Vasoconstriction: tightening the noose through MMPs

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This editorial refers to ‘Maintenance of adrenergic vascular tone by MMP transactivation of the EGFR requires PI3K and mitochondrial ATP synthesis’ by P.R. Nagareddy et al., pp. 368–377, this issue.

Arterial tone is dependent on a balance between agents that lead to relaxation of arterial vascular smooth muscle cells (VSMCs) and agents that cause contraction of the same. The process of contraction at a mechanical level requires interaction of structural proteins including myosin light chain 2 (MLC2) and actin. The interaction of these leads to force transduction and cell shortening, ultimately causing vessel diameter narrowing and increased resistance to blood flow. Physiological vasoconstrictors, such as norepinephrine, work through binding cell receptors on VSMCs and activating G-protein-coupled receptors (GPCRs). These in turn interact with several classes of heterotrimeric G-proteins to affect a diverse range of cell responses.1,2

Phenylephrine, a synthetic surrogate of physiological agonists like norepinephrine, acts to induce vasoconstriction by binding to adrenergic receptors (α1) and activating Gαq, which in turn increases phospholipase C (PLC) activity and formation of inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). These events result in the release of calcium from intracellular stores (Figure 1).

In their article published in Cardiovascular Research, Nagareddy et al.3 provide evidence that MMP–EGFR (matrix metalloproteinase–epidermal growth factor receptor) signalling contributes to phenylephrine-induced vasoconstriction. The present work builds upon prior findings by the same group that MMP cleavage and EGFR activation can promote vasoconstriction by a mechanism that involves mitochondrial reactive oxygen species (ROS) generation.4 Here, they show that MMP–EGFR-dependent vasoconstriction is dependent on phosphoinositide 3-kinase (PI3K) activation and subsequent mitochondrial ATP generation. Although elucidation of the signalling downstream from MMP–EGFR is interesting, it is not yet clear if this pathway is a major contributor to acute modification of arterial tone. As the authors note, previous studies and new results show that blocking EGFR can neither alter MLC2 phosphorylation nor inhibit phenylephrine-stimulated changes in ATP generation, although pre-contracted vessels dilate in response to the same.3

Although the authors establish a link between MMP transactivation of EGFR-induced PI3K/Akt activation and vasoconstriction, it has also previously been shown in vascular cells that the PI3K pathway, which activates the serine/threonine protein kinase Akt, can enhance the production of the signalling molecule nitric oxide (NO) through the phosphorylation of the enzyme NO synthase.5,6 This is interesting to note since this ubiquitous biogas is an important regulator of vascular health that works through the suppression of both inflammation and thrombosis and through the enhancement of blood flow by stimulating arterial dilation. Consistent with this protective effect of NO, recent work links PI3K/Akt activation with concurrent NO production in VSMCs and angiotensin II (Ang II) resistance in arterial segments.7 These seemingly contradictory effects of PI3K/Akt signalling remain the subject of active research and may be explained by temporal or compartmental differences. As a rapid-acting paracrine signalling molecule, NO mediates vasodilation acutely through the reversible activation of soluble guanylate cyclase (sGC) and the accumulation of cGMP in the cytosol. This acute effect may be diminished over time by conditions such as chronic ROS generation. In addition, NO may have pro-constrictive effects in certain compartments. In the mitochondrion, NO is an important regulator of organellar function that has been hypothesized to increase ROS generation through its binding to cytochrome c oxidase, which leads to the accumulation of electrons within the respiratory chain.8 In this manner, the production of low levels of NO may increase mitochondrial ROS generation, which could act as a feed-forward mechanism for PI3K/Akt signalling. In addition, several studies suggest that NO can be pro-proliferative, which could further drive arterial hypertrophy chronically.9,10 These chronic effects could outweigh the acute protective effects of NO in some conditions, contributing to pathology.

Consistent with the authors’ suggestion that the pathway described herein may represent a means by which the VSMC phenotype is altered on a chronic basis, leading to mural...
thickening and heightened arterial tone, recent analysis in human subjects determined a link between increased MMP activity and several vascular-based diseases, including hypertension, diabetes, and kidney failure. Although further research will determine the role of PI3K in the balance between vasoconstriction and NO-mediated vasodilation, this study along with published clinical data suggests that the MMP–EGFR pathway could potentially be a novel therapeutic target for treating chronic vasculopathy.

References