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ORIGINAL RESEARCH

Calsequestrin, a key protein in striated muscle health and disease

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Abstract
Calsequestrin (CASQ) is the most abundant Ca^{2+} binding protein localized in the sarcoplasmic reticulum (SR) of skeletal and cardiac muscle. The genome of vertebrates contains two genes, *CASQ1* and *CASQ2*. CASQ1 and CASQ2 have a high level of homology, but show specific patterns of expression. Fast-twitch skeletal muscle fibers express only CASQ1, both CASQ1 and CASQ2 are present in slow-twitch skeletal muscle fibers, while CASQ2 is the only protein present in cardiomyocytes. Depending on the intraluminal SR Ca^{2+} levels, CASQ monomers assemble to form large polymers, which increase their Ca^{2+} binding ability. CASQ interacts with triadin and junctin, two additional SR proteins which contribute to localize CASQ to the junctional region of the SR (j-SR) and also modulate CASQ ability to polymerize into large macromolecular complexes. In addition to its ability to bind Ca^{2+} in the SR, CASQ appears also to be able to contribute to regulation of Ca^{2+} homeostasis in muscle cells. Both CASQ1 and CASQ2 are able to either activate and inhibit the ryanodine receptors (RyRs) calcium release channels, likely through their interactions with junctin and triadin. Additional evidence indicates that CASQ1 contributes to regulate the mechanism of store operated calcium entry in skeletal muscle via a direct interaction with the Stromal Interaction Molecule 1 (STIM1). Mutations in CASQ2 and CASQ1 have been identified, respectively, in patients with catecholamine-induced polymorphic ventricular tachycardia and in patients with some forms of myopathy. This review will highlight recent developments in understanding CASQ1 and CASQ2 in health and diseases.

Keywords Sarcoplasmic reticulum · Excitation–contraction coupling · Store operated calcium entry · Ryanodine receptor

Calsequestrin structure and expression

Identification and tissue distribution

It is been about 50 years since David MacLennan published his first article on the discovery of an acidic protein, unique of the sarcoplasmic reticulum (SR), able to bind up to 970 nmol of Ca^{2+} per mg, which he elegantly named calsequestrin (CASQ) (MacLennan and Wong 1971). From that time on, a number of studies agreed that CASQ represents the major Ca^{2+} binding protein of muscle cells. It specifically concentrates in the junctional cisternae of the SR facing the T-tubules (Franzini-Armstrong et al. 1987), although with some difference between skeletal and cardiac muscles. Actually, purification and sedimentation experiments showed that approximately only 30% of CASQ2 remained associated with cardiac SR junctional membranes, compared to approximately 70% of CASQ1 in skeletal muscle (Wei et al. 2009a). In the latter, it reaches a concentration of about 6 mM, with a total content estimated to reach 0.5 mg of calsequestrin per gram of wet weight, as measured in frog skeletal muscles (Volpe and Simon 1991).

CASQ is present in invertebrates and in all vertebrates, and a calsequestrin-like protein was identified even in plants (Furlan et al. 2016; Krause et al. 1989; Henson et al. 1989). Two CASQ genes are present in mammalian genomes: CASQ1 and CASQ2. These two isoforms are co-expressed in neonatal skeletal muscles; however, in rodents fast-twitch fibers, the CASQ2 isoform disappears between 2 and 4 weeks postnatally, while CASQ1 continues to be expressed (Sacchetto et al. 1993). On the contrary, slow twitch fibers maintain the expression of both isoforms even in the adult (Damiani et al. 1990). In cardiac muscle, only the CASQ2 isoform is expressed. The two isoforms differ in their amino

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acid composition and biochemical properties with CASQ1 being apparently more able to bind Ca^{2+} than CASQ2.

CASQ polymerization and Ca^{2+} binding

CASQ is characterized by its high capacity and low affinity for Ca^{2+}. It can coordinately bind and release 40–50 Ca^{2+} ions per molecule per cycle with a Kd of about 1.1 mM under physiological conditions (Volpe and Simon 1991). These features make CASQ unequivocally suitable for its function, that is to manage the large amounts of Ca^{2+} necessary for muscle contraction. Hence it has been estimated that, at the beginning of each cycle of muscle contraction, the amount of Ca^{2+} released by calsequestrin is about twenty times higher than the pool of free Ca^{2+} in the SR (Pape et al. 2007).

