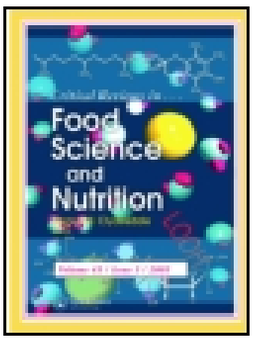

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REVIEW

Could partial nonstarch polysaccharides ameliorate cancer by altering m^{6}A RNA methylation in hosts through intestinal microbiota?

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ABSTRACT

There is a growing scientific view that the improvement of cancer by nonstarch polysaccharides (NSPs) is mediated by intestinal microbiota. Intestinal bacteria affect the supply of methyl donor substances and influence N^6-methyladenosine (m^{6}A) RNA methylation. As one of the epigenetic/epitranscriptomic modifications, m^{6}A RNA methylation is closely related to the initiation and progression of cancers. This review summarizes the cancer-improving effects of NSPs through modulation of intestinal microbiota. It also summarizes the relationship between intestinal bacteria and the supply of methyl donor substances. Moreover, it also provides a summary of the effects of m^{6}A RNA methylation on various types of cancer. The proposed mechanism is that, dietary consumed NSPs are utilized by specific intestinal bacteria and further reshape the microbial structure. Methyl donor substances will be directly or indirectly generated by the reshaped-microbiota, and affect the m^{6}A RNA methylation of cancer-related and pro-carcinogenic inflammatory cytokine genes. Therefore, NSPs may change the m^{6}A RNA methylation by affecting the methyl donor supply produced by intestinal microbiota and ameliorate cancer. This review discussed the possibility of cancer improvement of bioactive NSPs achieved by impacting RNA methylation via the intestinal microbiota, and it will offer new insights for the application of NSPs toward specific cancer prevention.

KEYWORDS

Cancer; intestinal microbiota; m^{6}A RNA methylation; methyl donor; nonstarch polysaccharides

Introduction

Cancer is among the leading causes of mortality worldwide, representing a major public health issue. The Global Burden of Disease evaluation estimated the incidence of cancer at 14.9 million cases, accounting for 8.2 million deaths and 196.3 million disability-adjusted life years, with prostate cancer and breast cancer having the greatest impact in men and women, respectively (Grosso et al. 2017). Accumulating evidence from epidemiological studies suggests the consumption of dietary fibers can significantly reduce the general cancer risk.

Dietary fibers are the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine, with complete or partial fermentation in the large intestine. Dietary fibers contain polysaccharides, oligosaccharides, lignin, and associated plant substances. Among them, polysaccharides are one of the well-sourced biomacromolecules. Polysaccharides are polymers usually connected by more than 10 monosaccharide residues with glycosidic bonds. They widely exist in plants, microorganisms, algae, and animals (Xie et al. 2016; Yu, Shen, et al. 2018). As one type of polysaccharides, nonglycemic carbohydrate or nonstarch polysaccharide (NSP) has been reported to have a broad spectrum of biological effects. Among them, the anti-tumor effects have attracted increasing attention. Multiple bioactive NSPs have been recognized as safe and nontoxic adjuvants in cancer treatment (Wang, Zuo, and Luo 2017).

NSPs can be daily consumed in diet while diet somewhat indirectly affected the cancer development in multiple ways. For example, some diets may influence endocrine related proteins which will further lead to obesity, one of the pro-carcinogenic factors (Font-Burgada, Sun, and Karin 2016). They may also trigger chronic inflammation or enhance immune response which also closely relate to cancer (Zitvogel, Pietrocola, and Kroemer 2017). Recently, NSPs, as one of the components in diet, are believed to exhibit their biological activity against cancer through intestinal microbiota. It is reported that, NSPs can be utilized by intestinal bacteria to generate some tumor-suppressive metabolites (O'keefe 2016). Additionally, the "polysaccharides-intestinal microbiota" axis has been proposed to lower the cancer risk by improving the leaky gut and reinforcing the body immune homeostasis through microbial metabolites (Liu, Li et al. 2019). Nevertheless, deeper insights on how microbial metabolites of NSPs modify the cancer-related genes or pro-carcinogenic factors are still inconclusive.

