Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Genetics & Development

Linking mitochondrial dynamics to mitochondrial protein quality control

Suraiya Haroon and Marc Vermulst

Over the last decade, countless discoveries have been made that have expanded our knowledge of mitochondrial biology, and more often than not, these discoveries provided fascinating new insights into the etiology of human disease. For example, advances in mitochondrial genetics exposed the role of mitochondrial mutations in cancer progression, and the discovery of mitophagy highlighted the role of mitochondrial quality control in Parkinson's disease. Additional discoveries underscored the importance of the mTor pathway in aging and disease, and more recently, the mitochondrial unfolded protein response was implicated in the regulation of mammalian lifespan. Some of the most fundamental discoveries though, were made in the context of mitochondrial fusion and fission. The balance between these two opposing forces shapes the mitochondrial population in our cells, and influences mitochondrial function at every level. Here, we highlight the basic biology that underlies mitochondrial fusion and fission, explain how these processes promote human health by solving a problem that is innate to multifarious organelles, and make a novel prediction: that fusion and fission are intimately linked to mitochondrial protein quality control.

Address
Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA 19104, USA

Corresponding author: Vermulst, Marc (vermulstm@chop.edu)

Current Opinion in Genetics & Development 2016, **38**:68–74

This review comes from a themed issue on **Molecular and genetic bases of disease**

Edited by **Jason Bielas** and **Carolyn Suzuki**

For a complete overview see the Issue and the Editorial

Available online 25th May 2016

http://dx.doi.org/10.1016/j.gde.2016.04.004

0959-437X/Published by Elsevier Ltd.

Cellular energy demands and the multiplicity of mitochondria

Our cells are addicted to energy. Whether it is protein synthesis, DNA replication, autophagy or signal transduction, almost every biological process is driven by the consumption of energy [1•]. To meet this demand, our cells contain hundreds, or even thousands of mitochondria that fuel our cells with ATP [2]. Since every compartment in our cells requires its own energy supply, mitochondria are usually distributed throughout the cell body, not unlike a power grid, to ensure that all demands are met [1•]. By rewiring this power grid [3] (or in other words, by changing the location of mitochondria), a cell can respond to changes in its environment or its own intrinsic needs; thus, the multiplicity of mitochondria, combined with their mobility, helps to solve the energy crisis of our cells.

All multifarious organelles suffer from a common problem

It is important to realize though, that this solution contains an inherent drawback. Most of us probably know that mitochondria contain approximately a thousand unique proteins [4••,5], and that the vast majority of these proteins are encoded in the nucleus [1•] and imported [6] into mitochondria after translation. Although these are rather mundane details, they are actually quite remarkable, because the logistics required to maintain mitochondrial proteomics must be mind-boggling. After all, how could a cell possibly ensure that each mitochondrion receives every one of these proteins? Certainly, no cell can scan hundreds of mitochondria simultaneously for the presence of a thousand proteins and adjust their concentration in real-time? Especially if these mitochondria are actively moving along the cytoskeleton and occupy the farthest corners of our cells. Moreover, these proteins do not only need to be present, they must be present in the right stoichiometry to function harmoniously. These considerations highlight a problem that is central to the biology of all multifarious organelles: the more organelles you create, the harder it is to control the quality of each individual unit. And this problem is especially relevant to mitochondria. After all, mitochondria do not only carry a large amount of proteins [4••,5], but they are also extremely abundant and widely dispersed throughout the cell [7]. Each of these factors makes it difficult to control protein content across the mitochondrial population. It is further important to note that the proteome of mitochondria is encoded by the nuclear, as well as the mitochondrial genome [1•], adding yet another layer of complexity to protein homogenization. Fortunately, our cells are able to solve this problem with the help of mitochondrial fusion and fission, two opposing forces that seem to have evolved specifically to promote mitochondrial homogeneity [8•,9].

