Editorial

KV1.3
A New Therapeutic Target to Control Vascular Smooth Muscle Cell Proliferation

William F. Jackson

Cellular proliferation requires an increase in expression and function of K⁺ channels. Blockade of K⁺ channels inhibits proliferation of many cell types, including vascular smooth muscle cells. Previous studies have shown growth factor-induced upregulation of KCa3.1 (sK4, IK1, locus KCN4) in cultured smooth muscle cells; selective inhibition of these channels reduces smooth muscle cell proliferation. Importantly, KCa3.1 blockers also attenuate restenosis after balloon injury in rat and pig models, and they limit atherogenesis in a mouse model of this disease. However, KCa3.1 does not appear to be the only K⁺ channel that can function in this role. In human uterine artery smooth muscle cells, KV3.4 (locus: KCNE3) appears to function similarly, as its expression is upregulated during proliferation, and selective blockade of these voltage-gated K⁺ channels inhibits proliferation. New research by the same group presented in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology further extends these findings to show that in both proliferating, cultured mouse smooth muscle cells and balloon-injured mouse arteries, expression of KV1.3 (locus: KCNC4) is upregulated and that selective blockade of these channels attenuates smooth muscle cell migration and proliferation. Smooth muscle cells join a long list of cell types in which KV1.3 is involved in proliferation. The findings of Cidat et al are particularly interesting given the importance of KV1.3 in T lymphocyte function, the significance of these immune cells in atherosclerosis, and the recent identification and development of selective inhibitors for these voltage-gated K⁺ channels. Thus, the therapeutic potential of KV1.3 as a target in vascular proliferative diseases is significant.

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Cidat et al. used a microarray-based screen to evaluate expression of 87 ion channels in both cultured mouse smooth muscle cells and cells from balloon-injured vessels compared with freshly isolated femoral arteries. Common to both the in vitro model of proliferation and the balloon-injured vessels was an increase in expression of message for KV1.3, data supported by the pharmacology of whole-cell K⁺ currents, immunohistochemistry, and results showing that both pharmacological inhibition of KV1.3 and short interfering RNA knockdown of this channel blunted migration and proliferation of vascular smooth muscle cells. Because blockade of KV1.3 also inhibited proliferation of smooth muscle cells from mesenteric and uterine arteries, the authors suggest that KV1.3 may be more generally involved in smooth muscle cell proliferation. What was surprising about this study was the lack of identification of KCa3.1 as a major player through the authors’ screen, despite extensive research regarding this channel and smooth muscle cell proliferation. This likely relates to the lack of fidelity of mRNA and functional protein expression, but it could also mean that differences in culture conditions or mouse strain account for differences relative to studies where KCa3.1 channels have shown to be involved. Furthermore, it is highly likely that multiple K⁺ channels participate in tuning the function of smooth muscle cells during proliferation, similar to the situation in nonproliferating contractile smooth muscle cells, where as many as 5 different classes of K⁺ channels operate in concert to regulate vascular smooth muscle tone.

As with prior studies, what remains unexplained is the precise mechanism by which smooth muscle cells transduce an increase in K⁺ channel expression and function into a signal for proliferation. Three non–mutually exclusive mechanisms have been proposed: membrane hyperpolarization, regulation of cell volume, and participation of K⁺ channels in signaling complexes. Studies in a number of systems support the hyperpolarization hypothesis. In this scheme, K⁺ channel-induced membrane hyperpolarization increases (or maintains) the electrochemical gradient for Ca²⁺ influx through non-voltage-gated, Ca²⁺-permeable ion channels as recently has been shown in prostate cancer cells. If this hypothesis is correct, blockade of active K⁺ channels should depolarize the cells and inhibit proliferation. Cidat et al. excluded this correlate by showing that depolarization, per se, using either elevation of extracellular K⁺ or application of nonselective K⁺ channel blockers, did not substantially inhibit smooth muscle cell proliferation, whereas blockade of KV1.3 slightly depolarized the cells and significantly blunted proliferation. As the authors did not study cell cycle–synchronized cells and did not measure membrane potential during the transition into the proliferative state, a role for transient membrane hyperpolarization as a signal for proliferation cannot be excluded. However, they did observe that elevation of extracellular K⁺ (which reduces the electrochemical gradient for K⁺ diffusion through K⁺ channels) blunted the inhibitory effect of KV1.3 channel blockade on proliferation. This observation suggests that K⁺ movement through the
KV1.3 channel is required, at least in part, for proliferation. Potassium channels also play significant roles in cell volume regulation,\(^7\) which is intimately connected to cell proliferation.\(^8\) Thus, KV1.3 may be involved in cell volume regulation that is required for proliferation. More intriguing is the possibility that KV1.3 may participate in signaling complexes and function independently from its role as an ion channel.\(^11,19\) For example, studies in T cells\(^20\) and melanoma and function independently from its role as an ion channel.\(^21\) have provided evidence that KV1.3 interacts with and activates, in a reciprocal fashion, B\(1\)-integrins involved in motility and adhesion. The binding partners associated with KV1.3 in smooth muscle cells to promote proliferation have not been established, but this area of investigation offers exciting possibilities for future research.

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