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Calcium dysregulation in heart diseases: Targeting calcium channels to achieve a correct calcium homeostasis

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ABSTRACT

Intracellular calcium signaling is a universal language source shared by the most part of biological entities inside cells that, all together, give rise to physiological and functional anatomical units, the organ. Although preferentially recognized as signaling between cell life and death processes, in the heart it assumes additional relevance considered the importance of calcium cycling coupled to ATP consumption in excitation-contraction coupling. The concerted action of a plethora of exchangers, channels and pumps inward and outward calcium fluxes where needed, to convert energy and electric impulses in muscle contraction. All this without realizing it, thousands of times, every day. An improper function of those proteins (i.e., variation in expression, mutations onset, dysregulated channeling, differential protein-protein interactions) being part of this signaling network triggers a short circuit with severe acute and chronic pathological consequences reported as arrhythmias, cardiac remodeling, heart failure, reperfusion injury and cardiomyopathies. By acting with chemical, peptide-based and pharmacological modulators of these players, a correction of calcium homeostasis can be achieved accompanied by an amelioration of clinical symptoms.

This review will focus on all those defects in calcium homeostasis which occur in the most common cardiac diseases, including myocardial infarction, arrhythmia, hypertrophy, heart failure and cardiomyopathies. This part will be introduced by the state of the art on the proteins involved in calcium homeostasis in cardiomyocytes and followed by the therapeutic treatments that to date, are able to target them and to revert the pathological phenotype.

1. Intracellular calcium handling and calcium cycling

1.1. Calcium from plasma membrane

Plasma membrane (PM, or sarcolemma in the cardiac muscle cells) is a selectively permeable structure which finely regulate the inner content of the cell by the concerted action of numerous systems of passive and active transport. More, the sarcolemma connects the basement membrane to other muscle cells and actively contribute to excitation and conduction of neuronal impulses. At PM, among all membrane-spanning proteins, there are a wide diversity of calcium (Ca^{2+}) channel types that diffuse Ca^{2+} ions down its electromechanical gradient from the extracellular space to the cytoplasm; these channels are mostly classified on the basis of their activation mechanism.

Voltage-gated Ca^{2+} channels (VGCCs) are transmembrane proteins activated by membrane depolarization; their activation allows Ca^{2+} influx in the cell, they are essential for the induction of physiological processes in the heart [1]. This is a peculiarity of excitable cells; cardiomyocytes, mainly express the L-type Ca^{2+} channels (LTCCs) $Ca_{V1.2}$ with major roles in excitation-contraction coupling (ECC) [2]. Conversely, in non-excitable cells the main pathway for Ca^{2+} influx is performed by store-operated calcium channels (SOCCs) [3] that

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generate the store-operated calcium entry (SOCE), activated in response to endoplasmic reticulum (ER)-Ca^{2+} stores depletion and following stimulation of PM receptors that couple to phosphatidyl inositol-bisphosphate (PIP_2) hydrolysis and inositol-triphosphate (IP3) generation [4]. The knowledge about presence and function of SOCCs and molecular partners in cardiomyocytes has undergone a remarkable evolution: in principle, they were excluded from this cell type; later, they have been reported to be expressed only in the embryonal cardiomyocyte with a progressive downregulation until shutdown in adult and differentiated cells. Nevertheless, latest discoveries highlight not only the presence of SOCE mechanism in cardiomyocytes but also its involvement in disease [5].

Molecular components of SOCE are the mammalian transient receptor potential canonical (TRPC) family of Ca^{2+} permeable channels (TRPC1–TRPC7), Stromal Interaction Molecule (STIM1) and ORAI Calcium Release-Activated Calcium Modulator 1 (ORAI1). The lowering of ER-Ca^{2+} concentrations stimulate STIM1 oligomerization and the interaction with ORAI1 and/or TRPC. Remarkably, TRPC and ORAI1 generate different patterns of Ca^{2+} motifs that are decoded for the regulation of precise cellular functions [6]. Several types of TRP exist; in this review we take into consideration the canonical family, considered its main contribution in cardiac diseases discussed below. TRPC3 is the most abundant form in the heart [7]; it was found at the sarcolemma of pacemaker cells and it triggers CaMKII activation by channeling Ca^{2+}; also, it provides for the phosphorylation of several proteins including PLB and RyR2 and thus increasing sarcoplasmic reticulum (SR) Ca^{2+} release [8]. There exist also evidence about TRCP3 involvement in sinoatrial node pacemaker activity trough SOCE and its kinase activity [8].

Postulated to be part of the SOCE pathway [9], Acid-sensing ion channel (ASIC) allows the passage of cations through the PM; ASICs generally sense changes in extracellular acidity (pH<7) and in cardiomyocytes they generate intracellular Ca^{2+} transients [10]. Since their expression is significant high in in neonatal cells and very low in adult cardiomyocytes, a role in development is supposed [11]. Widely expressed in neurons, they were found also in cardiomyocytes with pivotal roles in development and cardioprotection [11,12].

P2X receptors (P2X7Rs) are PM trimeric assemblies, defined as ATP-gated channels inasmuch they bind ATP for ionic permeation through the PM. There are seven P2XR subunits with very different trafficking properties and, consequently, different membrane subcellular distributions (PM, ER, endosomes and lysosomes) [13]. Their activation allow for Na^+ and Ca^{2+} influx into the SR and cytosol, contributing to stimulate sarcomere contraction [14]. ATP-induced Ca^{2+} mobilization can also induce pathological states [15]. ATP is therefore one of the most important elements in controlling intracellular Ca^{2+} and this is also reflected in the extrusion of this important second messenger from the intracellular to the extracellular environment.

The Na^+/Ca^{2+} exchanger (NCX) is a PM ion transporter that works in two directions. Normally, the exchanger transports one Ca^{2+} ion in the extracellular environment and three Na^+ ions into the cell and this is known as the Ca^{2+} exit, or "forward" mode. However, under certain conditions, the exchanger can reverse and transport Ca^{2+} ions into the cell putting into action what is called the "Ca^{2+} entry mode" [16].

PM Ca^{2+} ATPase (PMCA) belongs to the superfamily of P-type ATPases and have a peculiar feature that make them unique as they are activated by calmodulin (CaM), which binds at a C-terminal extension that functions as a pump autoinhibitory domain. PMCA undergo conformational changes during the reaction cycle for which energy is provided by ATP forming a high energy acyl phosphate to permit the pumps to transfer Ca^{2+} across the membrane against the Ca^{2+} ion gradient [17]. In mammals there exist 4 different isoforms (PMCA1–4) where the most represented in the heart are PMCA 1 and PMCA4 [18]. Overall, consequently to indirect findings which attributed to NCX and SR the greater ability to remove "useless" cytosolic Ca^{2+}, it is believed that PMCA contributes only minimally to Ca^{2+} cycling in the heart. However, increasingly evidence due to the discovery of mutations in the genes encoding PMCAs found among a wide variety of ethnics groups, show its their differential expression or activity produces severe defects in cardiac function [18,19].

1.2. Contacts with sarcoplasmic reticulum: a functional role

Sarcolemma invaginates to face some highly specific region of the SR (called junctional SR, jSR) with transversal tubules (TT). Here, the most percentage of $Ca_{V1.2}$ are located on TT and are very close to Ryanodine Receptors (RyRs). In jSR is located a large amount of Ca^{2+} which is bound to calsequestrin (CSQ), a protein able to store most of Ca^{2+} needed for rapid and frequent contractions [20].

In turn, SR perform contacts also with mitochondria. While playing different biological roles and being two distinct organelles, mitochondria and the SR are not completely independent structures; specifically, the dynamic and tight association between both organelles give rise to a microdomain called mitochondria-associated ER/SR membranes (MAMs) [21]. MAMs play a crucial role in many signaling pathways, providing an excellent platform for the SR-mitochondria crosstalk and, in this way, allowing the rapid exchange of biological molecules to maintain cellular health. It has been described, especially in recent years, as the correct signaling between mitochondria and SR guaranteed by the passage of the second messenger Ca^{2+}, is a biological event of fundamental importance for the maintenance of normal physiological functions; the perturbation of this delicate balance leads to pathologies [22].

Focusing on SR-mitochondria contact sites, the SR locally canalize Ca^{2+} signals through the RyRs to Voltage Dependent Anion-selective Channel (VDAC) on the mitochondrial side after both electrical and chemical cell stimulation. SR is the major intracellular Ca^{2+} storage organelle; on its lumen Ca^{2+} is accumulated via active Ca^{2+} transport mediated by ER Ca^{2+} ATPases (SERCA) followed by intraluminal Ca^{2+} buffering by calnexin, calreticulin and CSQ [20]. The cardiac specific isoform of SERCA in the heart is SERCA2a. RyRs are the most important Ca^{2+} outflow channels on the SR surface, mediating Ca^{2+} release to the cytoplasm following the functional interaction of agonists on the PM receptors and intracellular second messenger IP3. In mammals exists three different isoforms of IP3R (IP3R1, −2 and −3) that are ubiquitously expressed [23] though in cardiomyocytes they are 50-fold less present [24] than the RyRs (RyR1 primarily expressed in skeletal muscles, −2 in cardiac muscle and −3 mostly in hippocampal neurons) [25]. A huge number of proteins modulate Ca^{2+} efflux from the ER/SR, at MAMs, through interactions with IP3Rs. An emblematic example is represented by the sigma-1 receptor (S1R), a protein defined as a Ca^{2+}-sensitive chaperone that exerts a protective function in cells in various ways, including the modulation of MAMs Ca^{2+} signaling [26]. In 2020, a systematic review and metanalysis on S1R function in cardiac pathologies, ascribed to it cardioprotective roles by triggering the Akt-eNOS pathway and the modulation of intracellular Ca^{2+} signaling [26].

The ER Ca^{2+} content preserves the ability to regulate the channel opening. While being IP3 and Ca^{2+} essential for IP3R channel activation, other physiological ligands are not essential but can finely modulate channel Ca^{2+} sensitivity; for example, the IP3R modulation by ATP is biphasic. ATP micromolar concentrations exerts a stimulatory effect of IP3Rs while inhibits channel opening in the millimolar range [27]. Thanks to SR proximity to mitochondria, that juxtapose at a distance that can range from ~10 to ~25 nm [28], Ca^{2+} is taken up into mitochondria through VDACs. Established proteins involved in maintaining the structure of MAMs which guarantee a correct tethering between the two organelles are the Vesicle-associated membrane protein-associated protein B/C (VAPB)- Protein tyrosine phosphatase interacting protein 51 (PTPIP51) complex [29] and Mitofusins (Mfn1-Mfn2) complex.

Thanks to the growing evidence that is increasingly characterizing MAMs, it is becoming more and more evident that the SR-mitochondria

interfaces have a crucial role in Ca^{2+} homeostasis regulation and are fundamental for different functional outcomes, such as cell metabolism or induction of cell death [22].

Summarizing the route of Ca^{2+} waves, what happens following an action potential along the sarcolemma and the TT of each cardiomyocyte, is the Ca^{2+} flow from $Ca_{V1.2}$ to stimulate RyR2 at jSR (forming diads), in turn releasing the ion from the SR and, at the same time, the accumulation by SERCA2a. In this way Ca^{2+} transiently reside in the cytosol and finely regulates ECC.

1.3. Mitochondrial calcium entry

The mitochondrial Ca^{2+} uptake plays a pivotal role in fundamental cellular processes, it modulates the metabolism, the Ca^{2+} homeostasis, cell fate and autophagy [30].

