Potassium Channels and Proliferation of Vascular Smooth Muscle Cells

William F. Jackson

Potassium channels play a major role in the immediate and long term regulation of vascular smooth muscle function. The activity of these ion channels determines and regulates cell membrane potential, which, in turn, regulates the open state probability of voltage-gated Ca\(^{2+}\) channels, Ca\(^{2+}\) influx, and intracellular Ca\(^{2+}\). The concentration of intracellular Ca\(^{2+}\) not only regulates the immediate contractile responses of smooth muscle cells (ie, vascular tone), but also the long term responses of these cells through control of gene expression. By their effect on membrane potential, K\(^{+}\) channels also establish the electrochemical gradient that determines the movement of other ions across the plasma membrane. In addition, potassium channels participate significantly in cell volume regulation.

Over the past two decades it has become apparent that K\(^{+}\) channels also play an important role in cell proliferation. In vascular smooth muscle cells, investigators have identified increased expression of intermediate conductance, Ca\(^{2+}\) -activated K\(^{+}\) (IKCa) channels (KCa3.1, locus: KCNN4) associated with proliferation, and recent studies have shown that selective inhibition of these channels prevents vascular smooth muscle proliferation associated with injury-induced restenosis. The study by Miguel-Velado et al in this issue of Circulation Research confirms an important role for K\(^{+}\) channels in vascular smooth muscle cell proliferation. The authors extend this area by showing that Kv3.4 channel (locus: KCNC4) expression is increased in proliferating smooth muscle cells from human uterine artery and that blockade of these channels inhibits proliferation. These Kv channels have also been implicated in proliferation of an oral squamous cell carcinoma, and their expression is increased in growth cones of retinal ganglion cells. Although Kv3.4 channels, and other members of the voltage-gated K\(^{+}\) channel superfamily of K\(^{+}\) channels such as Kv1.3, Kv10.1, and Kv11,5 have been implicated in proliferation of other cell types, the study by Miguel-Velado and associates is the first to suggest that the Kv3 family participates in proliferation of smooth muscle cells. This finding is significant for several reasons. First, it suggests that there may be regional or cell-specific differences in the K\(^{+}\) channels that are used during smooth muscle proliferation. Such differences offer the potential for development of regional or cell-specific inhibitors of K\(^{+}\) channels, or the signaling pathways associated with their upregulation, that might be used to control pathological proliferation of vascular smooth muscle cells associated with diseases such as atherosclerosis, hypertension, and cancer. Second, the study by Miguel-Velado et al adds to the large body of evidence for a crucial role of K\(^{+}\) channels in cell proliferation. Although there remains little doubt that increased K\(^{+}\) channel expression and function are necessary for cells to proliferate, the mechanistic role for K\(^{+}\) channels in this process remains unclear (see below). By having a new target K\(^{+}\) channel in smooth muscle, it may be possible, through comparative studies using genomic and proteomic approaches, to define commonalities among different K\(^{+}\) channels and proliferation in one cell type. Finally, the study by Miguel-Velado and colleagues reinforces the notion that proliferating smooth muscle cells in culture are a poor model system in which to study normal ion channel expression and physiological function.

What remains to be established in smooth muscle and in other cells is the mechanistic link among increased K\(^{+}\) channel expression, K\(^{+}\) channel function, and proliferation. Several hypotheses have arisen based on the known functions of K\(^{+}\) channels including effects on membrane potential and calcium signaling, effects on cell volume regulation, and effects related to formation of signaling complexes (Figure). Studies from lymphocytes and tumor cells suggest that progress into G1 of the cell cycle requires K\(^{+}\) channel-induced membrane hyperpolarization. Hyperpolarization does not appear to account for the impact of Kv3.4 channel expression in the study by Miguel-Velado et al, because proliferating smooth muscle cells were found to be depolarized compared with freshly isolated cells. However, transient hyperpolarization associated with entrance into G1 was not excluded by Miguel-Velado et al, as the cells studied were not synchronized and the cell cycle state in which membrane potential was measured was not assessed. Although not established by the present study, the rapid voltage-dependent inactivation of Kv3.4 channels might actually contribute to the depolarized phenotype in the proliferating cells. In smooth muscle cells from pulmonary arteries, inhibition and decreased expression of other Kv channels results in membrane depolarization, elevated intracellular Ca\(^{2+}\), and increased proliferation. This mechanism also does not appear to be a viable alternative in uterine artery cells, because Kv3.4 channel blockade inhibited, rather than enhanced, proliferation. Decreased K\(^{+}\) channel function in pulmonary smooth muscle cells limits the ability of the cells to reduce cell volume, an effect that inhibits apoptosis, amplifying cell...
Mechanisms by which increased Kv3.4 channel expression might increase cell proliferation. Growth factors, such as those present in serum, trigger expression of Kv3.4 channels. The increased expression of Kv3.4 channels then has the potential to impact cell membrane potential, volume regulation, and formation of proliferation-related macromolecular signaling complexes. Changes in membrane potential, or its regulation, could then affect cell calcium signaling, or other membrane potential-sensitive mechanisms. Changes in cell volume, or its regulation, could alter concentrations or associations of signaling molecules, or produce other effects that might enhance proliferation. Finally, Kv.3.4 channels might interact with other signaling proteins involved in proliferation to form unique signaling complexes and in this way promote cell proliferation.

References


Key Words: potassium channels • vascular smooth muscle • proliferation • cell division • KV.3.4 • KCNC4
Potassium Channels and Proliferation of Vascular Smooth Muscle Cells
William F. Jackson

_Circ Res._ 2005;97:1211-1212
doi: 10.1161/01.RES.0000196742.65848.56

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/97/12/1211

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/