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Investigating the role of activating transcription factor 6 in CRC using a humanized transgenic mouse model

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Purpose: Alterations in the intestinal microbiota, called dysbiosis, have been implicated in the pathogenesis of colorectal cancer (CRC). Numerous bacteria such as *Fusobacterium nucleatum* as well as toxin-producing *Bacteroides fragilis* and *Escherichia coli* have been associated with tumor initiation, however mechanistic insights are lacking. Activating transcription factor 6 (ATF6) is one of three stress sensors involved in the unfolded protein response of the endoplasmic reticulum (er-UPR). er-UPR itself has also been associated with CRC, and we found alterations in the ATF6 gene in approximately 10 % of CRC patients. Tissue-specific overexpression of the active form of ATF6 (nATF6) in mice initiated inflammation-independent tumorigenesis only in homozygous $nATF6^{IEC\ tg/tg}$ (tg/tg) mice, but not in heterozygous $nATF6^{IEC\ tg/wt}$ (tg/wt) mice. In addition, nATF6 expression caused dysbiosis in tg/tg mice even before the initiation of tumor formation. Further, tumorigenesis requires microbial signals as mice raised under germ-free (GF) conditions did not develop tumors. Moreover, the transfer of SPF cecal microbiota from ATF6 mice into GF ATF6 mice restored the tumor phenotype in tg/tg mice suggesting tumor induction in tg/tg mice is microbiota-driven (Coleman et al., 2018).

Methods: Fecal samples will be analyzed by 16S rRNA gene sequencing with the aim of identifying distinct bacterial species involved in tumorigenesis in the humanized ATF6 mouse model. Phenotypic alterations between the groups will be analyzed by numerous approaches including immunohistochemistry, real-time quantitative PCR and metabolomics.

Results: To further support the role of ATF6 in CRC in the context of human disease, we plan to repeat the transfer microbiota experiments with human fecal microbiota from CRC patient and non-CRC controls. Murine and human microbiota show great similarity on higher taxonomic levels, but become distinct on the species level. With these experiments we hope to establish whether human microbiota can be stably transferred into our mouse model and if the dysbiosis observed in CRC patients can induce tumorigenesis in tg/tg mice.

Conclusion: We hypothesize that nATF6 expression causes metabolic alterations in tg/tg mice leading to a susceptible environment in which microbial triggers can initiate tumorigenesis.

Quotes (optional):

1 Coleman, O. I., Lobner, E. M., Bierwirth, S., Sorbie, A., Waldschmitt, N., Rath, E., Berger, E., Lagkouvardos, I., Clavel, T., McCoy, K. D., Weber, A., Heikenwalder, M., Janssen, K. P., and Haller, D. 2018. Activated ATF6 Induces Intestinal Dysbiosis and Innate Immune Response to Promote Colorectal Tumorigenesis. Gastroenterology. https://doi.org/10.1053/j.gastro.2018.07.028.