Cristae Dynamics

Subjects: Cell Biology

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Recent studies using fluorescence super-resolution (SR) microscopy techniques showed unexpected fast movement of cristae and CJs, collectively termed as cristae dynamics. Cristae undergo continuous cycles of membrane remodelling often assisted by the dynamics of CJs in a MICOS-dependent manner, which led to the proposal of the ‘Cristae Fission and Fusion’ (CriFF) model. The field of cristae dynamics is still in infancy, future experiments could provide better insights about the consequences of the reduced cristae or CJ dynamics in the knockouts (KOs) of the MICOS subunits and their relevance in many pathologies associated with the MICOS complex.

Keywords: mitochondria ; MICOS ; cristae ; cristae dynamics ; cristae biogenesis

1. Introduction

Mitochondria are important organelles that perform vital functions including energy conversion, cellular metabolism, apoptosis, calcium buffering and iron–sulfur cluster biogenesis. The mitochondrial ultrastructure is very versatile and thought to be optimally designed to perform many known mitochondrial functions. The hallmark feature of double membrane-enclosed mitochondria is the invaginations of the inner membrane (IM) into the matrix termed cristae. The rest of the IM that runs parallel to the outer membrane (OM) is termed the inner boundary membrane (IBM), which is compositionally and functionally distinct from the cristae membrane (CM) [1][2]. The CM and IBM are connected by small pore-like openings termed crista junctions (CJs) [3]. CJs restrict the entry of metabolites into the lumen of cristae due to their small diameter of 12–40 nm and hence potentially regulate many mitochondrial functions [4].

Cristae can vary in their shape, size and packing density [5] and undergo constant remodeling to adapt to varying energy demands and physiological cues [4][6][7][8][9][10]. Cristae are important identities containing the respiratory chain complexes (RCS) where oxidative phosphorylation (OXPHOS) occurs [1][2][11]. Altered cristae structures are found in many human diseases such as Parkinson’s disease, diabetes and cancer [12]. Although the ultrastructural features of cristae and CJs were described long ago [13], the fundamental question of how they are formed is not yet fully understood. The formation of cristae must be envisaged as a complex process involving a coordinated interaction of proteins and lipids helping to establish the curved nature of the CM and CJs. The latter display an approximately 90° bend in the membrane with both the leaflets exhibiting significant positive or negative curvature. Additionally, the rim/tip of the crista that seals the crista lumen from the matrix shows strong membrane curvature [14][15]. A team of various scaffolding protein complexes and phospholipid (PL) moieties could be envisioned to sculpt these membrane structures. Multiple models to explain cristae formation have been proposed [5] but have not been duly tested due to the technical challenges associated with addressing this fundamental question. The dynamin-like GTPase OPA1, the F_1F_O ATP synthase complex and the MICOS complex are the three main known mediators of cristae formation thus far (**Figure 1**) [16].

