Review

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Apoptosis inducing factor and mitochondrial NADH dehydrogenases: redox-controlled gear boxes to switch between mitochondrial biogenesis and cell death

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Abstract: The mitochondrial complex I serves as entry point for NADH into the electron transport chain. In animals, fungi and plants, additional NADH dehydrogenases carry out the same electron transfer reaction, however they do not pump protons. The apoptosis inducing factor (AIF, AIFM1 in humans) is a famous member of this group as it was the first pro-apoptotic protein identified that can induce caspase-independent cell death. Recent studies on AIFM1 and the NADH dehydrogenase Nde1 of baker's yeast revealed two independent and experimentally separable activities of this class of enzymes: On the one hand, these proteins promote the functionality of mitochondrial respiration in different ways: They channel electrons into the respiratory chain and, at least in animals, promote the import of Mia40 (named MIA40 or CHCHD4 in humans) and the assembly of complex I. On the other hand, they can give rise to pro-apoptotic fragments that are released from the mitochondria to trigger cell death. Here we propose that AIFM1 and Nde1 serve as conserved redox switches which measure metabolic conditions on the mitochondrial surface and translate it into a binary life/death decision. This function is conserved among eukaryotic cells and apparently used to purge metabolically compromised cells from populations.

Keywords: cell death; complex I; MIA40; mitochondria; protein import; redox.

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Introduction

The strange case of Dr. Jekyll and Mr. Hyde is a famous novel by Robert Louis Stevenson about a person of remarkable dual nature: Dr. Jekyll is a doctor with amiable personality who helps others and has many friends. But sometimes, he converts into Mr. Hyde who is shockingly evil and brings death to others. Several mitochondrial NADH dehydrogenases are likewise of dual nature. They are enzymes of the respiratory chain and, at least in animal cells, promote mitochondrial biogenesis. However, under certain conditions they can convert into pro-apoptotic factors that induce irreversible DNA fragmentation and cell death.

The mitochondrial respiratory chain utilizes the flow of electrons from NADH to oxygen to pump protons into the IMS. The return of these protons to the matrix is used to generate ATP. The capacity of this system is impressive. In a single human being, about 60 kg of ATP are produced in a single day, by far most of these in mitochondria. Despite the huge amount of the end product ATP, the substrates of the respiratory chain, oxygen and NADH, are often not limiting in well-fed organisms. On the contrary, high NADH levels and correspondently, low levels of NAD^+, are not beneficial but associated with pathological conditions and premature aging (Katsyuba et al. 2018). Cells employ alternative pathways to oxidize surplus NADH and NADPH, such as the production of lactate from pyruvate or that of α-hydroxybutyrate from α-ketobutyrate or acetoacetate (Thompson Legault et al. 2015). Many organisms use mitochondrial enzymes that bypass the respiratory chain, i.e., they transport electrons but do not pump electrons. Since these enzymes are running idle they have the potential to quickly and efficiently reduce the NAD(P)H redox potential. NAD(P)H dehydrogenases are shortcuts that bypass complex I (from NADH to ubiquinone) and alternative oxidases act downstream of ubiquinone to bypass complexes III and/or IV. These enzymes are ubiquitously

present in plants and fungi, but are also found in some animals where they can play a role in thermogenesis (Bertsova et al. 2004; Nguyen et al. 2020): In humans, brown adipose cells are specialized in heat production. They dissipate energy via the uncoupling protein UCP1 which serves as proton leak in the inner membrane. In addition to UCP1, these cells express AIFM2, a special isoform of an NADH dehydrogenase, to speed up electron flow through the respiratory chain. AIFM2 and its more ubiquitously expressed homolog AIFM1 presumably play a so far poorly analyzed physiological role in metabolism in many cells. Recent studies suggests that these enzymes are part of an OXPHOS paralleling system that reduces the risk of phospholipid peroxidation and ferroptosis, although this system is still poorly characterized (Bersuker et al. 2019; Doll et al. 2019). Despite this 'life-saving' function as ferroptosis suppressor, apoptosis inducing factors were initially identified as factors that can trigger a unique, caspase-independent apoptotic program.

In this review we will discuss these different functions of mitochondrial NADH dehydrogenases on the basis of recent discoveries made on mammalian and fungal isoforms.

