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Review

Calcium signaling and cell proliferation

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ABSTRACT

Cell proliferation is orchestrated through diverse proteins related to calcium (Ca^{2+}) signaling inside the cell. Cellular Ca^{2+} influx that occurs first by various mechanisms at the plasma membrane, is then followed by absorption of Ca^{2+} ions by mitochondria and endoplasmic reticulum, and, finally, there is a connection of calcium stores to the nucleus. Experimental evidence indicates that the fluctuation of Ca^{2+} from the endoplasmic reticulum provides a pivotal and physiological role for cell proliferation. Ca^{2+} depletion in the endoplasmatic reticulum triggers Ca^{2+} influx across the plasma membrane in an phenomenon called store-operated calcium entries (SOCEs). SOCE is activated through a complex interplay between a Ca^{2+} sensor, denominated STIM, localized in the endoplasmic reticulum and a Ca^{2+} channel at the cell membrane, denominated Orai. The interplay between STIM and Orai proteins with cell membrane receptors and their role in cell proliferation is discussed in this review.

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1. Mechanisms of cytosolic Ca^{2+} entry involved in cell proliferation

Cell proliferation is a complex mechanism orchestrated by several proteins related to Ca^{2+} signaling in different parts of the cell. In the 1970's, initial experimental evidence suggested that cell proliferation might be regulated by Ca^{2+} ions [1,2]. This concept was later elucidated when the involvement of Ca^{2+} channels was observed in normal and pathological cell proliferation [3]. Specifically, it was observed that normal cells require high external Ca^{2+} concentrations [4–7] to trigger cell proliferation while tumor cells demand much less Ca^{2+} influx [2,5]. In light of these evidences, it is clear that an understanding of Ca^{2+} signaling during cell proliferation is critical in order to explain cell physiology in health and disease.

While Ca^{2+} concentrations in the extracellular space, endoplasmic reticulum (ER) lumen, Golgi apparatus and acidic organelles are in the millimolar range, the cytosolic concentration of the ion is kept typically around 100 nM [8]. Ca^{2+} signaling involving membrane proteins, in particular the signaling between the ER and plasma membrane (PM) or between the ER and mitochondria, has been implicated in the regulation of direct Ca^{2+} transfer between organelles. This mechanism has the advantage of maximizing the efficiency of Ca^{2+} signaling and

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interorganellar exchange while avoiding excessive or prolonged changes in the overall concentration of cytosolic Ca^{2+}, which could be detrimental for the cell [9,10].

The major Ca^{2+} entry mechanism in nonexcitable cells is SOCE (store-operated calcium entries), where intracellular Ca^{2+} store reduction activates external Ca^{2+} entry through plasma membrane Ca^{2+} channels. These voltage-dependent Ca^{2+} channels are expressed in several non-excitable, depolarized cellular types (i.e. mesenchymal and cancer stem cells, lymphocytes and breast cancer cells) [11–13] and are essential for cell activation, exocytosis, gene regulation, and cell proliferation [14–17]. Agonist-stimulated Ca^{2+} influx through SOCE allows these cells (i.e. T-cells, mesenchymal, cancer stem cells, hepatocytes) to proliferate by initiating re-entry into the cell cycle [13,18]. In line, blockage of L- and T-type voltage-dependent Ca^{2+} channels and SOCE have potential antiproliferative effects on various cell types.

Capiod's group raised some interesting issues about Ca^{2+} signaling requirements in mammalian cell proliferation [19,20]. First, they demonstrate that cell cycle arrest is associated with a decreased SOCE amplitude [21] and, second, cell proliferation could be inhibited by Ca^{2+} channel blockers [22]. Capiod's group suggests that SOCE is more important factor for cell proliferation than external Ca^{2+} and channel function. Furthermore, Capiod's group believes that cell proliferation rates could depend on the relative balance between Ca^{2+} influx and Ca^{2+}-sensing receptor activation. In this scenario, the C- and N-terminals of the channel proteins may promote enzymatic reactions or participate in cell–cell interactions, which could influence many cellular processes including the regulation of intracellular Ca^{2+} homeostasis [23] and gene expression [24] or act as transcription factors [25].

In nonexcitable cells, several membrane receptors mediate the depletion of intracellular Ca^{2+} stores and modulate SOCE activity levels [26–28]. Particularly, stromal interaction molecule 1 (STIM1) proteins, a Ca^{2+} sensor in the ER, play a critical role in this phenomenon [29,30]. During low Ca^{2+} concentrations, STIM1 proteins sense the depletion of Ca^{2+} stores and spatially redistribute to the ER to activate Orai proteins [31–36], which perforate the PM and establish Ca^{2+} release-activated channels (CRAC) [31,37] (Fig. 1). The connection between ER and PM through CRAC will produce intracellular calcium transient ion flow [31,32,38–40]. In this way, Ca^{2+} depletion in the ER acquires available Ca^{2+} from extracellular space which enters into the cytosol and reloads the ER stores via sarcoplasmic/ER Ca^{2+} ATPases [10,25,41–46] (Fig. 2). In all of these cases, Ca^{2+}-dependent proteins are closely localized to Ca^{2+} channels rapidly transducing the local Ca^{2+} signal into a physiological output [47,48].