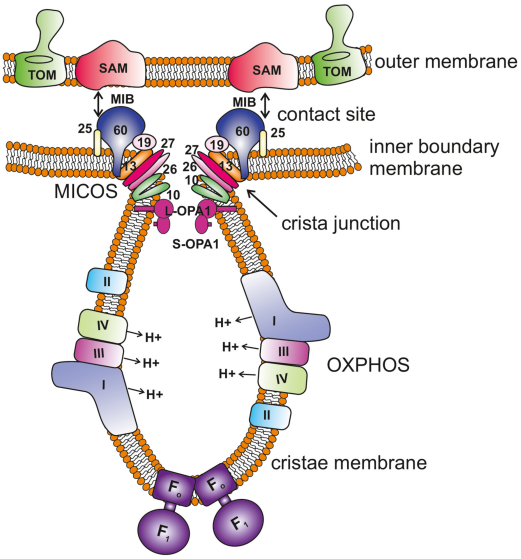

Figure 1. Key regulators of mitochondrial cristae organization. The scheme shows the organization of mitochondrial membranes where the cristae are formed by invagination of the inner membrane towards the matrix. The MICOS (mitochondrial contact site and cristae organizing system) complex resides at the crista junctions (CJs) and is composed of seven subunits, MIC10, MIC13, MIC19, MIC25, MIC26, MIC27 and MIC60 (only the numbers are depicted in the figure for the ease of legibility). MICOS is required to stabilize the CJs and form the contacts between the inner and outer membranes via interaction with the SAM (sorting and assembly machinery) complex. This interaction between MICOS and the SAM complex forms the larger complex called the mitochondrial intermembrane space bridging complex (MIB) that encompasses the intermembrane space. OPA1 is also enriched at the CJs, and interaction between membrane-bound long (L-) forms and soluble short (S-) forms is required to maintain the width of the CJs. F_1F_O ATP synthase plays an important role in the formation of positive membrane curvature at the tip/rim of cristae. The OXPHOS (oxidative phosphorylation) machinery resides in the cristae membrane.

2. Understanding Cristae Architecture Using Recent Technological Advancements

In recent years, many technical advancements that include live-cell imaging using super-resolution (SR) nanoscopy, focused ion beam-scanning electron microscopy (FIB-SEM), electron tomography (ET), single-particle tracking (SPT) and fluorescence recovery after photobleaching (FRAP) have been used to address the fundamental questions about cristae biogenesis and dynamics [17][18][19][20][21]. These techniques have allowed unexpected insights into the dynamic nature of cristae and have changed our view of cristae being static entities that only display different shapes under varying circumstances. An important change in perception occurred with the discovery that cristae can undergo dynamic membrane remodeling at a timescale of seconds in a MICOS-dependent manner [21]. The MICOS subunit MIC13 was identified as a central regulator in these processes in mammalian cells.

2.1. Application of Fluorescence Super-Resolution Techniques to IM Reveal Novel Insights

SR techniques provide crucial insights into the organization and distribution of the MICOS complex in the IM, showing a typical rail-like arrangement of MIC60 and other MICOS subunits across the mitochondrial length, mimicking the arrangement of CJs in electron micrographs [17][22][23][24]. Specifically, dual staining of MIC60 and cristae showed that, as expected for a CJ protein, most of MIC60 is found associated with cristae except a few instances where MIC60 spots were found in the IBM [18]. The two-sided distribution of MIC60 on either side of the mitochondrial length and its colocalization with OM protein remained unaltered in the *MIC10* KO, showing the important role of MIC60 in marking the sites for nascent CJs and contact sites [17][24][25]. The arrangement of MIC60 within an individual CJ was identified using the powerful MINFLUX nanoscopy technique that could attain a resolution of around 5 nm by employing the combinational advantages of photo-activated localization microscopy (PALM), stochastic optical reconstruction microscopy (STORM) and stimulated emission depletion (STED) microscopy [26]. Multiple MIC60 molecules were arranged in a ring-like pattern with a diameter of around 40–50 nm that could surround a CJ [26]. MIC19 was in close proximity of MIC60 compared to MIC10.

2.2. MICOS Complex Regulates Apparent Cristae Fusion and Fission Cycles

Recent studies using SR techniques showed unexcepted dynamics of cristae [17][19][21][27][28][29]. Both cristae and CJs constantly changed their position within mitochondria, confirming that they are highly dynamic within seconds [17]. Tracking movements of CJs using live-cell STED nanoscopy showed that they repeatedly come together and then move

apart in a balanced and reversible manner. Interestingly, two CJs coming together bring with them the adjoining cristae so that the cristae appear as the letter ‘Y’, as visualized using a time-lapse movie of mitochondria expressing MIC13-SNAP, which dually marked cristae and CJs (**Figure 2**). Deletion of MIC13, impairing, e.g., MICOS assembly, leads to a drastic reduction in merging and splitting events of cristae and CJs, identifying MICOS as the first molecular player that is required for the dynamics of cristae and CJs (Figure 2). Evidence showing exchange of content between cristae during merging events led to the proposal of Cristae Fission and Fusion (‘CriFF’) model [17].