Ca^{2+} transiently enters the mitochondrial matrix driven by the electronegative mitochondrial membrane potential (MMP), which favors the Ca^{2+} transit across the permeable outer mitochondrial membrane (OMM) and impermeable inner mitochondrial membrane (IMM) relying on the activity of selective channels [31]. In basal condition, the mitochondrial Ca^{2+} uptake is limited, it rapidly rises when the cytosolic Ca^{2+} concentration ($[Ca^{2+}]$) reaches orders of micromolar in close proximity to mitochondria. This is due to the dynamic apposition between the main intracellular Ca^{2+} stores, such as the SR, Golgi or lysosomes, and the mitochondria that permit to generate Ca^{2+} hot spots, microdomains of high $[Ca^{2+}]$ formed, for example at TT-SR and MAMs by which born the mitochondrial Ca^{2+} signals [32].

Ca^{2+} presumably across the OMM mediating an inert diffusion via VDAC. VDAC is the most abundant protein at the OMM, which also allows the exchange of ATP and ADP as well as electron transport chain (ETC) substrates pyruvate, malate, succinate, and NADH [33–35]. When open, the channel is typically anion-selective but becomes cation-selective when the channel assumes a half-open state, favoring the diffusion of Ca^{2+} and other cationic metabolites [36]. Three individual genes codify for the three mammalian isoforms of VDAC (VDAC1, −2 and −3), respectively. The three isoforms display similarities in both structure and function, but each VDAC isoform presents a tissue-specific expression pattern and plays a distinct role in mitochondrial processes, including metabolism or apoptosis. In general, VDAC1 and VDAC2 show a higher protein expression level than VDAC3 with exception in the testis [37]. Among the three isoforms, only VDAC2 is lethal in embryonic knockout model while VDAC1 and VDAC3 knockout mice present only bioenergetic defects and/or infertility [38–40]. All three isoforms are expressed in the heart.

To date, it is still unknown whether VDAC really plays an active role in Ca^{2+} regulation or it is only an inert Ca^{2+} diffusion pore. Tom40 could be a further candidate for the Ca^{2+}-transfer across the OMM. Component of the Translocase of Outer Membrane (TOM complex), this channel shows high cation selectivity, resulting a more favorable candidate for active Ca^{2+}-transport respect to the anion-selective VDAC [41]. VDAC is distributed at the level of SR-mitochondria contact sites and it is inserted in the multi-protein complex containing the ER-IP3R1 and the adaptor protein GRP75, responsible of SR-mitochondria Ca^{2+} microdomains [42]. Experiments performed in VDACs knockout cells showed that the IP3-induced Ca^{2+}-transfer to mitochondria was impaired while the overexpression of individual isoform increased the mitochondrial Ca^{2+} uptake, without affecting the number of SR-mitochondria contact sites [43]. These data indicate that VDAC is important for Ca^{2+} transfer to mitochondria because increase the permeability of OMM to Ca^{2+}. In particular, VDAC2 and VDAC3 had a slightly higher effect on mitochondrial Ca^{2+} uptake respect to VDAC1, being the last more anionic and thus less Ca^{2+} selective among the three isoforms [44]. Mediating immunoprecipitation assay it has been validated that VDAC1, but not VDAC2 or VDAC3, is responsible of Ca^{2+} transfer to mitochondria from lysosomes, via Transient Receptor Potential Mucolipin 1 (TRPML1) channel at the mitochondria-lysosomes contact sites [45]. All these data suggest that the distinct role of each isoform dependents by their differential regulation and interaction with specific protein partners. Only VDAC1 and VDAC3 seem to have high specificity for the skeletal muscle. Their influence the Ca^{2+}-transfer to mitochondria forming specific multiprotein complex with Ca^{2+} channels express in several organelles or binding cytosolic and/or OMM proteins, such as the cytosolic free dimeric tubulin and PD-associated protein a-synuclein or the OMM protein Translocator Protein 18 kDa (TSPO) [44,46,47].

The permeability of IMM to Ca^{2+} is more stringent, the Ca^{2+}-transport across this membrane is mediated by a highly Ca^{2+} selective channel, the mitochondrial calcium uptake (MCU) complex [48]. MCU complex is present in almost all mammalian tissues, it exists in a large multiprotein complex of ~500 kDa, composed by the pore forming MCU subunits (known as CCDC109A), the mitochondrial calcium uptake proteins MICU1, MICU2 and MICU3, the essential MCU regulator (EMRE) and additional partners, including the MCU dominant negative subunit, MCUb, and the MCU regulator, MCUR1 [30]. In these last years, it has been determined the structure of human MCU complex in presence or in absence of Ca^{2+}, using cryo-electron microscopy [48]. In presence of Ca^{2+}, the Ca^{2+} activated open state of the channel is compatible with a V-shaped MCU-EMRE subcomplex dimer that bridges a heterotetramer MICU1-MICU2 complex while in absence of Ca^{2+} the channel is inhibited by two MICU1-MICU2 dimers. In resting condition, a single heterodimer of MICU1-MICU2 is sufficient to gate an MCU-EMRE tetramer, where MICU1 shuts the mitochondrial Ca^{2+} uniport covering the aspartate ring on the MCU pore entrance of the MCU-EMRE subcomplex. Upon Ca^{2+} increase, the ion binds the MICU1-MICU2 heterodimer promoting a conformational change that weaken the interactions between MICU1 and MCU, leading to Ca^{2+}-activation state of the uniporter. The heterodimer MICU1-MICU2 appears to be more stable in absence of Ca^{2+}, but upon Ca^{2+} elevation, the heterodimer MICU1-MICU2 further dimerizes to form the heterotetramer mediating Ca^{2+} binding and stabilization of MICU2 [49]. The MCU complex activity is regulated by intracellular Ca^{2+} concentration, as described until now, but it may be also influenced by the levels of Ca^{2+} into the mitochondrial matrix [50]. The mitochondrial Ca^{2+} concentration ($[Ca^{2+}]_m$) influences the MCU Ca^{2+} current in a biphasic manner, where the minimum MCU Ca^{2+} current is about 400 nM, which constitutes the point of "maximal suppression" while the minimal point is at normal resting (about 100 nM), and that this point changes when is altered the composition of MCU complex, suggesting that exist a coupled of Ca^{2+} regulatory mechanism that act at level of intermembrane space and matrix, respectively.

MCU complex features depend on the tissue, in fact recent findings showed that the number of Ca^{2+} activate open MCU channels is regulated by intracellular Ca^{2+} concentration in skeletal muscle but not in the heart, indicating that the MCU complex presents a functional diversity specific for the different tissues [51]. Indispensable for MCU complex Ca^{2+} transport is the contribution of the EMRE binding to MCU [52]. The interaction between EMRE and MICU1 helps to shut MCU pore in absence of Ca^{2+}, and upon Ca^{2+} elevation prevents the dissociation of MICU1 from the subcomplex [48]. To maximize the uniporter's exposure to intracellular Ca^{2+} hot spots, the uniporter can dimerize, favoring its distribution towards IMM and OMM contact sites. This spatial arrangement should facilitate the effective inter-organelle Ca^{2+} transfer [48].

1.4. Mitochondrial calcium efflux

The recovery of Ca^{2+} homeostasis into mitochondrial matrix is guarantee by efficient Ca^{2+}-efflux pathway, which the molecular identification is occurred only in the last decade and albeit still open to further investigations. Findings demonstrated that PM NCX isoforms are also expressed on mitochondria where contribute to Ca^{2+} and Na^{+} handling [53]. In mammalian exist three NCX isoforms, named NCX1, NCX2 and NCX3, differently redistributed in the tissues. NCX1 is a

ubiquitous isoform while NCX2 is mainly expressed in the brain and NCX3 is essentially found in skeletal muscles and brain [54].

Their catalyze the bidirectional and rheogenic exchange of three Na^+ and one Ca^{2+} ions across the membranes, primarily working in forward mode, where their operate the Ca^{2+}-efflux from matrix and Na^+-influx from cytosol [55]. When the membrane potential changes and/or the mitochondrial Na^+ or Ca^{2+} concentration is altered, the NCX activity may change direction, operating in reverse mode, where the Ca^{2+} is imported to mitochondria while Na^+ is extruded.

The first evidence that documented the existence of a mitochondrial Na^+-dependent Ca^{2+} efflux was published in the 1974, where Carafoli et al. showed that Na^+ and Li^+, but not K^+, Mg^{2+} and Rb^+, were able to evoke an efficient mitochondrial Ca^{2+} release in isolated cardiac mitochondria [56,57]. In the years findings have continuously supported that PM NCX isoforms localized also within mitochondria, contributing to mitochondrial Ca^{2+} handling in different cell types [58]. The pioneering Carafoli's findings was supported by Garlid et al. that in the 1992 identified an additional mitochondrial Ca^{2+} efflux system in heart beef mitochondria, a 110 kDa Na^+/Ca^{2+} antiporter, successively identified as $Na^+/Ca^{2+}/Li^+$ exchanger (NCLX) [59,60]. Encoded by Slc8b1, NCLX is expressed at the IMM and catalyzes Li^+/Ca^{2+} exchange as well as Na^+/Ca^{2+} exchange at similar rate, transporting Ca^{2+} outside the matrix [59,61]. The two identified mitochondrial Ca^{2+} efflux systems may cooperate in the Ca^{2+} handling, both expressed within IMM, there can form hetero or homomeric complexes. Modulating the activity or expression of one exchanger is possible to interfere with the activity of the other [62]. These exchangers exhibit similar distinctive features, including the ionic regulation of their activity, potentiated by K^+, their activity is inhibited by Ni^{2+}, Mg^{2+}, Ba^{2+} and La^{3+} [63–65]. Also, the H^+ can significantly regulate the activity of both exchangers [66,67]. Structurally, both have two transmembrane hydrophobic regions separated by a hydrophilic loop, in which are contained the catalytic regions involved in ions transport [68,69]. Differences are emerged in lipid and kinases regulation, where lipid molecules may affect function and localization of NCX but it not clear whether the same effects are addressed to NCLX; or about Protein Kinase A (PKA) that typically stimulates NCLX activity while for NCX activity the effects are controversial [66,70,71]. A peculiar difference between NCX and NCLX is due to variations in ion-coordinating regions involved in exchange activity. NCX is allosterically regulated by Ca^{2+} mediating the binding with Calcium Binding Domain (CBD) 1 and CBD2 while in NCLX seems lack the CBD domains and the Ca^{2+} ion should act as an indirect modulator [66]. Future findings will aim to perform the molecular characterization of these exchangers, shedding light on the real scenario of mitochondrial Ca^{2+}-efflux that involves the tandem, NCX and NCLX, in Ca^{2+} handling.

Taken together, all these systems that allow Ca^{2+} to enter and escape from the cell constitute an essential toolkit for the maintenance of Ca^{2+} homeostasis (Fig. 1) and their perturbation often leads to imbalances and various pathologies.

