Ryanodine Receptors: Structure, Expression, Molecular Details, and Function in Calcium Release

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Ryanodine receptors (RyRs) are located in the sarcoplasmic/endoplasmic reticulum membrane and are responsible for the release of Ca^{2+} from intracellular stores during excitation-contraction coupling in both cardiac and skeletal muscle. RyRs are the largest known ion channels (>2MDa) and exist as three mammalian isoforms (RyR 1–3), all of which are homotetrameric proteins that interact with and are regulated by phosphorylation, redox modifications, and a variety of small proteins and ions. Most RyR channel modulators interact with the large cytoplasmic domain whereas the carboxy-terminal portion of the protein forms the ion-conducting pore. Mutations in RyR2 are associated with human disorders such as catecholaminergic polymorphic ventricular tachycardia whereas mutations in RyR1 underlie diseases such as central core disease and malignant hyperthermia. This chapter examines the current concepts of the structure, function and regulation of RyRs and assesses the current state of understanding of their roles in associated disorders.

Intracellular Ca^{2+} is an important secondary messenger for signal transduction and is essential for cellular processes such as excitation-contraction coupling (E-C coupling). The major source of intracellular Ca^{2+} is the sarcoplasmic reticulum (SR) in striated muscle and the endoplasmic reticulum (ER) in other cell types. There are two major Ca^{2+} release channels localized in the SR/ER, the ryanodine receptors (RyRs) (Otsu et al. 1990) and inositol 1,4,5-triphosphate receptors (IP_3Rs) (Nixon et al. 1994). The present article reviews the structure, regulation, expression, and function of the RyRs. RyRs exist in three isoforms (RyR 1-3) and are named after the plant alkaloid ryanodine, which binds to RyRs with high affinity and specificity and displays preferential interactions with the open state of the channel allowing its usage to evaluate the functional state of the channel (Imagawa et al. 1987; Inui et al. 1987; Lai et al. 1988; Chu et al. 1990). Ryanodine at nanomole concentrations locks the channel in an open subconductance state and inhibits the channel at high concentrations (>100 μM) (Meissner et al. 1986; Lai et al. 1989; McGrew et al. 1989). RyRs are homotetamers with a total molecular mass of >2 MDa (each subunit is >550 kDa) (Inui et al. 1987; Lai et al. 1988). RyRs are modulated (see Fig. 1) directly or indirectly by the dihydropyridine receptor

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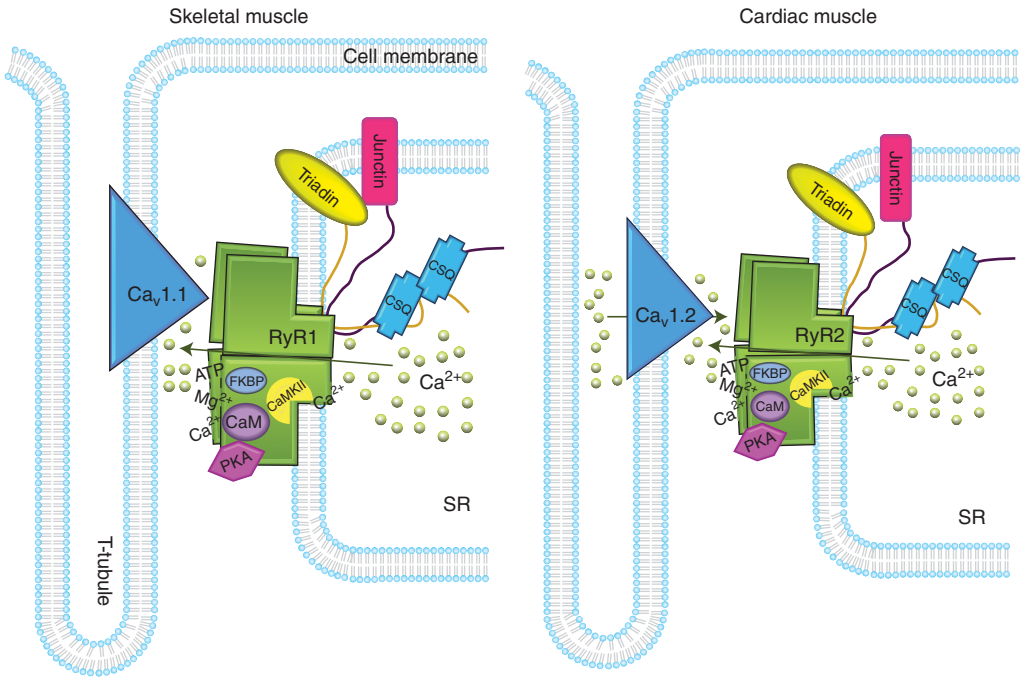

Figure 1. Schematic figure of the interaction between RyR and various modulators. *Left* panel illustrates skeletal muscle and *right* panel shows cardiac muscle. Modulators bind to the RyR tetramer but are for simplicity only depicted on one monomer.

(DHPR; also known as L-type Ca^{2+} channel, $Ca_V1.1/1.2$) and by various ions, small molecules and proteins, e.g., Ca^{2+}, Mg^{2+}, protein kinase A (PKA), FK506 binding proteins (FKBP12 and 12.6), calmodulin (CaM), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), calsequestrin (CSQ), triadin, junctin (Smith 1986; Tanabe et al. 1990; Ikemoto et al. 1991; Sabbadini et al. 1992; Wang and Best 1992; Brillantes et al. 1994; Chen and MacLennan 1994; Yang et al. 1994; Ma et al. 1995; Mayrleitner et al. 1995; Tripathy et al. 1995; Timerman et al. 1996; Nakai et al. 1998; Moore et al. 1999b; Rodney et al. 2000). RyR1 and RyR2 are crucial for E-C coupling in both skeletal and cardiac muscle, respectively. The action potential travels to transverse tubules (t-tubules) resulting in SR Ca^{2+} release, either by mechanical coupling to DHPR in skeletal muscle (Rios and Brum 1987) or by Ca^{2+} induced Ca^{2+} release in cardiac muscle (Endo 1977). Increases in cytoplasmic Ca^{2+} initiate muscle contraction. Ca^{2+} is then pumped back to the SR by sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) leading to relaxation (Nakai et al. 1998; Fill and Copello 2002). RyRs also play important roles in signal transduction in the nervous system and in osteoclasts where they contribute to secretion, synaptic plasticity, learning, and apoptosis (Zaidi et al. 1992; Chavis et al. 1996; Schwab et al. 2001).

