EDITORIAL

Modalities of cell death, survival and adaptation:

The role of the Ca^{2+}-signaling toolkit

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It is well-established that intracellular Ca^{2+} plays a central role in cell death, survival and adaptation decisions, including, but not limited to, fertilization [1, 2], modulation of metabolism in health and disease [3, 4], the control of autophagy [5-9], and the regulation/induction of various forms of cell death [6-8, 10]. While these topics have been extensively investigated for nearly three decades, exciting new insights and important developments have emerged in the last few years.

Already in 2017, Editor-in-chief Shmuel Muallem had invited us to guest edit for Cell Calcium a Special Issue on the topic. The overwhelming number of positive responses spurred the development of two distinct Special Issues, entitled "Ca^{2+} signaling and cell death: Focus on Ca^{2+}-transport systems and their implication in cell death and survival" [11] and "Ca^{2+} signaling and cell death: Focus on the role of Ca^{2+} signals in the regulation of cell death & survival processes in health, disease and therapy" [12].

Last year, Shmuel Muallem asked us to provide an update on the topic and we were glad and honored by this invitation. With great enthusiasm, we therefore present, exactly five years since the publication of the previous Special Issues, a new collection of timely and authoritative articles that delve deeper into this subject. In developing this Special Issue, we again converged and integrated the knowledge of more than 20 experts in the field, of whom we are happy to say they all accepted at once to contribute. The contributed articles are centered around 3 themes.

Theme 1 focuses on the role of Ca^{2+} signaling in controlling cell death and survival outcomes. After an introduction about Ca^{2+} signaling and cell death modalities in a primer article [13], further articles highlight the role of different Ca^{2+}-dependent processes in cell death, including store-operated Ca^{2+} entry [14] and endoplasmic reticulum (ER)-mitochondrial Ca^{2+} signaling [15]. Also, Ca^{2+} signals and/or deranged organellar Ca^{2+} homeostasis can intersect and direct different cell death processes in response to cell stress including ferroptosis [16], lysosomal-dependent cell death [17] and the unfolded protein response (UPR), a pathway activated by ER stress [18]. While UPR triggers cell death in conditions of persistent or excessive ER stress, it can also act as an adaptive, coping response to restore ER homeostasis and thus sustain cell survival in conditions of transient or mild ER stress. In addition to UPR, the cell can also activate senescence to enable cell survival when cells are exposed to cellular stress [19]. However, when cellular stress persists and/or can only partially be resolved, malignant properties may arise such as epithelial-mesenchymal transition, an early step in oncogenesis [20].

Theme 2 addresses the role of the main organellar Ca^{2+}-transport systems in cell death versus survival. The transport systems that are highlighted are the IP_3 receptor residing at the ER [21],

the mitochondrial calcium uniporter complex [22] and the mitochondrial permeability transition pore [23], both present at the inner mitochondrial membrane, and the lysosomal two-pore and TRPML channels [24].

Theme 3, finally, provides an update about the involvement and role of Ca^{2+} signals in pathogenesis and pathology. A wide spectrum of diseases is discussed, including breast cancer [25], neurological disorders, such as Alzheimer's disease [26] and Parkinson's disease [27], chemotherapy-induced neuropathy [28], hepatic diseases [29], cardiac diseases [30], polycystic kidney disease [31], pancreatic diseases [32] and auditory diseases [33].

We anticipate that this compendium of primer and review articles will be a great resource for the dynamic research community working on, dealing with or captivated by the intricate interplay between Ca^{2+} signals and the realm of cell death, survival and adaptation. Together with the authors, our aspiration was to provide a timely account of the current state-of-the-art in the field with attention for knowledge gaps. As such, we hope the Special Issue will spark the interest of a wide readership ranging from the interested newcomer to the seasoned expert leader, thereby driving future research in deciphering the role of intracellular Ca^{2+} signaling in cell survival versus cell death and in health versus disease. Finally, we wish to thank all authors for their time, efforts and dedication to prepare and develop these high-quality, authoritative and thoughtful reviews.

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