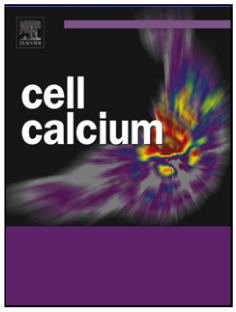

Title: To die or not to die SGK1-Sensitive ORAI/STIM in Cell Survival

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To die or not to die SGK1-Sensitive ORAI/STIM in Cell Survival

Running head: SGK1-sensitive upregulation of ORAI/STIM1

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Summary

The pore forming Ca^{2+} release activated Ca^{2+} channel (CRAC) isoforms ORAI1-3 and their regulators STIM1,2 accomplish store operated Ca^{2+} entry (SOCE). Activation of SOCE may lead to cytosolic Ca^{2+} oscillations, which in turn support cell proliferation and cell survival. ORAI/STIM and thus SOCE are upregulated by the serum and glucocorticoid inducible kinase SGK1, a kinase under powerful genomic regulation and activated by phosphorylation via the phosphoinositol-3-phosphate pathway. SGK1 enhances ORAI1 abundance partially by phosphorylation of Nedd4-2, an ubiquitin ligase priming the channel protein for degradation. The SGK1-phosphorylated Nedd4-2 binds to the protein 14-3-3 and is thus unable to ubiquinate ORAI1. SGK1 further increases the ORAI1 and STIM1 protein abundance by activating nuclear factor kappa B (NF-κB), a transcription factor upregulating the expression of STIM1 and ORAI1. SGK1-sensitive upregulation of ORAI/STIM and thus SOCE is triggered by a wide variety of hormones and growth factors, as well as several cell stressors including ischemia, radiation, and cell shrinkage. SGK1 dependent upregulation of ORAI/STIM confers survival of tumor cells and thus impacts on growth and therapy resistance of cancer. On the other hand, SGK1-dependent upregulation of ORAI1 and STIM1 may support survival of neurons and impairment of SGK1-dependent ORAI/STIM activity may foster neurodegeneration. Clearly, further experimental effort is needed to define the mechanisms linking SGK1-dependent upregulation of ORAI1 and STIM1 to cell survival and to define the impact of SGK1-dependent upregulation of ORAI1 and STIM1 on malignancy and neurodegenerative disease.

Introduction