The machinery of mitochondrial dynamics

As mitochondria travel along the cytoskeleton, they frequently collide in an end to end fashion. These collisions

are important events, because they provide mitochondria with an opportunity to fuse, and create a single contiguous organelle [8•,9] (Figure 1). Each fusion event requires two reactions: the first reaction fuses the outer membranes together, while the second reaction fuses the inner membranes together [8•,9]. These reactions are primarily catalyzed by dedicated GTP-ases that are embedded in the inner and outer mitochondrial membrane. In mammals, the mitofusins Mfn1 and Mfn2 regulate fusion of the outer mitochondrial membrane [10,11], while OPA1 regulates fusion of the inner mitochondrial membrane [12•,13•]. Genetic ablation or depletion of any of these molecules strongly inhibits mitochondrial fusion [14,15]. Mitochondrial fusion is opposed by mitochondrial fission, a process by which a single mitochondrion is split into two separate organelles [16]. In mammals, this process is primarily mediated by Drp1, a protein that constricts the mitochondrial membrane, and promotes mitochondrial scission [17•,18•,19•]. Mitochondrial fission is further enhanced by Fis1 [20,21], Mff [22,23], MiD49 and MiD51 [24–26], which contribute to fission in numerous ways, including the recruitment of Drp1 to the mitochondrial membrane. Together, the opposing forces of fusion and fission control the shape, size and number of mitochondria in our cells. If this balance favors fission, mitochondria are fragmented into short tubules, or small, spherical organelles [15]. If it favors fusion though, mitochondria appear elongated, and coalesce into an extensively interconnected network [15]. Mitochondrial dynamics affect more than mere morphology though. In fact, what is so unique about mitochondrial dynamics, is that it seems to affect almost every aspect of mitochondrial biology, including energy production [27•,28••,29••], apoptosis [30–32], mitophagy [33–37], stress resistance [38–40], mitochondrial movement, mtDNA stability [29••] and the tolerance of cells to mtDNA mutations [29••]. It is not surprising then, that genetic disruption of genes involved in fusion and fission has a pronounced effect on mammalian health. For example, the ablation of fusion genes results in embryonic death in mice [41], while less severe disruptions cause a variety of neuromuscular diseases in humans [8•]. For instance, mutations in OPA1 cause dominant optic atrophy (DOA) [12•,13•], a disease that is characterized by a progressive loss of vision due to the degeneration of retinal ganglion cells [42]. Ultimately, this degeneration causes atrophy of the optic nerve and results in premature blindness. Recent studies further indicate that DOA can be accompanied by various extra-ocular symptoms, including hearing loss, mitochondrial myopathy and peripheral neuropathy [42]. Interestingly, mutations in Mfn2 cause a disease with similar symptoms: Charcot Marie Tooth disease type 2A (CMT2A) [43••]. CMT2A is primarily characterized by peripheral neuropathy and the loss of sensation in distal limbs, which is a symptom that DOA patients can experience as well, although to a greatly lesser degree [42]. Patients that suffer from CMT2A may also display optic atrophy and mitochondrial myopathy [43••], two additional symptoms that are seen in patients with DOA as well, further confirming their common etiology.

Mitochondrial dynamics and content mixing

Initially, it was a little puzzling to find that mitochondrial fusion and fission affect so many aspects of mitochondrial biology, because the proteins that drive fusion and fission do not play a role in all of the pathways they affect. For example, deletion of Mfn1 and Mfn2 causes a significant decrease in mtDNA stability [29••]; however, neither Mfn1 nor Mfn2 plays a direct role in mtDNA maintenance. We think that the solution to this puzzle lies in content mixing, a basic consequence of mitochondrial dynamics that optimizes mitochondrial homogeneity [27•,29••]. When mitochondria fuse, they share their membranes with each other and create a common matrix and inter-membrane space [8•]. These compartments contain all the contents of the original fusion partners, including their lipids, proteins, DNA and RNA. By mixing these molecules together, mitochondria can ultimately divide them equally over their daughter organelles once fission occurs; thus, the net result of one cycle of fusion and fission, is that the original fusion partners are replaced by two daughter organelles, which contain the same amount of proteins as their parents, but these proteins are now distributed in a homogeneous manner. By repeating these cycles over and over, mitochondria can homogenize their content across the entire mitochondrial population. A cartoon of this process is depicted in