2. Calcium dysregulations in cardiac diseases

2.1. The importance of the calcium cycling and the bioenergetics in the heart

The heart is one of the highest energy-demanding organs as it beats continuously throughout the entire course of a lifetime and heavily reliant on mitochondria which provide the most energy to the heart [72]. This is evident as mitochondria occupy ~30% of the cardiomyocyte's volume and supply > 90% of the ATP required for cardiac contraction [73]. In addition, they are suited close proximity Ca^{2+} release, such as SR and SERCA2a pumps which actually requires an adequate ATP/ADP ratio in the cytoplasm [74]. Thus, the coupling of Ca^{2+} dynamics with mitochondrial bioenergetic is crucial for the functioning of cardiomyocytes both in health and disease conditions. The cardiac contraction (systole) is activated by an intracellular Ca^{2+} transient ($[Ca^{2+}]_i$) which triggers cross bridge cycling (binding of the protein complex to actin-binding sites followed by myosin head to bridge the gap) under load and ATP consumption by the myosin ATPases. Ca^{2+}, by traveling across the sarcolemma, TT, SR and cytosol, is thus an

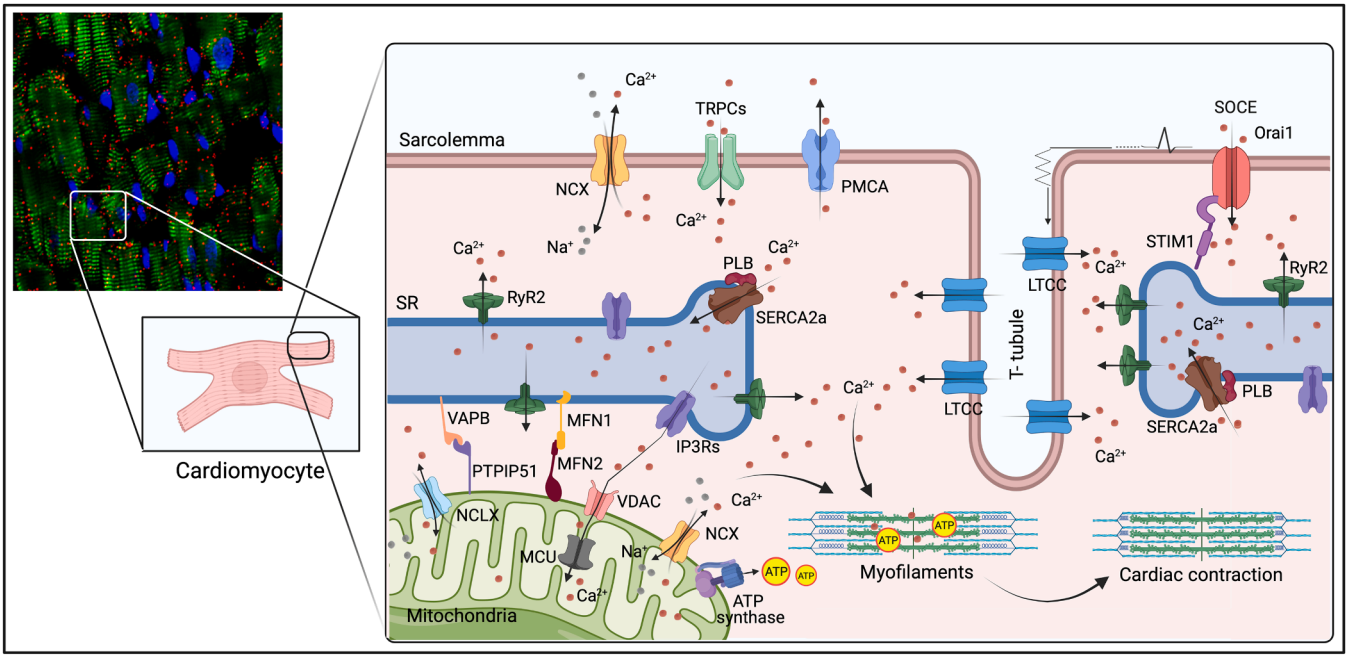

Fig. 1. Calcium cycling and calcium handling in the heart. The figure depicts all channels, pumps and exchangers involved in cardiomyocyte calcium homeostasis. On the left, a transversal section of cardiac tissue was imaged in confocal microscopy which highlights in green the sarcomeric alpha actin, in blue the nuclei and in red the ATP synthase dimers. On the right, three "levels" of calcium regulation are showed: the sarcolemma and TT with NCX, TRPCs, PMCA, Orai1 and LTCCs; the SR with SERCA2a, RyRs and IP3Rs; the mitochondrial level with VDAC, MCU complex, NCX and NCLX. Calcium fluxes coupled with ATP consumption transduce electrical impulses in mechanical force to establish the ECC.

excellent signal for the cell to control contractile behavior of the heart. Also, it can enter the mitochondrial matrix and influence the behavior of key enzymes. Studies have shown that $[Ca^{2+}]_m$ is known to exert a complex activation of several dehydrogenases of tricarboxylic acid (TCA) cycle indirectly, increasing membrane potential [75,76] and to directly drive ATP production through an ATP synthase inhibitory factor, termed Ca^{2+} binding inhibitor which has been described to dissociate into monomers upon Ca^{2+} binding, leading to the activation of the ATP synthase [77]. Thus, rises in mitochondrial matrix Ca^{2+} regulates the respiration capacity [78]. A series of studies demonstrated Ca^{2+} sensitivities of the proteins and complexes associated with the ETC. Studies on skeletal muscle show the dose-response effect of Ca^{2+} sensitivity for all three proton pumps (Complexes I, III, and IV) in the ETC [79]. In addition to potentially regulating the ETC proton pumps, the effects of Ca^{2+} on oxidative phosphorylation were investigated in isolated porcine heart. Ca^{2+} has been indicated to critically regulate the F_1F_0 ATP synthase through increased ATP production and adenylate translocase activity [80]. One novel protein, S100A1, a Ca^{2+} sensing protein of the EF-hand family and its interaction with mitochondrial F_1-ATPase, found to affect F_1-ATPase activity and cellular ATP production. In particular, cardiomyocytes that overexpress S100A1 exhibited a higher ATP content than control cells, whereas knockdown of S100A1 expression decreased ATP levels. Consistently, ATP synthase activity is reduced in cardiomyocytes from S100A1 knockout mice [81]. Furthermore, $[Ca^{2+}]_c$ fluctuations are relayed to the mitochondria by MCU, closely coupling cytoplasm's Ca^{2+} dynamic to the cells energetic demands [82]. Moreover, the selection of energetic substrates in cardiomyocytes is a fundamental and fatty acids (FA) are known to be the main source of energy when the heart is at rest and during fasting periods. Most of the acetyl CoA that enters the TCA cycle comes from the β-oxidation of free FA within the mitochondria. Furthermore, Ca^{2+} activation of TCA cycle dehydrogenases controls NADH production, which in turn influences cellular detoxification (anti-oxidant) capacity and mitochondrial reactive oxygen species (ROS) production. In relation to energy production, ROS signaling triggers mitochondrial matrix Ca^{2+} sparks which also include MCU and NCX [83].

During diastole, to reach an optimal muscle relaxation, $[Ca^{2+}]_i$ should be removed and should return to resting levels. In this, proteins involved in Ca^{2+} removal from the cytosol are of fundamental importance and include in order of importance SERCA2a (ATP-dependent), NCX and PMCA (ATP-dependent) (Fig. 1).

2.2. Calcium dysregulation in myocardial infarction

Myocardial Infarction (MI) is responsible for over 15% of mortality each year. The etiologies leading to the partial or complete block of the coronary circulation are manifold but they share the presence of common pathophysiological evolving features: the myocardial ischemia and the reperfusion injury (RI) [84,85].

Indeed, the occlusion of coronary vessels determines the arrest of either whole or partial blood flow to the heart inducing the ischemic condition, an imbalance of the ratio between oxygen demand and supply. After a brief period of ischemia (about 15–20 s), the only energy source of the heart becomes the anaerobic glycolysis. The limited amount of ATP produced by this process is not sufficient to satisfy the elevated ATP demand of the cardiac tissue [86]. Therefore, cardiomyocytes which do not adapt, die. The first line of clinical and mechanical intervention against ischemia is reperfusion, in which an early and fast restoration of the blood flow is induced [87]. However, this second phase can aggravate the damage of cardiac tissue, worsening the patient's condition as consequence [88]. During reperfusion, the oxidative phosphorylation of mitochondria reaches levels comparable to the pre-ischemic condition within seconds, meanwhile the myocardium does not reacquire the normal contractile functions immediately [89]. This postischemic condition is named stunned myocardium, in which the excessive H^+ accumulated during the aerobic glycolysis in the ischemic attack is transported outside the cardiac cell.

One of the most known Ca^{2+} dysregulated mechanisms in MI is the progressive intracellular Ca^{2+} overload priming during ischemia, and increasing with a more extent during the reperfusion phase [90]. In ischemia, to normalize the intracellular pH that has become acid, H^+ is inefficiently exchanged with Na^+ through the H^+/Na^+ exchanger (HNX). Again, intracellular Na^+ increases as the Na^+/K^+ is inhibited in the absence of ATP; the bidirectional NCX at the sarcolemma is active, but works in reverse mode causing cytosolic Ca^{2+} overload. At reperfusion, the sudden nutrient availability and oxygen restore the oxidative phosphorylation causing a burst in ROS generation and further Ca^{2+} accumulation due to the recovering of MMP.

Oxidative stress exacerbate Ca^{2+} fluxes by the hyperactivation of the opening of the RYR2 channels inducing Ca^{2+} leak from SR [91]. This pattern is dependent on the oxidation status of the RyR2 channel, this state would regulate the release threshold of Ca^{2+} [91]. Ca^{2+} released from the SR accumulates into the cytosol where can activate phospholipase A and protein kinase C, which mediate the destruction of cell membrane, with consequent release of toxic substance such as prostaglandins, ROS and leukotrienes. Additionally, $[Ca^{2+}]_c$ increase activates calpains, endonucleases, kinases and caspases, potentiating the activation of cell death events [90]. Among them, a particular role has been assigned for the CaM kinase type II (CaMKII) family. Indeed, it has been demonstrated that an increase in $[Ca^{2+}]_i$ may activate the isoform C, which is responsible to phosphorylate proteins of the apoptotic cascade [92] and those from which depend Ca^{2+} homeostasis and pathological consequences of MI (i.e., tissue remodeling, fibrosis, arrhythmia). An example is given by the impairment of the functioning of RyR2 channels, thereby provoking Ca^{2+} leakage from the SR that can contribute to cardiomyocyte contractile dysfunction and apoptosis [92]. At the same time, also the isoform B may be activated by Ca^{2+} overload. In this case, CaMKIIδB is responsible for maladaptive changes of the heart after MI, like hypertrophy that can lead to heart failure (HF) [93].

Intracellular Ca^{2+} during reperfusion also accumulates in the mitochondrial compartment via MCU. Consequently, mitochondria are subjected to an overload of Ca^{2+} that results in mPTP opening, mitochondrial dysfunctions and cardiomyocyte death [94,95].

Indeed, it has been investigated that up-regulation of MCU promotes downregulation of mitochondrial functioning and activation of apoptotic process throughout activation of the Ca^{2+}-dependent thiol-protease family calpains that, in turn, alter the functioning of the Optic Atrophy Protein 1 (OPA1), a master regulator of mitochondrial fusion [96]. Consistently, downregulation of expression of OPA1 was found in both humans with coronary disease and rat model of HF [97], and mice harboring $OPA^{delTTAG}$ mutations showed altered Ca^{2+} dynamics and increased infarct size than WT littermates [98]. In detail, cardiomyocytes from left ventricle with OPA1 deletion showed lower amplitude of Ca^{2+} transients, decreased SR Ca^{2+} uptake, increased cytosolic Ca^{2+} removal by NCX and impaired mitochondrial Ca^{2+} uptake. This has significant repercussion on the heart which results more sensitive to I/R and the number of the arrhythmias occurrence. Furthermore, genetic overexpression of OPA1 as well as the genetic ablation of its protease, OMA1, exert cardioprotective effects in in vivo ischemia reperfusion (I/R) model [99]. In contrast to OPA1, genetic ablation of mitofusins (MFNs), other regulator of mitochondrial fusion, have been shown to protective against I/R [100]. These unexpected effects may be explained by the fact that MFNs have pleiotropic non-fusion effects, including the preservation of ER/SR-mitochondria juxtaposition, which are fundamental for the Ca^{2+} transfer into mitochondria. Indeed, the ablation of MFNs reduced the proximity of mitochondria and SR protected from Ca^{2+} overload during I/R [100], thereby suggesting a close relationship between SR-mitochondria Ca^{2+} homeostasis and mitochondrial dynamics during I/R (Fig. 2).

