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Aging and the Microbiome: precondition for gastrointestinal carcinogenesis

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ABSTRACT

This review summarizes how aging-related changes in the gut microbiome contribute to gastrointestinal carcinogenesis. We highlight that cancer risk in aging is shaped not only by chronological age but largely by diet, lifestyle, environment, and their impact on microbial ecology. In healthy aging, microbial diversity is preserved with functional redundancy among short-chain fatty acid-producing commensals that support barrier integrity, immune regulation, and metabolic homeostasis. In unhealthy aging, loss of beneficial taxa, expansion of pathobionts, and accumulation of pro-inflammatory and genotoxic metabolites promote chronic inflammation, epithelial dysfunction, and DNA damage, thereby facilitating tumour development. Key microbial drivers include pks $^{+}$ *Escherichia coli*, enterotoxigenic *Bacteroides fragilis*, and *Fusobacterium nucleatum*, acting through genotoxic, inflammatory, and immune-evasive mechanisms. Although microbiome-targeted interventions such as diet modification, probiotics, faecal microbiota transfer, and phage-based strategies are promising, current evidence remains largely preclinical or observational. Overall, the gut microbiome is a central, modifiable mediator of aging-associated gastrointestinal cancer risk, but longitudinal studies are needed to establish causality and therapeutic efficacy.

1. Introduction: aging, cancer risk, and gut microbiome

The global population is shifting towards older age groups, a phenomenon known as population aging. By 2080, individuals aged 65 years or older are projected to outnumber those under 18 [1]. Thus, countries are facing challenges in preventing and treating age-related disorders, such as frailty and age-related diseases, such as cancer. Ageing implicates a cumulative lifetime molecular and cellular damage, making it the most important non-modifiable risk factor for cancer [2]. In 2022, 65% of cancer diagnoses and 74% of cancer-related deaths occurred in persons aged 60 or older [3]. Worldwide, the second-leading cause of cancer death is colorectal cancer [4]. However, mechanisms linking aging to carcinogenesis remain incompletely understood. Increasing evidence suggests that age-associated alterations of the gut microbiome contribute to chronic inflammation, metabolic dysregulation, and genomic instability, thereby creating a permissive environment for gastrointestinal cancer initiation and progression [2]. Yet, evidence suggests that physical activity and diet shape a healthy microbiome that is usually found in young persons, but also in healthy older people, and can counterbalance carcinogenic trajectories [5]. These findings are linked to a concept of healthy aging implicating a proactive health management that may be beneficial for physical and mental well-being [6]. This review provides an overview of how aging-microbiome interactions impact gastrointestinal carcinogenesis, focusing on permissive and preventive clinical associations as well as underlying molecular and cellular mechanisms.

2. Aging-related microbial shifts

2.1. Adult and aging microbiome

The young and middle-aged adult gut microbiome is highly diverse, stable, and resilient to short-term perturbations in diet, but is shaped by long-term diet, physical activity, cognitive training, and living environment [7–12]. The impact of long-term environmental changes has been illustrated in Asian people post US immigration, who exhibit a time-dependent decrease in microbiome diversity and replacement of native microbiota by Western microbiota, e.g. *Bacteroides* [13]. Over

