Molecules and Cells

Journal Club

Migrating Cells Dispose of Damaged Mitochondria into the Surrounding Environment

Mitochondria quality control coupled with cell migration in mammalian *in vivo* model

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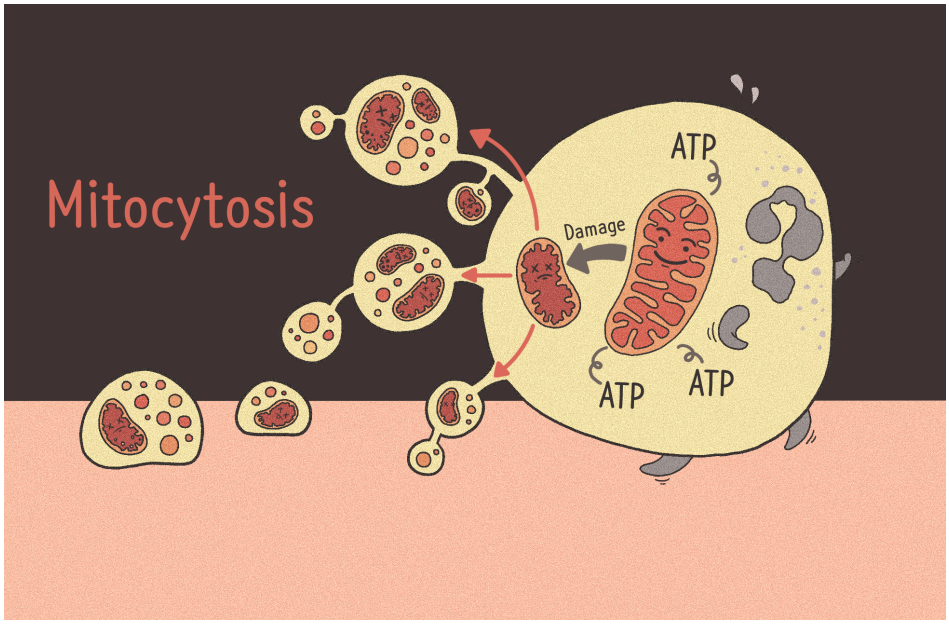

Discovery of mitocytosis: cell migration results in mild mitochondrial damage. To sustain mitochondrial function during migration, cells pack and dispose of damaged mitochondria in vesicle structures called migrasomes.

Mitochondria are at the center of cellular metabolism and signaling cascades (Song et al., 2021). Mitochondrial quality is monitored and maintained through various mechanisms. At the molecular level, mitochondrial retrograde signaling mediates mitochondrial stress response in the nucleus, where the response genes are transcribed. Mitochondrial proteins

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are tightly regulated by cytosolic proteasomes and mitoproteases. At the organelle level, mitochondria undergo fission and fusion to adapt to stress. For example, mitochondrial fission is promoted by nutrient overload, and by mitochondrial uncouplers. Mitochondrial fusion increases under limited nutrient conditions to increase energy generation efficiency (Meyer et al., 2017). Damaged mitochondria are targets of lysosomal degradation called mitophagy (Song et al., 2021).

Critical roles of mitochondria in cell migration, and mechanisms of mitochondrial regulation during cell migration have been revealed (Denisenko et al., 2019). For example, increases in mitochondrial fission, reactive oxygen species (ROS) production, and mitochondrial unfolded protein response signaling are associated with more strongly metastatic phenotypes in cancer cells.

A novel regulation mechanism by which migrating cells eliminate damaged mitochondria was revealed and defined as "mitocytosis" by Jiao et al. (2021). Through mitocytosis, cells dispose of damaged mitochondria into the surrounding environment.

