

Supplementary information

Molecular mechanisms of mitochondrial dynamics

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Supplementary informations for Molecular mechanisms of mitochondrial dynamics

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Supplementary Box

Supplementary Box 1: Non-core regulators of mitochondrial fission and fusion

Mitochondrial morphology is mainly regulated by the coordinated action of large GTPases, however, additional proteins are also involved in the modulation of mitochondrial dynamics, either by controlling post-translational modifications of the core fission and fusion machinery (**see Table S2**) or by directly altering mitochondrial shape.

The mitochondrial fission regulator 1 (MTFR1) family is comprised of three members that are all found in the outer mitochondrial membrane (OMM) and associated with the control of mitochondrial morphology: MTFR1, MTFR2, and the most divergent MTFR1L (ref. ¹). MTFR1 and MTFR2 participate in dynamin-related protein 1 (DRP1)-dependent mitochondrial division^{1,2}, identifying these two proteins as pro-fission factors. In contrast, loss of MTFR1L leads to mitochondrial elongation and hyperbranching induced by increased fusion events and upregulation of OPA1 levels³, suggesting MTFR1L as a negative regulator of mitochondrial fusion^{3,4}. Interestingly, MTFR1L has been identified as an AMP-activated protein kinase (AMPK) substrate^{5,6,7}, transducing AMPK-dependent metabolic changes through regulation of mitochondrial dynamics³. Finally, although all MTFR1 members interact with mitochondrial Rho GTPase 1 (MIRO1), only MTFR1L requires MIRO1 as an adaptor for its mitochondrial localization⁸. Human MIRO1 and MIRO2 are atypical GTPases, inserted in the OMM through a single transmembrane (TM) domain and coordinating mitochondrial transport across microtubules^{9,10}. Moreover, MIRO1 and 2 have recently been found to be involved in the control of mitochondrial shape^{11,12,13} and their yeast ortholog Gem1p also regulates mitochondrial morphology¹⁴, suggesting a link between mitochondrial structure and motility.

Ganglioside-induced differentiation associated protein 1 (GDAP1) is a tail-anchored OMM protein facilitating mitochondrial division^{15,16}. Its overexpression triggers mitochondrial fission factor (MFF)-dependent mitochondrial fragmentation and its downregulation leads to both peroxisomal and mitochondrial elongation^{15,16}. Recent findings suggest that GDAP1 loss causes defective F-actin recruitment to mitochondria, decreasing DRP1 recruitment and therefore leading to mitochondrial elongation¹⁷.

Similar to mitochondrial carrier homolog 2 (MTCH2) (**see Box 3 in the main text**), the mitochondrial outer membrane protein, solute carrier family 25 member 46 (SLC25A46), is an atypical member of the solute carrier protein family. It is exclusively localized to and inserted within the OMM,

and has also been suggested to be orthologous to the yeast protein Ugo1 (refs. ^{18,19}). Interestingly, similar to how Ugo1 interacts with orthologs of mitofusin 2 (MFN2) (Fzo1) and of optic atrophy 1 (OPA1) (Mgm1) in yeast to control mitochondrial fusion^{20,21}, human SLC25A46 also co-immunoprecipitates with both MFN2 and OPA1, and its presence has been reported at both fusion and fission sites²², highlighting the complex role of this protein in mitochondrial dynamics. Intriguingly, patient cells harbouring pathogenic *SLC25A46* mutations display mitochondrial elongation accompanied by decreased recruitment of DRP1 to mitochondria¹⁸, whereas knock-out cells show mitochondrial fragmentation, associated with an altered oligomerization status of OPA1 and MFN2 (ref. ²²). In addition, SLC25A46 loss-of-function alters mitochondrial lipid profiles, suggesting that it may facilitate lipid trafficking at mitochondria-ER contact sites (MERCs) to ensure an adequate lipid availability required for mitochondrial membrane remodeling^{18,22}.

