



# Colorectal cancer associated pathogenic bacteria and potentially beneficial bacteria

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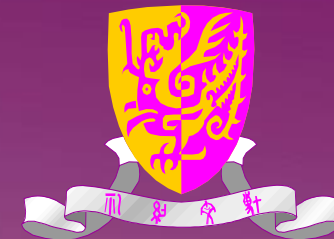
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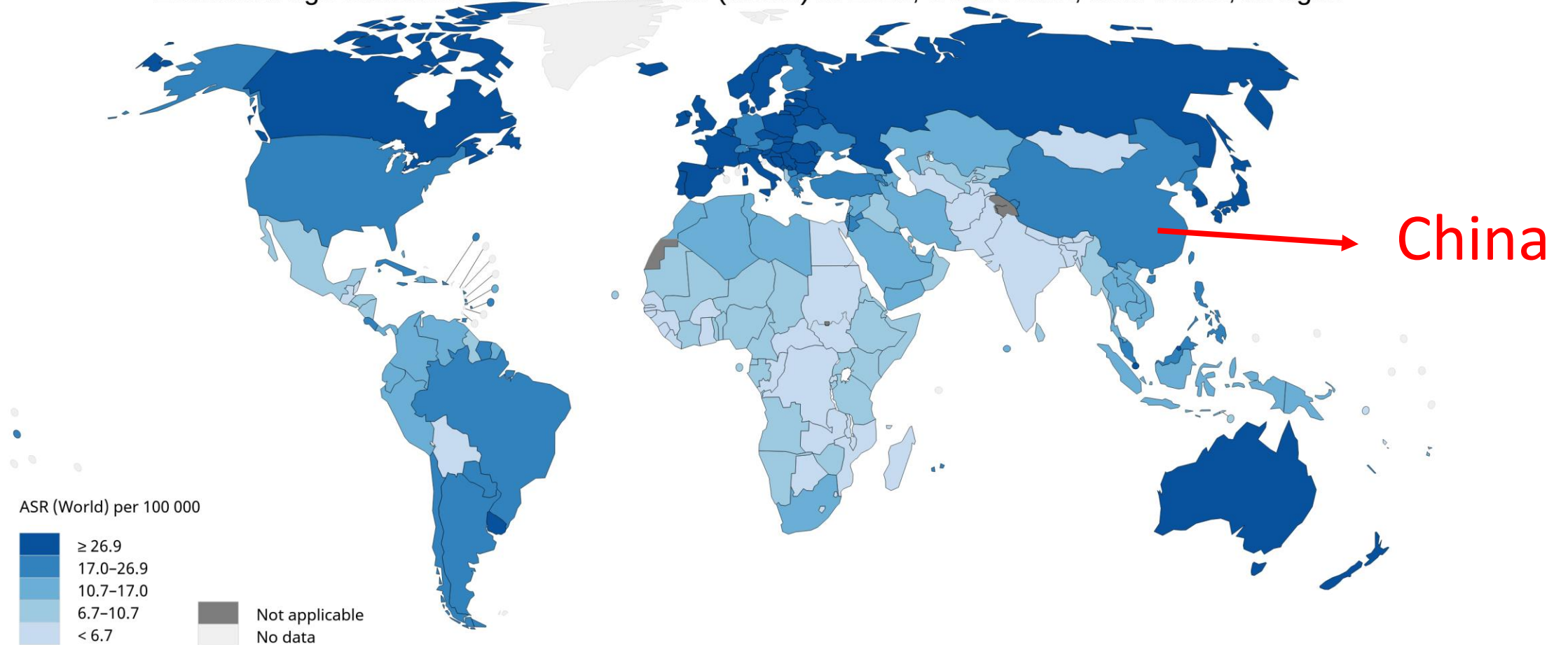
**Faculty of Medicine**

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# Background

Estimated age-standardized incidence rates (World) in 2020, Colorectum, both sexes, all ages



