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Signalling pathways involved in Kv1.3-induced proliferation

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Vascular smooth muscle cells (VSMCs) have the ability to switch from a contractile to a proliferative phenotype, in a process known as phenotypic modulation (PM) which associates with several cardiovascular diseases. We have previously demonstrated that changes in the expression of voltage-dependent potassium (Kv) channels associated with this proliferative phenotype. These results were validated in transfected HEK293 cells: Kv1.5 decreased proliferation and Kv1.3 increased cell proliferation independently of ion flux (Cidad et al., 2012). Our data suggested that the movement of Kv1.3 channels voltage-sensor could be coupled to signaling pathways leading to proliferation.
To test this hypothesis we studied: 1) the molecular determinants linking the functional expression of Kv1.3 channels to cell proliferation, 2) the signaling cascades involved in the pro-proliferative effects of Kv1.3 and 3) the effect of changes on membrane potential on Kv1.3-induced proliferation.
Taking advantage of the opposing effects on proliferation of Kv1.5 and Kv1.3 channels we designed chimeric Kv1.3-Kv1.5 channels as well as point-mutant Kv1.3 channels of consensus phosphorylation sites. Our results indicated that the molecular determinants of Kv1.3-induced proliferation are located in the carboxy-terminal domain. In particular, we identified two closed residues (Y447 and S459) whose mutation abolished proliferation. Furthermore, proliferation was increased with chimeric Kv1.5 mutants containing these residues (the YS segment) but only when located at specific place within the channel. We also found that Kv1.3-induced proliferation and PTyr labelling of the channel were impaired by MEK/ERK signal inhibition. In agreement with these data, Kv1.3 phosphorylation increases upon voltage-dependent transition from close to open conformation (i.e. depolarization), while membrane hyperpolarization reduced Kv1.3-induced proliferation. Finally, under conditions promoting channel phosphorylation, Kv1.3 associates with ERK1/2 and with the scaffold protein IQGAP3.
Altogether these data confirm that the signaling pathway linking Kv1.3 channels with proliferation requires voltage-induced conformational changes, and identify some of the associated proteins.

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