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Sarcoplasmic reticulum and calcium signaling in muscle cells: Homeostasis and disease

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Contents

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Abstract

The sarco/endoplasmic reticulum is an extensive, dynamic and heterogeneous membranous network that fulfills multiple homeostatic functions. Among them, it compartmentalizes, stores and releases calcium within the intracellular space. In the case of muscle cells, calcium released from the sarco/endoplasmic reticulum in the vicinity of the contractile machinery induces cell contraction. Furthermore, sarco/endoplasmic reticulum-derived calcium also regulates gene transcription in the nucleus, energy metabolism in mitochondria and cytosolic signaling pathways. These diverse and overlapping processes require a highly complex fine-tuning that the sarco/endoplasmic reticulum provides by means of its numerous tubules and cisternae, specialized domains and contacts with other organelles. The sarco/endoplasmic reticulum also possesses a rich calcium-handling machinery, functionally coupled to both con-

traction-inducing stimuli and the contractile apparatus. Such is the importance of the sarco/endoplasmic reticulum for muscle cell physiology, that alterations in its structure, function or its calcium-handling machinery are intimately associated with the development of cardiometabolic diseases. Cardiac hypertrophy, insulin resistance and arterial hypertension are age-related pathologies with a common mechanism at the muscle cell level: the accumulation of damaged proteins at the sarco/endoplasmic reticulum induces a stress response (termed endoplasmic reticulum stress), which impairs proper organelle function, ultimately leading to pathogenesis.

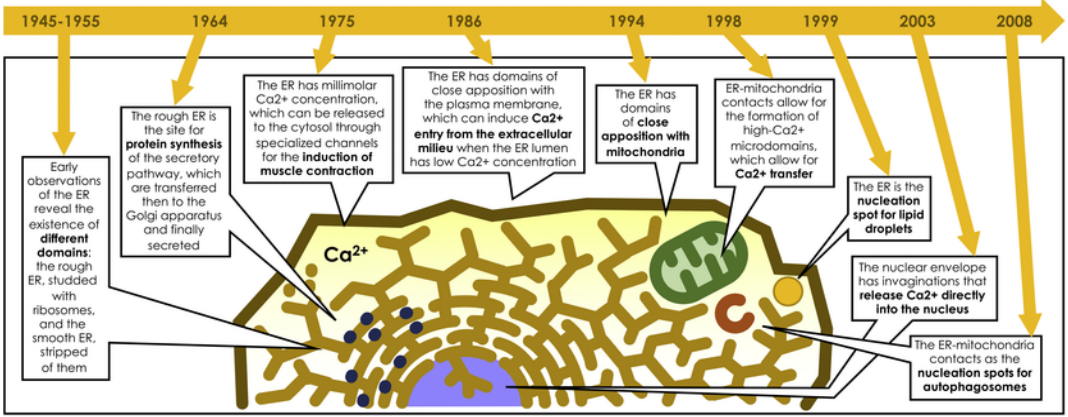
1. INTRODUCTION

1.1. SR/ER: A highly heterogeneous and complex structure

A general characteristic of eukaryotic cells is the presence of membrane-lined internal structures, termed organelles, which compartmentalize different cellular functions. Among organelles, the endoplasmic reticulum (ER) is the largest one, comprised by a continuous narrow lumen, enclosed by a single membrane. It was identified in the mid-20th century, in the dawn of cell electron microscopy, as a structure that gives cells their "rugged" appearance (Palade, 1955; Porter et al., 1945). Since its discovery, many functions of the ER have been described (Fig. 1A), which are addressed in the following pages, with special emphasis on Ca^{2+} handling in muscle cells. In the case of cardiac and skeletal muscle cells, termed myocytes, the ER is particularly dense and ordered, giving them their distinctive striated appearance. Because of this unique specialization, the ER in these cells is named sarcoplasmic reticulum (SR), a term that stems from the Greek word *sarco*, which means "flesh," which associates with muscle.

In nucleated cells, and not only in myocytes, the sarco/endoplasmic reticulum (SR/ER) is continuous with the nuclear envelope (NE), which encloses the genetic material. In non-muscular cells, the perinuclear ER consists of stacks of cisternae with sheet morphology, known as the lamellar ER, mainly in charge of protein synthesis. Because of that, it exhibits multiple ribosomes attached to its surface, thereby termed "rough" ER. In contrast, peripheral ER mainly consists of a network of tubules, thus known as tubular ER and since this domain is stripped of ribosomes, it is commonly termed "smooth" ER. When muscle cell precursors, termed myoblasts, differentiate into myocytes, their ER also differentiates into SR, acquiring a structure capable of supporting cell contraction. In both skeletal and cardiac myocytes, the SR becomes highly or-

A **Timeline of SR/ER discoveries**



B **Lifecycle of the SR/ER**

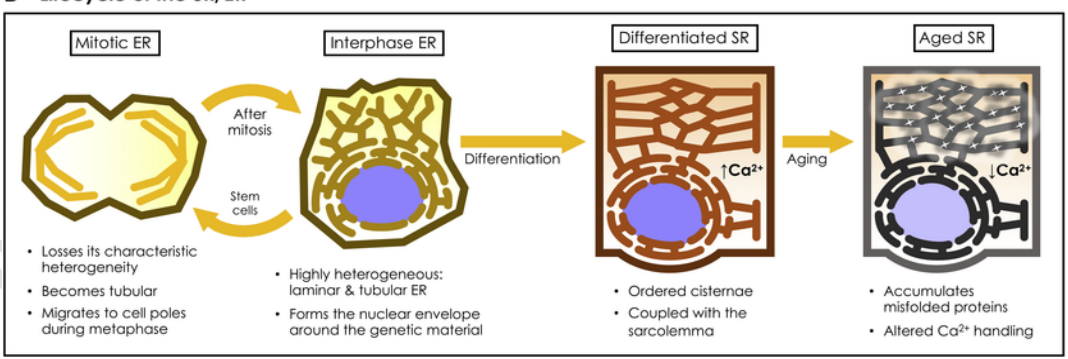


Fig. 1. The sarco/endoplasmic reticulum through time. (A) Timeline of the sarcoplasmic/endoplasmic reticulum (SR/ER) discoveries. The SR/ER was identified during the first observations of cells using electron microscopy in the mid-1900s. A decade later, radiographic tracking of proteins within the cell showed that the SR/ER is a key structure for protein synthesis. Around the same time, pioneer studies on isolated SR-derived vesicles showed the mechanism of Ca^{2+} accumulation in the SR, which became the basis for the elucidation of its role in muscle contraction. Ensuing research in parotid slices showed that ER Ca^{2+} depletion induces extracellular Ca^{2+} entry as a refilling mechanism. Subsequent investigation depicted that this process occurs owing to close contacts between the ER and the plasma membrane. Likewise, during the 1990s, biochemical analyses pointed out the existence of domains of close association between ER and mitochondria. Later on, advances in confocal fluorescence microscopy showed that said sites allow for the efficient Ca^{2+} transfer from ER to mitochondria. During the last two decades, mounting evidence showed that the ER is part of a complex signaling network with other organelles, serving as a nucleation site for both lipid droplets and autophagosomes. Moreover, the ER has also shown to regulate intranuclear Ca^{2+} signaling, through invaginations into the nucleus, termed nucleoplasmic reticulum. (B) Lifecycle of the SR/ER. As a dynamic organelle, the SR/ER undergoes several changes during the cell cycle and differentiation. First, the ER is segregated into daughter cells during mitosis, and then organizes as a mature ER, specializes as a SR, and ultimately experiments time-associated damage.

dered and aligns with the cell's longitudinal axis. In non-striated muscle cells, termed smooth muscle cells (SMC), the SR is not oriented in a single direction, as in other non-myocytes. These different types of SR organization are related to the ability of myocytes to exert mechanical forces, resulting in either axial or concentric contractions.

1.2. Calcium: A rapid and complex intracellular messenger governed by the SR/ER

Muscle contraction has fascinated researchers since the primal physiological studies. Along with ATP, calcium was early identified as one of the key participants at the biochemical level (Szent-Györgyi, 1975). In its soluble form, calcium exists as a cation (Ca^{2+}), which can form electrostatic interactions with negatively charged moieties of molecules (e.g., carboxyl groups). Thereby, varying Ca^{2+} levels can induce conformational changes in proteins, thus acting as a regulator of their function. Such is the case of the muscle contraction machinery, which contracts upon Ca^{2+} binding.

Interestingly, Ca^{2+} forms insoluble crystals with phosphate, which is a key intermediate in many cellular reactions (e.g., covalent regulation of protein function through phosphorylation and dephosphorylation). In accordance with that, cells maintain low Ca^{2+} levels in their cytosol (around 100 nM), but high levels in the extracellular milieu (around 10 mM, 10,000 times higher) (Szent-Györgyi, 1975). Because of this compartmentalization, a concentration gradient drives fast Ca^{2+} entry to the cytosol upon opening of specialized channels in the plasma membrane of myocytes, termed sarcolemma. This allows Ca^{2+} to act as a rapid second messenger.

Apart from timing, localization is also important for effective signal transduction. In the case of Ca^{2+} signals, different mechanisms regulate their spatiotemporal patterns: (i) the localization and selective activation of entry channels, (ii) limited Ca^{2+} diffusion to the cytoplasm (Al-Baldawi and Abercrombie, 1995; Donahue and Abercrombie, 1987), and (iii) pumps extrude Ca^{2+} and maintain its low resting levels (Szent-Györgyi, 1975). This system allows for spatially confined and temporally limited Ca^{2+} signals, which can be orchestrated into complex patterns to regulate multiple processes occurring at overlapping times.

Moreover, Ca^{2+} entry from the extracellular milieu is not the only source of intracellular Ca^{2+} signals. Certain organelles store Ca^{2+} at

high levels, and thus, can readily release it to the cytosol using the aforementioned concentration gradient. The SR/ER is one of such organelles, with a resting Ca^{2+} concentration around 1–2 mM (Szent-Györgyi, 1975). Similar to the plasma membrane, it harbors pumps that remove Ca^{2+} from the cytosol into its lumen. Thus, the SR/ER is the largest intracellular Ca^{2+} reservoir, and its lumen acts in a similar fashion as the extracellular milieu in terms of Ca^{2+} compartmentalization.

1.3. The SR/ER houses various Ca^{2+}-regulated cellular processes

The SR/ER is not only a key player in Ca^{2+} homeostasis, but also participates in many cellular processes. Most notably, the SR/ER is the primary site of synthesis of secretion proteins, as well as those targeted to cellular membranes (Caro and Palade, 1964). Ribosomes attached to the cytosolic side of the ER synthesize peptide chains that are co-translationally translocated to the ER lumen, or inserted at its membrane (Bravo et al., 2013). At the ER lumen, nascent peptides fold into their native conformation assisted by chaperones, which are proteins that prevent the formation of stable misfolded intermediates, prone to aggregation. In the ER, folding proteins become glycosylated in order to reach their native conformation. Furthermore, redox modifications of folding proteins also take place at the ER via enzymes termed foldases, which form and breakdown disulfide bonds. Finally, folding proteins interact with lectins that recognize their glycosylated moieties. These lectins serve as the ER quality control machinery, retaining protein folding intermediates, while letting terminally folded proteins advance to the rest of the secretory pathway (i.e., the cargo-managing organelle, the Golgi apparatus). Given its high concentration at the ER lumen, Ca^{2+} also plays a relevant role in protein folding, serving as a cofactor for chaperones, foldases and lectins.

Because of the redox reactions occurring at the ER lumen, this site is a privileged environment in terms of redox state. On the one hand, disulfide bond formation requires oxygen as an electron acceptor, which leads to the formation of oxygen reactive species (ROS) (Zeeshan et al., 2016). On the other hand, this mechanism converts the ER lumen in an oxidative environment, which differs from the cytosol (Hwang et al., 1992). Thus, the ER is not only a source of ROS, but its function is also highly sensitive to oxidative stress.

Along with from Ca^{2+} and protein homeostasis, the ER is also a key site for lipid synthesis. Diglycerides and triglycerides, which are the main components of lipid droplets, are synthesized at the ER surface. The route of phospholipid production also initiates at the SR/ER surface, beginning with the synthesis of phosphatidic acid, which then converts to phosphatidylinositol, phosphatidylcholine, phosphatidylethanolamine or phosphatidylserine (Vance and Tasseva, 2013). Furthermore, the SR/ER also participates in the synthesis of sphingolipids, ceramides and cholesterol (Jacquemyn et al., 2017).

1.4. Dynamics of the SR/ER

The SR/ER is a highly dynamic organelle that undergoes extensive remodeling with each cell division cycle (Fig. 1B). During mitosis, the ER remains as a group of extended sheets with homogeneous architecture, in striking contrast with the interphase ER described above. These sheets then distribute between the daughter cells by migrating to the poles of the dividing cell (Lu et al., 2009). Interestingly, the ER apparently retains its interconnected nature during mitosis, which contrasts with other organelles that disperse into smaller structures. Of note, although the nuclear envelope (NE) is a very distinct compartment of the SR/ER, its proteins disperse throughout the rest of the SR/ER network during mitosis, and must be reassembled at the end of the process (Yang et al., 1997).

During interphase, the ER maintains its structure through processes such as growth, which requires the synthesis of new lipids and proteins, and degradation, which occurs through selective degradation of ER portions by the lysosomal machinery (termed ER-phagy) (Bravo et al., 2013). ER tubules are also remodeled via branching, fusion and fission, resulting in the interconnected network typical of the tubular ER.

Due to decreased efficiency of quality control, degradation and/or renewal mechanisms, damage accumulates as time passes, in an aging path that occurs at the organismal, cellular and organellar level. A general feature of aging is the accumulation of misfolded proteins and/or protein aggregates that interfere with proper cell function (Agbulut et al., 2000). In the case of the SR, aging results in altered Ca^{2+} handling, which leads to a slower contraction (Narayanan et al., 1996). When damage accumulation becomes a critical burden, it leads to pro-inflammatory signaling, which, being an adaptive response to clear out damaged structures, also jeopardizes tissue homeostasis (Isaac et al., 2016). Finally, when cellu-

lar stress becomes unsolvable, it triggers cell demise pathways (Bravo et al., 2013).

1.5. SR/ER as a signaling hub

Since the SR/ER constitutes the largest intracellular Ca^{2+} reservoir, extending throughout the whole cell, it provides localized domains of Ca^{2+} signaling. The basic element of Ca^{2+} signaling is the opening of a single Ca^{2+} channel, which creates a small microdomain of high Ca^{2+} concentration at the SR/ER surface, thus allowing for fine-tuning of the local Ca^{2+}-responsive machinery. These Ca^{2+} signals can also induce the opening of neighboring Ca^{2+} channels, creating a wave of high Ca^{2+} concentration across the cell that most notably induces myocyte contraction (Mulder and de Tombe, 1989). Furthermore, these two kinds of Ca^{2+} signals often coexist, as in the case of cardiac myocytes, which experience never-ending cycles of Ca^{2+} waves and contraction, yet being able to regulate other local Ca^{2+}-depending events.