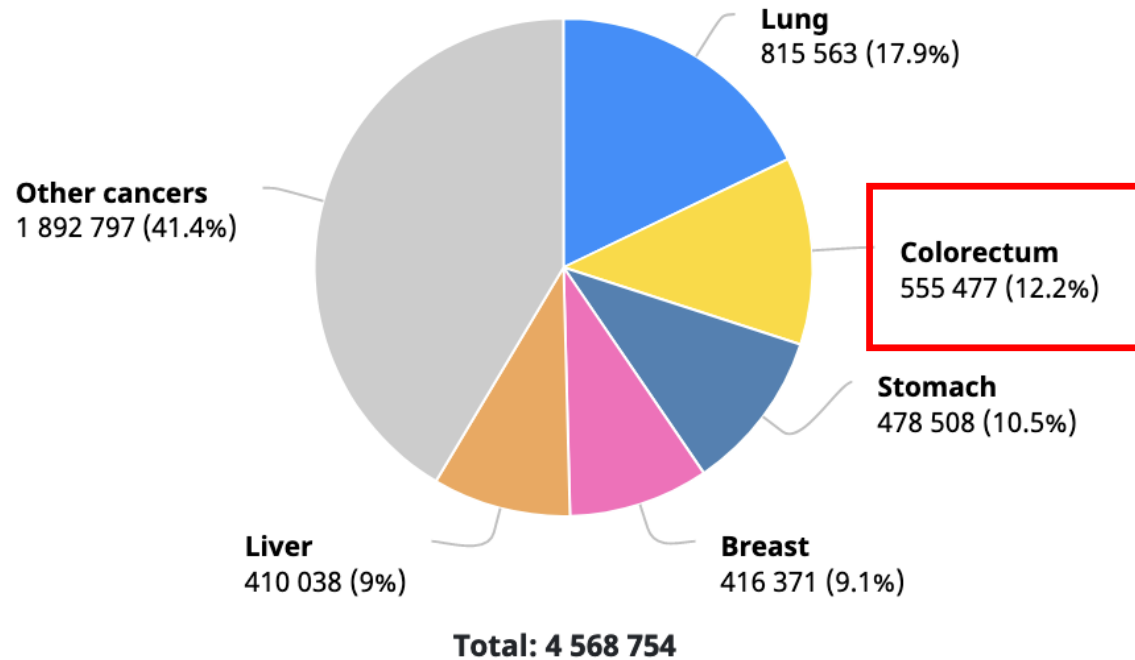
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Data source: GLOBOCAN 2020  
Graph production: IARC  
(<http://gco.iarc.fr/today>)  
World Health Organization

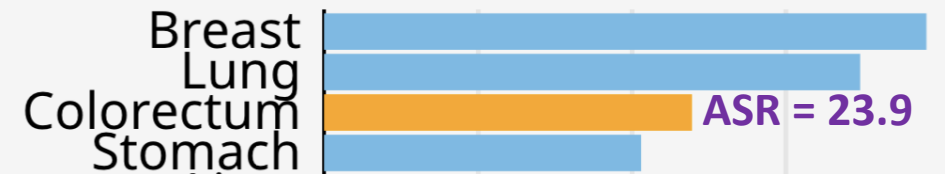
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<https://gco.iarc.fr/>

# Background



ASR (World) per 100 000, both sexes, all ages



ASR: Age-standardised Rate

# BACKGROUND

- Important roles of gut microbiota in the initiation and development of colorectal cancer (CRC).
- *Fusobacterium nucleatum* (*F. nucleatum*) promotes CRC development
  - ➔ Tumor initiation, development, metastasis, recurrence, chemotherapy resistance, immune response
- Some gut bacteria decreased in CRC, such as *Streptococcus thermophilus* (*S. thermophilus*), *Faecalibacterium prausnitzii* (*F. prausnitzii*), *Eubacterium rectale* (*E. rectale*)
  - ➔ Anti-pathogenic bacteria effects, anti-inflammatory function
- Many studies demonstrated gut bacteria's value in diagnosing CRC as a novel biomarker.