Figure 1

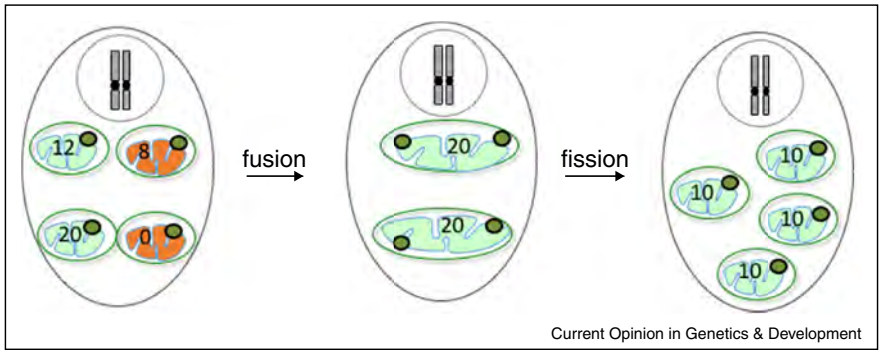
Mitochondrial fusion and fission control the size, shape and number of mitochondria housed within our cells. Although mitochondria are frequently depicted as static, kidney bean shaped organelles in textbooks, they are actually highly dynamic in nature. Most notably, they undergo continuous cycles of fusion and fission. When they collide in an end to end fashion, mitochondria can fuse their membranes together, to create a single contiguous organelle with a single matrix and inter membrane space. As a result, their contents (including their lipids, DNA, RNA and proteins) are mixed together, visualized here as a green and red mitochondrion giving rise to a single yellow organelle. This process is opposed by mitochondrial fission, during which a single mitochondrion is split into two separate organelles. Each of these mitochondria receives an identical share of protein, lipid, DNA and RNA molecules.

Figure 2. To demonstrate this process experimentally, we decided to infect fibroblasts with retroviruses that target CFP, EGFP and dsRed to the mitochondrial matrix. In WT cells, these fluorophores were distributed over the mitochondrial population in a relatively homogeneous fashion, so that each mitochondrion displayed a similar color. In fusion deficient cells though, we noticed that each mitochondrion displayed a unique color, indicating that the fluorophores were less homogeneously distributed. For example, some mitochondria displayed a blue color, indicating an abundance of CFP molecules, and the relative absence of GFP and dsRed molecules. Other mitochondria displayed a yellow color, indicating an abundance of GFP and dsRed molecules, and the absence of CFP molecules. This heterogeneity ultimately resulted in the 'Christmas lights-like' patterns seen in fusion deficient cells. We made similar observations when we monitored mitochondrial protein heterogeneity with native proteins [29••]. These observations highlight how important mitochondrial dynamics are to homogenize protein content across the mitochondrial population, and explain how fusion and fission can improve the efficiency of every process that occurs inside mitochondria, without directly regulating them. Since content mixing seems to be the primary function of mitochondrial fusion and fission, we suspect that reduced content mixing is one of the primary sources of the pathology experienced by patients DOA and CMT2A. In addition, it is possible that reduced content mixing contributes to various other diseases that are associated with abnormal mitochondrial dynamics, including Parkinson's disease, Alzheimer's disease and Huntington's disease [44,45]. Finally, it is important to note that even WT cells experience some variation in protein content (Figure 3a). Although this variation is relatively minor, it is easy to imagine how its cumulative effect over the lifetime of an organism could have detrimental consequences. For example, small variations in the presence of DNA repair proteins could allow mtDNA mutations to accumulate over time and thereby contribute to age-related pathology. Mitochondria may even experience greater protein heterogeneity as we age, which would accelerate this process. Although these considerations explain why mitochondrial fusion and fission ultimately affect every aspect of mitochondrial biology, we think there is a special connection between mitochondrial dynamics and the mitochondrial quality control. For example, it is already known that mitochondrial fission plays an important role in mitophagy, a broad term that generally refers to the selective degradation of dysfunctional mitochondria [46••]. During mitophagy, PINK1 and Parkin label dysfunctional mitochondria for degradation [47], and mitochondrial fission contributes to this process by separating damaged segments of mitochondria from healthy ones [48,49]. Enhanced fission (and reduced fusion), further allows mitochondrial dynamics to reduce the size of dysfunctional mitochondria, so that they can be engulfed by the autophagosome and the lysosome [48,49]. In addition though, we suspect that mitochondrial fusion and fission are also connected to a second quality control mechanism, the mitochondrial unfolded protein response (UPR^{mt}). This fascinating quality control mechanism has recently hugged the limelight because of its remarkable effect on organismal lifespan [50••,51,52]. In the paragraphs below, we would like to explain why we think this connection exists, how it affects cellular health, and how additional research in this area may be able to identify new avenues of treatment for patients that suffer from diseases that are caused by abnormalities in mitochondrial dynamics.