NADH dehydrogenases, a conserved group of enzymes

Alternative (or type II) NADH dehydrogenases are single or oligo subunit enzymes which catalyze the same reaction as complex I but they do not pump protons across the inner membrane (Figure 1A). Unlike complex I, they lack flavin mononucleotide (FMN) and iron-sulfur clusters as reactive groups. Instead, they contain a flavin adenine dinucleotide (FAD) cofactor to mediate the electron transfer from NAD(P)H to ubiquinone. While complex I is deeply integrated into the inner membrane, alternative NADH dehydrogenases are not membrane-embedded, but rather associated to the membrane surface, either on the IMS side (external NADH dehydrogenases) or the matrix side (internal NADH dehydrogenases). They often are firmly attached to the membrane (this is where ubiquinone serves as their electron acceptor) by N-terminal transmembrane anchors or/and by a C-terminal hydrophobic membrane-binding region. NADH dehydrogenases belong to a large group of oxidoreductases sharing the Rossmann fold (Mate et al. 2002; Rossmann and Argos, 1978; Sorrentino et al. 2015, 2017). This group also includes enzymes such as thioredoxin reductase, dihydrolipamide dehydrogenase (the E3 component of pyruvate dehydrogenase), sulfide:quinone oxidoreductase and flavin-dependent monooxygenases (e.g., Coq6 in yeast).

Alternative NADH dehydrogenases are ubiquitously expressed in fungi and plants (Figure 1B). In baker's yeast, three homologues are well characterized: two external (Nde1 and Nde2) and one internal (Ndi1) isoforms (Luttik et al. 1998; Saladi et al. 2020). Since baker's yeast has no complex I, they serve as predominant entry sites for NADH electrons into the respiratory chain. Thereby, Nde1 and Nde2 presumably accept NADH that is synthesized by glycolysis in the cytosol and Ndi1 electrons produced by the TCA cycle in the matrix, however, all three enzymes are functionally redundant. Whereas single mutants (in

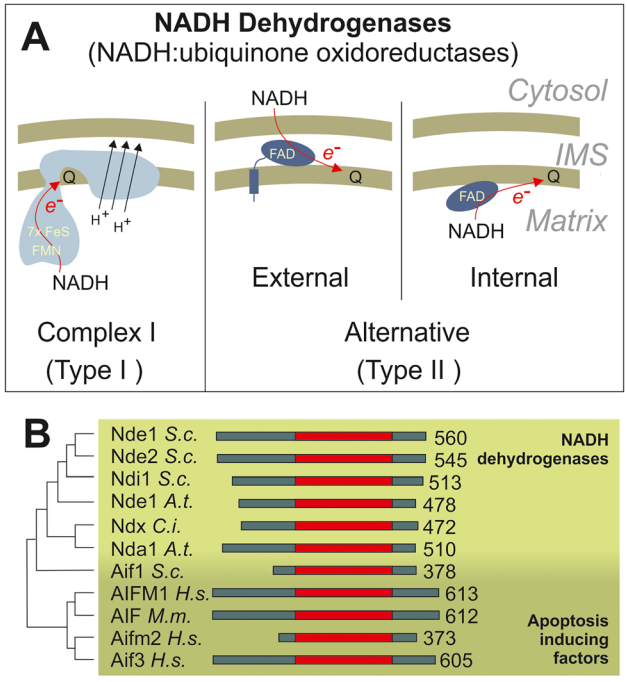

Figure 1: NADH dehydrogenases transfer electrons from NAD(P)H to ubiquinone. (A) In most organisms, the mitochondrial complex I serves as the sole or predominant entry point for electrons into the respiratory chain. However, external or internal NADH dehydrogenases provide additional, alternative electron transfer routes. These structurally rather simple flavoproteins do not pump electrons. They are ubiquitously found in fungi and plants, but also in some animals. Baker's yeast lost complex I and uses exclusively alternative NADH dehydrogenases for respiration. Q, ubiquinone. (B) Structural overview of NADH dehydrogenases and apoptosis inducing factors. All these proteins share the FAD- and NADH-binding region (shown in red) that are characterized by conserved Rossmann folds. The flanking regions are more variable, however, they consistently present matrix-targeting signals on their N-termini followed, in the case of external dehydrogenases and apoptosis inducing factors, by membrane-anchoring hydrophobic regions. The sequences shown are that of Nde1, Nde2, Ndi1 and Aif1 of baker's yeast (S.c.), Nde1 and Nda1 of *Arabidopsis thaliana* (CAA18713.1 and At1g06820), Ndx of *C. intestinalis* (XP_002122465.1), AIFM1, AIFM2 and AIF2 of *Homo sapiens* (NP_004199.1, AAH23601.1, NP_653305.1) as well as of murine AIF (NP_036149.1).