Mitochondrial fission process protein 1 (MTFP1, also known as MTP18), is an integral inner mitochondrial membrane (IMM) protein, initially considered a pro-fission factor^{23,24}. Indeed, its overexpression triggers DRP1-dependent mitochondrial fragmentation, whereas its loss leads to a hyperfused mitochondrial phenotype, characterized by excessive mitochondrial branching^{23,24,25}. Proposed to act upstream of DRP1 (ref. ²⁵), MTFP1 couples mitochondrial morphology to several pathways driving cell fate decisions, such as mammalian target of rapamycin complex 1 (mTORC1)²⁵, mitophagy²⁶, cell death^{27,28} and cancer progression^{29,30,31}. However, recent studies have revealed that MTFP1 is not a pro-fission factor per se^{27,32}, but rather coordinates IMM fusion inhibition with the OMM division machinery to promote peripheral mitochondrial division³² (**see Box 2 in the main text**). Mechanistically, it has been proposed that MTFP1 negatively regulates mitochondrial fusion, by controlling cardiolipin distribution and OPA1-driven IMM fusion³².

Stomatin-like protein 2 (SLP2) forms the SPY complex within the IMM together with the protease presenilin-associated rhomboid-like protein (PARL) and the ATP-dependent zinc metalloprotease YME1L³³. SLP2 is required for stress-induced mitochondrial hyperfusion (SIMH), a pro-survival mechanism that adapts the mitochondrial network to resist cellular stress and enhance ATP production, by limiting the proteolytic inactivation of OPA1 by overlapping activity with m-AAA protease 1 (OMA1) (ref. ^{34,33}). Similarly, prohibitins (PHBs) can form ring-like complexes at the IMM and cristae, which sequester OMA1 and thus impair OPA1 processing, preventing mitochondrial fragmentation^{35,36}.

Due to space limitations, it is difficult to describe in detail all proteins associated with mitochondrial morphology regulation in this section. However, the following proteins should also be considered and readers are referred to the following references: ABHD16 (fission and fusion, described

in **Box 2**)³⁷, BAX and BAK (fusion^{38,39} and fission^{40,41}), CDC42 (fission)⁴², Endophilin B1 (fission)⁴³, FUNDC1 (fission and fusion)^{44,45}, GTPBP8 (fission)⁴⁶, LETM1 (maintain tubular structure)^{47,48}, MSTO1 (fusion)^{49,50}, MIGA1/2 (fusion, described in **Box 3**)⁵¹, MTCH2 (fusion, described in **Box 2**)^{52,53}, PGAM5 (fission⁵⁴ and fusion⁵⁵), RAB11 (fission)⁵⁶, ROMO1 (fusion)⁵⁷, and TMEM135 (fission)^{58,59}.

Supplementary Box 2: Evolutionary divergence of mitofusin (MFN) topology

It has been traditionally thought that both the yeast mitofusin Fzo1 and mammalian MFNs share a similar topology, with both the amino and carboxy termini facing the cytosol, and both domains being involved in outer mitochondrial membrane (OMM) tethering and membrane fusion^{60,61,62}. Based on the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNARE)-like model of MFN2 and the homology to the bacterial dynamin-like protein (BDLP) crystal structure, studies have proposed that the antiparallel interaction between the heptad repeat 2 (HR2) and HR1 domains within the same MFN2 molecule led to the local bending of the HR1 domain^{62,63}. This constrains the HR2-binding region within the core MFN2 globular structure, restraining it in a closed and fusion-incompetent conformation⁶³. Destabilization of the intramolecular interactions between HR1 and HR2 induces an “open” or fusion-permissive state, with the HR2 extending into the cytosol, which permits HR2 *trans*-oligomerization and mitochondrial tethering⁶³. In fact, an anti-HR1 minipeptide or small molecule targeting this interface inhibits the closed conformation, driving mitochondrial fusion and rescuing mitochondrial defects in cellular models of Charcot–Marie–Tooth disease type 2A (CMT2A) caused by MFN2 mutations^{63,64}. However, the proposed mechanism of the minipeptides is inconsistent with a series of recent structural studies indicating that MFN tethering is mediated via the G domain (see main text of the review).

