Keratin 8-deletion Leads to Colonic Inflammation Predisposing to Colorectal Cancer Enforced by the IL-22 / P-STAT3 Pathway

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Background: Keratins (K) are intermediate filament proteins important in cell stress protection, and consequently keratin mutations predispose to e.g. human liver diseases. In colonic epithelia, K8, K18 and K19 are main keratins, and these proteins are central also in intestinal health since the K8-knockout (K8⁻/⁻) mouse manifesting early chronic colitis similar to the human inflammatory bowel disease (IBD). K8⁻/⁻ colonocytes hyperproliferate, are resistant to apoptosis and have abnormal differentiation patterns. Since IBD is a risk factor for developing colorectal cancer (CRC), we hypothesize that the K8-deficiency related-colitis phenotype predisposes to CRC.

Methods and Results: Young or old K8⁻/⁻ mice did not spontaneously develop colonic neoplasms, however, treatment with azoxymethane (AOM) induced a significantly higher incidence of colonic adenomas with high grade dysplasia in K8⁻/⁻ mice compared to K8⁺/⁺ or K8⁺⁻. When crossed with ApcMin⁺/+ (FVB/n) mice K8⁻/⁻ ApcMin⁺/+ mice developed abundant tumors in the distal colon, while no tumors were observed in K8⁺/+ ApcMin⁺/+ and K8⁺⁻ ApcMin⁺/+ mice. The NLRP3-component caspase-1 was activated and interleukin (IL)-18 was increased in both K8⁻/⁻ and K8⁻/⁻ ApcMin⁺/+ mice. Moreover, an upregulation of IL-22 and a complete loss of its negative regulator, the IL-22 binding protein (IL-22BP), were observed in K8⁻/⁻ and K8⁻/⁻ ApcMin⁺/+ colon suggesting an activation of the IL-22 pathway. This activation was confirmed by increased levels of phosphorylated STAT3 essential in proliferation and tissue regeneration.

Conclusions: K8⁻/⁻ mice do not develop CRC spontaneously but have a greatly increased susceptibility to induced tumorigenesis in two CRC models. K8-deficiency is, thus, a potent risk factor in CRC driven by activated NLRP3-inflammasome and the IL-22/P-STAT3 pathway.