RYANODINE RECEPTOR GENES AND ISOFORMS

There are three known mammalian isoforms of RyR: RyR1, RyR2, and RyR3. RyR1 was first detected in skeletal muscle (Takeshima et al. 1989; Zorzato et al. 1990), RyR2 was first found in cardiac muscles (Nakai et al. 1990; Otsu et al. 1990), and RyR3, previously referred to as the brain isoform, was found in brain (Hakamata et al. 1992). RyR1 is the most thoroughly examined isoform because of its high expression levels and ease of purification from skeletal muscle. In humans, the gene encoding RyR1 is located on chromosome 19q13.2 and spans 104 exons.

The gene encoding RyR2 is located on chromosome 1q43 and spans 102 exons, whereas the RyR3 gene with 103 exons is on chromosome 15q13.3-14. RyR1, 2, and 3 are located in chromosomes 7A3, 13A2, and 2E4 in mice (Mattei et al. 1994). In nonmammalian vertebrates RyRα and RyRβ are highly homologous to the three mammalian isoforms (Oyamada et al. 1994; Ottini et al. 1996). RyRs have been identified in *Drosophila (D) melanigaster*, *Caenorhabditis (C) elegans,* and *Homarus americanus* (Takeshima et al. 1994; Maryon et al. 1996; Quinn et al. 1998). The three mammalian isoforms are 65% identical in sequence (Hakamata et al. 1992) with three major regions of diversity: D1, between residues 4254 and 4631 in skeletal sequence and 4210 and 4562 in cardiac sequence; D2 between residues 1342 and 1403 in skeletal sequence and residues 1353 and 1397 in the cardiac sequence; D3, between residues 1872 and 1923 in skeletal sequence and 1852 and 1890 in the cardiac sequence. Region D2 is critical for the mechanical interaction between RyR1 and $Ca_V1.1$ (Perez et al. 2003) and mutations in D1 alter Ca^{2+} and caffeine sensitivity of RyR1 (Du et al. 2000). D3 may contain Ca^{2+} dependent inactivation sites (Hayek et al. 1999). In addition to these diverse regions, the large cytoplasmic domain is the site of both interaction with a large number of the modulators of channel activity, and many of the mutations that underlie the RyR channelopathies. Four-fifths of the RyR protein is cytoplasmic with ~one-fifth luminal and membrane spanning domains.

EXPRESSION OF RYANODINE RECEPTORS

The RyR1 isoform is primarily expressed in skeletal muscles (Takeshima et al. 1989; Zorzato et al. 1990) and is located in the junctional region of the terminal SR (Franzini-Armstrong and Nunzi 1983). RyR1 also appears to be expressed at low levels in cardiac muscle, smooth muscle (Neylon et al. 1995), stomach, kidney, thymus (Nakai et al. 1990; Giannini et al. 1995), cerebellum, Purkinje cells, adrenal glands, ovaries, and testis (Marks et al. 1989; Takeshima et al. 1989; Furuichi et al. 1994; Ottini et al. 1996). Recently it has been shown that RyR1 is also expressed in B-lymphocytes (Vukcevic et al. 2010).

The predominant form of RyR in cardiac muscle is RyR2 (Nakai et al. 1990; Otsu et al. 1990). Recently a splice variant of RyR2 was identified in the heart that increases susceptibility to apoptosis (Valdivia 2007). RyR2 is also expressed at high levels in Purkinje cells of cerebellum and cerebral cortex (Lai et al. 1992; Nakanishi et al. 1992; Sharp et al. 1993; Furuichi et al. 1994) and in low levels in stomach, kidney, adrenal glands, ovaries, thymus, and lungs (Kuwajima et al. 1992; Giannini et al. 1995).

RyR3 is expressed in hippocampal neurons, thalamus, Purkinje cells, corpus striatum (Hakamata et al. 1992; Lai et al. 1992; Furuichi et al. 1994), skeletal muscles (highest expression in the diaphragm) (Neylon et al. 1995; Marks et al. 1989), the smooth muscle cells of the coronary vasculature, lung, kidney, ileum, jejunum, spleen, stomach of mouse and aorta, uterus, ureter, urinary bladder, and esophagus of rabbit (Giannini et al. 1992; Hakamata et al. 1992; Giannini et al. 1995; Ottini et al. 1996).

Nonmammalian vertebrates, such as birds, fish, and chickens express isoforms RyRα and β (O'Brien et al. 1993). RyRα is abundant in skeletal muscles and its expression is lower in brain (cerebellum) (Oyamada et al. 1994). RyRβ is expressed in various tissues including skeletal and cardiac muscles, cerebellum, lungs, and stomach (Oyamada et al. 1994). In *C. elegans* RyRs are found in body wall, vulval, anal, and pharyngeal muscles (Hamada et al. 2002). In *D. melanogaster* a single isoform of RyR is expressed in digestive tract and nervous system (Vazquez-Martinez et al. 2003).

ROLE OF RYANODINE RECEPTORS IN HUMAN DISEASES

Mutations in both RyR1 and RyR2 are associated with a number of human diseases. Mutations in the RYR1 gene underlie several debilitating and/or life-threatening muscle diseases including malignant hyperthermia (MH) (MacLennan et al. 1990), heat/exercise induced exertional rhabdomyolysis (Capacchione et al. 2010), central core disease (CCD) (Zhang et al.

1993), multiminicore disease (MmD) (Ferreiro et al. 2002), and atypical periodic paralyses (APP) (Zhou et al. 2010). Mutations in RyR2 cause/are associated with catecholaminergic polymorphic ventricular tachycardia (CPVT) and arrhythmogenic right ventricular dysplasia type 2 (ARVD2) (Phillips et al. 1994, Zhang et al. 1993, Magee et al. 1956). Today around 300 mutations have been identified and linked to diseases associated with RyR (Fig. 2).

MH is an autosomal dominant disease in which genetically susceptible individuals respond to inhalation anesthetics (e.g., halothane) and muscle relaxants (e.g., succinylcholine) with sustained muscle contractions (Mickelson and Louis 1996). More than 150 different point mutations in the RYR1 gene have been identified and linked to MH (Fig. 2). The majority of RyR1 mutations linked to MH cluster in the cytoplasmic domains of RyR1 (amino acids 35 to 614 and 2129 to 2458). Another cluster of mutations is found near the carboxyl terminus (4637 to 4973) (Phillips et al. 1994; Quane et al. 1994; Lynch et al. 1999; Monnier et al. 2000; Scacheri et al. 2000; Tilgen et al. 2001). MH is often a silent disorder that goes undetected until the patient undergoes surgery or is exposed to high ambient temperatures (~37°C) (Jurkat-Roth et al. 2000). The underlying physiological consequence of MH is abnormal calcium homeostasis with increase sensitivity of channel opening in response to activators (Tong et al. 1999).

