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Review

Mitochondrial Proteins Containing Coiled-Coil-Helix-Coiled-Coil-Helix (CHCH) Domains in Health and Disease

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Members of the coiled-coil-helix-coiled-coil-helix (CHCH) domain-containing protein family that carry (CX_9C) type motifs are imported into the mitochondrion with the help of the disulfide relay-dependent MIA import pathway. These evolutionarily conserved proteins are emerging as new cellular factors that control mitochondrial respiration, redox regulation, lipid homeostasis, and membrane ultrastructure and dynamics. We discuss recent insights on the activity of known (CX_9C) motif-carrying proteins in mammals and review current data implicating the Mia40/CHCHD4 import machinery in the regulation of their mitochondrial import. Recent findings and the identification of disease-associated mutations in specific (CX_9C) motif-carrying proteins have highlighted members of this family of proteins as potential therapeutic targets in a variety of human disorders.

Trends

The bioenergetic and metabolic activities of the mitochondrion are crucial for cellular survival and adaptation to stress.

The vast majority of mitochondrial proteins are encoded by the nuclear genome and hence must be imported.

In humans, dysfunction of the mitochondrial protein import process has been associated with mitochondriopathies, neurodegeneration, diabetes, aging, and cancer.

The import of small cysteine motif-carrying proteins into the mitochondrial intermembrane space is controlled by the phylogenetically conserved disulfide relay-dependent Mia40/CHCHD4 import machinery.

This import machinery interacts with a variety of proteins, many of which contain CHCH domains, the CHCHD proteins.

In humans, CHCHD4 substrates constitute an emerging class of disease-associated proteins.

Mitochondrial Protein import: Historical Background and its Discovery

Mitochondria play a quintessential role in normal metabolism [1,2] and lethal signaling processes in the context of physiological or pathological cell death [3,4]. Mutations in mitochondrial proteins, be they encoded by the mitochondrial or nuclear genomes, have been associated with multiple diseases including cancer, metabolic disorders, neurodegenerative pathologies, diabetes, and premature aging [5–8].

A hypothetical reconstruction of cellular evolution postulates that some 2 billion years ago the organelle appeared in the eukaryotic cell by the engulfment of an endosymbiotic prokaryotic organism. This endosymbiotic relationship was consolidated by the progressive incorporation of originally bacterial genes into the nuclear genome [9,10], thereby improving the integration of mitochondria in various aspects of cellular metabolism [1,2,6,9–12]. Modern cells control mitochondrial function at several levels by regulating (i) the transcription of nuclear genes, (ii) the cytoplasmic translation of mRNAs, as well as (iii) the import of the proteins into one of the four subcompartments, namely the outer and inner membranes, the matrix, and the intermembrane space [5,13,14].

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The mitochondrial genome of human cells encodes only 13 proteins, while the function of the organelle requires the import of >1000 nucleus-encoded proteins [13,14]. Studies in yeast revealed that most of the nucleus-encoded mitochondrial proteins pass into the organelle through one general entry gate at the outer membrane, the outer-membrane translocase (TOM), which contains the protein Tom40 (also known as TOMM40 in mammals) as its central protein-conducting channel. However, after engaging with the TOM translocon, mitochondrial proteins follow different sorting routes that are dictated by specific targeting codes in their sequence or overall structure that guide them to their final destination. Additional translocase machineries, including the sorting and assembly machinery (SAM) complex in the outer membrane, the presequence translocase TIM23 complex and the carrier translocase TIM22 complex that are both located in the inner membrane, and the MIA40 complex located in the intermembrane space (IMS), decode the import signals to finally dispatch each protein toward the appropriate submitochondrial compartment [1,2,11,12]. Recently, the mitochondrial import (MIM) complex that is localized in the outer mitochondrial membrane was revealed to be necessary for the import of α-helical outer-membrane proteins that bypass the TOM complex [2]. Mitochondrial import activity can be influenced by the differentiation and activation states of the cell or be affected by pathological conditions such as oxidative stress, aging, and imminent cell death [2]. Human disease-associated mutations can affect either the mitochondrion-targeting segment of the nucleus-encoded proteins or specific components of the import machinery [2,6,8,15,16].

The characterization of the mitochondrial import process has led to the discovery of a family of nucleus-encoded proteins, the CHCH domain (CHCHD)-containing proteins, which are imported into the mitochondrial intermembrane space where they participate in activities such as mitochondrial biogenesis, bioenergetics, dynamics, and quality control. These proteins are imported with the help of the evolutionarily conserved redox-active Mia40/CHCHD4 import machinery that catalyzes their oxidative folding through a disulfide relay system [1,16] (Figure 1, Key Figure). We review here current knowledge on this fascinating family of proteins.

Import into the Mitochondrial Intermembrane Space

The intermembrane space (IMS) constitutes an essential crossroads for the physiological communication of mitochondria with the rest of the cell [16,17], as well as for lethal signaling processes [4]. Upon mitochondrial outer-membrane permeabilization (MOMP), which is generally associated with apoptosis [3], a series of proteins that are normally confined in the IMS such as apoptosis-inducing factor (AIF), cytochrome *c*, endonuclease G, HtrA2 peptidase, and Diablo homolog are released from the IMS into the extramitochondrial space, where they contribute to cellular dismantling [18,19].

Proteomic analyses conducted in *Saccharomyces cerevisiae* [20] or in human cells [21] revealed that all IMS-confined proteins are nucleus-encoded, with their number ranging between 50 to 130. IMS proteins that carry an N-terminal mitochondrial localization sequence (MLS) engage with the matrix-targeting TIM23 complex, but then either become attached to the inner membrane facing the IMS or are released into the IMS as soluble proteins following the proteolytic cleavage of their N-terminal presequence [1,2]. A second class of IMS-localized proteins do not possess such an N-terminal targeting sequence. Instead, their import is coupled to cofactor-triggered or redox-regulated folding events that stabilize and trap them in the IMS [16,17,22]. Cofactor-triggered IMS entrapment is exemplified by the heme-dependent import and maturation of cytochrome *c*, which is orchestrated by the activity of cytochrome *c* heme lyase (CCHL) [17]. The oxidation-driven import of cysteine motif-carrying proteins depends on a 'disulfide relay' pathway that is controlled by the evolutionarily conserved oxidoreductase Mia40/CHCHD4 [1,16,17,22].

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