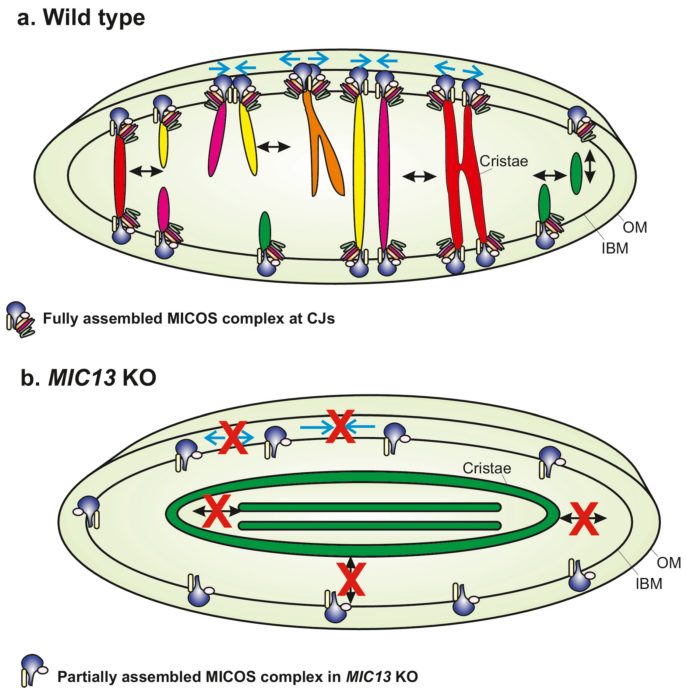

Figure 2. The MICOS complex regulates apparent cristae fusion and fission cycles. (**a**) Scheme depicts the various kinds of crista and CJ dynamics that are found in a mammalian cell. CJs formed by the MICOS complex move towards and away from each other in order to undergo merging and splitting events, respectively, as shown by cyan arrows. Similarly, cristae show a dynamic movement that involves continuous fusion and fission cycles in a balanced and reversible manner. In various instances, merging CJs can bring with them the adjoining cristae and facilitate their fusion along their length, resulting in the formation of a cristae network that resembles the ‘X’ or ‘Y’ letter. Cristae fusion is immediately followed by fission or vice versa. Cristae can also detach from the inner boundary membrane (IBM) to form cristae vesicles (shown as green cristae). These cristae vesicles can re-fuse to the IBM. OM represents outer membrane. (**b**) In *MIC13* KO, cristae are arranged as concentric rings or internal stacks that are not connected to the IBM. The movement of CJs and cristae is drastically reduced in *MIC13* KO cells.

2.3. Possible Implications of Cristae Dynamics

As the field of cristae dynamics is still in infancy, future experiments could provide better insights about the consequences of the reduced cristae or CJ dynamics in the KOs of the MICOS subunits and their relevance in many pathologies associated with the MICOS complex. Cristae dynamics may serve vital functions in mitochondria at different levels. Cristae housing OXPHOS complexes might, for example, employ cristae dynamics to dilute the local accumulation of dysfunctional OXPHOS complexes by mixing with optimally functioning complexes or subunits representing an efficient intramembrane complementation system. In addition, cristae dynamics may help to dynamically regulate the accessible surface of the IM and, conversely, the ability to trap protons efficiently. The transient formation of cristae vesicles could control the volume of the intermembrane space and the intracristal space, containing various metabolites, and thereby regulate their exchange with the cytosol. Protons as well as pools of ATP or other metabolites could be trapped efficiently in this way. Conversely, by fusion of cristae to the IBM, a larger ‘exchange-capable’ IM surface is generated. Overall, this could help to make oxidative phosphorylation more efficient and, importantly, presumably more tunable within a short timescale. An overview of the various possible implications of cristae dynamics has been discussed in more detail before [21].

3. Conclusions

The understanding of how cristae are formed and remodeled has progressed rapidly after the discovery and characterization of the first MICOS subunit about a decade ago. Several new findings have revealed that cristae are highly dynamic entities and that a central role regulating this can be attributed to the MICOS complex. These studies have

opened up many new avenues to explore exciting questions pertaining to cristae remodeling during various physiological conditions. Cristae are highly dynamic and undergo apparent fusion and fission cycles at the timescale of seconds. The question remains as to how these fast cristae dynamics mediated by the MICOS complex influence cristae formation and biogenesis and vice versa. The precise function of cristae dynamics and the mechanisms of how this is brought about by the MICOS complex are also exciting to explore further. The MICOS complex has been increasingly associated with many pathological conditions and human diseases. The changes in cristae dynamics and biogenesis could influence the pathobiology of these diseases.

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