One possibility lies on the epigenetic programming including histone modification or DNA/RNA methylation. On one aspect, it was proposed that diet-microbiota

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interactions mediate global histone modification (histone acetylation and methylation) in multiple host tissues, and short chain fatty acids (SCFAs) were implied to be the mediator (Krautkramer et al. 2016). On the other aspect, it was concluded that diet affected cancer most likely through DNA methylation, and the direct mechanism was closely related to the methyl donor substances (Sapienza and Issa 2016). Therefore, it seems there are more than one mechanism in "NSP-microbiota-cancer" axis and the mediators are varied in different epigenetic programming.

Similar to the DNA methylation, RNA methylation is about the modification of nucleic acids with methyl groups offered by the methyl donor substances. It is the most abundant internal modification of mRNA and has become a widespread way to regulate gene expression in diverse physiological processes (Zaccara, Ries, and Jaffrey 2019). A question is now raised whether bioactive NSPs ameliorate cancer by alteration of RNA methylation through affecting methyl donors supplied by intestinal microbiota. This review will discuss the possibility of cancer improvement of bioactive NSPs achieved by impacting RNA methylation via the intestinal microbiota.

NSPs ameliorate cancer via intestinal microbiota modulation

NSPs are able to ameliorate various types of cancer

It has been long reported that the consumption of resistant starch, one of the NSPs, could protect against colon cancer (Birt et al. 2013). Actually, an increasing number of studies have reported that NSPs have immune function and activate host immunity, which is probably one of the biology of cancer outcome improvement by NSP intervention. Apple polysaccharide (AP) could protect mice against azoxymethane/dextran sodium sulfate (AOM/DSS)-induced carcinogenesis and keep the colon in a moderative inflammatory state through toll-like receptor 4 (TLR4) signaling by reducing the number of T cells and macrophages and shifting macrophage polarization toward M1 phenotype (Li et al. 2020; Sun et al. 2020). Tea polysaccharide suppressed inflammation-related interleukin-6/signal transducer and activator of transcription 3 (IL-6/STAT3) pathway, resulting in the colitis-associated cancer attenuation both in vivo and in vitro (Liu, Eckert, et al. 2018). Crude polysaccharides from *Cantharellus cibarius* were found to inhibit the proliferation of colon cancer cells probably by reducing the expression of two inflammation-related proteins, cyclooxygenase-1 (COX-1) and cyclooxygenase (COX-2) (Nowacka-Jechalke et al. 2018). Corn pectic polysaccharide inhibited tumor invasion and metastasis to lung by the modulation of inflammation cytokines nuclear factor kappa-B (NF-κB) which responsible for proliferative potency of B12F10 melanoma cells (Jayaram, Kapoor, and Dharmesh 2015). *Sargassum fusiforme* polysaccharides (fucoidan) inhibited the tumor growth in nude mice inoculated with HepG2 cells and nasopharyngeal carcinoma CNE cells by modulating inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) (Fan et al. 2017) and inflammation-related toll-like receptor-2/TLR4 (TLR2/TLR4) receptor pathway (Fan et al. 2018), respectively.

In addition, the intake of NSPs can further trigger the programmed cell death of cancer cells via apoptosis. Modified apple polysaccharide was reported to significantly protect ICR mice against 1,2-dimethylhydrazine/DSS (DMH/DSS)-induced colorectal cancer by lowering the tumor incident. It could inhibit the binding of galectin-3 to its ligand and enhance the apoptosis of the cancer cells (Li et al. 2012). *Sargassum fusiforme* polysaccharides (SFPS) could stimulate the apoptosis of HepG2 cells by regulating the expression of B-cell lymphoma-2-associated X (Bax) and B-cell lymphoma-2 (Bcl-2) and induce apoptosis of the cancer cells (Fan et al. 2017). Another type of *Sargassum fusiforme* polysaccharides (SFPS-B2) inhibited the growth of human gastric cancer cell line SGC-7901 by inducing the cancer cell apoptosis such as increasing the activity of Caspase-9 and Caspase-3, up-regulating the expression of Bax and down-regulating the expression of Bcl-2 (Ji, Ji, and Yue 2014).