Additionally, a recent study has challenged the prevailing idea that both amino and carboxy termini are exposed into the cytosol, proposing that in metazoans, MFNs contain only one transmembrane (TM) domain spanning the OMM, resulting in an N-out and C-in topology⁶⁵. Biochemical approaches have confirmed that human MFNs possess a single TM domain, placing the 12 kDa carboxy terminus and the HR2 domain within the intermembrane space (IMS)⁶⁵ (**see Fig. 2b in the main text**). This new model aligns with findings showing that the HR2 domain alone does not induce liposome fusion⁶⁶ and raises an important question: What is the role of the HR2 domain in the IMS? In this regard, the revised MFNs topology suggests that before mitochondrial docking, redox-sensitive cysteine residues in the HR2 domain can form disulfide bridges with other MFN molecules forming homo-oligomers in *cis*, which may act as a “priming” mechanism to trigger MFNs *trans*-dimerization and OMM fusion⁶⁷. In fact, these findings corroborate earlier studies linking reactive oxygen species and oxidative stress to mitochondrial fusion^{68,57,69}. Finally, the projection of the carboxy

terminus of MFN1 into the IMS may provide a molecular bridge to interact with OPA1 at the IMM, ensuring that both membranes fuse in a sequential and coordinated manner⁶⁵. It is important to note that, whereas in yeast Ugo1 appears to facilitate the interaction between Fzo1 and Mgm1, driving the coordinated fusion of both OMM and IMM^{20,70}, in mammals two potential orthologs have been identified: MTCH2 and SLC25A46 (**see Supplementary Box 2**), but their precise role in mitochondrial fusion needs to be further elucidated.

Supplementary Tables

Gene	OMIM	Inheritance	Disease	Phenotype MIM number	Link to full list of symptoms	Refs
DNM1L	603850	AD, AR	Encephalopathy due to defective mitochondrial peroxisomal fission-1	614388	https://www.omim.org/clinicalSynopsis/614388	71 72 73 74 75 76
		AR	Optic atrophy-5	610708	https://www.omim.org/clinicalSynopsis/610708	77 78
MFF	614785	AR	Encephalopathy due to defective mitochondrial and peroxisomal fission-2	617086	https://www.omim.org/clinicalSynopsis/617086	79 80 81 82
MIEF1	615497	AD	Optic atrophy-14	620550	https://www.omim.org/clinicalSynopsis/620550	83
MIEF2	615498	AR	Combined oxidative phosphorylation deficiency-49	619024	https://www.omim.org/clinicalSynopsis/619024	84
MFN2	608507	AD	Charcot-Marie-Tooth disease, type 2A2A	609260	https://www.omim.org/clinicalSynopsis/609260	85 86 87 88 89 90 91
		AR	Charcot-Marie-Tooth disease, type 2A2B	617087	https://www.omim.org/clinicalSynopsis/617087	92 93 94
		AD	Charcot-Marie-Tooth disease, type 6A	601152	https://www.omim.org/clinicalSynopsis/601152	95
		AR	Lipomatosis, with or without peripheral neuropathy	151800	https://www.omim.org/clinicalSynopsis/151800	92 96 97 98
OPA1	605290	AR	Mitochondrial DNA depletion syndrome 14*	616896	https://www.omim.org/clinicalSynopsis/616896	99
		AR	Behr syndrome	210000	https://www.omim.org/clinicalSynopsis/210000	100 101
		AD	Optic atrophy-1	165500	https://www.omim.org/clinicalSynopsis/165500	102 103 104 105 106
		AD	Optic atrophy plus syndrome	125250	https://www.omim.org/clinicalSynopsis/125250	107 108 109 110 111 112 113 114 115
			Glaucoma susceptibility	606657		116 117
GDAP1	606598	AD, AR	Charcot-Marie-Tooth disease, type 2K	607831	https://www.omim.org/clinicalSynopsis/607831	118 119 120 121 122
		AR	Charcot-Marie-Tooth disease, axonal, type 4A	607706 214400	https://www.omim.org/clinicalSynopsis/607706	123 124
		AR	Charcot-Marie-Tooth disease, intermediate A	608340	https://www.omim.org/clinicalSynopsis/608340	125 126 127

