Ruprecht-Karls-Universität Heidelberg Medizinische Fakultät Mannheim Dissertations-Kurzfassung

Bone Morphogenetic Protein (BMP)-9 acts tumour-suppressive by enhancing the ID1/Noggin ratio in colorectal cancer

Autor: Chen Cai
Institut / Klinik: II Medizinische Klinik
Doktorvater: Priv.-Doz. Dr. K. Breitkopf-Heinlein

CRC is one of the most lethal tumours and for later disease stage patients, promising therapy is still missing. The role of BMP-9 in tumourigenesis in general is quite controversial, although there were few indirect researches supporting a protective effect of BMP-9 in CRC. We investigated BMP-9s' functions in CRC and its underlying mechanisms. Using N- and T- paired patients' 3D Organoids as models and BMP-9 knockout mice samples we investigated the direct effect of BMP-9 on the intestinal epithelium. Before BMP-9 application, we first established the colon Organoids model. Though 3D Organoids can better mimic the in vivo situation than regular monolyer culture, the possible influence of the complex culture medium on signalling pathways of the TGF-β family of cytokines was not clear. Therefore, in our stimulation/co-culture experiments, only Advanced medium was used containg a strongly reduced number of factors. The Organoids' morphology and viability using this medium were controlled before starting the experiments. In order to better characterize the model, we analysed the cell types, cell characteristics and CMS subgroups of our Organoids. In silico data from GENT, STRING and GEPIA and TCGA-COAD+READ cohorts, showed an adjustability of BMP-9 signaling in Organoids and basal expression level of the BMP- 9 signaling pathway components were used for predictions. BMP-9s' anti-proliferation effects were proven by: 1. Enriched gene sets for proliferation in non-BMP-9 treated organoids; 2. Reduced Ki67 expression in BMP-9 treated Organoids and 3. Inhibited proliferation in the stem cell/TA zone of the colon epithelium in BMP-9 KO mice. The mechanism of BMP-9s' anti-proliferation/tumourigenesis activity was explored through: 1. In silico data, showing that an increased ID1/Noggin ratio is associated with longer patient disease free survival times; 2. An increased ratio of ID1/Noggin after BMP-9 stimulation and 3. Up-regulated expression of ID1 in CAFs in the presence of BMP-9.
In summary, our data confirm that patient-derived Organoids from normal and matched tumour-biopsies represent highly suitable models to study individual responses and therefore such Organoids will most likely further advance personalized medicine approaches in the future. BMP-9 profoundly affects the normal as well as the malignant gut mucosa and these effects, including up-regulation of the ratio of ID1/Noggin, are supposedly tumour-suppressive, implying that BMP-9 mimetics might represent promising tools for future therapy approaches against initiation and progression of CRC in patients.