Between cancer and therapy: Studies of the colon
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Colorectal cancer (CRC) is one of the leading causes of cancer related deaths worldwide. Surgical resection is the primary treatment modality, but can only be curative in the earliest stages of CRC. As these early stages often occur asymptptomatically, much effort is being put into earlier detection by population based screenings. Nonetheless, the vast majority of diagnosed CRCs will need additional chemo-radiation therapy. Although more and more specific anti-cancer therapies are being developed, the standard of care remains treatment with cytotoxic agents that target both cancer and healthy cells resulting in severe toxicity. Therefore, in order to combat cancer better, we should aim our research goals at increasing knowledge on mechanisms involved in cancer development as well as enhance the understanding of therapy-sensitivity and, importantly -resistance.

The first two chapters of this thesis are an introduction. Chapter 1 introduces basic concepts of stemness and differentiation in the healthy intestinal epithelium and in cancer. These concepts form the basis of our experimental research described in chapter 7. Chapter 2 reviews the literature on the influence of sex hormones on CRC.

Several risk factors have been described to be associated with the incidence of colorectal cancer. Some risk factors are modifiable such as smoking, physical inactivity and western diet, whereas non modifiable risk factors include older age and male gender. In line with this, postmenopausal hormone replacement therapy (HRT) has been found to be associated with a reduced risk of CRC suggesting a protective role of female hormones as a potential mechanism. Further understanding on how these risk factors mechanistically act will increase our understanding of CRC development and can help us develop personalized treatment strategies predicting which patients will respond to which therapy. In Chapter 3 we investigated which endogenous hormones are responsible for gender differences in the incidence of CRC. Interestingly, we find gender differences to be dependent on male hormone promotion and not female hormone protection. This contrasts with the clinical observation that female hormone replacement protects from CRC. In Chapter 4 this apparent discrepancy is further investigated and explained by a pivotal role for postmenopausal hormone status in CRC protection by progestins. This indicates that in contrast to postmenopausal women, fertile women may not benefit from progestins. Oncogenic pathways involved in sporadic CRC development may differ from those involved in the pathogenesis of CRC in the context of chronic inflammation. Indeed, in contrast to sporadic cancer we find estrogens to promote colitis and subsequent colitis associated cancer, this is further described in Chapter 5.

Some patient groups are genetically predisposed to the development of CRC due to a mutation in the APC gene causing the development of up to hundreds of intestinal adenomas. To ultimately prevent from CRC, these so called FAP (familial adenomatous polyposis)-patients require surgical resection of their colon. In Chapter 6 we tested and disprove the hypothesis that azathioprine would protect from CRC in a mouse model with a similar mutation in the Apc gene.
In the last decades a multitude of new therapeutical strategies have emerged resulting in better efficacy, less side effects and longer overall survival. Even when tumors seem to have been completely eradicated based on radiologic imaging, relapses are relatively common. This implies that a very small population of tumor cells, invisible to current imaging techniques, is capable of withstanding the toxic effects of chemotherapy and eventually causing regrowth of the tumor. Important players in tumor relapse are the so-called cancer stem cells. In chapter 7 we focus on these therapy resistant cancer stem cells that are also believed to be responsible for tumor-initiation, and -growth. In this chapter a strategy is proposed to sensitize resistant colorectal cancer stem cells to the effects of conventional chemotherapy, namely by ER-stressed induced differentiation.

In this thesis, our ultimate goal was to contribute knowledge that allows for the development of more efficient and more specific (adjuvant) drugs in the treatment or prevention of colorectal cancer with fewer side effects. This will lead to new treatments specific to cancer cells and thereby narrows the gap between cancer development and response to therapy.

Figure. Schematic overview of the thesis