

## Mini Review

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# Shaping Up Mitochondrion in Motion

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### ABSTRACT

We previously reported that hair follicle dermal papilla cells (HFDPCs) show two types of mitochondria, which are filamentous (untangled) and rounded (tangled) mitochondria. Platelet-derived growth factor-AA (PDGF-AA) shifts the population balance toward the filamentous type that produces more adenosine triphosphate (ATP) than the other. In addition, the cells show filamentous mitochondria during the process of cellular migration. Furthermore, here we demonstrated that an inner membrane protein, optic atrophy 1 (OPA1), is involved in the filamentous-rounded transition of the organelle. We suggest that OPA1 confers longitudinal rigidity on the filamentous mitochondria. Other cells such as breast cancer cells utilize small fragmented mitochondria, instead of a filamentous form, in the migration process. Regarding the apparent inconsistency with those other reports on the morphological change upon the onset of cellular migration, we discuss communal feature of the regulation of mitochondrial morphology in different cellular systems: all previous reports showed that the organelle become slender or smaller in the energy-demanding activity.

**KEYWORDS:** Mitochondria; Morphology; Lymphocytes; Dermal papilla; Migration; OPA1.

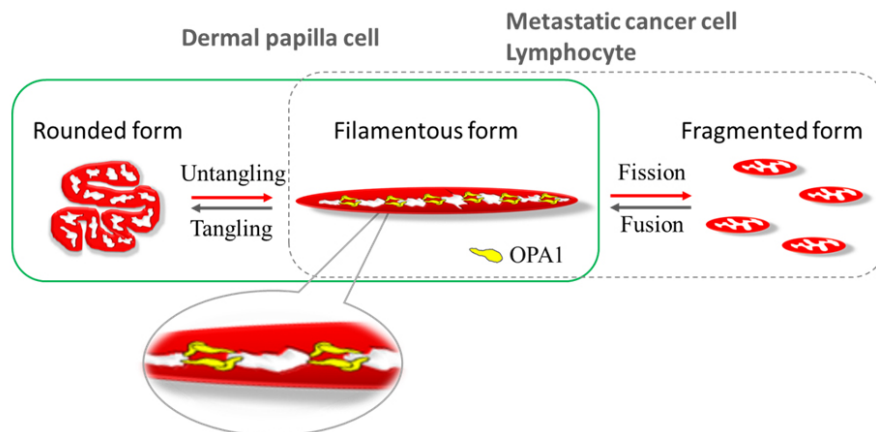
**ABBREVIATIONS:** ATP: Adenosine Triphosphate; HFDPC: Hair Follicle Dermal Papilla Cell; MMP: Mitochondrial Membrane Potential; OPA1: Optic Atrophy 1; PDGF-AA: Platelet-Derived Growth Factor-AA; RNA: Ribonucleic Acid; ROS: Reactive Oxygen Species; MTOC: Microtubule-organizing center.

### SUMMARY

The morphological balance of mitochondria is physiologically essential, which is ingeniously maintained by the fission/fusion regulations. The morphological balance can be abruptly changed upon cellular needs and/or environmental stimuli.<sup>1-5</sup> Mitochondrial functions, such as ATP synthesis, reactive oxygen species (ROS) production, calcium regulation, heme-synthesis and apoptotic induction, are closely coupled with the morphology of the organelle. Undoubtedly, a further understanding of the multi-faced organelle will contribute to the applications in the health and therapeutic worlds.<sup>6-11</sup>

We have demonstrated that HFDPCs show mainly two different mitochondrial morphologies, i.e., filamentous and rounded forms.<sup>12</sup> PDGF-AA shifts the balance of the population toward the filamentous form. The filamentous mitochondria produce more chemical energy than the rounded mitochondria while the levels of mitochondrial membrane potential (MMP) and ROS production are kept unchanged. Importantly, the fibroblast-like cells make use of the elongated mitochondria in the process of energy-demanding migration (Figure 1, green box). On the contrary, it was previously reported that other cells, such as metastatic cancer cells and lymphocytes, utilize fragmented mitochondria in the migration process, at the leading edge and trailing edge, respectively.<sup>13</sup> Therefore, it seems that the regulation of mitochondrial morphology depends on the types of cells.

