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Loss of DNA Mismatch Repair (MMR) Signaling Sensitizes the Colon Epithelial Cells to Transformation by Impacting the Colonic Homeostasis

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Loss in DNA mismatch repair (MMR) has long been linked to colon cancer, however, what is the specific role of MMR in the regulation of the colonic homeostasis remains unclear. It has been shown that inactivation of MMR leads to WNT-driven abnormal proliferation that highly predisposes the colon epithelial cells to transformation. While, the causative mechanism behind this phenomenon remains unknown, it suggests that MMR system may play an important role in the regulation of the equilibrium between proliferation, differentiation and apoptosis. To investigate the impact of the MMR pathway on the colonic homeostasis we used mice that harbor genetic mutation of one of the major MMR genes, namely Msh2 and completely abolishes the MMR function. Furthermore, using gene expression analysis, western blot, immunofluorescence and electron microscopy techniques we show that MMR deficiency does not lead to aberrant WNT activation but rather to inability to be negatively regulated due to loss of expression of the WNT inhibitor Dickkopf1 (DKK1). As a result, excessive levels of activated β-catenin promote strong crypt progenitor-like phenotype and suppress cell differentiation. Under these conditions, the normal development and function of the goblet cells is highly affected. We observed significant reduction in the number of goblet cells, that however, produce and secret substantially more mucin 2 (Muc2). We also show that under MMR deficient background the colon epithelial cells respond to the increased proliferation rate by boosting their apoptosis, mediated by enhanced Bone Morphogenetic protein signaling.

Biography:

Antoaneta Belcheva obtained her PhD in Molecular Biology from York University in Toronto, Canada in 2009. From 2009-2015 she completed a postdoctoral fellowship at the University of Toronto where she become a recipient of the BD Bioscience postdoctoral lecture prize for her research achievements in the area of gut microbiota and colon cancer. Antoaneta Belcheva is currently an Assistant Professor at the University of Southern Denmark. The major focus of her research is to better understand the complex interplay between cancer predisposing mutations, diet and the gut microbiota in the initiation and development of colorectal cancer.