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Role of Perivascular Adipose Tissue on Vascular Reactive Oxygen Species in Type 2 Diabetes: A Give-and-Take Relationship

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COMMENTARY

A major complication of type 2 diabetes (T2D) is atherosclerotic vascular disease, which develops earlier and more rapidly in patients with T2D than in subjects without diabetes (1). One of the characteristic features of T2D is excessive generation of reactive oxygen species (ROS) in the artery wall and the resultant oxidative stress, which contributes to the development of endothelial dysfunction and atherosclerosis (2–5). Moreover, activity of NADPH oxidase, the primary ROS-generating enzyme in vascular cells, has been shown to be increased in T2D (2–5). Notably, behavioral and pharmacological interventions that reduce vascular NADPH oxidase expression and activity demonstrate improvements in endothelial function and reduced atherogenesis (6–8). Furthermore, mice lacking components of the NADPH oxidase subunits are protected against hypertension, and when crossed to the apoE$^{-/-}$ background, they have a marked reduction in vascular ROS production, enhanced nitric oxide bioavailability, and reduced atherosclerotic lesion formation (9,10), thus demonstrating that excessive NADPH oxidase–derived ROS is detrimental to vascular health. Although the recognition that increased vascular NADPH oxidase is an important contributor to vascular complications in T2D, the mechanisms regulating its enzyme activity remain poorly understood.

Recent studies implicate adipose tissue adjacent to the artery wall (i.e., perivascular adipose tissue [PVAT]) as playing an important role in the pathogenesis of vascular diseases (11–13). The PVAT serves not only as a structural support for most arteries but also as a source of an abundance of molecules with varied paracrine effects on the underlying vascular cells (11–14). Indeed, the absence of a separating fascia layer promotes direct paracrine communications between the PVAT and the associated vasculature. Among the plethora of adipose tissue–secreted factors are both proinflammatory and anti-inflammatory vasoactive molecules. As such, the vascular effects of the PVAT are complex, involving changes in vasomotor tone, smooth muscle proliferation and migration, vascular inflammation, and oxidative stress (11–14). Importantly, atherosclerotic lesions develop primarily in arteries encased by the PVAT (15), supporting the contention that the PVAT plays an integral role in lesion development. In addition, current data indicate a positive relationship between the PVAT volume and the severity of vascular disease (16,17). In the setting of obesity and T2D, adipocyte hypertrophy is associated with both the infiltration of proinflammatory immune cells and a reduced expression of anti-inflammatory factors (e.g., adiponectin) in the PVAT (11–13). Adiponectin is secreted by adipocytes and has potent anti-inflammatory, insulin-sensitizing, and cardioprotective effects (18), and circulating levels are significantly reduced in obesity and T2D (19). Accordingly, decreased expression and secretion of adiponectin from the PVAT may provide a permissive environment for vascular inflammation and dysfunction (12,20,21).

In this issue of *Diabetes*, Antonopoulos et al. (22) examine the effect of T2D on NADPH oxidase in human vessels and explore potential mechanisms of this interaction. The authors harvested internal mammary arteries (IMAs) with their PVAT from 386 patients with and without diabetes who were undergoing coronary bypass surgery. This comprehensive investigation also includes

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genetic analyses. Not entirely surprising, patients with T2D had low levels of circulating adiponectin and increased vascular NADPH oxidase–derived ROS. Notably, genetic variability of the gene coding for adiponectin (*ADIPOQ*) and circulating adiponectin were independent predictors of NADPH oxidase–derived ROS. In an elegant set of ex vivo experiments, the authors were able to pinpoint a mechanism by which adiponectin protected against ROS production. That is, treatment of human IMA segments with recombinant adiponectin suppressed NADPH oxidase activity in all layers of the vascular wall by preventing activation/membrane translocation of Rac1 and downregulating $p22^{phox}$ in a phosphoinositide-3 kinase/protein kinase B–dependent manner. Somewhat paradoxically, increased vascular NADPH oxidase–derived ROS in the artery wall was positively associated with adiponectin mRNA levels in the PVAT that surrounded it. Next, experiments involving the coincubation of IMA and PVAT demonstrated that activation of arterial NADPH oxidase leads to the local production of oxidation products (e.g., 4-hydroxynonenal), which, in turn, upregulates adiponectin expression in the adjacent PVAT in a peroxisome proliferator–activated receptor-γ–mediated manner.