In this article, we describe a communal feature of the morphological regulation of mitochondria in the process of cellular migration. Firstly, the rounded mitochondria we discov-



**Figure 1:** Morphological regulation of mitochondria in cellular migration. Dermal papilla cells utilize tangling-untangling transition (green box). OPA1 plays a role in maintaining the rigidity of filamentous mitochondria by linking the neighboring inner membranes together. Without the inner fusion protein, mitochondrion become less stiff and thereby tangled. In contrast, metastatic cancer cells and lymphocytes use the fission-fusion regulation (dotted box). In all cases, mitochondria become less obstructive in response to the onset of migration process (red arrows).

ered in the primary hair follicle cells are totally different from typical fragmented mitochondria. Indeed, live cell imaging demonstrated that the rounded mitochondrion is formed by the process of tangling or curling-up of a filamentous mitochondrion, therefore, the round form is considerably big and fat. The tangled mitochondrion is untangled to become a filamentous mitochondrion (Supplementary video S1). In contrast to the rounded mitochondria, the apoptotic HFDPCs show typical fragmented mitochondria along with the remarkable reduction of MMP and the elevated level of reactive oxygen species. Therefore, the rounded mitochondria and fragmented mitochondria are to be discriminated both in size and configuration (Supplementary Figure S1, Figure 1). In this sense, rounded mitochondria that were previously reported are to be re-scrutinized whether they are the tangled type or not.

It is noteworthy that mitochondria become slenderer or smaller in the process of cellular migration in the different cellular types (Figure 1, red arrows). In the metastatic cancer cells, it was demonstrated that the regulation by dynamin-related protein-1 (Drp 1) and mitofusin-1 (Mfn 1) triggers the fragmentation of mitochondria and that the small organelles readily relocate into extended actin-rich area, i.e. lamellipodia.<sup>14</sup> In lymphocytes, the fragmented mitochondria are relocated at tubulin-rich microtubule-organizing center (MTOC).<sup>15</sup> On the other hand, HFDPCs spread the filamentous mitochondria over the large body with a small portion of fragmented mitochondria at the tip of filamentous mitochondria near the edge of the cells (Supplementary Figure S2). In addition, filamentous mitochondria dominate the dermal papilla cells when autophagy is induced. These results regarding the energy-demanding activities make sense since the filamentous mitochondria produce a higher level of ATP compared to the tangled mitochondria as described above. It seems that the tangling-untangling regulation is more beneficial to dermal papilla cells than fusion-fission regulation. This is possibly because HFDPC maintains sufficient ATP supply and avoids the excessive production of reactive oxygen species from fragmented mitochondria (it is generally known that the fragmented mitochondria produce less ATP and more ROS).

In contrast, it would be essential for metastatic cancer cells to provide the narrow leading edge of the cells with the organelle that produce energy as quick as possible.

Finally, as for the tangling-untangle transition, silencing OPA1 gene in HFDPCs suppressed the formation of filamentous mitochondria, which suggests that the inner membrane protein confers longitudinal rigidity on mitochondria (Figure 1, enlarged view). Consistently, the hair follicle cells up-regulated OPA1 antisense ribonucleic acid (RNA1) and simultaneously down-regulated the gene expressions of OPA1 upon spheroid formation, which leads the cell to the quiescent stage along with the elimination of filamentous mitochondria (unpublished data). In other cells, it is well known that OPA1 plays a role in the mitochondrial fusion process,<sup>16</sup> in which the protein would give the longitudinal stiffness to elongated filaments (Figure 1, dotted box). The novel role of OPA1, along with the orchestrated mechanisms of those regulatory proteins, is to be further investigated.