The ability of CASQ to bind Ca^{2+} is mainly due to the complex quaternary structure that this protein assumes in the SR lumen. Electron microscopy analysis of CASQ1 distribution in the SR of skeletal muscles showed that it is arranged in intricate gels, with repeated nodal points connecting short segments of linear polymers (Perni et al. 2013). Interestingly, Ca^{2+} dissociation experiments revealed that the presence of CASQ at high concentrations in a restricted space, such as when bound to the junctional membranes of the SR, accelerates Ca^{2+}dissociation presumably as a result of cooperative molecular interactions (Beltrán et al. 2006). A number of reports based on biochemical data confirm that CASQ exists in a wide range of high-molecular-mass clusters (Sato et al. 1998; Maguire et al. 1997; Maguire et al. 1998). The first crystals of calsequestrin were obtained from canine cardiac muscle (Hayakawa et al. 1994) and rabbit skeletal muscle (Wang et al. 1998). These revealed the presence of three highly negative thioredoxin-like domains surrounding a hydrophilic center. Following Ca^{2+} binding, the three domains collapse and CASQ monomers start to polymerize. Accordingly, Park and co-workers proposed a model where Ca^{2+}-induced formation of one front-to-front contact between two monomers leads to dimerization followed by Ca^{2+}-induced formation of a second contact, this time following back-to-back interactions among dimers, to bring polymerization in a ribbon like structure (Park et al. 2003). The assembly in large polymers represents a pivotal factor in determining the Ca^{2+} buffering capacity of CASQ. Analysis of the primary sequence and of the crystal structure of CASQ1 revealed the presence of low and high affinity Ca^{2+} binding sites; in addition, $^{45}Ca^{2+}$ overlay assays indicated that the asp-rich or CAS (consecutive aspartate stretch at the C-terminus) region, localized at the interface of back-to-back dimers, represents a major Ca^{2+} binding motif in CASQ. Further experiments showed that front-to-front and back-to-back polymerization can induce the formation of negatively charged cavities that may accommodate additional Ca^{2+} binding sites (Park et al. 2003; Sanchez et al. 2012a). This observation was further supported by the model described by Kumar and collaborators. They showed that, at low Ca^{2+} concentration, the CAS region can accommodate 6 to 8 Ca^{2+} ions and acquires a compact structure. Under these conditions, the negative charges of the CAS region get neutralized, thus allowing back-to-back stacking. The remaining regions of CASQ1 contain additional Ca^{2+}-binding sites that can progressively bind more Ca^{2+} ions as the [Ca^{2+}] increases, thanks to the formation of additional Ca^{2+}-dependent Ca^{2+} binding sites (Kumar et al. 2013).

Structural modeling of CASQ1 and CASQ2 suggested that the differences in the Ca^{2+} binding capacity observed in the two calsequestrin isoforms may be explained by differences in their ability to form front-to-front and back-to-back interfaces (Park et al. 2003, 2004). In particular, the different composition of the CAS region in CASQ1 and CASQ2 may correlate with isoform-specific Ca^{2+}-dependent polymerization properties (Bal et al. 2015). Finally, glycosylation and phosphorylation of CASQ were also proposed to correlate with polymer formation and/or Ca^{2+} binding capacity (Sanchez et al. 2011, 2012b; McFarland et al. 2011; Beard et al. 2008).

Ca^{2+} binding and polymerization have been suggested to also regulate the SR retention of CASQ (Gatti et al. 1997, 2001; Houle et al. 2006). At difference with many proteins of the ER, CASQ lacks the Golgi retrieval COOH-terminal signal KDEL; original studies proposed that it may travel from the Golgi to SR by clathrin-coated vesicles; however, the molecular mechanisms responsible for general ER/SR retention and trafficking of CASQ have not been completely defined yet (Thomas et al. 1989; Tijskens et al. 2003; Nori et al. 2004; Ram et al. 2004). On the other hand, it appears to be quite clear that neither polymerization, nor post-translational modifications are strictly involved in CASQ1 sorting to the junctional SR in skeletal muscle cells (Nori et al. 1999, 2000, 2001, 2006); this, in turn, has been proposed to depend on protein interactions with the ryanodine receptor, triadin and junctin (Cho et al. 2007; Boncompagni et al. 2012; Oddoux et al. 2009; Cacheux et al. 2020).

The quaternary Ca^{2+} release complex and the regulation of the excitation–contraction coupling mechanism

CASQ interactions with RyR, triadin and junctin

In striated muscles, CASQ is part of a quaternary complex composed of the ryanodine receptor calcium release channel and of two single transmembrane domain proteins of the junctional SR, triadin and junctin (Zhang et al. 1997; Mitchell et al. 1988; Glover et al. 2002; Jones et al. 1995).

These four proteins were found to directly and indirectly interact one with each other and their reciprocal interactions were shown to be important for regulation of Ca^{2+} release during muscle contraction. Indeed, within this quaternary complex, CASQ plays a dual role, that is to keep the large amount of Ca^{2+} necessary for muscle contraction in close proximity of RyRs and to directly and/or indirectly regulate channel opening and activity.