Apart from Ca^{2+} signaling, the ER is also functionally connected with the rest of the secretory pathway through vesicle traffic. It provides proteins and lipid precursors to the Golgi apparatus, endosomal system, lysosomes, peroxisomes and plasma membrane (Bravo-Sagua et al., 2014). This traffic is essential for proper organelle function and structure. For example, inhibition of cargo export from de ER leads to the disappearance of the Golgi apparatus, and also induces ER stress due to protein accumulation in its lumen. Additionally, the SR/ER allegedly also provides nucleation sites and membranes for other structures, such as lipid droplets (otherwise termed adiposomes) (Murphy and Vance, 1999) and autophagosomes, the latter being engulfing membranes that isolate cytoplasmic material for lysosomal degradation (Axe et al., 2008).

Given that the SR/ER also forms the NE, it has nuclear invaginations termed the nucleoplasmic reticulum, which allows local Ca^{2+} signaling within the nucleus, thus regulating transcription factors and gene expression (Echevarría et al., 2003). Furthermore, the SR/ER also communicates with other structures through close apposition between membranes, without actual membrane fusion. Within the plasma membrane, contact points allow for localized extracellular Ca^{2+} entry, in order to refill SR/ER stores (Putney, 1986). Such mechanism activates upon SR/ER Ca^{2+} depletion, and is thus termed, store-operated Ca^{2+} entry (SOCE, originally termed capacitative Ca^{2+} entry). The interface between the SR/

ER and mitochondria also requires close proximity to allow efficient lipid and Ca^{2+} transfer from the SR/ER to the mitochondria (Rizzuto et al., 1998; Rusiñol et al., 1994). In the mitochondrial matrix, Ca^{2+} stimulates oxidative metabolism and ATP production. In muscle cells, this communication is particularly important, as mitochondria must be positioned near the contractile machinery to provide enough ATP. This proximity is highly dynamic and its remodeling is an adaptive mechanism to cope with varying cellular needs (Bravo et al., 2011). When adverse conditions surpass the cellular adaptive capacity (e.g., chronic ER stress), it leads to sustained SR/ER-to-mitochondria Ca^{2+} transfer, which in turn, triggers mitochondrial dysfunction and cell death (Bravo-Sagua et al., 2013). Therefore, SR/ER-mitochondria communication serves as a double-edged sword that regulates both cell survival and death.

In sum, Ca^{2+} handling is spatially and temporally complex, requiring the communication of various organelles. Among them, the SR/ER plays a central role, being highly heterogeneous and dynamic. Through Ca^{2+} signals, the SR/ER controls a diverse array of functions, such as protein homeostasis, energy metabolism, gene expression and cell fate. Moreover, in muscle cells, all these regulatory networks coexist with whole-cell Ca^{2+} waves, which allow for cell contraction. In the following pages, we will describe Ca^{2+} handling in the SR/ER of the three muscle cell types (skeletal fibers, cardiac myocyte and SMC), explore their differences and analyze how their particularities associate with their function and pathological processes.

2. SR/ER STRUCTURE

2.1. ER-shaping proteins and dynamics

The SR/ER requires a plethora of specialized proteins to acquire and maintain its shape. In terms of ER laminar structures, the protein Climp63 has been identified as a molecular spacer that maintains the width of the ER sheets. Moreover, Climp63 knock-down in the monkey kidney cell line COS-7 leads to decreased luminal width, without fully eliminating the sheet-shaped ER. Conversely, its overexpression leads to a marked increase in the number of ER sheets (Shibata et al., 2010). Of note, Climp63 S-palmitoylation acts as a switch for its ER morphogenic effect, allowing for the interconversion between sheets and

tubules (Sandoz et al., 2018). The ER tubular structure has been successfully recreated in vitro by using proteoliposomes containing purified yeast ER proteins, specifically the GTPase Sey1p, the curvature-stabilizing protein Yop1, and the proteins known as reticulons (Rtns). This process is evolutionarily conserved, as the Sey1p vertebrate orthologue Atlastin also generates GTP-dependent tubular structures (Powers et al., 2017). Furthermore, Rtn1 overexpression leads to partial conversion of ER sheets into tubes, and in vitro experiments pinpoint Rtn5a as a key mediator of tubule formation, thereby suggesting that the relative abundance of these proteins determines ER morphology (Shibata et al., 2010; Voeltz et al., 2006).

Additionally, the ER is also a dynamic organelle characterized by the constant formation of new structures. Evidence indicates that the ER resident GTPase Rab10 localizes along the microtubules and marks both the branching position for newly-synthetized ER tubules and the fusion site between tubules. Indeed, Rab10 knock-down generates a phenotype similar to the knock-down of Rtns or other curvature-stabilizing proteins, but in this case, the anomaly is due to blunted tubule synthesis (English and Voeltz, 2013). Other presumable regulator of ER fusion is Mitofusin 2 (MFN2), a GTPase that mediates both mitochondrial fusion and the proximity between ER and mitochondria. MFN2 knock-out triggers ER fragmentation in mouse embryonic fibroblasts, in addition to the expected mitochondrial fission (de Brito and Scorrano, 2009). Moreover, Ngoh et al. showed that ER stressors increase *mfn2* mRNA levels, and MFN2 elimination, but not MFN1 (another MFN isoform involved in mitochondrial fusion), induces the ER stress response (Ngoh et al., 2012), thus highlighting its importance for ER function.

2.2. SR organizational features in striated muscle

Striated muscle cells possess a highly specialized architecture, in consonance with their mechanical function. Skeletal myocytes fuse into one long muscle fiber, and the arrangement of several of these fibers ultimately forms a muscle. Cardiomyocytes, on the other hand, do not fuse, and form interconnected branched fibers. Both cell types possess contractile units called sarcomeres, comprised of parallel hyper-structured proteins that form a long fibrillar arrangement able to exert mechanical force (myofibrils). The SR can be divided in two morphological types according to its localization respect to sarcomeres: (i) longitudinal SR, lo-

cated around the contractile units and participates in contraction and relaxation, and (ii) junctional SR (jSR), located in tight proximity to the sarcolemmal invaginations termed transverse tubules or T tubules (TT) that regulates contraction initiation (Rossi et al., 2008). To fulfill their functions, both SR regions have distinctive protein localization patterns (Fig. 2). The longitudinal SR is rich in ligand-gated Ca^{2+} channels, termed Inositol 1,4,5-trisphosphate receptors (IP3R), which release Ca^{2+} mainly to regulate signaling pathways distinct from sarcomere contraction. SR/ER Ca^{2+} ATPase (SERCA) is also abundant in this region, pumping Ca^{2+} back to the SR against a huge concentration gradient, thus consuming high levels of ATP (Salanova et al., 2002). The jSR, on the other hand, is continuous with the longitudinal SR and corresponds to a singular terminal cisterna that runs parallel and in close proximity to the TT (Flucher et al., 1993). In skeletal muscle fibers, two terminal cisternae associate with one TT, forming multicomplex structured membranes termed triads. This structure provides close proximity between sarcolemmal voltage-gated L-type Ca^{2+} channel (LTCC) Cav1.1, otherwise known as dihydropyridine receptor (DHPR), present in the TT, and ryanodine receptor 1 (RyR1) Ca^{2+} channels of the jSR membrane. Cav1.1 and RyR1 channels physically interact, forming a complex maintained by bridge proteins of the Triadin family, such as Triadin95 (Fourest-Lieuvin et al., 2012), Junctophilin (JPH) and others (Golini et al., 2011; Takeshima et al., 2015).

In cardiac muscle, the organization of the jSR differs from the skeletal muscle triads, which are replaced with dyads, formed by one terminal cisterna and a single TT. In the heart, the predominant isoforms of LTCC and RyR are Cav1.2 and RyR2, respectively, and the membrane junctional complex is composed of JPH2 as the main molecular bridge. Accordingly, JPH2 knock-out mice present embryonic lethality, and the cardiac myocytes derived from these mice have deficient junctional complexes and impaired Ca^{2+} ion transients (Takeshima et al., 2000; van Oort et al., 2011). Recent reports indicate that Nexilin (NEXN) participates in the formation of heart TT, as a protein essential for Ca^{2+} handling and proper architecture of the junctional complexes (Liu et al., 2019).

To maintain jSR composition, striated myocytes have developed a complex protein transport circuit. Calsequestrin (CSQ), for instance, is a Ca^{2+}-binding protein that acts as a Ca^{2+} buffer in the SR lumen.

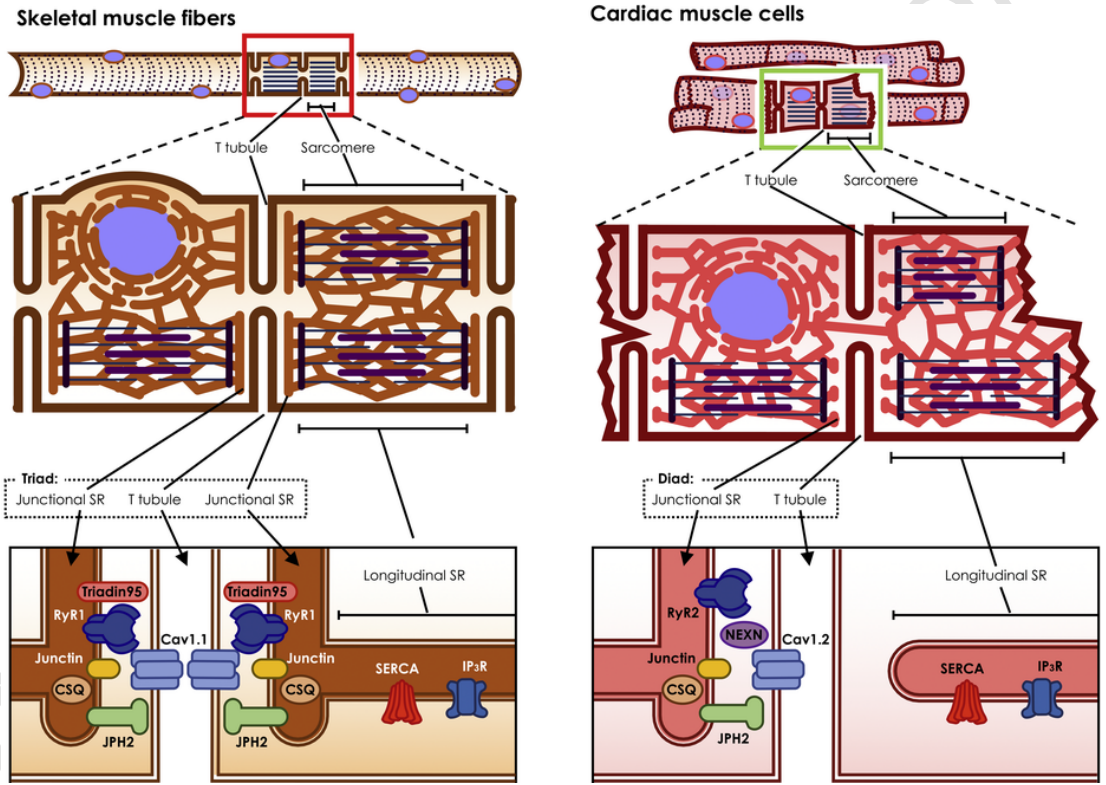

Skeletal muscle fibers
T tubule
Sarcomere
Triad:
Junctional SR
T tubule
Junctional SR
Triadin95
RyR1
Cav1.1
Junctin
CSQ
JPH2
Triadin95
RyR1
Junctin
CSQ
JPH2
Longitudinal SR
SERCA
IP3R
Cardiac muscle cells
T tubule
Sarcomere
Diad:
Junctional SR
T tubule
RyR2
NEXN
Cav1.2
Junctin
CSQ
JPH2
Longitudinal SR
SERCA
IP3R

Fig. 2. Striated muscle cells structure and sarcoplasmic reticulum organization. Skeletal muscle cells fuse to form a long linear fiber, while cardiac myocytes form an interconnected mesh of fibers. Both muscles have contractile units (sarcomeres) aligned parallel to the long axis of the fiber. Between every pair of sarcomeres, the sarcolemma forms invaginations termed T tubules. The bulk of the sarcoplasmic reticulum (SR) that surrounds the sarcomeres is termed longitudinal SR, and harbors the SR/ER Ca^{2+} ATPase (SERCA) pump and Inositol 1,4,5-trisphosphate receptor (IP_3R) channels. Specialized *cisternae* in close proximity with T tubules are termed junctional SR, and contain the Ryanodine receptor 1 (RyR1) and RyR2 channels in skeletal muscle and cardiomyocytes, respectively. The complex of one T tubule with two junctional SR *cisternae* is known as a triad in skeletal muscle, whereas in cardiac muscle one T tubule forms a complex with only one junctional SR cisternae, termed dyad. Many common proteins maintain the structure of triads and dyads, such as Junctin, Calsequestrin (CSQ) and Junctophilin 2 (JPH2), while others such as Triadin95 and Nexilin (NEXN) are exclusive to the triad or dyad, respectively. These complexes allow for the close proximity between the T tubule voltage-gated L-type Ca^{2+} channel Cav1.1 and RyR1 in the skeletal muscle, and between Cav1.2 and RyR2 in the cardiac muscle.

This protein is synthesized in perinuclear cisternae of the SR, and distributed to the jSR later on (McFarland et al., 2010). Triadin and Junctin, other two jSR markers, behave similarly (Sleiman et al., 2015). The same pattern of perinuclear protein synthesis in the rough SR followed by traffic to jSR has been observed in skeletal muscle cells (Kaisto and Metsikkö, 2003), suggesting that striated myocytes possess a structural organization in which rough SR functions are concentrated in the perinuclear portion of the SR membranous system.

2.3. ER organizational features in smooth muscle

Contrary to striated myocytes, SMC lack myofibril-forming sarcomeres, and thus have a different arrangement of their ER. Indeed, the ER of SMC is not considered a proper SR because it is almost indistinguishable from the ER of non-contractile cells. Electron microscopy studies have shown that the rough ER is perinuclear in SMC from rat *vas deferens*, whereas smooth ER concentrates in proximity to the plasmalemma (Villa et al., 1993). SMC lack TT, but display smaller plasma membrane structures, termed *caveolae*, which tightly interact with peripheral ER in rat mesenteric arteries, and are essential for Ca^{2+} oscillations and tension increase (Shaw et al., 2006). In replacement of jSR-TT membrane structures, SMC also have nanojunctions, which are organized portions of the ER and plasma membrane in 10–30 nm of proximity. These membrane portions are rich in Ca^{2+} transporters (Fig. 3), which confine Ca^{2+} elevations to a specific cytoplasm area, for activation of particular signaling pathways or local changes in tension generation (van Breemen et al., 2013).