Understanding the detailed mechanism and maintaining a sound balance in the properties of mitochondrial morphology function will contribute to human health. Therefore, locomotion would be promising as they are on a slimming diet.

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#### CONFLICTS OF INTEREST

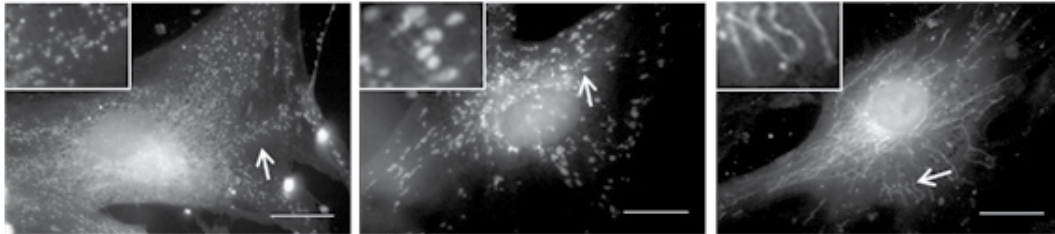
The authors declare that they have no conflicts of interest.

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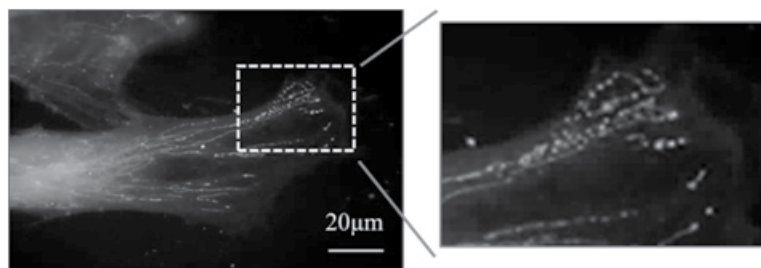
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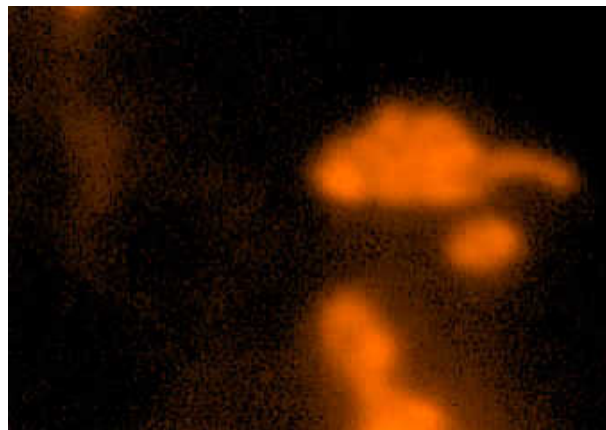
## Supplementary Data



**Supplementary Figure S1:** Apoptotic dermal papilla cells show fragmented mitochondria. When apoptosis was induced with the 1  $\mu$ M staurosporine treatment for 3 hours the cells showed small fragmented mitochondria (left), which are different from big rounded mitochondria (middle). Filamentous mitochondria are also shown (right). Scale bar is 20  $\mu$ m. Adapted from the previous report.<sup>12</sup>



**Supplementary Figure S2:** Migrating dermal papilla cells spread over filamentous mitochondria. In the process of migration, filamentous mitochondria dominate the hair follicle cells. The elongated filaments are expanded throughout the cell body. Fragmented mitochondria, in a small minority of the population, can be seen near the edge of the cell. The view in the dotted square is enlarged (right).



**Supplementary Video S1:** Formation of a filamentous mitochondrion by untangling. The live cell imaging shows a rounded mitochondrion transforming into a filamentous mitochondrion via untangling. Thirty images were recorded every 10 seconds.

Also you could view this video by clicking the following link:  
<https://www.youtube.com/watch?v=1heWGPB43cs&feature=youtu.be>

**Note:** To best view

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