Cell Calcium 63 (2017) 70–96

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

Crosstalk between calcium and reactive oxygen species signaling in cancer

Nadine Hempel [a,c,*], Mohamed Trebak [b,c,*]

[a] Department of Pharmacology, Penn State College of Medicine, Hershey PA 17033, United States
[b] Department of Cellular and Molecular Physiology, Penn State College of Medicine, Hershey PA 17033, United States
[c] Penn State Hershey Cancer Institute, Penn State College of Medicine, Hershey PA 17033, United States

ARTICLE INFO

Article history:
Received 7 December 2016
Received in revised form 13 January 2017
Accepted 14 January 2017
Available online 18 January 2017

Keywords:
Calcium signaling
Calcium channels
Reactive oxygen species signaling
Mitochondria
NADPH oxidase
Cancer
Tumorigenesis

ABSTRACT

The interplay between Ca^{2+} and reactive oxygen species (ROS) signaling pathways is well established, with reciprocal regulation occurring at a number of subcellular locations. Many Ca^{2+} channels at the cell surface and intracellular organelles, including the endoplasmic reticulum and mitochondria are regulated by redox modifications. In turn, Ca^{2+} signaling can influence the cellular generation of ROS, from sources such as NADPH oxidases and mitochondria. This relationship has been explored in great depth during the process of apoptosis, where surges of Ca^{2+} and ROS are important mediators of cell death. More recently, coordinated and localized Ca^{2+} and ROS transients appear to play a major role in a vast variety of pro-survival signaling pathways that may be crucial for both physiological and pathophysiological functions. While much work is required to firmly establish this Ca^{2+}-ROS relationship in cancer, existing evidence from other disease models suggests this crosstalk is likely of significant importance in tumorigenesis. In this review, we describe the regulation of Ca^{2+} channels and transporters by oxidants and discuss the potential consequences of the ROS-Ca^{2+} interplay in tumor cells.

Contents

Abbreviations: AMPK, 5′ adenosine monophosphate activated protein kinase; ASK1, apoptosis signal-regulating kinase 1; Atg, autophagy Related Cysteine Peptidase; BIRD-2, Bcl-2/IP3R disrupter; CaM, calmodulin; CaMKII, Ca^{2+}/Calmodulin-dependent kinase II; Cat, Catalase; CRAC, Ca^{2+} release activated Ca^{2+}; DAG, diacylglycerol; ER, Endoplasmic Reticulum; Ero, ER oxidoreductase; ETC, Electron Transport Chain; GPCR, G-protein coupled receptor; GPx, Glutahione Peroxidase; GR, glutathione reductase; Grx, glutaredoxin; GSH, Glutathione; HK, Hexokinase; H_2O_2, hydrogen peroxide; HOCl, hypochlorous acid; HIF, Hypoxia Inducible Factor; IP_3, inositol 1,4,5-trisphosphate; IP_3R, IP_3 receptor; Lamp1, lysosomal-associated membrane protein 1; LC3-II, Microtubule-associated proteins 1A/1B light chain 3B; MAM, mitochondria associated membrane; MCUR1, MCU Regulator 1; MICU, Mitochondrial Ca^{2+} Uptake; mPTP, mitochondria Permeability Transition Pore; mTOR, mechanistic target of rapamycin; NCLX, Na^+/Ca^{2+} Li^+ Exchanger; NCX, Na^+/Ca^{2+} exchanger; NAD, nicotinamide adenine dinucleotide; NO, •nitric oxide; NOS, Nitric Oxide Synthase; Nox, NADPH oxidase; O2, •−superoxide; •OH, hydroxyl radical; $ONOO^-$, peroxinitrite; PARP, poly(ADP-ribose) polymerases; PDH, Pyruvate dehydrogenase; PDI, protein disulfide isomerase; PERK, RNA-dependent protein kinase (PKR)-like ER kinase; PI3K, Phosphoinositide 3-kinase; PLC, phospholipase C; PKC, Protein kinase C; PTEN, phosphatase and tensin homolog; Prx, Peroxidase; PMCA, plasma membrane Ca^{2+} ATPase; RNS, Reactive nitrogen Species; ROS, reactive oxygen species; RNS, reactive nitrogen species; RyR, Ryanodine Receptor; SERCA, Sarco/endoplasmic reticulum Ca^{2+}-ATPase; SOCE, store operated calcium entry; Sod, Superoxide dismutase; TFEB, transcription factor EB; TRP, Transient Receptor Potential; Trx, thioredoxin; VDAC, voltage-dependent anion channel.

