If you, or your relatives are suffering from inflammatory bowel diseases (IBD) such as ulcerative colitis or Crohn's disease (CD), than you probably know that those are chronic, incurable disorders. IBDs, and especially CD, are the diseases with complicated and not fully understood etiology that typically strike young adults (after twenty). Although being thoroughly studied within the last few decades, the causes of IBD are not fully elucidated. Yet we know that among the symptoms is intestinal fibrosis that may end up with intestinal obstruction. This potentially lethal complication requires repeated surgical interventions during patients' live. Therefore, knowledge how to prevent intestinal fibrosis may bring benefits to patients with IBD, especially CD.

We should be aware that intestinal fibrosis is not an abrupt phenomenon, but its development requires time and simultaneous appearance of processes such as increased cells proliferation, improper production of extracellular matrix components, hyperactivation of immunological system or overproduction of proinflammatory cytokines. The last two listed may also disrupt redox homeostasis leading to oxidative stress, DNA damage and premature senescence of the gut cells. Importantly, so far there is no drug that can reverse intestinal fibrosis. Therefore, identification of causes of fibrosis and cellular senescence in *in vivo* and *in vitro* has an important diagnostic and therapeutic potential. We believe that Nrf2 signaling molecule may be a promising candidate.

Our preliminary data show that inactive activity of Nrf2 leads to dramatic changes in colon morphology and length. Moreover, as such changes are observed in four day old pups, it suggests impaired development of gastrointestinal tracks. Therefore, determining if Nrf2 deficiency influences colon development seems crucial. Still, at first glance, despite colon abnormalities, Nrf2 transcriptional knockout mice seem to function properly and they don't develop IBD. Therefore, we ask if such morphological abnormalities have impact on colon functionality and what could be responsible for possible colon protection. As deficiency of IL-10 leads to development of IBD and our data showed that Nrf2 transcriptionally knockout mice have higher expression of IL-10 therefore, we hypothesized that Nrf2 deficiency may lead to increased production of IL-10 which protects healthy mice from development of IBD.

To verify our hypotheses we will use mice lacking transcriptional activity of Nrf2 (tKO) or IL-10, which spontaneously develop IBD, and their wild type littermates. First, we will verify if the observed changes in colon morphology of Nrf2 tKO mice are associated with impaired deposition of extracellular matrix components in muscular mucosa which may be triggered by several processes including fibrosis, oxidative stress or premature senescence. We will verify which process is present in Nrf2 and IL-10 lacking mice, and analyze which one has a dominant role. Secondly, lack of transcriptional Nrf2 causes colon edema in mice but it seems to not influence stool water resorption as those mice have no signs of diarrhea or constipation. Therefore, we hypothesize that Nrf2 tKO changes water absorption and accumulation within colon. Those symptoms may be associated with increased permeability of epithelial barrier, impaired water resorption, and increased water accumulation. In this part we will use techniques of molecular biology, biochemical methods and histological analysis, which enable us to compare similarities and differences between both genotypes.

Surprisingly, our Nrf2 tKO mice at first glance, despite colon abnormalities, seem to function as their wild type counterparts. Therefore, we will answer the question how altered colon morphology of Nrf2 tKO mice, influences colon functionally e.g. motility, weight loss, anemia or anal fissures. We will examine colon motility *in vivo* by testing time of passage of the non-absorbable color dye, and *in vitro* response of isolated colon rings to excitatory transmitters.

As our results presented that four day old pups lacking Nrf2 transcriptional activity had significantly longer colon and altered colon morphology, we hypothesize that Nrf2 tKO may influence gut development by inhibiting Notch-dependent cell proliferation during gestation. Therefore, we will investigate the role of Nrf2 in intestine development.

Finally, we want to investigate the mechanism of Nrf2-dependent protection against inflammatory colon diseases. Our results indicate that mice lacking Nrf2 transcriptional activity have higher expression of IL-10, which was clinically tested as a potential drug for IBD as it may inhibit disease progression. Therefore, we will investigate if Nrf2 deficiency prevents colon diseases by up-regulating IL-10 production. These experiments will be performed on primary colonic epithelial organoids (colonoids) isolated from Nrf2 wild type and Nrf2 tKO mice.

We strongly believe that the new knowledge arising from this study will help to better understand the pathology of colon diseases, especially Crohn's disease, as better drugs for inflammatory bowel diseases are still needed.