INF2	610982	AD	Charcot-Marie-Tooth disease E with segmental glomerulonephritis	614455	https://www.omim.org/clinicalSynopsis/614455	128
			Focal segmental glomerulosclerosis-5	613237		129
MYOIIA	160740	AD, AR	Congenital myopathy-6 with ophthalmoplegia	605637	https://www.omim.org/clinicalSynopsis/605637	130 131 132 133
DNM2	602378	AD	Centronuclear myopathy-1	160150	https://www.omim.org/clinicalSynopsis/160150	134
		AD	Charcot-Marie-Tooth disease, type 2M	606482	https://www.omim.org/clinicalSynopsis/606482	135 136
		AR	Lethal congenital contracture syndrome-5	615368	https://www.omim.org/clinicalSynopsis/615368	137
PI4KB	602758	AD	Autosomal dominant deafness-87	620281	https://www.omim.org/clinicalSynopsis/620281	138
ARF1	103180	AD	Periventricular nodular heterotopia-8	618185	https://www.omim.org/clinicalSynopsis/618185	139
ABHD16	142620	AR	Spastic paraplegia-86	619735	https://www.omim.org/clinicalSynopsis/619735	140 141 142
AFG3L2	604581	AD	Optic atrophy-12	618977	https://www.omim.org/clinicalSynopsis/618977	143 144 145 146
		AR	Spastic ataxia-5	614487	https://www.omim.org/clinicalSynopsis/614487	147 148
		AD	Spinocerebellar ataxia-28	610246	https://www.omim.org/clinicalSynopsis/610246	149 147
SLC25A46	610826	AR	Charcot-Marie-Tooth disease, type 6B	616505	https://www.omim.org/clinicalSynopsis/616505	19 150 151 152 153
		AR	Pontocerebellar hypoplasia, type 1E	619303	https://www.omim.org/clinicalSynopsis/619303	154 155
YME1L1	607472	AR	Optic atrophy-11*	617302	https://www.omim.org/clinicalSynopsis/617302	156
MSTO1	617619	AD, AR	Mitochondrial myopathy and ataxia	617675	https://www.omim.org/clinicalSynopsis/617675	50 157 158 159

Supplementary Table 1: Pathogenic mutations associated with fission and fusion factors.

A list of diseases associated with the principal identified pathogenic mutations in genes encoding regulators of mitochondrial morphology. AD: autosomal dominant; AR: autosomal recessive; OMIM: Online Mendelian Inheritance In Man®. * Relationship between the phenotype and gene is provisional.

