

## Defining the dynamics behind Ryanodine Receptor modulation by small molecules

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Ryanodine receptors (RyRs) are calcium release channels that mediate the rapid release of calcium from the endoplasmic/sarcoplasmic reticulum into the cytosol. RyRs are essential for excitation-contraction coupling and are modulated by numerous auxiliary proteins and small molecules. There are over 200 reported mutations within the channel's skeletal isoform (RyR1) associated with altered channel function. However the molecular mechanism by which these mutations influence RyR1 response to channel's many modulators remains unclear. We employed mass spectrometry and cryo-electron microscopy to identify the direct and long-range allosteric consequences of ligand binding within RyR1. We determined that ligand binding within RyR1 regions, despite being distinct from mutated residue, are likely responsible for the altered function. These findings further support that significant long-range cooperatively across RyR1 domains is required for normal channel activity.