Blocking potassium channels: a new principle for treating restenosis?

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This editorial refers to ‘Potent suppression of vascular smooth muscle cell migration and human neointimal hyperplasia by Kv1.3 channel blockers’ by A. Cheong et al., pp. 282–289, this issue.

Vascular smooth muscle cells are important for the structural integrity of the tunica media, but they are also central to vascular remodelling in response to injury. Although they are highly differentiated cells with the ability to regulate vascular tone and synthesize extracellular matrix, smooth muscle cells are also very plastic cells. This enables them to switch from a contractile to an invasive, migrating, and proliferating phenotype in response to local injury. Ion channels in the plasmalemma of smooth muscle cells have been implicated in this active process. There is evidence of profound changes in the types of ion channels that are expressed or functionally important during vascular smooth muscle cell transition resulting in occlusive vascular pathologies. In the systemic circulation, vessel restenosis remains a major factor limiting the success of balloon angioplasty/stenting of coronary, carotid, and femoral arteries. A critical event seems to be replacement of the K_Ca1.1 (BK_Ca) with the intermediate-conductance Ca^{2+}-activated potassium channel K_Ca3.1 and the loss of Cav1.2 (the L-type voltage-dependent) calcium channels. This event confers functional dominance on other types of calcium channels, including the channel components transient receptor potential (TRP) C(canonical)1, STIM1, and Orai1. When cellular electrophysiologists think of potassium channels in the setting of arterial smooth muscle, they may focus on Kv channel inhibition leading to depolarization of the cell membrane and Ca^{2+} entry though voltage-gated calcium channels, which results in contraction. However, in the absence of L-type calcium channels, hyperpolarization, which is related to the activity of channels such as K_Ca3.1 or Kv1.3, by increasing the electrical gradient can facilitate Ca^{2+} entry through non-voltage-gated calcium channels such as the TRPC channels (Figure 1).

An intensive effort over the past 20 years has focused on the potential role of potassium channels in the regulation of contractile responses in vascular pathologies. Recent in vitro and in vivo evidence highlights the effects of potassium channels in pulmonary circulation, and we recognize vasoconstriction and proliferative remodelling as hallmarks of pulmonary arterial hypertension. However, the role of potassium channels in the generation of intimal fibrosis mediated by smooth muscle cells has not been addressed. Cheong et al. report their exciting discovery that blockade of the voltage-gated potassium channel Kv1.3 reverses neointimal hyperplasia by reducing migration of vascular smooth muscle cells. After injury associated with angioplasty or venous coronary bypass grafting, occlusive vascular disease such as atherosclerosis, or neointimal hyperplasia, and restenosis, smooth muscle cells may shift from a contractile to a synthetic phenotype that is characterized by smooth muscle cell proliferation and migration. These processes also involve various proliferation signal cascades, and there is a substantial support for a central regulatory role of cytoplasmic Ca^{2+} in these processes.

Many publications, including the other work from the same group, support the effectiveness of calcium antagonists in reducing smooth muscle proliferation.

To establish the function of Kv1.3 in smooth muscle cells, Cheong et al. performed experiments comparing the expression of Kv1.3 potassium channels in the contractile and proliferating phenotypes of vascular smooth muscle cells from mouse aorta and of human saphenous vein. A minor criticism is that one would prefer that they had used smooth muscle cells from a resistance artery such as the coronary rather than the aorta. They show up-regulated channel protein expression when the cells switch to their proliferating and migratory phenotype. The authors also provide evidence that Kv1.3 is functional by obtaining patch-clamp recordings of voltage-dependent potassium current. The current is associated with partial sensitivity to the Kv1.3 channel inhibitor margatoxin. Similar results were obtained when two other inhibitors of the Kv1.3 channel were applied. In intracellular [Ca^{2+}] measurement experiments, margatoxin significantly suppressed Ca^{2+} entry, consistent with the concept that the unblocked Kv1.3 current increases the electrical gradient, thus favouring the inward movement of the positively charged Ca^{2+} ion. Finally, Cheong et al. have provided the proof of principle for Kv1.3.
blockade in the treatment of vascular injury, because expression of Kv1.3 was enhanced in neointimal lesions from patients and in organ culture and its inhibitors (margatoxin or correloid compound C) reduced neointimal formation in the human saphenous vein. These are the first data to suggest a potential beneficial role for the inhibition of Kv1.3 in the treatment or prevention of human neointimal hyperplasia.

This study also raises many additional questions. For instance, the authors have previously observed similar effects with the blockade of another potassium channel, KCa3.1, and have provided the proof of principle for the treatment of vascular injury by inhibition of this channel. In addition, they showed that TRPC1 expression was enhanced in injured vessels and its blocking antibody (TI13) reduced neointimal formation in the human saphenous vein. Does this mean that all three channels should be targeted?

Unfortunately, intima remodelling is very complex and smooth muscle cell migration and proliferation is just one aspect. This view is being challenged by papers describing a contribution to intimal fibrosis by circulating cells that transdifferentiate into myofibroblasts once they have attached to the intimal lesion. In pulmonary hypertension, it also apparent that complex intimal remodelling can involve endothelial cells, as exemplified in plexiform lesions. In addition, calcium is just one of the variables in proliferative vascular disease. Since various proliferation signal cascades (including Src phosphorylation) are also involved in proliferation and Src affects potassium channel function, the question arises of how does the signalling upstream from the inhibition of the potassium channels alter smooth muscle cell migration?

What are the potential clinical implications of the current finding? The pharmacological actions of margatoxin could exceed blockade of Kv1.3, and the safety of such a drug is unknown. It is possible that blockade of Kv1.3 in other tissues may have deleterious effects, although incorporation of margatoxin or a similar blocker in the stent itself might obviate this potential problem. However, it is also possible that this new approach may turn out to be a breakthrough in the therapy of intimal proliferation and may influence our thinking of the importance of potassium channels for the vasculature.

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References


