Small but complete - the detail and future of mitochondrial quality control

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Abstract

Since mitochondria is the major power house in eukaryotic cells and unhealthy mitochondria would cause several severe diseases including neurodegeneration, cardiovascular disorders and some cancers, mitochondrial health maintenance can be considered as one of the most important mechanism we need to study. In this review we discussed current progress we know so far, and we focused on the detail of proteolytic aspect of the study which we call it mitochondrial protein quality control (MQC) and its relationship with ageing and mitochondria-related diseases in order to emphasize the future direction for the study and studies related to mitochondrial health.

Introduction

Mitochondria are dynamic organelles and play many different important roles in all eukaryotic cells including ATP production, metabolic and cofactor-generating pathways integration, regulation of ion homeostasis such as Ca2+ and apoptosis regulation.(Balaban et al., 2005; Wallace, 2005; Qian et al., 2006) Dysfunction of mitochondria will leads to several severe diseases including cardiovascular disease (CVD) such as cardiomyopathy and heart failure, some typical cancers, type II diabetes, and neurological and neurogenerative diseases including Parkinson's disease and Alzheimer's disease.(Balaban et al., 2005; Zhao, 2002) Since these diseases will more likely to happen with older people, mitochondrial health has also been studied with ageing. (Tatsuta and Langer, 2008) With the statements above, it is critical to maintain mitochondrial health and as far as the field developed, several interdependent mechanisms interact with each other – from molecular level to organellar level. That being said, these mechanisms are concluded as mitochondrial quality control. (MQC)

Basically, there are three main challenges to mitochondrial functions and therefore MQC monitoring is necessary. (**Fig.1**) The first challenge is continuous generation of reactive oxygen species (ROS) by the electron transport chain (ETC) complexes of OXPHOS. During the oxidative phosphorylation, some electrons would leak from the ETC and progressively react with oxygen. With ROS formation, it will further promote other ROS formations together with reactive nitrogen species (RNS). Many reports showed that there are about 0.3%-2% of the mitochondrial oxygen are converted into ROS and these harmful ROS together with RNS are highly harmful to nucleic acids, proteins and lipids which are fundamental building blocks for all cells.(Wallace et al., 2014; Zhang and Darley-Usmar, 2011; Hao et al., 2009) While even with free radical-scavenging mechanism which can eliminates ROS and RNS, these harmful species can not be fully removed. In contrast, ROS/RNS now are recognized as signaling molecules important for intracellular