The mitochondrial unfolded protein response

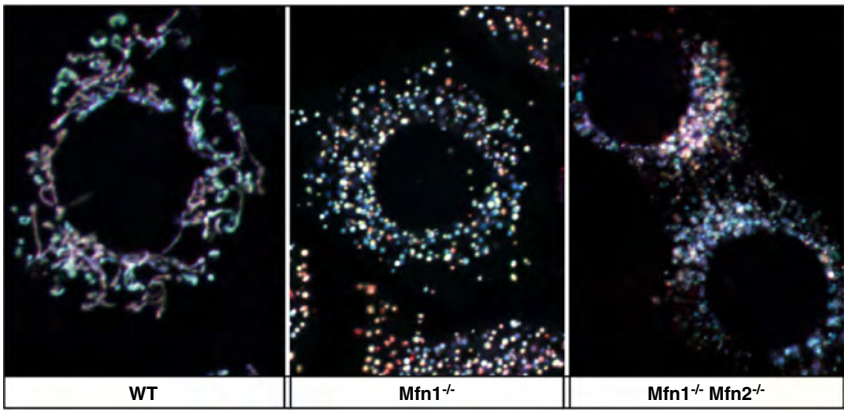
Every compartment in our cells, including mitochondria, struggle to maintain protein homeostasis [53]. Fortunately,

Figure 2



Protein homogenization by mitochondrial fusion and fission. In this diagram, a single cell is depicted that contains 4 mitochondria. Going from left to right, these mitochondria undergo one cycle of mitochondrial fusion and fission. During this cycle their protein contents are mixed together, and divided up over the daughter organelles, leading to increased protein homogeneity. Initially, each mitochondrion contained different amounts of a single hypothetical protein (either 0, 8, 12 or 20 copies). As a result, the mitochondria with the lowest copy number are dysfunctional (orange mitochondria) However, after one round of fusion and fission, this protein is homogenized over the entire population and this problem is solved. Gray oval: nucleus, green and orange ovals: functional and dysfunctional mitochondria, green circles with green filling: mtDNA.

Figure 3



Increased protein heterogeneity in fusion deficient cells. Each cell line was transfected with 3 retroviruses, each of which carries a single fluorescent protein that is targeted to the mitochondrial compartment (CFP, EGFP, dsRed). If these proteins are homogeneously distributed over the mitochondrial population, each mitochondrion would carry equal amounts of blue, green and red fluorescent proteins and display a similar color. On the other hand, if these proteins are not homogeneously distributed, each mitochondrion would display a different color, due to imbalanced protein content.

mitochondria normally produce misfolded proteins at a relatively low level, but in times of stress [54,55] (for example, when mtDNA is depleted [56], the electron transport chain is perturbed [57], or oxidative stress intensifies [58]), misfolded proteins can accumulate and threaten mitochondrial health [54]. To prevent this problem, mitochondria rely on the mitochondrial unfolded protein response (UPR^{mt}) to stimulate the transcription of genes that alleviate proteotoxic stress [55,59]. In mammals, this response is stimulated by two events: the accumulation of misfolded proteins in the matrix, and the accumulation of misfolded proteins in the inter-membrane space [60]. Each of these events elicits a unique response. When misfolded proteins accumulate in the matrix, they are cut into tiny peptides by the protease ClpP [60]. These peptides activate two kinases, JNK and PKR, which ultimately upregulate the integrated stress response and activate the transcription factor CHOP-10 [61], which regulates the expression of stress-resolving genes such as mitochondrial proteases and chaperones [54,60,62]. The mitochondrial sirtuin SIRT3 seems to play a similar role [63]. If misfolded proteins accumulate in the inter-membrane space though, mitochondria respond by activating ER-α [64], a protein that increases the expression of the HTRA2/Omi [65] protease and the transcription factor NRF1 [64]. HTRA2/Omi, along with the mitochondrial biogenesis genes regulated by NRF1 resolves the proteotoxic stress experienced by inter-membrane space.

