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Role of apoptosis regulators of the Bcl-2 family in the control of cell motility during development and tumor progression

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Local invasion can be considered as an initial and essential step in the malignancy of carcinomas, leading to the generation of distant metastasis. Metastasis remains the major cause of cancer-related mortality and currently, there is a lack of therapies that can efficiently prevent this process.The molecular mechanisms governing tumor progression, including metastasis development, are still poorly understood. During this process, cells acquire apoptosis resistance which is often correlated with alteration of Bcl-2 family proteins status. Bcl-2 family members are the main regulators of apoptosis. Upregulation of the anti-apoptotic members in wide range of cancers including breast cancer is often correlated with chemotherapy resistance and poor prognosis. Thus targeting the activity of Bcl-2 family proteins represents promising strategies for the elaboration of cancer therapeutic.

Bcl-2 proteins have been studied intensively for the past two decades owing to their importance in the regulation of apoptosis, tumorigenesis and cellular responses to anti-cancer therapy. However, increasing data suggest additional roles, including regulation of the cell cycle, metabolism and cytoskeletal dynamics. Using zebrafish as a vertebrate model we demonstrated that two Bcl-2 homologs, Nrz and Bcl-wav, orchestrate morphogenic movements by controlling the intracellular Ca2+ trafficking during early development. Nrz silencing causes development arrest followed by detachment of the entire blastomeres from the yolk sac. Time-lapse and confocal microscopy experiments demonstrated that this phenotype is due to the premature formation of actin-myosin complexes, giving rise to a contractile structure that squeezes the embryo margin and prevents epiboly progression. At the ER membranes, Nrz interacts with the IP_3 binding domain of the IP_3R1 Ca^{2+} channel. This interaction regulates the time course of Ca^{2+} transients in the yolk sac that consecutively controls the formation of actin-myosin cables via the CaMKII-MLCK pathway.

Put into a broader context our results established for the first time that members of the Bcl-2 family are able to control cell migration in a calcium dependent manner via their direct interaction with intracellular Ca2+ channels and thus independently of their involvement in the regulation of cell death. Together our results may also contribute to a better understanding of the molecular mechanisms underlying metastasis formation.

Biography:

Dr. Germain GILLET is a Professor in the Université Claude Bernard Lyon 1 (UCBL), France and Chair, Scientific Council UCBL ; Group leader at CRCL. His current research is focused on The molecular mechanisms governing tumor progression, including metastasis development, are still poorly understood. We showed that some members of the Bcl-2 family are able to control cell migration in a Ca^{2+}-dependent manner via their direct interactions with Ca^{2+} channels, independently of their involvement in apoptosis. Using genetically engineered mouse and zebrafish models, we are analyzing the molecular mechanisms by which members of the Bcl-2 family influence cell survival and cell migration. We intend to (i) identify the signaling networks that lead to the modulation of Ca^{2+} homeostasis and cell movements by Bcl-2 family proteins (ii) identify the factors involved in apoptosis progression and cell migration (iii) review the roles played by these factors, depending on the pathophysiological context.

It is anticipated that this work will lead to the identification of novel prognosis markers and might deliver potential molecular targets for the control of tumor-growth and formation of metastases.