In 2015, the same research group defined the "migrasome" as a vesicular membrane structure left behind by the retraction fiber of the migrating cell (Ma et al., 2015). The migrasome contains structural and membrane proteins, including tetraspanins (Tspans), which are used as migrasome markers. After years of research, the authors found that the migrasome mediates the expulsion of mitochondria from cells and defined it as "mitocytosis." Extensive optical and biochemical analyses have revealed that mitocytosis is tightly coupled with migration capacity and occurs in various types of mammalian cells, including cancer cell lines, immortalized normal cells, and immune cells. Furthermore, cells employ mitocytosis only under basal and mild stress conditions, such as low concentrations of carbonyl cyanide 3-chlorophenylhydrazone. Severe mitochondria-damaging conditions halt cell migration and induce mitophagy to eliminate damaged mitochondria.

Under mild mitochondrial stress, mitochondria are pulled to the peripheral edge of cells and enter the migrasome. This process is mediated by cellular transporters and the cytoskeleton. The authors suggested that kinesin family member 5B (KIF5B) pulls mitochondria to the plasma membrane, and myosin 19 (Myo19) mediates mitochondrial attachment to cortical actin. Here, dynamin-related protein 1 (Drp1)-mediated fission of mitochondrial tubules allows the tip to enter the migrasome. The authors revealed that affinity to dynein is reduced in damaged mitochondria, which are then pulled to the bottom rear periphery where migrasomes are generated.

By employing Tspan9 knock-out (KO) mice—in which migrasome generation is reduced—the authors revealed *in vivo* evidence of mitocytosis and its protective roles. Bone marrow-derived macrophages (BMDMs) from monocytes require mobility and mitocytosis to maintain mitochondrial quality. Tspan9 KO BMDMs, however, exhibit impaired mitocytosis and reduced mitochondrial function. The authors also observed migrasomes filled with damaged mitochondria directly in peripheral tissue; these migrasomes are generated by neutrophils. Tspan9 KO neutrophils showed reduced membrane potential and viability.

In summary, the authors showed the function of mitocytosis both *in vitro* and *in vivo*. The authors suggest that questions on mitocytosis still remain regarding its implication in immune response against pathogens, its roles in other types of migrating cells *in vivo*, and the detailed molecular mechanisms of selective elimination of damaged mitochondria.

This study showed the huge potential of migrasome research. Mitocytosis and migrasomes in immune cells would have further functions in addition to the mitochondrial quality control presented in this study. Migrasomes might contain further content, such as exhausted metabolites and signaling molecules. Migrasomes might then be transferred to or detected by the surrounding cells, as suggested by the authors. The migrasome levels detected by the surrounding tissue and other cells may then provide these cells with hints regarding the concentration, activity, or the rate of migration of the immune cells in the tissue. This possible intercellular communication between immune cells and the microenvironment via the migrasome might be an interesting research area.

This study also showed that immune cells do not handle "small problems," such as basal mitochondrial damage, while they are hurrying to their destination. Other cells must eliminate the migrasomes filled with the damaged mitochondria from the microenvironment. It would be an example of an intercellular metabolic interplay to support highly active cells suffering metabolic burden associated with and subsequently eliminated by cell migration.

As the authors suggested, detailed mechanisms of mitocytosis in immune cells might have critical implications in the study of the immune response. Furthermore, when immune cells are activated, they consume a large amount of energy to eliminate pathogens (Jung et al., 2019). Immune cells may modify mitocytosis and other functions of the migrasome to support their activity and metabolism.

In addition, it is not only immune cells that migrate inside an organism (Trepat et al., 2012). Researchers have already shown the function of migrasomes in the developing embryos (Jiang et al., 2019). Further roles of the migrasome in regulating embryo and tissue development are to be analyzed. Regulation of metabolic and ROS stress in metastatic cells may depend heavily on mitocytosis and migrasomes. Furthermore, the roles of mitocytosis and migrasomes in blood cancer cells with migration ability may be a potential target for therapy development. Wound healing also requires cell migration, and mitocytosis, therefore, has critical implications. Thus, research on mitocytosis and migrasomes has great potential for understanding human physiology and pathology.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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