Protein	Modification	Modifying enzyme	Effect on mitochondrial morphology	Biological context	Refs
DRP1	Phosphorylation of Ser637	PKA	Prevents mitochondrial Drp1 recruitment; decreases fission	Starvation	160 161 162
	Phosphorylation of Ser616 isoform 1, Ser590 isoform 2, Ser579 isoform 3 (Human); Ser585 (Rat)	CDK1-cyclin B, PKC δ , ERK1/2, CDK5, or MAPK1	Increases fission	Mitosis (CDK1-cyclin B), Oxidative stress (PKC δ), Tumor growth (ERK1/2, CDK5, MAPK1), Huntington's disease (MAPK1)	163 164 165 166 167 168 169
	Phosphorylation of Ser600 (Rat)	CaMKI α ROCK1	Enhances Drp1 recruitment; increases fission ¹⁷⁰	Synaptic activity/plasticity (CaMKI α), Hyperglycaemia (ROCK1)	171 172
	Phosphorylation of Ser693 (Human)	GSK3 β	Reduces Drp1 GTPase activity; inhibits fission	Oxidative stress	173
	Phosphorylation of Ser656 (rat, African green monkey)	PKA	Decreases fission	Stress and exercise	174 161
	Dephosphorylation of Ser637	Calcineurin	Increases fission	Apoptosis, Circadian clock	161 175
	SUMOylation (Lys532, Lys535, Lys558, Lys568, Lys594, Lys597, Lys606, Lys608)	MAPL, SENP2, SENP3, or SENP5	Increases fission	Apoptosis (MAPL), Neuronal cell death (SENP2), Ischaemic cell death (SENP3), Cell cycle (SENP5)	176 177 178 179 180 181
	<i>O</i> -GlcNAcylation (Thr585 and T586)	<i>O</i> -GlcNAc transferase (OGT)	Increases fission	Hyperglycaemia	182 183
	De- <i>O</i> -GlcNAcylation	<i>N</i> -acetylglucosaminidase (OGA)	Decreases fission	Hyperglycaemia	183
	Acetylation (Lys642)		Increases fission	Lipotoxicity	184
	S-Nitrosylation (Cys644)	Protein disulfide isomerase (PDI)	Increases fission	Neurodegeneration	185 170 186
	Ubiquitination	MITOL/MARCH5 or Parkin	Promotes proteasomal degradation; decreases fission	Mitochondrial quality control	187 188 189
	Ubiquitination	APC/C(Cdh1)	Promotes proteasomal degradation; decreases fission	Cell cycle	190
	S-palmitoylation	Zn ²⁺ -finger DHHC-domain-containing proteins (ZDHHC)	Enhances Drp1 recruitment	Maintenance of neurological function	191
MFF	Phosphorylation (Ser155 and Ser172, and Ser275)	AMPK or PKD	Increases fission	Starvation (AMPK), Mitosis (PKD)	192 193
MiD49	Ubiquitination	MARCH5/MITOL	Decreases fission	Stress-induced apoptosis	194

INF2	Phosphorylation (Ser1077)	AMPK	Increase fission	Endometrial cancer proliferation	195
MFN1	Phosphorylation (Thr562)	ERK	Decreases fusion	Apoptosis	196
	Phosphorylation (Ser86)	PKC isoform-β2	Decreases fusion	Ischaemia-reperfusion injury	197
	Deacetylation (Lys222, Lys491)	Histone deacetylase 6 (HDAC6)	Stabilises Mfn1; increases fusion	Glucose deprivation	198
	Ubiquitination	Parkin	Promotes proteasomal degradation; decreases fusion	Mitophagy	199
	Ubiquitination	MARCH5/MITOL	Promotes proteasomal degradation; decreases fusion	Mitochondrial quality control	200
MFN2	Phosphorylation (Ser27)	JNK	Promotes proteasomal degradation; decreases fusion	Apoptosis	201
	Phosphorylation (Ser442)	PKA	?	Vascular muscle cell proliferation independent of mitochondria morphology	202
	Phosphorylation (Thr111, Ser442, Tyr448)	PINK1	Promotes MFN2 and Parkin interaction; decreases fusion	Mitophagy	203
	Ubiquitination	Huwei1	Promote proteasomal degradation; decrease fusion	Apoptosis	201
	Ubiquitination	MARCH5/MITOL	Promotes proteasomal degradation; decreases fusion	Mitochondrial quality control	204
	Ubiquitination	Parkin	Promotes degradation of depolarized mitochondria	Mitophagy	203
OPA1	Cleavage	YME1L	Requires for fusion and cristae maintenance	Mitochondrial homeostasis	205 206
	Cleavage	OMA1	Decreases fusion	Apoptosis	207
	Proteolysis	PARL	Decreases cristae remodelling	Apoptosis	208
	Acetylation (Lys926 and Lys931)	?	Decreases fusion	Cell death	209
	De-acetylation (Lys926 and Lys931)	SIRT3	Increases OPA1 GTPase activity and fusion	Cell death	209
OMA1	Ubiquitination	?	Increase OPA1 expression and fusion	Heart failure	210

Supplementary Table 2: Post-translational modifications associated with fission and fusion factors.

The main post-translational modifications of the fission and fusion machineries, associated effects on mitochondrial morphology and biological contexts are listed.

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