In skeletal muscle, a direct interaction was described between CASQ1 and triadin. In particular, the CAS sequence in CASQ1 was found to bind a region containing a KEKE motif localized in the lumen of skeletal muscle triadin (Guo and Campbell 1995; Shin et al. 2000; Beard and Dulhunty 2015; Rossi et al. 2014a). Interaction of CASQ1 with triadin was proposed to be important to anchor the protein at the junctional region of the SR and to promote the junctional coupling between calsequestrin and the RyR (Guo and Campbell 1995; Kobayashi et al. 2000).

A region homologous to the KEKE motif observed in triadin is also present in the luminal domain of junctin, suggesting that interaction between CASQ1 and junctin can also occur via KEKE motifs (Dulhunty et al. 2009), while the junctin binding site in CASQ has been proposed to include the CAS region and a region encompassing amino acids 86–191 (Beard and Dulhunty 2015; Shin et al. 2003). It has been also proposed that CASQ phosphorylation may enhance binding to junctin at low Ca^{2+} concentration (Beard et al. 2008). Finally, a direct interaction was reported between CASQ1 and RyR1 (Herzog et al. 2000).

The same network of interactions between CASQ2, triadin, junctin and RyR2 was described in cardiac muscle, where it plays a key role in the regulation of the cardiac excitation–contraction coupling (Kobayashi et al. 2000; Rani et al. 2016; Handhle et al. 2016).

Functional role of CASQ in the regulation of RyR activation

The specific functional role of CASQ in the context of the quaternary protein complex in both skeletal and cardiac muscle has been investigated and debated for a long time. For example, CASQ was originally described to act as an endogenous activator of RyR in isolated heavy SR vesicles (Kawasaki and Kasai 1994). However, further studies based on lipid bilayer experiments suggested that, at low Ca^{2+} concentrations, CASQ1 may function as a Ca^{2+} sensor that prevents RyR1 to increase its activity in order to preserve the intracellular SR Ca^{2+} store (Beard et al. 2002, 2005; Wei et al. 2006, 2009a). Finally, in another study, CASQ1 was found not to exert any significant regulation of RyR1 channel opening (Qin et al. 2009). Distinct effects on channel regulation have been also reported when comparing different CASQ or RyR isoforms. Single channel lipid bilayer experiments showed that CASQ2 can increase the open probability of both RyR1 and RyR2 channels (Wei et al. 2009a). RyR2 channels show an increase in open probability in the presence of either CASQ1 or CASQ2 (Qin et al. 2009). Similar to what observed for CASQ1 in skeletal muscle, CASQ2 in cardiac muscle is believed to act as a SR Ca^{2+} sensor, inhibiting RyR2 opening at low Ca^{2+} concentrations (Györke et al. 2004a). More recently, Chen and collaborators reported that CASQ2 association with RyR2 determined a reduction in sensitivity to cytosolic Ca^{2+} activation, while RyR2 from CASQ2 knockout mice were significantly more sensitive to cytosolic Ca^{2+} activation and had significantly longer mean open times than RyR2 from control mice (Chen et al. 2013).

Finally, CASQ polymerization was shown to be a reversible process; however, since Ca^{2+}-binding sites of different affinities are present in the CASQ1 polymers, under physiological conditions, CASQ1 can sequester and deliver Ca^{2+} ions without the need to completely depolymerize (Kumar et al. 2013). Nevertheless, in conditions of critical SR depletion, when the intraluminal Ca^{2+} concentration decreases in a significant manner, CASQ can actually depolymerize. Interestingly, in both cardiac and skeletal muscle, SR depletion is paralleled by a progressive closure of the ryanodine receptors (RyRs) and a consequent reduction in Ca^{2+} release, to prevent dangerous SR exhaustion (Canato et al. 2010; Sztretye et al. 2011; Zima et al. 2010); on this line, and it has been proposed that CASQ1 depolymerization may represent the intracellular switch to induce channel closing (Manno et al. 2017).

The combined role of CASQ, triadin and junctin in the regulation of RyR activation

As described at the beginning of this chapter, in striated muscles, CASQ is present at the junctional SR together with two other proteins, triadin and junctin. Hence, when considering the combined role of calsequestrin, triadin and junctin on RyR activation and in the regulation of the excitation–contraction coupling, the scenario becomes quite complex. Calsequestrin was found to increase [^{3}H]ryanodine binding to solubilized heavy SR vesicles, but this effect was abolished by the presence of triadin (Ohkura et al. 1998). Similarly, addition of triadin and calsequestrin to purified RyRs resulted in channel inhibition, an effect that was not observed on channels depleted of triadin, suggesting that calsequestrin may reduce channel activity by binding the luminal domain of triadin (Beard et al. 2002; Györke et al. 2004b). Finally, more recently, Wei and collaborators showed that while both triadin and junctin appeared to increase the open probability of RyR1 channels, the presence of CASQ1 abolished the activation induced by junctin, but not that induced by triadin (Wei et al. 2009b). In conclusion,

results from all these studies, although in some cases conflicting, converge to the idea that the regulation of RyR activity in physiological conditions may actually depend on a complex combination of biochemical, structural or functional components. A more detailed discussion on this point is reported in a comprehensive review by Gaburjakova and collaborators, who critically analyze the functional meaning of protein interactions examined under distinct experimental conditions (Gaburjakova et al. 2013).

