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The ABC of Solute Carriers

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The sodium/calcium exchanger family—SLC8

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Abstract The Na^+/Ca^{2+} exchanger gene family encompasses three distinct proteins, NCX1, NCX2, and NCX3, which mediate cellular Ca^{2+} efflux and thus contribute to intracellular Ca^{2+} homeostasis. NCX1 is expressed ubiquitously while NCX2 and NCX3 are limited to brain and skeletal muscle. NCX1 exchanges 3 extracellular Na^+ for 1 intracellular Ca^{2+}. In addition to transporting Na^+ and Ca^{2+}, NCX1 activity is also regulated by these cations. NCX1 is especially important in regulating cardiac contractility.

Keywords Calcium · Sodium · Antiport · Myocardium · Sodium-calcium exchange

Discovery of the *SLC8* family

A Na^+/Ca^{2+} countertransport mechanism was first described in heart [75] and squid axon [2]. NCX1 was cloned by screening an expression library with an antibody [62]. NCX2 was isolated by screening a brain cDNA library at low stringency with a probe derived from NCX1 [46]. Degenerate oligonucleotide primers to an α-repeat region and the exchanger inhibitory peptide (XIP) region of NCX1 and NCX2 (see below) were used to screen brain cDNA libraries and identify the other isoform, NCX3 [64]. No other members of this family are likely to exist in humans.

SLC8 together with SLC24 constitute a superfamily of Na^+/Ca^{2+} countertransporters. The latter also transports K^+ (see this volume). There is a cluster of orthologous genes (COG0530) containing 23 members which are named Ca^{2+}/Na^+ antiporters although functional data have not yet been presented. An NCX-like protein in plants that is a Mg^{2+}/H^+ antiporter has been described [80].

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Functional characteristics

NCX1 is the most highly characterized member of this family (Fig. 1), though NCX2 and NCX3 appear to have

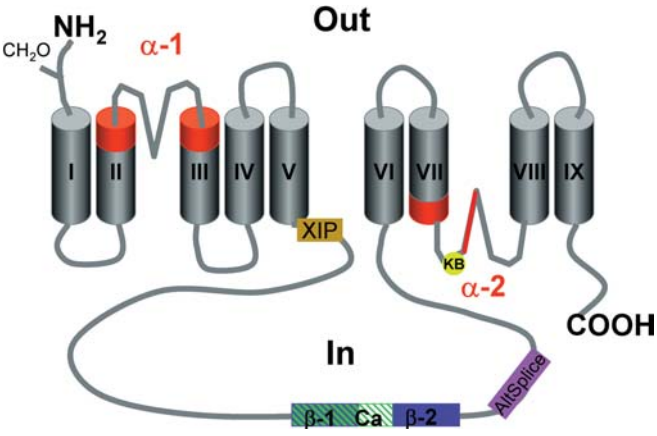

Fig. 1 Topological model of the Na^+/Ca^{2+} exchanger NCX1. NCX1 has 9 transmembrane segments (TMSs, *Roman numerals*) with a large intracellular loop connecting TMSs 5 and 6. The α-repeats (*red*) are each composed of two homologous segments connected by a variable region. A residue involved in binding KB-R7943 (*yellow*) is in α-2. The *large intracellular loop* contains the regulatory Ca^{2+} binding site (*green*), β-repeats (*blue*), alternative splice site (*pink*) and endogenous exchange inhibitory peptide (*XIP*) region (*brown*)

similar characteristics. NCX1 catalyzes the consecutive exchange of 3 Na^+ for 1 Ca^{2+} ([35, 71]; though see [18]). A current is generated during transport. Physiological electrochemical gradients result primarily in forward (cellular Ca^{2+} efflux) exchange activity though both forward and reverse Na^+-Ca^{2+} exchange currents are readily measured in giant membrane patches [23]. The stereotypic reverse Na^+/Ca^{2+} exchange current displays Na^+ $_i$-dependent inactivation (I_1; [26]) and Ca^{2+} $_i$-dependent enhancement (I_2; [24, 25]). All three NCX isoforms display I_1 and I_2 regulation [48].