Connecting mitochondrial dynamics to the unfolded protein response

The UPR^{mt} pathway has received an unusual amount of attention in recent years, because it has been suggested that the mitochondrial unfolded protein response is directly linked to the regulation of mammalian lifespan [50••,51,52,55,66,67,68••]. The most recent evidence for this exciting connection was made when a combination of bio-informatics, genetics and molecular biology revealed that mutations in a gene called *Mrps-5* can extend the lifespan of mice and worms [50••]. *Mrps-5* encodes mitochondrial ribosomal protein S5, a relatively unassuming protein that contributes to the translation of polypeptides encoded by the mitochondrial genome. It was subsequently discovered that manipulation of *Mrps-5* can reduce the efficiency of mitochondrial translation, which changes the ratio of proteins that are derived from the nuclear and the mitochondrial genome [50••]. Although this 'mito-nuclear imbalance' sounds innocuous, it actually deprives many proteins of their usual binding partners, which compromises their stability and activates the mitochondrial unfolded protein response. This chronic activation of the unfolded protein response (which was dubbed mitohormesis), increased the lifespan of mice with *Mrps-5* mutations by >25% [50••,51,52]. Further experiments even suggested that the lifespan extending effect of *sir2.1*, the homolog of SIRT1 in *C. elegans*, were partially mediated by the mitochondrial unfolded protein response [66].

What we can learn in the future and how it can benefit patients

When you place these observations in the context of mitochondrial dynamics, you will find several startling connections. First, the experiments on *Mrps-5* demonstrate that an imbalance in protein content is a powerful source of proteotoxic stress [50••,51,52]. Excitingly, a similar imbalance is present in fusion deficient cells

[29••] (Figure 3), which suggests that they are likely to suffer from proteotoxic stress as well. This possibility is further strengthened by the observation that loss of mitochondrial fusion decreases mtDNA stability and reduces mtDNA copy number [29••], which is a potent source of proteotoxicity as well. Thus, it is highly likely that mitochondria of fusion deficient cells contain a large amount of destabilized proteins. These destabilized proteins could be a powerful source of mitochondrial dysfunction, and contribute to the pathology of patients with DOA or CMT2A. In addition, it is likely that these destabilized proteins would activate UPRmt, and that this activation would help to suppress disease caused by abnormalities in mitochondrial dynamics. It will be extremely important to test this possibility, because if this hypothesis is correct, it may be possible to activate this pathway further as an auxiliary tool to improve the lives of patients. Moreover, there are various other diseases that are associated with abnormalities in mitochondrial dynamics, including Parkinson's disease, Alzheimer's disease and Huntington's disease. It is tempting to speculate that a similar rationale applies to these diseases. In the context of therapy, it is also important to point out that misfolded proteins inside the mitochondrial compartment are a powerful activator of mitophagy [69], which underscores how intimately mitochondrial dynamics and mitochondrial quality control are related. Understanding these relationships in greater detail, and ultimately exploiting them, holds great promise for the treatment of diseases that are caused by mitochondrial dysfunction. The most exciting aspect of the relationship between mitochondrial dynamics and the UPR^{mt} though, is that it can be tested in a fairly quick and straightforward manner. For example, in one experiment, the UPR^{mt} of fusion deficient cells could be disrupted, while in another experiment one could disrupt mitochondrial fusion and fission in UPR^{mt} deficient cells. We hope that this review will inspire researchers to perform these experiments and contribute to future efforts to understand the biological basis of mitochondrial disease.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. • Wallace DC: **A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine**. *Annu Rev Genet* 2005, **39**:359-407.

Dr. Wallace's reviews on mitochondrial genetics are a great starting point for anyone interested in the relationship mitochondrial biology and human disease.

2. McBride HM, Neuspiel M, Wasiak S: **Mitochondria: more than just a powerhouse**. *Curr Biol* 2006, **16**:R551-R560.

3. Frederick RL, Shaw JM: **Moving mitochondria: establishing distribution of an essential organelle**. *Traffic* 2007, **8**:1668-1675.

4. •• Mootha VK *et al.*: **Integrated analysis of protein composition, tissue diversity, and gene regulation in mouse mitochondria**. *Cell* 2003, **115**:629-640.

The first of numerous authorative papers by Dr. Mootha on the mitochondrial proteome.

5. Rhee HW *et al.*: **Proteomic mapping of mitochondria in living cells via spatially restricted enzymatic tagging**. *Science* 2013, **339**:1328-1331.

6. Schmidt O, Pfanner N, Meisinger C: **Mitochondrial protein import: from proteomics to functional mechanisms**. *Nat Rev Mol Cell Biol* 2010, **11**:655-667.

