

Tumor-biological role of proteases in peritoneal carcinomatosis

Cancer-associated proteolytic enzymes play an important role in tumor growth, invasion, and metastasis. Recently, we have shown that some members of the tumor-associated serine proteases including certain members of the kallikrein-related peptidases (KLK) family, primarily known for their clinical use as biomarkers in many cancers, drives colon cancer progression by targeting diverse substrates including a small family of GPCRs, the protease-activated receptors (PARs) (*Gratio et al. 2010-2011, Chung et al.2012 and Walker et al.2014, Delauney et al ,2018*). Colorectal cancer patients also contribute to a higher number of patients with peritoneal involvement due to the high incidence of these cancers overall. These observations provide reason for investigation of the role of the KLKs enzymes in the development of colonic Peritoneal Carcinomatosis (PC), a late stage manifestation of abdominal cancer associated with poor prognosis.

Our main objectives are :

- To characterize endogenous tumour and nodule-derived proteases including members of the KLK family, as early markers of colon cancer peritoneal dissemination. A focus will be put on KLK6 for which a correlation was established between its elevated expression and aggressivity of the colonic tumors and poor patient outcome. And we will also analyze the correlation between the mutational profile of colonic tumors from patients and KLK6 expression, since the activating K-RAS mutations have been shown to induce KLK6 in colon cancer cells *in vitro*. -To analyze role of KLK6 on PC steps in 2D cell culture, and three-dimensional models to mimic the colon PC microenvironment of patients.-To characterize the KLK6 pathways and drivers leading to the metastatic behavior-To validate the role of KLK6 in mouse models.-To test the newly emerging inhibitors to block tumor-associated proteolytic systems hereby to develop new therapeutic targets to improve tumor progression and patient survival.

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