Towards the human colorectal cancer microbiome

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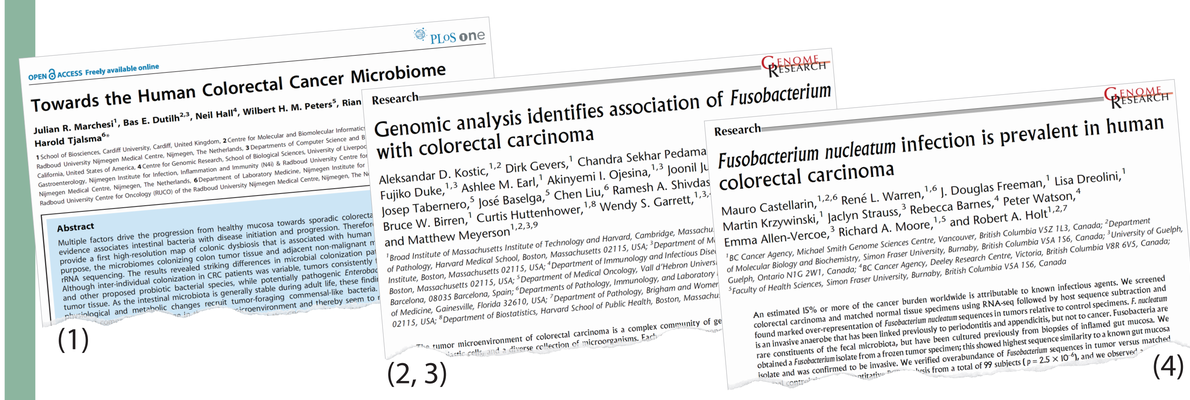
Introduction

Human colorectal cancer (CRC) is the 4th most commonly diagnosed cancer in the world. It is initiated by **driver mutations** in the stem cells at the base of the villus crypt. During the progression from adenoma to carcinoma, these cells become immortal and accumulate additional **passenger mutations** (Fearon 2011, Vogelstein & Kinzler 1993). The triggers for these mutations remain elusive.

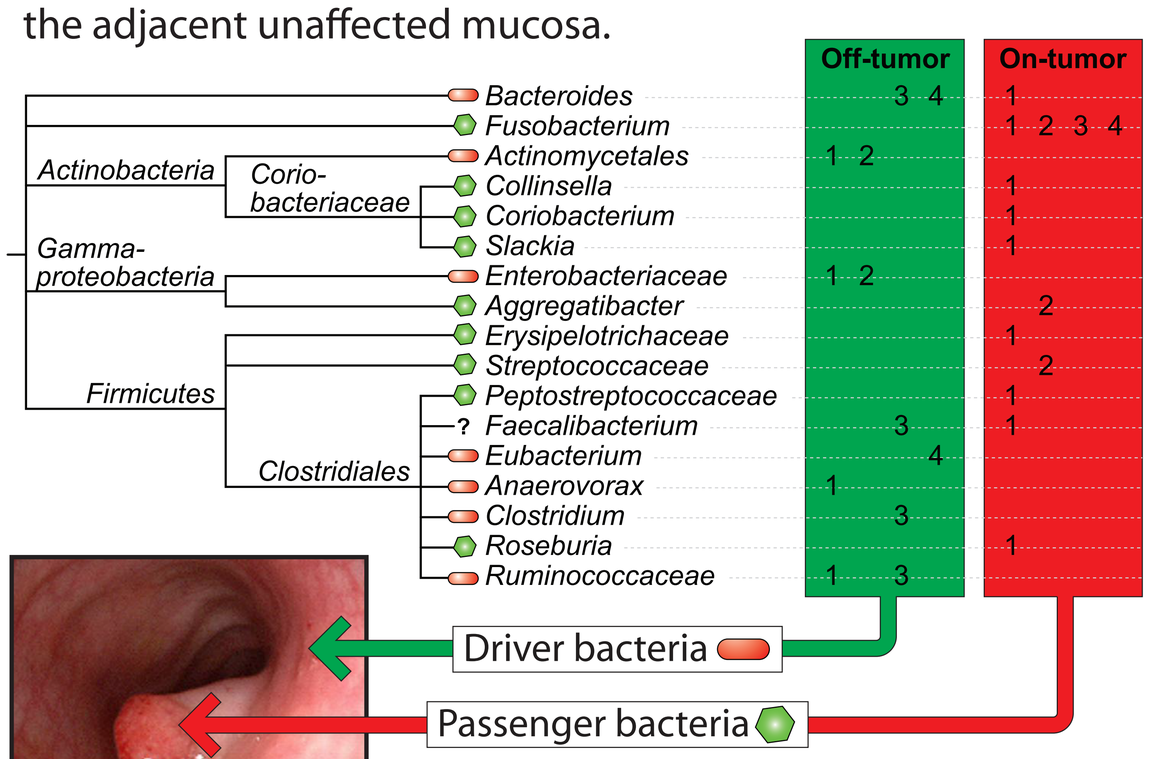
In 2011, four large-scale data sets were published that describe the microbiota associated with CRC tumors.



