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Biography

Philippe Juin obtained his PhD degree in 1995 for his work on mitochondrial assembly. During his post-doc in the UK, he defined the mitochondrial apoptotic pathway as one major intrinsic tumor suppressor mechanism triggered by oncogene deregulation. As an Associate Researcher at INSERM, he led increasingly ambitious investigations of the regulation of the mitochondrial apoptotic pathway by Bcl-2 family members in human cancer cells and he created in 2012 an INSERM team that specifically focusses on the role of this pathway in stress adaptation and tumor escape. This team gained international recognition for its fundamental and translational research on the regulation of therapeutic response and tumor progression by BCL-2 family members (Nature Rev. Cancer 2013, Cell Rep. 2016, EMBO Rep. 2018 in press). This team contributed to establish that changes in mitochondrial apoptotic priming are at the core of breast cancer cells response to cytotoxic stress and treatments, being influenced by oncogene signaling, tumor suppressor pathways, therapy and tumor context. This team recently established a new function of BCL-2 members, that contributes contributing to the self renewal of breast cancer initiating cells, and defined the molecular events involved (Nature Comm., 2017).

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BCL-XL DIRECTLY MODULATES RAS SIGNALLING TO FAVOUR CANCER CELL STEMNESS

In tumours, accumulation of chemoresistant cells that express high levels of anti-apoptotic proteins such as BCL-XL is thought to result from the counter selection of sensitive, low expresser clones during progression and/or initial treatment. We herein show that BCL-XL expression is selectively advantageous to cancer cell populations even in the absence of pro-apoptotic pressure. In transformed human mammary epithelial cells BCL-XL favours full activation of signalling downstream of constitutively active RAS with which it interacts in a BH4 dependent manner. Comparative proteomic analysis and functional assays indicate that this is critical for RAS-induced expression of stemness regulators and maintenance of a cancer initiating cell (CIC) phenotype. Resistant cancer cells thus arise from a positive selection driven by BCL-XL modulation of RAS-induced self-renewal, and during which apoptotic resistance is not necessarily the directly selected trait.