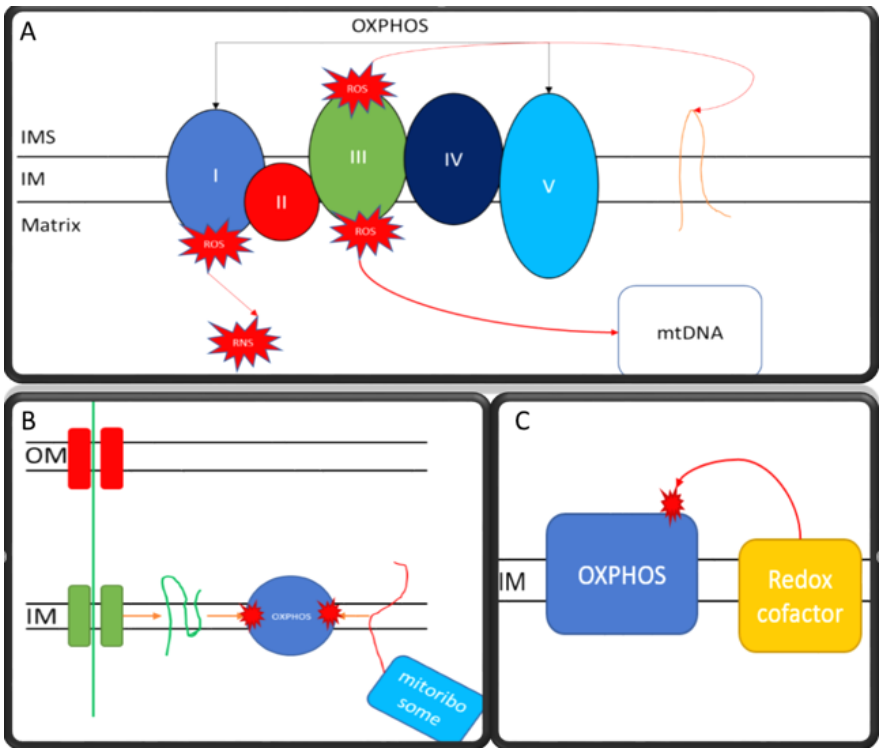

Figure 1: **Figure 1.** Three typical challenges that may cause mitochondrial dysfunction. These three conditions are the main reason why MQC is considered as critical mechanism for cell. **A.** Reactive ROS which made by OXPHOS is harmful for every kind of building blocks of cells. **B.** Double biogenesis pathways for subunits of ETC complex may cause unfolded and/or orphaned subunits which trend to aggregate and/or misfold. **C.** Improperly assembled redox cofactors can act as pro-oxidants which will promote ROX production.

communication and stress responses. (Harper et al., 2018; Endert, 2005) Therefore, MQC is downstream of radical-scavenging mechanism – it only deals with excessive ROS.

The second challenge is caused by dual genetic origin of several OXPHOS complexes. Biogenesis of these complexes needs precisely coordinated expression, sorting and folding from both mtDNA- and nuclear-coded polypeptides, and their further assemble within mitochondrial inner membrane (IM) with correct order. If any steps above failed, unfolded, or orphaned complex units are trend to misfolding and aggregate. (Yates, 2003; Wilkinson, 2011) The third challenge is caused by redox cofactors embedded in mitochondrial inner membrane. Disordered redox cofactors can act as prooxidants which disrupt the mitochondrial homeostasis and promote deleterious chemical environment. (Wallace, 2005; Qian et al., 2006)

In this review, we will mainly focus on the up-to-date knowledge of MQC mechanisms by giving details of each level of MQC and their functions toward the mitochondrial health maintenance. Furthermore, we more discuss the future direction and ageing focus of mitochondrial research field.

Overview of Mitochondrial Quality Control

Because of the complexity of mitochondrion, the quality control mechanism contains survey, repair or eliminate damaged mitochondria within several different layers from mitochondrial inner membrane (IM) including mitochondrial proteases and chaperones (**Figure 2A**) to cytosolic proteolytic systems such as