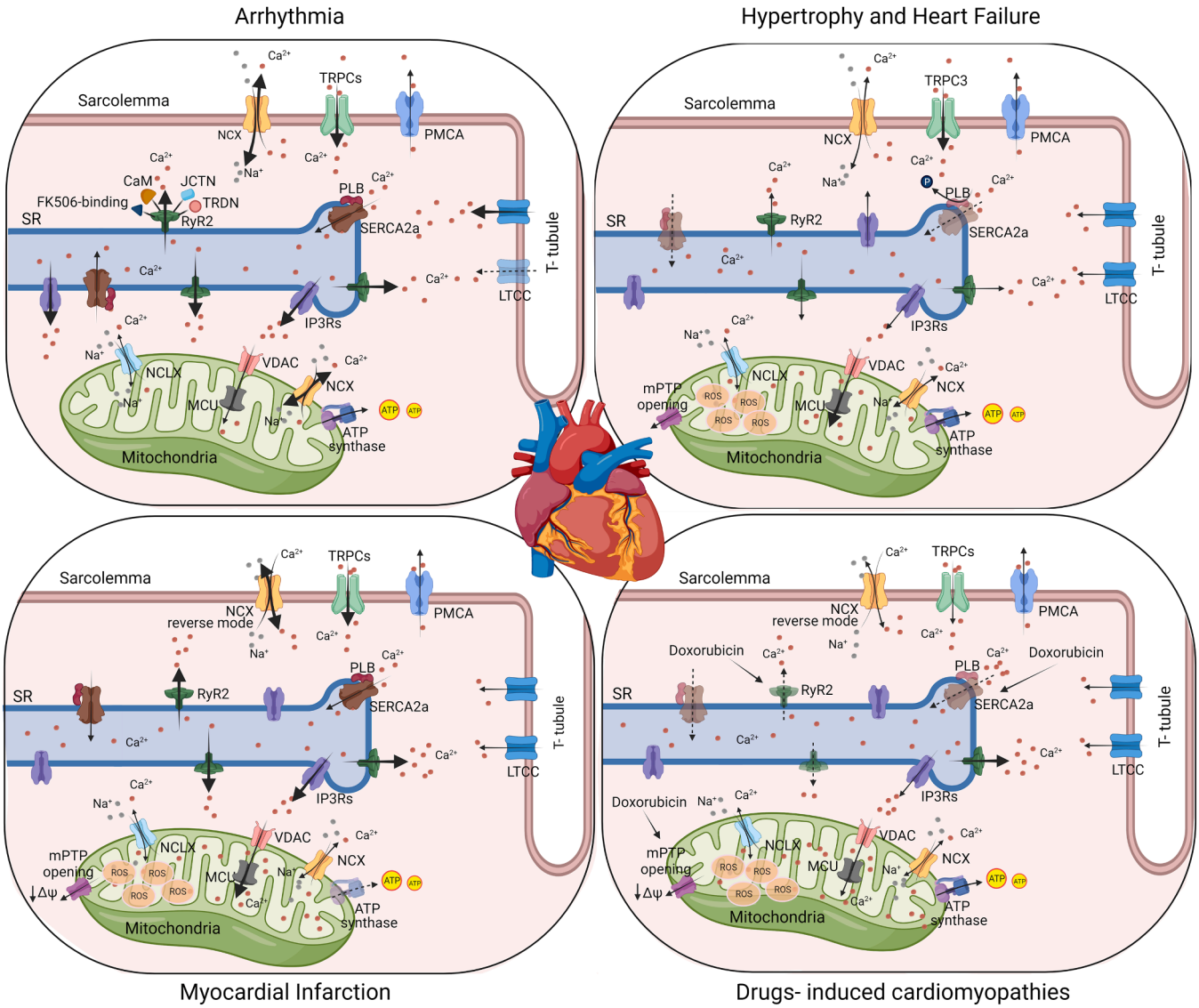

Fig. 2. Calcium dysregulation in cardiac diseases. The figure summarizes the main mechanisms known about calcium dysregulation occurring in cardiomyocytes in pathologies. From the diseased heart in the middle, four schematic views resume chapter 2 reviewed in the text. Clockwise, the first panel highlights the excessive propagation of action potentials derived by NCX and LTCCs and spontaneous Ca^{2+} increases in the cytosol arising from the Ca^{2+}-induced Ca^{2+}-release from SR. In the second, defects in SERCA2a expression or impaired function trigger increased and static intracellular calcium transients in heart failure. The third shows the significant cytosolic and mitochondrial calcium overload leading to mPTP opening and cell death following I/R. The last picture summarizes the increased susceptibility to calcium-dependent mPTP opening and an altered Ca^{2+} transport, the inhibition of RyR2 and SERCA2a activities by a direct interaction of doxorubicin with the channels, downregulation of SERCA2a and other proteins resident at the SR and a significant increase of calcium into the cytosol due to excessive RyR2 release.

2.3. Calcium dysregulation in Arrhythmia

The regular heart contraction is permitted by a process in which the electrical activation (excitation) is converted into mechanical force (contraction) [101]. Ca^{2+} is an indispensable element for each ECC event. Substantially, arrhythmia (AT) is an irregular heartbeat; this pathological condition is caused by several factors, but in the middle lie the dysregulation of Ca^{2+} homeostasis. Although there are different methods to categorize ATs, we will refer to those related to ventricles because they are more lethal and differentiated by the mechanism of action in: reentry, triggered activity and automaticity [102].

Reentry ATs identifies cardiac area characterized by re-excitation after the initial depolarization event. They can be the consequence of predisposing genetic factors or can happen after cardiac remodeling that cause impaired refractoriness and conduction, thereby provoking the reentry event. Abnormal intracellular increase as well an enhanced SR Ca^{2+} release are fundamental factors to elicit ATs reentry.

Indeed, LTCCs downregulation induces shortening of the action potential duration, provoking reentry [103]. An opposite effect is obtained when small-conductance Ca^{2+}-dependent K^+ channels (SKc) are inhibited. SKc are sensitive to submicromolar [Ca^{2+}] and play a role in atrial repolarization. It has been demonstrated that by using the specific SKc inhibitor, NS8593, canine ATs may be reduced [104]. However, a subsequent study performed in adult rat ventricular myocytes demonstrated not only that SR Ca^{2+} release is also determinant in SKc activation, but it suggests that SK up-regulation may have anti-arrhythmic effect [105].

Triggered activity are caused by early (E) or delayed (D) afterdepolarization (AD) events, which occur before and after full repolarization, respectively. DAD is mainly caused by spontaneous excessive Ca^{2+} increases arising from the Ca^{2+}-induced Ca^{2+}-release from SR, which activates the NCX. These spontaneous Ca^{2+} movements are the result of Ca^{2+} hot spots, which accumulate near Ca^{2+} releasing sites [106–108]. EAD are generally provoked by an excessive propagation of

action potentials derived by NCX and LTCCs and by Na^+ and K^+ currents, which permit Ca^{2+} to enter [109,110]. Furthermore, EAD are also associated with an excessive phosphorylation activity of CaMKII and an over activation of LTCCs, thus accelerating the recovery after their shutdown [111].

Automaticity consists of spontaneous depolarizations during the diastolic phase.

At demonstration that intracellular Ca^{2+} handling can affect different cardiac ATs, mutations in genes encoding Ca^{2+} transporters, channels and regulatory proteins have been discovered in different inherited ATs syndromes. For example, catecholaminergic polymorphic ventricular tachycardia (CPVT), one of the most-deadly arrhythmias known, manifests mutations in RyR2 [112,113]. These mutations cause in increased SR Ca^{2+} leak, thereby causing frequent Ca^{2+} releasing events that activate NCX and, finally, induce ventricular ATs [114] (Fig. 2). Mutations were also found for CaM. In this case, the mutations impair the Ca^{2+} binding of CaM and result in a compromised interaction between the protein and RyR2 [115]. Since RyR2 exists as a macromolecular complex and interacts with other members including CaM, FK506-binding protein-12.6 (FKBP12.6 or Calstabin2), junctin (JCTN) and triadin (TRDN) [116], also the onset of mutations in each of these components, such as TRDN [117] carry out ATs phenotypes. All mutational profiles are already reviewed in [118].

Lastly, also TRPC proteins take part in Ca^{2+} dysregulation-mediated ATs; they have been reported as overexpressed in patients affected by atrial fibrillation, especially the first and third isoform [119], they also may contribute to DAD events [120].

2.4. Calcium dysregulation in hypertrophy and heart failure

Cardiac hypertrophy (CH) is the process of heart remodeling in response to either increased workload (i.e., intended as physiological adaptation following chronic and sustained physical exercise or during pregnancy) or pressure overload (i.e., as consequence of hypertension and valvular diseases [121]). Macroscopically, physiologic CH differs from pathological hypertrophy because it induces changes that are reversible, and which involves also the ventricular chamber enlargement besides the walls thickness. Moreover, the cardiac structure remains normal and cardiac function is enhanced. From a molecular point of view, several pathways regulate CH and they, in part, differ between physiology and pathology as reviewed in [122]. Also, CH in pregnancy significantly differ from that occurs after exercise due to hormones contribution [123]. Regarding Ca^{2+} signaling, in physiologic CH there is an adaptation signaling pathway aimed to sustain enhanced cardiac function and workload; indeed, $[Ca^{2+}]_i$ are increased and SR Ca^{2+} uptake optimized [124]. A concomitant upregulation of RyR2 and SERCA2 proteins are reported in the mild and adaptative stages of CH.

Otherwise, physiologic CH can result in a diseased phenotype where the intracellular Ca^{2+} overload is reported to be involved in this transition; increased and prolonged $[Ca^{2+}]_i$ lead to the activation of pro-hypertrophic factors which, in turn, further stimulate CH. In this scenario, CaM and calcineurin are the mainly involved Ca^{2+} signaling proteins and once they become activated, they trigger NFAT nuclear translocation and its activation [125,126]. Also their expression is reported to increase in CH pathological states [126–128]. These changes in Ca^{2+} homeostasis due to Ca^{2+} overload are responsible for mitochondrial dysfunctions, anomalies in cardiac contraction and cellular damage. In turn, developed pathologic CH supports VEGF secretion through mechanical stretch and in a NFkB-dependent manner [129].

After chronic insults, deep changes in thickness and elasticity of the walls of the heart degenerate in HF, a condition in which the heart fails to efficiently pump the blood to the systemic circulation. Indeed, CH is the main risk factor for HF and for these reasons they share also several similarities in terms of molecular pathways become impaired. In the literature are reported several dysregulations of Ca^{2+} signaling accompanying this process of maladaptation: they refer to several proteins involved and mainly focused on the impaired Ca^{2+} sequestration by SR.

The diastolic dysfunction and the correlated disturbance in ventricle relaxation are one aspect that characterize some types of HF [130]. As mentioned in the introductive paragraphs, the diastole phase which is responsible for a correct ventricle filling [131], is guaranteed by a rapid reduction of cytosolic Ca^{2+} channeled in the SR of the cardiomyocyte. In CH and HF this does not occur; the most accredited hypothesis is that reduced levels of SERCA2a and not functional ATPase activity of the remaining expressed protein, impair the correct Ca^{2+} homeostasis with consequent increased stasis of $[Ca^{2+}]_i$. Indeed, in failing hearts, severe metabolic derangements occur [72] and these prompt a real energy crisis. Since the functioning of some proteins involved in Ca^{2+} homeostasis is ATP-dependent, their activity result to be impaired and the contractile heart function as well. The decline of the respiratory chain function and ATP depletion prevent the above mentioned Ca^{2+} removal from the cytosol which is essential in diastole for muscle relaxation before the next heartbeat [132]. A similar scenario is caused by the impaired action of PMCA and actomyosin, the other two ATP consuming proteins. It follows the absence of transients and a diminished contractility of the heart [133,134].

Nevertheless, other mechanistic insights are suggested in the literature. From the analysis of tissues of failing myocardium, it emerged a key role for an interactor of SERCA2a, phospholamban (PLB). PLB has the peculiarity to inhibit the Ca^{2+} transport trough the pump by decreasing its affinity for the bivalent ion when it is dephosphorylated. On the contrary, when PLB is phosphorylated, it allows Ca^{2+} spread. In failing hearts, the phosphorylation status of PLB is significantly reduced as the kinetics of SERCA2a Ca^{2+} transport [135,136]. At the center of this regulatory pathway, the Serine (Ser) 16 and Threonine (Thr) 17, both phosphorylated by PKA and by CaMKII, respectively [137].