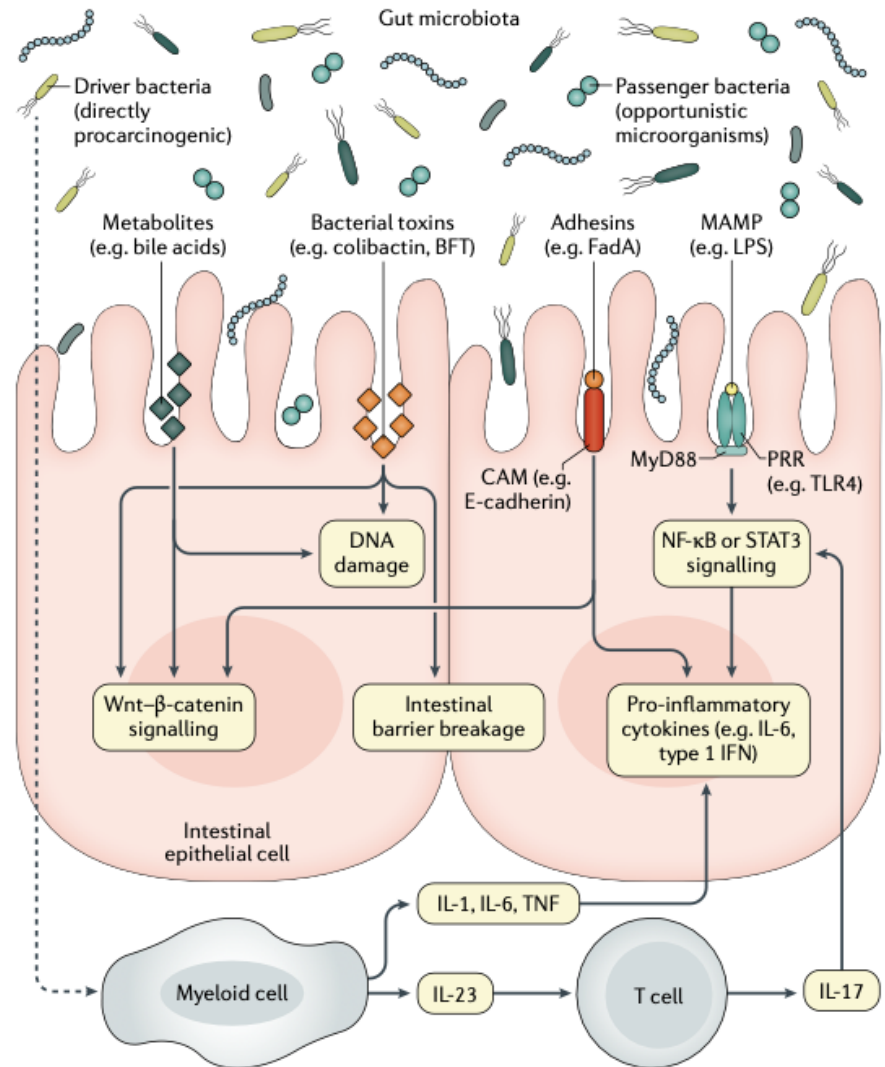
# CRC associated pathogenic and beneficial bacteria

Pathogenic bacteria	Beneficial bacteria
<i>Fusobacterium nucleatum</i>	<i>Streptococcus thermophilus</i>
<i>pks<sup>+</sup> Escherichia coli</i>	<i>Lactobacillus</i>
<i>Enterotoxigenic Bacteroides fragilis</i>	<i>Bifidobacterium</i>
<i>Peptostreptococcus stomatis</i>	<i>Eubacterium rectale</i>
<i>Peptostreptococcus anaerobius</i>	<i>Faecalibacterium prausnitzii</i>

# CRC associated pathogenic bacteria

- *Escherichia coli* (*E. coli*): strains with polyketide synthase island (*pks*<sup>+</sup>)
- *Fusobacterium nucleatum* (*F. nucleatum*)

# Microbiota-associated mechanisms involved in the pathogenesis of colorectal cancer



PRR, pattern recognition receptor  
BFT, *Bacteroides fragilis* toxin  
TLR4, Toll-like receptor 4

STAT3, signal transducer and activator  
of transcription 3  
LPS, lipopolysaccharide

NF-κB, nuclear factor-κB  
FadA, *Fusobacterium* adhesin A  
MAMP, microbe-associated molecular pattern