particular *Δndi1*) show mild respiration defects (Marres et al. 1991), triple deletion mutants in which all three enzymes are deleted are unable to grow on non-fermentable carbon sources. Aif1 is a fourth member of this family. It shows the highest similarity to the human AIFM1 and a function in electron transport is not unambiguously demonstrated, though appears likely (Wissing et al. 2004). Yeast mutants lacking Aif1 show a synthetic growth defect in the absence of Gsh1, the enzyme that carries out the first step in glutathione synthesis (Costanzo et al. 2010). This points to a physiological role of Aif1 in redox homeostasis, in line with a function of Aif1 in NAD(P)H metabolism.

Alternative NADH dehydrogenases were also found in many animals, in particular in sessile marine organisms (Matus-Ortega et al. 2011; McDonald and Gospodaryov, 2019). These enzymes are presumably not required for growth at the hypoxic conditions of these life forms, however, they might serve as important valves on the respiratory chain when oxygen tensions suddenly rise. This hypothesis is supported by experiments in *Drosophila melanogaster* (which normally lacks alternative NADH dehydrogenases): expression of the enzyme of the tunicate *Ciona intestinalis* in flies provides resistance to specific stresses and can prolong life (Gospodaryov et al. 2020).

It is likely, that apoptosis inducing factors play a similar 'physiological' role in cellular redox metabolism (Cheung et al. 2006; Elguindy and Nakamaru-Ogiso, 2015; Miramar et al. 2001). In mice, AIF is essential and homozygous mutants are embryonically lethal (Joza et al. 2001). Heterozygous deletion mutants (so-called harlequin mice) are viable but show severe defects in mitochondrial functionality (Coughlan et al. 2016). In humans, mutations in the AIFM1 locus on the X chromosome (at position Xq26.1) lead to diseases that show symptoms such as mitochondrial encephalomyopathy, axonal sensorimotor neuropathy, ataxia or deafness. These diseases are phenotypically similar to those caused by mutations in other mitochondrial components. They include syndromes such as the *Combined Oxidative Phosphorylation Deficiency 6* (Ghezzi et al. 2010), *X-linked recessive Charcot-Marie-Tooth disease-4* or Cowchock syndrome (Rinaldi et al. 2012), and *X-linked Deafness 5* (Zong et al. 2015). These defects might in part be due to the role of AIFM1 in the biogenesis of complex I and the mitochondrial disulfide relay system (see below), but presumably also due the physiological relevance of AIFM1 in electron transport from NADH (and to a lower degree NADPH) to ubiquinone. However, since the different paths by which electrons are funneled into the respiratory chain are highly redundant, the individual share of each enzyme in electron flux under physiological conditions is not known.

AIFM1, a partner of MIA40 in the mitochondrial disulfide relay

AIFM1 resides in the mitochondrial IMS. It is synthesized on cytosolic ribosomes as a 613 amino acid long precursor protein. Its import into the IMS depends on an N-terminal bipartite mitochondrial targeting sequence (AIFM1-MTS) (Susin et al. 1999). The AIFM1-MTS drives the AIFM1 precursor across the mitochondrial outer membrane and anchors it in a translocase of the inner mitochondrial membrane (TIMM23)-dependent manner in the inner mitochondrial membrane. There, the matrix-localized presequence of the AIFM1 precursor is removed by the matrix processing peptidase MPP resulting in the mature membrane bound form of AIFM1 that lacks the first 54 amino acid residues compared to the precursor (Otera et al. 2005).