2.4. Nuclear envelope and the nucleoplasmic reticulum

The NE is highly interconnected with the ER, constituting a continuous Ca^{2+} storage system (Wu and Bers, 2006). Emerging from the NE, the nucleoplasmic reticulum (NR) forms a complex network of invaginations localized deeply within the nuclear matrix (Malhas et al., 2011). Three-dimensional imaging has provided strong evidence for the existence of a functional NR in both cardiac myocytes and skeletal fibers (Fig. 4A). The structure of the NR depends on the abundance of the NE protein Emerin, whose knock-down significantly decreases the number of nuclear invaginations in primary cultured cardiac myocytes. This phenotype is also present in induced pluripotent stem cell (iPSC)-derived car-

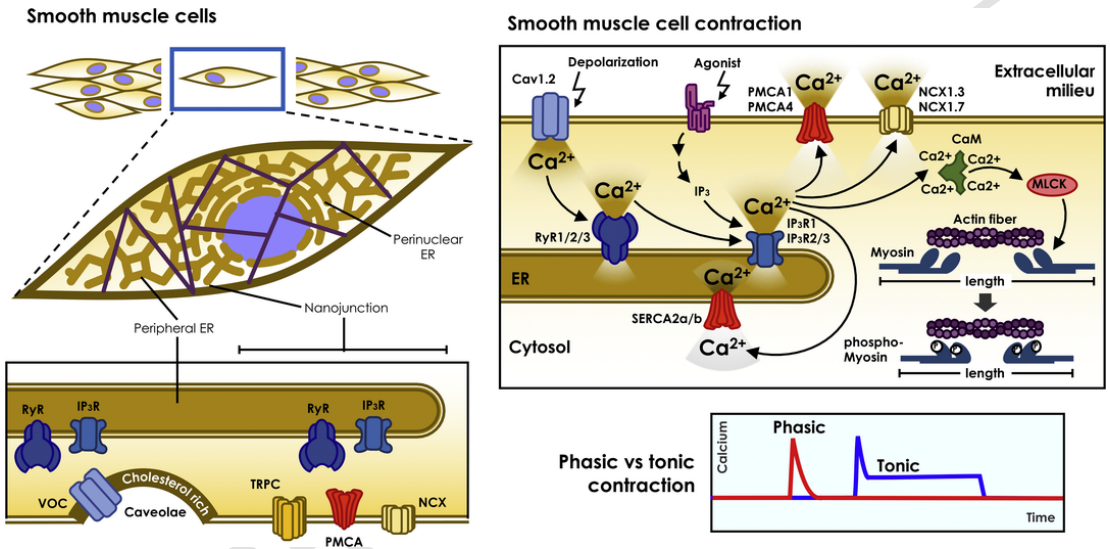
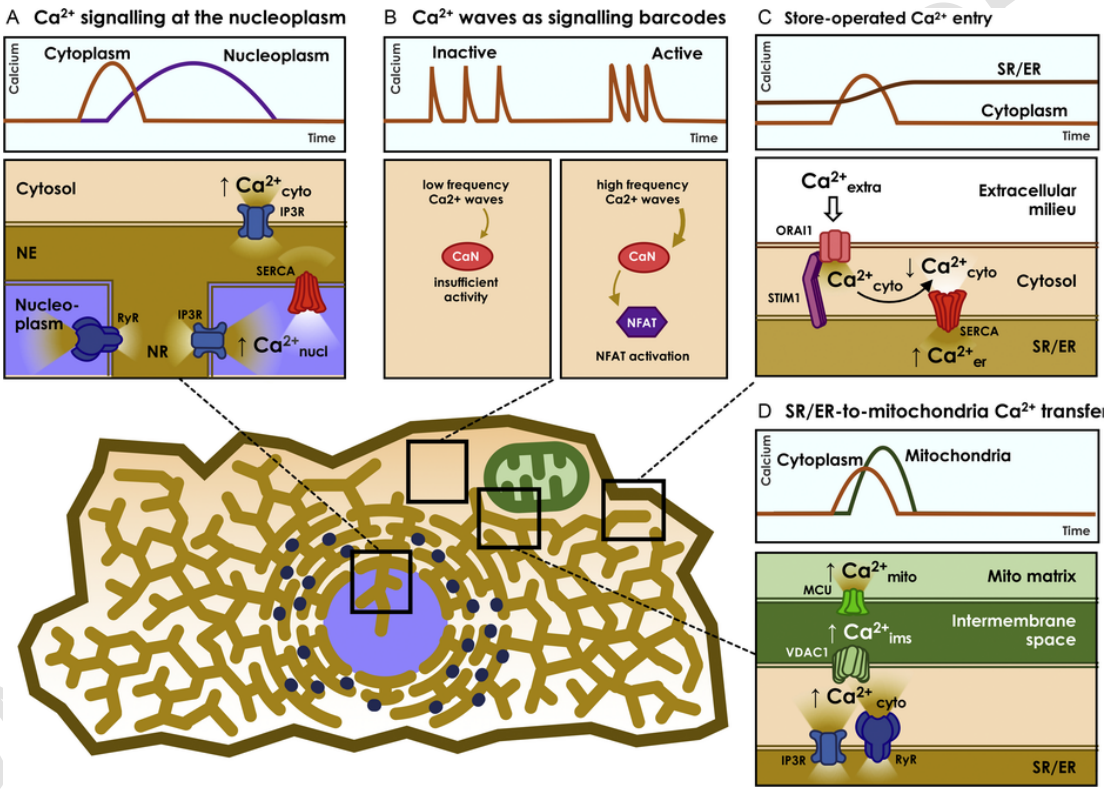


Fig. 3. Calcium handling and contraction in smooth muscle cells. Smooth muscle cells (SMC) have disordered contractile fibers, which allow concentric shortening of cell size. In these cells, the Ca^{2+}-handling machinery concentrates at points of close apposition between the endoplasmic reticulum (ER) and the plasma membrane. These sites can be at cholesterol-rich plasma membrane invaginations, termed *caveolae*, or points in which the distance between both membranes is around 10–30 nm, termed nanojunctions. Membrane depolarization leads to activation of voltage-operated Ca^{2+} channels (VOC), namely, Cav1.2 or Cav3.1, depending on the SMC type. This activation induces Ca^{2+} entry to stimulate Ca^{2+} release from Ryanodine receptors (RyR1, RyR2 or RyR3) channels. The rise in cytosolic Ca^{2+} can then activate the Inositol 1,4,5-trisphosphate receptors (IP_3R1, IP_3R2 or IP_3R3), recruiting them for generalized Ca^{2+} release throughout the cell. Alternatively, endogenous or exogenous agonists can stimulate SMC by stimulating G protein-coupled receptors (GPCR), thus leading to the production of inositol 1,4,5-trisphosphate (IP_3), which then activates IP_3R. In SMC, Ca^{2+} induces contraction by binding to Calmodulin (CaM) and then activating myosin

light chain kinase (MLCK) and myosin phosphorylation. Phosphorylated myosin binds to actin fibers, leading to fiber contraction. As in striated muscle cells, Ca^{2+} is extruded through the plasma membrane Ca^{2+} ATPase (PMCA1 or PMCA4) and the Na^{+}/Ca^{2+} exchanger (NCX1.3 or NCX1.7), or is pumped back to the ER through the SR/ER Ca^{2+} ATPase (SERCA2a or SERCA2b), allowing for a new cycle of muscle contraction. Some SMC are classified as phasic since they experiment an acute Ca^{2+} wave upon stimulation, which induces an acute contraction event. Tonic fibers, in turn, experiment an acute Ca^{2+} increase, followed by sustained Ca^{2+} elevation of around 50% of the initial Ca^{2+} peak.


A Ca2+ signalling at the nucleoplasm
Calcium
Cytoplasm
Nucleoplasm
Time
Cytosol
↑ Ca2+cyto
IP3R
NE
SERCA
Nucleo-plasm
RyR
IP3R
NR
↑ Ca2+nucl
B Ca2+ waves as signalling barcodes
Calcium
Inactive
Active
Time
low frequency Ca2+ waves
CaN
insufficient activity
high frequency Ca2+ waves
CaN
NFAT
NFAT activation
C Store-operated Ca2+ entry
Calcium
SR/ER
Cytoplasm
Time
Ca2+extra
Extracellular milieu
ORAI1
Ca2+cyto
↓ Ca2+cyto
Cytosol
STIM1
SERCA
↑ Ca2+er
SR/ER
D SR/ER-to-mitochondria Ca2+ transfe
Calcium
Cytoplasm
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Time
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MCU
Mito matrix
↑ Ca2+ims
Intermembrane space
VDAC1
↑ Ca2+cyto
IP3R
RyR
SR/ER

Fig. 4. A plethora of sarcoplasmic/endoplasmic reticulum-mediated Ca^{2+} signals. (A) Excitation-transcription coupling in striated muscle cells is a process in which Ca^{2+} waves associated with contraction modulate gene expression. Each wave of Ca^{2+} elevation in the cytosol preludes s Ca^{2+} wave in the nucleus. This Ca^{2+} is released from the nucleoplasmic reticulum (NR) through inositol 1,4,5-trisphosphate receptors (IP_3R) and regulates the activity of Ca^{2+}-activated transcription factors. (B) Ca^{2+} waves act as signaling barcodes, where different frequencies of Ca^{2+} elevations induce different responses. For example, in cardiac myocytes, high Ca^{2+} concentrations in the cytosol are known to activate the calcineurin A (CnA)/nuclear factor of activated T-cells (NFAT) signaling pathway. However, low frequencies of Ca^{2+} waves are insufficient to activate NFAT. On the contrary, high frequencies of Ca^{2+} waves induce NFAT activation. (C) Store-operated Ca^{2+} entry (SOCE) is the process by which decreased Ca^{2+} levels at the SR/ER lumen stimulate Ca^{2+} entry to the cytosol. Low SR/ER Ca^{2+} levels lead to oligomerization of STIM1 at the SR/ER surface. These complexes interact with ORAI1, which leads to Ca^{2+} entry from the extracellular milieu. Then, elevated Ca^{2+} in the cytosol enters into the SR/ER lumen through pumps such as the SR/ER Ca^{2+} ATPase (SERCA), restoring normal Ca^{2+} levels. (D) Excitation-metabolism coupling in striated muscle cells is a process in which Ca^{2+} waves associated with contraction modulate metabolism. Ca^{2+} released from sarco/endoplasmic reticulum (SR/ER) stores to the cytosol through IP_3R enter mitochondria through the voltage-dependent anion channel 1 (VDAC1). This Ca^{2+} transfer is possible due to the close proximity between SR/ER and mitochondria. Ca^{2+} then goes through the mitochondrial intermembrane space (ims) and enters into the mitochondrial matrix through the mitochondrial Ca^{2+} uniporter 1 (MCU1). In the mitochondrial matrix, Ca^{2+} stimulates oxidative phosphorylation, thus increasing ATP generation.

diac myocytes from patients with Emery-Dreyfuss muscular dystrophy (EDMD) caused by an Emerin mutation. Interestingly, cardiac myocytes from an EDMD patient autopsy also display a similar pattern (Shimojima et al., 2017). As the NR is the site of Ca^{2+} release into the nucleus through IP_3R in precise sub-domains, any disturbance in its structure may alter both gene transcription and other aspects of nuclear physiology (Echevarría et al., 2003).

In cardiac myocytes, nuclear Ca^{2+} has been implicated in mediating the transcriptional effects of Insulin-like growth factor-1 (IGF-1). Activation of IGF-1 receptors at the sarcolemma leads to a selective increase in nuclear Ca^{2+} levels mediated by IP_3R activation. This direct sarcolemma-nucleus signaling is possible due to plasma membrane invaginations containing IGF-1 receptors in the proximity of the nucleus (Ibarra et al., 2013). More recently, nuclear Ca^{2+} regulation in human iPSC-derived ventricular cardiac myocytes has given controversial results: in these cells, IP_3R are located in the SR, in contrast to RyR2, which are located in the NR. Apparently, RyR2 is the only receptor responsible for nuclear Ca^{2+} signaling in these cells (Li et al., 2019a,b). Moreover, in the skeletal muscle cell line C2C12 differentiated to myotubes, the NR is also present, endowed with a functional RyR1. Indeed, activation of RyR1 inside the nucleus leads to a Ca^{2+} elevation in the nucleoplasm (Marius et al., 2006). Furthermore, SERCA2a, ORAI1 and STIM1 have recently been found within the nucleus, suggesting the participation of SOCE in the regulation of these nuclear Ca^{2+} transients (Lee et al., 2018).

In SMC, evidence shows that tubular ER structures exist in the nucleus, endowed with functional IP_3R and RyR. Stimulation of these receptors in vascular smooth muscle cells (VSMC) from human aorta leads to nuclear Ca^{2+} elevations (Avedanian et al., 2011). Interestingly, data from rabbit aortas suggest that nuclear Ca^{2+} signaling is associated with RyR and SERCA, instead of IP_3R (Abrenica et al., 2003). Altogether, these evidences stress the importance of the NE in providing a functional and spatial compartmentalization for Ca^{2+} release in the nucleus. Moreover, evidence supports the idea of common Ca^{2+} handling mechanisms in the nucleus among the different muscle cell types; however, structure and protein compartmentalization within the nuclear membrane systems appear to be the differential factor.

2.5. Non-mitochondrial ER-organelle communication

Multiple investigations have shown the importance of ER-mitochondria communication in pathogenesis (López-Crisosto et al., 2017), which we will discuss in the upcoming sections. However, the communication between SR/ER and other organelles requires further research. These "pan-organelle" SR/ER interactions are termed membrane contact sites (MCS), and have only recently been described mediating lipid transport and metabolism (Phillips and Voeltz, 2016). The lysosomal protein Niemann-Pick type C 1 (NPC1), for instance, tethers late endocytic organelles, like the lysosomes, with the ER membrane. This tethering process is mediated by the ER protein Gramd1, and regulates cholesterol transport (Höglinger et al., 2019). The oxysterol binding protein (OSBP), on the other hand, forms bridges between the ER and the Golgi apparatus, allowing for lipid transfer between these two organelles (Mesmin et al., 2013).

Peroxisomes are the organelles that catabolize very long-chain fatty acids, and are extensively attached to the ER through MCS. The molecular entities mediating this interaction are ACBD5 in the peroxisome side and the ER protein VAPB. In this case, the MCS participate in peroxisome motility and peroxisome expansion, which requires a constant lipid supply from the ER (Costello et al., 2017). Finally, lipid droplets also display an extensive network of MCS with ER membranes. The acyl-CoA synthetase FATP1 and the diacylglycerol acyltransferase DGAT2 form a triglyceride synthesis complex at the ER-lipid droplet interface, where they mediate lipid droplet expansion; however, no tether function has been yet confirmed (Xu et al., 2012). Instead, the protein DFCP1 has shown to participate not only in the generation of nascent lipid droplets in the ER, but also to form a complex with Rab18 that acts as the molecular tether between ER and lipid droplet (Li et al., 2019a,b).

