Going With the Flow
Smooth Muscle TRPM7 Channels and the Vascular Response to Blood Flow

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Blood vessels sense and respond to the flow of circulating blood, and increases in flow most commonly lead to vasodilatation and increased vascular conductance. The main sensor of flow is the endothelial lining of the blood vessel lumen, which sits at the interface between the vessel wall and flowing blood. The fluid shear stress associated with an increase in flow is detected as a mechanical stimulus by the endothelial cells, which release endothelium-derived relaxing factors onto the nearby smooth muscle cells, causing them to relax. Because the smooth muscle cells lie below the endothelial cell layer they are normally protected from direct exposure to the fluid shear stresses caused by flowing blood. They may however sense significant shear stress from the pressure-driven flow of interstitial fluid through the vessel wall, the magnitude of which may be influenced by blood flow.3 Smooth muscle cells become exposed directly to the shear stresses of flowing blood when the endothelial cell layer is damaged, which occurs at the anastomoses of vascular grafts, in vessels subject to balloon angioplasty, and in atherosclerotic lesions. Under these conditions, direct effects of fluid shear stress on smooth muscle cells are likely to become important.

Whereas acute changes in blood flow influence vessel diameter and tone, more persistent changes in flow lead to chronic and profound alterations in blood vessel structure, involving cell proliferation, apoptosis, altered extracellular matrix, and even arteriogenesis.4 These adaptations have generally been investigated in relation to the effects of fluid flow on endothelial cells. Although little studied to date, fluid flow also affects smooth muscle cells directly. For example, exposing cultured human aorta myocytes to physiological levels of flow-induced shear stress results in a reduced rate of cell proliferation.5 This has important implications for the consequences of vascular injury and may explain why high flow inhibits the development of neointimal hyperplasia after balloon injury6 and why atherosclerosis progresses more rapidly in regions of low shear stress.7

Direct exposure to fluid flow causes several biochemical changes in vascular smooth muscle cells, each of which could contribute to the acute or long term regulation of smooth muscle cell activity, especially in vessels lacking a healthy endothelium. For example, physiological levels of flow-induced shear stress (<10 dyn/cm²) elevates the cytosolic Ca²⁺ concentration in rat aorta smooth muscle cells through a mechanism that appears to involve, at least in part, Ca²⁺ entry through a gadolinium-sensitive pathway.8 This direct effect on vascular myocytes could underlie the vasoconstrictor response to flow that has been observed in a number of resistance arteries and small veins in vitro, as these responses were retained after removal of the endothelium, required Ca²⁺ influx, and were inhibited by agents that block Ca²⁺ entry into smooth muscle cells.9 Indeed, flow has been shown to contract cultured aortic smooth muscle cells, although higher levels of shear stress (≥11 dyn/cm²) were required to produce this effect and it appeared to involve a Ca²⁺-independent signaling mechanism.10 An elevated Ca²⁺ concentration could also be involved in the production of nitric oxide, prostacyclin, and other mediators that are reportedly elevated in cultured aortic myocytes in response to fluid flow.11,12

Although a number of effects of flow on smooth muscle cells have been described, the signal transduction mechanisms involved are poorly understood. In this issue of Circulation Research, Oancea et al13 report that functional TRPM7 channels, which are expressed in vascular smooth muscle cells, accumulate rapidly at the plasma membrane in response to physiological levels of fluid flow. Because TRPM7 channels are permeable to Ca²⁺ the increased TRPM7 activity is likely to mediate a rise in cytoplasmic Ca²⁺ concentration, which may well trigger smooth muscle contraction and/or stimulate the production of mediators or activate signaling pathways involved in the smooth muscle adaptation to flow. The sensitivity of TRPM7 channels to gadolinium14 is consistent with the inhibitory effect of this ion on the flow-induced elevation of smooth muscle Ca²⁺ concentration.8

Unusually for an ion channel, the TRPM7 protein not only contains a pore-forming divalent cation-selective channel domain, but also possesses an enzymatically active protein kinase domain at its C terminus.14 Functional interactions between these domains are the subject of debate, but it is clear that the activity of the kinase could potentially be modulated by Mg²⁺ entering the cell through the channel.15 Thus in addition to stimulating Ca²⁺ influx, the increased membrane activity of TRPM7 caused by flow-induced shear stress may result in altered protein kinase activity. TRPM7 proteins are therefore multifunctional and well placed to integrate the multiple signaling pathways that are activated in smooth muscle cells, directly or indirectly, after vascular injury.

Several members of the transient receptor potential (TRP) family of cation channels have been implicated in the regulation of vascular function in health and disease.16 TRPM7 is a ubiquitously distributed member of the melastatin-related TRP subfamily (TRPM) of these channels.14 It is highly permeable to Mg²⁺ and until now, in vascular smooth muscle, it has mainly been implicated in Mg²⁺ homeostasis.17 The novel discovery that its activity is enhanced by flow-induced shear stress gives it particular relevance to vascular disease. Altered Mg²⁺ homeostasis appears to be a risk factor in...
The discovery that fluid flow stimulates TRPM7 incorporation into the plasma membrane was enabled by the novel use of green fluorescent protein (GFP)-tagged TRPM7 in conjunction with total internal reflection fluorescence (TIRF) microscopy, which conferred the ability to visualize translocation of the channel from vesicular structures within the cell. Consequently this response to flow could only be visualized in cell lines transfected with the GFP construct. Nevertheless, using immunostaining the authors were able to demonstrate a similar vesicular pattern of native TRPM7 expression in A7R5 aortic smooth muscle cells and flow-induced shear stress in the physiological range (15 dyn/cm²) was shown to increase the amplitude of a native TRPM7-like current. Endothelial cells, in contrast, displayed low levels of TRPM7-like current, which was not increased by flow-induced shear stress. The rapid membrane accumulation of TRPM7 channels, leading to increased TRPM7 current, appears therefore to be specific to the smooth muscle cell. The rapid time course of the response suggests that it is an early event in the response to increased flow and is therefore likely to contribute to the acute response of smooth muscle cells to flowing blood, encountered after vascular injury.

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