SIDEROFLEXINS AND MITOCHONDRIA

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The mitochondrion has long been studied for its central role in energy supply but it has many other functions (iron metabolism, lipids metabolism, calcium homeostasis, apoptosis for example). Mitochondria form a highly dynamic structure whose shape is under the control of fusion and fission mechanisms. Mitochondrial dysfunction and alteration of the fusion/fission balance are found in numerous diseases (mitochondrial disorders, neurodegenerative disease, cancers). Furthermore pathogens (like Listeria monocytogenes for example) can affect mitochondrial dynamics.
Our recent projects aimed at studying the mitochondrial activities of the tumor suppressor p53.

First we studied the mechanisms whereby p53 regulates the mitochondrial pathway of apoptosis. We wanted to understand how p53-dependent apoptosis is regulated by growth factors and in particular by the Fibroblast Growth Factor 1 (FGF1). FGF1 is overexpressed in various cancers and is able to inhibit the p53-dependent cell death. We

have shown that FGF1 is able to decrease the stability and transcriptional activities of p53 in some cellular models or to decrease mitochondrial localization of p53 in others (Rodriguez-Enfedaque *et al.*, 2009 ; Rodriguez-Enfalque *et al.* 2012 ; Delmas *et al.* 2016; Pirou *et al.*, 2017; Manousakidi *et al.*, 20108).

Secondly, we also investigated the mitochondrial functions of p53 in the absence of cell death induction. We highlighted the presence of a mitochondrial pool of p53 even when the cell was not undergoing apoptosis. We also showed that p53 can regulate the oxidative phosphorylation and can interact with the OSCP subunit of the ATP synthase (Ferecatu *et al.*, 2009 ; Bergeaud *et al.*, 2013).

Our current projects aim at deciphering the role of the mitochondria and of its interactions with the endoplasmic reticulum in the control of cell fate. In this context, our objectives are to understand the functions of a family of evolutionarily conserved mitochondrial proteins named sideroflexins. In humans, some sideroflexins have been found deregulated in diseases that involve mitochondrial defects.
Sideroflexins' functions are investigated using a methodology based on complementary models (yeast, fruit fly, rodents and human cells) and a multi-scale approach (molecular, cellular, organismal levels). Mitochondrial functions of the sole fungal sideroflexin are studied in collaboration with N. Bonnefoy (I2BC, Gif-sur-Yvette). Moreover, the role of sideroflexins in neuronal physiology and neurodegeneration is studied using fruit fly (a model perfectly mastered in the LGBC lab) and rodent models (in collaboration with G. Liot, CEA, Fontenay-aux-Roses).

Current collaborations:
- Nathalie Bonnefoy et Geneviève Dujardin (I2BC, Gif-sur-Yvette)
- Géraldine Liot (CEA, Fontenay-aux-Roses)
- Marie-Pierre Golinelli (ICSN, Gif-sur-Yvette)
- Ioana Ferecatu (Faculté de Pharmacie Paris 5, Paris)