3. CA^{2+} CELL PHYSIOLOGY IN STRIATED MUSCLE CELL

3.1. Differential spatiotemporal Ca^{2+} handling

Ca^{2+} exerts its functions through the regulation of several Ca^{2+}-sensitive proteins with specific domains, such as EF-hand, C2 and annexin Ca^{2+}-

binding domains. Each domain exhibits distinct Ca^{2+} binding dynamics, which allows for the fine regulation of intra- and/or inter-molecular interactions (Carafoli and Krebs, 2016). Therefore, these domains are probably susceptible to oscillatory Ca^{2+} changes consisting in series of Ca^{+2} spikes (Ca^{2+} transient elevations of certain amplitude and frequency) in response to different stimuli (i.e., adrenergic, trophic factors or hormones, among others) (Jacobus et al., 1975; Toyofuku et al., 1993). Each Ca^{2+}-binding protein decodes the Ca^{2+} signal based on spike duration, subcellular compartment, molecular environment and oscillation periods (time between spikes). In turn, Ca^{2+}-sensitive proteins modulate the duration and spacing of the spikes, thus increasing the complexity of Ca^{2+} signaling. Basically, Ca^{2+} waves are one of the most sophisticated codes within the cell and are subordinated to specific mechanisms controlling Ca^{2+} release and SR Ca^{2+} homeostasis in time and space (Berridge et al., 2000). In the heart, the transcription factor nuclear factor of activated T-cells (NFAT) has been proposed as a Ca^{2+} oscillation decoder through a phosphorylation/dephosphorylation-based cycle in vitro (Smedler and Uhlén, 2014). Increases in cytosolic Ca^{2+} ($[Ca^{2+}]_{cyto}$) activate the phosphatase calcineurin, which dephosphorylates NFAT, inducing its activation. Consequently, a single Ca^{2+} spike leads to the activation of a fraction of the cytosolic NFAT pool; however, due to the short duration and low baseline frequency of the spikes, NFAT is rapidly re-phosphorylated by cytosolic kinases, resulting in null net NFAT activation. At higher frequencies of Ca^{2+} oscillations, the number of dephosphorylation events increases, ultimately leading to the accumulation of active NFAT over time (Fig. 4B). Studies in other in vitro models show that NFAT has an optimal frequency of activation, with higher frequencies resulting in less activation. An accepted explanation for this behavior is that higher frequencies might trigger opposing processes. NFκB, CaMKII, MAPK and calpain have also shown to distinctly respond to Ca^{2+} oscillations; however, their relevance in striated muscle cells has not been assessed yet (Smedler and Uhlén, 2014).

3.2. Ca^{2+} homeostasis

Ca^{2+} release from SR/ER stores to the cytosol occurs spontaneously due to the steep concentration gradient between both compartments. This process requires the opening of RyR or IP_3R. These channels differ in their activation stimuli, Ca^{2+} release kinetics and the distribution of

their isoforms. In the heart, RyR2 is the predominant isoform and is activated by Ca^{2+} itself, a mechanism termed Ca^{2+}-induced Ca^{2+} release (CICR). In skeletal muscle, the predominant isoform is RyR1, which is activated by protein-protein interactions with Cav1.1 located in the TT. Regardless of the isoform, Ca^{2+} release events from a cluster of RyR are termed "sparks" (Berridge, 2006). On the other hand, IP_3R-mediated Ca^{2+} release is directly stimulated by inositol 1,4,5-trisphosphate (IP_3), a soluble second messenger derived from phosphatidylinositol located at the plasma membrane. Ca^{2+} release events from a cluster of IP_3R are termed "puffs" (Berridge, 2006). In all cases, every single Ca^{2+}-release event produces a local depletion of Ca^{2+} in the SR/ER lumen, known as a "blink." Of note, due to poor diffusion across the cytosol, Ca^{2+} released from SR/ER stores accumulates in a confined space, forming a microdomain of high Ca^{2+} concentration. Nonetheless, certain stimuli (such as membrane depolarization in myocytes) can evoke Ca^{2+} release events strong enough to activate adjacent clusters of Ca^{2+}-release channels, which amplifies the original Ca^{2+} signal. This amplification leads to recruitment of further neighboring Ca^{2+} channels, thereby propagating a Ca^{2+} wave that spreads through most of the cell (Cheng et al., 1996).

Contrary to Ca^{2+} release, SR/ER refilling requires energy expenditure because it occurs against the concentration gradient. SERCA is the main transporter involved in this process, pumping two Ca^{2+} ions into the SR/ER lumen at the expense of hydrolyzing one ATP molecule (Stammers et al., 2015). This Ca^{2+} transport depends on the Ca^{2+} buffer capacity of the SR/ER lumen, which relies on two Ca^{2+} binding proteins: CSQ and Calreticulin. Both proteins are essential to set the intraluminal free Ca^{2+} concentration ($[Ca^{2+}]_{SR/ER}$) and directly impact on RyR, IP_3R and SERCA functions (Wray and Burdyga, 2010). $[Ca^{2+}]_{SR/ER}$ not only regulates Ca^{2+} release and refill mechanisms, but also drives SOCE (Fig. 4C). This mechanism consists of a Ca^{2+} influx from the extracellular milieu in response to SR/ER luminal Ca^{2+} depletion (Elliott, 2001). The fall in SR/ER Ca^{2+} induces the formation of stromal interaction molecule 1 (STIM1) tetramers at the SR/ER surface. These oligomers directly activate store-operated Ca^{2+} (SOC) channels, also known as Ca^{2+}-release activated Ca^{2+} channels (CRAC), in the plasma membrane. The best described SOC channel is Ca^{2+}-release activated Ca^{2+} channel protein (ORAI), which, upon activation, leads to Ca^{2+} entry to the cytosol for its ensuing transport to the SR/ER lumen (Avila-Medina et al., 2018).

3.3. Excitation-contraction coupling

Excitation-contraction (EC) coupling refers to a well-organized process aimed to transform the electrical stimulation of the sarcolemma into muscle contraction (Fig. 5). In cardiac muscle, this process starts by an action potential that depolarizes the sarcolemma, activating Cav1.2 that drives extracellular Ca^{2+} entry to the cell, inducing the CICR mechanism mediated by RyR2 (Eisner et al., 2017). The same process describes EC coupling in skeletal muscle, with the exception that RyR1 does not require Ca^{2+} as a ligand to generate RyR1-mediated Ca^{2+} release; it only requires the interaction between Cav1.1 and RyR1 (Bannister, 2016). These two mechanisms that operate in cardiac and skeletal cells trigger a RyR-dependent increase in $[Ca^{2+}]_{cyto}$ concentration, leading to an increment in the amount of Ca^{2+} bound to troponin, which induces the sliding of thick myosin and thin actin filaments to produce contraction. EC coupling in striated muscle depends on the functional coupling of the junctional ER with sarcolemma structures; dyads and triads in cardiac and skeletal cells, respectively. After contraction, $[Ca^{2+}]_{cyto}$ returns to basal via SERCA-mediated pumping back into the SR, or via extrusion through plasma membrane Ca^{2+} ATPase (PMCA) and the Na^{+}/Ca^{2+} exchanger (NCX). This process induces a transient contraction and leaves myocytes on a state ready to initiate another contractile cycle. In skeletal muscle, however, high-frequency stimulation (tetanic) can lead to a sustained $[Ca^{2+}]_{cyto}$ elevation, resulting in sustained contraction.

According to previous evidence, the regulation of EC coupling is often related to the regulation of each of the RyR isoforms in striated muscle. In the case of cardiac RyR2, cyclic AMP dependent protein kinase (PKA) phosphorylation can increase the Ca^{2+} leak in the diastolic phase, thus producing an impairment in EC coupling, which has been corroborated by the development of an age-associated cardiomyopathy in a transgenic mouse mimicking the phosphorylated receptor (Shan et al., 2010). Similarly, in skeletal muscle, PKA-dependent phosphorylation of RyR1 increases the open probability of the channel from 0.34 to 0.72, and has been associated with defects in skeletal muscle contraction in heart failure patients (Reiken et al., 2003). Oxidation of the RyR2 also generates a leaky receptor related to the generation of arrhythmia post ischemia/reperfusion injury (Bovo et al., 2018). Moreover, another report indicates that RyR2 oxidation is responsible for dystrophic cardiomyopa-

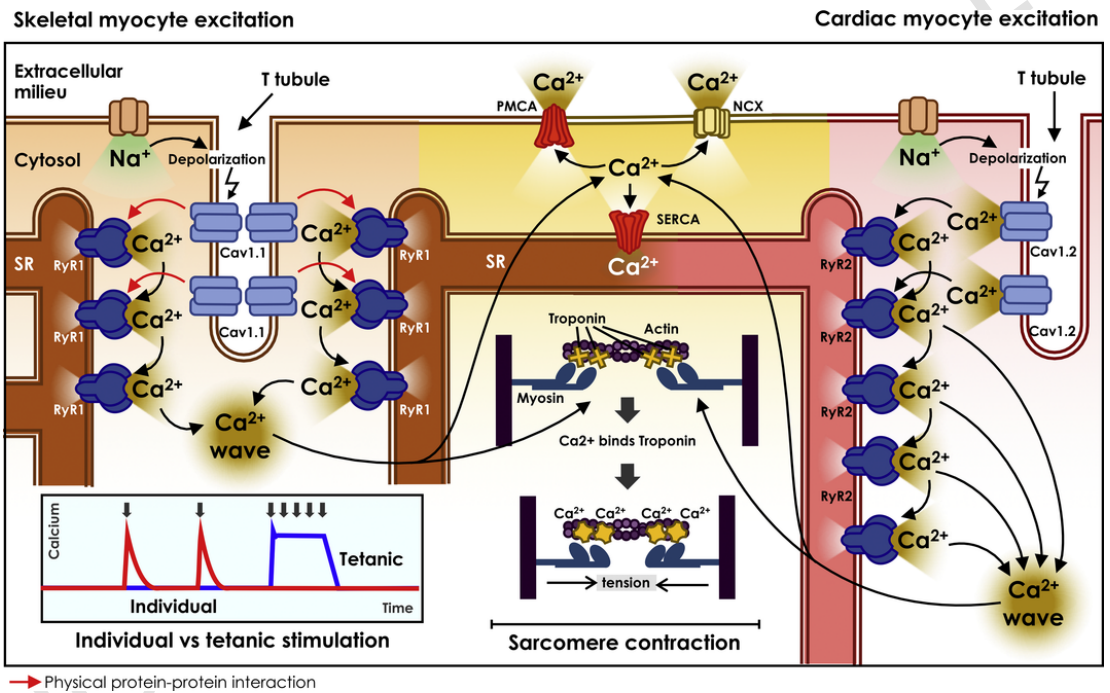

Fig. 5. Striated muscle cells contraction. In the skeletal muscle, depolarization due to Na^+ entry leads to voltage-gated L-type Ca^{2+} channel Cav1.1-mediated activation of the ryanodine receptor 1 (RyR1) via physical interaction. This triggers a wave of SR Ca^{2+}-induced Ca^{2+} release through RyR1 that propagates throughout the cell. In cardiomyocytes, in turn, fiber depolarization leads to Cav1.2 activation and concomitant Ca^{2+} entry, which activates RyR2, thus triggering a Ca^{2+} wave propagated by RyR2. Once Ca^{2+} reaches the sarcomeres, it induces a conforma-

tional change in troponin, thereby allowing for the interaction between actin and myosin fibers, leading to sarcomere shortening. Cytosolic Ca^{2+} is then extruded through the plasma membrane Ca^{2+} ATPase (PMCA) and the Na^{+}/Ca^{2+} exchanger (NCX), or is pumped back to the SR through SR/ER Ca^{2+} ATPase (SERCA), enabling for a new muscle contraction cycle. Each stimulation event of the muscle fiber induces a single contraction round; however, in skeletal muscle, if the stimulation events are frequent enough (termed tetanic), it leads to sustained muscle contraction. On the contrary, the cardiac muscle normally does not experience tetanic contraction, as its function is to rhythmically and constantly contract, from foetal development, until death.

thy by exacerbating the response of the receptor to CICR (Kyrychenko et al., 2013). Calmodulin (CaM) is another important regulator of RyR that at high Ca^{2+} concentrations has an inhibitory effect. However, at lower Ca^{2+} concentrations, CaM activates RyR1, whereas RyR2 remains inhibited, probably due to the presence of EF hands in RyR1 specific sequences (Brohus et al., 2019; Gong et al., 2019). In this regard, the structural basis for RyR2 interaction with CaM was recently discovered using Cryo-EM techniques (Gong et al., 2019).

EC coupling can be studied by simultaneous measurements of three of the most relevant transient endpoints generated in the process: the action potential, intracellular Ca^{2+} increase and the contraction generated. To this end, van Meers et al. developed a method to identify drugs affecting contractility by using human iPSC-derived cardiac myocytes. With this model, they observed that the use of the three parameters generates a better prediction than each one on its own (van Meer et al., 2019).

3.4. Excitation-transcription coupling

The molecular signals responsible for excitation-transcription coupling are similar to those of EC coupling, because the Ca^{2+} released from internal stores during EC coupling also regulates gene expression, and thereby shapes the transcriptome (Chin, 2010; Gundersen, 2011). In response to exercise, for instance, skeletal muscle shows plasticity, and reprograms gene expression via Ca^{2+}-dependent signaling pathways (Bassel-Duby and Olson, 2006; Dunn et al., 2001; Liu et al., 2001; Rana et al., 2009; Schiaffino et al., 2007). Thus, exercise drives the expression of structural proteins and energy metabolism enzymes (Pette, 1998; Pilegaard et al., 2000; Spina et al., 1996), which is essential to maintain muscle integrity and function (Bacou et al., 1996; Foehring et al., 1988; Jóhannsson et al., 1996; Roy et al., 1996). Genomic analysis has identified dozens of transcription factors that regulate hundreds of genes (Dolmetsch, 2003). Various components of Ca^{2+}-dependent signaling pathways and multiple transcription factors, coactivators and corepressors have involved in skeletal muscle remodeling (Bassel-Duby and Olson, 2006; Schiaffino et al., 2007; Shen et al., 2006).

The Ca^{2+} transients in skeletal myocytes can be evoked by two different mechanisms: one where RyR1 is directly activated by Cav1.1, and another that requires a G protein (Eltit et al., 2006) that activates phosphatidylinositol 3-kinase (PI3K) and phospholipase C (PLC) to pro-

duce IP_3, which diffuses through the cytoplasm and nucleoplasm and reaches IP_3R located both at the SR and the NE (Araya et al., 2003). Downstream of Ca^{2+} elevations, the best-characterized transcriptional pathways are Calcineurin A (CnA) and Ca^{2+}/CaM-dependent protein kinase II (CaMKII), both dependent on Ca^{2+}/CaM (Chin, 2010; Gundersen, 2011; Liu et al., 2005; Shen et al., 2006). The CnA pathway activates the transcription factors NFAT and myocyte enhancer factor 2 (MEF2) to control slow-type muscle fiber gene expression (Chin et al., 1998; Rana et al., 2009; Shen et al., 2010). On the other hand, the CaMKII pathway activates histone deacetylases and the transcription factors Serum response factor, NFAT and MEF2 (Chin, 2005; Liu et al., 2005; Shen et al., 2006) to regulate the metabolic responses to exercise (Chin, 2010; Rose et al., 2006). Another Ca^{2+}-dependent signaling pathway involves transient activation of ERK, transcription factor CREB and an increase in the mRNA levels of *c-fos*, *c-jun*, and *egr-1* early genes as well as the mRNA levels of late genes encoding Troponin I, Interleukin 6, Hmox, and Hsp-70 (Carrasco et al., 2003; Jorquera et al., 2009; Juretić et al., 2006, 2007). The regulation of specific Ca^{2+}-regulated genes has revealed that transcriptional regulation is finely tuned by the spatiotemporal features of Ca^{2+} signals, permitting a wide variety of responses through a handful of mediators (Carrasco and Hidalgo, 2006; Chin, 2010).