Mouse models to study CASQ function in skeletal and cardiac muscle

CASQ1-related mouse models

To investigate the role of CASQ in striated muscles, different mouse models have been generated. CASQ1 knockout mice have a normal motor activity. Nevertheless, they show a profound remodeling of the excitation contraction coupling apparatus, which is characterized by narrower terminal cisternae and by the appearance of multilayered junctions, likely due to a compensatory effect in response to a reduction in Ca^{2+} storage capacity. Although muscle performance is not significantly impaired, measurement of Ca^{2+} release parameters revealed that the average amplitude of Ca^{2+} release following either low frequency electrical stimulation or caffeine treatment was reduced (Paolini et al. 2007; Tomasi et al. 2012). Nevertheless, CASQ1 knockout mice were unable to sustain prolonged muscle activity; actually, the time parameters of twitch were significantly longer compared to wild type mice, with a significant increased rate of SR Ca^{2+} depletion, likely due to a reduced inhibition of the RyR1 Ca^{2+} release activity (Canato et al. 2010). Together these observations suggest that ablation of CASQ1 correlated with a reduction in the SR Ca^{2+}content associated with an impaired Ca^{2+} re-uptake by the SR, possibly due to a decreased efficiency of SERCA pumps and/or of the SOCE refilling process (Paolini et al. 2007, 2011; Protasi et al. 2011; Canato et al. 2010). In slow twitch skeletal muscle fibers, expression of CASQ2 in addition to CASQ1 may further support intraluminal Ca^{2+} buffering. However, depletion of both isoforms in double knockout mice resulted in a decrease in Ca^{2+} store amplitude and SR refilling, with kinetics similar to CASQ1 knockout mice, suggesting that the role of CASQ2 in slow twitch muscle fibers may not be determinant (Canato et al. 2010). On the contrary, in C2C12 cells CASQ2 seems to play a more relevant role than CASQ1 in determining the SR Ca^{2+} store, since depletion of CASQ1 following small interfering RNA transfection does not result in a significant depletion of the SR (Wang et al. 2006). It has to be mentioned, however, that muscle fibers devoid of CASQ1 or CASQ2 or both can still sustain Ca^{2+} release and muscle contraction, suggesting that other molecules, such as the Histidine Rich Calcium (HRC) Binding Protein may provide reversible Ca^{2+} binding and luminal Ca^{2+} buffering together with or in alternative to CASQ (Canato et al. 2010; Royer and Ríos 2009).

One of the most interesting phenotypic traits of CASQ1 knockout mice is their increased susceptibility to undergo hypermetabolic crises in response to halothane, heat-exposure and physical exertion, a syndrome remarkably similar to human malignant hyperthermia (MH) and environmental/exhertional heat-stroke (Paolini et al. 2011; Dainese et al. 2009; Protasi et al. 2009; Michelucci et al. 2015, 2017a, b; Guarnier et al. 2018). Loss of inhibition of RyR1 activity due to CASQ1 ablation (Beard et al. 2002) and SR Ca^{2+} depletion (Canato et al. 2010) may explain this MH-like phenotype in CASQ1 knockout mice, although the exact mechanisms still need to be elucidated.

However, despite evidence that CASQ1 knockout mice clearly show typical traits of human MH, no mutations in CASQ1 have been associated to human Malignant Hyperthermia, although reports of variants of unknown significance have detected in some patients (Kraeva et al. 2013; Lewis et al. 2015; Bjorksten et al. 2016).

CASQ2-related mouse models

CASQ2 knockout mice are viable and display normal SR Ca^{2+} release and contractile function under basal conditions. Nevertheless, these mice show an increased SR volume and absence of triadin and junctin. Exposure to catecholamines caused increased diastolic SR Ca^{2+} leak, resulting in premature spontaneous SR Ca^{2+} release, a condition that closely mimics human arrhythmias (Knollmann et al. 2006; Chopra et al. 2007). On the contrary, transgenic mice for CASQ2 showed cardiac hypertrophy and alteration of the beta-adrenergic receptor signaling, together with a reduction in Ca^{2+}-induced-Ca^{2+} release and frequency of Ca^{2+} sparks (Jones et al. 1998; Cho et al. 1999; Wang et al. 2000; Schmidt et al. 2000). A more recent model of CASQ2 knockout mice showed that the same alterations in Ca^{2+} release can be detected both in the atrium and in ventricle, indicating a more extended role of CASQ2 in cardiac Ca^{2+} physiology (Gergs et al. 2017). Moreover, a role of CASQ2 in the cardiac conduction system was described. In particular, CASQ2 deletion was found to give rise to sinus and atrio-ventricular nodal dysfunctions, which, together with alterations occurring in ventricular cardiomyocytes, correlate with development of the catecholaminergic polymorphic ventricular tachycardia (CPVT) phenotype (Glukhov et al. 2015; Faggioni et al. 2013; Flores et al. 2018).