An MH episode is characterized by elevations in body temperature, metabolic acidosis, hypoxia, tachycardia, skeletal muscle rigidity, and rhabdomyolysis (Denborough et al. 1962; Ellis et al. 1988; Pamukcoglu 1988; Britt et al. 1991; Ryan and Tedeschi 1997) and is life threatening if not immediately treated with dantrolene, currently the only clinically approved treatment for MH (Ward et al. 1986; Zhao et al. 2001; Paul-Pletzer et al. 2002). The incidence of MH is ~1 in 15,000 anesthetized children and ~1 in 50,000 to 100,000 anesthetized adults (MacLennan 1992; Strazis and Fox 1993; Rosenberg et al. 2007). Another disorder related

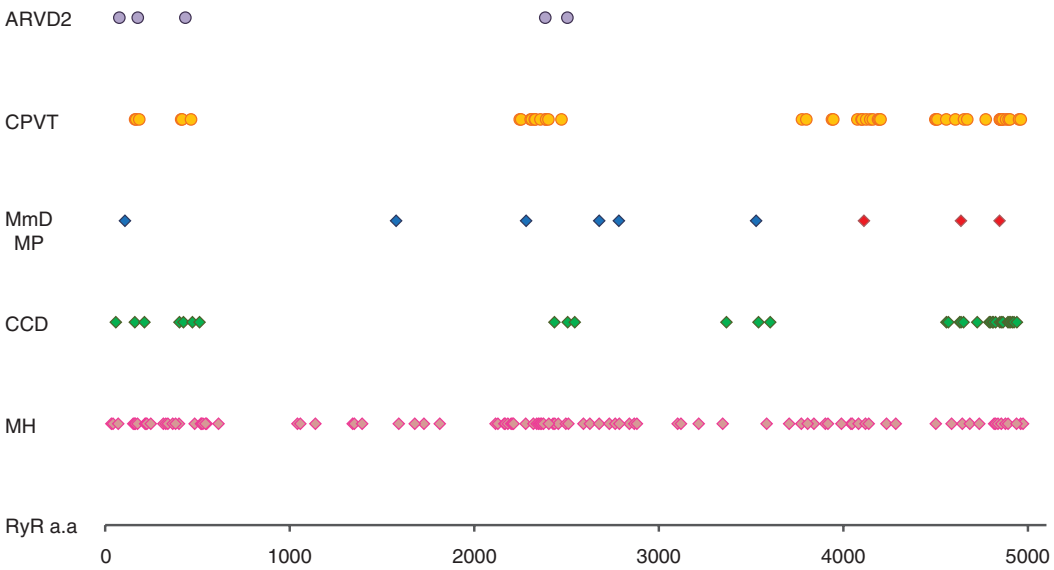

Figure 2. Linear presentation of RyR primary sequence outlining known mutations associated with skeletal and cardiac muscle diseases. Diamond shaped dots represent RyR1 mutations associated with: MH (151 mutations), CCD (63 mutations), and MmD (blue, 6 mutations) or other myopathies (MP, red, 4 mutations). Circles represent RyR2 mutations associated with: CPVT (53 mutations) and ARVD2 (5 mutations). Data collected from HGMD® (database of human gene mutation data) until 2006, UniProt 2007–2009, and publication by Vukcevic et al. 2010).

to MH is heat/exercise-induced exertional rhabdomyolysis; a clinical syndrome where heat/exercise-induced triggers breakdown of striated muscles that results in renal failure, hyperkalemia, and multi-organ failure. Approximately 26,000 cases are identified per year in United States (Capacchione et al. 2010).

CCD is a congenital myopathy in humans, and is characterized by hypotonia and muscle weakness of lower extremities leading to delayed attainment of motor skills (Dirksen and Avila 2002; Lueck and Dirksen 2004; Robinson et al. 2006). Slow-twitch (type I) skeletal muscles (e.g., soleus) of CCD of patients exhibit amorphous areas (central cores) that lack mitochondria and oxidative enzyme activity (Magee and Shy 1956; Shuaib et al. 1987). In some cases SR and t-tubules also degenerate and resting Ca^{2+} concentrations elevate with or without luminal store depletion (Tong et al. 1999). The majority of CCD causing mutations are in the pore-forming domain of RyR1 (Lynch et al. 1999; Monnier et al. 2000; Scacheri et al. 2000; Tilgen et al. 2001). Incidence of CCD is ~1 in 16,000 of total congenital myopathies and ~1 in 100,000 live births (Jungbluth 2007a).

MmD is an autosomal recessive myopathy characterized by weakness in axial and proximal limb muscles, hypoxia, and muscle biopsies showing characteristic mini cores due to lack of oxidative enzyme activity (Jungbluth 2007b; Sharma et al. 2007).

APP are dominant and genetically heterogeneous conditions characterized by muscle weakness and are divided into hypokalemic periodic paralysis and hyperkalemic periodic paralysis. Mutations on SCN4A and CASNAS1S gene that codes for α1s subunit of DHPR have been identified as general cause of hypokalemic- and hyperkalemic-periodic paralysis, respectively. Recently in a patient suffering from MmD the RyR1 mutation Arg2939Lys has been identified and clinical features of the patient are reminiscent of hyperkalemic periodic paralysis, suggesting a new RyR1-related form of periodic paralysis with additional myopathy features (Zhou et al. 2010).

Mutations in RyR2 produce altered Ca^{2+} homeostasis leading to ARVD2 (Dalla Volta et al. 1961; Marcus et al. 1982; Fontaine et al. 1984) and CPVT (Marks et al. 2002; Priori et al. 2002; Laitinen et al. 2003). ARVD2 an autosomal dominant cardiac disease characterized by replacement of myocytes with fibrofatty tissue leading to ventricular arrhythmias (Corrado et al. 2000). Mutations in RyR2 are detected at three regions that are homologous to the mutations on RyR1 associated with MH and CCD. Studies in ARVD2 suggest that Ca^{2+} leakage from myocardial SR via dysfunctional RyR2 is associated with development of ventricular arrhythmias (Tiso et al. 2001). The incidence of ARVD2 is ~1 in 10,000 adults in United States (Fontaine et al. 2001). CPVT is characterized by stress-induced ventricular tachycardia (Marks et al. 2002; Priori et al. 2002; Laitinen et al. 2003). Roles for protein kinase A (PKA) and Ca^{2+}/calmodulin dependent protein kinase II (CaMKII) phosphorylation and enhancement of RyR2 open probability in these arrhythmias has been suggested (Valdivia et al. 1995; Marx et al. 2000; Wehrens et al. 2004). In single channel recordings it has been shown that CPVT RyR2 mutation Arg4496Cys increases open probability at low Ca^{2+} concentrations (~5 nM) but not at higher concentrations (~150 nM) (Jiang et al. 2002; Wehrens and Marks 2003). In patients with CPVT increased PKA phosphorylation and leaky RyR2 channels was observed during β-adrenergic stress and exercise. Binding studies in vitro suggested that the mutant RyR2 associated with CPVT have lower affinity for FKBP12.6 (Wehrens et al. 2003). Later studies suggested that CPVT RyR2 expressing cells are more sensitive to β-adrenergic receptor stimulation (by either isoproterenol or forskolin) and have prolonged Ca^{2+} transients under these conditions. This sensitivity does not appear to be caused by differences either in RyR2 phosphorylation or loss of FKBP12.6 (George et al. 2003). Nonsense or missense mutations in the calsequestrin 2 gene have also been associated with autosomal recessive form of CPVT (Lahat et al. 2001; Postma et al. 2002).