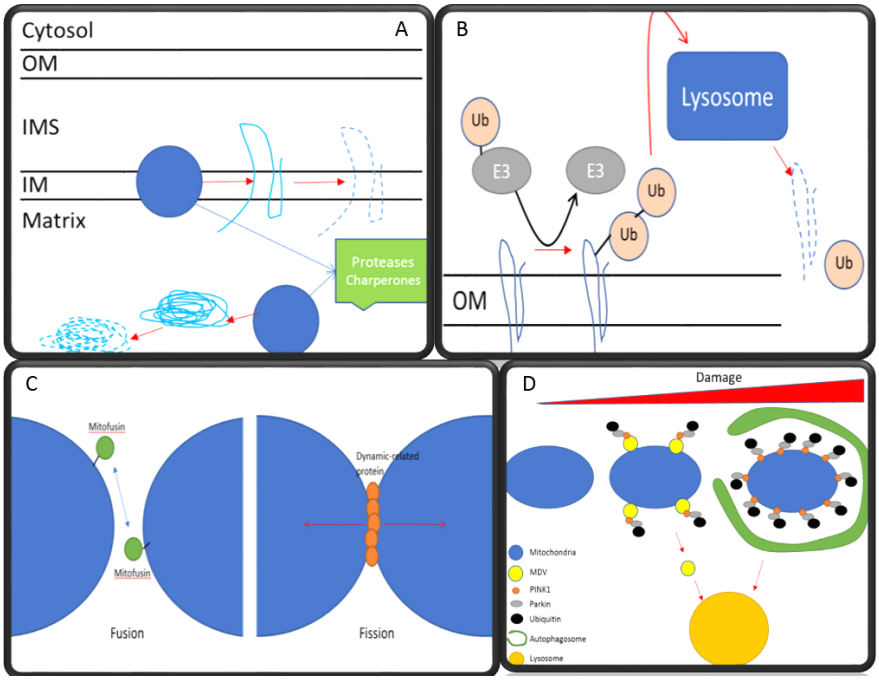

Figure 2: **Figure 2.** Models of MQC systems. MQC system has several models depend on different levels. **A.** Mitochondrial proteases and chaperones play the most important role to control mitochondrial quality represent one level. **B.** Removal of outside proteins localized on the OM is meditated by USP system which can is be second level. **C.** At organellar level, mitochondrial fission and fusion is the major way to maintain the mitochondrial network's homeostasis. **D.**Newly discovered mechanism which is called MDV allows selective fragment of mitochondria rather than go mitophagy which will degrade the whole mitochondria during the moderate damage.

ubiquitin-proteasome system (UPS) which interacts with mitochondrial outer membrane (OM). (**Figure 2B**) Other than proteolytic systems, MQC also includes mito-mito interaction like fusion and fission,(**Figure 2C**) and mitochondria-derived vesicles (**Figure 2D**) which will be discussed at the end of this session briefly.

Protein MQC can be classified as two parts: 1. ATP-dependent chaperones and 2. Mitochondrial proteases. For chaperones, mtHsp70 and Hsp60 families are in charged for sorting, folding, and disaggregation of proteins in the mitochondrial matrix, while Hsp70-types and Hsp90-type chaperones are for cytosol. The mitochondrial proteases part of protein MQC can also be divided into two different classes: I. ATP-dependent proteases, which known as AAA+ (ATPase associated with diverse cellular activities) and II. ATP-independent proteases. For ATP-dependent proteases, there are several different proteases discovered within each compartment of mitochondria and classified where they were found: ClpX and ClpP have been found in the matrix and they functionalize as degrader of oxidatively damaged or aggregated polypeptides. Matrix AAA protease has active site at matrix side of inner membrane where it performs its quality control functions. Lon has been found in mitochondrial inner membrane which has the similar function as Clpx and ClpP. (Baker et al., 2012) With the name they have, their proteolytic activities are associate with ATP hydrolysis, and this gives them a chaperone-like functions which including recongnization of misfolded or unassembled proteins and refold it, together with extract these polypeptides from phospholipid bilayers. ATP-independent proteases are less ordered than AAA+, and they can be classified as three types: i. processing peptideases which are involved in sequential removal and/or degradation of mitochondrial targeting sequences and then proper biogenesis, sorting, and stabilization of matrix- and IM-targeted proteins; ii. soluble peptidases that contribute to MQC in the intermembrane space; iii. IM-bound proteases which has

the function that control IM proteome quality and regulation of mitochondrial dynamics. (Kenniston et al., 2003; Osiewacz, 2010)

Many publications indicated that UPS also plays a critical role of protein MQC. UPS has been found that it removes several mitochondrial-targeted proteins. And UPS can access the OM subproteome and mediate retrotranslocation and degradation of OM proteins. This process is also called mitochondria-associated degradation. (MAD) (201, 2014; Casari et al., 1998)

Except from molecular level which discussed above, several MQC mechanisms are on the organellar level. Fusion and fission are coupled activity which can control mitochondrial dynamics and biogenesis, and even redistribution of mtDNA and proteome of the whole mitochondrial network in the cell. (Bohovych et al., 2014) Fusion allows relieve single mitochondrial damage through the whole network which is called hyperfusion. During the certain stresses like oxidative stress or starvation, mitochondria may tend to fuse together in order to increase content mixing, ATP production, and protecting mitochondria from autophagic removal. (Bota and Davies, 2002) Fission comes after when hyperfusion is not sufficient to protect damaged mitochondria. It removes damaged mitochondria through mitochondrial fragmentation.(ZHANG, 2008) Mitochondrial fission segregates the whole mitochondrial network and detect the damaged mitochondria then eliminate them through UPS which is called mitophagy – a mitochondria-specific type of autophagy. (Prinz, 2012; Ieva et al., 2013; MUNN, 1974)

