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GSK3 inhibition triggers both apoptotic and autophagic signals in pancreatic cancer cells

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Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading cause of cancer-related death worldwide and the only malignancy with a 5-year survival rate still in the single-digit i.e., 6%. These statistics have not improved over the last 40 years and, although the identification of the most frequently mutated genes in PDAC (KRAS, p53, p16, SMAD4) provided important insights into PDAC pathogenesis, they have not lead to improvement of diagnostic or treatment. Consequently, PDAC is still lately diagnosed and highly resistant to current chemotherapeutic agents. Finding the Achilles heel of pancreatic cancer cells and/or new therapeutic options to sensitize pancreatic cancer cells to chemotherapeutic agents will definitively help in our quest to improve PDAC patients fate. We and others have previously demonstrated that inhibition of glycogen synthase kinase-3 (GSK3) impairs pancreatic cancer cell growth providing a rationale for evaluating the potential clinical utility of GSK3 inhibitors in the setting of PDAC patients. Notably, we have shown that GSK3 inhibition triggers JNK-dependent apoptosis of pancreatic cancer cells. Recently, we found out that exposure to a GSK3 inhibitor concomitantly elicits an autophagic response independently of the JNK-cJUN pathway. Preventing this autophagic response sensitizes pancreatic cancer cells to apoptosis suggesting a pro-survival role for autophagy upon GSK3 inhibition. Interestingly, we found that treatment with GSK3 inhibitors impacts on the transcription factor EB (TFEB) recently identified as a master regulator of autophagy and lysosomal biogenesis. Our results underline the need to better define the downstream GSK3's effectors in order to propose better combination therapy for PDAC patients.

Biography

Marie-Josee Boucher completed her PhD in Cell Biology at the University of Sherbrooke, Canada and then pursued Post-doctoral training at the Umea Center for Molecular Medicine, Sweden. She is now an Associate Professor at the University of Sherbrooke, and devotes her career to the identification of key signaling pathways involved in the maintenance of the transformed phenotype of pancreatic cancer cells. She is the Deputy Director of research of the Medicine Department, University of Sherbrooke. She is currently serving as an academic editor for PLoS ONE and on the editorial board of *Advances in Medicine: Gastroenterology*.

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