Growing evidence indicates that a robust SOCE response is responsible for the stimulation of proliferation, survival and invasion of cancerous cells like melanoma [49], breast [50], colon [51], lung [52] and hepatocellular carcinoma cells [53]. For instance, one of these first reports demonstrated that STIM1 protein activation in the ER of melanoma cells was capable of triggering Ca^{2+} influx and Ca^{2+}/calmodulin (CaM)-dependent activation of the proto-oncogene tyrosine-protein kinase (Src)/protein phosphatase 2 (PP2A)/protein kinase B (PKB) cascade [54], a critical cascade for melanoma malignancy. Also notable, stimulation of CaM by SOCE stimulates the nuclear factor of activated T cells (NFAT) and nuclear factor-kappaB (NF-κB) transcription factors (Figs. 2 and 3) [55].

Decrease of ER Ca^{2+} content caused by pathological conditions can activate SOCE, but some compensatory mechanisms can counterbalance this ER depletion [56–58]. Although poor evidence exists for ER Ca^{2+} depletion during cell cycle, it is known that suppression of tumor cell proliferation by cell cycle arrest at the G0/G1 phase may occur upon CRAC inhibition. Furthermore, inhibition of CRAC let to inhibition of tumor cell metastasis in leukemic [59], breast cancer [60] and prostate

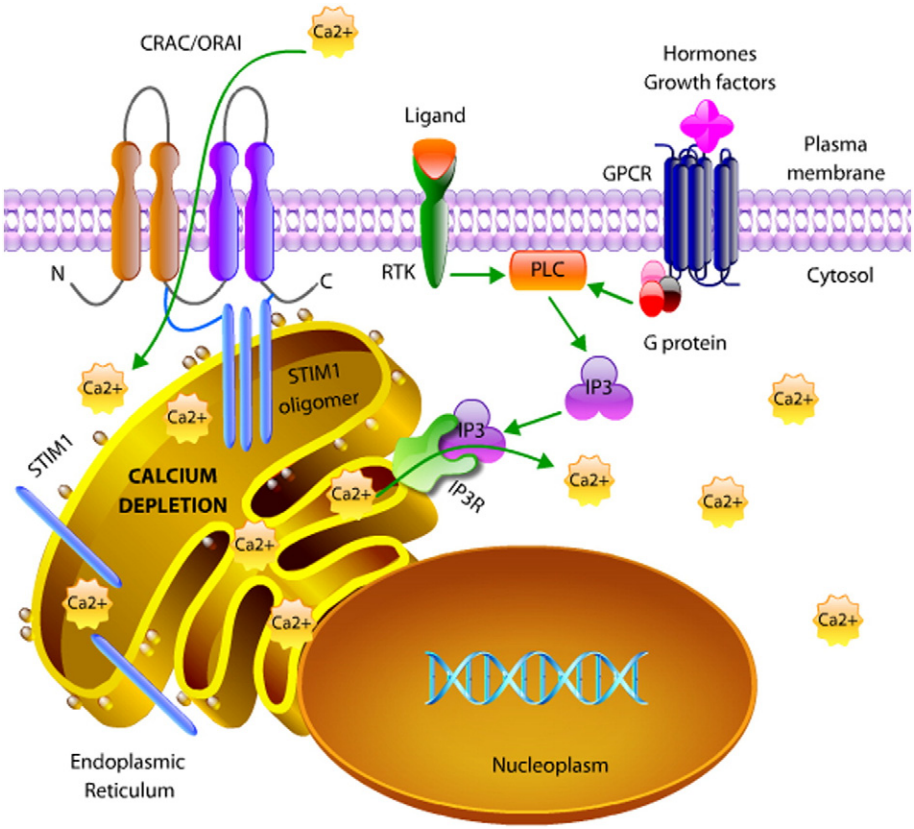

Fig. 1. Intracellular mechanisms controlling the increase of cytosolic Ca2+ concentration $[Ca^{2+}]_{cyt.}$ $[Ca^{2+}]_{cyt.}$ increases by entry through the PM or Ca^{2+} release from intracellular stores. The activation of PM receptors (RTKs-receptor tyrosine kinases and GPCRs- G-protein-coupled receptors) by their ligands promotes a cascade of events resulting in production of IP_3 (inositol 1,4,5-triphosphate). In the ER, IP_3 binds to its receptor (IP_3R) causing the release of stored Ca^{2+}. The decrease of ER Ca^{2+} concentration is perceived by receptors for stromal interaction molecule 1 (STIM1), which translocate to the membrane forming oligomers (puncta). STIM1 binds to the CRAC/Orai complex promoting SOCE.

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