Further investigations on genetic profile in humans predisposing to HF phenotype, highlighted the importance of the mutational profile of PLB in the inhibition of SERCA2a and thus in adverse events accompanying HF. The most known are two missense variations R9C and the R14del [138,139]. The first one is able to block the PKA-mediated phosphorylation of the wild type PLB; the second one consisting in the deletion of arginine 14 on PLB failed the interaction PLB-SERCA2a. An additional mutation Leu39stop, identified in humans with a hereditary form of HF, entails severe HF with consequent need of heart transplant in young age when expressed in homozygosity [140]. If expressed in heterozygosity, signs of CH have been described. Here, low levels of PLB expressed were redirected to the PM causing Ca^{2+} dysregulation.

Histidine-rich calcium (HRC) binding protein is recognized as an additional negative regulator of SR Ca^{2+} uptake interacting with SERCA2a. This 170 kDa protein is able to localize at SR thanks to its amino-terminal domain, while an histidine-rich sequence is supposed to have Ca^{2+} binding properties although there isn't a real Ca^{2+} binding motif [141,142]. Its overexpression in the heart is reported to decrease Ca^{2+} uptake into SR with consequent impairment of muscle relaxation and contractility [143].

Restoring $[Ca^{2+}]_i$ for a correct ECC depends in a lower percentage also by NCX. However, literature investigating its expression in tissues from failing hearts, reported controversial results. On one hand, an increased expression seems act as compensatory mechanism to help the cardiac contractility during HF, but it inevitably results in Na^+ overload [144]; on the other hand, no appreciable differences have been detected in similar experiments [145].

In a scenario where $[Ca^{2+}]_i$ are increased and static and that SR is unable to accumulate Ca^{2+}, mitochondria may be in the position to buffer Ca^{2+} and suffer from these oscillations [146]. Indeed, Ca^{2+} overload prompts mPTP opening together to oxidative stress inducing apoptosis and cardiomyocytes loss [147] (Fig. 2).

Increased activity of TRPCs is reported to additionally contribute to CH and its remodeling. They are able to inward great amount of Ca^{2+} inside cells and stimulate hypertrophy and fibrosis via the calcineurin-NFAT axis [148–150]. TRPC3 in particular, mediates CH also by

modulating $Ca_{V1.2}$ activity and the reverse mode of action of NCX resulting in more Ca^{2+} entry [151].

2.5. Calcium dysregulation in drug-induced cardiomyopathies

In agreement with Elliot's classification established in 2008 [152], cardiomyopathies (CMs) are classified in dilated (DCM), hypertrophic (HCM), restrictive (RCM), arrhythmogenic (ACM) and those remained unclassified. It is clear CMs consist of a heterogenous group of disorders joined together by an improper functionality of the heart due to ultrastructural abnormalities. Despite some criteria in their classification have changed during last years, our priority is not the discussion of what differences exist among them but what types of Ca^{2+} signaling dysregulation occur and contribute to the maladapted phenotype of drug-induced CMs.

Indeed, it is known that CMs may be the side effect of chronic assumption of some classes of drugs and unhealthy lifestyle which cause a progressive and prolonged state of cardiotoxicity. Drug-induced CMs are potentially reversible but in most cases leads to HF.

Unhealthy lifestyle, like the abuse of alcohol consumption, may induce adverse effects in the adult heart and it is considered a risk factor for CMs also in women during pregnancy. To unveil Ca^{2+} dysregulation, alcohol-dependent cardiac toxic effects have been studied in culture with cardiomyocytes treated with ethanol [153]. In the study, 69% of Ca^{2+} transients analyzed in cardiomyocytes treated with ethanol were abnormal. As cause of this phenotype, a deep change of protein expression profile has been observed; among the interested proteins, Annexin 6 was downregulated by 40% and ATP1A2 by 29% [153]. Both proteins are involved in Ca^{2+} transport: the first one modulating Ca^{2+} influx through the LTCCs and its release from SR by RyR2 and NCX [154]; the second protein is part of the Na^{+} pump that can regulate intracellular Ca^{2+} and muscle contractility [155].

A problem currently considered of great importance is the cardiotoxicity of some classes of drugs in the long-term treatment of oncologic patients, such as anthracyclines. A general consensus is their use in therapy despite they are responsible for progressive accumulation of several mitochondrial dysfunctions [156], mostly mediated by a strong oxidant action. Although in principle they are potentially reversible changes, often they concur to the onset of severe CMs.

An example of cardiotoxicity from anthracyclines is given by doxorubicin. Patients experiencing chronic exposure to doxorubicin show the following dysregulations regarding Ca^{2+} signaling: i) increased susceptibility to Ca^{2+}-dependent mPTP opening and an altered Ca^{2+} transport: these effects are dose-dependent [157]; ii) inhibition of RyR2 and SERCA2a activities by a direct interaction of doxorubicin with the channels: this action is oxidative stress-mediated and already in the nanomolar range has a deleterious effect [158]; iii) ROS- and Mitogen Activated Protein Kinase (MAPK) axis- mediated downregulation of SERCA2a mRNA in hearts treated with doxorubicin [159]; iv) a large-scale mRNA downregulation of Ca^{2+}-dependent proteins resident at SR, not only limited to SERCA2a but also including RyR2, PLB and CSQ have been found in a rabbit model of doxorubicin-induced CM [160] and v) $[Ca^{2+}]$ increase into the cytosol due to excessive RyR2 release [161]. All these changes prompt a sever Ca^{2+} homeostasis perturbation inside cells which are related in concurring several clinical symptoms, cell death (Fig. 2) [162].

Other links between drug-induced CMs and Ca^{2+} dysregulation are described also for other drugs such as arsenic trioxide [163], mitoxantrone [164], abuse of cocaine [165], methamphetamine [166], despite mechanistic insights are not completely addressed.

2.6. References to the calcium-mediated PTPC

One of the best-characterized effectors of Ca^{2+}-mediated cardiac stress is the mPTP. This is a supramolecular entity assembled at the interface between the inner and outer mitochondrial membrane responsible for abrupt increase of permeability of the inner mitochondrial membrane, also known as mitochondrial permeability transition (MPT). In response to high $[Ca^{2+}]_m$, mPTP opens allowing the deregulated exchange of small solutes (up to 1.5 kDa) between the mitochondrial matrix and cytosol, along their electrochemical gradients. The mPTP is believed to open with 2 different configurations: one at low conductance, believed to operate mostly in physiological conditions to allow the equilibration of Ca^{2+}, mitochondrial pH and ROS; the second at high conductance, which causes immediate and complete dissipation of the $\Delta\Psi_m$, osmotic swelling of the mitochondrial matrix and inhibition of oxidative phosphorylation [167]. When a few mitochondria undergone MPT do not cause major cellular alterations [168] because they can be efficiently removed by the autophagy machinery and are proposed to participate in cell physiology (for a further discussion see [169]). On opposite, widespread MPT initiates cell death via regulated necrosis or apoptosis [170]. Regulated necrosis is characterized by MPT-mediated block of mitochondrial energy production with the consequent arrest of its dependent activities [171]. Conversely, MPT-driven apoptosis mainly depends on the release of mitochondrial intermembrane proteins, especially cytochrome c, apoptosis-inducing factor, mitochondrion-associated, 1 (AIFM1, best known as AIF), and diablo, an IAP-binding mitochondrial protein (DIABLO, also known as Smac) [172].

A role for mPTP has been demonstrated in several cardiac conditions, foremost reperfusion injury [94]. The most accepted model is that during cardiac ischemia mitochondria uptake Ca^{2+} and produces ROS (a strong sensitizer of mPTP) but MPT is blocked by the simultaneous accumulation of mPTP endogenous inhibitors as ADP and acidic matrix pH. At the reperfusion phase, the re-flow of oxygen favors a ROS burst and a mild restoration of pH and ADP levels which ultimately cause the massive opening of mPTP. Thanks to the identification of cyclosporine A (CsA) as a strong inhibitor of MPT, this mechanism has been proven as responsible for most of the necrotic area (and possibly a large fraction of apoptosis) in the myocardia undergoing reperfusion injury [95].

Pieces of evidence link mPTP also to reperfusion induced arrhythmia. Exposure to the mitochondrial uncoupler FCCP induces arrythmias in explanted mouse hearths. FCCP causes dissipation of mitochondrial membrane potential which in turns favors the opening of the mPTP. It results the inability of IMM to hold a Ca^{2+} gradient between mitochondrial matrix and cytosol. The alteration of $[Ca^{2+}]_c$ in response to FCCP is believed a major determinant in FCCP-induced arrythmias. Genetic inhibition of mPTP (via deletion of the gene *Ppif* coding for Cyclophilin D, CypD, the target of CsA) results in significant resistance of explanted hearth to the insurgence of arrythmias [173]. Contrasting investigation have tested the pharmacological inhibition of mPTP by CsA on reperfusion induced arrhythmias on different animal models. Arteaga and co-workers originally reported a significant effect of CsA on rat heart which were not confirmed by other investigation in rat [174] guinea pig [175] and rabbit [176]. Overall, these piece of evidence calls for additional investigation, tough should be noted that obtaining and experimental design able to discriminated the impact of mPTP in reperfusion damage or reperfusion-induced arrythmia is challenging.

A similar mechanism is proposed for drug-induced cardiotoxicity. Compounds as doxorubicin [177,178], naproxen, diclofenac, celecoxib [179] and sorafenib [180] are proposed to elevate ROS production and affect Ca^{2+} homeostasis in cardiomyocytes, ultimately leading to mPTP opening and cell death. The exposure to mPTP inhibitors (as CsA) or antioxidants have been indeed shown to protect against drug-induced cardiotoxicity in different animal models. The MPT is also proposed to play a role in the necrotic cell death that is present in chronic HF. Cardiomyocytes isolated from dogs with chronic HF displayed increased opening of the mPTP, decreased mitochondrial membrane potential, and decreased mitochondrial cytochrome c oxidase and respiration. All the mitochondrial phenotypes were reverted by the administration of CsA [181,182].

However, a mechanism for mPTP opening in HF is not clear.

Tamoxifen-dependent conditional deletion of the mitochondrial NCX cause the rapid onset on CH and HF in mouse heart by causing excessive accumulation of mitochondrial Ca^{2+} and mPTP opening [183]. In addition, the mitochondrial NAD^{+}-dependent deacetylase SIRT3, was demonstrated to target CypD - thus exerting a regulatory activity on mPTP and prevents age-related CH [184]. Despite this evidence, mice knock out for *Ppif* displayed propensity in develop HF, CH, fibrosis, and reduction in myocardial function in response to pressure overload stimulation [185]. This phenotype is proposed to be mediated by a chronic remodeling of energy metabolism (possibly mediated by mPTP) rather than a direct regulation of cell death.

3. Approaches to correct calcium dysregulation: potentially many targets in cardiac diseases

Since the 90 s, it is becoming increasingly clear that targeting intracellular Ca^{2+} can be a valid strategy for the treatment of several diseases, including in the heart. The knowledge of the previous mentioned studies has led to the development of regulators, more or less selective, of exchangers, pumps and channels with the aim to revert the pathologic phenotype and clinical symptoms of most cardiac diseases (Table 1). Moreover, the recent identification of the genetic component of the mitochondrial uniporter and other mechanistic insights about Ca^{2+} cycling allowed the better understanding the biological roles of Ca^{2+} regulation and to create more selective molecules that regulate its activity [186–192].