Taken together, in their sequence of experiments, the authors eloquently put forth that reduced adiponectin in T2D leads to increased vascular NADPH oxidase–derived ROS, while the PVAT "senses" increased NADPH oxidase activity in the underlying vessel and responds by upregulating adiponectin gene expression (Fig. 1). The finding that oxidation products released from the artery wall represent "rescue signals" to increase PVAT adiponectin represents an exquisite self-control mechanism designed to attenuate vascular oxidative stress in the setting of T2D. This convincingly illustrates that the cross talk between the PVAT and associated vasculature is bidirectional (i.e., outside-in and inside-out). The finding that PVAT-derived adiponectin reduces vascular NADPH oxidase–derived ROS, in part via the downregulation of $p22^{phox}$, is remarkable in light of *1*) the mounting evidence, discussed above, indicating that excessive vascular NADPH oxidase–derived ROS is a major contributor to vascular complications in T2D and *2*) the recent and exciting data reported by Youn et al. (23), also published in *Diabetes*, demonstrating that vascular ROS plays a causal role in the development of obesity and metabolic syndrome. Youn et al. (23) showed that mice overexpressing $p22^{phox}$ in vascular smooth muscle are highly susceptible to obesity and insulin resistance. Reciprocally, mice with vascular smooth muscle–targeted deletion of $p22^{phox}$ are protected against high-fat diet–induced weight gain and T-cell infiltration into the PVAT. Therefore, it appears that increased vascular ROS in obesity and T2D may further exacerbate metabolic dysfunction, hence highlighting the importance of identifying signals (e.g., adiponectin) involved in regulating vascular redox.

Collectively, the study by Antonopoulos et al. (22) demonstrates, for the first time, the important role of adiponectin in the regulation of vascular NADPH oxidase activity and ROS, suggesting that reduced secretion of adiponectin from adipose tissue plays an important role in the development of vascular complications associated with T2D. Further, the authors demonstrated that the PVAT senses oxidation products derived from the underlying artery wall and responds by increasing expression of adiponectin, thus suggesting the existence of a local protective mechanism to prevent vascular oxidative stress. Future research should determine whether disruption of this PVAT-artery give-and-take relationship puts the arteries at greater risk for atherosclerosis and identify strategies that may serve as therapeutics by "hijacking" this intricately controlled mechanism to enhance adiponectin-vascular signaling.

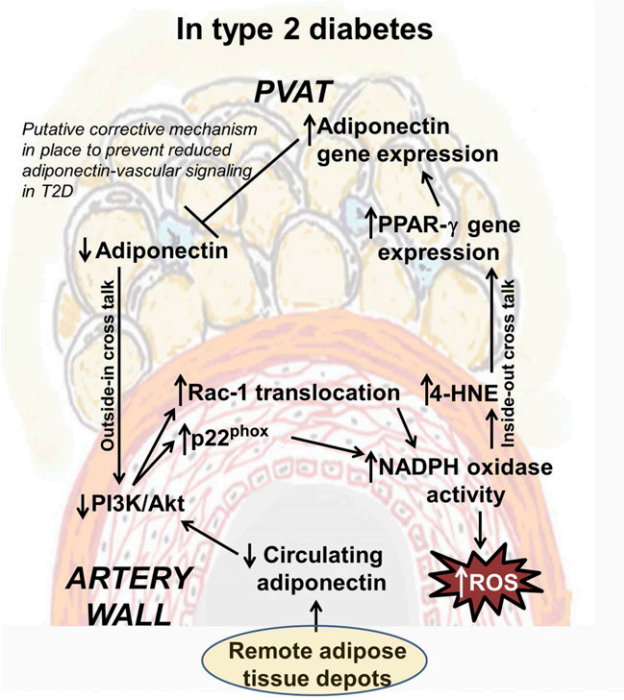

Figure 1—Proposed novel cross talk between the PVAT and vascular wall. 4-HNE, 4-hydroxynonenal; PI3K/Akt, phosphoinositide-3 kinase/protein kinase B; PPAR-γ, peroxisome proliferator–activated receptor-γ.

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