Recently, a new MQC mechanism has been described which is called mitochondrial derived vesicles (MDV). (Zhang et al., 2014) Studies have shown that mitochondria can produce vesicles which carry selected oxidized cargo drive the cargo to lysosomes. This phenomenon has been reported to facilitate MQC and MDV appears to function at both normal and oxidative stress conditions which is independent to mitochondrial stresses and dynamics. Even MDV has not been fully studied, this gives us a new aspect to study MQC strategy in order to manage mitochondrial damage. (Zhang et al., 2014)

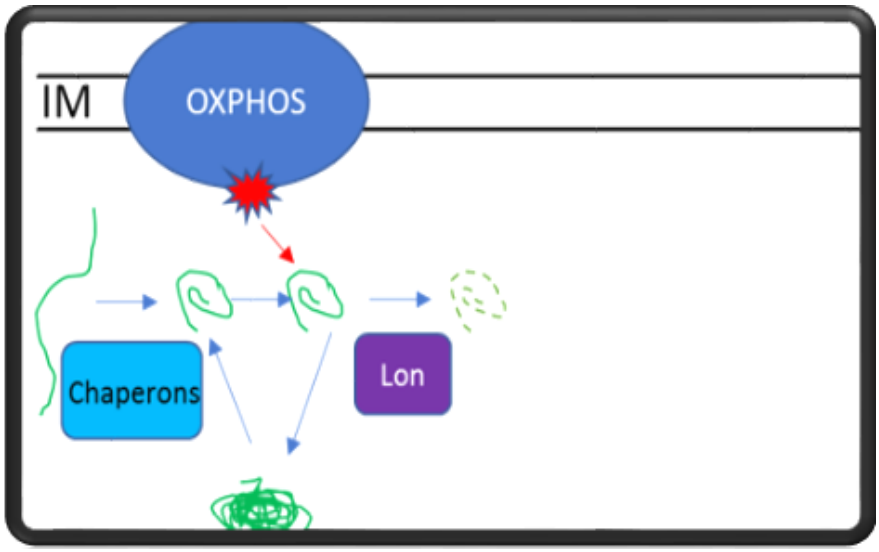

Figure 3: **Figure 3.** MQC in matrix. Multiple proteases and chaperones regulate the matrix. The whole process including maturation of accumulation of precursor proteins, aggregated protein detection, misfolded proteins degradation and finally oligopeptides degradation.

Details of protein mitochondrial quality control in each layer

Matrix (**Figure 3**)

When misfolded, damaged or aggregated protein was formed, chaperones will try to fix it back to normal first. If the damage cannot be fixed, two conserved AAA+ serine proteases, Lon and ClpXP will degrade the target protein. While the character of ClpXP needs to be identified, the Lon protease targets heat-damaged or oxidatively damaged proteins. But how does Lon recognize misfolded protein remain to be identified. Studies show that Lon cooperates with ClpB-type AAA+ chaperone Hsp78 and mtHsp70 to accelerate disaggregation and degradation of damaged proteins. (Baker et al., 2012; Bateman et al., 2002)