Novel roles of CASQ in muscle physiology and Ca^{2+} homeostasis

Store-operated Ca^{2+} entry (SOCE) represents an important mechanism for the refilling of depleted intracellular-reticulum Ca^{2+} stores. In muscle fibers, this process is necessary to maintain the Ca^{2+} stores at steady state levels as well as for generation of long-lasting Ca^{2+} signals and contractile function during tetanic stimulation and fatigue (Launikonis and Ríos 2007; Stiber et al. 2008; Stiber and Rosenberg 2011; Pan et al. 2014; Michelucci et al. 2018). The SOCE pathway is operated by the coordinated activity of two main molecules: stromal interaction molecule 1 (STIM1) and calcium release-activated calcium channel protein 1 (Orai1) whose activation should be tightly regulated. The process that supports SOCE activation in non-excitable cells is slow (Lunz et al. 2019), as it requires a sequence of events starting from STIM1 sensing a drop of endoplasmic reticulum (ER) Ca^{2+} levels by intraluminal EF-end motifs that triggers structural rearrangement and oligomerization; the cytoplasmic C-terminus acquires an extended conformation that exposes a STIM–Orai1 activating region (SOAR) that, in turn, induces Orai1 cluster formation and channel activation. In skeletal muscle, a longer form of STIM1 (STIM1L) exists and forms permanent STIM1L–Orai1 clusters (Darbellay et al. 2011): this could explain the rapid SOCE activation that sustains repetitive bursts of tetanic stimulations by compensating for Ca^{2+} efflux occurring during normal muscle contraction (Launikonis et al. 2010). More recently, intense exercise was found to induce formation of intracellular junctions in skeletal muscle between stacks of SR cisternae and extensions of transverse-tubules; these were proposed to increase co-localization of proteins required for SOCE and thus to optimize Ca^{2+} entry and SR refilling during acute exercise (Boncompagni et al. 2017, 2018; Michelucci et al. 2019).

Given that CASQ has a key role in regulating the intraluminal Ca^{2+} concentration, it can be expected that it may also play a role in SOCE. Indeed, it was originally proposed that CASQ may provide a retrograde signal to regulate this process (Ma and Pan 2003; Shin et al. 2003). This early idea was later supported by experiments showing that knockdown of CASQ1 in *flexor digitorum brevis* (FDB) muscle fibers increased Ca^{2+} entry across the sarcolemma (Zhao et al. 2010). Additional evidences demonstrated that monomeric CASQ1 that forms following Ca^{2+} store depletion can actually interact with STIM1 and inhibit STIM1/Orai1 interaction (Wang et al. 2015; Zhang et al. 2016). In particular, amino acid residues 362–396 of CASQ1 were proposed to be responsible for CASQ1-STIM1 association, since expression of CASQ1 proteins deleted in this region did not result in SOCE inhibition (Zhang et al. 2016).

More recently, the ER stress response sensor IRE1α was identified as a novel interactor of CASQ in cardiac and skeletal muscle. Interaction with CASQ1 prevents IRE1α oligomerization and activation, suggesting that this may represent a cell approach to avoid IRE1α activation in response to the constant fluctuations in the Ca^{2+} concentration that occur in the SR during muscle contraction and relaxation cycles (Wang et al. 2019).

