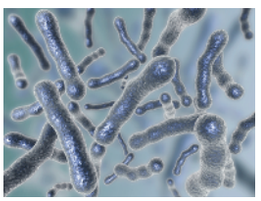
Inflammation

Major finding: Microbial products enhance colorectal cancer growth by activating IL-23 and IL-17 signaling.

Mechanism: Barrier degeneration occurs early in tumors and allows microbial products to invade tumors.

Impact: Tumor initiation triggers loss of barrier function to stimulate a protumor immune response.

MICROBIAL PRODUCTS PROMOTE IL-23 AND IL-17–MEDIATED TUMOR GROWTH



Colorectal cancers exhibit increased immune infiltration and elevated expression of inflammatory genes, many of which are characteristic of colitis-associated cancer and are associated with tumor progression, such as the T-helper 17 (T_H17) signature. To investigate the mechanisms underlying activation of this protumor immune response, Grivennikov and colleagues used a mouse model of spontaneous colorectal cancer driven by loss of the adenomatous polyposis coli (APC) tumor suppressor. In a similar manner to human colorectal cancer samples, mouse adenomas showed upregulation of interleukin (IL)-23, a positive regulator of T_H17 cells, in tumor-associated myeloid cells and increased tumoral expression of its downstream target IL-17. Ablation of the genes encoding IL-23, the IL-23 receptor, or the IL-17 receptor impaired colorectal tumor formation, indicating that IL-23 signaling enhances tumor growth via activation of an IL-17 response. Interestingly, genetic inactivation of Toll-like receptors or the adaptor protein myeloid differentiation primary response gene 88 (MYD88), which sense microbial products, also attenuated tumor formation and decreased IL-23 expression, suggesting that IL-23 upregulation is dependent on intestinal microflora. Consistent with this notion, elimination of commensal bacteria using antibiotics suppressed IL-23 and IL-17 expression and diminished tumor incidence. Furthermore, tumor-bearing mice exhibited increased blood levels of endotoxin and invasion of bacteria into early adenomas, suggestive of defects in the colonic epithelial barrier. Indeed, junctional proteins and the barrier protein mucin 2 were downregulated in mouse and human colorectal tumors but not in healthy tissue, coincident with induction of IL-23 and IL-17. In addition, loss of barrier function was observed in early adenomas and aberrant crypts and was induced in transformed cells upon APC inactivation. These results identify a broad role for microbial-dependent inflammation in colorectal cancer and suggest an additional mechanism by which cancer-initiating genetic lesions promote tumor progression. ■

Grivennikov SI, Wang K, Mucida D, Stewart CA, Schnabl B, Jauch D, et al. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17–mediated tumour growth. Nature 2012 Oct 3 [Epub ahead of print].

Breast Cancer

Major finding: The majority of breast cancer risk alleles affect FOXA1 chromatin affinity.

Clinical relevance: A risk SNP that increases FOXA1 enhancer binding suppresses the putative tumor suppressor TOX3.

Impact: Analysis of genomic features associated with linked SNPs will aid functional characterization of risk loci.

BREAST CANCER–ASSOCIATED SNPs AFFECT FOXA1 BINDING

The vast majority of cancer-associated single-nucleotide polymorphisms (SNP) identified in genome-wide association studies map to noncoding regions, hindering their functional classification. Growing evidence suggests that risk-associated SNPs may affect the activity of lineage-specific regulatory elements. Breast cancer provides a unique opportunity to study the effect of SNPs on regulatory regions because cell-specific binding of the pioneer factor forkhead box A1 (FOXA1) and estrogen receptor α (ERα) at enhancer regions is thought to contribute to disease progression. Cowper-Sal Lari and colleagues first used haplotype data to expand the list of breast cancer–associated SNPs and identified clusters of SNPs in linkage disequilibrium. Integration of these variant clusters with cistromic and epigenomic maps revealed that approximately 40% of the clusters were significantly and specifically associated with FOXA1 and ERα binding and histone H3 lysine 4 monomethylation (an epigenetic feature predominantly associated with enhancer regions) in breast cancer cells. The effect of reference and variant alleles on FOXA1 binding affinity was then determined computationally by averaging FOXA1 binding at various DNA sequences across the genome. Strikingly, most of the variant clusters contained SNPs that were predicted to affect FOXA1 binding affinity. An allele-specific increase in FOXA1 binding to chromatin was validated in the majority of breast cancer–associated SNPs, including rs4784227, a SNP lying in a regulatory element upstream of the *TOX3* gene. This element was shown to physically interact with the *TOX3* promoter, and the variant allele was significantly associated with decreased *TOX3* expression. Knockdown of *TOX3* significantly increased breast cancer cell proliferation, indicating that the variant allele of rs4784227 SNP may increase breast cancer risk by downregulating TOX3 tumor-suppressor activity. The integration of genome-wide data with disease-associated variants and linked SNPs can thus help assign functions to cancer risk alleles. ■

Cowper-Sal Lari R, Zhang X, Wright JB, Bailey SD, Cole MD, Eeckhoute J, et al. Breast cancer risk-associated SNPs modulate the affinity of chromatin for FOXA1 and alter gene expression. Nat Genet 2012 Sept 23 [Epub ahead of print].