Abstract

Colorectal cancer (CRC) is the third most common cancer and one of the most lethal. Inactivation of mismatch repair (MMR) genes is frequently observed in CRC, and indeed predisposes to this type of cancer more than others. MMR pathway repairs mutations that arise during DNA replication, but also has an important role in the DNA damage response that inhibits the cell cycle and facilitates DNA repair and apoptosis. Hence, failure to trigger cell cycle arrest and apoptosis is recognized as mechanisms through which MMR deficiency contributes to CRC. On the other hand, little is known about its role in regulation of colon homeostasis. However, this is important to understand in order to clarify the mechanistic linkage between MMR deficiency and CRC development. It has been shown that loss of MMR promotes proliferation of colon epithelial cells (CECs) that renders them highly susceptible to cancer development. This PhD project aimed to elucidate the causative factors. Using a MMR deficient mouse model ($Msh2^{-/-}$), we analyzed colon homeostasis and cell cycle regulation of CECs, which revealed several factors responsible for the hyperproliferation. We found that loss of MMR leads to methylation induced promoter silencing of the WNT/β-catenin inhibitor Dickkopf1 (DKK1). As a result, excessive levels of active β-catenin promote strong crypt progenitor-like phenotype mediating increased proliferation. This overactivation of WNT leads to increased Bone morphogenetic protein (BMP) activity in $Msh2^{-/-}$ mice. The physiological meaning of this crosstalk likely plays a role in maintenance of colon homeostasis, and these events were found to impact the normal goblet cell development and function. Further analysis indicated that BMP signaling also triggers apoptosis in $Msh2^{-/-}$ mice. This response likely functions as a mechanism to prevent abnormal tissue growth from enhanced proliferation. We found that the increased apoptosis comes from accelerated cell turnover supplied by faster

progression of cells through the cell cycle and migration in the colonic crypt. This promoted progression is another mechanism contributing to increased proliferation of MMR deficient CECs. Further analysis revealed that under MMR deficient background cells are forced to premature G1/S transition and uncontrolled division due to deregulated G2/M checkpoint. These effects might be enhanced through WNT induced $p21^{CIP1/WAF1}$ inhibition of cyclin-dependent kinase (CDK)/Cyclin complexes required for G1 and G2 cell cycle arrest. Consequently, cells with accumulated DNA lesions will be allowed to divide and transmit mutations into their progeny a process highly facilitating cancer development. Ultimately, this PhD thesis provides important aspects concerning the increased proliferation of MMR deficient CEC and why they are predisposed to cancer development.