Calsequestrin and human diseases

CASQ2 mutations in cardiac diseases

The importance of calsequestrin in the regulation of Ca^{2+} handling in striated muscles is supported by identification of mutations in both CASQ1 and CASQ2 genes associated to human diseases (see Table 1). The first mutations in CASQ were identified in the CASQ2 gene in patients affected by CPVT, a form of cardiac arrhythmia which occurs in the absence of structural abnormalities (Lahat et al. 2001, 2003, 2004; Eldar et al. 2003; Viatchenko-Karpinski et al. 2004; Houle et al. 2004; Postma et al. 2002). At present, more than ten different mutations have been identified in both recessive and dominant forms of CPVT. The characterization of some of these mutations confirmed that CASQ2 regulates the SR Ca^{2+} store both by acting as an active Ca^{2+} buffer, which controls the amount of releasable Ca^{2+} upon each stimulation and by controlling SR re-charging and RyR2 channel sensitivity to luminal Ca^{2+} (Györke et al. 2004a, b). The first mutation in CASQ2, the D307H mutation, was identified in a patient affected by a recessive form of CPVT and was characterized in rat myocytes and, more recently, through generation of hIPSC-derived cardiomyocytes from affected patients (Maizels et al. 2017). Expression of the mutant protein resulted in a decrease in SR Ca^{2+} storage capacity and Ca^{2+} release, with signs of delayed afterdepolarization likely due to abnormal Ca^{2+} polymerization and buffering of the mutant protein at high Ca^{2+} concentrations (Viatchenko-Karpinski et al. 2004; Houle et al. 2004; Dirksen et al. 2007; Kalyanasundaram et al. 2009; Novak et al. 2012; Maizels et al. 2017). On the contrary, expression of the R33Q mutation in CASQ2 led to an increase in Ca^{2+} release and occurrence of spontaneous Ca^{2+} sparks, suggesting that the R33Q mutation lost its ability to inhibit RyR2 at low Ca^{2+} concentrations (Terentyev et al. 2006). Accordingly, an enhanced sensitivity of RYR2 to cytosolic [Ca^{2+}] and longer RyR2 open times were observed in CASQ2 R33Q knock-in mice (Chen et al. 2013). An even more significant reduction in the ability of CASQ2 to inhibit RyR2 activity was observed for the L167H mutation (Qin et al. 2008). Cristal structures obtained for the D307H and the R33Q mutant proteins revealed that they had a reduced

Table 1 CASQ mutations in striated muscle disease

Mutation	Genetics	Clinical phenotype	Proposed mechanism	References
CASQ1 D244G	Heterozygous	Vacuolar myopathy, mild myopathy accompanied by muscle cramping, reduced muscle strength, fatigue, and elevated plasma creatine kinase (CK) levels. Presence, mainly in type II fibers, of vacuoles that does not stain by routine histochemical analysis and contain aggregates of SR proteins	D244G mutation weakens the hydrophobic core of domain II and shows a novel dimeric interaction, which alters protein polymerization. This causes the protein to form large aggregates with reduced Ca^{2+} binding ability	Rossi et al. (2014b), Lewis et al. (2015) and D'Adamo et al. (2016)
CASQ1 D44N	Heterozygous	Tubular aggregate myopathy with muscle fatigue and diffuse exercise- induced myalgia	Decreased Ca^{2+} dependent polymerization leading to decreased Ca^{2+} binding ability and loss of SOCE inhibition	Barone et al. (2017)
CASQ1 N56Y	Heterozygous	Tubular aggregate myopathy with muscle weakness in proximal muscles of lower limbs	Decreased Ca^{2+} dependent polymerization	Bohm et al. (2017)
CASQ1 D103G	Heterozygous	Tubular aggregate myopathy with exercise-induced muscle pain, stiffness, and early fatigue	Decreased Ca^{2+} dependent polymerization leading to decreased Ca^{2+} binding ability	Barone et al. (2017) and Bohm et al. (2017)
CASQ1 I385T	Heterozygous	Tubular aggregate myopathy with myalgia and proximal muscle weakness	Moderately increased Ca^{2+} dependent polymerization leading to decreased Ca^{2+} binding ability and loss of SOCE inhibition	Barone et al. (2017)
CASQ2 W361X	Homozygous mutation	Syncopal episodes since childhood. ECG at rest withleft axis deviation and QT-U prolongation. Polymorphic ventricular ectopy, which progressed to polymorphic ventricular tachycardia	Not tested	Fujisawa et al. (2019)
CASQ2 K87X and W361X	Compound heterozygous	Proband lost consciousness at his nursery school while playing with other children and was found to have pulseless pVT in the emergency room	Not tested	Kawamura et al. (2013)
CASQ2 Y55C and P308L	Compound heterozygous	Exercise stress testing revealed the onset of monomorphic ventricular premature beats progressing into polymorphic non-sustained VT. The patient experienced syncope during whilst running, despite having taken sotalol as prescribed	Altered conformation mainly due to the P308L substitution	de la Fuente et al. (2008)
CASQ2 D307H	Homozygous mutation	Early age at onset and a high mortality rate when untreated, resting bradycardia and a mild prolongation of the QTc segment	Decrease in SR Ca^{2+} storage capacity and Ca^{2+} release due to reduced Ca^{2+} binding capacity due to altered polymerization	Lahat et al. (2001)
CASQ2 62delA	Homozygous	Exercise-induced syncope	Total absence of functional CASQ2 protein	Postma et al. (2002)
CASQ2 532+1 G/A	Homozygous intronic base pair change	Exercise-induced syncope	Total absence of functional CASQ2 protein	Postma et al. (2002)
CASQ2 R33X	Heterozygous	Exercise-induced syncope	Reduction of functional CASQ2 protein	Postma et al. (2002)

Table 1 (continued)

