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Bacterial invaders drive CRC progression

Matthew Meyerson[1,2,3,*]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA

[2]Departments of Genetics and Medicine, Harvard Medical School, Boston, MA 02115, USA

[3]Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA.

Abstract

The oral bacterium *Fusobacterium nucleatum* is often found in colorectal cancer (CRC). In the 21 July 2020 issue of *Science Signaling*, Casasanta *et al*. show that CRC cell-resident *F. nucleatum* promote cytokine secretion that may potentiate tumor growth and metastatic progression in patients.

The gut is filled with bacteria. Current estimates suggest that there are roughly 40 trillion bacterial cells in the average adult human colon (1), with over 1000 different species that have been identified (2). It is therefore natural to wonder whether any of these abundant bacterial populations might promote the growth of intestinal cancers. High-throughput genome and transcriptome sequencing of the tissue microbiome provided an initial clue. Almost a decade ago, two independent laboratories found through the comparison of RNA (4) and DNA (5) from tumor and normal colon tissues that the bacterial species *Fusobacterium nucleatum* is highly abundant in specimens of colorectal tumors surgically removed from patients.

There are several questions raised by the association of *F. nucleatum* with colorectal cancer (CRC). First, *F. nucleatum* is known to be able to invade colonic epithelial cells (6,7). What is the connection between cellular invasion and carcinogenesis? Second, *F. nucleatum* abundance is associated with higher levels of expression of inflammatory genes, including many interleukin genes, such as *IL1B* and *IL6* (8). Could the induction of inflammation-associated transcripts be a factor by which *F. nucleatum* promotes colorectal carcinogenesis?

Casasanta *et al*. (3) tackle these questions. Until recently, there was no systematic method to perform targeted gene deletions in *Fusobacterium.* Based on a recently reported method for gene deletion in *Fusobacterium* (9), the authors further developed an elegant way to generate gene deletions and replacements in *F. nucleatum* genomes. In brief, wild-type fusobacteria cannot grow in the presence of 2-deoxy-D-galactose. Deletion of the *galKT* operon means that the bacteria cannot generate 2-deoxy-galactose-1-phosphate, the toxic metabolic

*Corresponding author. matthew_meyerson@dfci.harvard.edu.

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product, so the fusobacteria now survive on medium containing 2-deoxy-galactose. Finally, the use of a plasmid targeting a specific locus by homologous recombination, positive selection for thiamphenicol resistance to get initial selection, and finally negative selection or a *galK* gene that has been introduced on deoxygalactose, leads to markerless deletion of the targeted gene.

Casasanta *et al*. used their method to evaluate which bacterial genes were required for the bacteria to invade CRC cells. The results revealed that the *fap2* gene is required for *F. nucleatum* to invade HCT116 CRC cells in culture (3). Given that *fap2* reportedly modulates the immune response to colorectal cancers (10), the authors went on to ask whether *F. nucleatum* could induce cytokine secretion. They demonstrated that not only does *F. nucleatum* induce the secretion of IL-8 and CXCL1 from CRC cells, but they also showed that this secretion is dependent on a functional *fap2* gene (3). They further showed that *F. nucleatum* induces the migration of HCT116 cells in a manner that is dependent on the secretion of IL-8 and CXCL1 (Figure 1), and that depletion of these proteins reduces migration. Thus, the findings that Casasanta *et al*. indicate that the presence of *F. nucleatum* in colorectal tumors might induce metastatic progression of the cancer in patients by promoting gut inflammation (3). If this concept holds, this could prove an important mechanism by which the microbiome leads to causation of intestinal cancers.

As the role of the microbiome in human cancer is increasingly understood, the methods and findings of the Casasanta study provide a rigorous and effective way to assess and dissect many of the claims that are now being made in the literature. Through their rigorous analysis, the authors confirmed some previous hypotheses in the literature and have refined our understanding of others. Similar studies will be needed to further explore and refine these findings in CRC and the broader context of the cancer-associated microbiome.

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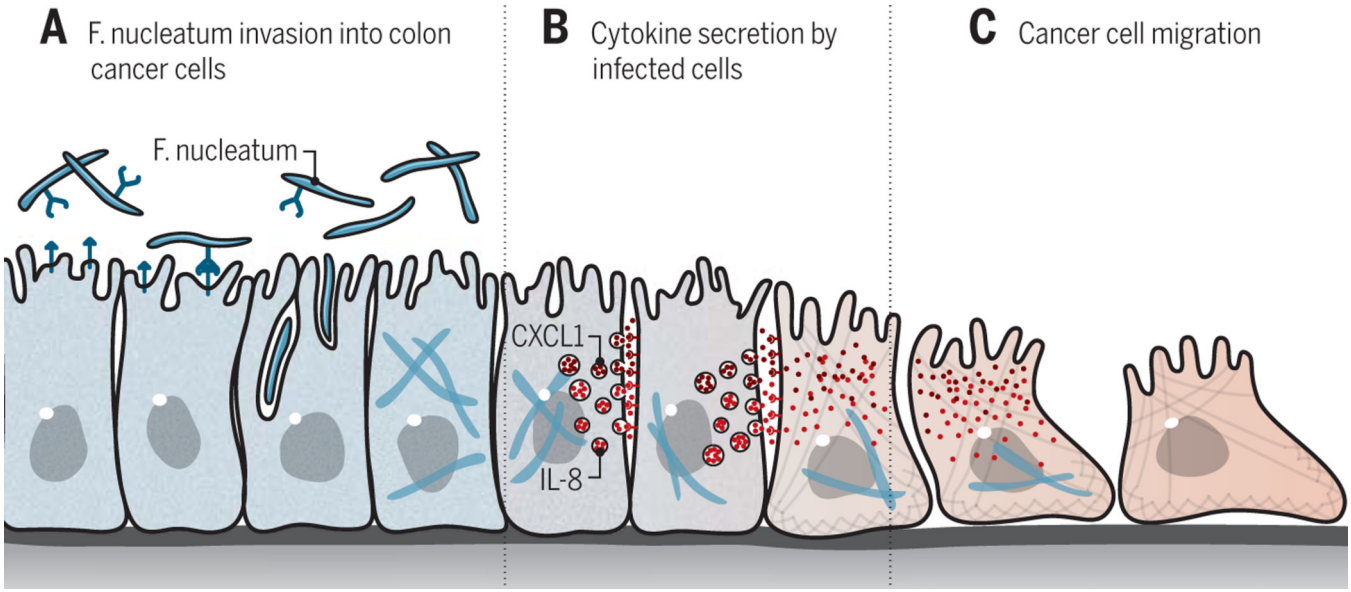

Figure 1: A model in which *Fusobacterium nucleatum* invasion into colorectal cancer cells induces cytokine secretion and invasion.

(A to C) A conceptual model of the findings of Casasanta *et al.* using a cultured CRC cell line, not actual CRC tissues. (A) *F. nucleatum* can invade CRC cells in a manner dependent on the bacterial adhesin protein FAP2. (B) Invasion of *F. nucleatum* induces secretion of IL-8 and CXCL1 by the host cell. (C) These cytokines, in turn, promote migration in both infected and uninfected cancer cells.