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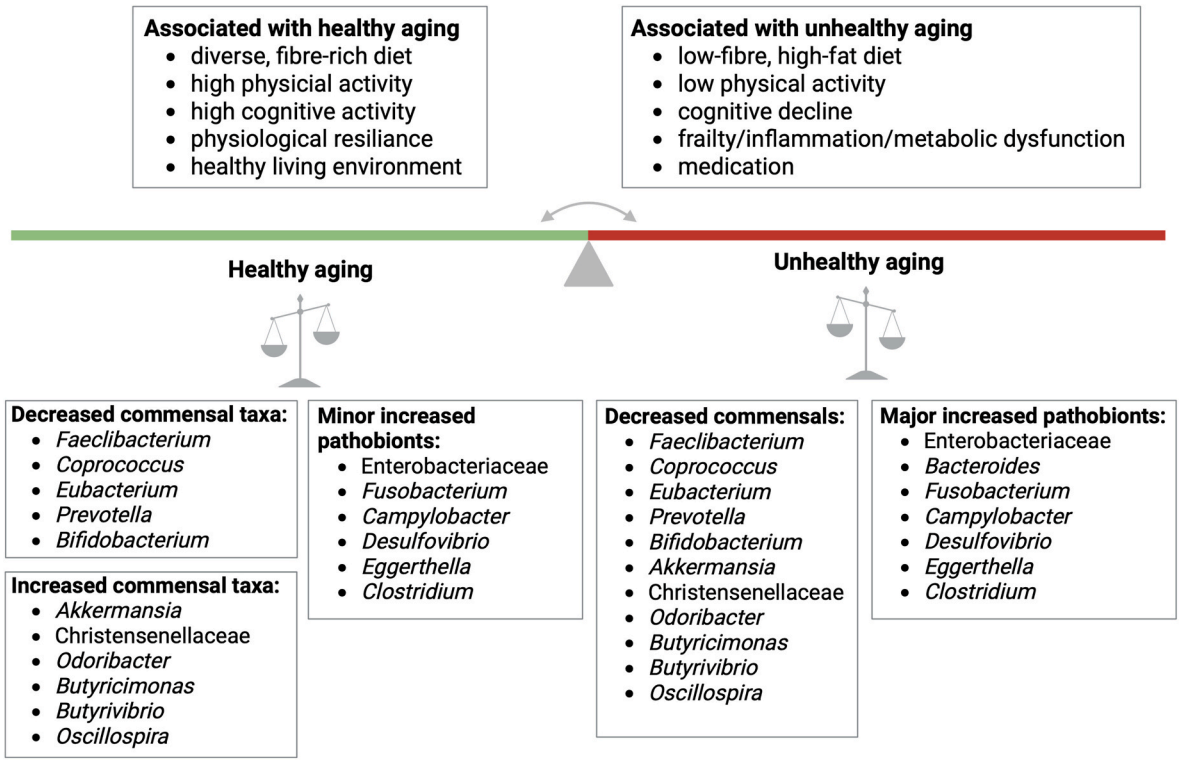

Fig. 1. Gut microbiota in healthy versus unhealthy aging. General aging-related changes are loss of dominant commensal taxa such as *Faecalibacterium*, *Coprococcus*, *Eubacterium*, *Prevotella* and *Bifidobacterium*. In a healthy environment and upon a healthy lifestyle this loss is compensated by an increase of a second group of commensals, such as *Akkermansia*, Christensenellaceae, *Odoribacter*, *Butyricimonas*, *Butyrivibrio,* and *Oscillospira* and a minor increase in pathobionts such as Enterobacteriaceae, *Fusobacterium*, *Campylobacter*, *Desulfovibrio, Eggerthella* and *Clostridium*. Shifts in unhealthy aging align with features of chronic inflammation, metabolic dysfunction, and frailty: loss of both primary and alternative commensals and major enrichment of pathobionts. Created with BioRender.com.

90% of gut bacteria belong to the phyla Bacteroidetes and Firmicutes; fewer present phyla are Actinobacteria and Proteobacteria [10,14]. *Bacteroides*, *Faecalibacterium*, *Eubacterium*, *Prevotella*, *Ruminococcus*, and *Bifidobacterium* are consistently dominant genera in healthy gut microbiomes [14,15]. These healthy communities are enriched in a diverse, plant-rich, and mixed diet and are key regulators of host energy metabolism, most importantly, involvement in fibre degradation, short-chain fatty acid (SCFA) production, and carbohydrate and protein metabolism. These healthy-taxa-derived metabolites are critical for gut-barrier maintenance, immune regulation, and energy homoeostasis in adults [10]. Importantly, acetate, propionate, and butyrate are the main SCFAs in the colon contributing to direct energy supply in host cells, including glucogenesis and lipogenesis, but also to systemic energy supply via absorption into the portal vein [16,17].

In older people (in developed regions often defined as age >65 years [18]), however, bacterial richness is decreased. Notably, most studies that analysed the microbiome in older people were cross-sectional studies, lacking longitudinal analysis. The composition of the gut microbiome in older people can be classified into two broad functional categories, which appear more accurate in terms of metabolic health than broad taxonomic descriptions: general changes in healthy aging, as well as changes in unhealthy aging related to age-associated disorders such as morbidity and frailty [5,19,20]. In addition to taxonomic reduction, mouse experiments have also revealed a reduced host ability to utilize microbe-derived metabolites upon aging e.g. impaired fatty acid oxidation and reduced synthesis of amino acids, vitamins, and SCFAs. This loss of microbial support is linked to age-related host changes: reduced tissue regeneration, impaired intestinal barrier, and increased inflammation [21].