Mutation	Genetics	Clinical phenotype	Proposed mechanism	References
CASQ2 K180R	Heterozygous	Sudden death	Not tested	Gray et al. (2016)
CASQ2 G112+5X	Homozygous	Exercise-induce syncopal episodes, rapid polymorphic ventricular tachycardia	CASQ2 G112+5X does not bind Ca2+ and leads to a reduction in SR Ca2+ release and calcium content. CASQ2 G112+5X lacks the amino acids involved in either front-to-front or back-toback interactions	di Barletta et al. (2006)
CASQ2 G112+5X L167H	Compound Heterozygous	Multiple syncopal events and runs of polymorphic ventricular tachycardia	Reduction in SR Ca^{2+} release and calcium content	di Barletta et al. (2006)
CASQ2 K206N	Heterozygous	Syncopes, in relation with emotion, stress, swimming and exercise	Reduced oligomers formation and Ca^{2+} binding capacity. Increase of the opening state of RyR2 calcium channels	Kirchhefer et al. (2010)
CASQ2 R33Q	Homozygous	Exercise-induced syncopal episodes	Reduction of the inhibitory effect on RyR2 resulting in enhanced sensitivity of the RyR2 channel to activation by luminal Ca^{2+}	Terentyev et al. (2006)
CASQ2 Q67X + 532+1 G/A	Compound heterozygous	The proband presented at age 11 with a history of palpitations and exercise syncope since the age of 3	Absence of CASQ2 due to presence of a stop codon mutation in one allele and alteration of the splicing process in the second allele	Josephs et al. (2017)

Ca^{2+} binding capacity due to altered polymerization. In particular, R33Q and D307H mutants did not form properly oriented dimers, while L167H mutant resulted in formation of high molecular weight aggregates (Kim et al. 2007). Molecular conformation studies confirmed that the R33Q mutation resides in a region of the protein responsible for the bidirectional transition from monomer to dimer (Bal et al. 2010). Finally, the K206N mutations creates an additional N-glycosylation site and it is associated with a reduction in oligomer formation and Ca^{2+} binding capacity. In cardiomyocytes, these alterations caused a reduction of the SR Ca^{2+} load and an increase in spontaneous RyR2 opening (Kirchhefer et al. 2010).

CASQ1 mutations in skeletal muscle myopathies

A mutation in CASQ1, D244G, was first described in patients affected by a mild myopathy characterized by the presence of inclusions containing an excess of SR proteins, including CASQ1 (Tomelleri et al. 2006; Rossi et al. 2014b; D'Adamo et al. 2016). The mutation affects a conserved high-affinity Ca^{2+} binding sites of CASQ1 and alters the kinetics of CASQ1 polymerization and Ca^{2+} release in muscle fibers and primary myotubes (Rossi et al. 2014b). In particular, D244G CASQ1 forms large aggregates, with atypical dimer interactions (Lewis et al. 2015) (Fig. 1). Additional CASQ1 mutations were later identified in patients affected by Tubular Aggregate Myopathy (TAM). TAMs were originally associated with mutations in STIM1, mostly in the Ca^{2+} sensing EF hand in the N-terminal luminal region (Bohm et al. 2013), or in Orai1 (Nesin et al. 2014; Lacruz and Feske 2015; Bohm et al. 2017; Bohm and Laporte 2018a). All these mutations resulted in SOCE hyperactivation; on the contrary, a mutation, in the cytoplasmic C-terminal inhibitory domain of STIM1, identified in a family with TAM, induced a decrease in Ca^{2+} influx (Okuma et al. 2016), suggesting a general dysregulation of SOCE and Ca^{2+} homeostasis in the pathogenesis of TAM (Lee and Noguchi 2016). Concerning CASQ1, four mutations, D44N, N56Y, G103D, and I385T have been identified in patient with TAM. Similar to the D244G mutation, alteration of CASQ1 polymerization was a typical trait of these mutations, resulting in a reduced ability to store Ca^{2+} (Barone et al. 2017; Bohm et al. 2018b). The altered Ca^{2+}-dependent aggregation of some of these mutated CASQ1 proteins was also associated with altered SOCE. In particular, two of these mutants (D44N and I385T), were shown to have lost the ability to inhibit SOCE, while the G103D mutant was still able to inhibit Ca^{2+} influx (Barone et al. 2017), further supporting that a general dysregulation of SOCE and Ca^{2+} homeostasis, either due to mutations in STIM1 and Orai1,

or to mutations in CASQ1 can be associated to development of TAM (see Table 1).

Additional proposed CASQ-related diseases

In addition to typical muscle diseases, the genomic region where the CASQ1 gene maps has been associated to type 2 diabetes susceptibility. *CASQ1* is localized to human chromosome 1 (Fujii et al. 1990). In particular, two SNPs in intron two of the *CASQ1* gene were found to be strongly associated in the Caucasian population in North America with type 2 diabetes; other SNPs were also found to be associated with the same disease in the Amish population. However, the molecular mechanisms explaining the correlation between CASQ1 and diabetes have not been defined yet (Das et al. 2004; Fu et al. 2004). In addition, in the Danish population this correlation apparently does not exist, suggesting that association of CASQ1 with type 2 diabetes may be a coincidence or may be restricted to specific populations (Sparsø et al. 2007).

