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Review

Altered calcium signaling in cancer cells☆

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ABSTRACT

It is the nature of the calcium signal, as determined by the coordinated activity of a suite of calcium channels, pumps, exchangers and binding proteins that ultimately guides a cell's fate. Deregulation of the calcium signal is often deleterious and has been linked to each of the 'cancer hallmarks'. Despite this, we do not yet have a full understanding of the remodeling of the calcium signal associated with cancer. Such an understanding could aid in guiding the development of therapies specifically targeting altered calcium signaling in cancer cells during tumorigenic progression. Findings from some of the studies that have assessed the remodeling of the calcium signal associated with tumorigenesis and/or processes important in invasion and metastasis are presented in this review. The potential of new methodologies is also discussed. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

Contents

1. Introduction

Tightly controlled regulation of the calcium signal is essential for appropriate cellular functioning, as evidenced by the role of changes in cytosolic free Ca^{2+} in processes such as cell proliferation, gene transcription and cell death [1–5]. Typically cells at rest maintain an intracellular calcium concentration ($[Ca^{2+}]_i$) of approximately 100 nM, while extracellular calcium concentrations are much higher, generally within the range of 1–2 mM [3–5]. Specialized calcium pumps, channels and calcium binding proteins are used by cells to both maintain cellular homeostasis and carry out specific cellular functions, and have been referred to as the "molecular toolkit" for calcium signaling [1,2] (Fig. 1). Changes in cytosolic free Ca^{2+} can involve global increases that may be transient or sustained, or highly localized such as calcium sparks and puffs, or they may occur as waves or oscillations [1,5]. These changes can be "decoded" by the cell, which allows the ubiquitous calcium signal to specifically regulate cellular processes [1,2]. This complexity in calcium signaling means that the deregulation of the calcium signal can be a feature of certain pathological states, including cancer [5–7]. Much of the research assessing calcium signaling in cancer has focused on determining changes in the expression levels of proteins responsible

Abbreviations: ATP, adenosine triphosphate; EGF, epidermal growth factor; EMT, epithelial–mesenchymal transition; IP_3R2, inositol 1,4,5-triphosphate receptor, type 2; PMCA, plasma membrane Ca^{2+} ATPase; SERCA, sarco/endoplasmic reticulum Ca^{2+} ATPase; SOCE, store operated Ca^{2+} entry; STIM1, stromal interaction molecule 1; TRP, transient receptor potential

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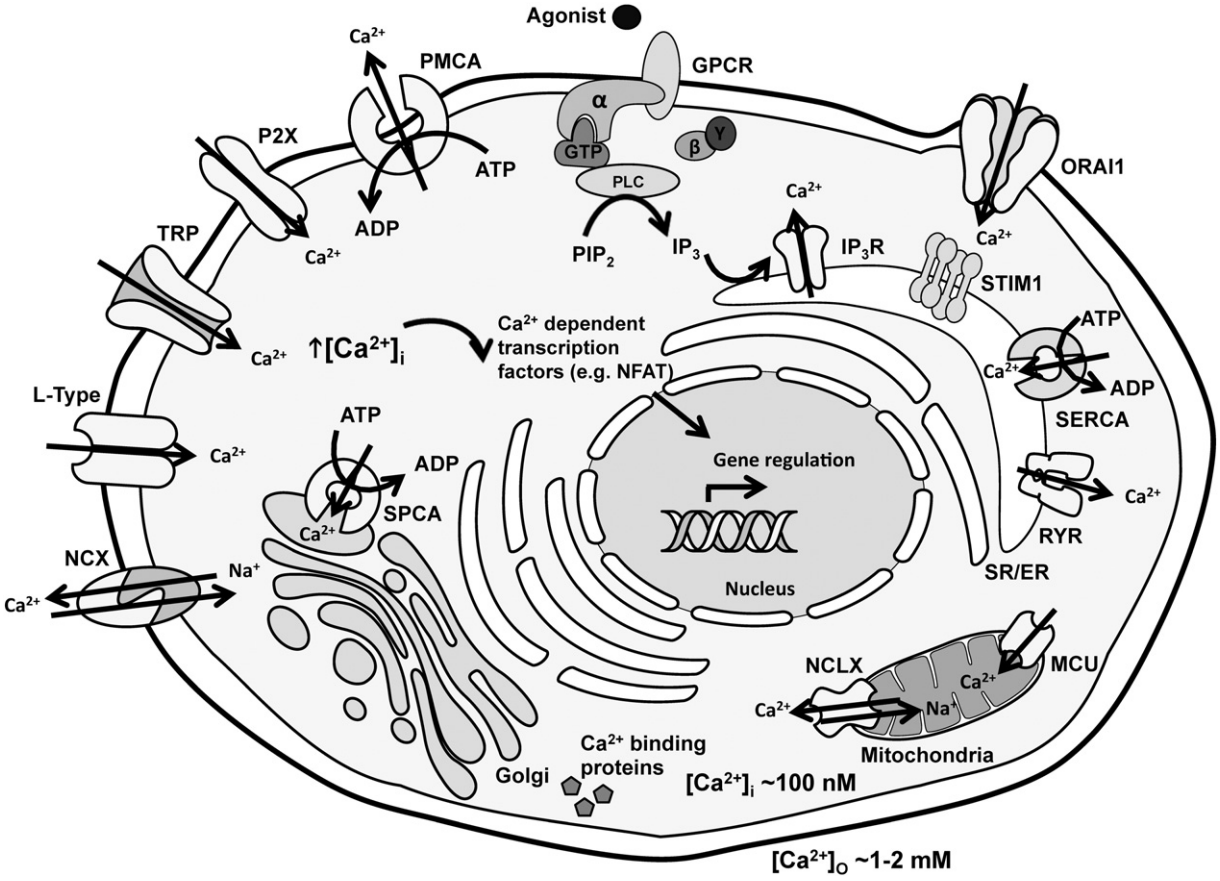