* Corresponding authors at: Penn State Hershey Cancer Institute, Penn State College of Medicine, Hershey PA 17033, United States.
E-mail addresses: nhempel@psu.edu (N. Hempel), mtrebak@psu.edu (M. Trebak).

http://dx.doi.org/10.1016/j.ceca.2017.01.007
0143-4160/

1. Introduction

The relationship between Calcium (Ca^{2+}) and reactive oxygen/nitrogen species (ROS/RNS) is well established and has been described in numerous disease models. Much of our knowledge has been gained from the cardiovascular system, where this interplay is an important aspect of pathophysiology, a prominent example being ischemia/reperfusion injury, where the Ca^{2+}- ROS interplay is involved in eliciting cell death [1]. Thus, apoptosis is one event where coordinated surges of ROS and Ca^{2+} have been observed and studied in great depth [2–4]. However, in addition to cell death, emerging evidence reveal that many diverse cellular signaling events are regulated by concomitant and localized increases in ROS and Ca^{2+} transients [5–8]. This Ca^{2+} – ROS interaction is evident by the fact that many regulators of Ca^{2+} signaling are redox modified, and reciprocally Ca^{2+} signaling is intricately involved in regulating ROS levels. Importantly, the subcellular location of Ca^{2+} stores and the sites of ROS production are closely linked, prominently the ER-mitochondrial interface and the plasma membrane [9,10].

Tight regulation of Ca^{2+} homeostasis lies at the center of cellular signaling. The type of signaling "output" is dependent on the duration, localization, amplitude and frequency of the Ca^{2+} signal [11,12]. Regulation of Ca^{2+} homeostasis is achieved by a number of ion channels, pumps and exchangers, found on both the cell surface and the organelles that act as primary intracellular Ca^{2+} stores. Similarly, subcellular regions of ROS/RNS production, such as the leading edge of migrating cells and the ER-mitochondrial interface, are emerging as hubs of signaling, and, as highlighted below, the type of reactive species and signal amplitudes influence the consequential signaling events and cellular responses [13–15]. While many studies have examined the redox control of Ca^{2+} homeostasis, relatively few studies have investigated this connection specifically as it pertains to carcinogenesis or metastatic progression. This may in part be due to the fact that the role of Ca^{2+} signaling in cancer is a relatively new field and that Ca^{2+} signaling mechanisms are complex and do not adhere to a "one size fits all" paradigm in cancer cells [16]. Much like changes in redox balance, this appears to be context and cancer type specific. Underlying genomic differences between tumor types, cellular heterogeneity of individual tumors, and the contribution of the tumor microenvironment likely contribute to this variability. Nevertheless, a number of studies have demonstrated that increased cytosolic Ca^{2+} is involved in processes such as proliferation, migration, invasion, and anchorage independent survival, clearly demonstrating that Ca^{2+} signaling is important in cancer progression [16–19]. In the present review, we focus on the interplay between Ca^{2+} and ROS in cancer, highlighting some of the discoveries pertaining to the redox regulation of Ca^{2+} transport mechanisms, and how Ca^{2+} signaling pathways in turn may regulate the cellular redox environment. Although much work is still required to firmly establish this relationship in different cancer types, two themes can be inferred from existing literature. 1) Coordinated ROS and Ca^{2+} surges are required for apoptosis initiation at the mitochondrial-Endoplasmic Reticulum (ER) interface, with evidence suggesting that this interplay is altered in cancer cells to enhance apoptosis resistance. 2) Localized, sub-lethal changes in both ROS and Ca^{2+} levels fine-tune signaling cascades that maintain proliferative and metastatic signals (Fig. 1).

2. Oxidants – the importance of what, where and how much

2.1. What and where?

The terms reactive oxygen species (ROS) and reactive nitrogen species (RNS), are often loosely used to describe a group of very different molecular species that vary in reactivity, half-life, site of production and detoxification reactions (Fig. 2). These oxidants can be either free radicals (containing an unpaired electron), such as superoxide anion ($O_2^{\bullet -}$) and hydroxyl radical ($^{\bullet}OH$), or non-radical oxidants, including hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl, primarily in neutrophils) and peroxinitrite ($ONOO^-$), the latter being generated in the presence of $O_2^{\bullet -}$ and nitric oxide ($NO^{\bullet}$). $NO^{\bullet}$ is produced by Nitric oxide synthase, of which two isoforms (nNOS/NOS1 and eNOS/NOS3) are regulated by Ca^{2+} in a calmodulin-dependent manner [20]. It should be noted that these species vary widely in their half-life, reactivity and diffusion rates, and their role on macromolecular oxidation is dependent on amounts and sites of generation, as well as the rate of oxidation and abundance of target moieties [21]. Moreover, the reaction with target molecules, such as other ROS, lipids, proteins and DNA, is dependent on the redox environment of the cell. For example, high abundance of reduced glutathione and fast reaction with more readily oxidized proteins, such as peroxiredoxins, may result in "scavenging" of the oxidant species before these are able to reach their target (Fig. 2) [21–23]. The relatively high reactivity of some oxidants limits their diffusion and role as true signaling molecules. This includes the highly reactive $^{\bullet}OH$ ($T_{1/2}$ 10^{-6}-10^{-9}sec). Similarly, $O_2^{\bullet -}$ has a half-life of micro to milli seconds, depending on its environment and interactions with cellular and extracellular components such as $NO^{\bullet}$, transition metals and ascorbic acid; while H_2O_2 has a half life in the order of seconds [24,25].