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Editorial

Ca²⁺ signaling and cell death: Focus on the role of Ca²⁺ signals in the regulation of cell death & survival processes in health, disease and therapy

Complex spatio-temporal Ca²⁺ signals control nearly every aspect of cellular physiology by acting as important inducers, regulators or terminators of crucial processes as fertilization, metabolism, secretion, contraction, transcription, etc. [1].

An important concept for the understanding of the cellular function of these Ca²⁺ signals is that they are not only limited in amplitude but also in space. Indeed, due to their propensity to bind to negative charges, Ca²⁺ ions demonstrate only a very limited intracellular mobility [2]. The resulting unique spatio-temporal profiles of the Ca²⁺ signals allow for highly specialized signaling outputs [3,4]. Depending not only on the signal strength, but also on the cellular architecture, on the expression levels of the various Ca²⁺-transporting and Ca²⁺-binding proteins and on their subcellular localization, the Ca²⁺ signal in a cell can therefore be limited to a smaller or larger part of the cytosol and/or be absorbed by any of the cellular organelles (endoplasmic reticulum (ER), mitochondria, lysosomes) [5].

In this second special issue of Cell Calcium on the theme of Ca²⁺ signaling and cell death, we will therefore first focus on the various pathways affecting cell life and death that are controlled or regulated by intracellular Ca²⁺ signals. Subsequently, we will see how the further regulation of Ca²⁺ signals affect cell survival/cell death processes and we will finish with a number of examples of the consequences of these highly regulated Ca²⁺-signaling pathways in disease, therapy and development.

Guido Kroemer and his co-workers start this issue with a comprehensive analysis of the various ways through which Ca²⁺ and calmodulin impact the cell cycle and its checkpoints, control cellular proliferation and participate in cell death processes when irreversible damage to the cell cycle occurs [6]. On a related topic, Nadine Martin and David Bernard discuss the involvement of Ca²⁺ in cellular senescence and in senescence-associated conditions [7]. Claudio Hetz and his co-workers explore in depth the complex interplay between Ca²⁺ signaling and the unfolded protein response [8]. The Ca²⁺ content in the ER on the one hand establishes the threshold for the onset of ER stress and on the other hand, after its transfer to the mitochondria at the ER-mitochondrial contact sites, Ca²⁺ modulates mitochondrial bioenergetics during the early adaptive phase while inducing apoptosis in the case of persistent ER stress conditions.

Another process involved in maintaining cellular homeostasis and in protecting cells against stress conditions is autophagy. As the role of Ca²⁺ signaling in the regulation of autophagy remains only very partially understood, the review by Martin Bootman and his collaborators is certainly timely [9]. In this review, the literature on the interrelation between Ca²⁺ signaling and autophagy is critically reviewed, potential methodological issues identified and future avenues for further research proposed.

Oxidative glutamate toxicity is a particular form of cell death occurring as a consequence of profound oxidative stress due to glutathione depletion. Displaying very similar characteristics to it, is ferroptosis, an iron-dependent form of cell death. These both forms of cell death can therefore be covered by the new term oxytosis. Axel Methner and collaborators highlight in their review the importance of Ca²⁺ in oxytosis, and in particular the crucial role of Ca²⁺ entry in the cell via the store-operated Ca²⁺ entry (SOCE) mechanism that occurs subsequently to ER depletion and mitochondrial dysfunction [10]. Finally, Paolo Bernardi and his team discuss the role of Ca²⁺ signals in regulating the opening of the mitochondrial permeability transition pore (mPTP), a crucial step in the process of Ca²⁺-induced apoptosis, and thereby provide key evidence for a direct effect of mitochondrial Ca²⁺ on mPTP opening [11].

In the framework of cell survival/cell death, Ca²⁺ signaling is itself the target of additional control by other pathways, including by ER proteins. Tomas Gutierrez and Thomas Simmen first demonstrate the general importance of ER chaperones in the regulation of ER-mitochondrial Ca²⁺ transfer [12]. Through the regulation of this step, the chaperones directly control ATP availability versus apoptosis induction, depending on the state of the ER. Subsequently, Matthew Pitts and Peter Hoffmann discuss the specific role of the seven ER-resident selenoproteins in the control of Ca²⁺ signaling and therefore of Ca²⁺-dependent processes as proliferation, survival and apoptosis [13].

Finally, the role of deranged intracellular Ca²⁺ signals underlying pathophysiological conditions and disease states is highlighted. Also, the contribution of Ca²⁺ signaling in therapeutic treatments and in development is discussed.

Neurons depend on Ca²⁺ signaling for synaptic plasticity, learning and memory. Not unexpectedly therefore, a dysregulation of neuronal Ca²⁺ signaling is highly detrimental for these processes [14]. Such a dysregulation is found in various neurodegenerative diseases as Alzheimer's, Parkinson's and Huntington's diseases. Ilya Bezprozvanny and his coworkers discuss in their review especially the role of SOCE and the possibility to target this pathway for therapeutic purposes [15].

Acute pancreatitis on the other hand is a serious condition in which inside the pancreatic acinar cells the digestive enzymes are untimely activated by an excessive and prolonged elevation of the cytoplasmic Ca²⁺ concentrations, established by an enhanced Ca²⁺ release from the ER and

the ensuing increased SOCE. In their review, Julia and Oleg Gerasimenko and their co-workers discuss the implication of Ca^{2+} signaling in the various causes for acute pancreatitis as well as potential therapies [16].

As several cancers are dependent on overexpression of anti-apoptotic members of the Bcl-2 protein family for their survival, Bcl-2 inhibitors have been developed as novel precision medicines to eradicate these cancers through apoptotic cell death. Anti-apoptotic Bcl-2 family members act either by binding mitochondrial pro-apoptotic family members and/or by suppressing excessive Ca^{2+} transfer from the ER to the mitochondria [17]. Vervloessem et al. present a state-of-the-art view on the action of Bcl-2 inhibitors on Ca^{2+} handling as part of their anti-tumoral action and also indicate the parallel risk of damaging healthy cells and tissues by adversely impacting Ca^{2+} homeostasis and dynamics [18].

Finally, Ca^{2+} signaling is essential for correct cochlea development. Fabio Mammano and Mario Bortolozzi discuss in their review the complex interrelation between Ca^{2+} signaling, connexin expression and the contribution of apoptosis and autophagy to establish correct hearing [19].

In conclusion, in a complementary approach to that of the previous special issue [20] that focused on the variety of Ca^{2+} -transporting mechanisms impacting cell death and survival, the present issue demonstrates how the modulation of the intracellular complex spatio-temporal Ca^{2+} signals can promote cell survival or provoke cell death by controlling an emerging list of processes including cell cycle progression, autophagy, unfolded protein response, cellular senescence, glutamate-induced toxicity/ferroptosis/oxytosis and mitochondrial membrane permeabilization. In addition, dysregulation of cellular Ca^{2+} homeostasis and dynamics has been implicated in several pathological conditions, disease progression and developmental aspects. Moreover, several articles emphasize how understanding the mechanisms underlying deranged Ca^{2+} signaling and how modulating Ca^{2+} signaling could bring solace to fight these diseases. Thus, strategies and drugs that act on Ca^{2+} signaling may ultimately result in the development of novel therapeutic approaches for disease management, including interventions to treat disease or at least delay disease onset and progression.

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