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AUTHOR'S VIEW

CHCHD4 links AIF to the biogenesis of respiratory chain complex I

Nazanine Modjtahedi[a,b,c,d,*] and Guido Kroemer[a,b,c,e,f,g,h]

[a]Equipe 11 labellisée Ligue Nationale contre le Cancer, Center de Recherche des Cordeliers, Paris, France; [b]Institut National de la Santé et de la Recherche Médicale, U1138, Paris, France; [c]Institut Gustave Roussy Cancer Campus, Villejuif, France; [d]Faculty of Medicine, University of Paris Sud, Kremlin-Bicêtre, France; [e]Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Campus, Villejuif, France; [f]Université Paris Descartes, Sorbonne Paris Cité, Paris, France; [g]Université Pierre et Marie Curie, Paris, France; [h]Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris, France

ABSTRACT

During the evolution from yeast to mammals the Mia40 protein, the regulator of the redox-sensitive mitochondrial intermembrane space import machinery, has lost its membrane-anchorage segment to become CHCHD4, which interacts with the flavoprotein apoptosis-inducing factor (AIF). Our results establish CHCHD4 as the missing link between AIF deficiency and dysfunctional biogenesis of respiratory chain complexes.

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Mitochondrial diseases are a group of heterogeneous inherited metabolic disorders that affect 1 in 5,000 individuals and are essentially caused by defects in the mitochondrial oxidative phosphorylation machinery.[1] Our poor understanding of these diseases and the lack of efficient therapeutic solutions reflect the uniqueness of the respiratory chain, which is the only metabolic machinery under the dual control of nuclear and mitochondrial genes. Among the 90 subunits that constitute the 5 respiratory chain complexes (CI to CV), 13 subunits are encoded by the mitochondrial DNA whereas the additional 77 are nuclear encoded and imported into the organelle.[1] Moreover, optimal performance of the organelle requires the import of more than 1,000 additional nuclear-encoded proteins that are indispensible for the biogenesis and/or the assembly of respiratory chain complexes, expression of the mitochondrial genome, regulation of mitochondrial ultrastructure, the finely tuned movement of mitochondria, and for crosstalk between the organelle and the nuclear compartment.[1,2]

Approximately 30% of human mitochondriopathies affect the complex CI (nicotinamide adenine dinucleotide (NADH): ubiquinone oxidoreductase; EC 1.6.5.3), a multiprotein complex that is composed of 7 mitochondrial- and 38 nuclear-encoded subunits and requires a series of "assembly factors" that are not contained in the mature complex for its assembly and maturation. One of the nuclear-encoded mitochondrial proteins that has been listed in the category of CI assembly factors is the redox-active flavoprotein apoptosis-inducing factor (AIF) that was initially discovered as a proapoptotic protein.[3] In mitochondria from healthy cells AIF is confined to the intermembrane space (IMS). In all investigated species, the loss or downregulation of AIF provokes severe CI-related respiratory defects that are caused by a post-translational loss of CI protein subunits.[3] Although complex CI remains the primary target of AIF dysfunction, losses of complex CIII (ubiquinol cytochrome c reductase; EC 1.10.2.2) and CIV (cytochrome c oxidase; EC 1.9.3.1) subunits were also observed in specific cell types.[3] In humans, mutations in AIF have been associated with severe X-linked pediatric mitochondriopathies.[4-6]

The recent isolation of the first mitochondrial interactor of AIF, a protein called coiled-coil-helix-coiled-coil-helix domain containing 4 (CHCHD4), has shed new light on the mitochondrial activity of AIF.[7] CHCHD4, which is the human homolog of yeast mitochondrial intermembrane space import and assembly protein 40 (Mia40),[8] plays a central role in the import and oxidative folding of a group of small nuclear-encoded proteins (substrates) that essentially carry 2 cysteine-x_3-cysteine $(Cx_3C)_2$ or 2 cysteine-x_9-cysteine $(Cx_9C)_2$ motifs and participate in a large panel of heterogeneous activities in the IMS[8-10] (Table 1). Given the vast number of mitochondrial processes that are covered by potential CHCHD4 substrates[8-10] (Table 1), AIF cannot be solely considered as a complex CI assembly factor but rather as a central component of the redox-active CHCHD4-dependent import machinery that, in addition to the biogenesis of respiratory chain subunits,[7] has the capacity to regulate additional processes ranging from protein import to intramitochondrial lipid homeostasis, antioxidant response, mitochondrial translation, or mitochondrial membrane organization.

Obviously, for a better understanding of the molecular impact of AIF activity on the CHCHD4-dependent import pathway, several questions need to be answered in the future. For instance, co-crystalization of AIF and CHCHD4 will reveal how AIF affects the structural maturation of CHCHD4 and its interaction with cofactors, its substrates, and its redox recycling

CONTACT Nazanine Modjtahedi Nazanine.MODJTAHEDI@gustaveroussy.fr; Guido Kroemer kroemer@orange.fr
*Present address: INSERM U1030 – Gustave Roussy Cancer Campus, Villejuif, France.