3.5. Excitation-metabolism coupling

Contraction of striated muscle is a highly ATP-consuming process, which requires a metabolic machinery that matches such energy demands. Because of the spatiotemporal complexity of contraction, myocytes require appropriate systems to provide ATP with every stimulation-contraction cycle, in the right place, and at the right time (Gehlert et al., 2015). One of these pathways is anaerobic glycolysis, which acts as a rapid source of ATP, starting from either glucose or glycogen. Ca^{2+} stimulates this process through indirect activation of phosphofructokinase (the pacemaker of glycolysis) and glycogen phosphorylase (which drives glucose generation from glycogen) (Gehlert et al., 2015). Importantly, many glycolytic enzymes tightly interact with the SR, where they fuel Ca^{2+} intake through SERCA in both skeletal and cardiac myocytes (Xu et al., 1995). Furthermore, in skeletal muscle, glycolytic enzymes are compartmentalized at triads, where they form ATP microdomains (Han et al., 1992). These evidences strongly suggest the existence of an excitation-glycoly-

sis coupling with every depolarizing event, which fuels the initiation of contraction.

Mitochondrial oxidative metabolism, on the other hand, provides ATP especially at the interfibrillar space, thereby fueling the contractile machinery. During contraction, $[Ca^{2+}]_{cyto}$ spikes are closely followed by mitochondrial Ca^{2+} elevations in both cardiac (Chacon et al., 1996) and skeletal muscle cells (Rudolf et al., 2004). In the mitochondrial matrix, Ca^{2+} reportedly stimulates oxidative phosphorylation and ATP production in striated muscle cells (Glancy et al., 2013; Territo et al., 2000), thus suggesting that excitation-induced Ca^{2+} spikes acutely increase mitochondrial ATP generation (Fig. 4D). Regarding the chronic effects of contraction on mitochondria, it is known that exercise induces mitochondrial biogenesis, assembly of respiratory chain supercomplexes and increases cristae surface (Díaz-Vegas et al., 2019). These changes are associated with improved mitochondrial function and increased Ca^{2+} uptake (Bravo-Sagua et al., 2017).

Therefore, mitochondrial Ca^{2+} homeostasis appears to be a key player in excitation-metabolism (EM) coupling. This notion is further supported by a study using transgenic mice lacking the mitochondrial Ca^{2+} uniporter (MCU). This channel is responsible for Ca^{2+} entry into the mitochondrial matrix, and its ablation impairs rapid mitochondrial Ca^{2+} uptake. Fibroblasts, skeletal myocytes and hepatic mitochondria obtained from $MCU^{-/-}$ mice do not exhibit significant alterations of basal oxidative metabolism; however, these mice display decreased performance during high-intensity exercise, which is indicative of reduced capacity of skeletal myocytes to cope with increased workload (Pan et al., 2013). These results reflect the importance of mitochondrial Ca^{2+} uptake for optimal muscle contraction. This effect might arise from a decreased capacity to adjust mitochondrial metabolism to muscle workload, due to defective Ca^{2+} entry to the mitochondrial matrix. An alternative explanation is that a lower mitochondrial Ca^{2+} buffering capacity might affect myocyte contractility. In either case, current evidence indicates that excitation-induced Ca^{2+} elevations are responsible for matching localized ATP production with energy demands in striated myocytes.

Although mitochondrial Ca^{2+} uptake after depolarization has already been described in isolated adult muscle fibers using electrical stimulation or high potassium medium (Casas et al., 2010; Mammucari et al., 2015), the role of intracellular Ca^{2+} channels in this response was poorly under-

stood. Contrasting with a previous report that ruled out IP_3R participation (Blaauw et al., 2012), Díaz-Vegas et al. recently showed that this process partly relies on both RyR1 and IP_3R function (Díaz-Vegas et al., 2018). Inhibition of either channel decreased basal respiratory rates, but only RyR1 inhibition decreased ATP-linked respiration during excitation-metabolism coupling (Díaz-Vegas et al., 2018). This process also includes Ca^{+2}-dependent mitochondrial transmembrane potential transfer from peripheral mitochondria (subsarcolemmal) to mitochondria located among the sarcomeres (intermyofibrillar). This process seems to participate in the energy distribution in response to the increased energy demands in the adult skeletal muscle fibers (Díaz-Vegas et al., 2018, 2019).

4. CA^{2+} CELL PHYSIOLOGY IN SMOOTH MUSCLE

4.1. Smooth muscle cell classification

Unlike striated muscle, SMC are very heterogeneous in relation to their location and function (in terms of contraction-relaxation times and mechanisms involved). These types of muscle cells do not have sarcomeres as contraction units; instead they present a network of actin-myosin that drives the contraction in a very particular way (Sweeney and Hammers, 2018). SMC can be classified in different groups; however, since the scope of this work is not the diversity of SMC, we will classify them according to their type of contraction and Ca^{2+} sources, specifically in terms of the "fast phasic" or "slow tonic." Golenhofen et al. early described these two types of contraction (Golenhofen et al., 1979) and three cell phenotypes: tonic, phasic and mixed. Tonic SMC, such as those in the vasculature and airways, develop a maintained tension in response to membrane depolarization and/or neurohumoral agonist stimuli preceded by $[Ca^{2+}]_{cyto}$ increase. In tonic SMC, agonist-stimulated Ca^{2+} release shows a $[Ca^{2+}]_{cyto}$-force relationship, described in two phases: phase 1 is a rapid $[Ca^{2+}]_{cyto}$ elevation from basal to maximum concentrations in response to IP_3R activation, correlated with a gradual increase in tension; and phase 2, when $[Ca^{2+}]_{cyto}$ gradually decreases from 100% to around 50%, but tension is maintained during a longer stimulation time (Ozaki and Karaki, 1993). On the other hand, phasic SMC are characterized by a repetitive spontaneous contraction-relaxation cycle with a minimum contribution of muscle tone in response to depolarization and agonist stim-

uli. Common examples of phasic cells are myometrium and gastrointestinal SMC (Ozaki and Karaki, 1993). Phasic SMC $[Ca^{2+}]_{cyto}$-force relationship is developed in three phases; in phases 1 and 2, $[Ca^{2+}]_{cyto}$ elevation precedes the increase of tension. However in phase 3, the tension decreases gradually, but $[Ca^{2+}]_{cyto}$ remains elevated (Ozaki and Karaki, 1993). The difference in Ca^{2+} sensitivity displayed by both types of SMC relies in different molecular mechanisms commented below.

Szymanski et al. analyzed the contractile protein content in phasic and tonic smooth muscles and found that phasic SMC have more Caldesmon (> 2.4-fold) compared to tonic SMC (Szymanski et al., 1998). This is a common actin-binding protein that maintains the attachment between actin and myosin, allowing tonic contraction. N-terminal phosphorylation of Caldesmon by Casein kinase 2 (CK2) and Mitogen-activated protein kinase (MAPK) interferes with the actin-myosin tether and prevents tonic contraction (Gusev, 2001). A higher proportion of γ-actin (> 1.4-fold) in phasic, compared to tonic SMC, has also been described (Szymanski et al., 1998). γ-Actin is highly expressed in veins and dilative tissues like the uterus, in which it would transduce the passive forces of stretching (Arnoldi et al., 2013). Phasic SMC also show a greater proportion of seven amino acid inserts in the myosin heavy chain isoform (> three-fold), which is related to an increase in contraction velocity (Szymanski et al., 1998). Recently, evidence has described a differential role of the SM22 Transgelin/Calponin protein in phasic and tonic muscles. SM22 is attached to actin filaments in non-stimulated phasic SMC, preventing actin-myosin interaction, and hence, the initiation of the basal tone state. However, in stimulated SMC, SM22 is phosphorylated in a serine residue by Rho-associated protein kinase (ROCK), breaking the interaction with actin filaments, thereby leaving it enabled to generate the basal muscle tone required (Rattan and Ali, 2015).

4.2. Ca^{2+} homeostasis

The ER from SMC is enriched around the nucleus; however, the ER also projects as a peripheral structure that is positioned about 20 nm from the plasma membrane, which is supported by a microtubule framework (Evans, 2017; Pritchard et al., 2017). These structures were already described in the 1970s (Devine et al., 1972; Gabella, 1971) as nanojunctions or peripheral junctions (Pritchard et al., 2017). These specialized microdomains are enriched in different Ca^{2+}-handling proteins

(NCX, PMCA and TRPC in the plasma membrane and SERCA, RyR, and IP_3R in the ER) that interplay in a complex process to produce a specific pattern of Ca^{2+} transients for each SMC type (Fameli et al., 2017). Nanojunctions work like a superficial Ca^{2+} buffer barrier that limits free Ca^{2+} diffusion and restrict the Ca^{2+} signal to defined microdomains, increasing local $[Ca^{2+}]_{cyto}$ four times more than in absence of the junctions (Kargacin, 1994). High $[Ca^{2+}]_{cyto}$ presents in the microdomains is related with the activation of Ca^{2+}-dependent ion channels, exchangers and pumps in the plasma membrane that regulate changes in membrane potential and cell excitability (Ghosh et al., 2017).

Ca^{2+} influx through the plasma membrane and this mechanism can be classified in three types: (a) Receptor-operated Ca^{2+} channels (ROC), such as Purinergic receptor (P2X1) channels (Large, 2002; Vulchanova et al., 1996) and transient receptor potential channels (TRPC) (Ghosh et al., 2017; González-Cobos and Trebak, 2010); (b) Voltage-operated Ca^{2+} channels (VOC), like the L- and T-type Ca^{2+} channels (Tykocki et al., 2017); and (c) SOC, as previously described. The relative relevance of each source depends on the specific function of the SMC analyzed. ROC have been described early in SMC studies. The P2Xs are purinergic-dependent cation channels that allow the entrance of monovalent cations and Ca^{2+} under ATP stimulation (North, 2016). The functional role of P2X-derived Ca^{2+} and Na^{+} influxes have been associated with increased levels of Ca^{2+} in the ER and the induction of the reverse function of the Na^{+}/Ca^{2+} exchanger (NCX); both mechanisms seem to have a refilling role, maintaining Ca^{2+} levels in the ER lumen of airway SMC (Flores-Soto et al., 2011). However, the direct role of P2X in SMC contraction is still unclear and most studies have not given a clear explanation for its function (Angus and Wright, 2015; Flores-Soto et al., 2011; Kwon et al., 2015). Finally, TRPC are highly expressed in SMC and have a clear role in the modulation of the surface membrane potential, tension and myogenic tone. In these processes, TRPC participate as ROC and SOC modulators (Earley and Brayden, 2015).

The main VOC expressed in SMC is the Cav.1.2 isoform. It is responsible for the first Ca^{2+} movement in the ECC mechanism. In SMCs, just like in cardiomyocytes, Cav.1.2 induces a contractile response driven by changes in membrane potential (mV) (Catterall, 2011). Ca^{2+} influx through Cav1.2 is defined as a "sparklet," which in SMC are small Ca^{2+} signals inside microdomains originated in specific places of the

plasma membrane. In vascular SMC, subpopulations of grouped Cav1.2 are regulated by diverse kinases and phosphatases modulated by agonists. They transduce the signals to a scaffold protein complex, localized in this microdomain, that generates the appropriate Ca^{2+} signal (Navedo and Amberg, 2013). T-type Ca^{2+} channels Cav3.1 are also expressed in SMC and have a relatively small Ca^{2+} current at negative membrane potentials, compared to Cav1.2. The role of these channels is unclear; nevertheless, in vascular SMC they have been endorsed with a myogenic regulator function (Ghosh et al., 2017).

In vascular and airway SMC, SOC channels are relevant to induce Ca^{2+} entry through the SOCE mechanism. ORAI is the main SOC channel described and the three isoforms of these channels are expressed (ORAI-1, 2 and 3) in SMC, of which ORAI-1 is the most relevant in pathological models (Sung et al., 2012; Wang et al., 2017). SOC channels regulate Ca^{2+} oscillations and contraction in airway and vascular SMC (Chen and Sanderson, 2017; Dominguez-Rodriguez et al., 2012). Interestingly, ORAI-1-induced Ca^{2+} influx modulates the activation of the NFAT pathway, impacting vascular SMC proliferation and repairing in vascular occlusive diseases (Zhang et al., 2011). In parallel, SOCE components also participate in the pathogenesis of vascular remodeling and atherosclerosis in a Ca^{2+}/CREB-dependent mechanism (Rodríguez-Moyano et al., 2013).

SMC plasma membrane also has two known Ca^{2+} efflux mechanism driven by PMCA and NCX. Both proteins cooperate to extrude Ca^{2+} and decrease $[Ca^{2+}]_{cyto}$; however, there is not much information about this mechanism in SMC. Vascular and bladder SMC express PMCA isoforms 1 and 4, of which is PMCA4 the main one (Liu et al., 2007; Pande et al., 2006). In SMC from portal vein, Liu et al. described a housekeeping role of PMCA1 in regulating basal $[Ca^{2+}]_{cyto}$, whereas PMCA4 might have a role in agonist-induced Ca^{2+} elevation and contraction (Liu et al., 2007). On the other hand, NCX is enriched in nanojunction microdomains and has a lower affinity and more capacity for Ca^{2+} transport than PMCA (Juhaszova et al., 1994; Szewczyk et al., 2007). Vascular SMC express NCX isoforms 1.3 and 1.7 (Szewczyk et al., 2007) and they seem to play a role in SMC contractility under non-physiological contexts (Blaustein and Lederer, 1999). NCX can also operate in reverse mode in SMC, being a source for extracellular Ca^{2+} entry. In SMC from asthma air-

way models, the NCX reverse mode allows Ca^{2+} entry in unstimulated conditions, favoring an increased muscle tone (Rahman et al., 2012).

4.3. Ca^{2+} release channels in ER

SMC have a large difference in the expression and distribution of RyR and IP_3R compared to striated muscles, because of the structure of the ER/plasma membrane microdomains and the presence of several SMC subtypes. SMC can express all the RyR and IP_3R isoforms; however, the expression of each isoform is limited to the origin of the SMC (Grayson et al., 2004; Westcott et al., 2012). In any case, IP_3R is widely expressed in SMC compared to RyR, achieving a stoichiometric ratio of 3:1–10:1, depending on the SMC type (Boittin et al., 1999). In SMC, the IP_3R plays a key role in different physiological processes such as contraction (Bergner and Sanderson, 2002; Boittin et al., 1999), transcriptional regulation (Gomez et al., 2002), migration (Espinosa-Tanguma et al., 2011) and proliferation (Wilkerson et al., 2006). These receptors are located both in the central and peripheral ER, but again, the isoform that prevails in each ER domain is cell type dependent (Narayanan et al., 2012). In the aorta, resistant arteries and intestine SMC, IP_3R1 is the predominant isoform (Gordienko et al., 2008; Tasker et al., 1999). On the other hand, IP_3R2 and IP_3R3 isoforms are expressed in portal veins and the ureter, respectively, but always in co-expression with IP3R1 (Morel et al., 2003).