Apart from its role in apoptosis induction, AIFM1 has been linked to assembly and maintenance of respiratory chain complexes. Human and mouse cells lacking AIFM1 exhibited reduced levels and activity of complex I (Kollias et al. 1992; Troulinaki et al. 2018; Urbano et al. 2005; Vahsen et al. 2004). Work in other model organisms such as *Saccharomyces cerevisiae*, *D. melanogaster* and *Caenorhabditis elegans* supported a role of AIFM1 in respiratory chain assembly and maintenance. Deletion of the AIFM1 homolog AIF1 in yeast resulted in altered growth on non-fermentable carbon sources like lactate and glycerol (Vahsen et al. 2004). AIF knockout in flies led to larval lethality due to loss of complex I and complex IV activities (Joza et al. 2008). Likewise, downregulation of the *C. elegans* homolog wah-1 decreased mitochondrial respiration (Troulinaki et al. 2018).

AIFM1 is no subunit of complex I and its molecular role in respiratory chain complex assembly is not fully understood. AIFM1 is not influencing the expression of OXPHOS genes (Vahsen et al. 2004) pointing to a posttranslational role of AIFM1 during respiratory chain assembly. Indeed, AIFM1 plays an important but indirect role for the import of respiratory chain subunits into the IMS as it facilitates the import of the oxidoreductase MIA40 (also CHCHD4) (Hangen et al. 2015; Meyer et al. 2015; Petrungaro et al. 2015). Owing to this functional connection, MIA40 and AIFM1 share very similar gene essentiality profiles in systematic CRISPR knockout studies (DepMap portal) (Dempster et al. 2019), supporting their relevance for the same cellular processes.

The mitochondrial disulfide relay is a machinery that mediates protein import into the IMS and concomitant oxidative protein folding (Edwards et al. 2020; Finger and Riemer, 2020; Fischer et al. 2013; Mesecke et al. 2005; Peleh

et al. 2017; Riemer et al. 2015; Rissler et al. 2005). It relies on the oxidoreductase MIA40 (also CHCHD4) which introduces disulfide bonds into newly imported IMS proteins. In addition, MIA40 serves as import receptor and binding site for substrates coming from the cytosol through the TOM channel. Using its oxidoreductase and chaperone activity, MIA40 catalyzes the oxidative folding of proteins and their insertion into different protein complexes in the IMS and the inner membrane (Erdogan et al. 2018; Habich et al. 2019; Okamoto et al. 2014; Peleh et al. 2016; Ramesh et al. 2016; Wrobel et al. 2016).

Yeast Mia40 contains an N-terminal bipartite mitochondrial targeting sequence that guides the protein into the IMS on the matrix-targeting pathway (Backes and Herrmann, 2017; Callegari et al. 2020; Mokranjac, 2020). Such a signal is lacking in MIA40 of animals. Instead, human MIA40 contains an N-terminal sequence of 40 residues which binds to an AIFM1 dimer that forms in the presence of NADH (Hangen et al. 2015); this interaction apparently drives the translocation of MIA40 through the translocase of the outer membrane (TOM) complex though details are not entirely clear (Figure 2). Removal of the N-terminal amino acids from MIA40 or the depletion of AIFM1 (by siRNA) strongly impairs MIA40 accumulation in the IMS. This reduction in mitochondrial MIA40 levels is also observed in the harlequin mouse model, however, there exists a surprising and unexplained heterogeneity in different tissues of the mice (Meyer et al. 2015; Wischhof et al. 2018).

Since MIA40 imports several complex I subunits (Friederich et al. 2017), the relevance of AIFM1 for complex I biogenesis is explained by the AIFM1-dependent MIA40 biogenesis. Accordingly, when MIA40 is overexpressed or imported as fusion with a bipartite presequence in an AIFM1-independent manner, AIFM1 was found to be largely dispensable for complex I biogenesis (Hangen et al. 2015; Meyer et al. 2015).

The substrates of the disulfide relay significantly vary in their dependence on MIA40 levels (Habich et al. 2019) and, again, strong differences among different tissues were described. For example, a patient expressing a cysteine mutant of the MIA40 substrate NDUFB10, a structural subunit of complex I, had no detectable NDUFB10 protein in his liver and muscle but normal levels in fibroblasts (Friederich et al. 2017).

