'MITOCHONDRIAL STRESS AND APOPTOSIS' AXIS

In the past years, our work had primarily focused on the study of two pro-apoptotic Bcl-2 family proteins-induced apoptosis in Drosophila. More recently, in the continuity of the work carried out by Jean-Luc Vayssière's group on the mammalian Rb protein, we changed our focus to study the functions of Rbf1, the Drosophila homologue of the mammalian tumor suppressor, in apoptosis and tissue homeostasis.

Inactivation of tumour suppressor genes is one of the fundamental steps in carcinogenesis. The proteins encoded by these genes most often limit cell proliferation and/or trigger apoptotic death of cells that are potentially harmful for the organism. The rb gene was the first tumor suppressor gene identified in 1987. The Rb tumor suppressor protein is a regulator of the cell cycle allowing, by binding to factors of the E2F family, a cell cycle arrest essential to differentiation of many types of cells. While its properties of negative regulator of the cell cycle are in agreement with its role of tumor suppressor, surprisingly, some studies suggest an anti-apoptotic role for Rb. In fact, the pro- or anti-

apoptotic activity of Rb could depend on the cellular context (Godefroy *et al*., 2006) and recent works highlight a direct role for Rb in genotoxic stress-induced apoptosis (Ianari *et al*., 2009 ; Ianari *et al*., 2013).

To better understand the physiological role(s) of Rb in the regulation of tissue homeostasis (i.e. its role in apoptosis and proliferation control), we use Drosophila as a model. The Rb/E2F pathway is conserved in fruitfly, however with a lesser genetic complexity (Chen *et al*., 2009 ; van den Heuvel & Dyson, 2008). We have shown that Rbf1, the Rb homologue found in Drosophila, can be pro- or anti-apoptotic and that its properties depend on the proliferative status of the cells (Milet *et al*. 2010) (comments: (Ianari & Gulino, 2010).

Post-translational modifications of Rb such as phosphorylations are decisive for the regulation of its activities. Cleavage of Rb by caspases may also modulate its properties in relation to apoptosis (Chau *et al*., 2002 ; LeFoch *et al*., 2010, Lemaire *et al*., 2005), probably by modifying the interactions of Rb with its multiple partners (E2F family members, factors involved in chromatin remodeling, cyclines, differentiation factors...). Furthermore, our results indicate that Rbf1 is cleaved during development and that some forms of Rbf1 exert antagonistic roles on apoptosis and display cell non-autonomous effects that alters the fate of surrounding cells (Milet *et al*, 2014).

We have also shown that Rbf1, in cooperation with dE2F2 and some members of the dREAM complex, can downregulate the anti-apoptotic genes *buffy* and *diap1*, and thus promote cell death in a proliferative tissue (Clavier *et al*., 2014). *Debcl* is necessary downstream of *buffy* to induces mitochondrial fragmentation by binding the pro-fission protein Drp1, which triggers the production of mitochondrial reactive oxygen species (ROS), thereby activating the JNK (c-Jun N-terminal kinases) pathway and cell death (Clavier *et al*. 2015). Finally, we have also shown that two different specific JNK activators are required to trigger apoptosis or compensatory proliferation in response to Rbf1 (Clavier *et al*. 2016b).

Our project should allow a better understanding of the complexity of Rbf1 functions, and potentially those of its mammalian counterpart Rb, in the control of cell fate .