Mechanisms, Regulation and Pharmacology of Calcium Transporting NCX Proteins

Positions
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Research
Calcium (Ca\(^{2+}\)) is a major regulator in the living cell. In many cell-types the Na\(^+\)/Ca\(^{2+}\) exchanger proteins (NCX) represent a major Ca\(^{2+}\) extruding system and thus, play a key role in regulating the Ca\(^{2+}\)-dependent events in the cell. Three NCX genes form numerous splice variants, which are expressed in a tissue-specific manner to regulate excitation–contraction coupling in heart, long-term potentiation and learning in brain, blood pressure, immune responses, neurotransmitter and hormone secretion, kidney Ca\(^{2+}\) reabsorption, mitochondrial bioenergetics, etc. Altered expression and regulation of NCX proteins is a chief contributor to Ca\(^{2+}\)-driven tissue-remodeling in heart failure, cerebral ischemia, hypertension, diabetes, renal malfunction, muscle dystrophy, etc. For example, in cardiac disease a single isoform/splice variant (NCX1.1) is overexpressed, thereby representing a primary concern for life-threatening arrhythmias and contractile malfunction. Selective pharmacological targeting of NCX variants is expected to recover Ca\(^{2+}\) homeostasis in predefined cell types and thus, may improve desired activity of altered tissues/organs. Since this breakthrough remains challenging our research efforts are focused on two principle issues: a) To resolve structure-activity relationships underlying the function and regulation of diverse NCX variants; b) To develop new experimental approaches for selective pharmacological targeting of tissue-specific NCX variants with a goal of providing new opportunities for preventing and effective treatment of harmful diseases. In this respect we investigate structure-activity relationships in the wild-type and mutated proteins by exploring a wide spectrum of techniques (stopped-flow and ion-flux assays, FRET, SAXS, ITC, X-ray crystallography, confocal microscopy, patch-clamp, etc). In searching the regulatory mechanisms of CBD1 and CBD2 domains we found that the tissue-specific splice segment, located on CBD2, shapes the regulatory specificity of the primary Ca\(^{2+}\) sensor located on CBD1. These findings may allow the identification of drug candidates targeting the disease-related NCX variants.

Publications


Reviews


Grants

2013-2017 Fields Center of Molecular Cardiology

2010-2015 USA-Israel Binational Science Foundation

2014-2018 Israeli Science Foundation