CAM, cell adhesion molecule  
IFN, interferon

## Epidemiology association of *pks*<sup>+</sup> *E. coli* with CRC

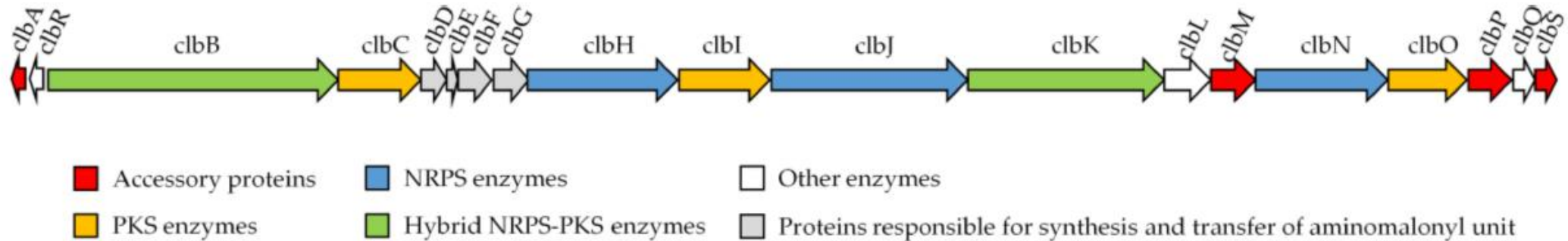
Study	Results	Note
Janelle C. Arthur et al.	<i>pks</i> island was 14 of 21 (66.7%) CRC patients <b>vs.</b> 5 of the 24 (20.8%) non-CRC controls harbored <i>pks</i> <sup>+</sup> <i>E. coli</i>	mucosa-associated
Christine M. Dejea et al.	17 of 25 (68%) familial adenomatous polyposis (FAP) <b>vs.</b> 5 of the 22 (20.8%) controls harbored <i>pks</i> <sup>+</sup> <i>E. coli</i>	mucosa-associated
Vincy et al.	22 of 39 (56.4%) colon cancer has <i>clbA</i> <sup>+</sup> <i>pks</i> island	stool-associated

- *E. coli* with *psk* island has a higher prevalence in CRC patients than control groups
- *pks*<sup>+</sup> *E. coli* may act as marker to help diagnose CRC



# Mechanisms of *pks* island in CRC initiation/development

## Organization of the *pks* island



- *pks* island is responsible for some virulent factors synthesis, including cyclomudlins
- Cyclomudlins include cytolethal distending toxin (CDT), cycle inhibiting factor (Cif), cytotoxic necrotizing factor (CNF), **colibactin**
- Colibactin-producing *E. coli* induce chromosomal instability and DNA damage in eukaryotic cells, which leads to senescence of epithelial cells and apoptosis of immune cells

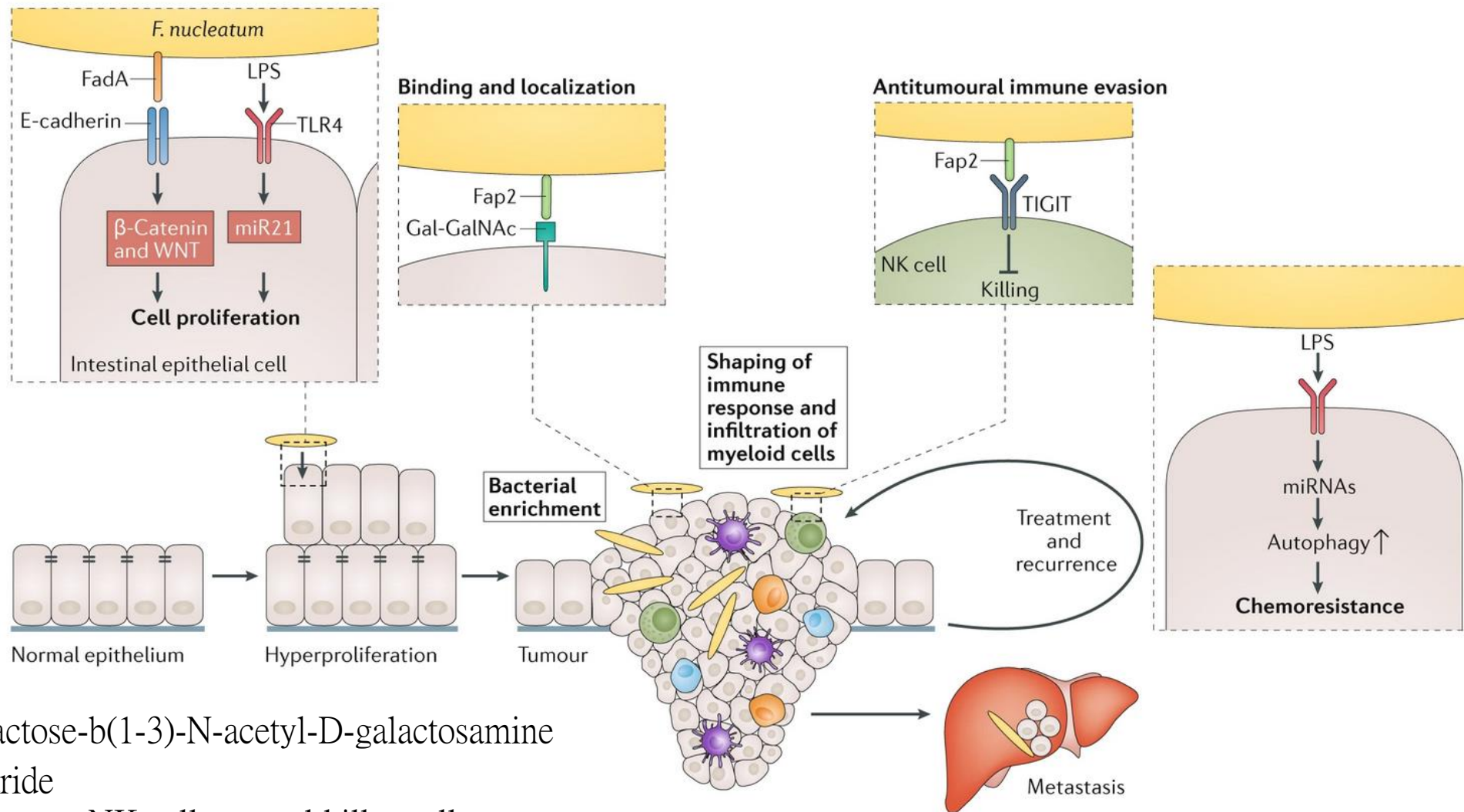
NRPSs: nonribosomal peptide synthetases

PKSs: polyketide synthases

# Epidemiology association of *F. nucleatum* with CRC

Study	Results	Study platform
Mauro castellarin et al.	overabundance of <i>Fusobacterium</i> sequences was verified in tumor versus normal control tissue by RNA sequencing, high-abundance <i>Fusobacterium</i> in tumor were more likely to have regional lymph node metastases	qPCR
Aleksandar et al.	<i>Fusobacterium</i> was enriched in colorectal tumors through whole genome sequencing analysis	whole genome sequencing
Liang et al.	Panel of four bacterial markers ( <i>F. nucleatum</i> , <i>Clostridium hathewayi</i> , <i>Bacteroides clarus</i> and an undefined species m7), AUC 0.89	qPCR

# *F. nucleatum's* role in tumor initiation or development



Gal-GalNAc: D-galactose-b(1-3)-N-acetyl-D-galactosamine

LPS, lipopolysaccharide

TLR4: toll-like receptor NK cell: natural killer cell

TIGIT: T-cell immunoreceptor with immunoglobulin and ITIM domains

ITIM: immunoreceptor tyrosine-based inhibition motif

# CRC associated potentially beneficial bacteria

- *Streptococcus thermophilus*
- *Eubacterium rectale*
- *Faecalibacterium prausnitzii*

# Characteristics of beneficial bacteria

	<i>S. thermophilus</i>	<i>E. rectale</i>	<i>F. prausnitzii</i>
Gram stain	positive	positive	positive
Oxygen sensitive	facultative anaerobe	Obligately anaerobic	Obligately anaerobic
Product	Lactic acid	Short chain fatty acids	Short chain fatty acids
Abundance in CRC	↓	↓	↓

# *Streptococcus thermophilus*

- It is generally used in yogurt production and can be found in fermented milk products;
- protect the gastrointestinal epithelium from enteroinvasive *E. coli*
- diminish the severity of methotrexate-induced small-intestinal mucositis in rats (2)
- Inhibits Colorectal tumorigenesis through secreting beta-galactosidase (1)

(1) <https://pubmed.ncbi.nlm.nih.gov/32920015/>

(2) <https://pubmed.ncbi.nlm.nih.gov/16627985/>

# Prevalence of *E. rectale* and *F. prausnitzii*

## My data:

- used qPCR to detect *E. ractale* and *F. prausnitzii* signal from 22 randomly selected fresh stool samples (the donors do not have gut diseases)
- 6/22 were *E. retale* positive
- 18/22 were *F. prausnitzii* positive

