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Letter to Editor
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ER-Mitochondria Contact Sites and Mitochondrial Mass a Mid-Term Regulation of Bio Energetic

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Letter to Editor

Mitochondrial activities are tightly regulated, regarding cell status like differentiation state, cellular fate and energetic requirements, at cellular and body levels. They produce ATP efficiently to the cells but they also contribute importantly in lipid metabolism (consumption and storage) and also in steroids production, phospholipid biosynthesis and calcium homeostasy. Of course, each metabolic pathway is itself regulated through growth factor and hormonal actions, but the mitochondrial "mass" seems to be conditioned too, depending on nutrition, activity, seasons or pathologies.

The mitochondrial mass is regulated by the synthesis and the degradation of mitochondria (mitophagy). Indeed, mitochondrial biogenesis is not so well known today and can be involved in much different pathology (diabetes, obesity, neuro- and myopathies like endocrine disturbances). These processes that allow mitochondrial biogenesis are extremely complex as they need of a complete co-regulation of mitochondrial replication/transcription/translation with the one related to nuclear genes. In fact, most of the mitochondrial protein is nuclear-encoded (13 encoded by mt DNA/1000 by the nucleus) and their synthesis pathways are just partially understood.

Many mitochondrial proteins are with unknown export pathway, especially some membranous ones. In parallel, mitochondrial biogenesis requires lipids, which are provided by the endoplasmic reticulum reservoir. To conciliate all these requirements, molecular models supporting mitochondrial biogenesis are emerging now [1] and a one new and major actor is the mitochondrial ATPase ATAD3 (ATPase family AAA Domain-containing protein 3).

ATAD3 protein was discovered in 2005 as an oncogenic marker of tumors [2,3] and mainly studied at cancer level [4,5]. Inserted in the inner mitochondrial membrane [6,7], ATAD3 is able to tether the outer mitochondrial membrane as well as endoplasmic reticulum structures [8]. By the way, ATAD3 supports mitochondrial biogenesis [9,10] and as can be expected, ATAD3 is vital as early as at the gastrula/implantation stage [11]. All these characteristics make ATAD3 a potent actor in a wild range of diseases.

Recent researches have shown how the cholesterol can transit from ER to mitochondria, for mitochondrial biogenesis as for other processes like steroids production [12-14]. These teams have shown that the transport of cholesterol can occur through ER-Mitochondria contact sites involving ATAD3. They found there a molecular complex supporting cholesterol transfer where ATAD3 is essential for this function. The more interesting is that this process can occur as a lipid-raft system, carrying neo-synthetized, nuclear encoded proteins [1,9].

Then, ATAD3 is the principal candidate protein to function as a link between inner/outer mitochondrial membranes and the endoplasmic reticulum, to support the transport cholesterol/proteins and to allow mitochondrial biogenesis. It is interesting therefore to see that ATAD3 can be a site for regulation of the mitochondrial mass, like can occur during cell cycle, differentiation and along hormone regulations. This process is also regulated by diet molecules like resveratrol [15] and is a known to be a site for stress response.

A focus on this protein and this system might be of particular interest to better understand this new site of metabolic regulation which regulates the mitochondrial mass. This would have to be considered in pathologies studies too.

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