SMC have several types of G protein-coupled receptors (GPCR) and many of them are coupled to Gq/11 proteins, which activate PLC to produce IP_3 as a potent second messenger that induces Ca^{2+} release from the IP_3R. As in striated muscle, SMC IP3R modulate Ca^{2+} levels in both the cytoplasm and ER lumen. In phasic SMC, the classical biphasic dependence on $[Ca^{2+}]_{cyto}$ can be detected, in which low $[Ca^{2+}]_{cyto}$ (50–300 nM) increases IP_3R-dependent Ca^{2+} release, and higher concentrations (> 300 nM) inhibit this IP_3R-dependent Ca^{2+} channel function (Iino, 1990). On the other hand, IP_3R modulation by $[Ca^{2+}]_{SR/ER}$ in SMC is limited (Iino et al., 1994; Itoh et al., 1992). Cholinergic stimulation of phasic intestinal SMCs also initiates a local rise in $[Ca^{2+}]_{cyto}$ and a subsequent Ca^{2+} wave from a specific spatial origin. Olson et al. showed that the origin of this Ca^{2+} wave is determined by the speed of local IP_3 rises, which is subordinated to the proximity between GPCR and IP_3R clusters in specific subcellular locations (Olson et al., 2012). The lat-

ter supports the idea that the effect of any agonist depends on the functional junctions formed between GPCR and IP_3R clusters, which are different depending on the SMC type. For instance in portal veins, IP_3R and RyR work cooperatively to originate spontaneous Ca^{2+} release events, where the RyR is responsible for Ca^{2+} signal propagation after IP3R activation in response to IP_3 (Gordienko and Bolton, 2002). On the contrary, RyR does not contribute to the propagation of Ca^{2+} signals initiated by a receptor-dependent cholinergic increase of IP_3 in airway SMC. This example reflects the large differences observed between IP_3R and RyR content and function in SMC originated from different anatomical places (Bai et al., 2009).

The three RyR isoforms are expressed in SMC, but they are expressed in different proportions. Only in vascular SMC there is a large difference regarding RyR isoform expression related to the type and tissue location of blood vessels. For instance, rat aorta SMC express RyR2 as the main isoform and a minimum level of RyR1/3 (Yang et al., 2005). In contrast, SMC from mesenteric arteries show a reciprocal expression pattern, with high expression levels of RyR1/3 compared to RyR2 (Li et al., 2015). Airway SMC express the three RyR isoforms, with greater RyR1 expression than RyR2, and higher levels of RyR2 compared to RyR3. In these cells, the three isoforms are involved in muscle contraction (Du et al., 2005). Intestine and urinary bladder SMC express almost exclusively RyR2, which plays a minimum role in muscle contraction (Aoyama et al., 2004; Chambers et al., 1999).

The regulation of RyR activity has been mainly studied in skeletal muscle fibers and cardiac myocytes, and is regulated by post-translational modifications, adenine nucleotides, protein-protein interaction and di/monovalent cations. However, there is limited information about these mechanisms in SMC (Meissner, 2017). The main stimulus that induces Ca^{2+} release from RyR (mainly, RyR 1 and 2) is the elevation of $[Ca^{2+}]_{cyto}$ (between 0,1 and 10 μM) in the vicinity of the cytoplasmic N- and C-terminal domains that contain the Ca^{2+} sensor sites (Hamilton and Serysheva, 2009; van Petegem, 2015). However, an excess of $[Ca^{2+}]_{cyto}$ (> 1 mM) has an inhibitory effect on RyR activity (Hamilton and Serysheva, 2009). Moreover, luminal ER Ca^{2+} content also modulates Ca^{2+} release by RyR and/or IP3R. Additionally, the regulation by divalent cations in the luminal and cytoplasmic compartments of the tetrameric RyR2 has been modeled, showing that each RyR subunit has four Ca^{2+} sensing sites: two activation sites (luminal and cytoplas-

mic) and two cytoplasmic inhibitory sites. Apparently, three activation sites need to be occupied in order to open the tetrameric RyR2 channel (Laver and Honen, 2008).

The functional role of RyR in SMC is different to that of striated muscles, mainly because these cells lack of specialized microdomains that allow effective coupling with the plasma membrane and the distribution of RyR clusters. Despite evidence that RyR amplifies Ca^{2+} sparks (Collier et al., 2000; Iino, 1989) and puffs (Boittin et al., 1999; Gordienko and Bolton, 2002) to induce contraction, this is not a common feature of SMC. RyR rarely participates in SMC contraction; however, through Ca^{2+} sparks, they modulate the activity of ion channels inserted in the plasma membrane. These channels generate two specific ions currents: the spontaneous transient outward current (STOC) and the spontaneous transient inward current (STIC); both of which modify the membrane potential, thereby influencing cell excitability and favoring muscle dilation or contraction, respectively (Wray and Burdyga, 2010).

4.4. Ca^{2+} refill mechanisms in ER

SERCA is the most relevant protein that refills the ER with Ca^{2+}, at the expense of huge amounts of ATP. However, this role is only possible due to the presence of two luminal ER proteins Calreticulin and CSQ. Both proteins have a high Ca^{2+} buffer capacity that relieves ATP expenditure from the SERCA pumping work. The main isoforms expressed in SMC are SERCA2a and 2b in vascular, uterine, airway and gastrointestinal systems (Burk et al., 1989; Eggermont et al., 1990). SMC also express phospholamban (PLB), a SERCA regulator protein described for cardiac myocytes. In its unphosphorylated state, PLB inhibits SERCA; however, its role in SMC is controversial (Chen et al., 1994; Eggermont et al., 1990; Ferguson et al., 1988). Inhibition of Ca^{2+}/CaM and CaMKII in airway SMC reduces PLB phosphorylation and ER Ca^{2+} reuptake. Thus, acetylcholine-induced intracellular Ca^{2+} oscillations (due to the primary activation of IP_3R and later RyR activation) is decreased in the presence of CaMKII inhibitors. Moreover, in knock-down PLB models, acetylcholine-induced Ca^{2+} oscillations also decrease, concomitant with an augmented rate of Ca^{2+} decreases, suggesting increased SERCA activity. This post-translational modulation of SERCA has not been observed in arterial SMC (Sathish et al., 2008).

SMC also express Calsequestrin, but considerable expression has only been observed in *vas deferens*. In aorta and stomach SMC, its expression is very low and even undetectable in the uterus and bladder (Volpe et al., 1994).

4.5. Excitation-contraction coupling

As in striated muscle, SMC tone and contraction also dependent on $[Ca^{2+}]_{cyto}$; however, stimulation of actin-myosin cross-bridges occurs in a completely different form. In SMC, myosin lacks intrinsic ATPase activity; hence, ATP hydrolysis takes place in the presence of actin interaction, albeit in a very slow way, which prevents fluent contraction (Ellison et al., 2000). SMC express myosin light chain (MLC) kinase (MLCK), a CaM-dependent kinase that induces MLC phosphorylation on Ser^{19}, increasing the ATP hydrolysis rate ~ 1000-fold (Sellers and Adelstein, 1985). The main stimulus for MLCK activation is $[Ca^{2+}]_{cyto}$ elevation and subsequent CaM activation, which binds to a CaM-binding domain of MLCK, thereby inducing tension in a Ca^{2+}-dependent manner (Van Lierop et al., 2002).

Several proteins regulate the Ca^{2+} sensitivity of MLC, such as MLC phosphatase (MLCP), which regulates the phosphorylation status of MLC and decreases the formation of actin-myosin cross-bridges. MLCP phosphorylation by several agonist-induced kinases such as ROCK, zipper-interacting kinases and integrin-liked kinases reduces its activity and, therefore, increases the Ca^{2+} sensitivity of MLC. In a reciprocal way, other kinases like cyclic GMP-dependent protein kinase (PKG) and PKA prevent the inhibition of MLCP and promote a decrease in Ca^{2+} sensitivity (Khromov et al., 2009). CaMKII-γ also regulates MLC Ca^{2+} sensitivity mediated by a $[Ca^{2+}]_{cyto}$ elevation through a still unknown mechanism. Nevertheless, CaMKII-γ auto-phosphorylation mechanisms may differ between phasic and tonic SMC, explaining the difference in MLC Ca^{2+} sensitivity between these two types of cells (Lorenz et al., 2002).

The primary source of $[Ca^{2+}]_{cyto}$ elevation for the activation of MLCK can have diverse origins. IP_3R activation by GPCR (α-adrenergic, muscarinic, serotoninergic, among others) is one of the main triggers of Ca^{2+} release from the ER, which in most cases leads to a Ca^{2+} wave (Berridge, 2008). Other sources of $[Ca^{2+}]_{cyto,}$ such as ROC (Ghosh et al., 2017; González-Cobos and Trebak, 2010; Large, 2002), VOC (Tykocki et al., 2017) and SOC (Feldman et al., 2017) also participate, by controlling Ca^{2+} influx. Berridge et al. proposed three mechanisms for the con-

traction-related increase of $[Ca^{2+}]_{cyto}$ in SMC (Berridge, 2008). The first depends on membrane depolarization and VOC activation, where external Ca^{2+} is the main source for contraction. Different tissues are modulated by this mechanism, like the *vas deferens* (Koslov and Andersson, 2013), bladder (Herrera et al., 2000; Kim et al., 2012) and myometrium (Wray et al., 2015). The second mechanism is mediated by ROC that induce $[Ca^{2+}]_{cyto}$ elevations from ER stores. This is a common mechanism of vascular and airway SMC for contraction and tension control (Hirshman et al., 1999; Lamont et al., 2003). Finally, the third mechanism requires cells known as interstitial cells of Cajal to generate membrane depolarization and transmit the ion current through gap junctions. This depolarization wave activates VOC channels to produce Ca^{2+} influx and contraction (Hashitani and Suzuki, 2007; Yamazawa and Iino, 2002). A typical example for this mechanism are SMC from the gastrointestinal tract (Sanders et al., 2006).

Unlike striated muscles, Ca^{+2} entry through VOC does not always trigger muscle contraction in SMC. This phenomenon is called "loose coupling" and refers to a low pass filter that conditions a minimum $[Ca^{2+}]_{cyto}$ elevation to induce Ca^{+2} waves. In SMC, the opening of hundreds of L-type channels does not generate Ca^{2+} waves if the duration of the aperture does not ensure enough Ca^{2+} entry for CICR by RyR (Kotlikoff, 2003). The mechanism behind this effect depends on the structure of Ca^{2+} microdomains and the distance between Cav1.2 and RyR. A possible explanation is that the distance between channels in SMC is larger than in cardiac myocytes (> 100 nm), and RyR clustering is lower. Therefore, only high-duration aperture or simultaneous activation of several Cav1.2 ensures a global change in $[Ca^{2+}]_{cyto}$ to induce a discrete CICR (low gain system) (Collier et al., 2000). The function of loose coupling depends on the capacity of SMC to discriminate between local and global Ca^{2+} changes (signal integration), and hence, differentiate its response according to these stimuli. For example, local Ca^{2+} changes are associated with STOC and STIC, whereas global Ca^{2+} changes are related with Ca^{2+} waves and muscle contraction (Collier et al., 2000; Imaizumi et al., 1998). Loose coupling is the reason why CICR is not the main way to induce SMC contraction, and accordingly, SMC require more than a single way to increase global $[Ca^{2+}]_{cyto}$ for contraction.

5. SR/ER DYSFUNCTION AND DISEASES

The SR/ER is a pivotal organelle in the regulation of intracellular Ca^{2+}, which is a key second messenger in several pathological pathways. Alterations in Ca^{2+} uptake or release lead to Ca^{2+} imbalance, thereby triggering dysfunctional responses in cells. Additionally, the SR is the organelle responsible for protein synthesis, which is a very delicate process. Correct protein folding is carried out by luminal chaperones such as Grp78, Grp94 and Calreticulin, whose activity is Ca^{2+}-dependent (Xu et al., 2005). Consequently, dysregulation of Ca^{2+} handling leads to the accumulation of unfolded proteins. This condition triggers activation of the IRE1α-XBP1, PERK-ATF4-CHOP and ATF6 pathways, which comprise the unfolded protein response (Xu et al., 2005). In this regard, ER stress has been observed in neurological and metabolic disorders. On the other hand, mitochondria-associated membranes (MAM) are structural and functional platforms of communication between the SR and mitochondria, allowing phospholipid and Ca^{2+} transfer. As in ER stress, alterations in MAM structure and function are implicated in pathologic conditions (López-Crisosto et al., 2017). Cardiac hypertrophy, insulin resistance and hypertension are pathologic chronic conditions with high worldwide prevalence that promote structural and functional alterations in cardiac myocytes, skeletal muscles and smooth muscle cells, respectively. These changes and their relationship with SR/ER dysfunction will be reviewed below (Fig. 6).

5.1. SR dysfunction and cardiac hypertrophy

Cardiac hypertrophy is a compensatory response of cardiac cells to mechanical stress and/or neurohumoral stimuli. Increased synthesis and reduced degradation of proteins lead to an increment in sarcomere number and size, which lead to heart enlargement along with biochemical, metabolic, and Ca^{2+}-handling alterations that ultimately result in heart failure (Heineke and Molkentin, 2006).