The three NCX isoforms have been compared in whole cells or vesicles isolated from stably transfected cells [30, 48]. The apparent affinities for transported ions at either membrane surface are similar in all three isoforms. Responses to chymotrypsin, pH, or the inhibitor Phe-Arg-Cys-Arg-Cys-Phe-$CONH_2$ (FRCRCFa) are also similar. Activities of NCX1 and NCX3 but not NCX2 are increased modestly by activation of protein kinases A or C. NCX1 and NCX2 but not NCX3 activities are modulated by intracellular ATP levels.

Expression patterns

The Na^+/Ca^{2+} exchanger family members NCX1, NCX2, and NCX3 are products of separate genes (Table 1) [64]. NCX1 mRNA is nearly ubiquitous and NCX2 and NCX3 mRNAs have been detected only in brain and skeletal muscle [41, 64]. The NCXs are plasma membrane proteins and exchange Na^+ for Ca^{2+}, though Ca^{2+}/Ca^{2+}, Na^+/Na^+, Na^+/Mg^{2+}, Na^+/Ba^{2+}, Na^+/Sr^{2+}, and Na^+/Ni^{2+} exchanges have been described [5, 14, 65, 81, 84]. In heart, NCX1 is localized to both surface and T-tubular sarcolemma of cardiomyocytes with increased density in T-tubules in some studies [16, 37, 79, 87]. In the kidney, NCX1 protein is expressed preferentially in the basolateral membrane of cells from distinct sections of the cortex [9, 17, 72]. In rat brain, NCX1 mRNA shows a specific regional pattern [50, 89] and NCX1 protein is distributed in discrete sites on the plasmalemma, some of which are in proximity to intracellular Ca^{2+} stores [32, 49]. Furthermore, NCX1, NCX2, and NCX3 proteins are expressed differentially in a cell-specific manner in distinct portions of rat brain [83]. The sarcolemma of rat skeletal muscle cells expresses both NCX1 and NCX3 in a muscle fiber-specific manner [11, 17]. A region at the C-terminus of the large intracellular loop of NCX1 and NCX3 undergoes extensive alternative splicing in a tissue-specific, developmentally regulated manner [38, 70]. Expression of mutually exclusive exons in NCX1 splice variants from kidney and brain gives rise to distinct ionic regulatory phenotypes [13].

Physiological implications

The Na^+/Ca^{2+} exchanger proteins primarily mediate cellular Ca^{2+} efflux and thus help maintain intracellular

Table 1 Characteristics of the *SLC8* gene family of Na^+/Ca^{2+} exchangers

Human gene name	Protein name	Aliases	Predominant substrates	Transport type/Coupling ions	Tissue distribution and cellular/subcellular expression	Human gene locus	Sequence accession ID	Splice variants and their specific features
SLC8A1	NCX1	NACA, NCE	Sodium, calcium	Exchanger/Na^+, Ca^{2+}	Ubiquitous tissue distribution. Plasma membrane of various cell types. In brain mainly in neurons and their dendrites.	2p23-p22	NM_021097.1	Exon A splice variants in excitable tissues. Exon B splice variants in all other tissues.
SLC8A2	NCX2		Sodium, calcium	Exchanger/Na^+, Ca^{2+}	Predominantly in brain (glial cells) and skeletal muscle. Low transcript levels in various other tissues.	19q13.3	XM_0038970	No splice variants found.
SLC8A3	NCX3		Sodium, calcium	Exchanger/Na^+, Ca^{2+}	Exclusively in brain (subpopulations of neuronal cells) and skeletal muscle.	14q24.1	NM_033262.2	Exon A splice variants in skeletal muscle. Exon B splice variants in skeletal muscle and brain.

