EDITORIAL

Endothelial NF-κB: the remote controller of the backyard fire in the vascular wall?

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This editorial refers to 'Importance of endothelial NF-κB signaling in vascular remodelling and aortic aneurysm formation' by T. Saito et al., pp. 106–114, this issue.

It has been established in the past few decades that the vascular endothelium, the monolayer of cells covering the inner surface of the vessel wall, functions as a master regulator to maintain the physiological integrity of vascular function and structure by actively releasing numerous vasoactive hormones that control smooth muscle cell contraction and proliferation and inflammatory cell adhesion and infiltration into the vascular wall.[1] Endothelial dysfunction, which usually refers to a decrease in bioavailability of the vasoprotective nitric oxide (NO) from endothelial NO synthase (eNOS) in the presence of cardiovascular risk factors such as hypertension, hypercholesterolaemia, hyperglycaemia, and ageing, includes also other functional alterations due to pro-inflammatory, pro-coagulant, and prothrombotic properties and plays an important role in promoting atherosclerotic vascular disease.[1] This endothelium-centric 'inside-out' injury paradigm of pathogenesis of vascular disease was initially proposed by Ross and Glomset in 1970s[2] and has led to the important concept that modification to preserve the luminal endothelial function would protect blood vessels from the development of vascular diseases. Indeed, emerging research from studies of recent years demonstrates that mice with endothelium-specific inhibition of functional nuclear factor-κB (NF-κB) signalling, the major transcription factor in mediating inflammation,[3] are protected from atherosclerosis,[4] hypertension-induced renal damage,[5] septic shock, and septic endothelial dysfunction.[6] Most recently, Katagiri's group showed that mice with endothelium-specific blockade—by transgenic expression of dominant-negative IκBα under the control of the Tie2 promotor/enhancer (E-DNIκB mice)—are also protected from the development of insulin resistance associated with obesity and ageing, and the mice have a prolonged lifespan.[7] The same group in the current issue of *Cardiovascular Research*[8] now further demonstrates that these mice with endothelium-specific inhibition of NF-κB signalling show attenuated intimal hyperplasia and aneurysm formation most likely through inhibition of vascular inflammation and matrix metalloproteinases (MMPs).

What are the major, special advances of this study compared with the previous studies? Unlike the conventional experimental approach, which induces intimal hyperplasia in arteries by damaging the endothelial layer through angioplasty, the authors introduce vascular injury from the adventitial side of the femoral artery in mice by placing a perivascular cuff surrounding the blood vessel. This is a typical vascular remodelling model in which injury initially occurs in the adventitia instead the endothelial layer. In addition, the aortic aneurysmal mouse model—hypercholesterolaemic, atherosclerosis-prone, ApoE-deficient mice with or without E-DNIκB, and treated with angiotensin II to facilitate vascular wall inflammation, a well-studied vascular remodelling model mainly associated with media and adventitial degeneration[9]—was also used to investigate the cross-talk between the endothelium and the media/adventitia. The term 'vascular remodelling' is considered a process that mainly occurs in adventitia and media, where chronic inflammation plays a key role.[10] It refers to a spatial reorganization of the vascular wall components resulting in geometric changes. Vascular remodelling can be either inward (constrictive), leading to lumen narrowing, or outward (expansive), leading to vascular lumen enlargement, and it is the crucial process responsible for *de novo* atherosclerosis, restenosis after coronary intervention, and aortic aneurysm formation.[11,12] Although the cellular and molecular mechanisms that control vascular remodelling are poorly understood, it has been suggested that myofibroblast proliferation, smooth muscle cell phenotype transformation, cell apoptosis, inflammatory cell infiltration, and secretion of inflammatory cytokines and MMPs, which modify extracellular matrix composition, act in concert to determine the pathological vascular remodelling process that leads to either vascular (re)stenosis or aneurysm formation.[12] The results of this study by Katagiri's group are of particular relevance towards understanding the regulatory mechanisms of vascular remodelling and indicate that the vascular endothelium is capable of sensing injury from adventitia through NF-κB signalling, participating in pathological vascular remodelling.

However, this concept remains to be fully proved and the following critical questions must be adequately addressed: (i) What are the initial signals generated from adventitial injury and from which cells do the signals derive? (ii) How are these signals transmitted to the endothelial cells and how is NF-κB signalling activated in these cells?

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(iii) What is the molecular mechanism of the NF-κB signalling blockade in endothelial cells responsible for the inhibition of pathological vascular remodelling and associated inflammation? Is this attributable to improved eNOS function, since eNOS expression is enhanced in the E-DNIκB mice and eNOS gene deficiency abolishes the effects of decreased systemic blood pressure and increased muscle blood flow in aged E-DNIκB mice[7] and functional intact eNOS is important for inhibition of vascular inflammation and ageing?[13] (iv) Is there a vicious circle between adventitial 'outside-in' injury and endothelial 'inside-out' injury? Although the answer is likely 'yes', it has to be proved. (v) Finally, the most critical question that remains unanswered is whether the inhibitory effects of vascular inflammation and pathological remodelling observed in this study are attributable, at least in part, to the functional preservation of the endothelial cells of the adventitial vasa vasorum in the E-DNIκB mice, since the vasa vasorum has been suggested to be an important player in mediating vascular wall inflammation and remodelling.[14] Answering these questions will further strengthen and prove the currently developed vascular 'outside-in' injury concept and will also have an important impact on understanding the mechanisms of pathogenesis of atherosclerosis and vascular complications associated with risk factors such as obesity and ageing in which perivascular tissue dysfunction in vascular diseases is implicated.[15]

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