5.1.1. SR shape alterations in cardiac hypertrophy

As aforementioned, RyR2 and Cav1.2 are in tight juxtaposition, allowing for the increase in cytoplasmic Ca^{2+} levels during cardiac myocyte contraction (Vega et al., 2011). Studies in hypertrophied rat cardiac my-

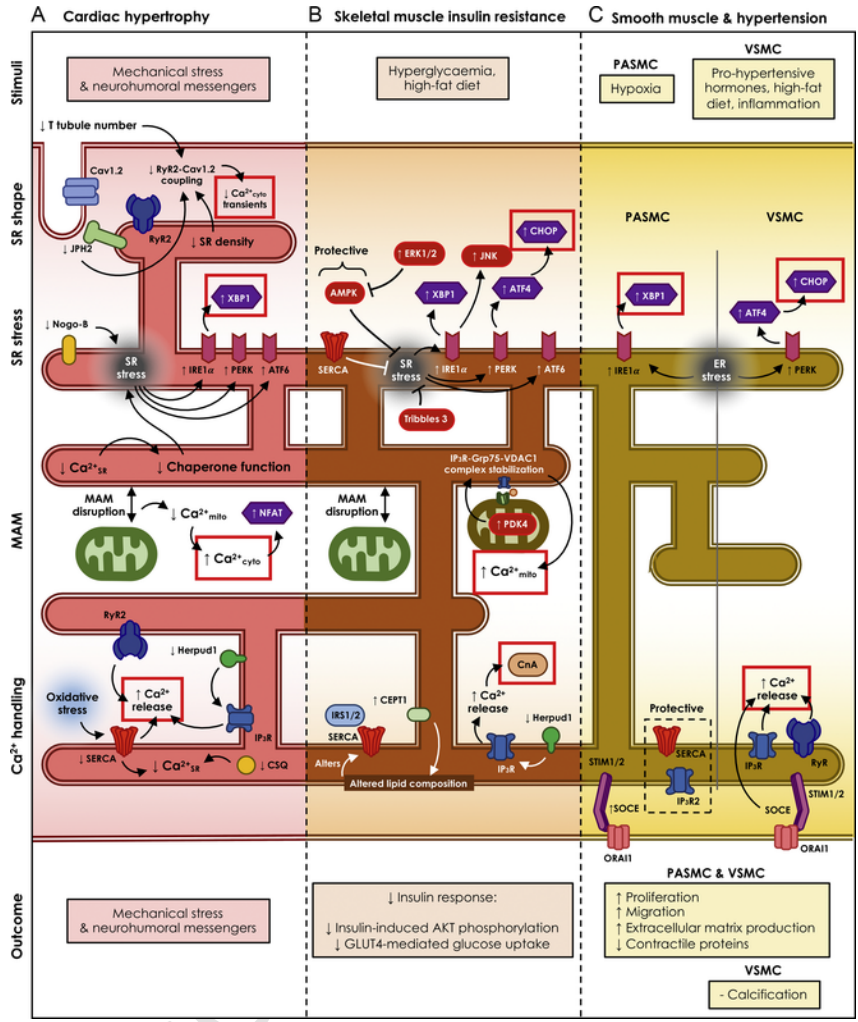

Fig. 6. Alterations in SR/ER function and Ca2 + homeostasis in pathological processes. (A) In cardiomyocytes, mechanical stress and neurohumoral messengers trigger hypertrophy through a decrease in T tubule number, sarcoplasmic reticulum (SR) density and Junctophilin 2 (JPH2) levels. These changes reduce the functional coupling between ryanodine receptor 2 (RyR2) and voltage-gated L-type Ca^{2+} channel Cav1.2, decreasing the magnitude of cytoplasmic Ca^{2+} transients and therefore the contractile force. Decreases in SR Ca^{2+} levels or in Nogo-B expression contribute to the hypertrophic process by aggravating SR stress, leading to the activation of its three canonical pathways: IRE1α-XBP1, PERK and ATF6. Also, during cardiac hypertrophy there is a disruption of the contact sites between SR and mitochondria, termed mitochondria-associated membranes (MAM). The ensuing reduction in SR-to-mitochondria Ca^{2+} transfer leads to Ca^{2+}

accumulation in the cytoplasm, resulting in nuclear factor of activated T-cells (NFAT) activation, which drives the hypertrophy genetic program. Alterations in Herpud1-mediated degradation of the inositol 1,4,5-trisphosphate receptor (IP_3R) channel, oxidative stress-mediated alterations in the SR/ER Ca^{2+} ATPase (SERCA) pump, and increased RyR2 activity also contribute to increase cytoplasmic Ca^{2+} levels. This, along with decreased calsequestrin (CSQ) expression, results in a decrease in SR Ca^{2+} concentration, which alters chaperone function and favors SR stress (B). In skeletal muscle, hyperglycaemia and high-fat diet trigger a decreased response to insulin. All three branches of SR stress contribute to this process, namely, IRE1α-XBP1-JNK, PERK-AFT4-CHOP and ATF6. In terms of organelle communication, skeletal muscle insulin resistance also displays MAM disruption; however, PDK4-mediated stabilization of the MAM complex IP_3R-Grp75-VDAC1 has also been reported, suggesting a complex role of this signaling axis. As in cardiac muscle, decreased Herpud1-mediated IP_3R degradation increases cytoplasmic Ca^{2+}, resulting in Calcineurin A (CnA) activation. Also, alteration of SR membrane lipid composition via CEPT1 upregulation alters the interaction between SERCA and Insulin receptor substrate IRS1/2, which is a key mediator of insulin signaling. (C) As in the other two muscle types, endoplasmic reticulum (ER) stress contributes to hypertension via the IRE1α-XBP1 and PERK-ATF4-CHOP pathways in pulmonary artery smooth muscle cells (PASMC) and vascular smooth muscle cells (VSMC), respectively. In PASMC, the activity of SERCA and IP_3R2 have a protective role, while store-operated Ca^{2+} entry (SOCE) mediated by ORAI1 and STIM1/2 are deleterious. In VSMC, elevated cytosolic Ca^{2+} levels promote hypertension, mediated by the increased SOCE and elevated Ca^{2+} release from the ER. The red rectangles mark the most relevant and common mechanisms that mediate the three pathologies.

ocytes show a reduction in cytoplasmic Ca^{2+} transients and a weaker contraction, associated with decreased Ca^{2+} entry (van Oort et al., 2011) and decreased JPH2 expression (Takeshima et al., 2015). Moreover, in early stages of cardiac hypertrophy induced by pressure overload in mice, both the numbers of TT and the density of the SR decrease without altering intracellular Ca^{2+} levels, suggesting that the first change in hypertrophy occurs at the structural level (Pérez-Treviño et al., 2015). Interestingly, computational simulation of cardiac myocytes originated from failing hearts show that disruption of TT leads to a reduced coupling between the Cav1.2 and RyR2 as well as an increase in $[Ca^{2+}]_{SR}$, causing alterations in Ca^{2+} transients (Nivala et al., 2015). In sum, these studies suggest that loss in TT-SR juxtaposition leads to alterations in Ca^{2+} signaling and EC coupling, thereby promoting hypertrophy in cardiac myocytes.

5.1.2. Ca^{2+} cycle alterations in cardiac hypertrophy

Hypertrophied hearts display alterations in function and/or expression of proteins that regulate Ca^{2+} release (Kim et al., 1994) and uptake (Scholz et al., 1991). SERCA levels, for instance, decrease in both hypertrophic hearts (Aoyagi et al., 1999; Kiss et al., 1995; Matsui et al., 1995; Qi et al., 1997) and in cultured neonatal rat cardiac myocytes treated with the hypertrophic stimulus endothelin-1 (ET1) (Hartong et al., 1996; Uehara et al., 2012; van Heugten et al., 1998). In hearts, however, alterations in SERCA occur only in the later stages of cardiac hypertrophy (Gupta et al., 2003). Oxidative stress in cardiac overload models mediates the loss of SERCA activity, which is prevented by catalase overexpression (Qin et al., 2014). PDPC5, a novel protein under NFAT regulation, also plays a role in SERCA2a stabilization, protecting the heart against hypertrophy (Ye et al., 2018). PLB phosphorylation together with SERCA activity are reduced in human failing hearts (Schwinger et al., 1998). PLB expression is reduced in cardiac hypertrophy (Kiss et al., 1995; Matsui et al., 1995), while in PLB knock-out mice, SERCA Ca^{2+} affinity is augmented (Vangheluwe et al., 2006). On the contrary, increased SERCA phosphorylation leads to a series of compensatory effects during early stages of hypertrophy (Boateng et al., 1997). In the same line, increased PLB phosphorylation associates with enhanced CaMKII and PKA activities in SR preparations from hypertrophic hearts (Currie and Smith, 1999). Decrease of SERCA activity promotes a reduction in SR Ca^{2+} content (Díaz et al., 2004).

Although RYR expression is reduced in cardiac hypertrophy induced by pressure overload (Hisamatsu et al., 1997), the gain of function of RYR isoforms promotes Ca^{2+} leak from the SR and the activation of pro-hypertrophic signaling pathways, such as CnA-NFAT (van Oort et al., 2010). Also, CaMKII and PKA regulate RYR, favoring Ca^{2+} leak from the SR; however, only CaMKII expression increase associates with the transition from human cardiac hypertrophy to heart failure (Fischer et al., 2013). Furthermore, IP_3R levels also increase due to hypertrophic agents such as ET1 (Harzheim et al., 2010). Interestingly, our group found that Herpud1 (a component of the SR degradation machinery) promotes IP_3R degradation, and increased levels of IP_3R are associated with cardiac hypertrophy in Herpud1 knock-out mice, suggesting a protective role of Herpud1 against hypertrophy (Torrealba et al., 2017).

CSQ expression is also decreased in hypertrophied hearts (Kiss et al., 1995); however, it has been reported that its overexpression leads to cardiac hypertrophy with increased expression of SERCA and PLB, effects that were associated with alterations in Ca^{2+} release from the SR and contractility (Sato et al., 1998). Of note, CSQ and SERCA1a (a skeletal muscle isoform) double-mutant mice show heart failure with left ventricular hypertrophy. Also, CSQ and PLB double knock-out mice show enhanced SERCA activity, but accompanied with RYR dysfunction that leads to cell death via apoptosis (Kalyanasundaram et al., 2013).

5.1.3. SR stress in cardiac hypertrophy

Cardiac myocytes increase their size in response to workload, a process that requires elevated protein synthesis (Görlach et al., 2006). Elevated protein synthesis and a larger SR suggest the participation of the SR stress response in cardiac hypertrophy induced by transverse aortic constriction (TAC) (Okada et al., 2004). In that model, increases in SR chaperones are observed 1 and 4 weeks after TAC, as well as in cultured cardiac myocytes treated with the pro-hypertrophic agent angiotensin II (Okada et al., 2004). Additionally, mRNA level of these chaperones are also increased in patients with heart failure (Okada et al., 2004). More recently, increases in GRP78 and XBP1 have been observed in cardiac hypertrophy induced by isoproterenol infusion or TAC (Duan et al., 2016). Additionally, other studies have shown that down-regulation of Nogo-B, a protein that maintains ER structure, promotes cardiomyocyte hypertrophy induced by norepinephrine and activates the PERK-ATF4 and ATF6 pathways (Li et al., 2018). These findings suggest the participation of SR stress in cardiac hypertrophy development. Interestingly, the SR stress inductor thapsigargin (a SERCA inhibitor) induces cardiomyocyte hypertrophy (Zhang et al., 2010), via increase $[Ca^{2+}]_{cyto}$ levels, elevated PLB expression, and activation of the pro-hypertrophic signaling pathway CnA-MEF2c (Zhang et al., 2010). Of note, chaperone proteins such as GRP78, Grp94, calnexin, GRP170/ORP150 and ERp57, which are responsible for proteins folding and quality control, contain multiple Ca^{2+}-binding sites (Bravo et al., 2013; Görlach et al., 2006). Therefore, maintenance of SR Ca^{2+} levels is important to prevent SR stress. Hence, these evidences suggest that the SR stress response is exacerbated in cardiac hypertrophy, which may be exacerbated by alterations in Ca^{2+} handling.

5.1.4. SR-mitochondria communication in cardiac hypertrophy

In recent years, SR communication with other organelles, especially mitochondria, has become relevant as a mechanism of Ca^{2+} regulation. As such, cardiac myocytes of rats with isoproterenol-induced hypertrophy undergo SR stress and apoptosis (Lu et al., 2013). These effects were also described with calindol, an activator of extracellular Ca^{2+}-sensing receptor, accompanied with a reduction in SR Ca^{2+} and an increase of mitochondrial Ca^{2+} levels. These changes suggest an augmented Ca^{2+} transfer from SR to mitochondria, which is responsible for SR stress apoptosis (Lu et al., 2013). On the other hand, our group has shown that the pro-hypertrophic agent norepinephrine induces a loss of the SR-mitochondria communication, with reduced Ca^{2+} transfer (Gutierrez et al., 2014), an effect associated with increased $[Ca^{2+}]_{cyto}$ and the activation of the CnA-NFAT signaling pathway (Garrido-Moreno et al., 2019).

5.1.5. SR-mitochondria communication in ischemia/reperfusion

Organelle communication has also been implicated in different other cardiac pathologies, such as coronary artery diseases or myocardial infarction, where ischemia-reperfusion (I/R), and in particular the early state of reperfusion has shown to induce a massive cardiomyocyte death (Vanden Hoek et al., 1996). Importantly, intracellular Ca^{2+} handling impairments participate in I/R injury (Garcia-Dorado et al., 2012). In this scenario, mitochondria have a protective role, acting as Ca^{2+} buffers via Ca^{2+}; however, mitochondrial Ca^{2+} overload, may lead to mitochondrial dysfunction and subsequent apoptosis (Hausenloy and Yellon, 2013). Several reports indicate that Ca^{2+} transfer from SR to mitochondria is responsible of mitochondrial Ca^{2+} overload during the cell death induced by reperfusion (Dong et al., 2010; Ruiz-Meana et al., 2009; Shintani-Ishida et al., 2012). Moreover, some proteins localized at MAM are associated with this process, such as cyclophilin D (CypD), a regulator of mitochondrial integrity that participate in SR-mitochondria tethering between the through its interaction with the complex consisting in IP_3R at the ER, the cytoplasmic chaperone Grp75, and voltage-dependent anion-selective channel 1 (VDAC1), the Ca^{2+} channel that mediates Ca^{2+} entry to mitochondria (Paillard et al., 2013). Accordingly, knock-down or inhibition of CypD, Grp75, IP_3R or the SR/ER-mitochondria tether MFN2 prevent the I/R-induced injury in H9C2 cell line (Paillard et al., 2013

). Moreover, the mitochondrial exchange protein activated by cyclic AMP 1 (Epac1) also promoted the Ca^{2+} transfer from SR to mitochondria through interaction with IP_3R/Grp75/VDAC1, leading to cell death. Consequently, the Epac1 KO mice are protected of myocardial cell death induced by I/R (Fazal et al., 2017).

On the other hand, protein tyrosine phosphatase-interacting protein 51 (PTPIP51) is overexpressed in mice hearts subjected to I/R, concomitant with SR-dependent mitochondrial Ca^{2+} overload and cell death. Thus, PTPIP51 ablation protects from I/R-induced heart dysfunction in mice, whereas its overexpression increases the SR-mitochondria contacts (Qiao et al., 2017). Inhibition of GSK3β has also reported to protect the heart damage induced by I/R (Tong et al., 2002), via reduction of IP_3R phosphorylation and activity (Gomez et al., 2016).

5.1.6. SR-mitochondria communication in diabetic cardiomyopathy (DCM)

This disease is characterized by an alteration in cardiac structure and function in diabetic patients without arterial hypertension and coronary arterial disease (Boudina and Abel, 2007). Hyperglycemia has shown to contribute to high mitochondrial ROS production in cardiac cells, activating cell death pathways during DCM pathogenesis (Boudina and Abel, 2007). Some proteins such as MFN2 and PERK, the latter also located in MAM, are involved in DCM, mainly associated with SR stress and mitochondrial ROS production (Liu et al., 2013; Yang et al., 2017). Moreover, intracellular Ca^{2+} homeostasis is also altered in this condition, generally due to SR dysfunction (Boudina and Abel, 2007). Interestingly, recent work found that Fundc1, a mitochondrial membrane protein involved in MAM formation, is elevated in the hearts of diabetic patients (Wu et al., 2019). In isolated mice cardiomyocytes incubated in high-glucose conditions, AMP-activated protein kinase (AMPK) function is suppressed, triggering an increase in Fundc1 protein levels (Wu et al., 2019). Cardiomyocytes from AMPK KO mice have also increased Fundc1 levels, more MAM structures, and augmented mitochondrial Ca^{2+} uptake (Wu et al., 2019). Conversely, cardiac-specific deletion of Fundc1 as well as AMPK-induced reduction in mitochondrial Ca^{2+} uptake via loss of MAMs diminished apoptosis and improved cardiac function of diabetic mice (Wu et al., 2019).

