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Review

Regulation of inositol 1,4,5-trisphosphate receptors during endoplasmic reticulum stress☆

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ABSTRACT

The endoplasmic reticulum (ER) performs multiple functions in the cell: it is the major site of protein and lipid synthesis as well as the most important intracellular Ca^{2+} reservoir. Adverse conditions, including a decrease in the ER Ca^{2+} level or an increase in oxidative stress, impair the formation of new proteins, resulting in ER stress. The subsequent unfolded protein response (UPR) is a cellular attempt to lower the burden on the ER and to restore ER homeostasis by imposing a general arrest in protein synthesis, upregulating chaperone proteins and degrading misfolded proteins. This response can also lead to autophagy and, if the stress can not be alleviated, to apoptosis. The inositol 1,4,5-trisphosphate (IP_3) receptor (IP_3R) and IP_3-induced Ca^{2+} signaling are important players in these processes. Not only is the IP_3R activity modulated in a dual way during ER stress, but also other key proteins involved in Ca^{2+} signaling are modulated. Changes also occur at the structural level with a strengthening of the contacts between the ER and the mitochondria, which are important determinants of mitochondrial Ca^{2+} uptake. The resulting cytoplasmic and mitochondrial Ca^{2+} signals will control cellular decisions that either promote cell survival or cause their elimination *via* apoptosis. This article is part of a Special Issue entitled: 12th European Symposium on Calcium.

1. Introduction

The endoplasmic reticulum (ER) forms an extensive intracellular network of tubules and cisterns, representing together the largest membrane system of animal cells [1]. The ER plays a crucial role in the synthesis, correct folding and sorting of proteins, but is also involved in many other functions like the synthesis of phospholipids, cholesterol and steroids, the degradation of glycogen, detoxification processes and, last but not least, intracellular Ca^{2+} signaling. Although the various functions are at least partly performed in different areas of the ER, they are not completely independent of each other [2–5]. Importantly, several of these functions are coupled to the ER Ca^{2+} level [1,3,5]. A concerted regulation of the ER Ca^{2+}-uptake and the ER Ca^{2+}-release mechanisms is therefore essential for correct ER functioning [6,7] and a decreased Ca^{2+} concentration in the ER can lead to a phenomenon called ER stress (see Part 3). Such an alteration in ER homeostasis is an upstream event in many pathological conditions [8–10], including many neurodegenerative diseases [11,12].

The most ubiquitously expressed Ca^{2+}-release channel of the ER is the inositol 1,4,5-trisphosphate (IP_3) receptor (IP_3R). The IP_3R and the IP_3-induced Ca^{2+} release (IICR) resulting from IP_3R activation have a central role in many cellular processes including the regulation of cell fate [13]. Their role in apoptosis and autophagy has been highlighted in a number of recent reviews [14–20]. The relation between the IP_3R on the one hand and ER stress and the subsequent processes occurring in the cell, globally named unfolded protein response (UPR), on the other, has however, to the best of our knowledge, not yet been systematically reviewed.

In this review, we therefore will first discuss the function of the ER as a Ca^{2+} store and the various proteins hereby involved, including the IP_3R in particular. We will then treat the phenomenon of ER stress and the subsequent UPR. Subsequently, we will go into further detail on how the IP_3R and IICR are regulated during ER stress, and on how this will affect UPR progression and subsequent cell fate. The importance of the IP_3R and IICR during the adaptive, pro-survival phase as well as,