RyR3 is the least studied ryanodine receptor, and consequently little is known of its function. Recently, RyR3 was suggested to play a role

in Alzheimer's disease, and up-regulation of RyR3 in cortical neurons is neuroprotective in TgCRND8 mouse model of Alzheimer's disease (Supnet et al. 2009).

ULTRASTRUCTURAL STUDIES ON RYANODINE RECEPTOR

The Size Challenge

RyRs, the largest known ion channels (Takeshima et al. 1989; Nakai et al. 1990; Otsu et al. 1990; Zorzato et al. 1990; Hakamata et al. 1992), are large conductance channels (Smith et al. 1985; Smith et al. 1986b) capable of creating rapid transient increases of cytosolic Ca^{2+}. Analysis of the primary structure of RyRs reveals several functional motifs seen in other proteins; but the role of these motifs in RyRs function has not yet been elucidated (see review Hamilton and Serysheva 2009). The importance of RyRs in mammalian physiology and disease drives the need for high resolution structural information. The massive size, multiple modulators, and the dynamic nature of RyRs make their structural analysis a challenge. Advances in single-particle electron cryomicroscopy (cryo-EM) and crystal structures of small fragments (~200 amino acids) of the protein (Amador 2009; Lobo and Van Petegem 2009) are beginning to elucidate many important structural features.

Structural Studies on RyRs

Most cryo-EM studies on RyRs, (Radermacher et al. 1992; Radermacher et al. 1994; Serysheva et al. 1995; Orlova et al. 1996; Sharma et al. 1998; Serysheva et al. 1999; Benacquista et al. 2000; Sharma et al. 2000; Ludtke et al. 2005; Samsó et al. 2005; Serysheva et al. 2005; Serysheva et al. 2008; Samsó et al. 2009) and all the subnanometer resolution analysis (Serysheva et al. 2008; Samsó et al. 2009) have focused on the RyR1, however, some progress has been made with RyR2 (Sharma et al. 1998; Liu et al. 2002) and RyR3 (Sharma et al. 2000; Liu et al. 2001). Overall, the structures of all three isoforms are similar, consistent with the high sequence homology (~65%). However, the small differences seen are important, because they reflect variations in the primary sequence and are likely to be related to the specialized functions of each isoform.

RyRs form homotetramers of square prism shape and are arrayed in the SR where they control the release of Ca^{2+}. The cytoplasmic area of the channel (280 Å × 280 Å × 120 Å) is connected with the transmembrane region (120 Å × 120 Å × 60 Å) (Fig. 3). The membrane region constitutes approximately one-fifth of the channel and is localized to the carboxy terminal of the protein and forms the ion-conducting pore. The cytoplasmic/sarcoplasmic area that is also called the "foot" is a huge area with cavities and micro-structures that facilitate interactions with solvent, small molecules, and protein modulators. The corners of the cytoplasmic area, also called "clamps" are connected through the "handle" domain that surrounds the "central rim" domain of the cytoplasmic area. This area is connected to the membrane region through the "column." These structural domains have been divided in to 15 subdomains. The clamps (Fig. 3, subdomains 5, 6, 7, 8, 9, 10) undergo major conformational changes during the opening and closing of the channel (Serysheva et al. 2008; Samsó et al. 2009), are likely to participate in intermolecular interactions with neighboring RyRs, and are the sites of interactions with modulators (Wagenknecht et al. 1994; Wagenknecht et al. 1996; Wagenknecht et al. 1997; Samsó and Wagenknecht 2002; Samsó et al. 2006; Sharma et al. 2006; Meng et al. 2009). Two of the areas of high divergence in the primary sequence of the RyR isoforms were mapped in the clamps (Zhang et al. 2003; Liu et al. 2004). At subnanometer resolution seven α-helixes and three β-sheets have been localized to the clamp domain (Serysheva et al. 2008).

The handle domain that is formed by subdomains 3 and 4 (Fig. 3) has been found to contain an expanded region of divergence (Liu et al. 2002), and a β-sheet mapped on the subdomain 4 (Serysheva et al. 2008). In total seven β-sheets and 36 α-helixes at various orientations have been mapped on the cytoplasmic region

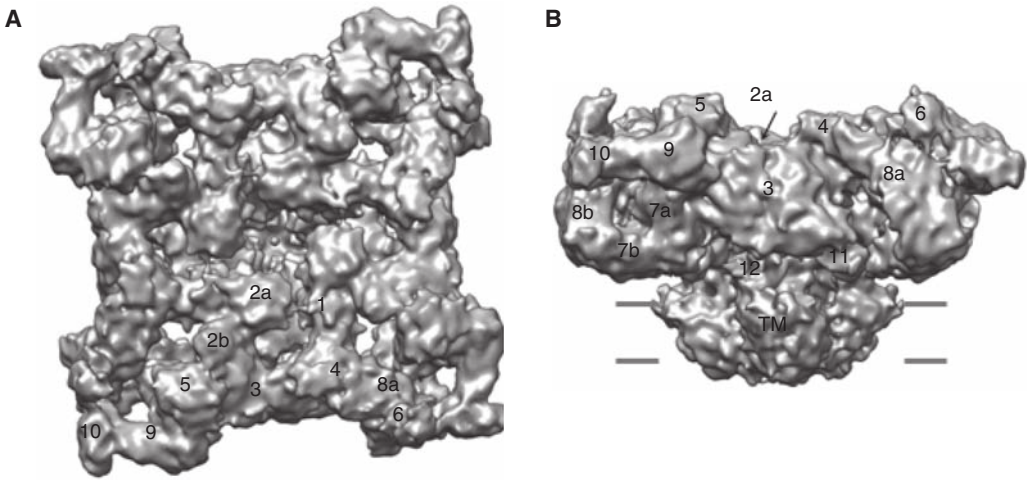

Figure 3. Cryo-EM reconstruction of RyR1 at 9.6 Å resolution. Cytoplasmic domain (*A*) and side view (*B*) of RyR1 with the different subdomains mapped by Irina Serysheva (See section "structural studies" for detailed information).

of the channel (Serysheva et al. 2008). These structures appear interconnected and merge toward the center of the molecule (Samsó et al. 2005). Two more β-sheets have been found in central rim (Fig. 3, subdomains 1,2) and one in the column (Fig. 3, subdomains 11,12), which also has eight α-helixes (Serysheva et al. 2008) that maintain the connection of the cytoplasmic and transmembrane regions (Samsó et al. 2005).

