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Ca²⁺ signaling and cell death:**Focus on Ca²⁺-transport systems and their implication in cell death and survival***Geert Bultynck, Jan B. Parys*

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Intracellular Ca²⁺ plays a pivotal role in a plethora of cellular and physiological functions in all living systems on earth, ranging from unicellular organism to humans [1, 2]. In the cytoplasm, free Ca²⁺ concentration ([Ca²⁺]) is maintained at very low levels (~100 nM) compared to intracellular stores like the endoplasmic reticulum (ER) or lysosomes (~500 μM) and the extracellular environment (1-2 mM). The low cytoplasmic [Ca²⁺] ([Ca²⁺]_{cyt}) is established and maintained by Ca²⁺-extrusion mechanisms (“Ca²⁺-off systems”), including P-type ATPases, like sarco/endoplasmic reticulum Ca²⁺ ATPases (SERCAs) and plasma membrane Ca²⁺ ATPases (PMCAs), and exchangers like Na⁺-coupled Ca²⁺ exchangers. As such, by using the high electrochemical driving force for Ca²⁺ flux into the cytosol, cells can employ rapid and transient elevations in [Ca²⁺]_{cyt} as a signal transduction mechanism [1]. This occurs with high spatiotemporal resolution via different Ca²⁺-sensing proteins present in the cytosol and in organellar compartments [3]. These Ca²⁺ signals are generated via “Ca²⁺-on systems”, including (i) Ca²⁺-permeable channels located at the plasma membrane for mediating Ca²⁺ influx, like the store-operated Ca²⁺-entry channel Orai and several members of the transient receptor potential (TRP) channel family and (ii) intracellular channels for mediating intracellular Ca²⁺ release, including IP₃ receptors (IP₃Rs) and ryanodine receptors (RyRs) at the ER membranes and two-pore channels (TPC) and other TRP members (like TRPMLs) at the lysosomes.

Besides the above-mentioned extrusion mechanisms, also the mitochondria play a central role in limiting $[Ca^{2+}]_{cyt}$ rises by taking up Ca^{2+} that is released from the ER or that enters from the outside. This mitochondrial Ca^{2+} transport involves voltage-dependent anion channels (VDACs) at the mitochondrial outer membrane and the mitochondrial Ca^{2+} uniporter (MCU) complex at the mitochondrial inner membrane [4]. Such cross-talk between organelles via Ca^{2+} signaling is highly facilitated by the presence of membrane contact sites and is not limited to ER and mitochondria, but also occurs between ER, lysosomes and extracellular environment [5-7]. The occurrence of local, inter-organellar Ca^{2+} signals in subcellular microdomains can even occur during basal growth conditions [8] and is important for the cellular response to stress and damage [9, 10]. For instance, ER-mitochondrial Ca^{2+} exchanges were found to be crucial in sustaining cells' bio-energetics and in cancer cells' survival [11, 12], while ER and lysosomal Ca^{2+} fluxes enable cells to adequately respond to stress caused by nutrient depletion [10, 13]. But, ER-mitochondrial Ca^{2+} exchanges, when occurring in an excessive manner for a prolonged period, can also allow cells to provide an adequate response to cellular damage, toxins or during stress by engaging cell-death processes [14]. This phenomenon is not only critical to maintain cellular and organismal health by preventing oncogenesis and malignant cell transformation and proliferation, but also underlies therapeutic effectiveness of anti-cancer regimens [15, 16]. The concerted action of the various Ca^{2+} -transport systems in a cell therefore fundamentally impact their ability to survive and proliferate, to cope with stress and damage, and to engage cell death pathways in situations of on-going stress or irreparable damage. Interestingly, the expression levels and/or activity of several Ca^{2+} -transport systems are influenced by cellular factors, including Ca^{2+} itself [17] and reactive oxygen species [18], enabling adequate regulation of bio-energetics and survival processes. Moreover, a plethora of proteins, including a growing list of tumor suppressors and oncogenes have been discovered as binding partners of these transporters, directly regulating their activity and/or enabling their post-translational modifications (phosphorylation, lipidation, ubiquitination, ...) [19, 20]. The formation of such protein complexes allows functional fine-tuning and dynamic control of their activity and expression, ultimately impacting the survival or demise of the cell. The function and regulation of the different Ca^{2+} -transport systems in these processes is exactly the topic of this first special issue of Cell Calcium on “ Ca^{2+} signaling and cell death”.

Our aim therefore was to provide a state-of-the-art view on (i) the role of Ca^{2+} -transport systems in controlling and regulating cell death and survival and (ii) how their dysregulation

is linked to different pathologies as a consequence of excessive cell death / impaired survival (like neurodegeneration) or suppressed cell death / enhanced survival and/or proliferation (like cancer and polycystic kidney disease). This special issue has been organized by focusing on the Ca^{2+} - or Ca^{2+} -controlled transport systems at (i) the plasma membrane, (ii) the ER, (iii) the mitochondria, and (iv) the lysosomes.

