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## Gut microbiome regulation of cancer stem cells and colon carcinogenesis

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Colorectal cancer (CRC) is a multi-step process resulting from accumulation of mutations during progression from normal epithelium to carcinoma. Loss or inactivation of the tumor suppressor gene in adenomatous polyposis coli (Apc) initiates genomic instability that is thought to produce the phenotypic appearance of an adenoma. Increasing evidence suggests that pluripotent cancer stem cells (CSCs) are involved in the development and progression of many types of malignancies, including CRC. Earlier, we reported that patients with  $\geq 3$  adenomas (High-risk for CRC) exhibited a marked increase in CSCs in the colon than those without adenomas, specifically the CD44+CD166- phenotype. Although the regulatory mechanisms for this increase in CSCs are poorly understood, we have suggested a role for secondary bile acids in the intestine, specifically deoxycholic (DCA) and lithocholic (LCA) acids, bio-transformed by gut microbiota, in regulating this process. Indeed, we observed a marked rise in *Fusobacterium nucleatum* and *Enterobacterium* (both are associated with CRC) in high-risk CRC patients. An opposite phenomenon was noted for the anti-inflammatory *Bifidobacteria* and for probiotic *Lactobacillus acidophilus*. Among the secondary bile acids, DCA and LCA are thought to be the most significant with respect to the development of CRC. Interestingly, we found the levels of DCA and LCA in the colon of high-risk (HR) CRC patients to be markedly higher than those at lower risk (LR) for CRC. We also found DCA and/or LCA to induce CSCs in normal human colonic epithelial cells, as evidenced by increased colonosphere formation and elevated expression of several CSC markers as well as MMP-2, accompanied by an induction in drug exclusion and increased expression of multiple drug resistance transporters ABCB1 and ABCG2. Our observations suggest, alterations in specific gut micro-organisms resulting in increase in DCA and LCA that induce CSCs in the colon play critical roles in the development and progression of sporadic CRC.

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