Current three-dimensional reconstructions at 8–10 Å resolution suggest five (Ludtke et al. 2005; Serysheva et al. 2008) or six α-helixes (Samsó et al. 2005) with different orientation in the transmembrane region of the closed channel. Although these studies (Ludtke et al. 2005; Samsó et al. 2005) were performed at similar conditions, they differ in interpretations, one study suggesting conformational similarity to the open K^+ channel (Ludtke et al. 2005) and the other suggesting a structure more similar to the closed K^+ channel (Samsó et al. 2005; Samsó et al. 2009). The conformation of the open RyR has so far only been proposed to resemble the conformation of the open K^+ channel (Samsó et al. 2009). The pore region has been predicted to consist of between 4 and 12 transmembrane segments (Takeshima et al. 1989; Zorzato et al. 1990; Tunwell et al. 1996; Du et al. 2002). Most of these models place both amino- and carboxy-termini in the cytoplasm. The ion conducting pore has been proposed to be located in the lumenal region and to include the GVRAGGGIGD amino acid sequence (4891–4900 human RyR1) (Zhao et al. 1999; Du et al. 2001) which is conserved between RyRs. The sequence GGIG has been proposed as the selectivity filter (Balshaw et al. 1999; Gao et al. 2000) based on the similarity with the consensus selectivity filter of K^+ channels. During channel opening, massive movements of cytoplasmic and transmembrane masses take place and result in a 4 Å increase of the ion gate (Samsó et al. 2009).

Crystal Structure of the Amino-Terminal Domain

The first crystal structures of RyRs are from the amino-terminal domain. The first 210 amino acids of the RyR1 structure (rabbit) was at 2.5 Å resolution (PDB ID code 3HSM) (Amador 2009), and a similar fragment (amino acids 9–205 of rabbit RyR1) was resolved at 2.9 Å resolution (PDB ID code 3ILA) (Lobo and Van Petegem 2009). The structure of the first 217 amino acids of mouse RyR2 was at 2.5 Å resolution (PDB ID code 3IM5) (Lobo and

Van Petegem 2009). These domains of RyR1 and RyR2 display the same overall fold, and consist of a β-trefoil domain flanked by a rigid α-helix. Furthermore, minor differences are seen in the loops connecting the various β-strands in the two isoforms (Amador 2009; Lobo and Van Petegem 2009).

Effects of Disease-Causing Mutations on the Structure of RyR1

An area rich in disease-associated mutations has been identified in the amino-terminal domain of RyR1 where mutations associated with MH and CCD have been located. Six are in a short loop between Gln156 and Asp167, and the rest either in different β-strands (Cys35, Arg178, and Tyr179) or loops (Leu14 and Arg45) (Amador 2009). Similar clustering of disease-causing mutations is seen in RyR2. Mutations found in RyR2 associated with CPVT and ARVD2, Arg169, and Arg176 (which correspond to Arg156 and Arg163 MH mutations of RyR1) are in a short loop with Pro164. Two more disease-causing mutations, Ala77 and Val186, are located in the rigid α-helix and in a small loop close to a β-strand, respectively (Lobo and Van Petegem 2009). These mutations in the amino-terminal of RyRs have been proposed to affect the interaction of RyR1 with modulators because they appear to cause only local changes in the structure (Amador 2009; Lobo and Van Petegem 2009). Another area of the amino-terminal region, amino acids 414–466 of RyR2 contains more than half of the amino-terminal mutations associated with cardiac arrhythmias and sudden death (Wang et al. 2007) and was mapped to a location between subdomains 5 and 9 using green fluorescent protein insertion into the primary structure and difference mapping of cryo-EM reconstructed structures (Wang et al. 2007). Notably, mutations at positions Glu161, Arg164, Arg402, and Ile404 of RyR1 and the mutations Arg169, Ile417, and Arg418 of RyR2 are located in the suggested FKBP binding pocket (Serysheva et al. 2008); whereas the Ile4898Thr CCD mutation appears to be located in the proposed selectivity filter in the pore region.

RYR REGULATION

RyRs, together with $Ca_v1.1/Ca_v1.2$, PKA, FKBP12 and 12.6, CaM, CaMKII, triadin, junction, and calsequestrin form the core of the macromolecular complex that regulates SR Ca^{2+} release. Thus, RyR structure, function and regulation are likely to be defined within this complex macromolecular set of interactions. Despite the ~65% sequence homology, the different RyR isoforms respond differently to some modulators. Most of the RyRs modulators interact with the cytoplasmic region of the channel, suggesting that they allosterically regulate channel gating. The locations of the binding sites for some of the modulators have been predicted from the primary structure, interactions with RyR1 fragments, and from difference mapping in the cryo-EM structures.

$Ca_v1.1$ and 1.2

The voltage dependent Ca^{2+} channels ($Ca_V1.1$ and $Ca_V1.2$, skeletal and cardiac isoforms respectively), also known as dihydropyridine receptors (DHPRs), are composed of multiple subunits: α_1, α_2/δ, β and γ for $Ca_V1.1$. $Ca_V1.2$ has α_1, α_2/δ, and β but the γ subunit has not been identified. The α_1 subunit is both the voltage sensing and the pore forming subunit. DHPRs and RyRs are targeted to either side of the narrow junctional gap that separates the external and internal membrane systems in striated muscle. They are arranged so that bidirectional structural and functional coupling can occur between the proteins. The molecular mechanism of E-C coupling is fundamentally different between skeletal and cardiac muscle (Rios and Brum 1987; Bers and Stiffel 1993; Garcia et al. 1994; Lamb 2000). In skeletal muscle a physical interaction between $Ca_v1.1$ and RyR1 is required for E-C coupling and SR Ca^{2+} release; referred to as voltage-induced Ca^{2+} release (Lamb 2000). In contrast, RyR2 Ca^{2+} release in cardiac muscle is initiated by Ca^{2+} influx via $Ca_V1.2$, designated Ca^{2+} induced Ca^{2+}-release (see review Bers 2002). Thus, cardiac E-C coupling is dependent on extracellular Ca^{2+} and functional coupling between $Ca_v1.2$

