Investigating autophagy and glutamine metabolism as therapeutic targets for pancreatic cancer

Mario A. Jardon, Steve E. Kalloger, Christina Iggulden, Nancy Erro Go, Paalini Sathiyaseelan, Donald T. Yapp, Daniel J. Renouf, David F. Schaeffer, Sharon M. Gorski
BC Cancer Agency, Canada

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest types of cancer, for which new therapeutic approaches are urgently needed. We are developing novel combination therapy approaches based on the inhibition of glutamine metabolism and autophagy, to improve current treatments for PDAC. Since both processes are key mediators of multiple cancer hallmarks, and have inter-related but non-redundant roles, this combination approach could result in a more efficient disruption of cancer cell resistance to treatments.

We interrogated the Pancreas Centre BC tissue micro-array (TMA), containing the epithelial component of 252 PDAC samples, for expression of three key glutamine-metabolizing proteins and two autophagy-related proteins: glutamine synthetase (GLUL), asparagine synthetase (ASNS), glutaminase C (GLS-GAC), microtubule-associated protein 1 light chain 3 beta (MAP1-LC3B or LC3B) and autophagy-related protein 4B (ATG4B). We found that these proteins were expressed in 31%, 58%, 99%, 51% and 73%, respectively, of PDAC samples. Furthermore, higher LC3B expression correlated with poor outcome. These observations indicate that glutamine metabolism and autophagy are clinically relevant in PDACs and may have potential as therapeutic targets.

While previous efforts by other groups have focused on GLS-GAC, the role of GLUL in cancer has remained less well understood. We thus investigated the functional relevance of GLUL in PDAC cells. Analysis of a panel of cell lines revealed that various PDAC cells express GLUL, which can be upregulated upon glutamine deprivation. In all cell lines tested, GLUL knockdown sensitized them to gemcitabine, as assessed by a long-term recovery assay.

In addition to investigating the role of GLUL in PDAC and potential strategies to target it, we are investigating interactions between glutamine metabolism and autophagy, including the exploration of the therapeutic potential of a new class of ATG4B inhibitors for the treatment of pancreatic cancers.

Supported by Pancreas Centre BC, BC Cancer Foundation and VGH Foundation.