Therefore, NSPs are able to ameliorate various types of cancer by inducing apoptosis or by regulating the pro-carcinogenic factors such as the inflammatory cytokines. However, as mentioned above, NSPs cannot be directly absorbed by human body due to the nature of the glycosidic bonds. There must be something acting as a "bridge" between NSPs and cancer improvement. Actually, the intestinal microbiota is the "bridge" since NSPs can be utilized as substrates for bacterial fermentation in the large intestine in humans.

Intestinal microbiota and cancer are closely related

There are a large number of intestinal bacteria in the human body. They are in a dynamic equilibrium state, and generally act to maintain human health. When the balance is broken and the intestinal microbiota is disturbed, this dysbiosis can elevate the risk of multiple tumors, and further stimulate their progression. Conversely, cancers can also cause changes of the intestinal microbiota.

The best-studied bacteria closely relating to the occurrence and development of gastric cancer (GC) is *Helicobacter pylori*. A study evaluating the relationship between fecal microorganisms of subjects with *H. pylori* infection and gastric lesions found that people at high risk for GC had more intestinal microbial species and a higher Shannon index compared to healthy people. Changes in the dominant bacteria of Bacteroidetes, Firmicutes, and Proteobacteria may be involved in the progression of GC caused by *H. pylori* (Gao et al. 2018). Researchers found that GC patients had obvious mucosal microbial abnormalities. They found 21 bacterial taxa were enriched while 10 were depleted. Among them, *Peptostreptococcus stomatis*, *Dialister pneumosintes*, *Slackia exigua*, *Parvimonas micra* and *Streptococcus anginosus* may play crucial roles in the GC development (Coker et al. 2018).

Bacteroides fragilis can induce intestinal epithelial neoplasia and may promote the occurrence of colorectal cancer (CRC) (Toprak et al. 2006). Additionally, a comparative study revealed that a high abundance of *Fusobacterium*

could be detected in the intestinal tract of CRC patients. Patients with intestinal flora structure disorders also have significantly elevated amounts of *Fusobacterium* and *Actinomycota* (Flanagan et al. 2014).

The intestinal microbiota also affect cervical cancer (CCa). A study of patients with CCa revealed a significant increase in intestinal microbial alpha diversity as well as the proportion of the phylum Proteobacteria. The relative abundance of bacteria in 7 genera, including *Escherichia–Shigella*, *Roseburia*, *Pseudomonas*, *Lachnoclostridium*, *Lachnospiraceae*_UCG-004, *Dorea* and *Succinivibrio*, was significantly different between CCa and healthy individuals (Wang, Wang et al. 2019).

The diversity of intestinal microbiota in postmenopausal breast cancer patients was significantly different from that in the healthy group, as well as the composition and function of the intestinal microbial community. *Ruminococcaceae* is more abundant in postmenopausal breast cancer case patients, while *Dorea* and *Lachnospiraceae* are less abundant (Zhu et al. 2018).

Intestinal microbiota may also regulate or respond to the host immune and metabolic balance to affect cancer. Some studies proved that the intestinal microbiota primes tumor-associated myeloid cells for CpG oligodeoxynucleotide (CpG ODN) or anti-interleukin-10 receptor (anti-IL-10R)-induced inflammatory cytokine production, mainly through the TLR4 pathway (Netea et al. 2016; Huo et al. 2019). The oral administration of *Alistipes shahii* to mice before exposure to antibiotics reconstituted the ability of tumor-associated myeloid cells to produce TNF, while *Lactobacillus fermentum* given to intact mice attenuated their response to CpG ODN and anti-IL-10R (Iida et al. 2013). Intestinal microbes can activate dendritic cells (DCs) and hence potentiate the function of T cells, thereby mediating cures in mice with tumors. Furthermore, the presence or absence of lipopolysaccharides (LPS) from Gram-negative (G^-) bacillus influenced the therapeutic effect of total body irradiation on tumor regression (Paulos et al. 2007).

Therefore, some harmful intestinal microorganisms cause mucosal damage and chronic inflammation, or they produce harmful substances, causing the initiation and development of tumors, whereas others will lower the cancer risk or ameliorate cancer in the host via the production of some beneficial metabolites and the regulation of the host inflammation status and immune response.

NSPs ameliorate cancer by modulating the intestinal microbiota

The biological functions of NSPs, including pro-carcinogenic factor reduction or even an anti-cancer effect, are believed to be related to their role as substrates for the intestinal microbiota. Several NSPs, together with their functions, are listed in Table 1.

