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Loss of DNA mismatch repair signaling impairs the WNT: Bone morphogenetic protein (BMP) crosstalk and the colonic homeostasis

Katrine Norgaard
University of Southern Denmark, Denmark

The mismatch repair (MMR) is an evolutionary conserved DNA repair pathway that repairs mutations generated during DNA replication but also maintains genome integrity. Inactivation of MMR has been recognized as a critical step in colorectal cancer initiation, however, little is known about its role in the regulation of the colonic homeostasis. The fine balance between proliferation, differentiation and apoptosis in the colonic epithelium is tightly controlled by the interplay between Wnt, Notch and bone morphogenetic protein (BMP) signaling. How these complex signaling networks coordinate the colonic homeostasis is still unclear, especially if cancer predisposing mutations are present. Loss of MMR function promotes activation of Wnt/β-catenin and increased proliferation in colon epithelial cells that renders them highly susceptible to transformation events. However, the mechanistic link between MMR and the enhanced Wnt still remains unclear. Using MMR deficient mouse model we show that loss of expression of Dickkopf1 (DKK1) leads to excessive levels of active β-catenin that promotes strong crypt progenitor-like phenotype, enhances proliferation and suppresses cell differentiation. Under these settings, the development and the function of the goblet cells are adversely affected. MMR deficient mice had fewer goblet cells, with enlarged mucins-loaded vesicles. Our study demonstrates that MMR inactivation impacts the WNT-BMP signaling crosstalk. The colon epithelial cells respond to the increased proliferation rate by boosting their apoptosis, mediated by BMP signaling. Although under these conditions the colonic homeostasis is disrupted the tissue size remains preserved.

Biography

Katrine Norgaard is a PhD student in Department of Biochemistry and Molecular Biology, University of Southern Denmark. Master's Thesis in Cancer Research with the title: The mechanistic role of S100A14 - a novel independent prognostic biomarker of the triple-negative breast cancer subtype. During her PhD, she did a collaboration with Dr. Lakshmi P. Kotra at University Health Network (UHN) at the University of Toronto (UofT). She went to Dr. Kotras laboratory for 3 weeks in April 2018 to May 2018.

knorgaard@bmb.sdu.dk

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