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Naringenin as a novel inhibitor of Two-Pore Channel 2 controlling the angiogenic process *in vitro* and *in vivo*

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Two Pore Channels (TPCs) are an emerging family of intracellular channels, expressed on acidic compartments, which mediate calcium signaling evoked by NAADP. In particular, we demonstrated that TPC2 isoform has a main role in angiogenesis (Favia et al. PNAS 2014 Nov 4;111(44):E4706-15). TPC2 inhibition is emerging as a key therapeutic step in a range of important pathological conditions including the progression and metastatic potential of cancer, Parkinson's disease, and Ebola virus infection. We introduce naringenin, a natural flavonoid, as a novel TPC2 inhibitor as shown by electrophysiological evidence in a heterologous system, i.e. Arabidopsis vacuoles lacking endogenous TPCs. In view of the control exerted by TPC2 on intracellular calcium signaling and angiogenesis, we demonstrate that naringenin dampens intracellular calcium responses of human endothelial cells stimulated with VEGF, histamine or NAADP-AM, but not with ATP or Angiopoietin-1. The ability of naringenin to impair TPC2-dependent biological activities was further explored in an established *in vivo* model in which VEGF-containing matrigel plugs implanted in mice failed to be vascularized in the presence of naringenin. Our present data suggest that naringenin inhibition of TPC2 activity and the observed inhibition of angiogenic response to VEGF are linked by impaired intracellular calcium signaling. The relationship we describe here between naringenin and TPC2 is therefore likely to have wider implications in systems other than the vascular system, thus representing a novel tool for experimental, and possibly even clinical, research purposes.

Keywords

Calcium signalling, acidic stores, flavanones