Enheten för Molekylär Neurobiologi
Institutionen för Medicinsk Biokemi och Biofysik
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Calcium Signaling in Development and Disease

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Abstract

The calcium ion (Ca^{2+}) is a highly versatile signaling messenger involved in a diverse range of physiological processes such as gene transcription/expression, proliferation, differentiation and cell death. Intracellular Ca^{2+} signals are generated through a 10 000 – 20 000 fold gradient across the cell membrane and via release from the external milieu and/or internal Ca^{2+} stores. Cells have a unique signaling toolkit to control Ca^{2+} homeostasis including a selection of ion channels, pumps, exchangers and Ca^{2+} binding proteins.

We have reported that ouabain, an endogenous steroid hormone and ligand to the Na^{+},K^{+}-ATPase, can trigger dendritic growth in cortical neurons through signal transduction. This involves a Ca^{2+}-dependent transcriptional program regulated by CREB and CRE-mediated gene activation, primarily regulated through Ca^{2+}/calmodulin-dependent protein kinases. The process also includes Ca^{2+} oscillations and phosphorylation of mitogen-activated protein kinases (ERK 1/2). These data suggest a novel role for Na^{+},K^{+}-ATPase and Ca^{2+} in dendritic growth during development.

Previous work has shown that treatment with protein kinase C (PKC) inhibitors results in a prolonged Ca^{2+} increase leading to calpain activation and release of apoptosis-inducing factor (AIF). We have demonstrated that hyperpolarization-activated cyclic nucleotide-gated (HCN) channel 2 is responsible for the Ca^{2+} influx. The influx is regulated via dephosphorylation of a residue in the intracellular C-terminal. This data shows a novel role for HCN channel 2 in cell death and a new possible drug target.

Bladder cancer is overall one of the ten most common cancers. We have shown that treatment with *Bacillus Calmette-Guerin* (BCG), currently the most effective intravesical agent against bladder cancer, induces an intracellular Ca^{2+} increase and reduces cell proliferation in urinary bladder cancer (T24) cells. Store depletion by SERCA inhibition blocked the BCG-triggered signal, thereby suggesting a role of the endoplasmic reticulum as a Ca^{2+} source. This signaling event was dependent on phospholipas C since pharmacological inhibition or small interference RNA-mediated gene silencing abolished the response. Finally EdU incorporation revealed that BCG-controlled cell proliferation was mediated via a Ca^{2+}- and PLC-dependent signaling cascade.

In summary this thesis presents three studies highlighting three different roles for Ca^{2+} signaling. They show that Ca^{2+} signaling is involved in processes critical for cell differentiation, cell proliferation, and cell death, three aspects highly coordinated with development and disease.

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