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Caveolin-1 in Cardiovascular Disease: A Double-Edged Sword

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Endothelial dysfunction, as manifested by an attenuation of nitric oxide (NO)–mediated vasodilation, is recognized to be a fundamental abnormality in the genesis of hypertension, atherosclerosis, and coronary artery disease (1). Metabolic risk factors, such as obesity, insulin resistance, and type 2 diabetes (T2D), can initiate and accelerate endothelial dysfunction leading to cardiovascular disease (CVD) (1). Endothelial dysfunction in association with metabolic abnormalities is typically caused by a combination of reduced production and increased destruction of NO leading to a decrease in NO bioavailability (1,2). NO production in response to various factors, such as increased shear stress, is mediated by endothelial nitric oxide synthase (eNOS), which is constitutively expressed in endothelial cells (ECs) and is tightly controlled by various membrane-bound receptors and regulatory proteins under physiological conditions (3). Caveolin-1 (Cav-1), an anchoring protein in the plasma membrane caveolae in ECs and vascular smooth muscle cells (VSMCs), attenuates endothelial NO production by occupying the calcium/calmodulin (Ca^{2+}/CaM) binding site of eNOS (4) (Fig. 1). Increases in caveolin and eNOS interaction, as may occur with hyperlipidemia, reduce NO production and promote endothelial dysfunction and atherosclerotic lesion formation. This process is mediated by increased lipoprotein trafficking across the vascular endothelium (5,6). Therefore, treating hyperlipidemia as an early intervention to help prevent endothelial dysfunction is an important strategy to reduce CVD.

In ECs, Cav-1 anchors eNOS in plasma membrane caveolae, which limits its translocation and phosphorylated activation and thereby reduces its capacity to generate NO (7) (Fig. 1). On one hand, increased cytosolic Ca^{2+}/CaM leads to eNOS activation and its dissociation from Cav-1 (6). On the other hand, an increase in Ca^{2+} induces eNOS translocation from the cell membrane to the cytosol or Golgi complex (8), where it is phosphorylated and fully activated by protein kinases that reside in caveolae, such as p38 mitogen-activated protein kinase, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt), cAMP-dependent protein kinase A, and 5′ AMP-activated protein kinase (7). It is now recognized that a major mechanism involved in eNOS activation is phosphorylation of eNOS at the Ser^{1177} residue (1,2). In addition to subcellular location and protein-protein interactions, several phosphorylation and dephosphorylation sites also modulate eNOS activity (9). For example, PI3K/Akt-mediated eNOS phosphorylation at Ser^{1177} increases the activity of the enzyme and reduces its Ca^{2+} dependency (9) (Fig. 1). Activated eNOS converts L-arginine to L-citrulline and increases NO, which diffuses into VSMCs and activates guanylyl cyclase, producing cyclic guanosine monophosphate and activating kinases responsible for vessel relaxation (9). Normally NO modulates the phosphorylated state of myosin light chain phosphatase to reduce myosin light chain kinase sensitization/activation. Thus, elevations in VSMC levels of intracellular Ca^{2+} and Ca^{2+} sensitization increase the ambient state of vessel constriction in states of obesity and T2D (9). Thus, direct binding of eNOS to the scaffolding domain of Cav-1 is a well-accepted mechanism for downregulating NO production and associated endothelial dysfunction and CVD (6). Consistent with this notion, insulin resistance and T2D induce oxidative stress and increase Cav-1 expression, and a peptide containing the region of the Cav-1 scaffolding domain that binds to eNOS inhibits acetylcholine-induced NO production and vasodilation (5,6), whereas Cav-1 knockout enhances acetylcholine-induced arterial relaxation (5,6). However, it is noted that hyperactive eNOS activity or excessive NO production can increase superoxide production and nitrosative stress and thus conversely impair NO bioavailability (10). Therefore, Cav-1 may maintain the normal vessel function through its ability to modulate NO production under normal physiological conditions.