Natalia Prevarskaya and co-workers prepared a comprehensive and integrated overview of the roles of different members of the TRP-channel family in survival, proliferation and apoptosis by means of altering $[\text{Ca}^{2+}]_{\text{cyt}}$ and impacting Ca^{2+} -dependent signaling pathways [21]. These TRP channels not only allow Ca^{2+} influx from the extracellular environment, but some family members also mediate Ca^{2+} release from intracellular stores, like ER, late endosomes, amphisomes, autophagosomes and autolysosomes. Particularly, in these acidic organelles, TRPML1/mucolipin-1 was found to play a key role by establishing a local Ca^{2+} -signaling domain that drives autophagy in a calcineurin-dependent manner, an aspect discussed in more detail by Diego Medina and co-workers [22]. In the plasma membrane, besides TRP channels, also Orai channels and their ER-located gating partner Stim have been implicated in several aspects of cell death and survival, including extrinsic & intrinsic apoptosis and apoptotic cell clearance by impacting the nature of the Ca^{2+} signals occurring in the cytosol, a topic considered by the team of Rajender Motiani [23]. Jason Bruce provided not only an overview of the role of PMCAs in cell death by antagonizing intracellular Ca^{2+} overload, but also emerging concepts on how PMCA function is affected by cytosolic Ca^{2+} , ROS and ATP, all cellular factors impacting and impacted by cell death [24]. The team of Barbara Ehrlich highlighted the state-of-the-art on the function of polycystin channels in Ca^{2+} -signaling in cell death and survival and how their dysfunction caused by genetic mutations results in polycystic kidney disease through dysregulation of Ca^{2+} signaling and other signaling pathways, ultimately leading to novel therapeutic opportunities [25]. Besides plasmalemmal Ca^{2+} fluxes, also the ER compartment and its Ca^{2+} content play a critical role in cell fate decisions. Djamel Lebecq and his team presented the recent discoveries on the contributions of SERCA to these decisions [26]. It has become increasingly clear that SERCA activity is dynamically regulated during exercise and stress and by a growing list of activators and inhibitors and is affected by disease-linked genetic mutations, impacting cell death and survival. The ER as the main intracellular Ca^{2+} -storage and Ca^{2+} -releasing organelle ultimately determines the mitochondrial metabolism and energy production, the apoptotic sensitivity and autophagic flux. This critically depends on the IP_3R -mediated Ca^{2+} delivery to

the mitochondrial compartment via ER-mitochondrial contact sites, which also harbor several oncogenes and tumor suppressors, a topic explained by Paolo Pinton and co-workers [27]. Ca^{2+} is eventually transported to the mitochondrial matrix across the mitochondrial inner membranes through the means of the MCU complex. Rosario Rizzuto, Diego De Stefani and co-workers covered this rapidly evolving area and provide a critical evaluation of the role of the MCU, of its essential regulator proteins and of mitochondrial Ca^{2+} handling in cell death and survival processes, including emerging *in vivo* and tissue-specific roles and their contribution to disease [28]. At the mitochondria, also VDAC1 plays a critical role in cell death and survival by (i) serving as a transport pathway for Ca^{2+} and metabolites and (ii) forming oligomers in a Ca^{2+} -dependent manner in response to apoptotic stimuli, promoting the release of apoptogenic proteins into the cytosol. Alterations in VDAC1 expression have been observed in several diseases, impacting mitochondrial Ca^{2+} and survival, as pointed out by Varda Shoshan-Barmatz and her team [29]. Finally, at the inner mitochondrial membranes, also Ca^{2+} -activated K^+ channels reside with important emerging roles in cell death and survival. As discussed by Amalia Dolga and co-workers, the opening of these mitochondrial K^+ channels has neuroprotective effects by maintaining the mitochondrial potential, reducing ROS and preventing mitochondrial Ca^{2+} overload [30].

An emerging theme is that even seemingly subtle changes in the activity, regulation or expression of Ca^{2+} -transport systems and their accessory proteins can have major adverse consequences, resulting in pathophysiological conditions and contributing to disease progression. For instance, it is sufficient that cells express a different isoform of a certain Ca^{2+} -transport system to change the modality of Ca^{2+} signaling, enabling proliferation and cell-death resistance, two cancer hallmarks. In concert with other aberrations, such alterations in Ca^{2+} -signaling profiles can promote neoplasia and oncogenesis [31].

As you will discover in this collection of articles, it is clear that recently many fascinating insights have emerged on the role of Ca^{2+} -transport systems in regulating cell death and survival processes with important impact on health and disease. These conceptual advances will undoubtedly lead to novel means and opportunities for therapeutic interventions to stabilize, treat or even prevent pathophysiological conditions and diseases.

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