7. Frazier AE, Kiu C, Stojanovski D, Hoogenraad NJ, Ryan MT: **Mitochondrial morphology and distribution in mammalian cells**. *Biol Chem* 2006, **387**:1551-1558.

8. • Chan DC: **Fusion and fission: interlinked processes critical for mitochondrial health**. *Annu Rev Genet* 2012, **46**:265-287.

Fom protein structure to organismal health, Dr. Chan has made remarkable discoveries regarding mitochondrial fusion and fission, and his reviews are required reading for anyone interested in this field.

9. Mishra P, Chan DC: **Mitochondrial dynamics and inheritance during cell division, development and disease**. *Nat Rev Mol Cell Biol* 2014, **15**:634-646.

10. Santel A, Fuller MT: **Control of mitochondrial morphology by a human mitofusin**. *J Cell Sci* 2001, **114**:867-874.

11. Rojo M, Legros F, Chateau D, Lombes A: **Membrane topology and mitochondrial targeting of mitofusins, ubiquitous mammalian homologs of the transmembrane GTPase Fzo**. *J Cell Sci* 2002, **115**:1663-1674.

12. • Alexander C *et al.*: **OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28**. *Nat Genet* 2000, **26**:211-215.

This paper links inner mitochodnrial membrane fusion and human disease.

13. • Delettre C *et al.*: **Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy**. *Nat Genet* 2000, **26**:207-210.

This paper links inner mitochodnrial membrane fusion and human disease.

14. Cipolat S, Martins de Brito O, Dal Zilio B, Scorrano L: **OPA1 requires mitofusin 1 to promote mitochondrial fusion**. *Proc Natl Acad Sci U S A* 2004, **101**:15927-15932.

15. Detmer SA, Chan DC: **Functions and dysfunctions of mitochondrial dynamics**. *Nat Rev Mol Cell Biol* 2007, **8**:870-879.

16. Richter V, Singh AP, Kvansakul M, Ryan MT, Osellame LD: **Splitting up the powerhouse: structural insights into the mechanism of mitochondrial fission**. *Cell Mol Life Sci* 2015, **72**:3695-3707.

17. • Bleazard W *et al.*: **The dynamin-related GTPase Dnm1 regulates mitochondrial fission in yeast**. *Nat Cell Biol* 1999, **1**:298-304.

This paper identified a key component of the mitochondrial fission machinery in yeast, providing the field with a weatlh of research opportunities.

18. • Sesaki H, Jensen RE: **Division versus fusion: Dnm1p and Fzo1p antagonistically regulate mitochondrial shape**. *J Cell Biol* 1999, **147**:699-706.

This paper describes how mitochondrial fusion and fission regulate mitochodnrial mirphology, a staple of mitochondrial dynamics.

19. • Labrousse AM, Zappaterra MD, Rube DA, van der Bliek AM: ***C. elegans* dynamin-related protein DRP-1 controls severing of the mitochondrial outer membrane**. *Mol Cell* 1999, **4**:815-826.

One of several papers by the van der Bliek lab to provide key insight into the nature of mitochondrial dynamics in worms.

20. Yoon Y, Krueger EW, Oswald BJ, McNiven MA: **The mitochondrial protein hFis1 regulates mitochondrial fission in mammalian cells through an interaction with the dynamin-like protein DLP1**. *Mol Cell Biol* 2003, **23**:5409-5420.

21. Stojanovski D, Koutsopoulos OS, Okamoto K, Ryan MT: **Levels of human Fis1 at the mitochondrial outer membrane regulate mitochondrial morphology**. *J Cell Sci* 2004, **117**:1201-1210.

22. Gandre-Babbe S, van der Bliek AM: **The novel tail-anchored membrane protein Mff controls mitochondrial and peroxisomal fission in mammalian cells**. *Mol Biol Cell* 2008, **19**:2402-2412.

23. Otera H *et al.*: **Mff is an essential factor for mitochondrial recruitment of Drp1 during mitochondrial fission in mammalian cells**. *J Cell Biol* 2010, **191**:1141-1158.

24. Palmer CS *et al.*: **MiD49 and MiD51, new components of the mitochondrial fission machinery**. *EMBO Rep* 2011, **12**:565-573.

25. Palmer CS *et al.*: **Adaptor proteins MiD49 and MiD51 can act independently of Mff and Fis1 in Drp1 recruitment and are specific for mitochondrial fission**. *J Biol Chem* 2013, **288**:27584-27593.

