Mechanisms of intestinal tumor initiation and progression in \( Apc^{MIN} \) mouse model of colorectal cancer

Avhandlingen baseras på följande delarbeten:


   **Targeting Zfp148 activates p53 and reduces tumor initiation in the gut.**


   **Zfp148 prevents cell cycle arrest by repressing ARF.**

   *In manuscript*


   **Dietary antioxidants accelerate growth of intestinal adenomas in \( APC^{Min/+} \) mice.**

   *In manuscript*
ABSTRACT

Colorectal cancer (CRC) is a cancer that occurs in the colon or rectum and is one of the most common cancer forms and a leading cause of cancer death in the Western world. The majority of CRCs are caused by inherited or somatic mutations in the APC gene. The Apc\textsubscript{Min} model is driven by a truncating mutation in the Apc gene and is considered to be one of the best mouse models of CRC. The aim of this thesis is to uncover novel mechanisms behind the initiation and progression of intestinal adenomas in Apc\textsubscript{Min/+} mice.

Clinical studies suggest that the transcription factor Zfp148 may play a role in CRC but the importance of Zfp148 for tumor development has not been properly investigated. We have previously shown that Zfp148 is a potent inhibitor of p53 and hypothesized that Zfp148 deficiency may protect against CRC by increasing p53-activity. In paper I, we show that deletion of one or both copies of Zfp148 markedly reduces tumor formation in Apc\textsubscript{Min/+} mice. The result shows that Zfp148 controls the fate of newly transformed tumor cells by repressing p53, and suggests that targeting Zfp148 might be useful in the treatment of colorectal cancer.

Previous studies show that Zfp148 inhibits activation of p53; however, the underlying mechanism is not understood. We have previously shown that transcription of Cdkn2a was increased in Zfp148 deficient MEFs. ARF is one of two products of Cdkn2a and is a major activator of the p53-pathway. Therefore, we hypothesized that Zfp148 inhibits p53 by repressing ARF. In paper II, we tested this hypothesis in mouse embryoblasts (MEFs) and found that Zfp148 regulates cell proliferation and p53 activity by repressing the transcription of ARF.

Finally, we addressed the role of antioxidants. Clinical studies on the ability of dietary antioxidants to prevent CRC show inconsistent results. To understand the effect of antioxidants, we gave two types of dietary antioxidants to Apc\textsubscript{Min/+} mice and investigated tumor development. Our results indicate that dietary antioxidants have no effect on tumor initiation but accelerate progression of existing tumors. The result raises concerns about the widespread use of dietary antioxidants, especially among high risk populations.