Abbreviations: a.a., amino acid; ATF, activating transcription factor; Bcl-2, B-cell lymphoma 2; Bcl-Xl, B-cell lymphoma-extra large; BH3, Bcl-2 homology 3; Bl-1, Bax inhibitor-1; BiP, immunoglobulin heavy chain-binding protein; CHOP, C/EBP-homologous protein; CSQ, calsequestrin; eIF2α, eukaryotic initiation factor 2α; ER, endoplasmic reticulum; ERO1α, ER oxidase 1α; GADD34, growth arrest and DNA damage-inducible 34; GIT, G-protein-coupled receptor kinase-interacting protein; GRINA, glutamate receptor, ionotropic NMDA-associated protein 1; GRP, glucose-regulated protein; IICR, IP_3-induced Ca^{2+} release; IP_3, inositol 1,4,5-trisphosphate; IP_3R, inositol 1,4,5-trisphosphate receptor; IRE1, inositol-requiring enzyme 1; MAM, mitochondria-associated membrane; PDI, protein disulfide isomerase; PERK, protein kinase RNA-like ER kinase; PML, promyelocytic leukemia; ROS, reactive oxygen species; RyR, ryanodine receptor; SERCA, sarco- and endoplasmic-reticulum Ca^{2+} ATPase; TMBIM, transmembrane Bax inhibitor motif-containing; UPR, unfolded protein response; XBP1, X box-binding protein 1

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when the ER stress can not be alleviated, in cell death will be highlighted.

2. The ER as central player in cellular Ca^{2+} homeostasis

In mammalian cells, the ER forms the main intracellular Ca^{2+} reservoir. To function as a dynamic Ca^{2+} store, the ER basically contains three types of proteins (Fig. 1): Ca^{2+} pumps allowing active Ca^{2+} uptake, Ca^{2+}-binding proteins allowing the storage of significant amounts of Ca^{2+} in its lumen, and, last but not least, Ca^{2+} channels allowing a controlled release of Ca^{2+} into the cytosol in response to well-determined stimuli [2,4,13,21–23]. Noteworthy, these proteins not only control the Ca^{2+}-loading level of the ER but are themselves often regulated positively or negatively by the luminal Ca^{2+} concentration [24].

2.1. Ca^{2+}-handling mechanisms of the ER

2.1.1. Ca^{2+} pumps

Active Ca^{2+} uptake in the ER is mediated by pumps, belonging to the sarco- and endoplasmic-reticulum Ca^{2+}-ATPase (SERCA) family (Fig. 1). Three different genes encode a SERCA pump (SERCA1, SERCA2, SERCA3) but the variety of Ca^{2+} pumps is increased by the existence of splice variants [25–27]. The crystal structure of SERCA1a was determined in various conditions, enabling the reconstitution of the almost complete reaction cycle at a structural level [28]. Structurally the SERCA pumps (molecular mass of ~110 kDa) are divided in the following domains: a