Table 1. Human proteins containing 2 (Cx_9C) and 2 (Cx_3C) motifs.

Symbol	Synonyms	Accession number	Cysteine motif	Function[#]	Chromosomal location
CHCHD1	FLJ25854	NP_976043	Cx_9C-Cx_9C	Mitochondrial translation	10q22.3
CHCHD3	MINOS3; Mic19	NP_060282.1	Cx_9C-Cx_9C	MICOS complex	7q33
CHCHD6	CHCM1; Mic25	NP_115719.1	Cx_9C-Cx_9C	MICOS complex	3q21.3
CHCHD4	MIA40; TIMM40	NP_001091972.1	Cx_9C-Cx_9C	IMS redox-regulated import	3p25.1
CHCHD10	N27C7–4	NP_001288268.1	Cx_9C-Cx_9C	Cristae morphology	22q11.23
NDUFA8	PGIV	NP_055037.1	Cx_9C-Cx_9C	CI subunit	9q33.2
NDUFB7	B18	NP_004137.2	Cx_9C-Cx_9C	CI subunit	19p13.12
NDUFS5	CI-15k	NP_001171908.1	Cx_9C-Cx_9C	CI subunit	1p34.3
UQCRH	QCR6	AAH93060	$Cx_{10}C$-Cx_9C	CIII subunit	1p34.1
COX6B1	COXG	NP_001854.1	Cx_9C-$Cx_{10}C$	CIV subunit	19q13.12
COX6B2	CT59	NP_653214.2	Cx_9C-$Cx_{10}C$	CIV subunit	19q13.42
COX17		NP_005685.1	Cx_9C-Cx_9C	CIV copper chaperone	3q13.33
COX19	MGC104475	NP_001026788	Cx_9C-Cx_9C	CIV copper chaperone	7p22.3
CHCHD7	COX23	NP_001011668	Cx_9C-Cx_9C	CIV copper chaperone	8q11.23
COA4	CMC3; E2IG2	NP_057649.2	Cx_9C-Cx_9C	CIV assembly factor	11q13.4
COA5	FLJ27524; Pet191	NP_001008216	Cx_9C-$Cx_{10}C$	CIV assembly factor	2q11.2
COA6		NP_001013003.1	Cx_9C-$Cx_{10}C$	CIV assembly factor	1q42.2
CMC1	MGC61571	NP_872329	Cx_9C-Cx_9C	CIV biogenesis	3p24–1
CMC2	MGC45036; DC13	NP_064573	Cx_9C-Cx_9C	CIV biogenesis	16q23.2
CHCHD2		NP_057223	CX_9C-CX_9C	CIV subunit expression and assembly	7p11.2
TRIAP1	MDM35	NP_057483	Cx_9C-Cx_9C	Mitochondrial lipid homeostasis	12q24.31
CHCHD5	MIC14	NP_115685.1	Cx_9C-Cx_9C	Unknown	2q14.1
CMC4	P8MTCP1	NP_001018024.1	Cx_9C-Cx_9C	Unknown	Xq28
UPF0545		NP_776154	Cx_9C-Cx_9C	Unknown	22q11.21
C17orf89		NP_001079990.1	Cx_9C-Cx_9C	Unknown	17q25.3
TIMM8A	DDP1	NP_001139423.1	Cx_3C-Cx_3C	Protein import	Xq22.1
TIMM8B	DDP2	NP_036591.2	Cx_3C-Cx_3C	Protein import	11q23.1
TIMM9	TIM9A	NP_001291414.1	Cx_3C-Cx_3C	Protein import	14q23.1
TIMM10	TIM10A	NP_036588.1	Cx_3C-Cx_3C	Protein import	11q12.1
TIMM10B	TIM10B; Tim9B	NP_036324.1	Cx_3C-Cx_3C	Protein import	11p15.4
TIMM13	Tim13	NP_036590.1	Cx_3C-Cx_3C	Protein import	19p13.3

[*]Data have been extracted from References 8 to 10, as well as from public databases.
CI, respiratory chain complex CI; CIII, respiratory chain complex CIII; CIV, respiratory chain complex CIV; IMS, intermembrane space; MICOS, mitochondrial contact site.