2.2. Microbial trajectories in healthy aging

General aging-related changes are loss of dominant commensal taxa such as the butyrate producers: *Faeclibacterium*, *Coprococcus*, *Eubacterium*, *Prevotella,* and the acetate-producing *Bifidobacterium* (recently categorized as Group 1 taxa [5]). This loss is compensated by an increase of a second group of commensals, such as acetate-producing *Akkermansia* and alternative butyrate producers: *Odoribacter*, *Butyricimonas*, *Butyrivibrio,* and *Oscillospira* (recently categorized as Group 3 taxa [5]), and a minor increase in pathobionts such as Enterobacteriaceae, *Fusobacterium*, *Campylobacter*, *Desulfovibrio, Eggerthella,* and *Clostridium* (recently categorized as Group 2 taxa [5]). This rearrangement of community structures upon aging has recently been validated in a worldwide meta-analysis of 79 studies that identified a shift from primary health-associated bacteria such as *Bifidobacterium* to alternative healthy taxa such as *Ruthenibacterium lactatiformans*, *Anaerotruncus*, and *Butyricicoccus* [10]. This indicates a functional redundancy in healthy older people with multiple species contributing to host resilience (Fig. 1). Interestingly, centenarians (individuals over 100 years) maintain a high diversity with high expression of beneficial taxa such as *Akkermansia* and Christensenellaceae [10]. Metabolites that are exchanged between host cells and gut microbes represent a link to longevity. Important host-derived metabolites are fatty acids, branched-chain amino acids, and microbe-derived SCFAs, polyamines, and polysaccharides, together modifying autophagy, mitochondrial maintenance, epigenetic regulation, and nutrient-sensing pathways such as mTOR and AMP-activated protein kinase (AMPK) pathway [22].

2.3. Microbial trajectories in unhealthy aging

Shifts in unhealthy aging align with features of chronic inflammation, metabolic dysfunction, and frailty: loss of both primary and