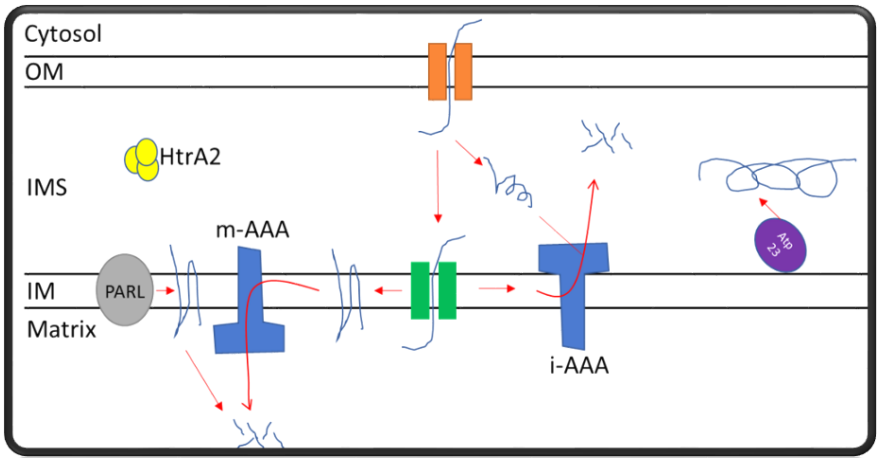

Figure 4: **Figure 4.** MQC in IM and IMS. Complexity of mitochondrial IM involves efficient system to maintain protein homeostasis. These include two AAA proteases which are matrix-facing AAA protease (m-AAA) and intermembrane space-facing AAA (i-AAA). These two proteases cooperate together to monitor the whole spaces interaction from Matrix to intermembrane space. Other IM protease complexes like OMA1, with overlapping function as m-AAA, is also proposed to play an important role in mitochondrial homeostasis during stresses. The mechanisms for HtrA2 and Atp23 are not clear.

Inner membrane (**Figure 4**)

Since the ETC complexes embed in the inner membrane, it is crucial to main IM homeostasis. There are two major mechanisms to assure mitochondrial biogenesis and maintenance. The first one is a class of chaperones and chaperone-like factors to help the assistance and regulation. The second one is a set of mechanisms by using proteolysis enzymes. For chaperones and chaperones-like factors, m-AAA and i-AAA play the major role to control the mitochondrial homeostasis which m-AAA surveys matrix and i-AAA surveys intermembrane space. (Bohovych et al., 2014; Kirkwood and Kowald, 1998) Studies showed that loss of AAA molecules in yeast is lethal which proved that AAA is important for quality control. For proteolysis enzymes, PARL is a well-studied module intrinsic to the IM. Recent studies showed that PARL in mammalian cells is constituent for removal of the phosphate and tensin homolog-induced putative kinase 1 (PINK1). (Vafai and Mootha, 2012; Zeng et al., 2007) PINK1 is a critical regulator of mitophagy and ETC turnover. PINK1 is translated in cytosol and imported into the mitochondria through TOM complex. Under normal situations, PINK1 is sorted to the IM after it gets degraded by PARL. But this pathway is blocked when mitochondria are depolarized and PINK1 is stabilized and accumulates on the OM. Then PINK1 recruits and activates E3 ubiquitin ligase Parkin/PARK2 which will trigger mitochondrial segregation and mitophagy of damaged mitochondria. Previously a recent study showed that removal of PINK1-Parkin pathway only inhibits formation of MDV under mitochondrial stress condition. (Quirós et al., 2012)

Intermembrane Space (**Figure 4**)

All the proteases are less studied. In this area proteases are ATP-independent enzymes, and the reason

behind this may be due to the separation between intermembrane space and ATP production area. HTRA2 is a trimeric protease with critical roles in the degradation of oxidized proteins. (Lu, 2017; Jou, 2011) Mouse cells with HTRA2 deficient accumulate mutations in mtDNA which suggest that HTRA2 is also important for keeping mtDNA integrity.(Bota et al., 2002) ATP23 is another protease while poor-studied in mammals. Its yeast orthologue participates in mitochondrial quality control by the degradation of lipid transfer proteins that are highly conserved during revolution.

Outer membrane (**Figure 2B**)

Although previously USP has been studied as prevention of misfolded or damaged proteins to the mitochondrion, recent study showed that mitochondrial localized polypeptides can be ubiquitylated and subsequently removed by the UPS which is named as MAD. Parkin is one of the USP recruitment factors and more factors need to be identified. And, MAD was found that it can remove several IM- and matrix-localized proteins while this study also needs to dig further. (Beckman and Ames, 2000; Viscomi et al., 2016)