(1) (2, 3) (4)

The CRC Microbiome

Studies (1) through (4) show that certain bacterial taxa specifically inhabit the tumor niche, while others are enriched in the adjacent unaffected mucosa.



CRC tumor inside the colon.

(1) 16S rRNA amplicons, 6 Dutch patients (Marchesi *et al.* 2011)
(2) Metagenome, 9 Spanish, American and Vietnamese patients (Kostic *et al.* 2011)
(3) 16S rRNA amplicons, 95 Spanish, American and Vietnamese patients (Kostic *et al.* 2011)
(4) Metatranscriptome, 9 American patients (Castellarin *et al.* 2011)

Bacterial Drivers of CRC

Bacterial drivers of CRC are gut bacteria with pro-carcinogenic features that may contribute to CRC development.

Driver bacteria may be outcompeted by passenger bacteria as the tumor progresses from an adenoma to a carcinoma.

Enterococcus faecalis	Extracellular superoxide	May cause DNA damage when converted to hydrogen peroxide
Escherichia coli	Colibactin	Induces DNA single strand breaks; encoded on the polyketide synthetase (pks) island in certain strains
Bacteroides fragilis (ETBF)	BFT (a metalloprotease; a.k.a. fragilysin)	Stimulates cleavage of E-cadherin (tumor suppressor)
Enterobacteriales (*Shigella*, *Citrobacter*, *Salmonella*)	Genotoxins	Prolonged inflammatory response; antibody titers against *Salmonella* are increased in early CRC patients

Bacterial Passengers of CRC

Bacterial passengers of CRC are relatively poor colonizers of a healthy intestinal tract, but gain a competitive advantage when the growing CRC tumor changes the local microenvironment (Tjalsma *et al.* 2012).

Passenger bacteria may either promote (opportunistic pathogens) or inhibit (preserve niche) tumor growth.

Fusobacterium	Production of butyrate (fuel for colon cells), pro-inflammatory (implicated in inflammatory bowel disease), stimulates metastasis, hitchhikes with metastasising cells throughout the body
Streptococcus gallolyticus subsp. *gallolyticus*	Cause of endocarditis, strong biomarker for adenomas or CRC (albeit rare), may escape immune system in blood stream, incidence associated with livestock
Clostridium septicum	Cause of bacteraemia associated with colorectal malignancies
Coriobacteriaceae (*Slackia*, *Colinsella*)	Probiotic bacteria, production of equol (strong antioxidant), butyrate (preferred fuel for colonic cells), these catabolites also have anti-carcinogenic properties

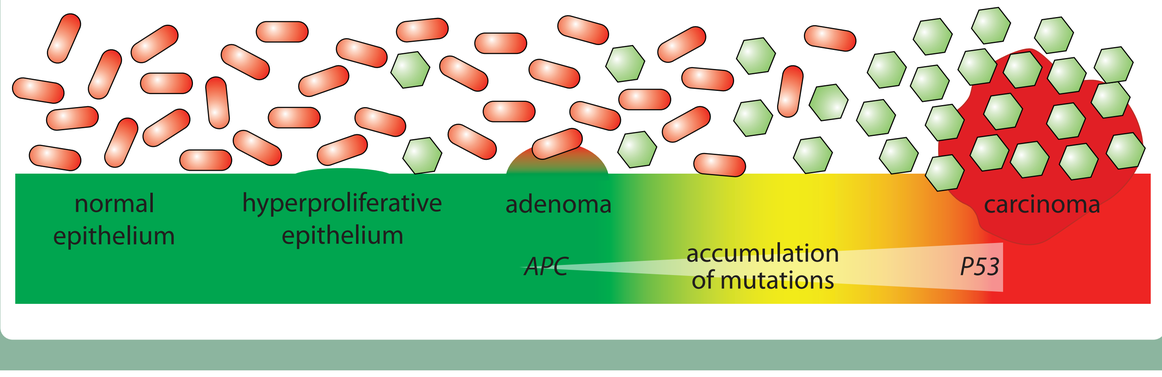
Conclusions

We propose that species found in the off-tumor samples are the typical colon microbiota for CRC patients. The identified species may act as **driver bacteria** for CRC. Screening for these species can identify patients with a high risk for developing CRC. They may be selectively targeted to prevent CRC.

Growth of the tumor alters the niche (loss of colonic barrier function, bleeding). This attracts **passenger bacteria** with a competitive advantage in the changed microenvironment.

Driver bacteria
Enterotoxigenic *Bacteroides fragilis* (ETBF) (Sears & Pardoll, 2011)
Enterobacteria
toxin-producing bacteria, pathogens

Passenger bacteria
Fusobacterium
Streptococcus
Coriobacteria
Tumor-foraging commensals
Opportunistic pathogens



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