Microbial networking in cancer: when two toxins collide

A recent study by Dejea et al. has demonstrated that two enterotoxigenic bacteria frequently associated with sporadic colorectal cancer, Bacteroides fragilis and pks+ Escherichia coli, are found together in biofilms on tissue from patients with familial adenomatous polyposis. In preclinical mouse models, these two bacteria and their corresponding toxins work synergistically to promote colon cancer.

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potential of \( \text{pks} + \text{E. coli} \). These results indicate that additional contributing factors, such as \( \text{bft} \), are required for carcinogenesis.

Overall, Dejea et al. demonstrated a synergistic interaction between two carcinogenic bacteria, and established the concept of microbial networks in carcinogenesis.

The authors’ findings suggest that the spatial distribution of bacteria within the colon, including their proximity to the host mucosal barrier as well as interactions with each other, should be investigated further in the context of CRC. Intestinal lumen and even oral microbial composition has previously distinguished healthy subjects from patients with CRC\(^{10}\); however, these studies were conducted to identify biomarkers, and did not address causation. The evidence that ETBF and \( \text{E. coli} \) are found within biofilms and mucosal tissue from patients with FAP, and have a combined synergistic effect in animal models of CRC (Fig. 1), suggest that screening for the presence of these two bacterial strains may help assess cancer risk in humans.

The events leading to increased microbial co-occurrence and development of CRC are unclear. One contributing factor appears to be host genetics, as FAP is driven by mutations in the tumour-suppressing adenomatous polyposis coli gene, and \( \text{Apc}^{\text{Min}} \) mouse models have increased \( \text{Bacteroides} \) and \( \text{Enterobacteriaceae} \) compared with WT mice.\(^{2} \) \( \text{B. fragilis} \) and \( \text{Enterobacteriaceae} \) members have also been identified within mucosal biofilms of intestinal biopsies collected from patients with inflammatory bowel disease,\(^{11} \) suggesting intestinal inflammation also influences host susceptibility. In mice, increased mucus penetrability and proximity of bacteria to the mucosal layer are side effects of both high-fat\(^{12} \) and western-style\(^{13} \) diets, which are both carcinogenic risk factors. Whether diets have similar effects within hereditary CRC patients, by predisposing them to bacterial colonisation of the mucosal surface, is unclear. Interestingly, administering the dietary fibre inulin was shown to ameliorate the negative impact that high-fat or western style diets have on the mucus barrier and bacteria localisation in mice.\(^{12,13} \) This may indicate a potential preventative approach.

The polymicrobial nature of CRC suggests additional microbial networking likely exists within the intestine, which could positively or negatively influence carcinogenesis outcomes. It would be important to characterise these microbial networks and identify specific nodes that could represent preventive or therapeutic targets. Dejea et al. provide invaluable information on the functional interaction between two carcinogenic microorganisms, and the study paves the way for future studies elucidating microbial networks in cancer.

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**ADDITIONAL INFORMATION**

**Competing interests:** The authors declare no competing interests.

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