26. Zhao J *et al.*: **Human MIEF1 recruits Drp1 to mitochondrial outer membranes and promotes mitochondrial fusion rather than fission**. *EMBO J* 2011, **30**:2762-2778.

27. • Chen H, Chomyn A, Chan DC: **Disruption of fusion results in mitochondrial heterogeneity and dysfunction**. *J Biol Chem* 2005, **280**:26185-26192.
First analysis of the basic biological consequences of reduced fusion in mammalian cells.

28. •• Chen H, McCaffery JM, Chan DC: **Mitochondrial fusion protects against neurodegeneration in the cerebellum**. *Cell* 2007, **130**:548-562.
Breakthrough paper describing, for the first time, how mitochondrial fusion affects mammalian health.

29. •• Chen H *et al.*: **Mitochondrial fusion is required for mtDNA stability in skeletal muscle and tolerance of mtDNA mutations**. *Cell* 2010, **141**:280-289.
In this paper, the authors expose the intimate relationship between mitochondrial dynamics and mitochondrial DNA instability.

30. Tait SW, Green DR: **Mitochondria and cell death: outer membrane permeabilization and beyond**. *Nat Rev Mol Cell Biol* 2010, **11**:621-632.

31. Lee YJ, Jeong SY, Karbowski M, Smith CL, Youle RJ: **Roles of the mammalian mitochondrial fission and fusion mediators Fis1, Drp1, and Opa1 in apoptosis**. *Mol Biol Cell* 2004, **15**:5001-5011.

32. Frank S *et al.*: **The role of dynamin-related protein 1, a mediator of mitochondrial fission, in apoptosis**. *Dev Cell* 2001, **1**:515-525.

33. Gegg ME *et al.*: **Mitofusin 1 and mitofusin 2 are ubiquitinated in a PINK1/parkin-dependent manner upon induction of mitophagy**. *Hum Mol Genet* 2010, **19**:4861-4870.

34. Chan NC *et al.*: **Broad activation of the ubiquitin-proteasome system by Parkin is critical for mitophagy**. *Hum Mol Genet* 2011, **20**:1726-1737.

35. Tanaka A *et al.*: **Proteasome and p97 mediate mitophagy and degradation of mitofusins induced by Parkin**. *J Cell Biol* 2010, **191**:1367-1380.

36. Poole AC *et al.*: **The PINK1/Parkin pathway regulates mitochondrial morphology**. *Proc Natl Acad Sci U S A* 2008, **105**:1638-1643.

37. Deng H, Dodson MW, Huang H, Guo M: **The Parkinson's disease genes pink1 and parkin promote mitochondrial fission and/or inhibit fusion in Drosophila**. *Proc Natl Acad Sci U S A* 2008, **105**:14503-14508.

38. Youle RJ, van der Bliek AM: **Mitochondrial fission, fusion, and stress**. *Science* 2012, **337**:1062-1065.

39. Tondera D *et al.*: **SLP-2 is required for stress-induced mitochondrial hyperfusion**. *EMBO J* 2009, **28**:1589-1600.

40. Gomes LC, Di Benedetto G, Scorrano L: **During autophagy mitochondria elongate, are spared from degradation and sustain cell viability**. *Nat Cell Biol* 2011, **13**:589-598.

41. Chen H *et al.*: **Mitofusins Mfn1 and Mfn2 coordinately regulate mitochondrial fusion and are essential for embryonic development**. *J Cell Biol* 2003, **160**:189-200.

42. Yu-Wai-Man P *et al.*: **Multi-system neurological disease is common in patients with OPA1 mutations**. *Brain* 2010, **133**:771-786.

43. •• Zuchner S *et al.*: **Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A**. *Nat Genet* 2004, **36**:449-451.
This paper links fusion of the outer mitochondrial membrane to human disease.

44. Itoh K, Nakamura K, Iijima M, Sesaki H: **Mitochondrial dynamics in neurodegeneration**. *Trends Cell Biol* 2013, **23**:64-71.

45. Chen H, Chan DC: **Mitochondrial dynamics – fusion, fission, movement, and mitophagy – in neurodegenerative diseases**. *Hum Mol Genet* 2009, **18**:R169-R176.

46. •• Narendra D, Tanaka A, Suen DF, Youle RJ: **Parkin is recruited selectively to impaired mitochondria and promotes their autophagy**. *J Cell Biol* 2008, **183**:795-803.
Breakthrough paper on selective mitophagy.