3.1. Targeting MCU

From the topics covered by this review it is clear that sustained mitochondrial Ca^{2+} overload is toxic for both tissues and cells in heart diseases, especially in I/R injury (IRI) where Ca^{2+} accumulation occur both in ischemia and reperfusion. Thus, although the inhibition of the MCU activity to treat this mitochondrial disfunction may be considered an innovative therapeutic approach, it is necessary to take note of a series of apparent controversial results which don't always do theory the practice [193]. For example, it is reported that constitutive cardiac MCU-deficient animal models are not protected by IRI [188,192,194] despite mitochondria are protected from Ca^{2+} entry. These findings claim that the role of mitochondrial Ca^{2+} in IRI is extremely complex and whether on one hand sustained Ca^{2+} overload is harmful, also the complete and chronic inhibition of Ca^{2+} uptake may be deleterious or assumes compensative adaptations. In support with this opinion, conditional knockout of the MCU or its transitory chemical inhibition, conferred the expected protective effects [195].

To date, several groups have developed molecules capable of reducing Ca^{2+} uptake into mitochondria through the inhibition of MCU. The most known and widely used is ruthenium red (RuRed), synthesized in 1892 [196]. RuRed is a substance that blocks Ca^{2+} uptake by MCU inhibition without affecting Ca^{2+} efflux and mitochondrial respiration [197–199]. The most important paper using RuRed against heart disease was by Grover et al. in which the treatment of perfused rat hearts with the compound in the micromolar range improved cardiac contractile function and oxygen efficiency at reperfusion after ischemia [200]. Despite its great potential, RuRed has shown low cellular permeability together with a poor selectivity for MCU and several off-target biological effects.

Subsequently, starting from RuRed another compound has been formulated and was called Ruthenium 360 (Ru360) [201,202]. The inhibition of MCU by Ru360 was highly selective and, unlike its predecessor, it did not induce changes in SR Ca^{2+} release, both actomyosin ATPase and NCX activity, LTCCs current and cytosolic Ca^{2+} dynamics [203]. The use of Ru360 as an intravenous single bolus (quantified in 15–50 nmol/kg) lasting 30 min before ischemia in rats, significantly reduced reperfusion-induced arrhythmias, mitochondrial damage and improved cardiac performance [201].

Recently, Woods et al. have synthesized and characterized the bioactivity of a new ruthenium-based MCU inhibitor, Ru265. This compound is structurally similar to Ru360 and would overcome it thanks to an increased selectivity, cell permeability associated to low toxicity detection [204]. It has been used as drug to prevent hypoxia/reoxygenation (H/R) in rat neonatal cardiomyocytes with a significant preservation from MMP lowering and mPTP opening [204].

Kon et al. have recently identified a novel cell permeable inhibitor of MCU, called DS16570511 [205]. Among the described effects ascribed to DS16570511 inhibition of mitochondrial Ca^{2+} uptake, the most common are increased heart contractility and reduction of RI when used in the range 3–30 μM. Its inhibition results reversible simply after washout.

However, two small compounds have been recently discovered through the screening of a library of about 44.000 substances for their capacity to regulate mitochondrial Ca^{2+} uptake. These compounds, called MCU-i4 and MCU-i11, directly bind a specific domain of MICU1, fundamental for the gating activity of MCU complex. Their interaction with MICU1 in muscle fibers has decreased Ca^{2+} influx altering the growth of myotubes [206]. MCU-i4, unlike -i11, impacts mitochondrial depolarization thus future investigations should be focused on the second one.

Santo-Domingo et al. have demonstrated that KB-R7943, a compound originally developed as inhibitor of the NCX, protects against myocardial I/R injury through the inhibition of MCU [207]. Inhibition of MCU by KB-R7943 may block the mitochondrial calcium uptake, the matrix overload and the subsequent opening of the mPTP, contributing to cardioprotective activity [207]. On the other hand, it has been seen that KB-R7943 inhibits Ca^{2+}-induced mPTP opening as primary and more direct function [208].

These data highlight that there is the need for new studies associated to the difficulty of finding permeable molecules that can inhibit the MCU, selectively, and without altering biological functions.

3.2. Targeting SERCA2a

As previously reviewed, SERCA2a is one of the main proteins to be dysregulated in CH and HF. Its function is impaired by an improper protein expression, an inhibitory action of molecular interactors and gene mutations. Malfunction of this protein is responsible for non-physiological $[Ca^{2+}]_i$ transients which have repercussion in muscle relaxation during diastole and thus heart pumping. For these reasons, the recovery of their function may improve cardiac contraction and clinical conditions of patients affected.

According to experimental researches made in the field, the restoration of the functions of the SERCA2a can be carried out by either acting directly or indirectly, by targeting some of its regulators.

3.2.1. Direct ways

The most accredited way for the maintenance or the recovery of SERCA2a levels, especially for translational applications in humans, is gene therapy, which is applied from 25 years in the cardiovascular field and attracting interest for always new clinical trials. In the 90's, for the first time, an adenoviral expression (AV) system is used in ventricular cardiomyocytes of HF patients, to directly increase SERCA2a levels [209]. The effect has been replicated also in cardiomyocytes from different species [210]. By this method, Del Monte et al., have shown that the overexpression of SERCA2a in isolated failing human cardiomyocytes has restored the $[Ca^{2+}]_i$, muscle relaxation and increased cardiac contractility [209]. Moreover, several studies have further verified the beneficial effects of SERCA2a gene transfer on cardiac performance also in animal models of HF, improving myocardial excitability and preventing ventricular arrhythmia in pigs [211,212], diastolic dysfunction in swine [213] and dose-dependent functional benefit in ovine models [214]. It has been shown that Adeno-Associated Virus (AAV)-based vectors, compared to AV technique, are safer and more

Table 1
Existing modulators of intracellular calcium to counteract cardiac diseases.

Modulators	Protein target	Main experimental model	Molecular effects	Physiologic effects
Ruthenium Red	MCU	Cells, perfused animal hearts of I/R	Inhibition of mitochondrial Ca^{2+} load, changes in SR Ca^{2+} release;	Improved cardiac contractility
Ru360 Ru265 DS16570511		Cells, whole body laboratory animals of I/R	Inhibition of mitochondrial Ca^{2+} load	Reduced RI, prevention of arrhythmias and mitochondrial damage (MMP lowering and mPTP opening), improved cardiac performance, increased heart contractility
MCU-i4	MICU1	Cells and muscle tissues	Inhibition of mitochondrial Ca^{2+} load, impairment of MMP	N/A
MCU-i11			Inhibition of mitochondrial Ca^{2+} load	
KB-R7943	MCU NCX	Cells, perfused animal hearts of I/R	Inhibition of mitochondrial Ca^{2+} load, inhibition of Ca^{2+}-induced mPTP opening Inhibition of the reverse mode of NCX	Protective effects following I/R by improving LV function, by reducing ventricular fibrillation and hypercontracture of cardiomyocytes
AV/SERCA2a	SERCA2a	Cells, large animal models of HF	Restore SERCA2a expression, restore of Ca^{2+} transients	Muscle relaxation, increased cardiac contractility, improved myocardial excitability, prevention of arrhythmia
AAV/SERCA2a	SERCA2a	Cells, large animal models of HF, humans		Improved vascular reactivity, restored cardiac ejection fraction, blood flow, eNOS expression, decreased apoptosis
AAV9/PLB shRNA Antisense RNA AV/S16E Aptamers	PLB	Cells, large animal models of HF	PLB inhibition/silencing PLB phosphorylation	Improved systolic and diastolic function, normalization of dilation and hypertrophy, reduced fibrosis
Hydralazine	SERCA2a	Patients with HF	Demethylation of the promoter region of SERCA2a	Ca^{2+} homeostasis correction
Glucocorticoids	PLB	Patients with I/R	PLB phosphorylation, Unaltered Ca^{2+} transients, reduced calpain activation	Improved myocardial function after cardiopulmonary bypass
Istaroxime	PLB Na^{2+}/K^{+}	Large animal models of HF, patients with HF	PLB inhibition, decrease of Na^{2+}/K^{+}-ATPase activity	Decreased heart rate, cardiac contractility, improved pulmonary capillary wedge pressure
Resveratrol	SIRT1 PI3 kinase-Akt-SERCA2a	Laboratory animals	Increased SERCA2a activity and Ca^{2+}transient	Improved contractile amplitude, reduced relengthening time and superoxide generation
Losartan/Enalapril	SERCA2a RAS	Patients	Prevented downregulation of SERCA2a, RyR2, PLB and CSQ	Partial improvement in LV function
N106	SUMO1	Cells, mouse model of HF	SUMOylation of SERCA2a	Improved hemodynamic performance and reduced mortality among the animals with HF
antagomiR-25	miR-25	Mice models of HF	SERCA2a restoring	Improved cardiac function and survival
Diltiazem	Calcium antagonist	Patients		
JTV519	RyR2 RyR2/ Calstabin2 complex	Large animals with AT	Decreased Ca^{2+} leak from SR Stabilization of the RyR2/Calstabin2 complex to prevent Ca^{2+} release	Improved cardiac function
S107	RyR2/ Calstabin2 complex	Humans with AT, HF and CPVT	Prevention of the Ca^{2+} leakage from the SR	
Dantrolene	CaM/RyR2 complex	Humans with CPVT, treatment of ATs following I/R in large animal models	Stabilization of CaM/RyR2 complex, inhibition of cytosolic Ca^{2+} sparks in diastole	Prevention of DAD, antiarrhythmic
Flecainide	RyR2	Patients	Correction of aberrant RyR2 activity, blocking the open state of RyR2, decreased spontaneous Ca^{2+} leak	Completely prevention ov CPVT
Tetracaine and derivatives (EL1–9), EL20	RyR2	Laboratory animals	Inhibition of RyR2 and Ca^{2+} leak	Prevented the induction of ventricular tachycardia without affecting heart rate or cardiac contractility
Benzothiazepines Dihydropyridines Phenylalkylamines	LTCCs	Patients with HCM, CHF, CH, angina pectoris and cardiac ATs	Ca^{2+} channel blockers	Decreased traits of hypertrophy, AT and improved contractility
SEA0400 SN-6 YM-244769	NCX	Cells, large animal models of I/R	Inhibition of NCX and Ca^{2+}-induced cell death	Recovery of LV function after reperfusion and decreased of infarct size and incidence of ventricular fibrillations.
GSK255B + GSK503A	TRCP3 TRCP6	Cell models of CH	TRCPs inhibitors, antagonize either the molecular signaling inducing CH or reduced the phosphorylation status of many proteins involved in Ca^{2+} handling	N/A
Pyr-3	TRCP3	Cells	TRCP3 inhibitor, inhibition of Ca^{2+} influx, modulation of NFAT	Reduced hypertrophy
C31	TRPC1/4/5 complex	Cells	N/A	N/A
KN-93	CaMKII LTCCs IP3Rs CaM	Cells	Inhibition of Ca^{2+} currents	N/A
AS105 GS-680	CaMKII	Cells, laboratory animals	Inhibition of CaMKII, reduced SR Ca^{2+} leak	

(*continued on next page*)

Table 1 (*continued*)

Modulators	Protein target	Main experimental model	Molecular effects	Physiologic effects
RA306				Reduced arrhythmia, increased contractility in failing myocardium, improved cardiac parameters linked to contractility
AIP AC3-I CN19o		Large animal with CH and ATs Cells	Interaction and block of CaMKII	N/A

successfully alter gene expression in cardiac tissue, in addition to reducing inflammation [215,216]. Among more than 100 wild-type AAV serotypes, some have been demonstrated to have distinct features on cardiomyocyte transduction [215]. AAV-1 vector was the most used and studied. In several congestive heart failure (CHF) animal models it has been seen that the intracoronary injection of AAV carrying SERCA2a acutely improves vascular reactivity. Also, long-term overexpression of SERCA2a by the same method, significantly restored cardiac ejection fraction, blood flow, eNOS expression in coronary arteries and decreased myocardial apoptosis [213,216–218]. Interestingly, SERCA2a gene transfer by improving Ca^{2+} signaling, directly influenced vascular endothelial and smooth muscle cell function [219]. Finally, AAVs/-SERCA2a infusion in animal models of HF, have improved the myocardial and coronary artery Ca^{2+} handling and consequently the cardiac function.

