

ATF6 ACTIVATION ALTERS COLONIC LIPID METABOLISM CAUSING TUMOR ASSOCIATED MICROBIAL ADAPTATION

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UEG Week Berlin 2025

Poster

Small Intestine & Nutrition

October 5, 2025

ATF6 signaling drives colorectal cancer development through lipid metabolism alterations that promote tumor-associated microbial dysbiosis, affecting 19-38% of late-onset and 11% of early-onset CRC patients.

KEY POINTS

- High ATF6 expression was identified in 19-38% of late-onset CRC patients and 11% of early-onset CRC patients across multiple independent German cohorts.
- Transgenic mouse models with intestinal epithelial cell-specific ATF6 activation developed spontaneous colon tumors with 100% incidence in specific pathogen-free conditions, while germ-free mice remained tumor-free, demonstrating microbiota dependence.
- ATF6 signaling upregulates fatty acid biosynthesis, leading to enrichment of long chain fatty acids in colonic tissue of both CRC patients and mouse models, confirmed by untargeted metabolomics and organoid cultures.
- FASN inhibition and microbiota transfer experiments confirmed the causal role of ATF6-induced lipid alterations in tumorigenesis, with reduced survival in recipient mice.
- Long chain fatty acids selectively promote expansion of tumor-relevant bacteria including *Desulfovibrio*, with BONCAT analysis revealing enhanced translational activity and growth of these bacteria in response to fatty acid exposure.

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