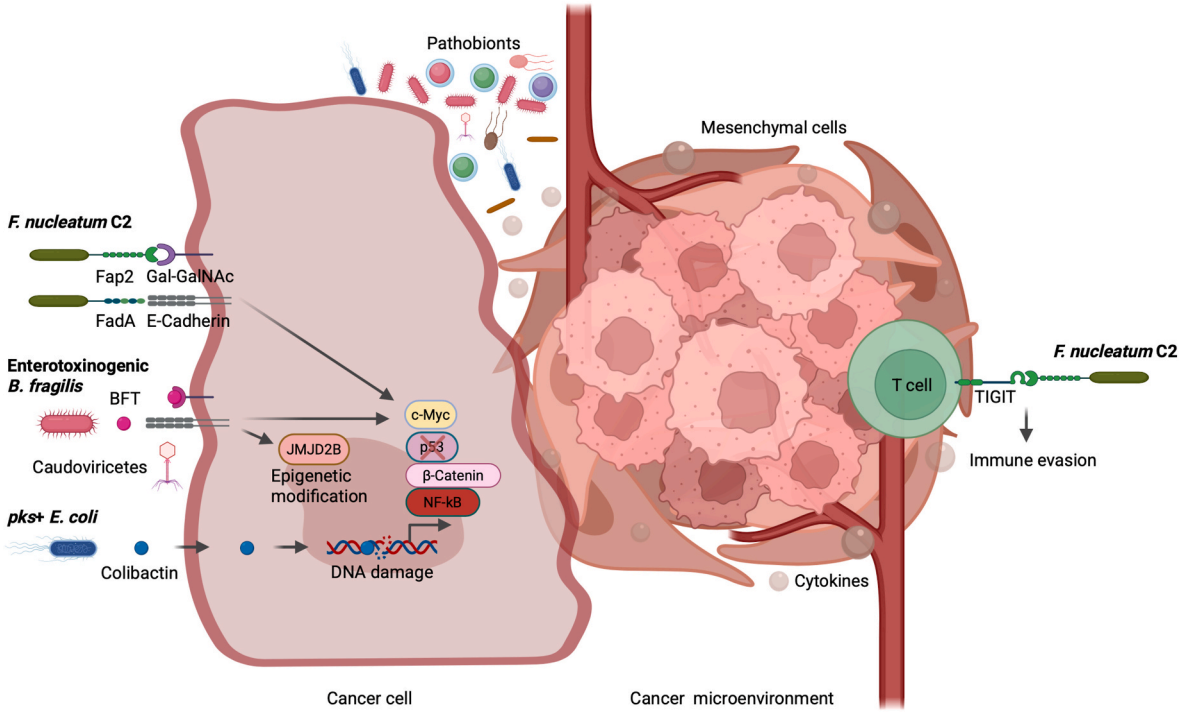

Fig. 2. Microbiota-driven molecular pathomechanisms in colorectal cancer. Core colorectal cancer (CRC)-associated taxa are *Pks* + *Escherichia coli* (*E. coli*), enterotoxigenic *Bacteroides fragilis* (*B. fragilis*), and *Fusobacterium nucleatum* (*F. nucleatum*). Cytotoxic *E. coli* harbours a genomic *pks* island. The *pks* island encodes Colibactin, a potent genotoxin that causes DNA interstrand cross-links. Colibactin drives mutations in key tumour suppressor genes like adenomatous-polyposis-coli (APC) and p53. Enterotoxinogenic *B. fragilis* renders epithelial signalling by binding E-cadherin, promoting activation of Wnt, c-Myc, and NF-kB signalling. Upregulation of the histone demethylase JMJD2B drives stemness in CRC. CRC-associated *B. fragilis* isolates have been found to be infected with specific Caudoviricetes prophages. *F. nucleatum* colonizes human CRC tissue via its lectin Fap2 and its adhesin FadA. The *F. nucleatum* clade C2 drives intestinal carcinogenesis via Wnt signalling, NF-kB signalling, and suppression of an anti-tumour immune response via binding to the immune checkpoint inhibitor T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT), allowing evasion of CRC cells from cytotoxic T-cells. Created with BioRender.com.

alternative beneficial butyrate and acetate producers (Group 1 and Group 3) and enrichment of inflammation-associated pathobionts (Group 2) [19,20,23] (Fig. 1). Decrease in intestinal barrier function upon loss of beneficial metabolites translocates inflammatory bacterial mediators such as lipopolysaccharide (LPS) specifically in older people, which drives the age-associated expression of pro-inflammatory cytokines like IL6 [24]. A prime example of unhealthy aging has been presented in the ELDERMET cohort that identified how diet, residence care, and health impact gut microbiota in Irish persons aged >65 years: a lower microbiome diversity and instability correlated with frailty and both have been especially detected in residence care persons that consumed a low-fibre, high-fat, and less diverse diet [25–27]. A well-studied harmful microbial metabolite is trimethylamine-N-oxide (TMAO). Gut bacteria ferment dietary nutrients like choline, L-carnitine, and betaine (found in animal-based diet) into trimethylamine (TMA). The host's liver then converts this into TMAO. The plasma detection of TMAO has been driven by an animal-based diet in German persons aged >65 years and has been associated with frailty in Chinese persons aged >65 years with cardiovascular disease, indicating detrimental effects of harmful metabolites, especially upon aging [28,29]. High TMAO levels are directly linked to the activation of the NLRP3 inflammasome, vascular calcification, and endothelial dysfunction, accelerating cardiovascular aging [30]. In nursing home residents' colonization with *Clostridium difficile* (*C. diff.*) correlates with reduced microbial diversity, depletion of SCFA-producers, and an increase in pathobionts such as *Escherichia coli* (*E. coli*), and *Bacteroides fragilis* (*B. fragilis*); not with antibiotic exposure alone, indicating that microbial shifts in unhealthy aging predispose to infections [31]. In addition to frailty and diet, polypharmacy (especially proton pump inhibitors (PPI), antipsychotics, and antidepressants) in older inpatients correlated with reduced bacterial diversity, including a reduction in SFCA-producers [32]. Together, this evidence indicates that unhealthy trajectories in aging are not per se driven by chronological aging, but in the context of lifestyle, diet, environment, and morbidity.

3. Cancer-associated microbiome signatures

3.1. From association to causality in microbiome-cancer research

Dysbiosis of the gut microbiome is a hallmark of cancer. It is now well established that cancer is accompanied by pathogenic shifts in the microbiome, while the functional capacity of many cancer-associated microbiota is not well explored. The diversity and variability of microbiota in non/pre-cancerous conditions due to diet, lifestyle, and aging, as described above, need to be considered when analysing microbiota in heterogeneous cancer cohorts [33]. It appears that the gut microbiota might display a potential link between environmental factors and carcinogenesis. Most findings in microbiome-cancer research derived from clinical associations and cross-sectional observational studies that lack proof of causality. More recently, new mechanistic studies have analysed direct effects on cells and the genome, e.g. via analysis of microbiota-derived pro-carcinogenic inflammatory responses and/or pro-carcinogenic metabolites, thus allowing separation of “driver” organisms from passengers and healthy microbiota [34–37]. So far, only a few drivers have been well characterized, although bacteria are increasingly recognised as key players in gastrointestinal carcinogenesis. In principle, since 1994, only one bacterium has been classified as a Group 1 carcinogen by the World Health Organisation (WHO): *Helicobacter pylori* (*H. pylori*) for gastric cancer (GC).

3.2. H. pylori as a paradigm for microbial carcinogenesis

The discovery more than 40 years ago that a bacterium manages to colonize the highly acidic environment of the stomach and causes a chronic gastritis that can culminate in cancer ushered in a paradigm shift that established bacteria as a potential carcinogen. Coordinated research has revealed the mechanistic principles through which *H. pylori* affects epithelial cells. Specific virulence factors such as CagA, VacA, and ADP heptose, that alter cellular signalling and DNA integrity, have been identified. In addition, *H. pylori* effects on the tissue level have been analysed, considering that the bacterium can colonize deep in gastric glands, directly interacting with stem and progenitor cells, leading to distinct pathogenic effects and disruption of gland homoeostasis in mice [38]. We have recently reviewed these general principles for *H. pylori*-driven gastric carcinogenesis: long-term gland colonization, evasion of host immune responses, evasion of the tissue barriers that protect long-lived stem cells, alterations of tissue homoeostasis and the ability to compromise the DNA integrity of long-lived cells as well as new insights into permissive interaction of *H. pylori* and associated tissue alterations (e.g. gastric atrophy) with other gastric microbiota such as *Streptococcus* that may contribute to carcinogenesis [39,40]. It is well established that *H. pylori*-driven GC takes decades, undergoing specific tissue pathological steps, called the Correa Cascade, leading to GC onset usually aged >60 years [41]. New analyses showed that *H. pylori* seropositivity, likely indicating chronic infection, has been associated with biomarker-based unhealthy aging in a large US cohort, linking *H. pylori*-driven systemic inflammation to accelerated aging and subsequent increased risk of death [42]. This effectively reclassifies *H. pylori* as a major driver of unhealthy aging.

3.3. Colorectal cancer-associated dysbiosis

The recognition of *H. pylori* as a driver of gastric cancer has prompted investigation of analogous microbial mechanisms in colorectal cancer (CRC). At the phylum level, Firmicutes, Bacteroidetes, and Fusobacteria predominate in CRC. While individual species are not inherently pathogenic, the acquisition of virulence factors, including toxin production, can directly contribute to carcinogenesis. CRC is associated with reduced microbial diversity, although a relatively higher diversity is observed in younger compared to older patients [43]. Notably, the spatial abundance of bacterial communities in CRC is not random, but highly organised in microniches interacting with epithelial and immune cells as revealed by spatial transcriptomics [44]. A recent Mendelian randomization study identified specific gut bacteria associated with increased colorectal cancer risk, while simultaneously linking these taxa to host genetic variation in immune, epithelial barrier, and metabolic pathways, suggesting a shared gene-microbiome axis in CRC susceptibility [45]. Core CRC-associated taxa, including *Pks* + *E. coli*, enterotoxigenic *B. fragilis*, and *Fusobacterium nucleatum* (*F. nucleatum*), are shared across age groups [46]. This review focuses on clinical associations and preclinical models of key Group 2 pathobionts implicated in CRC, which are particularly enriched in unhealthy aging (Fig. 2). However, no CRC-associated microbe has yet been classified as a Group 1 or 2 carcinogen by the WHO, reflecting the lack of longitudinal human evidence and the frequent presence of these species in healthy individuals. This indicates that data on proven microbial-driven CRC are still limited.

Cytotoxic *E. coli* harbours a genomic *pks* island. The *pks* island encodes Colibactin, a potent genotoxin that causes DNA interstrand crosslinks by alkylating adenine residues on opposite strands of host epithelial cell DNA. After *pks* + *E. coli* infection, distinct mutational signatures, promoting Wnt independence, can be detected in murine and human cells and organoids [47,48]. These signatures are enriched in patients with CRC, particularly in young patients, providing the first direct genomic evidence that bacterial toxins leave a traceable imprint in human cancer [47]. Colibactin-induced genomic damage occurs early

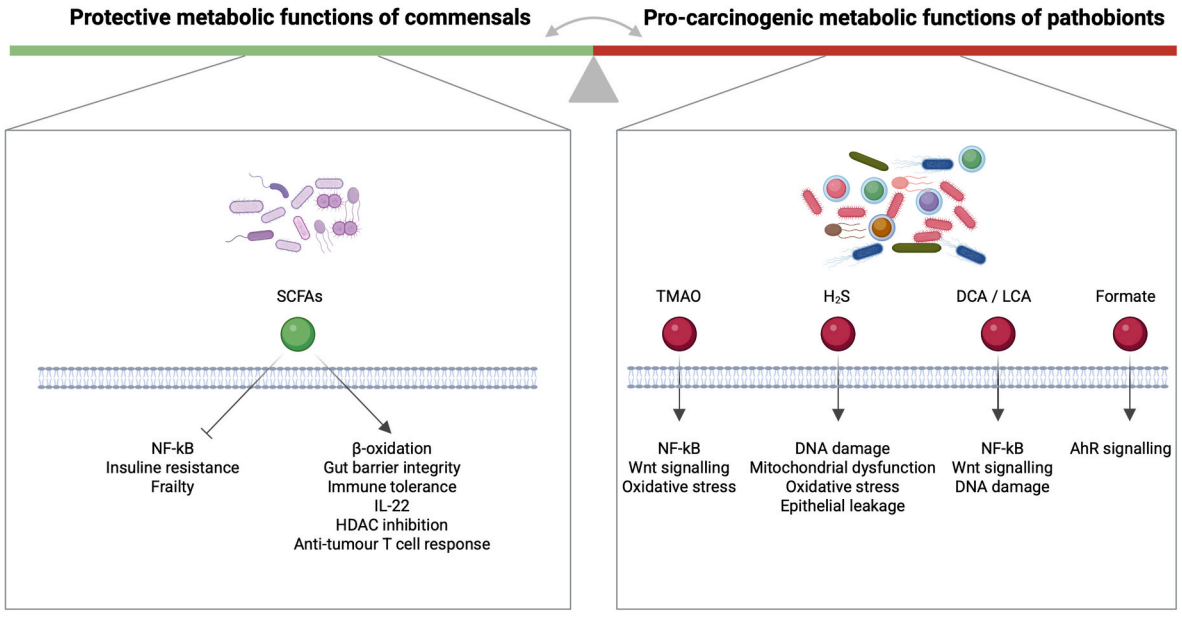

Fig. 3. Commensal versus pathobiont metabolic functions. Beneficial microbes are less expressed upon unhealthy aging and produce short-chain fatty acids (SCFAs) through fermentation of fibre in the colon. SCFAs prevent aging-related physiological decline, pro-inflammatory signals via NF-kB inhibition, and stimulate immune tolerance, while promoting colonocytes and barrier function via IL-22 production and activation of β-oxidation, which supports microbial diversity via induction of an anaerobic environment. Intestinal leakage and induction of a pro-inflammatory state drive pathology, e.g. insulin resistance or frailty. Cancer-preventing actions of SCFAs are histone deacetylase (HDAC) inhibition directly in tumour cells and PD1 induction on T cells. Pathobiont metabolites promote tumourigenesis by modulating host cellular pathways. Trimethylamine-N-oxide (TMAO) promotes chronic inflammation, oxidative stress, and epithelial proliferation via Wnt signalling, creating a microenvironment favourable to tumour development. Sulfide-producing bacteria can convert sulfur-containing compounds into hydrogen sulfide (H_2S), which at high levels damages DNA, disrupts mitochondrial function, and impairs the intestinal epithelial barrier. Harmful secondary bile acids such as deoxycholic acid (DCA) and lithocholic acid (LCA) directly contribute to colonic epithelial cell transformation. The one-carbon metabolite formate drives tumour stemness via activation of the aryl hydrocarbon receptor (AhR) pathway. Created with BioRender.com.

in CRC initiation by generating early driver mutations in key tumour suppressor genes like APC and p53 [49]. In persons with early onset of CRC (before 50 years), specifically the SBS88 and ID18 signatures, inactivating one copy of APC have been identified [33]. Currently, the role of Colibactin in older adults, including its interaction with morbidity and environmental factors, is not well explored. It may interact with enterotoxinogenic *B. fragilis*, as both co-localize in colonic biofilms in familial adenomatous polyposis (FAP) patients and have a synergistic oncogenic effect in mice [50].

Enterotoxinogenic *B. fragilis* renders epithelial signalling by binding E-cadherin, promoting activation of Wnt, c-Myc, and NF-kB signalling, thus not per se altering the genome [51], but generating a chronic pro-proliferative, pro-inflammatory (IL17-dominant) colonic mucosal environment predisposing to carcinogenesis most likely upon further hits [52–54]. In addition, epigenetic modification promotes stemness in CRC stem cells, e.g. upregulation of the histone demethylase JMJD2B that drives the expression of CD44 and Sox2 [55]. Recently, CRC-associated *B. fragilis* isolates have been found to be infected with specific Caudoviricetes prophages, significantly more often than in CRC-negative controls [56]. This points to a more complex, toxin-independent role of *B. fragilis* than expected so far and raises the question if other bacteria may also carry phages that promote CRC carcinogenesis.

F. nucleatum is an anaerobic gram-negative inhabitant of the human oral cavity, but also specifically colonizes human CRC tissue via its lectin Fap2 and its adhesin FadA [57,58]. While evidence in mice suggest a promotion of intestinal carcinogenesis via Wnt signalling [59], NF-kB signalling [60,61] and suppression of an anti-tumour immune response via binding to the immune check point inhibitor T cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT), allowing evasion of CRC cells from cytotoxic T-cells and NK cells [61], the mechanistic oncogenic capacity of *F. nucleatum* in humans is not well explored [62]. Somatic genetic susceptibility has been exemplified in CRC tumours carrying a KRAS p.G12D mutation, that represents a risk factor for *F. nucleatum*-driven cancer progression via binding to DHX15, an RNA helicase protein in tumour cells, providing a basis for precision medicine accounting the genetic background [63]. Recently, it has been identified that *F. nucleatum* is bifurcated into two distinct genetic clades, arguing against the dogma of *F. nucleatum* translocation from the mouth to the colon: *Fna* C1, which is largely restricted to the oral cavity, and *Fna* C2, which dominates the human CRC niche, particularly in advanced cancer stages [64,65]. The pro-oncogenic capacity of *Fna* C2 has been functionally validated in mice, indicating that specifically the *Fna* C2 clade should be analysed in future studies [64].

4. Aging-related microbiota mechanisms driving carcinogenesis

4.1. Loss of protective microbial functions with age

Beneficial Group 1 and Group 3 microbes are less abundant upon unhealthy aging [26] and produce SCFAs through fermentation of non-digestible carbohydrates (dietary fibre) in the colon. Notably, SCFA-producers can increase rapidly upon a plant-based or Mediterranean diet [66,67]. SCFAs prevent an aging-related physiological decline [68], pro-inflammatory signals via NF-kB inhibition [69], and stimulate immune tolerance via Treg expansion [70]. They also support colonocyte health and intestinal barrier function, primarily through PPARγ--driven β-oxidation, which maintains an anaerobic environment favourable to microbial diversity, and through free-fatty acid receptor 2 (FFAR2)-mediated regulation of IL22 production [71,72]. Thus, numerous benefits are diminished upon reduction of beneficial microbes, with potential detrimental effects on healthy aging and longevity (Fig. 3). In turn, intestinal leakage and induction of a pro-inflammatory state drive pathology, e.g. insulin resistance upon loss of *Akkermansia* in mice [73] or frailty in older persons [74]. Cancer-preventing actions of SCFAs have been identified, most importantly histone deacetylase (HDAC) inhibition directly in tumour cells [75] and PD1 induction on T cells [76]. In line with this, treatment of CRC cells with SCFAs increased their ability to activate an anti-tumour T cell response [77]. In addition, mice lacking Ffar2 were shown to have an increased tumourigenesis, probably due to increased barrier damage and decreased immunosurveillance [78]. Despite this amount of protective evidence, it should be noted that a simplified view of a per se protective role of SCFAs has been challenged in the specific context of two *Porphyromonas* species, that in a mouse model induced butyrate-driven cellular senescence and a pro-tumour secretory phenotype [79].

4.2. Pathobiont expansion and pro-carcinogenic metabolites

Decreased levels of SCFAs enhance susceptibility to pathogenic bacteria, e.g. via reduction of PPARγ, leading to an oxygen-rich gut lumen that favours outgrowth of aerobic pathobionts such as *pks*$^{+}$ *E. coli*. In mice, a fibre-free diet in the presence of *pks*$^{+}$ *E. coli* increased colonic polyp formation, while fibre-supplementation counterbalanced this effect [80]. Interestingly, more polyps were identified in mismatch repair (MMR) deficient mice, a genetic condition that increases upon human aging [81], together linking age, host genetics, nutrition, and pathobionts in the complex interplay of CRC carcinogenesis. Although not yet validated in human studies, these new insights may extend the role of Colibactin beyond early CRC patients to unhealthy aging and older aged cancer cohorts.

In addition, some pathobiont metabolites promote tumourigenesis by modulating host cellular pathways. TMAO, e.g. generated by *Clostridium* species e.g. from dietary choline promotes chronic inflammation, oxidative stress, and epithelial proliferation via Wnt signalling, creating a microenvironment favourable to tumour development [82,83]. Sulfide-producing bacteria such as *Desulfovibrio* can convert sulfur-containing compounds into hydrogen sulfide (H_2S), which at high levels damages DNA, disrupts mitochondrial function, and impairs the intestinal epithelial barrier, further contributing to carcinogenesis, which is particularly pertinent in older populations [84,85]. Harmful secondary bile acids with genotoxic potential, directly contributing to colonic epithelial cell transformation, are created in the colon and upregulated upon a high-fat diet [86]. Especially deoxycholic acid and lithocholic acid, created by some *Clostridium* species (Group 2), may represent a metabolic link between unhealthy aging and CRC [87]. Recently, the *F. nucleatum*-derived one-carbon metabolite formate promoted tumourigenesis in mice via activation of the aryl hydrocarbon receptor (AhR) pathway driving stemness [88] (Fig. 3).