partner, the sulfhydryl oxidase ERV1/ALR.[8] The second question concerns the organo-specific impact of AIF deficiency on the biogenesis of specific respiratory chain complexes. Such tissue specificity is well described in the case of the AIF hypomorphic Harlequin (Hq) mouse model.[3] CI deficiency was detected only in the brain and retina of Hq mice, but not in other organs, correlating with the tissue-specific degeneration that characterizes the phenotype of this mouse model.[3] Is this peculiarity explainable by tissue-specific expression of certain CHCHD4 substrates? During the evolution from yeast to mammals, $(Cx_9C)_2$ motif-containing proteins have almost doubled in number. Beyond the evolutionary-conserved substrates implicated in the biogenesis of complex CIV (conserved between yeast and mammals), substrates corresponding to the subunits of complex CI (absent from yeast) have made their appearance (Table 1). An in-depth characterization of CHCHD4 substrates and their redox-regulated mitochondrial import in mammals should help us better understand the tissue-specific effect of AIF dysfunction on CI. Is this effect caused by the loss of CI subunits that are directly imported in a CHCHD4-dependent manner or is it an indirect effect provoked by the loss of other substrates? As recent progress in the field tends to support the notion that the assembly of complex CI is dependent on the formation of supercomplexes with CIII and CIV, an open alternative question concerns the potential crosstalk between complexes CI and CIV to explain the phenotype of AIF-deficient cells.

The molecular characterization of the physical and function interaction between AIF and CHCHD4 may spur new therapeutic strategies for the correction of respiratory defects that are caused by the loss or downregulation of AIF. As our results show that *in vitro* transfection of cells with a modified CHCHD4 whose mitochondrial import does not rely on AIF can repair the respiratory defect of AIF-deficient cells,[7] we believe that strategies for the correction of CHCHD4-dependent import pathway should be considered as a potential therapeutic strategy for the treatment of mitochondriopathies that are caused by the loss or downregulation of AIF.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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References

1. Schon EA, DiMauro S, Hirano M. Human mitochondrial DNA: roles of inherited and somatic mutations. Nat Rev Genet 2012; 13:878-90; PMID:23154810; http://dx.doi.org/10.1038/nrg3275
2. Pagliarini DJ, Calvo SE, Chang B, Sheth SA, Vafai SB, Ong SE, Walford GA, Sugiana C, Boneh A, Chen WK, et al. A mitochondrial protein compendium elucidates complex I disease biology. Cell 2008; 134:112-23; PMID:18614015; http://dx.doi.org/10.1016/j.cell.2008.06.016

3. Hangen E, Blomgren K, Benit P, Kroemer G, Modjtahedi N. Life with or without AIF. Trends Biochem Sci 2010; 35:278-87; PMID:20138767; http://dx.doi.org/10.1016/j.tibs.2009.12.008
4. Modjtahedi N, Giordanetto F, Kroemer G. A human mitochondriopathy caused by AIF mutation. Cell Death Differ 2010; 17:1525-8; PMID:20835254; http://dx.doi.org/10.1038/cdd.2010.88
5. Berger I, Ben-Neriah Z, Dor-Wolman T, Shaag A, Saada A, Zenvirt S, Raas-Rothschild A, Nadjari M, Kaestner KH, Elpeleg O. Early prenatal ventriculomegaly due to an AIFM1 mutation identified by linkage analysis and whole exome sequencing. Mol Genet Metab 2011; 104:517-20; PMID:22019070; http://dx.doi.org/10.1016/j.ymgme.2011.09.020
6. Rinaldi C, Grunseich C, Sevrioukova IF, Schindler A, Horkayne-Szakaly I, Lamperti C, Landouré G, Kennerson ML, Burnett BG, Bönnemann C, et al. Cowchock syndrome is associated with a mutation in apoptosis-inducing factor. Am J Hum Genet 2012; 91:1095-102; PMID:23217327; http://dx.doi.org/10.1016/j.ajhg.2012.10.008
7. Hangen E, Feraud O, Lachkar S, Mou H, Doti N, Fimia GM, Lam NV, Zhu C, Godin I, Muller K, et al. Interaction between AIF and CHCHD4 regulates respiratory chain biogenesis. Mol Cell 2015; 58:1001-14; PMID:26004228; http://dx.doi.org/10.1016/j.molcel.2015.04.020
8. Herrmann JM, Riemer J. Three approaches to one problem: protein folding in the periplasm, the endoplasmic reticulum, and the intermembrane space. Antioxid Redox Signal 2014; 21:438-56; PMID:24483706; http://dx.doi.org/10.1089/ars.2014.5841
9. Longen S, Bien M, Bihlmaier K, Kloeppel C, Kauff F, Hammermeister M, Westermann B, Herrmann JM, Riemer J. Systematic analysis of the twin cx(9)c protein family. J Mol Biol 2009; 393:356-68; PMID:19703468; http://dx.doi.org/10.1016/j.jmb.2009.08.041
10. Cavallaro G. Genome-wide analysis of eukaryotic twin CX9C proteins. Mol Biosyst 2010; 6:2459-70; PMID:20922212; http://dx.doi.org/10.1039/c0mb00058b