NSPs may reduce the cancer risk by ameliorating those cancer-related diseases such as obesity and intestinal mucosal injury through intestinal microbiota modulation. Gut dysbiosis and chronic inflammation are normally found in high-fat-diet feeding obese rats (Wang, Li et al. 2017). Apple polysaccharide (AP) increased the abundance of Bacteroidetes and *Lactobacillus* while reduced that of Firmicutes and *Fusobacterium*, resulting in inhibition of gut dysbiosis caused by obesity (Wang, Li et al. 2017). Flaxseed polysaccharide (FP) also had anti-obesity effect and the elevation of the *Clostridium* abundance seemed to be the key to this process (Luo, Li et al. 2018). Intestinal mucosal injury can increase the colon cancer risk (Bibi, Du, and Zhu 2018). Fucoidan increased the abundance of *Coprococcus*, *Rikenella*, and *Butyricicoccus* and mitigated intestinal mucosal injury caused by cyclophosphamide (Shi et al. 2017), while *Ganoderma lucidum* polysaccharide (GLP) increased *Ruminococcus_1*, reduced pathogens such as *Escherichia-Shigella* and relieved intestinal mucosal injury in dextran sodium sulfate (DSS)-treated colitis rats (Xie et al., 2019).

Additionally, NSPs exhibited cancer alleviation directly in animal tumor model by regulating the intestinal microbiota. Jujube polysaccharides (JP) reduced the abundance of bacteria in the Herpotrichiellaceae, Enterobacteriaceae, Aspergillaceae and Lachnospiraceae families and increased that of bacteria in the Lactobacillaceae family in CRC model mice treated with AOM and DSS (Ji et al. 2020). Both guar gum (GG) and GLP alleviated CRC by suppressing the abundance of cecum *Oscillospira* and one unknown genus of *Desulfovibrionaceae* (Luo et al. 2020; Luo, Zhang et al. 2018). GLP also reversed the changes in Firmicutes and Bacteroidetes caused by breast cancer. Specifically, GLP recovered the abundance of *Alistipe*, and increased that of *Prevotellaceae_ucg-001* as well as *Bacteroides*. *Zizyphus jujuba* cv. Muzao polysaccharides (ZMP) specifically increased the abundance of *Actinobacteria* and *Tenericutes*, *Bifidobacterium*, *Bacteroides*, *Lactobacillus*, and *Clostridium*_sp_K4410MGS-306, and decreased the ratio of the Firmicutes/Bacteroidetes (Ji et al. 2019).

These NSPs, which regulated the composition of intestinal microbiota, further changed the expression of some inflammation or cancer-related genes. AP downregulated the inflammatory cytokines, such as plasma lipopolysaccharide-binding protein (LBP), TNF-α, monocyte chemotactic protein-1 (MCP-1), chemokine C-X-C-motif ligand-1 (CXCL-1) and interleukin-1β (IL-1β) (Wang, Li et al. 2017), while fucoidan also downregulated multiple inflammatory cytokines including interferon-γ (IFN-γ), interleukin-4 (IL-4), TNF-α, and IL-1β (Shi et al. 2017). FP reduced the concentration of serum TNF-α, IL-6 and IL-1β (Luo et al. 2019). Same cytokines (TNF-α, IL-6 and IL-1β) were also reduced in the serum and colon tissues after ZMP consumption (Ji et al. 2019). The intake of GLP resulted in the upregulation of six inflammation-related genes (*Ccl5*, *Cd3e*, *Cd8a*, *Il21r*, *Lck* and *Trbv*), downregulation of five inflammation-related genes (*Ccl3*, *Gro*, *Il11*, *Mhc2* and *Ptgs*) and four cancer-related genes (*Acaa1b*, *Fabp4*, *Mgll* and *Scd1*) in colonic epithelial cells (Xie et al., 2019; Luo, Zhang et al. 2018). GLP can also increase the level of phosphorylated extracellular regulated protein kinases (ERK), c-JunN-ternimalkinase (JNK), p38 mitogen-activated protein kinase (p38 MAPK) and p65, resulting in inhibition of the growth of cancer (Li et al. 2018). Different from the GLPs, GG regulated the expression of five epithelial genes (*Il10*, *Cytl1*, *Ighv1-14*,

Table 1. Improvement of NSPs on cancer-related diseases and cancer through intestinal microbiota.