On the basis the data obtained in preclinical models, Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease -Trial (CUPID) was established as first clinical trial in humans, to test the efficiency of recombinant AAV1/SERCA2a in HF [220,221]. The purpose of the clinical trial was intended of monitoring safety and efficacy of high doses of AAV1/SERCA2a administration as therapeutic approach. The result of the Phase I and Phase IIa trials showed reduced adverse cardiac events [220,221]. However, the double-blind randomized and placebo-controlled phase IIb clinical trial, named CUPID2, failed to show significant improvement in ventricular remodeling. Consequently, CUPID2 were terminated prematurely [222]. Despite the failure of these clinical trials, the field of cardiac gene therapy has gained valuable knowledge on AAV gene delivery in the heart and on safety in advanced HF population [223]. In recent years is emerging a new gene delivery method using other viral vectors mainly based on lentivirus. In a rat model of HF, it has been shown that lentivirus can integrate the gene of interest in the host genome with long-term effect of gene transduction [224–227]. In addition, in a model of I/R, the overexpression of SERCA2a reduced the incidence of the ventricular arrhythmia and improved hemodynamics [228–230].

3.2.2. *Indirect ways*

PLB is a SR membrane protein which modulates SR Ca^{2+} uptake, contractility and relaxation by SERCA2a inhibition [231]. In its dephosphorylated state, it lowers the affinity of SERCA for Ca^{2+}, thereby inhibiting the uptake of the latter [231]. On the contrary, its phosphorylation relieves PLB-mediated inhibition of SERCA2a, thereby increasing the activity of the channel.

Several studies have demonstrated that to increase SERCA2a activity in treating HF, either increase PLB phosphorylation or its knockdown might be a promising therapeutic approach [232]. Indeed, all studies in large animals reported similar data output describing enhanced $[Ca^{2+}]_i$, improved systolic and diastolic LV function, the normalization of dilation and hypertrophy and reduced cardiac fibrosis; all clinical stages that act synergistically to reverse HF phenotype. Methods used are multiple and include the depletion of PLB through either AAV9-mediated shRNA [233] or antisense RNA directed to PLB mRNA [234], the use of an AV-mediated phosphorylated mutant of PLB which is constitutively active [235] and cell-permeable aptamers [236]. Nevertheless, attention should be maintained in the use of some methods due to the possible presence of side effects [237].

In addition to this, several drugs may act indirectly on SERCA2a activity. Some of these are: Hydralazine, glucocorticoids, Istaroxime and resveratrol. Hydralazine is a drug already used in the treatment of patients affected by HF, it acts indirectly being an inhibitor of DNA methylation [238]. Demethylation of the promoter region of SERCA2a increases its mRNA levels and leads to a correct Ca^{2+} homeostasis [238]. Glucocorticoids have been shown to restore the phosphorylation status of PLB together to SERCA2a when used as treatment in IRI or cardiac arrest [239].

Istaroxime is utilized for the treatment of acute HF syndromes, it increases function of SERCA2a by acting on PLB inhibition and decreases of Na^{2+}/K^{+}-ATPase activity [240,241]. The results are clear and various; in principle administered in dogs, they have highlighted the absence of arrhythmic events associated with improved heart function [242]. In addition, also humans benefit from this [243] as evidenced by a clinical trial in patients with HF which has shown that the administration of Istaroxime decreases heart rate, improves pulmonary capillary wedge pressure besides demonstrating safety and beneficial effects on cardiac contractility [244,245]. Likewise, other drugs like Losartan and Enalapril can prevent the downregulation of SERCA2a protein and the mRNA levels through blockage of the renin–angiotensin system (RAS) and an angiotensin II receptor blocker (ARBs) [246]. Moreover, the administration of Resveratrol in diabetic mice has shown an increase in SERCA2a expression and an improvement of the cardiac function through activation of SIRT1 [247,248]. In addition to this, in diabetic rat cardiomyocytes, the treatment with insulin-like growth factor 1 (IGF-1) through activation of the PI3 kinase-Akt-SERCA2a signaling pathway enables the increase the SERCA2a levels [249]. Lastly, in a rat model of chronic HF also the anti-inflammatory agent named Oxymatrine, improves the SERCA2a expression and cardiac function [250].

However, recent studies have focused the attention on possible SERCA2a post-translational modifications. Studies have shown that in cardiomyocytes the activity and levels of SERCA2a are modulated through SUMO1; SUMOylation of SERCA2a is reduced in HF and with it also the protein amount [251]. Kho et al., have developed a molecule that induced the activation of SUMO1, called N106, that leads to the SUMOylation of SERCA2a with consequent stimulation of the activity of the latter [252]. In addition to this, also the gene therapy through AAV9 gene transfer the SUMO1 levels are increased, leading to of SERCA2a normal levels. Consequently, induces an improved hemodynamic performance and a reduced mortality among the animals with HF. Likewise, it has been proven that increased expression of S100A1, a Ca^{2+} binding protein involved in intracellular Ca^{2+} regulation, improves the activity of both SERCA2a and RyR2, restoring the correct $[Ca^{2+}]_i$ transients and Ca^{2+} at the SR [253]. This is translated into a long-term reversal of LV dysfunction with improvements of contractile function in a pre-clinical model of ischemic CM. These data indicate that S100A1 can be another target for therapy of the human HF [254,255].

Furthermore recent studies have discovered that many microRNAs (miRs) are dysregulated with HF [256,257]. In particular, experiments in cardiomyocytes of both mice and humans, have detected high levels of miR-25 that delays Ca^{2+} re-uptake kinetics with consequently increased HF phenotypes. Wahlquist et al. have demonstrated that the use of antagomiR-25 in a mouse model improves cardiac function and survival through restoring SERCA2a activity [258].

3.3. Targeting RyR2

RyR2 plays a central role in the dysregulation of Ca^{2+} homeostasis found mainly in ATs [259]. Indeed, the pathological leak of Ca^{2+} from RyR2 is at the basis of arrhythmogenesis.

Several groups of research have developed compounds and drugs with the potential of regulating RyR2 channel activity, to maintain the normal SR Ca^{2+} release during systole and inhibit it during diastole [260].

From the study of the pluriannual use of Diltiazem in clinic, a 1,5-benzothiazepine-derivate and Ca^{2+} antagonist [261], led to the discovery of further additional benzothiazepine derivatives with potential therapeutic properties for the treatment of ATs. Among them, JTV519 is a 1,4-benzothiazepine compound that shows its cardioprotective effects against atrial fibrillation through the finely regulation of RyR2 properties without altering the capacity to the propagation of Ca^{2+} waves [262]. This piece of evidence on the molecular mechanism adopted by JTV519 in preventing the onset of ATs in cardiac diseases, seem not to be the only one existing. It has been seen that in dogs, after four weeks of chronic right ventricular pacing, the administration of JTV519 controlled RyR2 opening by restoring Calstabin2 levels and stabilized the RyR2/FKBP12.6 complex, improving cardiac function and decreasing SR Ca^{2+} with recorded reduced RyR2 hyperphosphorylation [263]. Subsequently, Wehrens et al. have shown that JTV519 stabilizes the closed state of RyR2 by promoting FKBP12.6 binding. The same group also demonstrated that in Calstabin2 knockout mice, JTV519 had no effects, highlighting the importance of Calstabin2 for the antiarrhythmic effect induced by this compound [264]. In recent years, in 2016, it has been reported an additional property for this drug, such as its partial and mild block of SERCA2a just enough to prevent SR Ca^{2+} overload and related harmful events in IRI; thus, as consequence, it has repercussion also on SR Ca^{2+} release modulation [265].

A second 1,4-benzothiazepine derivative is S107; it has the same function of JTV519, or preventing the Ca^{2+} leakage from the SR, by promoting the Calstabin2-RyR2 binding. S107 has high specificity for RyR2 and no off-target activity [266]. But the real innovation concerning this novel drug is the ability to create a complex RyR2-Calstabin2 and thus blocking pathological Ca^{2+} leakage and serious ATs also in the presence of a mutated form of RyR2, which is the main responsible for CPVT [266,267]. These compounds may have great promise for treating patients with CPVT and not only, indeed, clinical trials studies for the treatment of HF and ATs are in phase 2. In addition to this, S107 can also prevent muscle weakness in aging, stress-induced cognitive dysfunction, Duchenne muscular dystrophy and the progression of HF [268–271].

Dantrolene is a hydantoin derivative that is clinically used for the treatment of malignant hyperthermia, a condition caused by mutations in the skeletal RyR1 [272]. Its mechanism of action involves CaM-dependent stabilization of the interaction between the amino terminal and central domains of RyR1, required for the closed state of the RyR Ca^{2+} channel [273]. Kobayashi et al. have shown that Dantrolene has a role against CPVT by binding also the mutated form of RyR2, specifically to domain 601–620 and resulting in the inhibition of cytosolic Ca^{2+} sparks in diastole and DAD [274]. However, it has been demonstrated by using the knock-in mouse model with a human CPVT-associated RyR2 mutation (R2474S) that pretreatment with Dantrolene inhibited CPVT-related tachycardia, induced by either epinephrine or exercise [275]. Subsequently, studies have been carried out on the therapeutic antiarrhythmic potential of Dantrolene in the treatment of CPVT. Dantrolene was administered intravenously and it reduced the number of premature ventricular complexes with antiarrhythmic effects in a subgroup of CPVT1 patients with specific RyR2 mutations [276]. These data showed comparable results even in experiments conducted in pluripotent stem cells (iPSC)-derived spontaneously beating cardiomyocytes generated from the same patients, proving once again the antiarrhythmic effects of Dantrolene [276]. Dantrolene has found useful also for the treatment of ATs following I/R in several animal models [277,278]. All these evidences underline that to attenuate Ca^{2+}-mediated arrhythmias associated with HF, this hydantoin derivative can be a possible therapy. Currently, a new clinical trial is in the recruitment phase to test the efficacy of Dantrolene in CPVT patients [279].

Flecainide is a trifluoroethoxybenzamide, an oral class Ic antiarrhythmic drug, already approved for medical use in the United States since 1984. Flecainide known as a Na^{+} channel blocker, is used in patients who do not have structural heart disease, for the treatment of atrial fibrillation/atrial flutter, paroxysmal supraventricular tachycardia, atrioventricular nodal reentrant tachycardia, AV reentrant tachycardia [280,281]. Recent data have shown both in iPSC-cardiomyocytes and in mouse models of CPVT that Flecainide acts either reducing or removing aberrant RyR2 activity, blocking the open state of RyR2 and decreasing spontaneous Ca^{2+} leak, thus preventing ventricular tachycardia [282,283]. Confirming its efficacy in CPVT is not only due by the blockage of the Na^{+} channel. In addition to this, treatment of two patients with Flecainide, who remained symptomatic with conventional drug therapy, has prevented CPVT with great success. Hence, these data provide clear evidence on the antiarrhythmic effectiveness of Flecainide in inhibiting defective RyR2 Ca^{2+} release channels in humans, identifying it as a possible currently available drug for fight CPVT [283].

A last class of drugs considered efficient in reducing spontaneous and pathological Ca^{2+} release are Tetracaine and derivatives (EL1–9) [284] for the treatment of ventricular tachycardia; they showed great affinity for RyR2 and few off-target side effects. The last one identified by Word et al., EL20, used at low nanomolar concentrations and also efficacy in cardiomyocytes harboring the R176Q variant from a CPVT patient [285].