47. Pickrell AM, Youle RJ: **The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease**. *Neuron* 2015, **85**:257-273.

48. Buhlman L *et al.*: **Functional interplay between Parkin and Drp1 in mitochondrial fission and clearance**. *Biochim Biophys Acta* 2014, **1843**:2012-2026.

49. Twig G *et al.*: **Fission and selective fusion govern mitochondrial segregation and elimination by autophagy**. *EMBO J* 2008, **27**:433-446.

50. •• Houtkooper RH *et al.*: **Mitonuclear protein imbalance as a conserved longevity mechanism**. *Nature* 2013, **497**:451-457.
Potentially important paper that describes the relationship between mitonuclear protein imbalances, UPR^{mt} and longevity.

51. Karpac J, Jasper H: **Aging: seeking mitonuclear balance**. *Cell* 2013, **154**:271-273.

52. Jovaisaite V, Auwerx J: **The mitochondrial unfolded protein response-synchronizing genomes**. *Curr Opin Cell Biol* 2015, **33**:74-81.

53. Kim YE, Hipp MS, Bracher A, Hayer-Hartl M, Hartl FU: **Molecular chaperone functions in protein folding and proteostasis**. *Annu Rev Biochem* 2013, **82**:323-355.

54. Zhao Q *et al.*: **A mitochondrial specific stress response in mammalian cells**. *EMBO J* 2002, **21**:4411-4419.

55. Schulz AM, Haynes CM: **UPR(mt)-mediated cytoprotection and organismal aging**. *Biochim Biophys Acta* 2015, **1847**:1448-1456.

56. Martinus RD *et al.*: **Selective induction of mitochondrial chaperones in response to loss of the mitochondrial genome**. *Eur J Biochem* 1996, **240**:98-103.

57. Pulliam DA *et al.*: **Complex IV-deficient Surf1(−/−) mice initiate mitochondrial stress responses**. *Biochem J* 2014, **462**:359-371.

58. Baker BM, Haynes CM: **Mitochondrial protein quality control during biogenesis and aging**. *Trends Biochem Sci* 2011, **36**:254-261.

59. Yoneda T *et al.*: **Compartment-specific perturbation of protein handling activates genes encoding mitochondrial chaperones**. *J Cell Sci* 2004, **117**:4055-4066.

60. Arnould T, Michel S, Renard P: **Mitochondria retrograde signaling and the UPR mt: where are we in mammals?** *Int J Mol Sci* 2015, **16**:18224-18251.

61. Horibe T, Hoogenraad NJ: **The chop gene contains an element for the positive regulation of the mitochondrial unfolded protein response**. *PLoS ONE* 2007, **2**:e835.

62. Aldridge JE, Horibe T, Hoogenraad NJ: **Discovery of genes activated by the mitochondrial unfolded protein response (mtUPR) and cognate promoter elements**. *PLoS ONE* 2007, **2**:e874.

63. Papa L, Germain D: **SirT3 regulates the mitochondrial unfolded protein response**. *Mol Cell Biol* 2014, **34**:699-710.

64. Papa L, Germain D: **Estrogen receptor mediates a distinct mitochondrial unfolded protein response**. *J Cell Sci* 2011, **124**:1396-1402.

65. Radke S *et al.*: **Mitochondrial protein quality control by the proteasome involves ubiquitination and the protease Omi**. *J Biol Chem* 2008, **283**:12681-12685.

66. Mouchiroud L *et al.*: **The NAD(+)/sirtuin pathway modulates longevity through activation of mitochondrial UPR and FOXO signaling**. *Cell* 2013, **154**:430-441.

67. Jovaisaite V, Mouchiroud L, Auwerx J: **The mitochondrial unfolded protein response, a conserved stress response pathway with implications in health and disease**. *J Exp Biol* 2014, **217**:137-143.

68. •• Durieux J, Wolff S, Dillin A: **The cell-non-autonomous nature of electron transport chain-mediated longevity**. *Cell* 2011, **144**:79-91.
Visionary paper on the relationship between mitochondrial function and longevity.

69. Pellegrino MW, Haynes CM: **Mitophagy and the mitochondrial unfolded protein response in neurodegeneration and bacterial infection**. *BMC Biol* 2015, **13**:22.