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## Dynamic regulation of the subunit composition of BK channels in smooth muscle

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### Keywords

Endothelin-1; Membrane Trafficking; Rab11A

Ion channels in vascular smooth muscle cells control membrane potential, which is a major determinant of the intracellular  $\text{Ca}^{2+}$  concentration and thus vascular tone. Membrane potential is modulated by a complex collection of endogenous vasodilator and vasoconstrictor pathways that ultimately dictate regional vascular resistance, organ blood flow, and systemic arterial pressure. Membrane potential in vascular smooth muscle is dominated by multiple types of  $\text{K}^+$  channels including those regulated by  $\text{Ca}^{2+}$  ( $\text{K}_{\text{Ca}}$ ), voltage ( $\text{K}_{\text{V}}$ ), and ATP ( $\text{K}_{\text{ATP}}$ ).<sup>1</sup> It is not surprising then, that  $\text{K}^+$  channels in vascular smooth muscle have been studied extensively as targets in normal vasoregulatory pathways and as end-effectors gone awry in diseases. Most investigations to date have focused on traditional intracellular signaling systems (e.g., cyclic nucleotides and their associated kinases<sup>2</sup>) and chronic changes in expression patterns (e.g., down regulation of subunits<sup>3</sup>).

In the present issue of *Circulation Research*, Zhai *et al.* examine the novel hypothesis that endothelin-1 elicits vasoconstriction, in part, by rapidly altering the subunit composition of vascular smooth muscle  $\text{K}^+$  channels, thereby reducing their functional activity.<sup>4</sup> The  $\text{K}^+$  channel under investigation is the large conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channel, known colloquially as BK (where the B stands for big, in contrast to IK and SK, which are abbreviations for  $\text{K}^+$  channels of intermediate and small conductance).<sup>1</sup> The subunit composition of BK channels has been established as an important factor regulating vascular tone.<sup>5</sup> Altering the subunit composition of BK channels can involve the cellular trafficking of subunits through mechanisms involving the small GTPase Rab11A.<sup>6, 7</sup> This GTPase controls the trafficking of ion channel subunits between endosomes and the sarcolemma of vascular smooth muscle cells.

Jonathan Jaggar's laboratory has been on the forefront of understanding BK channels in smooth muscle, their functional roles, and regulation by numerous mechanisms, including cellular trafficking.<sup>6, 7</sup> Previous efforts by the Jaggar laboratory have established that

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Rab11A regulates BK channels in nitric oxide-induced relaxation of cerebral arteries. BK channels are composed of pore-forming ( $\alpha$ ) and auxiliary (e.g.,  $\beta$ 1) subunits. The  $\beta$ 1 subunit increases the apparent  $\text{Ca}^{2+}$  sensitivity of BK channels, such that when it is part of the multi-protein channel complex, the open probability is higher at a given  $\text{Ca}^{2+}$  concentration and membrane potential. BK channel opening is associated with membrane hyperpolarization and vascular smooth muscle relaxation.<sup>1, 5</sup>

The previous view was generally that BK  $\alpha$  and  $\beta$ 1 subunits are co-assembled prior to emerging on the sarcolemma. However, recent studies from the Jaggar laboratory demonstrated that although most BK  $\alpha$  subunits were indeed present in the sarcolemma, the  $\beta$ 1 subunits were surprisingly located intracellularly.<sup>7</sup> Moreover, the vasodilator nitric oxide stimulated rapid surface trafficking of  $\beta$ 1 subunits, enhancing BK channel function and leading to vasodilation.<sup>7</sup> Thus, Jaggar's team established that rapid, dynamic  $\beta$ 1 subunit trafficking is a unique mechanism to control functional surface ion channel activity and mediate vasodilation.

Their work raised an interesting question. That is, can the converse be true for the roles of Rab11A, the  $\beta$ 1 subunit, and BK channel function in smooth muscle contraction? Specifically, might dynamic  $\beta$ 1 subunit trafficking be held responsible for some portion of vasoconstriction? This is the exciting and novel aspect of the contribution of Zhai *et al.*<sup>4</sup> They have now demonstrated that Rab11A plays a significant role in modulating BK channel function and smooth muscle contraction. Zhai *et al.* show that endothelin-induced constriction of cerebral arteries is mediated, at least partially, through the inhibition of BK channel function by Rab11A. Using vertically integrated approaches, they determined that endothelin-1 stimulates PKC-dependent phosphorylation of Rab11A at serine 177, which in turn leads to decreased surface trafficking of  $\beta$ 1 subunits, the inhibition of transient BK currents, and cerebral vasoconstriction. Interestingly, this dynamic control of BK channel subunit composition appears to function in the presence of competing stimuli (endothelin-1, nitric oxide donor, depolarization),<sup>6, 7</sup> supporting the idea that regulation of  $\beta$ 1 trafficking is an important physiologic mechanism that is actively regulated by a variety of influences (see Figure). Presently, it is unclear what controls the removal of  $\beta$ 1 subunits from BK channels.