and RyR2, which is assumed to rely on spatial proximity between the proteins rather than physical interaction. Because of the role of the direct physical interaction between $Ca_V1.1$ and RyR1 in skeletal muscle, E-C coupling can proceed for long periods in the absence of extracellular Ca^{2+} (Armstrong CM 1972; Dulhunty and Gage 1988). The $Ca_V1.1$ and RyR1 interaction in skeletal muscle is dependent on the strict geometrical alignments between the two proteins, which has been shown with electron microscopy in different muscle preparations (Takekura et al. 1994; Protasi et al. 1998) A critical determinant of E-C coupling in skeletal muscle is the α_{1S} II-III loop of $Ca_v1.1$, with a minor involvement of the α_{1S} I-II loop (Tanabe et al. 1990; Nakai et al. 1998; Kugler et al. 2004). Other parts in addition to the α_{1S} II-III loop are also suggested to be able to interact with RyR, e.g., the carboxyl terminus and the α_{1S} III-IV loop (Slavik et al. 1997; Leong and MacLennan 1998). The β_{1a} carboxyl terminus is also important for E-C coupling (Beurg et al. 1999; Sheridan et al. 2003). Multiple regions of RyR1 are likely to be involved in the interactions with $Ca_v1.1$ (Nakai et al. 1998; Proenza et al. 2002; Protasi et al. 2002; Perez et al. 2003; Sheridan et al. 2006). The sites of interaction appear to be distributed over a large part of the cytoplasmic region, among them the divergent region 2 (Sheridan et al. 2006), which has been mapped to the clamp domains (Liu et al. 2004). Freeze-fracture studies suggest subdomains 4 and 6 as the most likely locations for contact with $Ca_V1.1$ (Paolini et al. 2004).

Mechanical E-C coupling may also play a role in other tissues that express Ca_v isoforms and RyR isoforms; for instance there is evidence for both cardiac-like Ca^{2+}-induced Ca^{2+}-release and skeletal-like protein–protein interactions in neurons (Chavis et al. 1996; Mouton et al. 2001).

Ca^{2+}, Mg^{2+}, and ATP

Ca^{2+}, Mg^{2+}, and ATP are important small molecule regulators of RyRs. Mg^{2+} and ATP modulate RyRs in the cytoplasm and Ca^{2+} regulates RyRs both in the cytoplasm and in the lumen of SR. The cardiac and skeletal isoform of RyR show some difference in the regulation by these ligands, which has been linked to the different characteristics of E-C coupling in the two isoforms (Lamb 2000; Laver et al. 2001). Ca^{2+} has both direct effects on RyRs and also regulates RyRs via CaM and CaMKII. RyR1 activity shows a bell-shaped dependence on Ca^{2+} concentration and is activated by low Ca^{2+} concentration ($\sim$1 μM) by binding to specific high-affinity Ca^{2+} sites, and inhibited by high Ca^{2+} concentration ($\sim$1 mM) by binding to less selective low-affinity Ca^{2+} sites (Meissner et al. 1986; Meissner 1994; Meissner et al. 1997). Luminal Ca^{2+}, i.e., SR Ca^{2+} is also suggested to stimulate Ca^{2+} release in skeletal and cardiac muscle. Single channel measurements with increased store Ca^{2+} load have shown an increase in the sensitivity of Ca^{2+} release in the presence of cytosolic agonists such as ATP and caffeine (Smith et al. 1986; Sitsapesan 1995; Györke and Györke 1998; Xu et al. 1998; Laver et al. 2004). However, there have been conflicting results regarding luminal Ca^{2+} regulation and the source of these discrepancies is unclear. These might reflect altered mechanisms because of different experimental conditions, for example, differences in membrane preparation that results in variation of the protein complexes formed between RyR and calsequestrin, triadin, and junctin that are known to regulate RyR via luminal Ca^{2+} (Györke et al. 2004). Mg^{2+} is believed to inhibit RyRs by two mechanisms: reducing RyR open probability by competing with high-affinity Ca^{2+} activation sites, or by binding to less selective low-affinity Ca^{2+} sites that also mediate Ca^{2+} inhibition (Meissner et al. 1986; Laver et al. 1997). Noteworthy, there is a predicted difference in Mg^{2+} inhibition among RyR1, RyR2, and RyR3. RyR2 and RyR3 are activated by Ca^{2+} to greater extent than RyR1 and require higher Ca^{2+} concentration for inactivation. Hence, at elevated cytoplasmic Ca^{2+} concentrations Mg^{2+} causes potent RyR1 inhibition and relatively little inhibition of RyR2 and RyR3 (Lamb 2000; Meissner 2002).

ATP is an activator of RyRs. Various other adenine nucleotides (ADP, AMP, cAMP, adenosine,

and adenine) also potentiate SR Ca^{2+} release but are less efficacious than ATP (Meissner 1984). In vitro studies have shown that skeletal muscle RyR1 can be activated by ATP in the absence of Ca^{2+}, but Ca^{2+} needs to be present for maximal activation (Meissner 1984; Meissner et al. 1986; Laver et al. 2001). Cardiac RyR is not activated by ATP in the absence of Ca^{2+}. However, ATP augments the Ca^{2+} induced activation of RyR2, but the effects are more modest than those seen with RyR1 (Xu et al. 1996; Kermode et al. 1998). In cells, most ATP is in complex with Mg^{2+}. Therefore, it is probable that under physiological conditions the MgATP complex rather than free ATP regulates Ca^{2+} release. The presence of high concentrations of free Mg^{2+} in cells and its inhibitory effects on RyR makes it difficult to determine the different effects of ATP and MgATP.

Calmodulin

CaM is a ubiquitously expressed 17-kDa Ca^{2+}-binding protein that regulates RyRs by direct binding. CaM is also known to bind to and regulate $Ca_v1.1$ and $Ca_v1.2$ (Tang et al. 2002; Ohrtman et al. 2008; Halling et al. 2009). CaM contains four EF-hand Ca^{2+} binding pockets (two in the carboxy-terminal domain and two in the amino-terminal domain of the protein) and binds to one site per RyR subunit (four per tetramer) (Moore et al. 1999a). All three RyR isoforms bind and are regulated by CaM both in its Ca^{2+}-free (apoCaM) and Ca^{2+}-bound (CaCaM) states (Tripathy et al. 1995; Yamaguchi et al. 2005). ApoCaM is a partial agonist whereas CaCaM is an inhibitor of RyR1 and SR Ca^{2+} release (Rodney et al. 2000). CaM binding site involves amino acids 3614–3643 of the RyR1 rabbit sequence (Takeshima et al. 1989; Moore et al. 1999b; Yamaguchi et al. 2003; Zhang et al. 2003). Cryo-EM difference mapping of the three-dimensional structures of RyR1 with and without added CaM has suggested that the CaCaM binding site is located in subdomain 3. The site seems to be displaced to ~33 Å in the presence of Ca^{2+} with respect to its position for apoCaM (Wagenknecht et al. 1994; Wagenknecht et al. 1997; Samsó and Wagenknecht 2002). This displacement could be caused by a movement of the CaM upon binding calcium and/or a movement of the CaM binding site when RyR1 binds Ca^{2+}. The structure of CaM bound to a RyR1 peptide (3614–3643) has been visualized by NMR residual dipolar coupling (Maximciuc et al. 2006). Amino acids 3615–3628 contact the carboxy lobe of CaM, whereas amino acids 3628–3637 bind the amino lobe of CaM. In cardiac muscle, CaM shifts the Ca^{2+}-dependence of RyR2 activation to higher Ca^{2+} concentrations and hence decreases the RyR2 opening at all Ca^{2+} concentrations (Balshaw et al. 2001; Yamaguchi et al. 2003). Recently reduced affinity for CaM binding to RyR2 with PKA phosphorylation was found in a CPVT-associated mouse model (Arg2474Ser), resulting in spontaneous local Ca^{2+} release events leading to lethal arrythmias (Xu et al. 2010). In addition to CaM, a number of other EF-hand containing proteins have been recognized to interact with and regulate RyR, including calumenin and S100A1 (Jung et al. 2006; Wright et al. 2008). S100A1 has been found to compete with CaM for the RyR binding site (Wright et al. 2008). The questions of which of these EF-hand proteins actually regulate RyRs in vivo have yet to be answered.