Thus, in mammalian cells, alternative NADH dehydrogenases serve as important, though not necessarily essential import receptors of MIA40. Here, mitochondria utilize the NADH-dependent interaction of AIFM1 and MIA40 to regulate the biogenesis of complex I subunits in dependence of the prevailing NADH concentrations.

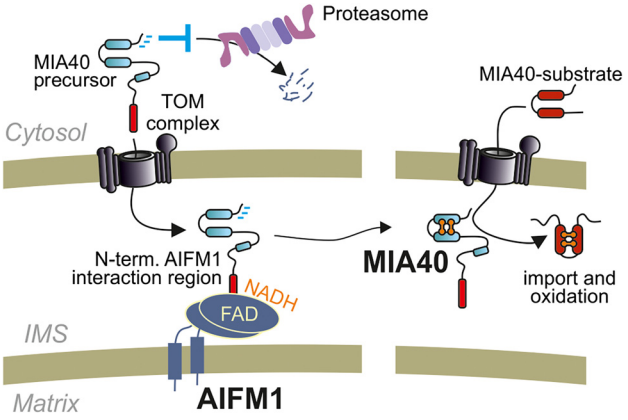

Figure 2: AIFM1 facilitates the import of MIA40, and indirectly that of complex I subunits into the IMS of mammalian cells. In humans, MIA40 carries an N-terminal stretch of 40 residues (shown in red) that serves as binding site for AIFM1. NADH-dependent dimerization of AIFM1 is a prerequisite for AIFM1 binding and, hence, the efficient import and oxidative folding of MIA40. Once imported and oxidized MIA40 drives the import and oxidation of its substrates. Non-imported MIA40 is stable in the cytosol as its C-terminal negatively charged regions prevents proteasomal degradation.

Apparently, mammalian mitochondria added this regulatory step to the MIA40 import pathway to allow its control by the metabolic conditions.

AIFM1/Nde1 can induce apoptosis

AIFM1 was initially identified as a mitochondrial protein that, to induce apoptosis, is released into the cytosol, from where it translocates into the nucleus in order to initiate DNA fragmentation and cell death (Susin et al. 1996, 1999). This pro-apoptotic role of AIFM1 is described in depth in several excellent review articles (e.g., Bano and Prehn 2018; Dawson and Dawson 2017; Hangen et al. 2010a; Norberg et al. 2010b). Like other factors that are relevant for apoptosis, such as cytochrome *c*, SMAC/Diablo and Htra2/Omi, AIFM1 is a protein of the IMS and initially it was proposed that in order to induce cell death, the outer membrane is ruptured to release a detrimental cocktail of killer proteins. This view is presumably too simplistic and incorrect. Rather, mitochondrial proteins are released into the cytosol in a more specific fashion which includes processes such as Bax/Bak-mediated outer membrane permeabilization.

AIFM1 is not involved in the 'canonical', caspase-dependent apoptosis program. Its role in pro-apoptotic signaling therefore is distinct from that of cytochrome *c* and caspases. Moreover, the release of AIFM1 from mitochondria is not triggered by a mechanical rupturing of the

outer membrane (that would spill the content of the IMS into the cytosol). Rather, the release of pro-apoptotic factors from the IMS into the cytosol, and in particular that of AIFM1, can occur in a well-controlled and specific manner which, despite many years of intensive research, is still not very well understood (Pena-Blanco and Garcia-Saez 2018).

The classical model for the release of AIFM1 from mitochondria (Figure 3A) proposes its calpain-mediated cleavage C-terminally of its membrane anchor in a calcium and oxidation-triggered reaction (Norberg et al. 2010a; Ozaki et al. 2008; Polster et al. 2005). Calpains are calcium-activated cysteine proteases. In mammalian cells, several isoforms exist which are present in the cytosol as well as in the matrix and the IMS of mitochondria. The relevance of calpain for AIFM1 cleavage *in vivo* was questioned in several studies. Nonetheless, at least *in vitro*, the addition of calpains to inner membrane vesicles leads to the generation of the identical G102↓L103 pro-apoptotic AIFM1 fragment that induces cell death *in vivo* (Polster et al. 2005). Moreover, inhibitory peptides that block the activity of calpains can protect rat retinal ganglion cells from AIFM1-dependent ischemia/reperfusion injury (Ozaki et al. 2009). However, in this context, it is very difficult to disentangle the molecular functions of AIFM1 unambiguously since it is involved in complex I assembly, in mitochondrial redox regulation and in pro-apoptotic signaling, thus in three processes that are directly relevant in the context of ischemia/reperfusion injury (Chen et al. 2019; Thompson et al. 2016).

