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Forum Editorial

Redox Regulation of Cardiac and Skeletal Sarcoplasmic Reticulum

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SIGNAL TRANSDUCTION for excitation-contraction coupling of cardiac and skeletal muscle is mediated by Ca^{2+} release from the sarcoplasmic reticulum (SR) in response to depolarization of sarcolemma. The Ca^{2+} release apparatus of the cardiac and skeletal SR is composed of the ryanodine receptor (Ca^{2+}-release channel) and associated molecules such as triadin, junctin, calsequestrin, FK506-binding protein, and calmodulin. Studies of fractionated SR vesicles, the purified ryanodine receptor incorporated into lipid bilayers, and isolated myocytes suggest that the Ca^{2+} release process is under redox regulation.

Historically, the redox modulation of the SR Ca^{2+} release was first described in skeletal muscle. In 1986, Trimm *et al.* reported that thiol-containing compounds such as cysteine, cyteamine, and homocysteine triggered Ca^{2+} release from the skeletal SR vesicles in the presence of Cu^{2+}. Dithiodipyridines, which specifically oxidize free sulfhydryl groups through a thiol-disulfide exchange reaction, were also found to induce Ca^{2+} release from the skeletal SR (Zaidi *et al.*, 1989). It was proposed that three different sulfhydryl groups in close proximity react through thiol oxidation and thiol-disulfide interchange to open or close the Ca^{2+}-release channel (Abramson and Salama, 1988, 1989).

Cardiac muscle SR Ca^{2+} release is also modulated by redox reactions. Similar to the action on the skeletal SR, dithiodipyridines were also found to release Ca^{2+} from cardiac SR vesicles (Prabhu and Salama, 1990). Boraso and Williams (1994) provided evidence for the redox regulation of the Ca^{2+}-release channel molecule by demonstrating that hydrogen peroxide (H_2O_2) increased open probability of the cardiac SR Ca^{2+}-release channel incorporated into planar phospholipid bilayers. Further, sulfhydryl oxidants were also found to activate the cardiac Ca^{2+}-release channel activity (Eager *et al.*, 1997).

More recently, the molecular mechanisms of redox modulation of the Ca^{2+} release channel have become apparent. In skeletal SR vesicles, the 450-kDa ryanodine receptor band was lost in the nonreducing sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) in response to H_2O_2 exposure of SR vesicles (Favero *et al.*, 1995), suggesting the production of high-molecular-weight species through the disulfide formation. Such disulfide formation may be mediated through the subunit–subunit contact within the ryanodine re-

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ceptor complex (Aghdasi *et al.*, 1997a) or through ryanodine receptor-triadin interactions (Liu and Pessah, 1994; Liu *et al.*, 1994).

Various reactive oxygen and nitrogen species can also influence Ca^{2+} release from the cardiac and skeletal SR, suggesting possible pathological as well as regulatory roles for redox modulation of Ca^{2+}-release channels. For instance, free radicals such as semidehydroascorbyl radicals (Stoyanovsky *et al.*, 1994) and hydroxyl radicals (Anzai *et al.*, 1998) have been shown to activate the SR Ca^{2+}-release channel. Nitric oxide also appears to activate skeletal (Aghdasi *et al.*, 1997b) and cardiac (Stoyanovsky *et al.*, 1997; Xu *et al.*, 1998) SR Ca^{2+}-release channels through modulation of sulfhydryl groups.

Modulation of Ca^{2+}-release events by redox reactions was also observed at the cellular level. In intact cardiac myocytes, oxidants such as H_2O_2 caused transient enhancement of Ca^{2+} channel-gated Ca^{2+} release; however, such transient enhancement of Ca^{2+} release was absent in whole-cell-clamped myocytes (Goldhaber and Liu, 1994). This may be due to a lack of cellular glutathione in whole-cell-clamped myocytes as the inclusion of physiological concentrations of glutathione in the internal solution appears to restore the ability of H_2O_2 to enhance the Ca^{2+} channel-gated Ca^{2+} release mechanism (Suzuki *et al.*, 1998). The calmodulin inhibitor W-7 appears also to enhance the gain of Ca^{2+}-induced Ca^{2+} release mechanism only in the absence of physiological concentrations of intracellular glutathione (Suzuki *et al.*, 1999), potentially suggesting that oxidation by constitutively generated reactive oxygen or nitrogen species influences the ryanodine receptor via a pathway mediated by calmodulin. Consistent with this idea, Kawakami and Okabe (1998) have shown that superoxide radicals trigger Ca^{2+} release from cardiac SR vesicles by decreasing their calmodulin content. A recent study by Zhang *et al.* (1999) demonstrated that oxidation blocks binding of calmodulin to the skeletal muscle ryanodine receptor.

The field of free radical biology had a paradigm shift during the 1990s leading to a novel concept of redox regulation of signal transduction (for review, see Suzuki *et al.*, 1997). Observations that redox reactions may regulate the ryanodine receptor activity, thus modulating Ca^{2+} release from the SR, suggest a possible regulatory role for biological oxidants and antioxidants in cardiac and skeletal muscle Ca^{2+} signaling events for muscle contraction as well as gene expression. The following "Forum on Redox Regulation of Cardiac and Skeletal Sarcoplasmic Reticulum" summarizes some of the recent contributions in understanding the regulation and modulation of the ryanodine receptor and Ca^{2+} release from the cardiac and skeletal muscle SR by reactive oxygen species, antioxidants, thiols, and nitric oxide. This Forum presents discussion on the molecular basis for the redox regulation of the ryanodine receptor and its associated molecules such as triadin and calmodulin and how such mechanisms may regulate signal transduction at the cellular level. We hope that this Forum will help the working investigators in the field to design novel experiments to probe and challenge some of the ideas discussed here by the contributing authors.

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ABBREVIATIONS

H_2O_2, Hydrogen peroxide; SDS-PAGE, sodium dodecyl sulfate-polyacrylamide gel electrophoresis; SR, sarcoplasmic reticulum.

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