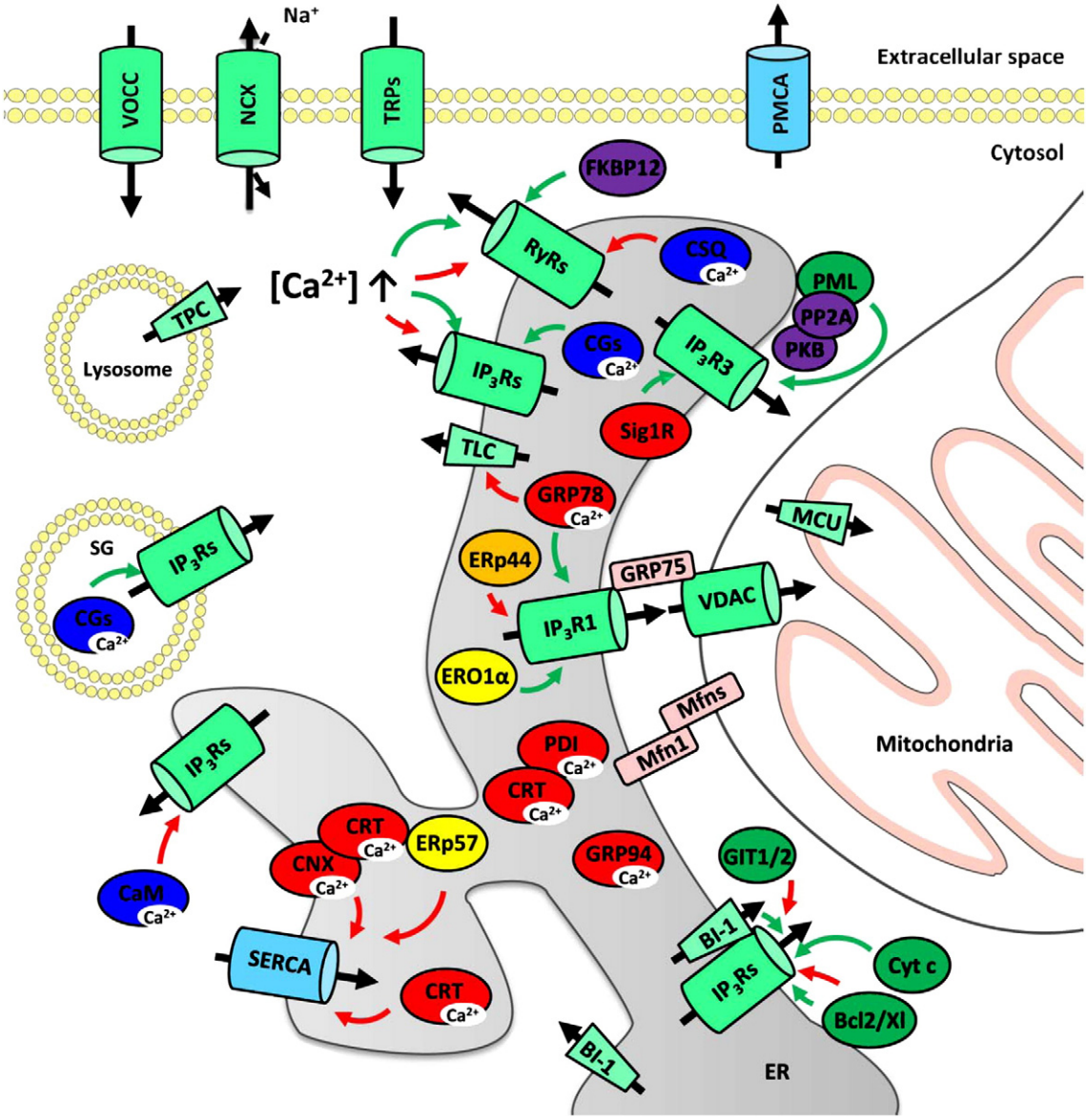

Fig. 1. Overview of the proteins involved in cellular Ca^{2+} handling. The ER and other membrane systems are represented with the main Ca^{2+}-transporting and Ca^{2+}-binding proteins, together with a number of regulatory proteins of importance for this review. Ca^{2+} channels and the Na^+/Ca^{2+} exchanger are in light green, ATP-dependent Ca^{2+} pumps are in light blue, Ca^{2+}-binding proteins are in dark blue, chaperones, including Ca^{2+}-binding chaperones, are in red, oxidoreductases are in yellow, thioreductases are in orange, anti- and pro-apoptotic proteins are in dark green, regulatory proteins are in purple and linker proteins in salmon. Ca^{2+} fluxes are shown by the large black arrows, regulatory arrows are green (stimulatory effect) or red (inhibitory effect), while the flux of the counterion Na^+ occurring at the level of the Na^+/Ca^{2+} exchanger is represented by a small black arrow. Abbreviations are as defined in the text, except for the following ones that are only used in the figure: Bcl2/Xl, anti-apoptotic proteins of the Bcl-2 family; CaM, calmodulin; CGs, chromogranins; CNX, calnexin; CRT, calreticulin; Cyt c, cytochrome c; FKBP12, FK506-binding protein; GRP78, BiP/GRP78; MCU, mitochondrial Ca^{2+} uniporter; Mfn, mitofusin; NCX, Na^+/Ca^{2+} exchanger; PKB, protein kinase B; PMCA, plasma-membrane Ca^{2+} ATPase; PP2A, protein phosphatase 2A; SG, secretory granule; Sig1R, sigma-1 receptor; TLC, translocon; TPC, two-pore channel; VDAC, voltage-dependent anion channel; VOCC, voltage-operated Ca^{2+} channels. For more information, see text.