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Functional properties of the IP3 receptor at membrane contact sites

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Abstract:

Statement of the Problem: The inositol 1, 4, 5-trisphosphate (IP3) receptors (IP3Rs) are ubiquitously expressed Ca2+ release channels of the endoplasmic reticulum (ER). Th e resulting Ca2+ signals are instrumental in the regulation of many intracellular processes. It is now becoming increasingly clear that contact sites between ER and mitochondria or between ER and lysosomes is very important for controlling mitochondrial energetics, autophagy and apoptosis. Anti-apoptotic Bcl-2 leads to increased cell survival by both blocking pro-apoptotic family members like Bax and Bak and by inhibiting IP3R mediated Ca2+ transfer to the mitochondria. As Bcl-2 is upregulated in a variety of cancers, including diff use large B-cell lymphoma (DLBCL) and chronic lymphocyticleukemia (CLL), we developed in collaboration with Clark W Distelhorst (Case Western Reserve University, USA) BIRD-2, apeptide tool that disrupts Bcl-2/IP3R interaction by binding to the Bcl-2 BH4 domain, increasing IP3 induced Ca2+ release and triggering apoptosis of DLBCL cells and of primary CLL cells. Interestingly, DLBCL cell lines with high expression levels of the high affi nity IP3R2 isoform, were the most sensitive to BIRD-2. In addition to high levels of IP3R2 expression, constitutive IP3 signaling downstream of the tonically active B-cell receptor increases sensitivity towards BIRD-2. Under standard growth conditions, this constitutive IP3 signaling fulfi lled a pro-survival role, since inhibition of phospholipase C using 2.5 μM U73122 caused cell death in various DLBCL cell lines and primary CLL cells, but at lower concentrations protected against BIRD- 2-induced Ca2+ release and apoptosis. Taken together, our data indicate that on the one hand, constitutive IP3 signaling is necessary for cancer cell survival and proliferation but that on the other hand to survive this chronic signaling the cancer cells are dependent on high Bcl-2 levels to prevent excessive Ca2+ release via IP3Rs. Disrupting Bcl-2/IP3R interaction switches constitutive IP3 signaling to a pro-death signal and may therefore lead to a novel therapeutic approach.

Biography:

Jan B Parys is a faculty member since 1997, ordinary Professor of Physiology since 2006 and Head of the Laboratory of Molecular and Cellular Signaling at the KU
Leuven, Belgium since 2013. His research always concerned the understanding of the mechanisms for Ca2+ homeostasis in general and the structure, function and regulation of the inositol 1, 4, 5-trisphosphate receptor (IP3R), a central player in the initiation and propagation of intracellular Ca2+ signals, in particular. More recently, he focused on the role of the IP3R in conjunction with other Ca2+-transporting proteins of the endoplasmic reticulum, the mitochondria and the lysosomes in cell survival and cell death, and especially in the processes of apoptosis and autophagy. Since 2010 he is Secretary-General of the European Calcium Society (ECS) and was organizeror co-organizer of multiple international workshops (2013) and meetings (2008, 2014, and 2016) of the ECS.

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