International Conference on Pancreatic Disorders and Treatment

October 17-19, 2016 Chicago, USA

Tumor cell-derived MMP3 orchestrates Rac1b and tissue alterations that promote pancreatic adenocarcinoma

Christine Mehner Mayo Clinic, USA

Pancreatic ductal adenocarcinoma (PDA) arises at the convergence of genetic alterations in KRAS with a fostering microenvironment shaped by immune cell influx and fibrotic changes; identification of the earliest tumorigenic molecular mediators evokes the proverbial chicken and egg problem. Matrix metalloproteinases (MMP) are key drivers of tumor progression that originate primarily from stromal cells activated by the developing tumor. Here, MMP3, known to be expressed in PDA, was found to be associated with expression of Rac1b, a tumorigenic splice isoform of Rac1, in all stages of pancreatic cancer. Using a large cohort of human PDA tissue biopsies specimens, both MMP3 and Rac1b are expressed in PDA cells, that the expression levels of the two markers are highly correlated, and that the subcellular distribution of Rac1b in PDA is significantly associated with patient outcome. Using transgenic mouse models, coexpression of MMP3 with activated KRAS in pancreatic acinar cells stimulates metaplasia and immune cell infiltration, priming the stromal microenvironment for early tumor development. Finally, exposure of cultured pancreatic cancer cells to recombinant MMP3 stimulates expression of Rac1b, increases cellular invasiveness, and activation of tumorigenic transcriptional profiles. Implications: MMP3 acts as a co-conspirator of oncogenic KRAS in pancreatic cancer tumorigenesis and progression, both through Rac1b-mediated phenotypic control of pancreatic cancer cells themselves, and by giving rise to the tumorigenic microenvironment; these findings also point to inhibition of this pathway as a potential therapeutic strategy for pancreatic cancer.

Biography

Christine Mehner has completed her MD at the University of Witten/Herdecke, Germany and became a Post-doctoral fellow at the Mayo Clinic Cancer Center, Jacksonville, FL. She has published multiple first author papers in the field of cancer research, in reputed journals that have been recognized by the Faculty of 1000 and have been featured in news and media. She has been serving as an Editorial Board Member and constant reviewer for various journals.

christine@gmail.com

Notes: