The Gut Virome: A Neglected Factor in Colorectal Cancer

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Outline

A) Brief on human virome and cancer risk factors

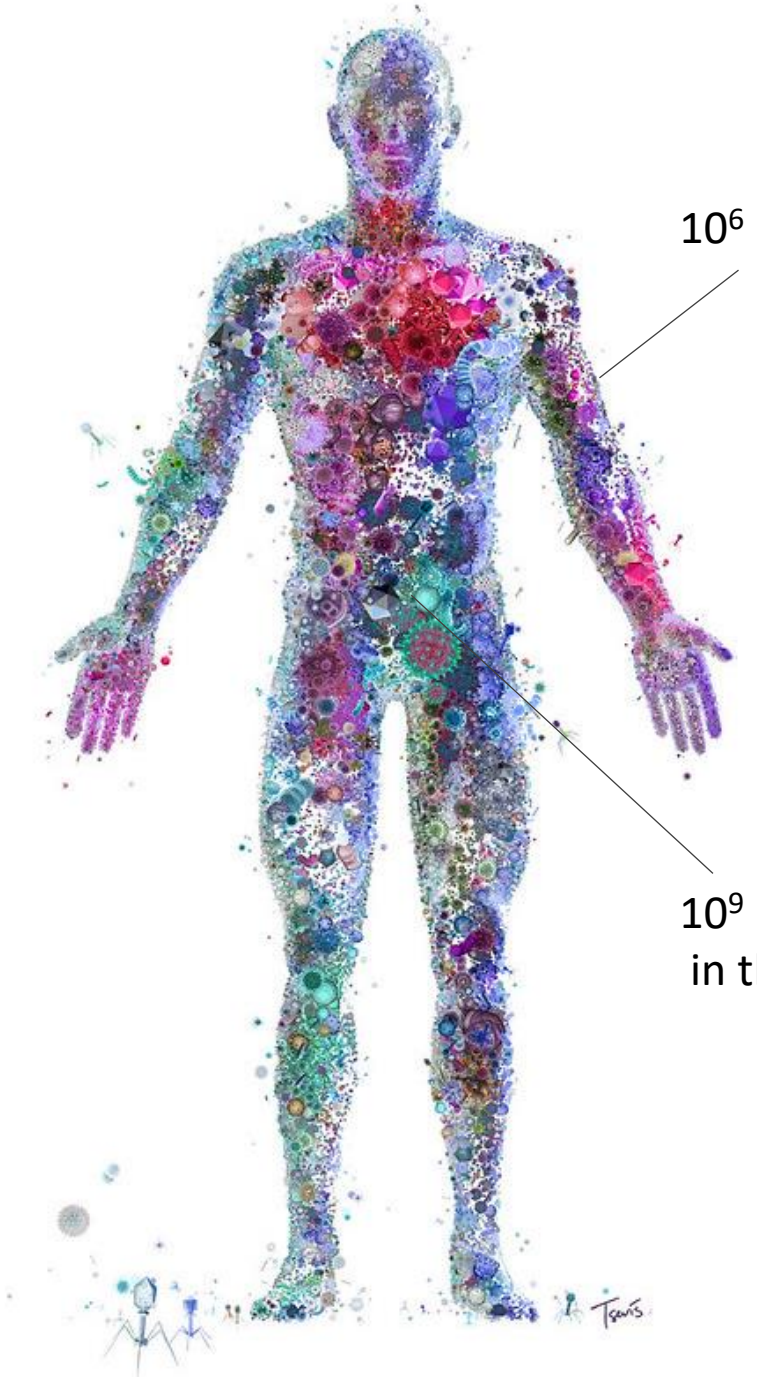
- Human Virome
- Virome-related diseases
- Cancer risk factors
- Mechanism of virome carcinogenesis

B) Gut virome and colorectal cancer (CRC)

- Microbiota in CRC
- Gut virome composition
- Gut virome in CRC

Brief on human virome and cancer

Gut virome and colorectal cancer (CRC)



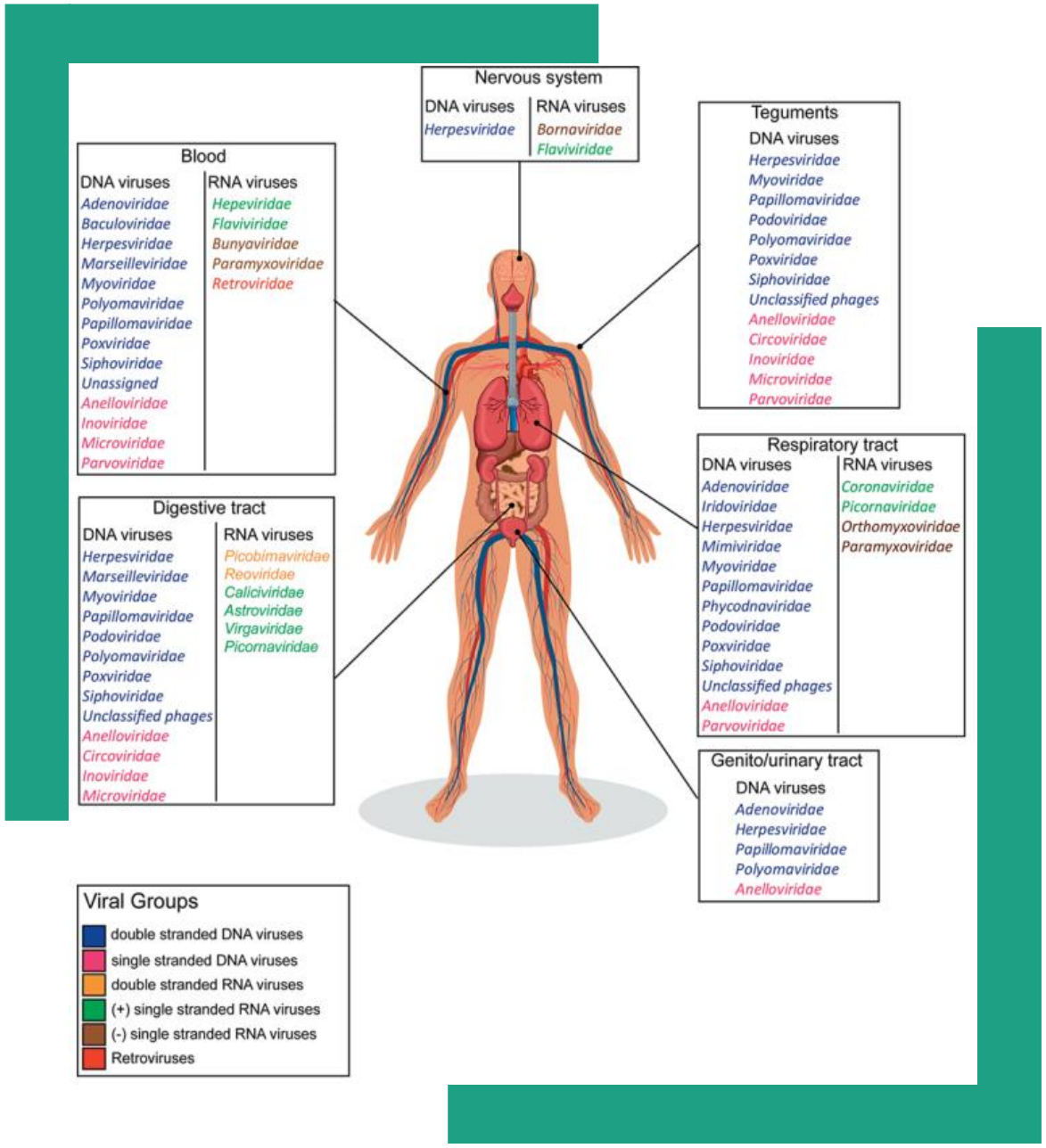
10^6 per cm^2 in the skin

10^9 particles per gram
in the intestinal content

Human cells ≈ 10^{13}

Bacterial cells ≈ 10^{14}

Viral particles ≈ 10^{15}

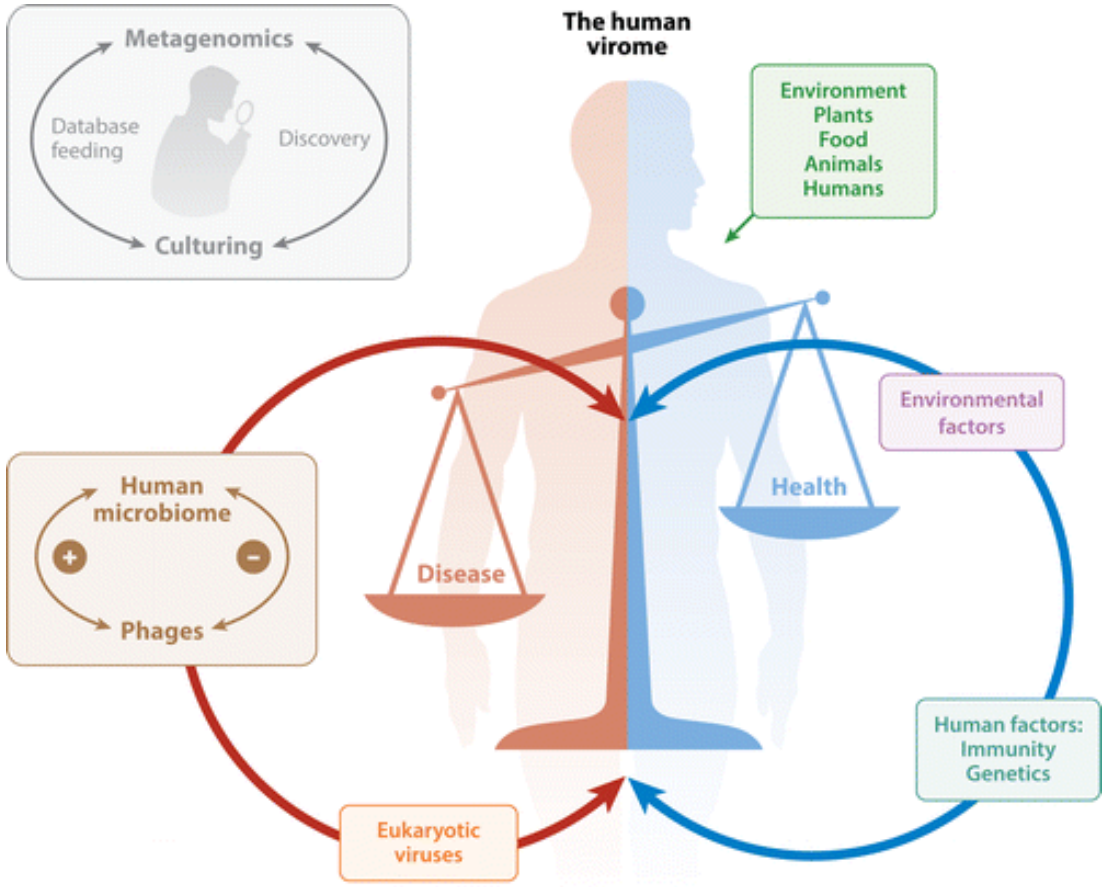


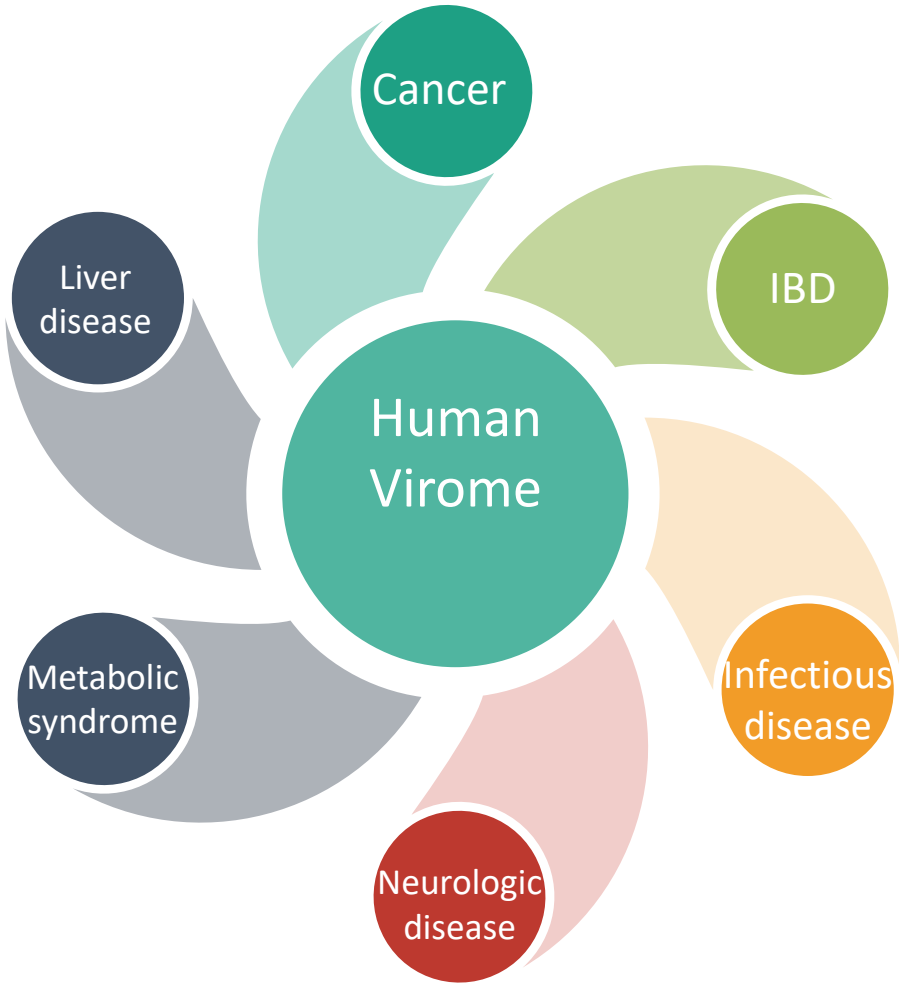
What is human virome?

- the repertoire of all viruses on the surface and inside our body
- Infect both human cells and microbes
- Some can cause disease, while others are asymptomatic
- Different composition due to anatomical sites

Popgeorgiev N, et al. 2013

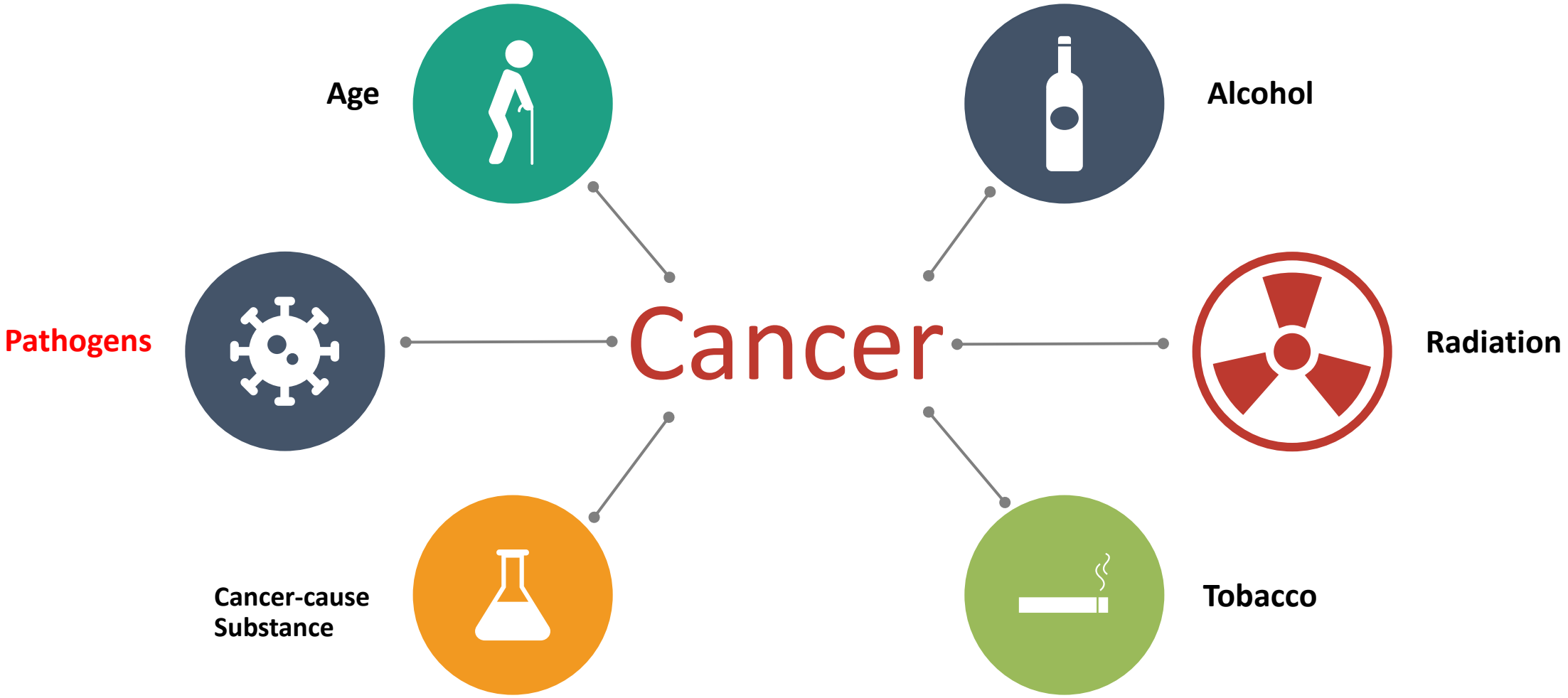
Human virome-related diseases



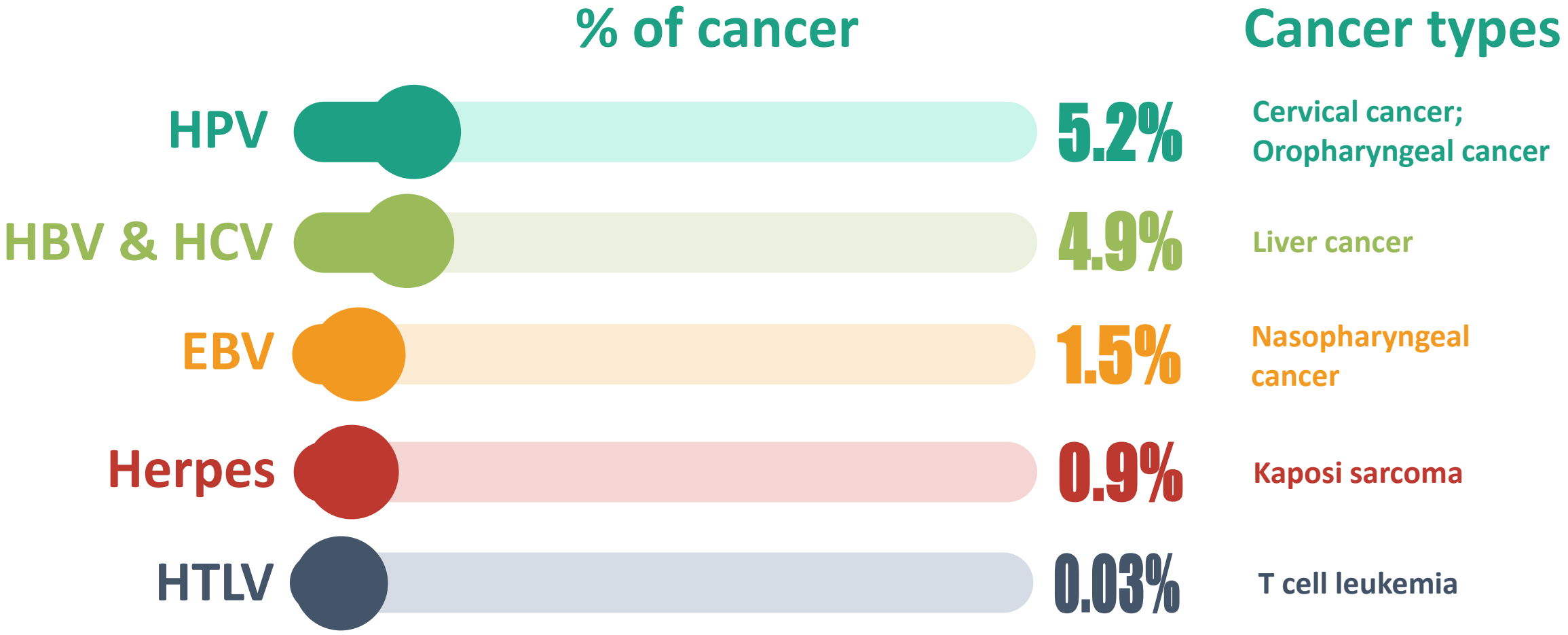


Rascovan N, et al. 2016

Cancer risk factors

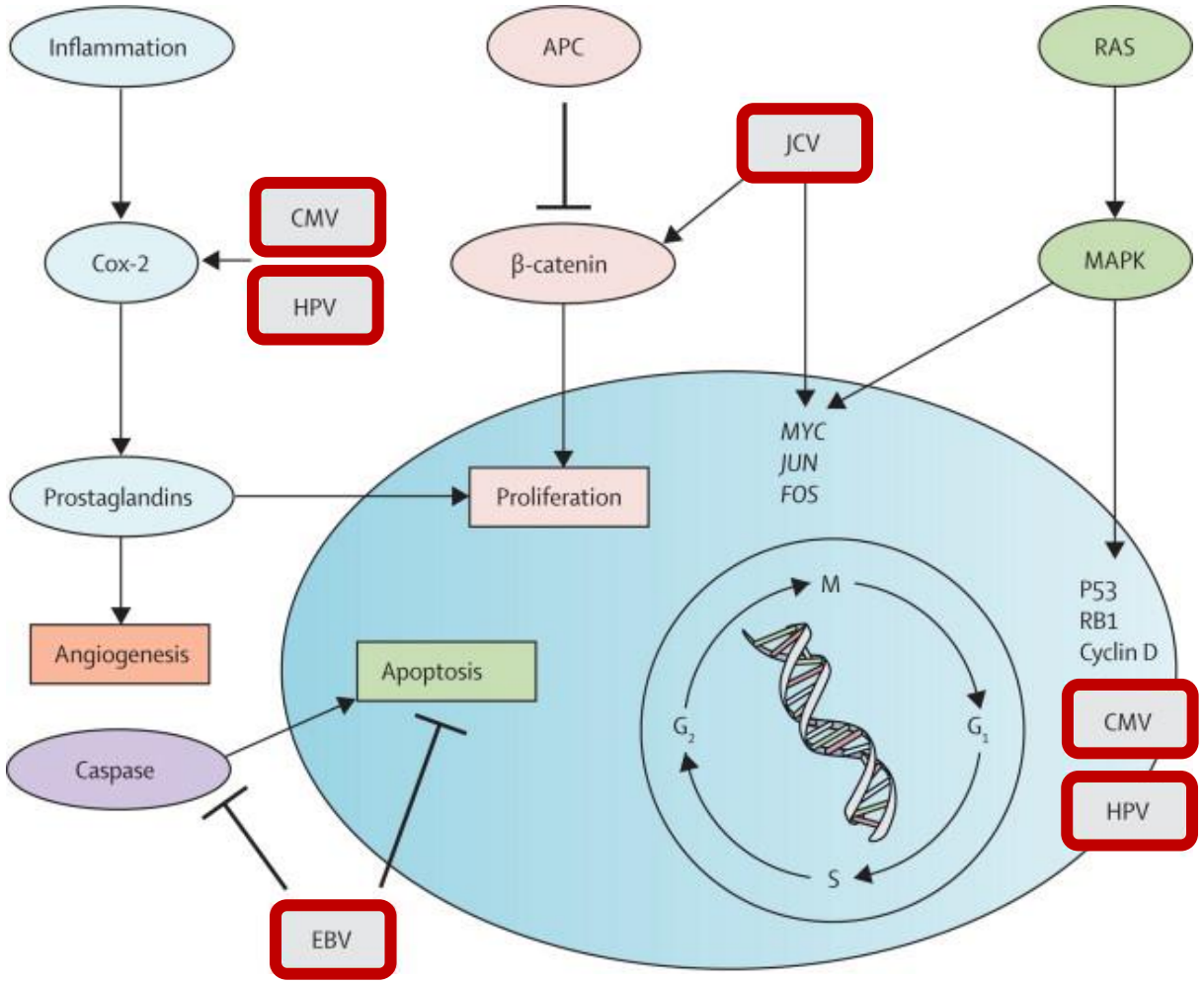


Oncoviruses



Ong H K, et al. 2017

Mechanism of viral carcinogenesis

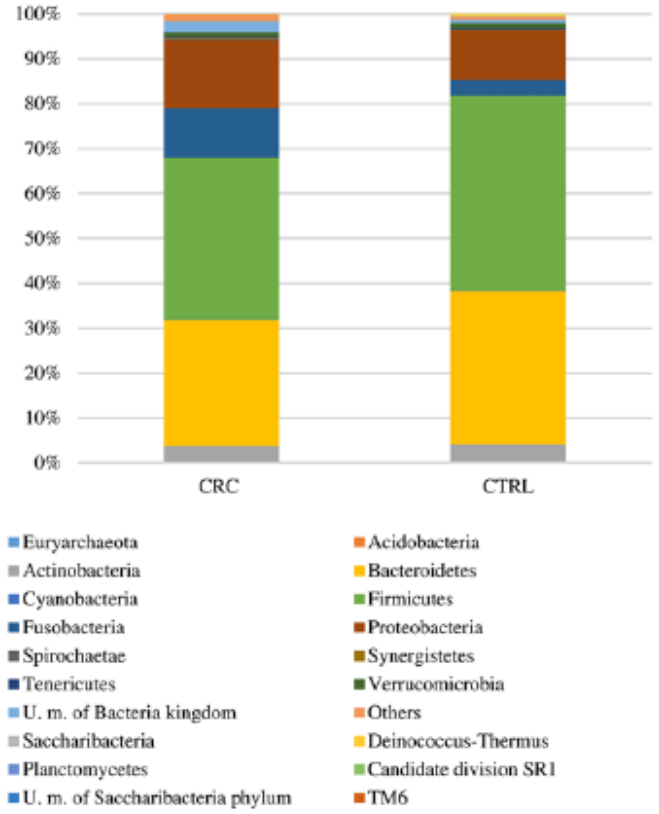


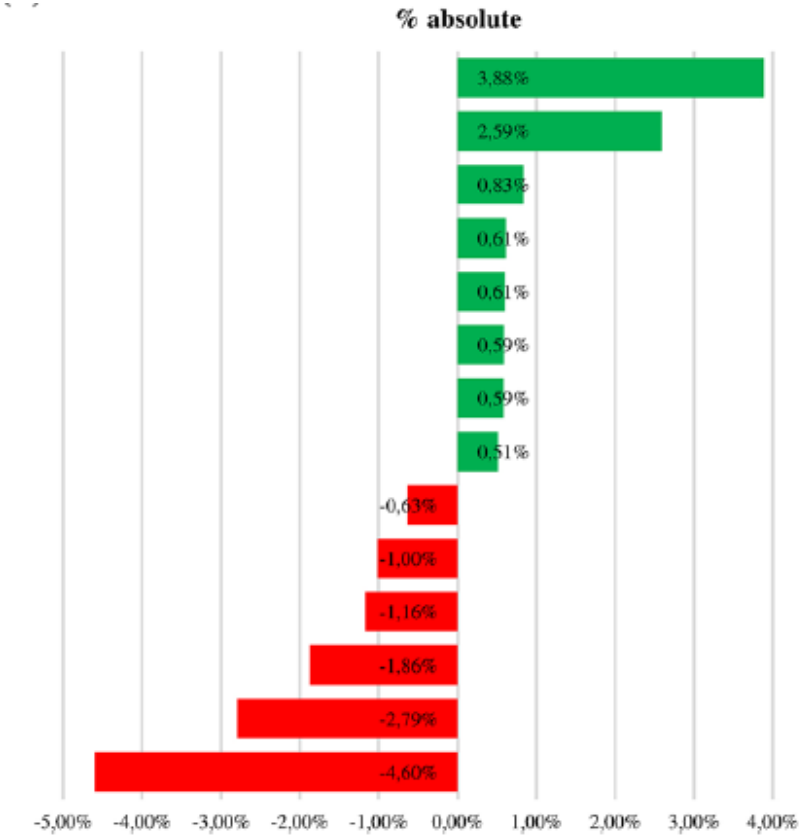
- Cell proliferation
- Apoptosis
- Cell cycle
- DNA damage

Collins D, et al. 2011

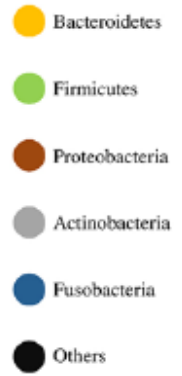
Brief on human virome and cancer

Gut virome and colorectal cancer (CRC)





Taxonomy	CRC	CTRL	p-value
Bacteroides	16.04%	19.93%	0.00
Faecalibacterium	3.33%	5.92%	0.00
Lachnoclostridium	2.41%	3.24%	0.04
Alistipes	1.19%	1.80%	0.01
U. m. of *Lachnospiraceae* family	1.49%	2.09%	0.03
Parabacteroides	1.05%	1.65%	0.00
Subdoligranulum	0.70%	1.29%	0.00
Sutterella	0.37%	0.88%	0.00
Others	1.41%	0.78%	0.05
Streptococcus	2.49%	1.49%	0.05
Leptotrichia	1.28%	0.11%	0.00
U. m. of Bacteria kingdom	2.48%	0.62%	0.00
U. m. of *Proteobacteria* phylum	6.18%	3.39%	0.02
Fusobacterium	6.73%	2.13%	0.00



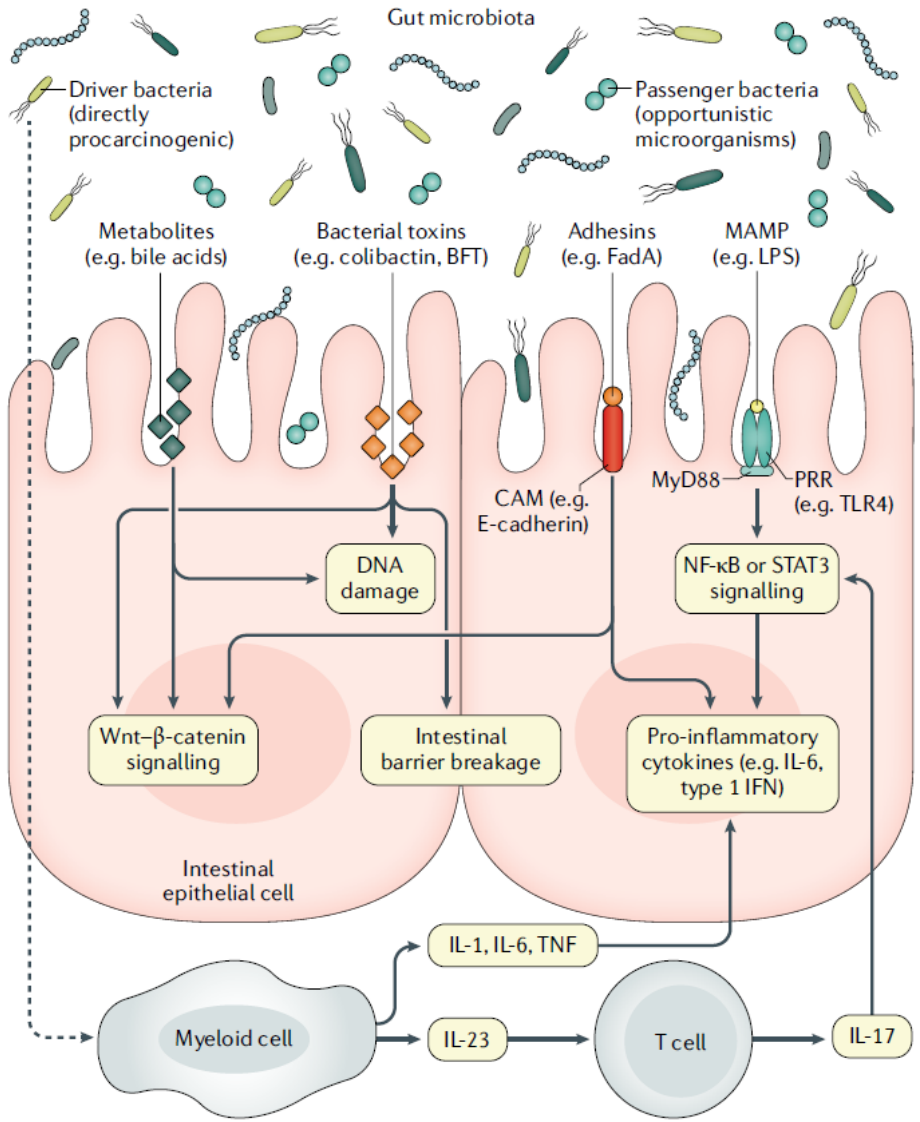
Microbiota in CRC

- The abundance of microbes in CRC tissue is different from normal tissue.
- Compared to health tissue, *Fusobacterium* is more abundant while *Bacteroides* is less abundant in CRC tissue.
- *Fusobacterium* is the key phylotype that contribute to the dysbiosis in CRC patients.

Mancabelli L, et al. 2017

Microbiota-related mechanisms in CRC carcinogenesis

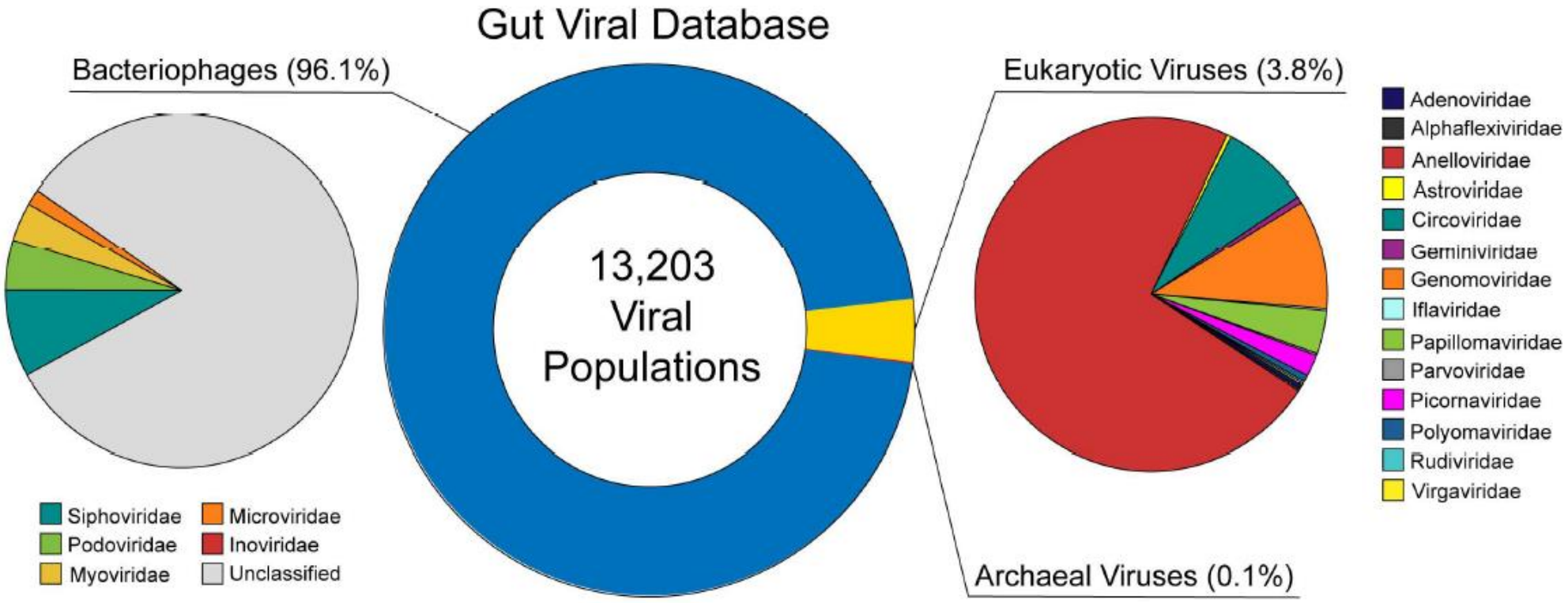
- By metabolites or genotoxins
- Procarcinogenic bacteria and opportunistic bacteria
- Activate carcinogenic signaling pathways
- Molecular changes lead to CRC progression



Wong S H, et al. 2019

Known bacteria in CRC

Unknown bacteria and virus in CRC



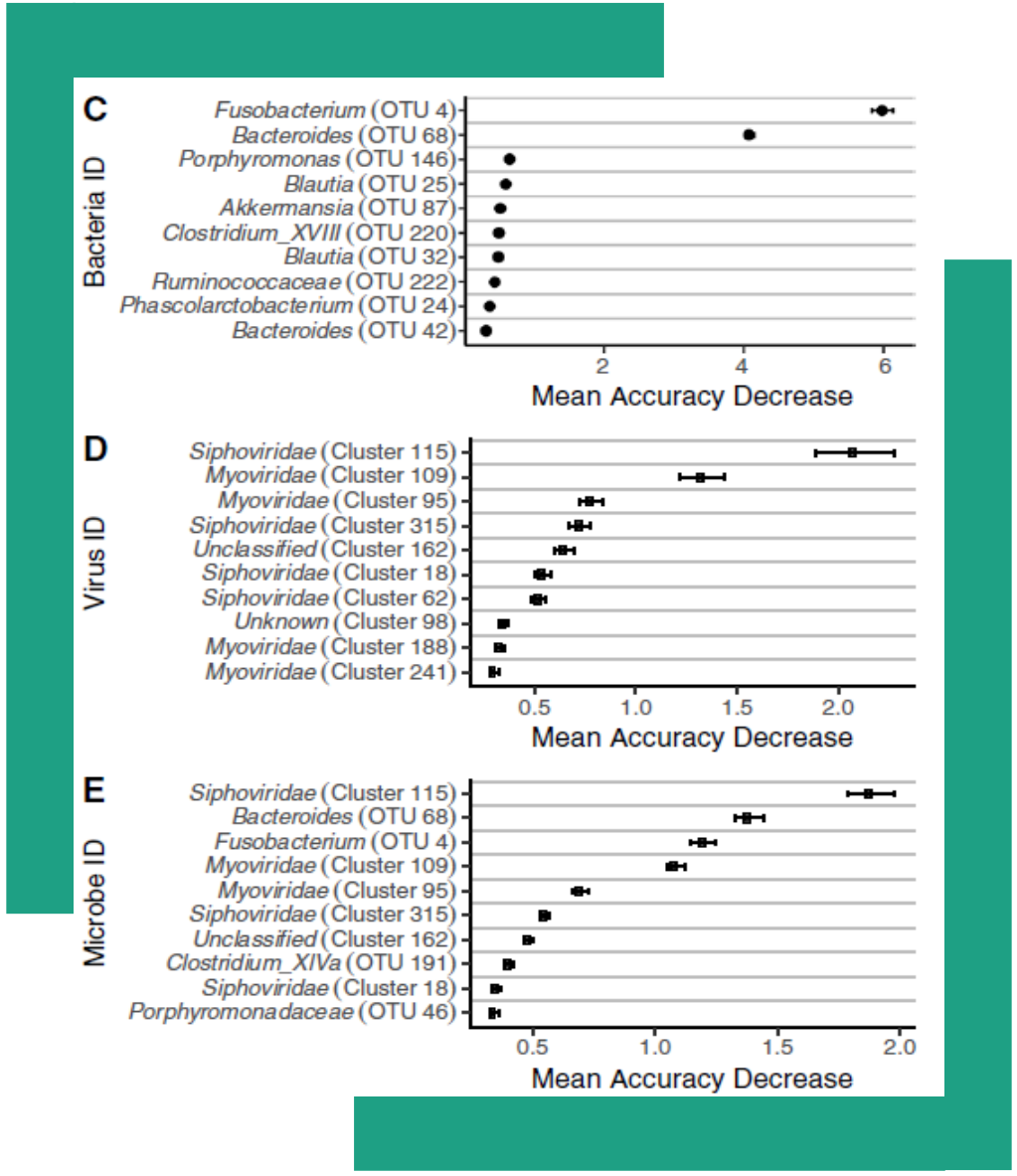
Gut Virome composition

- Gut virome contains 13204 viral populations, including prokaryotic viruses and eukaryotic viruses.
- 96.1% of gut viral populations are bacteriophages, 3.8% are eukaryotic viruses.

Gregory, A. C., et al. 2019 (under peer review)

Viruses in CRC

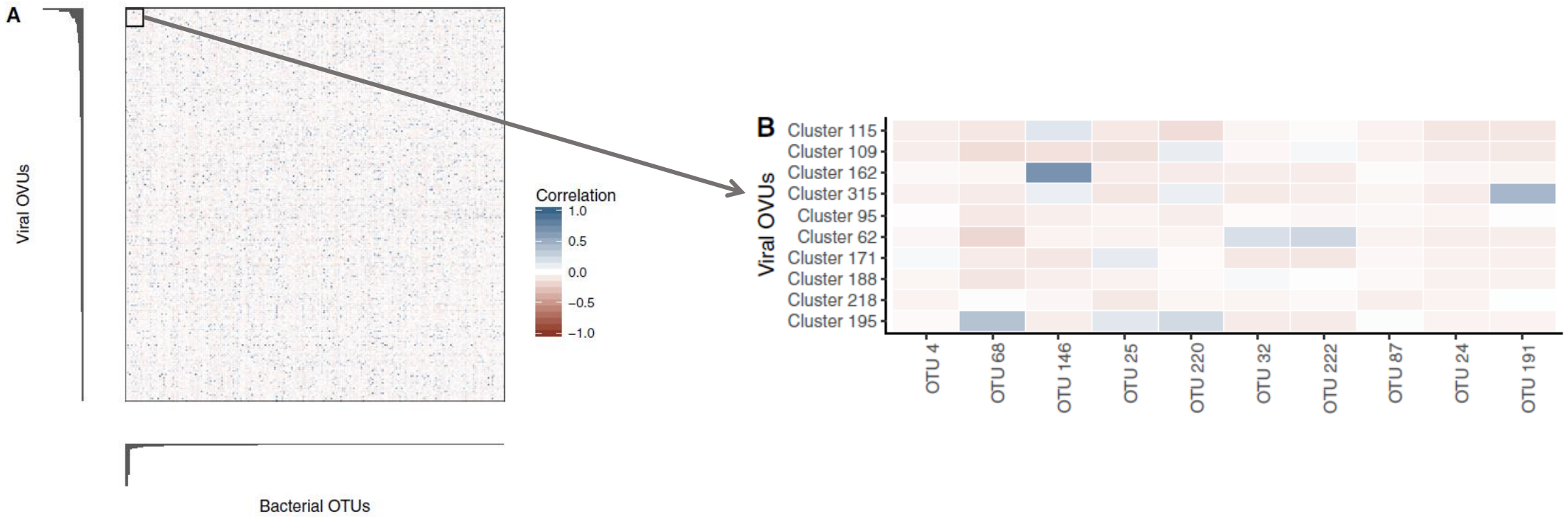
- Several eukaryotic viruses can be detected in CRC samples
- Negative association with these viruses



Bacteriophage in CRC

- *Fusobacterium* was the primary driver of the bacterial association with colorectal cancer
- Bacteriophages(belong to *Siphoviridae* and *Myoviridae)* play a role in tumorigenesis
- Both bacterial and viral microbes were found to drive the community association with cancer

Hannigan G D, et al. 2018



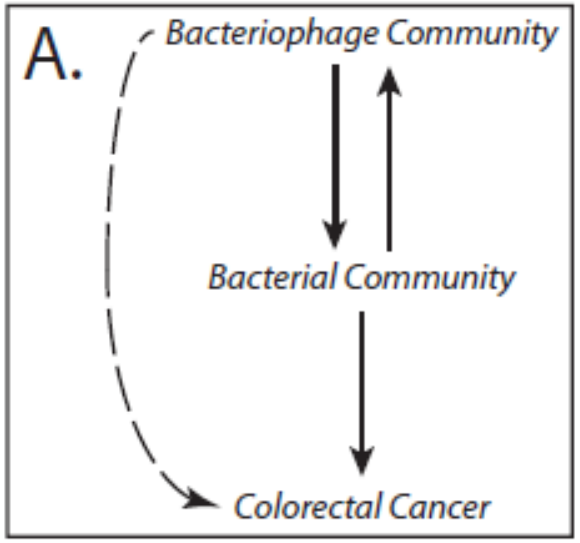
Bacteriophages and bacteria in CRC

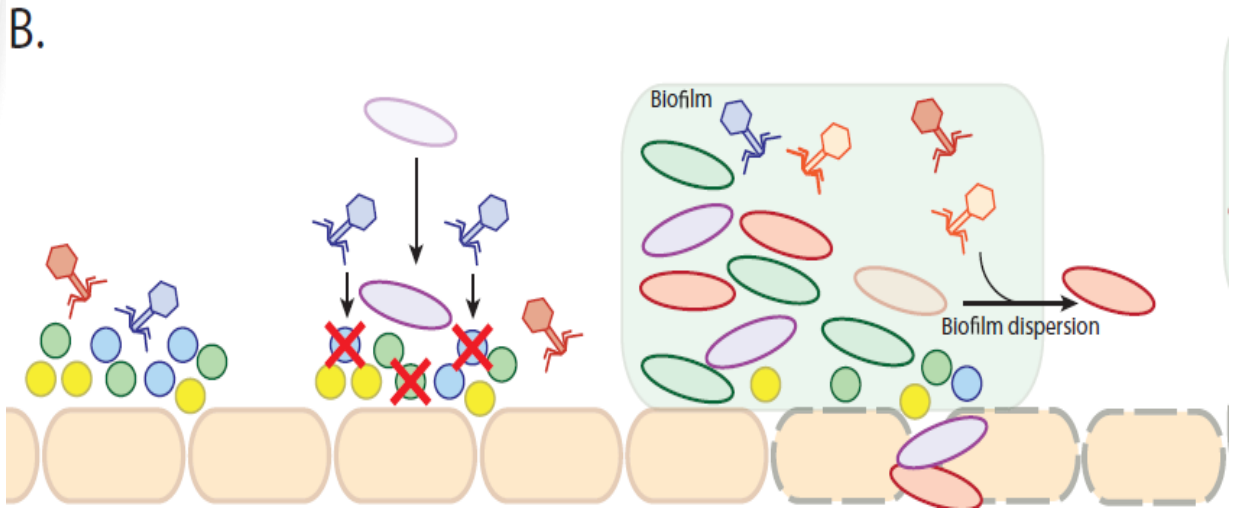
- low correlation between bacterial and viral relative abundances

Hannigan G D, et al. 2018

How bacteriophage promotes CRC

- Phages alter bacterial community
- Space for opportunistic bacteria
- Adhere, colonize and may establish biofilm
- Oncogenic bacteria transforms epithelial cells and disrupt tight junctions.





Hannigan G D, et al. 2018

Other conceptual models

Kill the winner

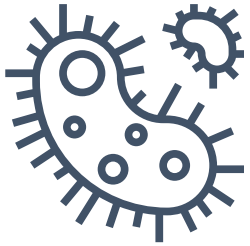
Phages act as predators of overgrowed bacteria

Biological weapon

Phages are used by commensal bacteria to kill bacterial competitor

Community shuffling

A host reaction induced phages to act negatively on their host



Emergence of new bacterial strains

Phages operate as reservoirs of genetic diversity, without killing bacteria

Columpsi P, et al. 2016

Summary

- Human virome has been associated with diverse cancers and diseases.
- Bacteriophages can alter gut bacterial community thereby promoting CRC progression indirectly.
- More researches need to be done to elucidate how phages influence CRC.

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Thanks for listening!