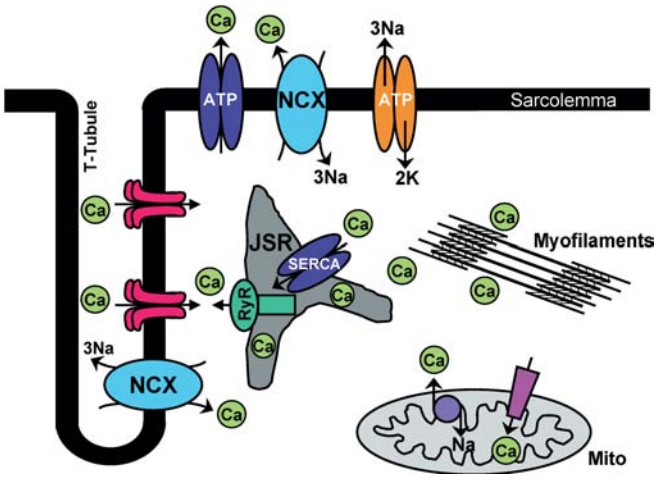

Fig. 2 Na^+/Ca^{2+} exchange and excitation-contraction coupling. The cartoon shows a ventricular cardiomyocyte and the relevant pathways of Ca^{2+} signaling during contraction and relaxation of the heart. Ca^{2+} enters the cell through voltage-gated Ca^{2+} channels (*red*) or possibly reverse Na^+/Ca^{2+} exchange (*NCX*) to initiate systole. Ca^{2+} influx triggers Ca^{2+} release from the junctional sarcoplasmic reticulum (*JSR*) via the ryanodine receptor (*RYR*). To produce diastole, Ca^{2+} is transported back into the SR by the SR Ca^{2+} ATPase (*SERCA*) or is removed from the cytosol by the Na^+/Ca^{2+} exchanger (*NCX*), the sarcolemmal Ca^{2+}-ATPase (*blue*), or by the mitochondrial Ca^{2+} uniporter (*pink*). *Orange*, Na^+/K^+-ATPase. Mitochondria also possess a poorly characterized Na^+/Ca^{2+} exchanger. The Na^+/Ca^{2+} exchanger is the dominant cellular Ca^{2+} efflux mechanism and regulates contractility. After D. Bers, with permission

Ca^{2+} homeostasis. In heart, NCX1 contributes to muscle relaxation by extruding Ca^{2+} that entered cardiomyocytes to initiate systole (Fig. 2). Transgenic mice or cultured cells over-expressing NCX1 show altered $Ca^{2+}{}_i$ transients [1, 77, 82, 83, 88] and SR Ca^{2+} content [82] as well as altered responsiveness to cardiovascular stresses [10, 20]. Furthermore, over-expression of a NCX1 mutant lacking I_1 and I_2 leads to alterations of cardiac contractile properties [55]. Homozygous NCX1 knockout mice are embryonic lethal at ≈11 days post-coitum [9, 40, 74, 85]. Heart tubes from day 9.5 NCX1 knockout embryos have been useful for studying excitation-contraction coupling in the absence of Na^+/Ca^{2+} exchange [40, 73, 74]. The functional role of NCX1 in other tissues is not as well defined as in the heart [5]. Although isoform-specific cellular expression patterns suggest distinct functions for each of the three exchangers [17, 83], the physiological roles of NCX2 and NCX3 in brain and skeletal muscle remain elusive.