3.4. Targeting LTCCs

LTCCs are the main mediators of VGCC-mediated Ca^{2+} influx into cardiac cells and are fundamental in certain mechanisms and electrical properties of the heart. These channels, thus are considered as an important target for the treatment of several diseases [286–288]. In the heart, the most expressed isoforms are $Ca_{V1.2}$ and $Ca_{V1.3}$ and their alteration is related to the onset of cardiac diseases related to the impairment of ECC and inotropy [289].

It is known that mutations in LTCC genes induce the dysfunctions of Ca^{2+} channels, resulting in the abnormal excitations of cardiomyocytes leading to the onset of cardiac ATs such as LQTS (Long QT syndrome) [290] and Brugada syndrome [291].

For decades antagonists of LTCCs have been used for the treatment of CH and I/R. However, in patients with HF, LTCC Ca^{2+} blockers are employed with great caution. In addition to this, the knockdown of LTCCs induces the secondary CH signaling through a compensatory increase in Ca^{2+} by RyR2 leak [292].

However, over the years, several organic molecules have been identified as modulators of LTCCs by blocking the inward Ca^{2+} current. These modulators bind to three separate receptor sites on LTCCs and can be grouped into three groups: benzothiazepines, dihydropyridines (DHP) and phenylalkylamines [286,293,294]. All binding sites are situated within the IIIS5, IIIS6, and IVS6 transmembrane segments and near to the pore [295]. These substances are used to treat several diseases, including HCM, CHF, CH, angina pectoris and cardiac ATs [296–299]. In particular, the non-dihydropyridines Ca^{2+} channel blockers that includes benzothiazepines and phenylalkylamines are used also for the treatment of ATs, but should not be used in patients with HF and atrial fibrillation united with preexcitation. Several studies have demonstrated that the use of non-dihydropyridines increase mortality and incidence of HF, due by their negative inotropic effects [300,301]. Indeed, to prevent further depression of cardiac function the non-dihydropyridines, are used only when β-blockers alone are

unsuccessful [302].

In addition to this, several studies have shown that in arrhythmic conditions the combination of different Ca^{2+} channel blockers can be a valid therapeutic treatment. Interestingly, in patients affected by CPVT, it has been reported that by adding verapamil to existing β-blocker therapy, the incidence of exercise-induced arrhythmias was reduced when compared to β-blocker therapy alone [303].

Despite the physiological role of the T-type Ca^{2+} channel in the human heart is still little documented, it is known they are present in the sinoatrial node, atrioventricular node and Purkinje fibers and are involved in the pacemaker activity. Mangoni et al., have highlighting the importance of the channel in cardiac rhythm, through $Ca_{V3.1}$ knockout mice [304]. In this animal, the genetic inactivation of the $Ca_{V3.1}$ result in a significant slowing of the heart rate and atrioventricular conduction [304].

3.5. Targeting NCX and PMCA

In addition to SERCA2a, both PMCA and NCX are important regulators of $[Ca^{2+}]_i$ intervening in Ca^{2+} removal when it exceeds, for instance after contraction. NCX has the adjunctive peculiarity to work in a bidirectional way creating inward and outward currents of Ca^{2+} and Na^+, depending on the intracellular concentrations of the ions exchanged and on membrane potential. Thus, both activators and inhibitors of this channel may result in cardioprotective effects. During I/R when it functions in reverse mode by increasing Ca^{2+} influx, its inhibition may result useful; otherwise, in HF Ca^{2+} extrusion may result impaired caused by high $[Na^+]$, in this scenario, stimulators of its activity may provide benefit.

There exist many NCX inhibitors, but most of them are not selective (i.e., Amiodarone, Bepridil, Aprindine) as they modulate also Na^+/K^+ and LTCCs currents and they are already reviewed in [305], although they retain good antiarrhythmic properties.

The first, but less selective inhibitor, is KB-R7943 developed by Watano T. [306]. Its administration has showed protective effects following I/R by improving LV function, by reducing ventricular fibrillation and hypercontracture of cardiomyocytes [307,308]. KB-R7943 in not considered too selective because it results also a potent MCU inhibitor; thus, it is difficult to discriminate if its cardioprotection following I/R (at a concentration of 10 μM) is dependent on the inhibition of mitochondrial Ca^{2+} uptake or on the modulation of NCX, or both; although that dose should not influence the exchanger as claim some reports [207].

To date, the most potent and selective compounds targeting NCX are named as SEA0400, SN-6 and YM-244769. Overall, in the heart, SEA0400 is considered to have a higher potency in the inhibition of NCX compared to SN-6, which result similar to KB-R7943 [305]. At the same time, also its selectivity is greater than SN-6 which in turn, is more selective of KB-R7943. Cardioprotective effects of SA0400 are multiple and range from cell cultures to large animals. Generally, its treatment led to Ca^{2+}-induced cell death inhibition [309], recovery of LV function after reperfusion and a decrease of the infarct size [310], and the incidence of ventricular fibrillations. To conclude, the newest YM-244769, firstly described in the brain and targeting preferentially NCX3 [311], showed protective action under H/R both in neuronal diseases and in the heart [312].

On the other hand, although NCX stimulators own cardioprotective features, they share many molecular mechanisms of protection which often fall back so far into the modulation of Ca^{2+} homeostasis [313].

Concerning PMCAs, PMCA1 and PMCA4 are primarily reported to be expressed in the heart. These proteins are considered minor contributors for Ca^{2+} efflux from the cell, thus they have always been of secondary importance to study in diseases and as target of cardioprotection. Nevertheless, it is reported the existence of interesting mutational profiles of the PMCA1 gene concerning cardiac disease. Genome wide association studies (GWAS) performed in several cohorts of the whole world population and taking into consideration different ethnicities, identified at least 10 SNPs in correspondence of intronic regions of the gene encoding for PMCA1. As consequence, they are significantly associated to hypertension, pre-eclampsia, salt sensitivity and leading to coronary artery diseases, myocardial infarction and also calcification. These SNPs are the following: rs1401982 [314–316] associated to artery stenosis, hypertension and arterial stiffness; rs2070759 [317,318] associated to hypertension in both Chinese and Japanese population; rs2681472 [319–321] responsible for hypertension and arterial stiffness; rs2681492 [322,323] involved in high blood pressure in people from Africa; rs7136259 [324–326] associated to premature coronary disease and atherosclerosis in multi-ethnic populations; rs10858911 [327], rs11105354 [328–331] with increased risk of cardiovascular disease; rs11105378 [317,332] with increased susceptibility to hypertension; the same for both rs12817819 [333] and rs17249754 [319,320,333]. Besides what reported above, more than 50 additional papers reported same findings on the association of PMCA1 to hypertension and coronary artery disease like MI. This evidence involve loss of function of PMCA1 or reduced amount of the protein at the PM that has, as direct effect, the increase in the expression of LTCCs and blood pressure, triggering CH and heart remodeling [334,335]. Overall, no reports classify these mutational profiles as deadly themselves, but it is clear that they significantly increase the onset of hypertension and premature coronary artery disease with all related consequences. Also PMCA4 plays key roles in heart physiology by controlling cardiac contractility [336]. In a scenario of established I/R, its overexpression alleviates all maladaptation of the heart included CH and HF [337]. However, to date there are no drugs able to induce PMCA overexpression.

3.6. Targeting TRP channels

Each of TRPCs has an individual role in cardiovascular pathologies, being differentially expressed in the diseased heart. On the basis of recent considerations made on TRPC targeting to prevent CH, fibrosis, heart remodeling and HF, there exist several pitfalls that obstacles the use of this target in human clinical trials, when compared to other strategies for other proteins. In particular, still very few drugs targeting these channels have been discovered where the majority are not selective, they do not exist cardiac-specific isoforms of these channels thus their targeting may involve severe off-target effects [8].

However, here we report what is known about advanced studies in cells. Deletion of the first isoform of TRCPs is able to deactivate the calcineurin-NFAT signaling axis in the progression of CH [338]. About TRCP3 there exists few inhibitors like GSK255B [339] which blocks the channel but does not led to any protective effect when administered alone. While, the synergistic inhibition with TRPC6 with GSK503A, antagonize the signaling inducing CH or reduced the phosphorylation status of many proteins involved in Ca^{2+} handling [340]. The second inhibitor Pyr-3, a pyrazole compound, mediate a plethora of effects ranging from Ca^{2+} influx, modulation of NFAT to reduce hypertrophy; Pyr-3 seems to acquire more selective skills [341]. Recently, it has been developed a selective compound 31, c31, that working in the picomolar range of concentrations it inhibits the assembly of TRPC1/4/5 complex, but no cardioprotective effects have yet been investigated [342].

3.7. Targeting CAMKII

CaMKII is a kinase reported as mainly involved in intracellular Ca^{2+}-dependent changes occurring during HF, CH and ATs and caused by its intense activity of phosphorylation towards proteins involved in Ca^{2+} handling. It has many targets (i.e., PLB, RyR2, SERCA2a) and, overall, it triggers SR Ca^{2+} leaking and the opening of LTCCs. It is clear that its inhibition constitutes the way to preserve physiological functions.

There are two types of CaMKII inhibitors: those grouped in the pharmacological area and those based on peptides structures. In the 90's, one of the first CaMKII pharmacological inhibitor was KN-93

[343]; if its use in basic research was spread, it had no future in clinical practice. Indeed, side effects targeting multiple proteins as LTCCs, IP3Rs and calmodulin have been described several times [344–346].

The second known pharmacological inhibitor is AS105 [347]; by working 1000-fold less concentrated than the first one, it successfully reduced SR Ca^{2+} leak in cardiomyocytes from mice with HF. Given the very low dose of use, no negative effects on ECC and SR Ca^{2+} loading were recorded.

Again, another similar binding molecule (which results in a ATP-competitive binding) is GS-680 [348]. It has been improved by Wagner S et al. with a strong selection against cardiac CaMKII and with beneficial effects reducing arrhythmia and increasing contractility in failing myocardium. Also, this compound worked efficiently in the low nanomolar range. Of the same class, RA306 was described for the first time by Beauverger P. and colleagues in 2020 [349]; by treating diseased mice with oral administrations, after few weeks it improved cardiac parameters linked to contractility.

Among the peptide-based inhibitors, autocamtide-2-related inhibitory peptide (AIP) [350] and autocamtide-3 derived inhibitory peptide (AC3-I) [351] interact with CaMKII and blocked its canonical activation. This resulted in a strong enzyme inhibition in several animal models providing evidence once again on the importance to target this protein to counteract pathological hypertrophy and lethal arrhythmias [352].

Across the end of 90's and the early 2000's, by using the catalytic domain of CaMKII as bait [353,354], proteins with inhibitory function against the enzyme have been unveiled; they were resident in the brain, but absent in the heart. For this reason, the first effort was an efficient delivery in the heart by the use of AAV vectors and by targeting the CaMKII once active and limiting I/R consequences and ATs [111,355]. Taking advantage from growing biomolecular methods, it was created a mitochondria-targeted inhibitory protein [356]. Its administration at reperfusion relieved CaMKII activation and thus its positive loop on MCU-mediated mitochondrial Ca^{2+} load and mPTP opening. Further studies in improving these peptides achieved a great result by creating the smallest sequence of 19 aa (named as CN19o) sufficient to exert all cardioprotective effects in the picomolar range [357].

4. Conclusions

From the literature reviewed above, it emerges that the knowledge of the tasks accomplished by each of Ca^{2+}-dependent proteins in the heart physiology and how they become differentially impaired in diseases is essential to draw a successfully targeted therapy. Indeed, Ca^{2+} cycling involves a finely tuned and dynamic spatio-temporal waves to achieve a proper contraction-relaxation with high frequency, thousands of times, every day. Overall, there is a good understanding about Ca^{2+} dysregulation in cardiac diseases; now, the efforts should be more directed towards drugs developing and in translating results from preclinical models to patients.

Also, proper drug delivery methods are needed to increase bioavailability, to better target only specific cardiac protein isoforms and minimize off-target effects.

Declaration of interest

The authors have no conflicts of interest.

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