Calsequestrin

Calsequestrin (CSQ) is the major intra-SR Ca^{2+} buffer. There are two genes encoding CSQ; type 1 CSQ (CSQ1) expressed in skeletal muscle and type 2 CSQ (CSQ2) expressed in cardiac and low levels in slow-twitch skeletal muscle. In addition to functioning as a Ca^{2+} buffer, CSQ forms oligomers in the lumen and interacts with the RyR anchoring proteins junctin and triadin embedded in the SR membrane. Together these three proteins appear to regulate RyR activity. The molecular details underlying these interactions have not been elucidated in either skeletal or cardiac muscle (Beard et al. 2009; Györke et al. 2009).

CSQ1 and CSQ2 appear to have unique isoform-specific properties in skeletal and cardiac muscle. CSQ1 reduces the activity of

RyR1 whereas CSQ2 increases the open probability of RyR1 and RyR2 (Wei et al. 2009). CSQ1-mediated inhibition of Ca^{2+} release during a single action potential may tune RyR1 activation to stimulation frequency and maintain Ca^{2+} release with repeated stimulation. In cardiac muscle CSQ2 may facilitate high rates of Ca^{2+} efflux through RyR2 during systole resulting in fast activation of contraction.

Recently, a mutation in the CSQ2 gene was linked to exercise-induced cardiac death caused by CPVT, although under basal conditions the cardiac contractility is apparently normal in subjects lacking functional CSQ2 (Postma et al. 2002). Knollmann and coworkers showed that *Casq2*-null mice are viable and display normal SR Ca^{2+} release and contractile function under basal conditions. However, exposure to catecholamines in *Casq2*-null myocytes caused increased diastolic SR Ca^{2+} leak, resulting in premature spontaneous SR Ca^{2+} releases that triggered beats indicating that these mice are susceptible to catecholaminergic ventricular arrhythmias (Knollmann et al. 2006).

FK506-Binding Protein 12 and 12.6 (FKBP12 and FKBP12.6)

FKBPs are named according to their molecular mass and belong to the immunophilins, a family of highly conserved proteins that bind immunosuppressive drugs such as FK506 and rapamycin. FKBPs are expressed in most tissues and are involved in a number of biochemical processes such as protein folding, receptor signaling, protein trafficking, and transcription. FKBP12 and FKBP12.6 (also known as calstabin 1 and 2, respectively) physically interact with all three isoforms of RyR but have different expression levels and binding affinity in different tissues (Chelu et al. 2004). FKBP12 copurifies with RyR1 (Jayaraman et al. 1992; Brillantes et al. 1994) and FKBP12.6 copurifies with RyR2 (Timerman et al. 1995; Timerman et al. 1996; Barg et al. 1997; Jeyakumar et al. 2001; Masumiya et al. 2003). Although somewhat controversial, a component of the FKBP12 binding site appears to be located between amino acids 2458 and 2468 of RyR1 (Rabbit sequence, SwissProt accession #P11716). Mutation of the amino acid Val2461 abolishes the FKBP12 binding (Gaburjakova et al. 2001; Avila et al. 2003). The amino-terminal and the carboxy-terminal regions of RyR2 have also been suggested to interact with FKBP12.6 (Masumiya et al. 2003; Xiao et al. 2004; Zissimopoulos and Lai 2005). Difference mapping of three-dimensional reconstructions of RyR with and without FKBP12 or 12.6 places the FKBPs binding site between subdomains 3, 5, and 9 (Wagenknecht et al. 1996; Wagenknecht et al. 1997; Samsó et al. 2006; Sharma et al. 2006). In agreement with this localization, FRET studies have localized the FKBP12 (Cornea et al. 2009) and the FKBP12.6 (Cornea et al. 2010) binding site to the same area as the model from Samsó et al 2006. Furthermore, both FKBP12 and 12.6 bind RyR1 and RyR2 in the same orientation (Cornea et al. 2010). Comparison of this location with the docking of the IP3 homology model, which includes the suppressor domain and the IP3-binding core region both with high sequence similarity to RyR1 amino-terminus, suggests a binding pocket for FKBP12 formed by Glu161, Arg164, Arg402, and Ile404 (Serysheva et al. 2008).

In mammals FKBP12 and 12.6 bind to RyRs with a stoichiometry of four FKBPs per RyR homotetramer (Jayaraman et al. 1992; Timerman et al. 1993; Qi et al. 1998). Under physiological conditions (i.e., the absence of immunosuppressive drugs), FKBPs are though to bind to RyRs with high affinity and stabilize the closed state of the channel (Ahern et al. 1994; Brillantes et al. 1994; McCall et al. 1996; Ahern et al. 1997; Marx et al. 1998; Marx et al. 2001). Removal of FKBP12, by preventing rebinding with an immunosuppressive drug or as the result of a genetic FKBP deficiency leads to greater open probability of the channel and longer mean open times (Ahern et al. 1997; Marx et al. 1998; Shou et al. 1998). Furthermore, FKBP12 displacement in skeletal muscle alters the coupling between RyR1 and $Ca_V1.1$. The consequences of these changes are dependent on muscle type and activity (Tang et al. 2004). In cardiac muscle, FKBP12 deficiency results in cardiomyopathy and ventricle septal defects

that mimic human congenital heart disorder (Shou et al. 1998).

PKA and CaMKII Phosphorylation

The importance of RyR phosphorylation in modulation of Ca^{2+} release from SR was first established in the heart (Takasago et al. 1989). The functional consequences of phosphorylation on RyR function and the identity of the enzymes involved have been the focus of considerable debate. RyRs have several potential phosphorylation sites in their cytoplasmic domains. PKA, CaMKII, and cGMP-dependent kinase (PKG) have all been shown to phosphorylate RyR isoforms (Rodriguez et al. 2003; Wehrens et al. 2004; Xiao et al. 2006; Huke and Bers 2007).

