CHCHD2 connects mitochondrial metabolism to apoptosis

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As the powerhouse of cells and gatekeeper for apoptosis, mitochondria control life and death. CHCHD2, a mitochondrial protein previously known to regulate metabolism, has recently been identified as an apoptosis inhibitor. New data suggest a model in which CHCHD2 performs a prosurvival function by acting as both a reactive oxygen species scavenger and BCL-XL activator.

Mitochondria are multifunctional organelles that serve as both the powerhouse of cells and a gatekeeper for apoptosis. The majority of cellular carbon sources are catabolized in the mitochondria to produce ATP and meanwhile generate reactive oxygen species (ROS). As a gatekeeper for apoptosis, mitochondria control the intrinsic apoptosis pathway through mitochondrial outer membrane permeabilization (MOMP), which is tightly regulated by the B-cell lymphoma 2 (BCL-2) family of proteins. In recent years, emerging evidence has suggested that metabolic networks are entangled with apoptosis pathways. Central to this connection, mitochondria appear to regulate important metabolic checkpoints to determine cell fate.2

Mitochondria consist of 4 major compartments: the matrix, the inner membrane (IM), the intermembrane space (IMS), and the outer membrane (OM). In contrast to our relatively thorough understanding of most other mitochondrial compartments, the contents of the IMS and their physiological and pathophysiological functions remain poorly defined. The best-known function of the IMS is the MOMP-associated release of apoptotic factors such as cytochrome c, second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pi (SMAC/DIABLO), HtrA serine peptidase 2 (HTRA2, also known as OMI), apoptosis inducing factor (AIF), and endonuclease G (ENDOG). In this issue of Cell Death & Differentiation, our laboratory reports the characterization of coiled-coil-helix-coiled-coil-helix domain containing 2 (CHCHD2), a novel CHCH domain-containing protein, as an inhibitor of mitochondrial apoptosis. CHCHD2 binds to BCL2-like 1 isoform 1 (BCL-XL) and inhibits the mitochondrial accumulation and oligomerization of BCL2-associated X protein (BAX). In the presence of apoptotic stimuli, CHCHD2 levels decrease and the protein becomes released from the mitochondria prior to MOMP. Downregulation of CHCHD2 expression interferes with the interaction between BCL-XL and BAX and consequently results in BAX oligomerization and initiation of the apoptotic cascade.

The CHCHD2–BCL-XL Complex Connects Metabolism to Apoptosis

CHCHD2 contains a CHCH domain, which is characterized by a twin CX9C motif (2 pairs of cysteines spaced by 9 residues). Similar to other CHCH domain-containing proteins, the CX9C motif is responsible for the import of CHCHD2 into the IMS through the MIA40-Erv-1 system.3 As it contains an amino-terminal mitochondrial targeting sequence and a transmembrane domain, CHCHD2 may be embedded in the IM, where the core electron transport chain (ETC) machinery assembles and functions. Like its yeast homolog MIC174 and its mammalian paralog CHCH domain containing 10 (CHCHD10),5 CHCHD2 promotes mitochondrial oxygen consumption. Recent studies have showed that CHCHD2 is involved in electron transport through 2 mechanisms: (1) CHCHD2 translocates to the nucleus and transcriptionally upregulates isoform 2 of cytochrome c oxidase subunit 4 (COX4I2), and (2) CHCHD2 binds to cytochrome c oxidase (COX) thereby maintaining COX enzymatic activity.3,6 Intriguingly, BCL-XL has also been
identified in the mitochondrial IM cristae, where it binds to the β subunit of ATP synthase to prevent wasteful ion flux and thus maintain the membrane potential for optimal ATP production. Given that CHCHD2 and BCL-XL interact with one another, co-localize to the IM, and play similar functions in metabolism and apoptosis, one could speculate that the CHCHD2–BCL-XL complex functions as a sensor to probe the status of mitochondrial metabolism and coordinate metabolism with apoptosis.

Does CHCHD2 Promote Cell Survival by Detoxifying ROS and Facilitating OXPHOS?

To understand how CHCHD2 coordinates mitochondrial metabolism with apoptosis, it is important to identify the metabolic cues monitored by CHCHD2. As the major by-product of mitochondrial oxidative phosphorylation (OXPHOS), ROS serve as signaling molecules for normal biological processes but also represent a potent damage-inducing agent for cellular metabolism and coordinate metabolism with apoptosis. These defensive functions are generally considered to be carried out by cellular detoxification enzymes (catalase, superoxide dismutase, and glutathione peroxidase) and by the low molecular weight thiol glutathione (GSH) or cysteine residues in the active sites of proteins such as thioredoxin and peroxiredoxin (Trx/Prx). In addition to GSH and the Trx/Prx proteins, recent evidence suggests that some proteins with thiols exposed on their surface could function to neutralize cellular ROS. Given that the characteristic feature shared by all CHCH domain-containing proteins is the twin CX3C or CX2C motif, which provides free thiols under reducing conditions, the many mitochondria-localized CHCH domain-containing proteins may function as an additional thiol pool to detect and scavenge cellular ROS in the IMS.

As shown in our study, downregulation of CHCHD2 sensitizes cells to apoptosis induced by a variety of stimuli, including UV irradiation, cisplatin, staurosporine, etoposide, and doxorubicin. Although these apoptotic stimuli induce cell death via different mechanisms, they all induce ROS, suggesting that CHCHD2 could function as a ROS scavenger. Consistent with this hypothesis, downregulation of CHCHD2 significantly increases cellular ROS levels. Additionally, oxidation of CHCHD2 by ROS could lead to a conformational change (our unpublished data), which correlates with the ROS-dependent translocation of CHCHD2 from the mitochondria to the nucleus, where CHCHD2 can transactivate the expression of genes involved in mitochondrial respiration. These data suggest that CHCHD2 is not only a ROS scavenger but also a prosurvival transcription factor that promotes oxidative phosphorylation and compensates for the energy crisis that results from ROS-induced DNA damage and mitochondrial dysfunction.

Based on our data showing that the mitochondrial protein CHCHD2 interacts with BCL-XL to facilitate cell survival, and on previous observations suggesting that CHCHD2 participates in the metabolic regulation of ROS, we propose a model whereby under unstressed conditions CHCHD2 promotes mitochondrial respiration whereas under oxidative stress CHCHD2 helps neutralize ROS through its CHCH domain (Fig. 1). Failure to maintain proper levels of CHCHD2 sensitizes cells to apoptotic cell death. Overexpression of CHCHD2 has been reported in many different cancers. Therefore, based on our data showing that inhibition of CHCHD2 can sensitize cancer cells to apoptosis, CHCHD2 could represent a novel therapeutic target for the treatment of cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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