Fig. 1. Diagrammatic representation of major Ca^{2+} influx/efflux/release and resequestration pathways involved in the regulation of $[Ca^{2+}]_i$ homeostasis in mammalian cells and their associated proteins. Major Ca^{2+} influx pathways include those mediated by the transient receptor potential (TRP) family of Ca^{2+} permeable ion channels, voltage-gated Ca^{2+} channels (e.g. L-type), purinergic receptors (e.g. P2X), and the SOCE pathway components Orai1 and STIM1. Activation of plasma membrane localized G protein-coupled receptors (GPCRs) leads to generation of inositol triphosphate (IP_3) and subsequent stimulation of IP_3 receptors (IP_3Rs) located on the endoplasmic reticulum (ER), resulting in Ca^{2+} store release. ER localized ryanodine receptors (RYR) and mitochondrial Na^+/Ca^{2+} exchanger (NCLX) also regulate Ca^{2+} in organelles. The sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA), secretory pathway Ca^{2+} ATPase (SPCA), and mitochondrial uniporter (MCU) all sequester cytosolic Ca^{2+} into intracellular organelles, while plasma membrane Ca^{2+}-ATPases (PMCA) actively extrude Ca^{2+} from the cytosol into the extracellular space, and together with the Na^+/Ca^{2+} exchanger (NCX) play a role in restoring resting $[Ca^{2+}]_i$. Ca^{2+} signaling also regulates various Ca^{2+} dependent transcription factors (e.g. NFAT) and Ca^{2+} binding proteins (e.g. calmodulin).
Adapted from references [8–10].

for regulating cytoplasmic free Ca^{2+} concentrations. Following the identification of aberrantly expressed calcium channels, pumps or exchangers, researchers often then rely on gene silencing approaches and/or chemical inhibitors/activators to evaluate their role in calcium signaling and cancer relevant processes (e.g. proliferation and migration). However, in the context of cancer, compared to some other disease states, there is a paucity of information regarding changes in the *nature* of the calcium signal that occurs in cancer cells compared to non-cancer derived cells. Elucidating such information would improve our understanding of the mechanisms underlying cancer progression, and may further help guide researchers to identify molecular targets not associated with changes in expression. This review will discuss the available evidence for the remodeling of the calcium signal in cancer, and briefly describe studies in other disease states to highlight potential approaches that could further improve our understanding of alterations in calcium signaling in cancer cells.

2. Remodeling of the calcium signal in disease

The development of Ca^{2+} sensitive indicators, such as the fluorescent dyes Fura-2 and Fluo-4, and genetically encoded Ca^{2+} indicators has been integral to our understanding and interpretation of intracellular calcium signaling by enabling quantitative analysis of Ca^{2+} in the cytoplasm and in subcellular organelles [11–16]. These tools have allowed a better understanding of how the nature of the calcium signal is remodeled in some diseases. A relatively well studied example of pathological remodeling of the calcium signal, reviewed in detail elsewhere [17–20], is that which occurs in smooth muscle cells as a consequence of vascular disease and injury, including pulmonary hypertension [21,22], atherosclerosis [23,24] and arterial restenosis following angioplasty [25,26].

Calcium signaling in smooth muscle cells regulates numerous cellular processes including proliferation, contraction and gene transcription [27–30]. During vascular injury (through mechanical stress and/or growth factors/cytokine exposure), vascular smooth muscle cells can undergo phenotypic switching from cells that are largely quiescent and contractile, to those exhibiting a more synthetic and proliferative phenotype [18,31,32]. This phenotypic switching [31], is associated with corresponding changes in the *nature* of the calcium signal, for example a transition from voltage-gated Ca^{2+} entry pathways typical of contractile cells to one resembling store-operated and receptor-operated Ca^{2+} entry (SOCE) in proliferating cells [20,33–35]. Kumar et al. demonstrated an example of such remodeling using an in vivo model of neointimal hyperplasia [25]. In this model, freshly isolated periadventitial cuff injured mouse carotid artery displayed increased $[Ca^{2+}]_i$ in response to reintroduction of Ca^{2+} following store depletion using the sarco/endoplasmic reticulum ATPase (SERCA) inhibitor thapsigargin, while K^+ induced depolarization failed to significantly increase $[Ca^{2+}]_i$ relative to uninjured arterial tissue [25]. These findings indicated a switch from a predominately voltage-gated calcium entry