The "fight or flight" response is a classic physiological stress pathway that involves activation of the sympathetic nervous system (SNS) that among other effects results in larger and faster Ca^{2+} transients and subsequently stronger and faster muscle contractions (Bers 2002). SNS activation causes β-adrenergic stimulation of the muscle, which via an intracellular signaling cascade results in activation of PKA. SNS-activated PKA phosphorylates RyR, altering its gating properties, but also phosphorylates several other key proteins involved in Ca^{2+} handling such as troponin I and phospholamban (Valdivia et al. 1995; Li et al. 2000; Kentish et al. 2001; Reiken et al. 2003). Modified RyR function is associated with increased SR Ca^{2+} leak in heart, which could contribute to reduced contractile function and increased propensity to arrhythmias. Altered phosphorylation of RyR2 has been suggested as one possible explanation for RyR dysfunction. Marks and colleagues propose that a hyper-adrenergic state that occurs in heart failure or during extreme stress, including exercise, leads to hyperphosphorylation of RyR serine residues (Ser2030, Ser2809 in RyR2 and Ser2843 in RyR1). They also suggest that hyperphosphorylation causes FKBPs to dissociate from RyRs, producing "leaky channels" (i.e., channels prone to open at rest). Such leaky channels could underlie increased risk for arrhythmias in heart failure and contribute to decreased muscle force production by reducing SR Ca^{2+} store content (Marx et al. 2000; Reiken et al. 2003). However, other groups have not found PKA-dependent hyperphosphorylation in failing hearts (Xiao et al. 2005). In addition, other laboratories suggest that CamKII-dependent phosphorylation of RyR2 is involved in enhanced SR Ca^{2+} leak and reduced SR Ca^{2+} load in heart failure and may contribute to arrhythmias and contractile dysfunction (Ai et al. 2005; Chelu et al. 2009; Curran et al. 2010; Neef et al. 2010). Phosphorylation of other targets of these kinases (troponin I, sarcolemmal Ca^{2+} channels, and phospholamban) could also alter the Ca^{2+} handling in cardiac and skeletal muscle.

CaMKII is modulated by changes in intracellular Ca^{2+} ($[Ca^{2+}]_i$), although little is still known quantitatively about the role of dynamic $[Ca^{2+}]_i$ fluctuations in the activation of CaMKII (Huke and Bers 2007; Aydin et al. 2007). CaMKII phosphorylates the same residues on RyR1 as PKA and also phosphorylates several other proteins such as troponin I, sarcolemmal Ca^{2+} channels, and phospholamban. Ser2808 on RyR2 was first described as a CaMKII phosphorylation site, but it was later shown that both PKA and PKG also phosphorylate this site (Witcher et al. 1991; Rodriguez et al. 2003; Wehrens et al. 2004; Xiao et al. 2006; Huke and Bers 2007). Ser2814, however, appears to only be phosphorylated by CaMKII whereas Ser2030 is only phosphorylated by PKA (Wehrens et al. 2004; Xiao et al. 2006).

Reactive Oxygen Species and Reactive Nitrogen Species

Sulfhydryl groups (SH, also called thiol) of cysteine (Cys) residues are potential targets for reduction/oxidation (redox) modifications of proteins. Alteration in the redox state of SH groups of two neighboring cysteine residues can lead to formation or breaking of disulfide bonds, which can modify both the structure and function of proteins. Low concentrations of redox active molecules (reactive oxygen species/reactive nitrogen species; ROS/RNS) constitute a basal endogenous redox buffering system that reversibly interacts with proteins.

Both RyR1 and RyR2 have nitric oxide (NO) covalently bound to cysteines (i.e., *S*-nitrosylation) and this posttranslational modification is reversible (Xu et al. 1998; Eu et al. 2000; Sun et al. 2008). High levels of ROS/RNS are able to irreversibly modify and even damage proteins in cardiac ischemia-reperfusion injury (Ferdinandy and Schulz 2003).

RyR is an established redox-sensitive channel and alterations in its redox state can result in either activation (Stoyanovsky et al. 1997; Eager and Dulhunty 1998) or inactivation (Boraso and Williams 1994; Marengo et al. 1998). Other key components of Ca^{2+} regulation and E-C coupling, e.g., SERCA and Ca_v's, are also redox modulated. RyR has ~100 cysteines per subunit and ~20 of them have been estimated to be free for redox modifications by oxidation, nitrosylation, or alkylation by the redox active molecule glutathione (Zable et al. 1997; Xu et al. 1998). A number of redox-sensitive cysteines have been identified in both the open and closed state of the channel and appear to be distributed across the primary structure of cytoplasmic region (Voss et al. 2004; Aracena et al. 2006). Several of these sites have been mapped to the clamp domains like Cys36 and Cys315 (Liu et al. 2005; Amador 2009; Hamilton and Serysheva 2009; Lobo and Van Petegem 2009), whereas the Cys3635 is located in the subdomain 3 in the CaM binding site (Moore et al. 1999b; Sun et al. 2001). *S*-nitrosylation of Cys3635 has been shown to reverse the CaM inhibition on RyR1 and to activate the channel (Moore et al. 1999b). The *S*-nitrosylation of Cys3635 appears to occur only at physiological tissue O_2 tension (pO_2; ~10 mm Hg) and facilitates muscle contraction (Eu et al. 2003). Moreover, increased *S*-nitrosylation-induced RyR1 activity is suggested to sensitize RyR1 to environmental heat stress and MH crises (Durham et al. 2008). Increased RyR1 nitrosylation has also been observed in muscle dystrophy and is thought to contribute to muscle weakness by increased SR Ca^{2+} leak (Bellinger et al. 2009). In comparison to RyR1, no specific redox sensitive cysteine residues have yet been identified for RyR2. RyR2 is also pO_2-responsive but is not activated or S-nitrosylated directly by NO; instead activation and *S*-nitrosylation of RyR2 requires *S*-nitrosoglutathione (Sun et al. 2008).

CONCLUDING REMARKS

Primary sequence and location of several mutations are identified for RyR, but unanswered questions and debated topics still remain regarding the tertiary structure, the macromolecular interactions, and the regulation of RyR. The large size of RyR makes it more challenging to study, but new insights into the detailed structure of RyR are emerging with the continuous improvement and refinement of technologies such as cryo-EM and FRET-based assays. Resolution of the structure of RyR is progressing steadily, and ultimately we will have a map including carbon backbones, side-chains, membrane spanning regions and binding sites of interacting molecules. Along with our understanding of RyRs structure, it is likely that the number of known modulators that interact with RyR will also increase. Although the basic role and function of RyR in E-C coupling in skeletal and cardiac muscle is well established, further refinement of our understanding of the many modulators of RyR will be important in the development of therapeutics for treatment of cardiac and skeletal muscle diseases.

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