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Gut microbiota and Toll-like receptors as regulators of colorectal cancer formation

Anna Sichler, Klaus-Peter Janssen
[1]***Department of Surgery, Klinikum Rechts der Isar, Tum, Munich, Germany***
[2]***Dept. of Surgery, Tum, Munich, Germany***

Purpose: Signals from commensal microbiota, as well as endogenous danger signals promote colorectal cancer initiation and progression through MyD88-dependent toll-like receptor (TLR) signaling and the activation of oncogenic, inflammation-associated epithelial pathways that include induction of lipogenesis. In contrast to tumor-promoting functions of MyD88, the contribution of TLR3 signaling, which is activated by dsRNA and relies on the adapter TRIF instead of MyD88, is still incompletely understood. In line with these results from genetic mouse models, components of the MyD88 pathway are overexpressed in human colorectal cancer, correlating with poor CRC prognosis. Here, we aim to characterize the mechanisms contributing to tumor-suppressive actions of TLR3 and TRIF.

Methods: Genetically engineered mouse models were generated, based on the "switch-on mutagenesis" approach that allow tissue-specific expression of *Tlr3* and its adapter *Trif* (Ticam1). These lines were interbred with the Apc^{1683N} mouse model for human digestive cancer. Furthermore, human colon cancer tissue samples and established cell lines were tested for TLR3 expression, and several cell lines were engineered by Crispr/Cas9 methodology to create TLR3-deficiency.

Results: Global deficiency of either *Tlr3* or its adapter protein *Ticam1* induced significantly increase tumor formation in the Apc^{1683N} mouse model, associated with increased morbidity and splenomegaly, indicating a tumor-suppressive role. In accordance, TLR3 expression in human colorectal cancer samples was found to be highly significantly decreased, as compared to normal colon mucosa. Of note, induction of enzymes of de novo lipogenesis was not affected by Tlr3/Trif signaling.

Conclusion: The two major adaptors of TLR-signalling, TRIF and MyD88, apparently have opposing roles in cancer formation. With the exception of TLR3, TLRs signal through MyD88 and activate pro-inflammatory and pro-tumorigenic programs through NF-κB and mitogen-activated protein kinases. In contrast, TLR3/TRIF has tumor-suppressive roles.