5. Microbiome-targeted strategies for cancer prevention and therapy in aging

The microbiome may represent a modifiable risk factor for unhealthy aging and gastrointestinal carcinogenesis. Administration of health-associated bacteria (probiotics) or substrates which promote the growth of selective microorganisms (prebiotics) or dietary interventions can theoretically promote health and longevity by “resetting” unhealthy-aging associated microbial shifts. This concept has been explored in aged mice that showed attenuated age-related cognitive impairments and reduced inflammation following faecal microbiota transfer (FMT) from young mice [89,90]. In line with this, administration of the probiotics *Bifidobacterium lactis* and *Lactobacillus acidophilus* led to enrichment of beneficial butyrate-producers in the gut mucosa and faecal samples [91] and to decreased pro-inflammatory cytokines in CRC patients [92].

However, convincing evidence for microbiome-based therapies in humans is sparse, often involving small cohorts of short durations. Most importantly, specific administration of probiotics or prebiotics (e.g. substrates of SCFA-producers) often lacks improvement in patient-oriented outcomes, due to mechanisms that are incompletely understood, probably because studies lack baseline and long-term high-

Practice points

- Consider the gut microbiome as a cancer risk factor in aging populations
- Lifestyle factors play a central role in shaping microbiome-related cancer risk
- Account for inter-individual variability and confounding factors in microbiome studies
- Specific bacterial factors can directly promote carcinogenesis
- Microbiome-targeted interventions show promise but require stronger clinical evidence

Research agenda

- Establish causal relationships between microbiome changes and carcinogenesis
- Identify and validate microbial "driver" species and their mechanisms of action
- Elucidate host-microbiome interactions across aging trajectories
- Develop and test effective microbiome-targeted interventions in humans
- Stratify cancer risk and treatment response based on microbiome profiles

CRediT authorship contribution statement

Jonas Wizenty: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft. **Michael Sigal:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

resolution profiling of taxonomic composition [5,9]. Despite this, promising data have been presented, particularly in older individuals. The one-year multi-centre "NuAge" trial has demonstrated that Mediterranean diet restores Group 1 and Group 3 microbes and suppresses Group 2 pathobionts in people over the age of 65 years, resulting in lower pro-inflammatory cytokines, less harmful metabolites such as secondary bile acids, and improved frailty scores [93].

In a large prospective cohort, specifically high fibre intake has been associated with reduced risk of *F. nucleatum* $^{+}$ CRC, suggesting that diet influences CRC risk via modulation of the gut microbiome [94]. Initial experiments on therapeutic modulation of specific gut bacteria by phage-guided nanotechnology in CRC in mice have been conducted, e.g. effective elimination of *F. nucleatum* by phages carrying chemotherapy [95]. Furthermore, studies have been conducted focusing on outcomes of cancer immunotherapy. Age-related microbiome changes can reduce the effectiveness of immunotherapies in mice due to poorer activation of anti-tumour immune pathways [96], while probiotic administration (here *Lactobacillus rhamnosus* GG) augmented immunotherapy via anti-tumour CD8^{+} T cell recruitment in a mouse model of CRC [97]. Primary resistance to immunotherapy in humans has been linked to unhealthy gut microbiome composition, e.g. reduction of *A. muciniphila*, while FMT of beneficial bacteria promoted response to immunotherapy in mice [98]. In melanoma patients, dietary fibre intake of at least 20g per day has also been associated with higher immunotherapy efficacy, most likely via altered function of bacterial metabolites with beneficial properties for anti-tumour immunity [99].

6. Conclusions and future perspectives

Here, we review how aging and the gut microbiome interact in gastrointestinal carcinogenesis. Both are key contributors to carcinogenic processes through multiple, interrelated mechanisms, and interactions among microbial species within individually susceptible hosts remain incompletely understood. Aging is associated with predictable changes in the gut microbiome, driven by diet, lifestyle, disease, and medication use. Gut dysbiosis contributes to carcinogenesis through chronic inflammation, metabolic disturbances, and DNA damage with genomic instability. These aging-associated mechanisms may be driven less by chronological aging itself than by adverse environmental and lifestyle factors, and may thus contribute to the increasing incidence and mortality of CRC in individuals under 50 years [4,100]. Conversely, a healthy diet-microbiome interaction may promote longevity by limiting inflammatory and genotoxic pathways. Insights from healthy and unhealthy aging research inform microbial contributions to carcinogenesis and highlight the microbiome as a promising target for cancer prevention and integration into multidimensional, potentially synergistic therapeutic strategies. Longitudinal human studies and mechanistic validation are now needed to establish causality and guide microbiome-targeted interventions in aging populations.

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Declaration of competing interest

None.

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