5.2. SR and insulin resistance in skeletal muscle cells

Skeletal muscle is the main contributor to glucose uptake stimulated by insulin. In physiological conditions, insulin induces the activation of signaling pathways that involve the phosphorylation of the Insulin receptor substrate-1 (IRS1) by the Insulin receptor (IR). In turn, IRS activates PI3K, leading to the formation of PIP_3, which then allows the activation of protein kinase Akt, ultimately leading to the translocation of GLUT4 to the sarcolemma in to promote glucose uptake (Defronzo and Tripathy, 2009). However, in pathological conditions, skeletal muscle loses its capacity to respond to insulin, in a process known as insulin resistance, the first step for the development of type-2 diabetes (Defronzo and Tripathy, 2009).

5.2.1. SR Ca^{2+} handling and insulin resistance in skeletal muscle

Several studies have revealed the importance of Ca^{2+} regulation by the SR on the insulin response in skeletal muscle. In this regard, the interaction of both IRS1 and IRS2 isoforms with SERCA1 in response to an insulin stimuli (Algenstaedt et al., 1997) and Ca^{2+} influx induced by insulin in skeletal cells has been implicated in glucose uptake and the translocation of GLUT4 to the sarcolemma (Lanner et al., 2006). Interestingly, the inhibitor of Ca^{2+} release from SR dantrolene abolishes glucose uptake induced by hyperglycaemia in skeletal muscle tissue (Nolte et al., 1995). Additionally, a knock-down of Herpud1 increases the output of Ca^{2+} levels through IP3R, thus increasing CnA phosphatase activity accompanied with a decrease in GLUT4 translocation (Navarro-Marquez et al., 2018).

On the other hand, the lipid composition of the SR also regulates Ca^{2+} homeostasis and insulin response in skeletal muscle. Skeletal muscle knock-down of choline/ethanolamine phosphotransferase-1 (CEPT1), an enzyme that participates in phospholipid synthesis at the SR, modifies SR lipid composition and Ca^{2+} handling (Funai et al., 2016). Additionally, obesity induction by a high-fat diet increases CEPT1 and decreases insulin sensitivity (Funai et al., 2016). Moreover, CEPT1 knock-out mice are protected from high-fat diet-induced insulin resistance, together with a decrease in Ca^{2+} uptake by SERCA (Funai et al., 2016).

5.2.2. SR stress and insulin resistance in skeletal muscle

SR stress and insulin resistance have been observed in mice fed with high-fat diet, in humans with obesity and type-2 diabetes (Koh et al., 2013), and in skeletal muscle cells (Gu et al., 2015; Peng et al., 2011; Salvadó et al., 2013), mouse C2C12 myotubes, the human myogenic cell line LHCN-M2 (Salvadó et al., 2013) and primary human myotubes (Mäkinen et al., 2017) treated with palmitate. All these models display SR stress markers, accompanied with a reduction in insulin response (Ebersbach-Silva et al., 2018; Gu et al., 2015; Mäkinen et al., 2017; Peng et al., 2011; Salvadó et al., 2013). These studies also showed increased expression SR stress markers such as IRE1α, XBP1, JNK, PERK, CHOP or Grp78, along with a reduction in the phosphorylation of Akt, GLUT4 expression and glucose uptake induced by insulin (Ebersbach-Silva et al., 2018; Gu et al., 2015; Mäkinen et al., 2017; Peng et al., 2011; Salvadó et al., 2013). In contrast to these findings, another study showed that palmitate effectively induces insulin resistance, but with a weak activation of the IRE1-JNK pathway (Hage Hassan et al., 2012). Additionally, glucosamine, a substrate for the hexosamine pathway, also induces SR stress and insulin resistance in myotubes. These effects are abolished with the synthetic chaperones TUDCA and 4-PBA (Kars et al., 2010; Raciti et al., 2010). This last report also showed the role of the ATF6 SR stress pathway on insulin resistance, because ATF6 silencing improved the insulin response (Raciti et al., 2010).

Some strategies that reverse both the ER stress response and insulin resistance have been used to investigate the mechanisms implicated in this relationship in skeletal muscle cells. As an example, the activation of AMPK, a fuel sensing protein kinase, by AICAR or A769662 reverses both insulin resistance and ER stress (Salvadó et al., 2013). The MEK1 inhibitor also U0126 improves AMPK activation, accompanied with a reduction of ER stress and activation of insulin signaling (Hwang et al., 2013). Moreover, both in vivo and in vitro evidences show that ERK1/2 phosphorylates the phosphatase PHLPP1, which is involved in the inactivation of Akt and AMPK, as well as in the induction of ER stress (Behera et al., 2018). These results suggest that the ERK pathway is implicated in AMPK action and ER stress associated with insulin response. In the same line, the antioxidants mito-tempo and tempol also pre-

vent ER-dependent insulin resistance by hindering ROS production in skeletal muscle cells (Mäkinen et al., 2017).

Finally, the expression of the pseudo kinase tribbles increases during SR stress, and is elevated in the skeletal muscle of mice fed with high-fat diet and in obese and diabetic patients with impaired insulin response. The development of insulin resistance triggered by a high-fat diet is not observed in tribbles three KO mice, suggesting that it has a role in insulin resistance induced by the activation of the ER stress pathway (Koh et al., 2013).

Despite the previous evidence shows a causative role of SR stress on insulin resistance in the skeletal muscle, two works depicted that lipotoxic stress induced by palmitate leads to insulin resistance in C2C12 and human myotubes, independently of SR stress. In these studies, chemical chaperones mitigate ER stress only, but not the insulin decreased response (Hage Hassan et al., 2012; Rieusset et al., 2012). In mice, 8-week diet with high levels of palmitate induces SR stress, but not insulin resistance, whereas, in C2C12 myotubes, lipotoxic stress with palmitate does induce SR stress accompanied with a decrease in insulin response. In this model, treatment with TUDCA or 4-PBA does not improve insulin desensitization (Rieusset et al., 2012).

5.2.3. SR stress, Ca^{2+} handling and insulin resistance in skeletal muscle

The association between Ca^{2+} regulation, SR stress and insulin response has been described in the liver, where the increment of SERCA2b activity associates with a decrease of ER stress and improvement in glucose tolerance (Park et al., 2010). This relationship has also been described in skeletal muscle. Flavones isolated from *Artemisia vestita* have hypoglycemic effects (Anaya-Eugenio et al., 2014), and also increase SERCA2b expression, reduce SR stress, and improve insulin sensitivity in skeletal muscle cells (Ouyang et al., 2017). In agreement with this, glyceollin (a soybean phytoalexin) also reduces ER stress, and increases AMPK activity and insulin sensitivity (Yoon et al., 2013). Interestingly, knock-down of Ca^{2+}/CaM-dependent protein kinase kinase (CaMKK) inhibits the effects of glyceollin on SR stress, AMPK activation and insulin sensitivity, suggesting a Ca^{+2}-dependent effect of glyceollin (Yoon et al., 2013). The treatment of C2C12 myotubes with the adipokine aprosin increases PKCδ activation and suppresses the expression of *ser-*

ca2 mRNA. This effect is accompanied with an increase in PERK activation, CHOP expression and alterations in the phosphorylation of IRS1 and Akt. These data suggest that impairment of insulin sensitivity is linked to the Ca^{2+}-handling protein SERCA2b and the ER stress response (Jung et al., 2019).

5.2.4. Mitochondrial associated membranes and insulin resistance in skeletal muscle

MAMs are the structural and functional communication between the SR and mitochondria, constituting a signaling platform implicated in the regulation of insulin resistance and SR stress. In different experimental models of diabetes in the skeletal muscle, disruption of SR-mitochondria communication preludes insulin resistance (Tubbs et al., 2018). Moreover, palmitate treatment promotes several MAM alterations in cultured myotubes (Tubbs et al., 2018). Interestingly in obese mice, increased PDK4 levels stabilize the IP_3R1-GRP75-VDAC1 complex at MAMs. PDK4 inhibition improves insulin signaling by preventing MAM-induced mitochondrial Ca^{2+} accumulation and ER stress (Thoudam et al., 2019). PDK4 KO mice show a reduction in MAM structure that is protective against diet-induced insulin resistance in skeletal muscle (Thoudam et al., 2019). Finally, forced MAM formation with a synthetic SR-mitochondria linker prevents the effects of PDK4 deficiency on insulin signaling (Thoudam et al., 2019). Overall, these findings suggest a critical mediatory role of PDK4 in the development of skeletal muscle insulin resistance via enhanced MAM formation.

5.3. ER in smooth muscle cell and hypertension

SMC are specialized cells that, under physiological conditions, exhibit a low proliferation rate and reduced protein synthesis (Rzucidlo et al., 2007). In pathological conditions, such as hypertension, SMC dedifferentiate and change their morphology, increment their proliferation rate, develop a migratory phenotype, increase their secretion of extracellular matrix components and lose several contractile proteins, thereby leading to vessel stiffness (Lacolley et al., 2017; Rzucidlo et al., 2007). Here, we will review the relationship between alterations in SR and Ca^{2+} homeostasis and SMC phenotypic changes.

5.3.1. ER stress and hypertension

Pulmonary arterial hypertension (PAH) is a type of hypertension that affects the SMC from pulmonary arteries (PASMC), and usually develops under hypoxic conditions. These cells are characterized by a hyperproliferative phenotype (Fan et al., 2011). In this regard, PASMC from rats subjected to hypoxia show phenotypic changes such as proliferation and remodeling that are associated with increased markers of ER stress, such as GRP78 (Fan et al., 2011). Similar results were obtained with PASMC isolated under hypoxia, that showed increased GRP78 expression, together with IRE1α activation and a decreased proliferation and migration (Cao et al., 2019). Treatment with the IRE1α/XBP1 inhibitor 4u8c abolished cell proliferation and migration, and triggered apoptosis in hypoxic conditions. These findings suggest the participation of this SR stress pathway in the pathologic phenotype associated with PAH (Cao et al., 2019).

A typical feature of arterial hypertension is the development of atherosclerosis, which is associated with vascular calcification. Here, vascular SMC (VSMC) adopt a calcific phenotype characterized by the production of calcific vesicles, reduction of mineralization inhibitors, and secretion of matrix components prone to calcification (Durham et al., 2018). Treatment of VSMC with the saturated fatty acid stearate leads to cellular mineralization associated with ER stress (Masuda et al., 2012). In this work, stearate induced ATF4, which promoted the calcific phenotype (Masuda et al., 2012). Another study on chronic kidney disease indicates that tumor necrosis factor-α (TNFα) promotes vascular calcification in VSMC via the induction of the PERK-ATF4-CHOP axis, and suppression of the expression of these proteins prevents the mineralization and osteogenesis induced by TNFα (Masuda et al., 2013).

5.3.2. Ca^{2+} homeostasis and hypertension

Cytoplasmic Ca^{2+} levels are associated with the induction of proliferation in arterial hypertension by activating Ca^{2+}-dependent signaling pathways (Song et al., 2018). Altered Ca^{2+} regulation associated with blood pressure increase has been observed in spontaneously hypertensive rats (SHR) (Traub and Webb, 1993). Similarly, changes in the modulation of Ca^{2+} release and uptake by the ER have been found in VSMC, using the same rat model (Hermsmeyer and Erne, 1989). VSMC iso-

lated from SHR treated with angiotensin II shows a proliferative phenotype that is accompanied by enhanced Ca^{2+} release from the ER (Côrtes et al., 1997). SOCE also plays an important role in the regulation of Ca^{2+} signaling that participates in VSMC differentiation associated with hypertension (Qian et al., 2003). SOCE is also important in Ca^{2+} signaling in SMC from pulmonary veins, and is implicated in PAH induced by hypoxia (Peng et al., 2010).

A recent study where IP_3R2 KO mice were subjected to hypoxia showed exacerbated PAH compared to wild type mice, suggesting a protective role of IP_3R2 in PASMC. Moreover, the activity of SOCE induced by thapsigargin was enhanced in these IP_3R2 knock-out mice. This effect was abolished by an inhibitor of the STIM-ORAI complex that was also able to induce PASMC apoptosis (Shibata et al., 2019). Evidence indicates that STIM1 is increased in distal hypoxic arteries with increased proliferation. Suppression of STIM1 expression in PASMC reduces Ca^{2+} influx by SOCE, hypoxia-induced proliferation, and inhibits NFATc3 translocation to the nucleus (Hou et al., 2013). Similar effects were also observed with STIM2 suppression (Song et al., 2018). Finally, SERCA has also been implicated in the regulation of PASMC phenotype, as SERCA2a overexpression using an adeno-associated virus type 1 (AAV1) shows beneficial effects on pulmonary arterial remodeling (Aguero et al., 2016).

6. CONCLUDING REMARKS

The SR/ER is a ubiquitous organelle composed of several domains, all of which are distinct in both composition and function. Moreover, the SR/ER undergoes profound specialization depending on the cell type, as well as extensive remodeling, according to both internal and external cues. Muscle cells take the versatility of SR/ER architecture to the extreme, ranging from an apparently disordered network to a densely packed array of parallel cisternae. In either case, the SR/ER participates in cell contraction, serving as a Ca^{2+} source for the contractile machinery. In accordance, the SR/ER spatial disposition perfectly suits the directionality of the applied force: either concentric, in smooth muscle cells, or axial, in skeletal and cardiac myocytes. In this scenario, the SR/ER acts as a hub for Ca^{2+} delivery at the sites where contraction occurs. Furthermore, the specialized Ca^{2+}-handling machinery of the SR al-

lows the generation of transient Ca^{2+} signals of varying amplitude and frequency, which act as a barcode for the regulation of cell function. For muscle cells, this complexity is undoubtedly required, as Ca^{2+} does not only regulate contraction, but also protein folding, gene transcription and energy metabolism, among other important functions. In other words, the extension and heterogeneity of the SR/ER provides a ground where unitary, discreet Ca^{2+} signaling events take place, and the sum of all of them paints the landscape of cellular life.

Because SR/ER function and Ca^{2+} homeostasis intertwine with physiological cell processes, their alterations are inextricably linked to pathological developments. In terms of age-related diseases, time-dependent accumulation of damage in the SR/ER leads to progressive loss of function, ultimately affecting Ca^{2+} handling and other signaling pathways. Nowadays, the best-characterized SR/ER alteration is the accumulation of misfolded proteins that leads to SR/ER stress. This process is known to reshape SR/ER structure and composition, thus impairing normal Ca^{2+} signals and leading to cardiometabolic chronic diseases such as cardiac hypertrophy, insulin resistance and arterial hypertension.

An emerging topic contributing the pathogenesis of the SR/ER-Ca^{2+} axis is the communication between mitochondria and SR/ER. Since contraction is an energy-demanding process, mitochondrial bioenergetics is fundamental for proper muscle function. Furthermore, mitochondria also participate in Ca^{2+} homeostasis by acting as sinks that buffer cytoplasmic Ca^{2+} signals, thereby contributing to regulate their temporal patterns. In accordance, alterations in SR/ER-mitochondria communication have also been identified as factors that promote cell dysfunction not only in muscular tissue, but in many other tissues. However, the mechanisms that lead to altered organelle communication in muscle cells are not fully understood. Therefore, one of the challenges that this field faces is the development of strategies to promote SR/ER-mitochondria interaction, not only as a potential treatment for different pathologic conditions, but also to assess the biological significance of this regulatory axis, which is fundamental for Ca^{2+} homeostasis and muscle cell function.

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