Finally, CASQ1 was found to be associated with Graves' ophthalmopathy, a disease associated with the thyroid autoimmune disorder Graves' disease. Significant levels of antibodies against CASQ1 or CASQ2 are present in the serum of patients affected by this disease; although the exact correlation with the pathological phenotype of these patients has not been defined, it has been suggested that these antibodies may contribute to eye muscle damage and/or cardiac complications associated with the disease (De Haan et al. 2010).

Concluding remarks

Since its initial identification as an intraluminal Ca^{2+} buffering protein, the role of CASQ in striated muscle has been continuously updated and novel functional aspects are being depicted. In this respect, the involvement of CASQ in the regulation of SOCE and ER stress response as well as in the cardiac muscle conduction system open new perspectives in the pathophysiology of striated muscle cells. Next generation sequencing approaches are constantly in progress to identify novel mutations in CASQ1 and CASQ2 genes associated with skeletal or cardiac myopathies. No target-specific therapeutic approaches have been identified so far. On this line, recent studies on the development and characterization of induced pluripotent stem cell lines generated from patients carrying CASQ2 mutations show that cardiomyocytes derived from these cells appear to recapitulate the main features of disease specific phenotypes thus representing a valuable model for personalized drug development and mutation screening.

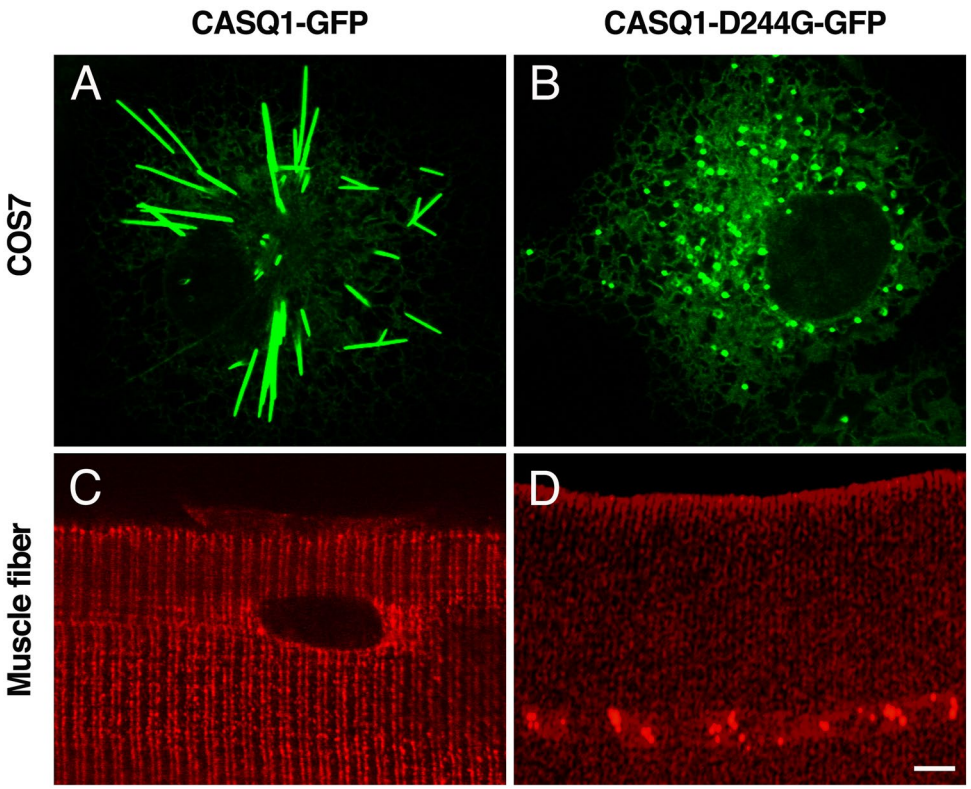

Fig. 1 Expression and localization of wild type and D244G CASQ1 in COS7 cells and in adult muscle fibers. Wild type CASQ1 distributed in regular linear structures resembling CASQ1 polymers in COS7 cells (**a**) and localized at triads in adult skeletal muscle fibers (**c**). The D244G CASQ1 mutation identified in patients affected by vacuolar myopathy affects CASQ1 polymerization. Expression of the D244G CASQ1 mutant in COS7 cells resulted in protein assembly in puncta (**b**), while in skeletal muscle fibers it formed large intracellular aggregates (**d**) (Tomelleri et al. 2006; Rossi et al. 2014b). Bar = 3.5 µm

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Compliance with ethical standards

Conflict of interest The authors declare not to have conflicts of interest or competing interests.

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