

Andrew R. Marks, M.D.

Wu Professor & Chair, Department of Physiology & Cellular Biophysics
Founding Director, Helen & Clyde Wu Center for Molecular Cardiology
Columbia University College of Physicians & Surgeons
Columbia University

Seminar Title

Ryanodine Receptor: Structure, Function & Therapeutic Targeting for Diseases of the Heart & Muscle

Abstract

Ryanodine receptor (RyR) channels are required for release of calcium from intracellular stores, a process essential for many cellular functions including excitation-contraction (EC) coupling in skeletal and cardiac muscle, and hormone and neurotransmitter release. They are the largest ion channels, comprised of the four identical -565 kDa channel-forming protomers, as well as regulatory subunits, enzymes and their respective targeting/anchoring proteins, in a macromolecular complex that exceeds three million daltons. We have obtained high-resolution cryo-electron microscopy (Cryo-EM) reconstructions from highly purified rabbit skeletal muscle RyR1 in the open and closed states. Our data reveal that RyRs are members of the six transmembrane family of ion channels and show a mechanism for channel gating suggesting that calcium binding facilitates mechanical coupling of conformational changes in the cytosolic region to opening of the channel gate. In heart failure and myopathies, the RyR channel is excessively phosphorylated, oxidized and nitrosylated and depleted of the RyR-stabilizing protein calstabin (FK506 binding protein 12/12.6). This remodeling of the RyR channel complex results in an intracellular SR Ca²⁺ leak and impaired contractility and defective learning and memory. A novel class of RyR-stabilizing drugs, Rycals, which reduce Ca²⁺ leak by stabilizing the RyR channels due to preservation of the RyR-calstabin interaction, have recently been shown to improve contractile function in both heart and skeletal muscle and to have anti-arrhythmic activity in animal models of atrial fibrillation. This opens up a novel therapeutic strategy for the treatment of contractile failure in disorders of cardiac and skeletal muscles.

Conflict of interest: A.R. Marks is a consultant for a start-up company, ARMGO Pharma Inc. This company is working on targeting RyR channels to treat heart disease and to improve exercise capacity in muscle diseases.

Biography

Andrew R. Marks, MD received his undergraduate degree from Amherst College where he was the first student in the history of the college to graduate with honors in two subjects (Biology and English), and his MD from Harvard Medical School. Following an internship and residency in internal medicine at the Massachusetts General Hospital (MGH), he was a post-doctoral fellow in molecular genetics at Harvard Medical School, and then a clinical cardiology fellow at the MGH. He is board certified in internal medicine and in cardiology.

Dr. Marks is Chair and Professor of the Physiology and Cellular Biophysics Department at Columbia University. From 2002-2007, Dr. Marks was Editor-in-Chief of the *Journal of Clinical Investigation*.

His honors include: ASCI, AAP, the National Academy of Medicine (2004), American Academy of Arts and Sciences (2005) and the National Academy of Sciences (2005). Doctor of Science *Honoris Causa* from Amherst College (2009), Docteur *Honoris causa*, del'Universite de Montpellier (2016), the ASCI Stanley J. Korsmeyer Award (2010), the Pasarow Foundation Award for Cardiovascular Research (2011), the Ellison

Medical Foundation Senior Scholar in Aging Award (2011), and the Glorney-Raisbeck Award from NY Academy of Medicine (2016). In 2015, Dr. Marks was chosen to present the Ulf von Euler lecture at the Karolinska Institute.

Research

Dr. Marks' identification of the mechanism of action of rapamycin's inhibition of vascular smooth muscle proliferation and migration lead to the development of the first drug-eluting stent (coated with rapamycin) for treatment of coronary artery disease. This substantially reduced the incidence of in-stent restenosis. In 2014, Dr. Marks reported the high-resolution structure of the mammalian type 1 ryanodine receptor/calcium release channel (required for excitation-contraction coupling in skeletal muscle) which he had cloned and worked on since 1989.

His research has contributed to new understandings of fundamental mechanisms that control muscle contraction, heart function, lymphocyte activation, and cognitive function. He discovered that "leaky" intracellular calcium release channels (ryanodine receptors) contribute to heart failure, fatal cardiac arrhythmias, impaired exercise capacity in muscular dystrophy, post-traumatic stress disorder (PTSD) and Alzheimer's disease. Dr. Marks discovered a new class of small molecules (Rycals), developed in his laboratory, that target leaky ryanodine receptor channels and effectively treat cardiac arrhythmias, heart failure, muscular dystrophy and prevent stress induced cognitive dysfunction and symptoms of Alzheimer's disease in pre-clinical studies. Rycals are now in Phase II clinical trials for the treatment of heart failure and cardiac arrhythmias, and entering clinical trials for the treatment of Duchenne Muscular Dystrophy.