A recent study in yeast proposed an alternative process by which the pro-apoptotic cytosolic fragment is generated (Figure 3B). The yeast NADH dehydrogenase Nde1 has a topology similar to that of AIFM1. It is integrated into the inner membrane by an N-terminal membrane anchor and exposes an oxidoreductase domain into the IMS. However, there is a considerable fraction of the protein which has a different topology as it exposes its oxidoreductase domain into the cytosol (Saladi et al. 2020; Zahedi et al. 2006). This species is generated by an incomplete translocation across the outer membrane. If the N terminal targeting segment of Nde1 is replaced by the 'strong' import sequence of the inner membrane protein Mia40, only the IMS species is generated. Thus, the Nde1 targeting sequence obviously generates on purpose two versions: an IMS-located form which serves as electron transfer protein from NADH to ubiquione, and a cytosol-exposed form which is catalytically inactive (since it is inaccessible to ubiquinone). Interestingly, this surface-exposed form is highly toxic and induces apoptosis in yeast cells. Under pro-apoptotic conditions, such as in the presence of acetic acid, it gives rise to a cytosolic fragment that is under control of the mitochondrial i-AAA protease and the proteasome system (Augustin et al. 2005; Gomes et al. 2013; Saladi et al. 2020). Such pro-apoptotic fragments can presumably also be generated from other NADH dehydrogenases in yeast such as Ndi1 or Aif1 (Cui et al. 2012; Li et al. 2006; Muzaffar and Chattoo 2017; Wissing et al. 2004).

The similarity of the Nde1-mediated apoptosis in yeast and the AIFM1-dependent cell death in animal cells is very

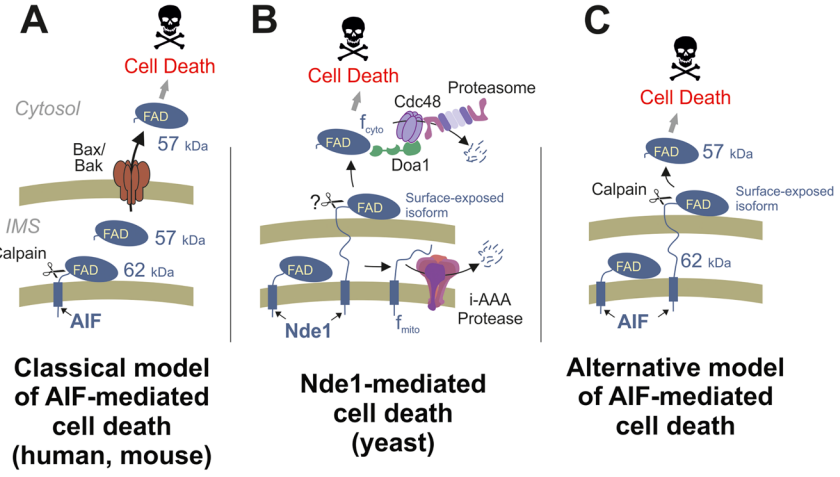

Figure 3: Pro-apoptotic signaling by NADH dehydrogenases. (A) According to the classical model, AIFM1 resides within the IMS. Upon induction of apoptosis, the calcium- and redox-regulated protease calpain releases a 57 kDa fragment from the inner membrane. This fragment is translocated through the outer membrane by the pro-apoptotic BCL-2 family effector proteins Bax/Bak (Pena-Blanco and Garcia-Saez 2018) into the cytosol from where it enters the nucleus to bind DNA. DNA fragmentation and chromatin condensation then initiate the irreversible cell death. (B) Nde1 forms two distinct topomers, one in the IMS and one exposed to the cytosol. The latter gives rise to two fragments (f_{mito} and f_{cyto}) which are under control of the i-AAA protease and the proteasome system, respectively. The fcyto-Fragment is particularly enriched in mutants with compromised mitochondria were the membrane potential is low (Saladi et al. 2020). It can efficiently induce cell death, for example in the presence of acetic acid or in aging cells. (C) An alternative model of AIFM1-mediated cell death proposes the generation of the 57 kDa fragment from a surface-exposed topomer. It should be noted that this alternative model and the classical Bax/Bad-depending process are not mutually exclusive and might be of relevance under different conditions or in different cell types.