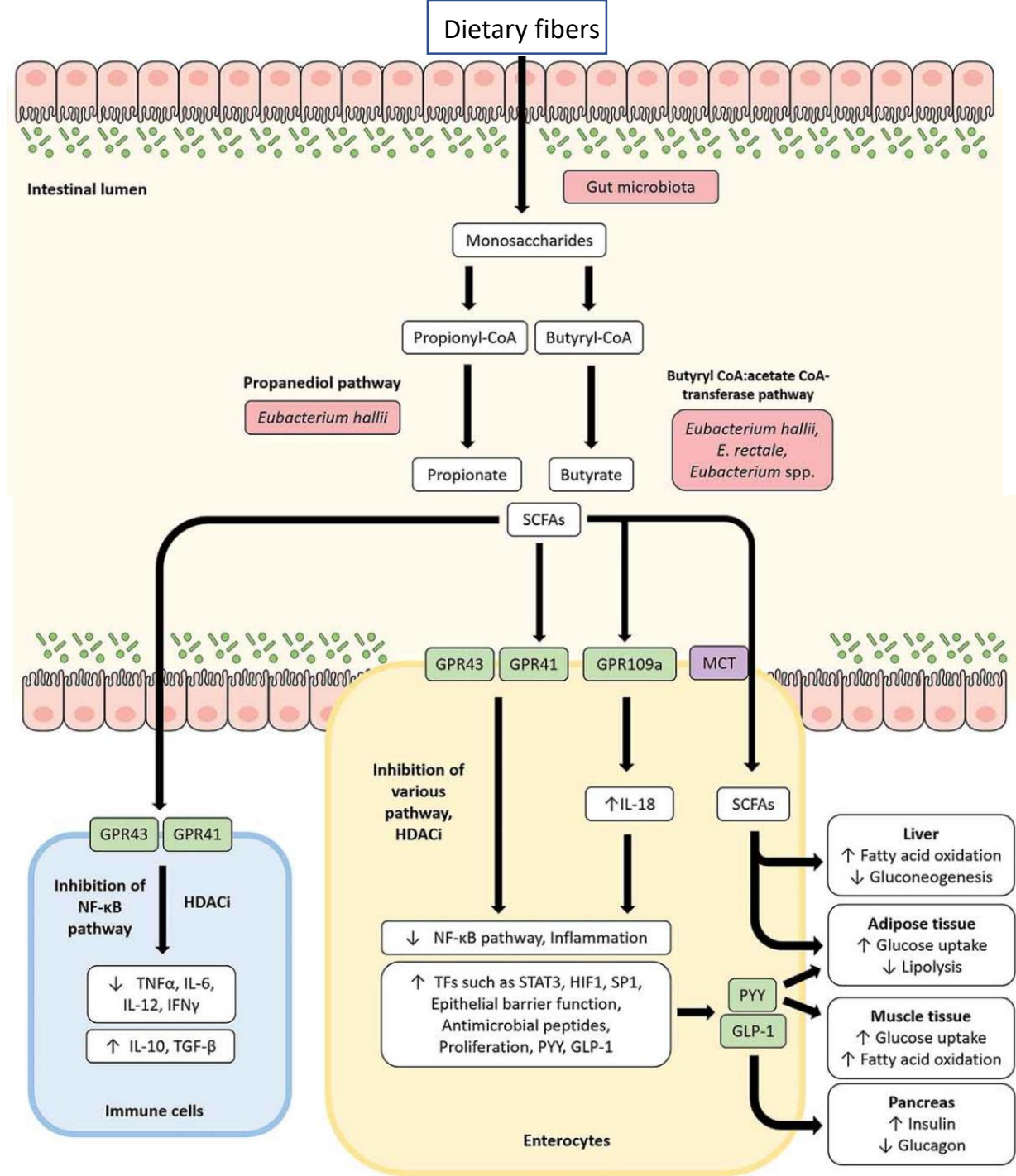
## Epidemiology association of *F. prausnitzii* with gut diseases

Disease	Phylogroup I	Phylogroup II	Total <i>F. prausnitzii</i>	Reference
Ulcerative colitis	-	-	↓	(4)
	-	-	↓	(1)
Crohn's disease	-	-	↓	(2)
	↓	↓	↓	(3)
Colorectal cancer	↓	↓	↓	(3)
	↓	No change	↓	(2)

(1) <https://pubmed.ncbi.nlm.nih.gov/24021287/> (2) <https://pubmed.ncbi.nlm.nih.gov/26595550/>

(3) <https://pubmed.ncbi.nlm.nih.gov/30245977/> (4) <https://pubmed.ncbi.nlm.nih.gov/23725320/>





PYY: peptide YY

SCFAs: short-chain fatty acids

GLP-1: glucagon-like peptide-1

MCT: monocarboxylate transporter

HDACi: histone deacetylase function

GPRs: G-protein-coupled receptors

<https://pubmed.ncbi.nlm.nih.gov/32835590/>

# Promising research direction: my opinion

- As biomarkers to help diagnose CRC at early stage with combination of pathogenic bacteria and potentially beneficial bacteria;
- Potentially beneficial bacteria can be used in clinic to protect our gut health like *lactobacillus* and *bifidobacterium*;
- Therapy targets in cancer treatment.

**Thank you for listening**