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TITLE
Microbial biofilms promote development of colorectal cancer: role of the bacterial gene fimH

HYPOTHESIS:
Intestinal mucosal bacteria promote the development of CRC though microbial factors favoring biofilm formation.

BACKGROUND/AIMS:
Biofilms have been found to be involved in a wide variety of microbial infections. A previous study found that presence of biofilms increased the risk of human of colorectal cancer (CRC) by more than five-fold. However, the role of biofilms in development of CRC is unclear. We previously observed that the adherent invasive E. coli NC101 containing the polyketide synthase genotoxik island promote CRC in mice. FimH, a manno-specific adhesin on type 1 fimbriae, have been reported to affect surface adhesion of bacteria, and therefore may affect biofilm formation. In this study, we investigated the impact of biofilm-forming bacterial communities on development of CRC and defined the role of FimH in biofilm formation.

METHODS:
Germ-free (GF) ApcMin/+, Il10−/− mice were orally gavaged with an inoculum of homogenized human tissue that was biofilm positive (BF+) tumor tissue, BF+ paired normal flanking tissue, BF+ normal colonoscopy, and BF- normal colonoscopy. Stool and distal colon samples were collected for 16S rRNA next-generation sequencing. Deletion of E. coli NC101 fimH gene was achieved by λ Red Recombinase System. Motility assay was conducted in 0.25% agar plate. Biofilm formation was evaluated through crystal violet assay. The morphology of the extracellular polysaccharide matrix was visualized by congo red staining.

RESULTS & CONCLUSIONS
Results: ApcMin+/+, Il10−/− mice associated with BF+ tumor, paired normal flanking and normal colonoscopy inoculums developed significantly more colonic tumors (means= 4.1, 2.8, and 3.7, respectively) compared to BF-bx associated mice (mean= 0, p< 0.01). 16S rRNA sequencing performed on stools and distal colon tissues showed 24 OTUs in ApcMin+/+, Il10−/− mice that were significantly different between the BF- and BF+ associated mice after transplantation. Six genera were significantly increased in both the stool and distal colon tissue compartments of BF+ associated mice (Clostridium XVIII, Erysipelotrichaceae incertae sedis, Escherichia/Shigella, Eubacterium, Parabacteroides, and Robinsoniella). To selectively assess a mechanism of biofilm formation, we used E. coli NC101 as a candidate microorganism. Compared to the well-known biofilm former LF82, NC101 showed comparable biofilm formation level. Genetic deletion of E. coli NC101 FimH (ΔfimH) showed ~65% reduced motility (p<0.0001) compared to WT E. coli. The crystal violet assay showed ~82% reduction in biofilm formation (p<0.0001) in E. coli ΔfimH compared to WT NC101. In addition, congo red staining showed reduction in extracellular polysaccharide level in E. coli ΔfimH compared to WT NC101.
Conclusions: Biofilm-associated microorganisms promote development of CRC, for which the microbial gene FimH may be an important contributor.