# Abstract

Colorectal cancer (CRC) is the third most common cause of cancer worldwide. Several factors such as host genetics, diet, the composition of the gut microbiota and host immune system have been described as the main drivers for CRC initiation and progression. Mutations in key components of the DNA mismatch repair (MMR) system are present in high percentage of CRC cases. However, the mechanistic links between MMR and CRC has not been elucidated. Indeed, based on the known roles of MMR system, it is still unclear why mutations in this pathway strongly predispose to CRC more than to other types of cancers. Some studies proposed that the colonic microenvironment interacts with these cancer-predisposing mutations and promote the transformation of the colon epithelial cells. Specific dietary regimens have the potential to shape the composition of the gut microbiota. Moreover, the gut microbiota possesses a wide variety of metabolic capacities that strongly affect the metabolism, proliferation and differentiation of the colonic epithelium. Specifically, the bacterially-produced metabolite butyrate is essential for the maintenance of the colonic homeostasis and it has been shown to play a key role in CRC. Interestingly, butyrate protects against CRC as well as it may act as an oncometabolite. In this regard, more research is needed to elucidate the mechanisms through which diet and gut microbiota interact with specific cancer-predisposing mutations to induce CRC.

In order to shed light on the mechanism by which butyrate affects the proliferation of colonic epithelial cells, we investigated the effects of a 10% low carbohydrate (10% LC) diet and of a normal diet supplemented with 10% pectin from apple (ND+10% Pec) on CRC progression and on the colonic homeostasis. We showed that although these dietary regimens had differential effects on the gut microbiota and the production of butyrate, they both reduced CRC development in an $APC^{Min/+}Msh2^{-/-}$ mouse model. The 10% LC diet reduced the number of goblet cells to a great extent while ND+10% Pec had no such effect. Interestingly, both regimens induced upregulation of Muc-2. However, the changes in the gut microbiota, butyrate levels and increased Muc-2 expression triggered endoplasmic reticulum (ER) stress. Specifically, our study showed that 10% LC diet induced PERK pathway while ND+10% Pec also activated the IRE1-α pathway by inducing the splicing of the XBP1. In addition, both diets mediated the dramatic expression of the heat shock proteins Hsp27 and Hsp70, which further results in an increased intestinal barrier function. Altogether, these events are likely to protect the cells and help them to cope with the changes in their surrounding microenvironment. As the induced cellular stress conditions are known to suppress cell proliferation, this could be a mechanism through which these regimens attenuate CRC. Moreover, we investigated the effects of butyrate on cells with different status of the MMR system in *in vitro* experiments. The data support the notion that the

genetic mutations are important for determining the effects of butyrate and further prove that the metabolic state of the cells also dictates the behaviour of this metabolite in colon cancer cells.

In conclusion, the results presented and discussed in this thesis highlight the complexity of the colonic microenvironment and the importance of the interplay between diet, the gut microbiota and host genetics in CRC development. Nevertheless, more research is needed in order to determine the mechanisms by which diet protects against CRC as well as to figure out whether dietary interventions could be safely used in cancer prevention.