striking, suggesting that the underlying principles are well conserved among eukaryotes. However, the mechanism by which the pro-apoptotic fragment is formed appears to be entirely different: In animals, the cleavage was proposed to produce the fragment initially in the IMS from where it is translocated across the outer membrane by Bax/Bak complexes or by mitochondrial permeability transition pores (Bidere et al. 2003; Moubarak et al. 2007). In contrast, the pro-apoptotic fragment of Nde1 is generated on the mitochondrial surface in the cytosol from a minor topomer, so that a translocation across the outer membrane is not required. Is it possible, that such an alternative mechanism (Figure 3C) is also of relevance in the context of AIFM1-mediated cell death? Indeed, a surface-exposed topomer of AIFM1 was described for neurons and it was proposed that this species gives rise to the pro-apoptotic fragment (Yu et al. 2009). Moreover, more recent studies on mouse models (Engel et al. 2010) challenge the initial *in vitro* data from which a critical relevance of proapoptotic Bcl-2 proteins such as Bid for AIFM1 translocation across the outer membrane were concluded. Thus, a minor surface-exposed topomer of AIFM1 might also exist in humans and be of direct relevance for the pro-apoptotic function of AIFM1. Since the IMS-localized form is predominant, such a 'moonlighting' second species might be difficult to identify biochemically. Immunoprecipitation and proximity labeling, however, did identify AIFM1 as an interactor of parkin on the mitochondrial surface, in line with the existence of a cytosol-exposed species (Guida et al. 2019). This species might be controlled by the proteasome (Liu et al. 2010) in the same way as the surface-exposed Nde1 topomer of yeast cells.

Interestingly, neurons express an alternative AIFM1 variant: AIF2 is a brain-specific isoform generated by alternative splicing (use of exon 2b) (Hangen et al. 2010b). This isoform is identical to the canonical AIFM1 except for the N-terminal transmembrane region which serves as stop-anchor sequence. It was proposed that the different properties of this membrane anchor bind the protein more tightly to the inner membrane explaining why AIF2 favors its physiological and disfavors its pro-apoptotic potential (Hangen et al. 2010b). This physiological function as an NADH dehydrogenase in an electron transfer route that parallels the respiratory chain is also supported by recent studies that showed that AIF2 reduces respiration-induced lipid peroxidation and ferroptosis (Bersuker et al. 2019; Doll et al. 2019). In its properties, AIF2 is very reminiscent to the Mia40-Nde1 fusion protein of yeast cells which prevented the formation of the surface-exposed topomer and therefore could not trigger cell death (Saladi et al. 2020).

Mitochondrial oxidoreductases as redox-controlled switches to commit life/death decisions

NADH dehydrogenases obviously have different conserved functions: (1) they serve as redox enzymes that bypass the respiratory chain. This valve-like role on the respiratory chain is particularly important during unstable oxygen conditions such as in marine organisms or in the context of pathological ischemia-reperfusion injury, but also relevant to prevent oxidative damage in mitochondria under physiological conditions. (2) NADH dehydrogenases serve as 'apoptosis inducing factors' in a poorly understood process that involves the formation of a toxic protein fragment on the outside or inside of the mitochondrial outer membrane. (3) In animals but not in yeast, AIFM1 serves as biogenesis factor for MIA40 and thus, indirectly, for many IMS proteins. Why did Nature entrust one protein with these seemingly unrelated functions? As valves on the respiratory chain, NADH dehydrogenases serve as sensors of the metabolic fluxes in mitochondria. It appears likely that this metabolic information is crucial to control their role as pro-apoptotic component as well as their function as MIA40 import receptor. According to this hypothesis, alternative NADH dehydrogenases serve as regulatory metabolic hubs on the mitochondrial surface that can exhibit "Dr. Jekyll and Mr. Hyde"-like activities depending on the local prevailing physiological conditions. This regulation of these exciting redox controlled gear boxes on the mitochondrial surface will have to be studied in more depth in the future.

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