A significant issue concerning these findings is whether this novel pathway regulating BK channel activity applies universally. For instance, does it apply to BK channels and endothelin-induced vasoconstriction of arteries from coronary, skeletal muscle, or other vascular beds? There is not enough evidence to support it at this time, but there is no reason to dismiss it either. While it is clear that rapid, dynamic  $\beta$ 1 trafficking controls BK channel function in cerebral arteries, significant differences in BK channel function and regulation, particularly with regard to the  $\beta$ 1 subunit, have been documented previously in other arteries. For example, while smooth muscle cells from cerebral and cremaster arteries have similar BK channel current densities, there is a reduced  $\beta$ 1: $\alpha$  ratio in myocytes from cremaster arteries.<sup>8, 9</sup> Moreover, it is very surprising that expression of the  $\alpha$  subunit protein in cerebral arteries is approximately 20 $\times$  higher than in cremaster.<sup>10</sup> Further, it seems that BK channels are more important regulators of tone in the cerebral bed compared to, for example, the coronary circulation. Specifically, while BK channels regulate metabolic control of cerebral blood flow,<sup>11</sup> they appear to have little, if any, impact on metabolic

regulation of coronary blood flow.<sup>12</sup> However, coronary vascular BK channels contribute to vasodilator responses to multiple agonists, for example, endothelium-dependent dilators such as bradykinin.<sup>13</sup> These findings suggest that there are some very fundamental differences in how BK channels are regulated and how they function in the smooth muscle cells of various vascular beds. Further, it is noted that the experiments by Zhai *et al.* were performed in cerebral arteries which can act quite differently than arterioles responsible for flow regulation; therefore, an important gap in knowledge deals with how these concepts apply to the microcirculation. Furthermore, given that BK channel function and subunit composition are altered in disease states such as hypertension<sup>14</sup> and obesity/type 2 diabetes<sup>15</sup>, this novel membrane trafficking mechanism merits intense future investigation, as it may be responsible for some key features of pathology.

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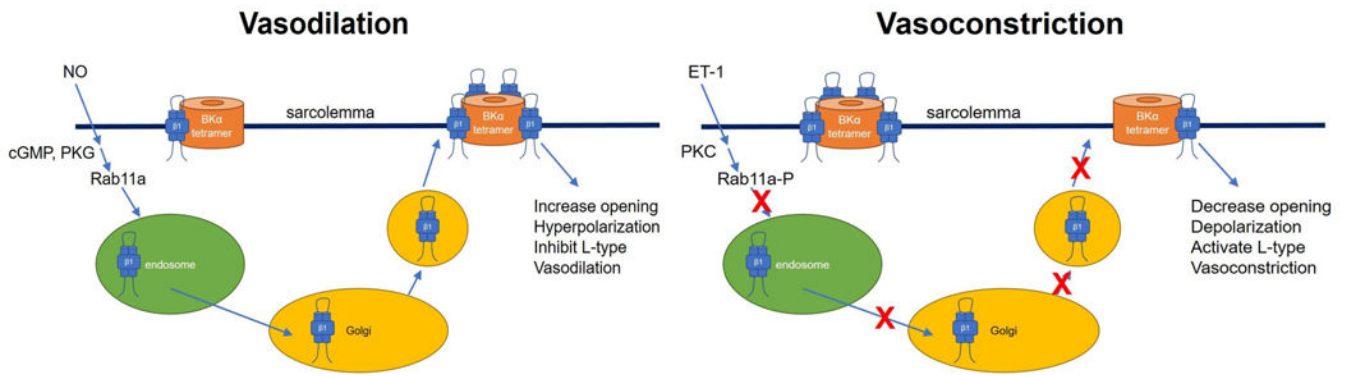
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**Figure. Schematic diagram of vasoactive mechanisms regulating the surface trafficking of  $\beta 1$  subunits in cerebral smooth muscle**  
 Dynamic regulation of BK channel subunit composition in cerebral artery smooth muscle by Rab11A. Changing the number of  $\beta 1$  subunits in BK channels contributes to both vasodilation and vasoconstriction.