"The role of kappa opioid receptors during chronic intestinal inflammation and colitis-associated colorectal cancer – focusing on different types of cell death and cell-cell interactions"

Ulcerative colitis belongs to a group of inflammatory bowel disease (IBD), which is diagnosed in 39-250 cases per 100 000 persons. Moreover, up to 25% of IBD patients develop colitis-associated colorectal cancer (CACRC). The cause of IBD is still not known, therefore the determination of the IBD pathogenesis as well as novel drug targets are urgently needed.

Opioids are considered now as drugs, which can find an application in IBD and cancer therapy. For centuries, opioids have been used to treat severe pain, nowadays they still constitute a gold standard in the therapy of severe cancer pain in order to improve patients' quality of life, even taking into the consideration that the use of opioids leads to numerous side effects such as constipation, drowsiness, nausea, itching, increased sweating and hormonal changes.

Within the group of opioid receptors – kappa opioid receptors (KOP) are not well characterized in the GI tract, but they are known to play a role in other immune diseases, for example rheumatoid arthritis or atopic dermatitis.

In our previous studies we revealed that stimulation of KOP receptors with a mixed agonist (having also binding affinity to MOP receptors) induced an anti-inflammatory response in experimental colitis in mice. We also found that expression of KOP receptors is impaired in the course of colitis and colitis-associated colorectal cancer.

The aim of the proposal is to determine the role of kappa opioid receptors (KOP) during chronic colitis and colitis-associated colorectal cancer. We will characterize the interactions between neuronal and epithelial cells and impact of KOP receptors modulation on the different cell death types and cell proliferation, moreover in further future to design new drugs targeting KOP receptors in the gastrointestinal tract.

Firstly, we would like to assess the anti-inflammatory and anti-tumor potential of known KOP ligands in the mouse model of ulcerative colitis and colitis-associated colorectal cancer. Secondly, we would like to determine how KOP ligands affect cell proliferation in in vitro studies using mouse colorectal cancer cell lines. In further perspective, we how like to elucidate how KOP receptors modulation will influence cell death. In next experiments, we would like to identify if any interactions between neuronal and epithelial cells upon kappa receptors activation occur.

And last, but not least, we would like to characterize an anti-inflammatory effect of novel designed KOP ligands in the chronic colitis and colitis-associated colorectal cancer in mice in order to find a new opportunities in the therapy of IBD and CACRC.