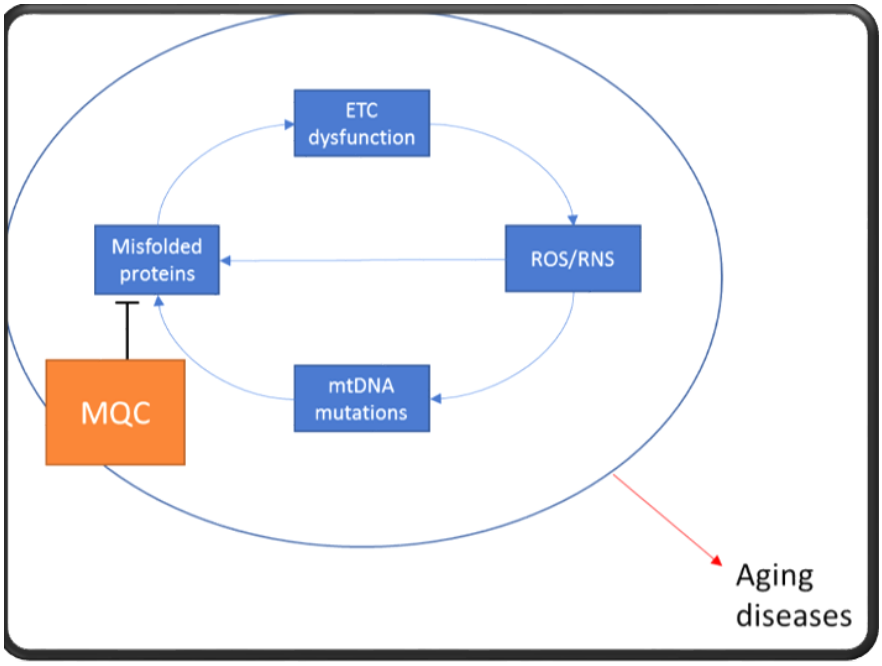

Figure 5: **Figure 5.** Relationship between mitochondrial dysfunction and aging. Once MQC cannot performs efficiently, damaging including ROS, misfolded proteins, mtDNA mutations can be accumulated be these can finally result aging-related diseases.

Mitochondrial quality control in Disease and Aging

Over time, accumulation of free radical damage, failing protein homeostasis, and mitochondrial and organellar quality control capacity can cause significantly to the onset of progressive age-associated pathologies, cellular aging instability of mtDNA and mitochondrial proteome. (**Figure 5**) Studies reported that reduced activity/abundance of Lon and ClpP proteases increased aging of rat hepatocytes. (Burton, 2001; Bonn et al., 2011) In contrast, overexpress of Lon significantly extended lifespan of the organism for Podospora anserina fungal model. (Liby, 2006) Studies in mice also indicate that the AFG3L2 of subunit of m-AAA is important for the survival of Purkinje cells and anterograde mitochondrial transport in murine cortical neurons which indicate the critical role of AAA function in late-onset neurodegeneration. (Bota et al., 2002;

Nagley and Zhang, 1998) Depletion of OMA1 in the mouse model reduces energy consumption and leads to obesity, hepatic steatosis, and altered thermogenesis/cold stress resistance. (Deas et al., 2010) These are due to inability to initiate mitochondrial network fragmentation in response to metabolic and oxidative stresses. The intermembrane space protease HtrA2/Omi has the potential in protecting neurons from degeneration and has been associated with Parkinson's disease. (22) Recently, mutations in PARL, PINK1, Parkin have also been reported as Parkinson's disease related. (Karbowski and Neutzner, 2011)

Conclusion

The importance of multilevel MQC mechanisms in maintaining mitochondrial health has becoming more crucial with the field emerging. It is worth noting that mitochondrial damage not only from aging but also can be found in young population. Aggressive chemical therapies for treating cancer and virus may enhance formation of dysfunction mitochondria during the treatments and this question should be considered before the therapy decision. And also, by maintaining healthy mitochondria could be a new perspective to get longer lifespan is the new field needs to be investigated.

But still, we have a lot of pieces of puzzle need to be found in order to solve the total MQC mechanism map. Such as How MQC components recognize the stress signals is still not fully understand. By looking into these questions, more of mitochondria-related diseases and cellular health problems would be solved.

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