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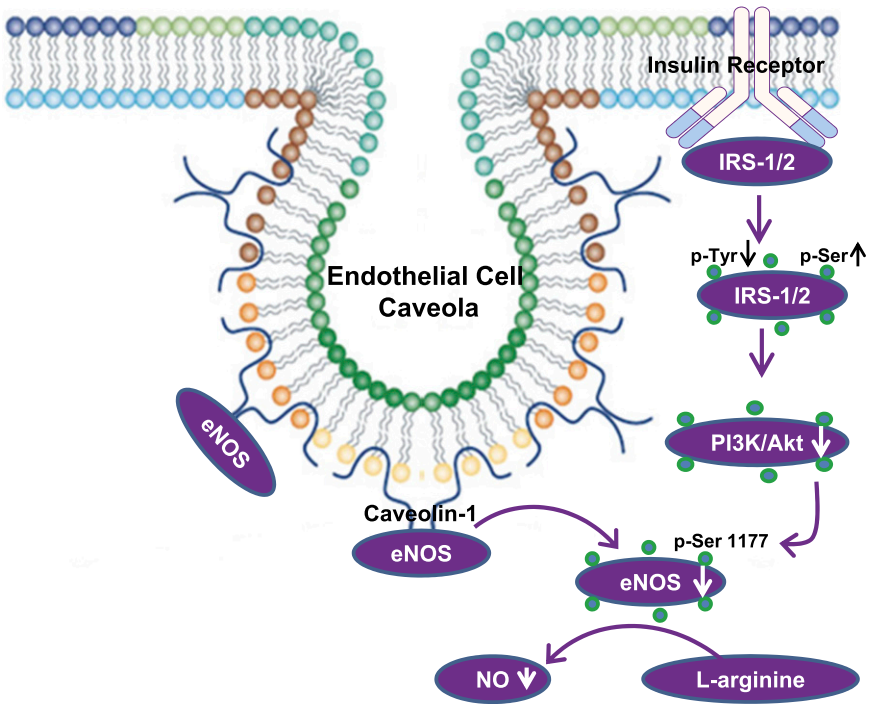

Figure 1—Proposed interaction of Cav-1 and eNOS in the pathogenesis of endothelial dysfunction. IRS-1/2, insulin receptor substrate 1/2.

In this issue of *Diabetes*, Sharma et al. (11) investigated the therapeutic effect of CavNOxin on the development of atherosclerosis by using an insulinopenic type 1 diabetes model and Western diet–induced T2D model. CavNOxin, a cell-permeable, Cav-1–derived peptide with T90,91,F92 substituted to alanines, has been shown to increase eNOS activity (12,13). The current study further demonstrated that CavNOxin normalized oxidative stress and attenuated diabetes-induced atherosclerosis by up to 86% in vivo, whereas eNOS inactivation rendered diabetic animals resistant to CavNOxin treatment. Mechanistically, CavNOxin lowered oxidative stress markers, inhibited the expression of proatherogenic mediators, and blocked leukocyte-endothelial interactions while preserving Cav-1–dependent biological activities such as caveolae formation. Therefore, these data indicate that CavNOxin can directly and specifically trigger the protective function of eNOS, suggesting that this interaction should be considered a direct pharmacological target to lessen the burden of diabetic end-organ injury, such as endothelial dysfunction, and associated atherosclerosis, hypertension, and CVD.

While these data highlight a central role of CavNOxin in the regulation of eNOS activity and NO production, several caveats need to be considered. For example, this study did not investigate the efficiency of CavNOxin in the inhibition of Cav-1 and upregulation of eNOS activity production, which is important in understanding the interaction of Cav-1 and eNOS and cross-talk signal regulation in eNOS activation. Indeed, impaired insulin metabolic downstream signaling can inhibit eNOS activity (2) (Fig. 1). Further, it is possible that CavNOxin treatment could inappropriately increase the activity of eNOS, resulting in superphysiologic levels of NO and increased generation of the reactive peroxynitrite radical ($ONOO^-$) (14). $ONOO^-$ has numerous detrimental effects in the cardiovascular system and plays a crucial role in the development of insulin resistance and diabetes-associated vascular diseases (1,2). To this point, hyperactivated eNOS has been implicated in several cardiovascular and pulmonary pathologies in Cav-1 knockout mice, and inhibiting excessive eNOS activation prevents these pathologies (7,15). Thus, it is very important to balance the interaction of Cav-1 and eNOS under normal physiological conditions.

In summary, these data identified a physiologic relevant role of Cav-1 in the regulation of eNOS activation and provided evidence that the interaction of Cav-1 and eNOS could be a novel target site for the regulation of CVD (11). Further studies are necessary to develop safe and clinically effective modulators of the Cav-1/eNOS interaction in vascular and whole-body insulin homeostasis in the population with T2D.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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