Regulation of expression

Expression of the NCX1 gene is controlled by alternative promoters [3, 60] in a tissue-specific [3, 41, 58] and transcription factor-specific manner [8, 57, 59]. The NCX1 heart promoter is sufficient to control cardiac-specific expression of NCX1 during development in mice and in hypertrophic hearts [56]. In vitro, the NCX1 heart promoter is regulated by adrenergic agents and the calcineurin inhibitor cyclosporin A [3, 8, 31, 57]. In many tissues, expression of NCX1 [6, 7, 39, 70], NCX2 [44], and NCX3 [11, 17] is regulated developmentally. Ca^{2+} is critical for the expression of all NCX isoforms in cerebellar neurons but only NCX2 transcription is controlled by calcineurin [44]. Elevated exchanger transcript and/or protein levels in animal models of heart failure, in the human failing heart [15, 21, 26, 66, 67], and in cardiac hypertrophy [34, 56, 86] have been reported.

Biochemical and structural characteristics

The amino acid sequences of the three NCX isoforms are about 70% identical. All biochemical and structural information comes from studies involving NCX1. The current topological model for NCX1 is shown in Fig. 1.

NCX models contain nine transmembrane segments (TMS) in two groups. Five TMSs near the amino terminus are separated from four near the carboxy terminus by a large intracellular loop. The extracellular amino terminus and the loop connecting TMSs 6 and 7 are linked via a disulfide bond [76]. The disulfide bond may aid in expression of the exchanger [68]. Each NCX contains two pairs of internal repeats, designated α- and β-repeats [78]. The α-repeats (PFAM01699) consist of two groups of highly conserved residues separated by a short unconserved linker and are located in the groups of TMS. The α-repeat regions have been implicated in ion binding and transport [61] and may form membrane reentrant segments [30, 63]. The α-2 domain is involved in determining the sensitivity of the exchanger to the inhibitor KB-R7943 [28]. The α-repeat regions interact with one another in the tertiary structure of the protein [69]. The β-repeats (PFAM03160) are in the intracellular loop and share sequence similarity with a motif found in β4 integrin [78]. The function of this motif is unknown.

The intracellular loop is involved in I_1 and I_2 inactivation [54]. Regulatory Ca^{2+} associated with I_2 binds to a portion of the intracellular loop comprised of β1 and the β1-β2 linker [42, 43, 53]. Two groups of three consecutive acidic amino acids are involved in binding Ca^{2+}.

Near the intracellular surface of the fifth TMS is a 20-amino acid region designated XIP. A peptide with the sequence of XIP inhibits the exchanger [47]. Mutations in the XIP region [52] or in the intracellular loop between transmembrane segments 1 and 2 [12] alter the properties of Na^+-dependent inactivation. The binding site on NCX1 for exogenously applied XIP is not known but XIP binds to vesicles containing PIP_2 [22]. PIP_2 stimulates NCX1 by removing Na^+-dependent inactivation [23]. NCX1 binds to ankyrin but the binding site has not been identified [45].

Pathological implications

NCX1 regulates cardiac contractility by regulating the amount of intracellular Ca^{2+}. Nevertheless, the role of an up-regulated exchanger in cardiac hypertrophy and heart failure is controversial. An increase in Ca^{2+} extrusion may preserve low diastolic $Ca^{2+}{}_i$ levels [21] but could also deplete sarcoplasmic reticular Ca^{2+} stores. There has been support for a role of reverse exchange, in which Ca^{2+} is transported into the cell via NCX1; reverse exchange through an up-regulated exchanger may contribute to Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum and could augment contractility in heart failure. These possibilities have been debated widely [4, 19, 27].

Pharmacological and pharmaceutical aspects

NCX activity is blocked non-selectively by amiloride or bepridil analogs [33] and by an isothiourea derivative (KB-R7943) [28]. NCX is also inhibited by the synthetic peptides XIP (see above) and FMRFa and its analogs [36]. SEA0400 is a recently described, potent exchange inhibitor still under investigation [51]. NCX1 knockout mice have been used to demonstrate that both KB-R7943 and SEA0400 are non-selective [73]. There is no known, clinically useful Na^+-Ca^{2+} exchange inhibitor. Further development of exchange inhibitors may be useful in combating the arrhythmias associated with heart failure.

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