor- α, interleukin-6, and interleukin-1β by adipose tissue (3).

In the last several years, studies have identified mechanisms of communication between endothelial cells, adventia, and perivascular adipose tissue (PVAT). The vascular adventia and PVAT are no longer viewed as passive tissues surrounding the blood vessel but as important producers of vasoactive factors and cytokines (4). PVAT is a thin sheet of adipose tissue that consists of adipocytes and stromal cells including fibroblasts, leukocytes, stem cells, and capillaries. It remains stable most of the time, but during obesity the mass of PVAT increases with a larger population of inflammatory tissue macrophages. This is observed in rats that become obese after a high-fat diet (HFD) (5) or in mice that are genetically predisposed to obesity, as in the *db/db* mouse (6). These responses are similar to those observed in omental white fat during high-fat feeding (7); however, the paracrine effects of PVAT on vessel wall functioning may be much stronger because of their close proximity.

In an effort to link obesity with cardiovascular disease, several adipokines have been experimentally shown to significantly impair endothelial function. These include leptin, resistin, and tumor necrosis factor-α (8), and all have been shown to reduce endothelial-dependent vasodilation. However, whether PVAT is the sole provider of these adipokines remains unanswered. Furthermore, despite compelling clinical observations suggesting reduced endothelial function during obesity, the mechanistic link between obesity and the development of endothelial dysfunction remains unclear. In an article in this issue of *Diabetes*, Wang et al. (9) demonstrate a significant role of P-selectin glycoprotein ligand-1 (PSGL-1) in mediating obesity-induced endothelial dysfunction, providing a mechanistic link between PVAT and the onset of endothelial dysfunction.

PSGL-1, a major selectin ligand on leukocytes, interacts with endothelial P-selectin, E-selectin, and L-selectin, and mediates leukocyte tethering and rolling (10,11). PSGL-1 is a mucin-like cell adhesion molecule expressed on the surface of leukocytes and endothelial cells, and PSGL-1 mRNA is expressed in a variety of tissues including bone marrow, brain, adipose, heart, kidney, and liver (12).

Although, the role of PSGL-1 in the formation and progression of atherosclerotic lesion (13) has been known for over a decade, recent studies suggest that PSGL-1 plays a role in increasing leukocyte recruitment into adipose tissue in obesity (14). *PSGL-1* gene expression is upregulated in epididymal white adipose tissue from *db/db* mice and C57BL/6 mice fed an HFD. PSGL-1–deficient mice fed an HFD showed a reduction of macrophage infiltration and inflammation in adipose tissue and improvement of insulin resistance compared with wild-type mice fed an HFD (15).

The absence of PSGL-1 not only reduces monocyte recruitment into gonadal adipose tissue but is also associated with reduced monocyte recruitment into PVAT as shown by Wang et al. As expected, a reduction of mesenteric PVAT inflammatory activation and reduced accumulation of macrophages attenuated the development of endothelial dysfunction in the mesenteric arteries during HFD, providing further evidence for a role of PVAT in reducing endothelial function during obesity. The carotid arteries from wild-type mice, which lack a robust PVAT pad in the presence of high-fat feeding, did not show endothelial dysfunction, whereas a robust mesenteric PVAT pad significantly reduced mesenteric endothelial function, suggesting that local PVAT contributes more to vascular dysfunction than systemic effects in obesity.

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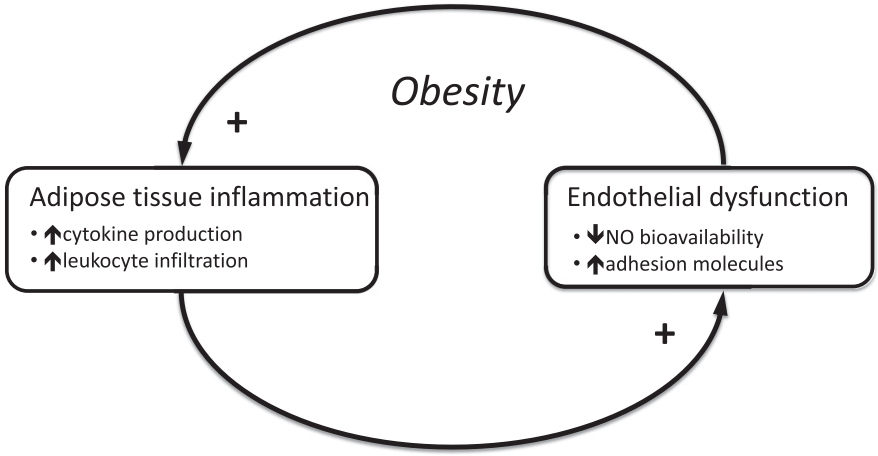


**FIG. 1. During obesity, adipose tissue becomes increasingly inflamed, characterized by increased adipokine production and macrophage infiltration. Increased adipose inflammation results in increased endothelial adhesion molecule expression and reduced NO bioavailability (endothelial dysfunction), which further increases adipose tissue inflammation.**

Presumably, PSGL-1 deficiency reduced endothelial dysfunction by reducing PVAT inflammation. Homogenized fat from obese PSGL-$1^{+/+}$ mice induces endothelial dysfunction ex vivo, whereas homogenized fat from obese PSGL-$1^{-/-}$ mice had little effect on endothelial function. This observation supports the concept that inflammatory fat-derived factor(s) trigger endothelial dysfunction. Identification of the factors downstream of PSGL-1 activation should be a high priority.

Finally, it is conceivable that there is bidirectional crosstalk between PVAT and blood vessels. In obesity, adipokine production and chronic inflammation represented by macrophage infiltration in adipose tissue reduce vascular function by altering local nitric oxide bioavailability or leukocyte-endothelium interaction as suggested by the current article and others (16). Conversely, restoration of NO bioavailability and endothelial function during an HFD using a superoxide scavenger reduces adipose tissue inflammation. Indeed, others have shown that increasing NO signaling pharmacologically (PDE5 inhibitor) or in genetic mouse models attenuates the development of adipose tissue inflammation during an HFD, suggesting a protective role of vascular NO in reducing adipose inflammation (17,18). These findings support a vicious cycle model between PVAT and blood vessels in the setting of obesity (Fig. 1). PVAT inflammation reduces endothelial NO resulting in increased PVAT inflammation leading to further reduction in NO. Infusing anti–PSGL-1 antibody as a strategy to reduce PVAT inflammation, as shown in the current work, increases endothelial NO levels, further reducing PVAT inflammation and breaking the vicious cycle between adipose tissue and vascular endothelium.

A thorough understanding of mechanisms of leukocyte-endothelium crosstalk in inflamed PVAT could have important clinical implications, leading to the development of therapeutic strategies aimed at reducing the cardiovascular diseases associated with obesity.

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