Types	Diseases	Results	References
AP	Gut dysbiosis and chronic inflammation	Increased the abundance of Bacteroidetes and *Lactobacillus*; reduced Firmicutes and *Fusobacteium*. Downregulated plasma LBP, TNF-α, MCP-1, CXCL-1 and IL-1β.	Wang, Li et al. 2017
FP	Obesity	Increased the abundance of *Clostridium*; Reduced the concentration of TNF-α, IL-6 and IL1-β in serum.	Luo, Li et al. 2018; Luo et al. 2019
Fucoidan	Intestinal mucosal injury	Increased the abundance of *Coprococcus*, *Rikenella*, and *Butyricicoccus*. Increased occluding and E-cadherin; Decreased IFN-γ, IL-4, TNF-α and IL-1β	Shi et al. 2017
GLP	Colitis	Increased *Ruminococcus_1*; Reduced pathogens such as *Escherichia-Shigella* Upregulated six inflammation-related genes (*Ccl5*, *Cd3e*, *Cd8a*, *Il21r*, *Lck*, and *Trbv*); Downregulated five inflammation-related genes (*Ccl3*, *Gro*, *Il11*, *Mhc2*, and *Ptgs*)	Xie et al. 2019
GG	Colorectal cancer	Altered the abundance of *Oscillospira* and an unknown genus of Desulfovibrionaceae, Upregulated the genes in host epithelial cells, including *Il10*, *Cytl1*, *Ighv1-14*, *Igfbp6* and *Foxd3*	Luo et al. 2020
GLP	Breast cancer	Recovered the abundance of *Alistipe*; increased the abundance of *prevotellaceae_ucg-001* and *Bacteroides*. Increased the expression of phosphorylated ERK, JNK, p38 MAPK and p65	Li et al. 2018
GLP	Colorectal cancer	Reduced the relative abundance of cecal *Oscillospira* and an unknown genus of *Desulfovibrionaceae*, Downregulated 4 genes related to cancer, *Acaa1b*, *Fabp4*, *Mgll* and *Scd1* of colonic epithelial cells	Luo, Zhang et al. 2018
JP	Colorectal cancer	Reduced the ratio of Firmicutes to Bacteroidetes by expanding Bacteroidetes Increased the abundance of Lactobacillaceae and reduced abundances of Herpotrichiellaceae, Enterobacteriaceae, Aspergillaceae and Lachnospiraceae on the family level	Ji et al. 2020
ZMP	Colon tumorigenesis	Increased the richness of *Bifidobacterium*, *Bacteroides*, *Lactobacillus*, *Actinobacteria*, *Tenericutes* and *Clostridium*_sp_K4410MGS-306; Decreased the *Firmicutes*/*Bacteroidetes* Inhibited the levels of IL1-β, IL-6, and TNF-α in serum and colonic tissues	Ji et al. 2019

AP: Apple polysaccharides; FP: Flaxseed polysaccharides; GG: Guar gum; GLP: *Ganoderma lucidum* polysaccharides; JP: Jujube (*Ziziphus jujuba* Mill.) polysaccharides; ZMP: *Zizyphus jujuba cv. Muzao* polysaccharides.

Igfbp6 and *Foxd3*) to exhibit its anti-CRC effect (Luo et al. 2020).

Therefore, the intake of NSPs can remodel the intestinal microbiota, such as the elevation of some health-beneficial bacteria proportion. It can further regulate the expression of cancer-related genes and the inflammatory cytokine genes, reduce the cancer risk, and reverse the tumor development. Bacterial metabolites such as SCFAs were generally believed to be one of the mediators during this process. However, in our previous research, we did not find SCFAs generated from FP fermentation by intestinal microbiota have a dose-dependent effect in amelioration of obesity, one of the pro-carcinogenic factors of cancer (Luo, Li et al. 2018). In this sense, there may be some bacterial metabolites besides SCFAs as the mediator to explain the cancer improvement during the interaction between NSPs and intestinal microbiota. Most recently, epitranscriptomic modifications as an additional level of interaction between commensal bacteria and their host has been highlighted. Specifically, the methylation profiles were altered with the lack of methyl donor substance, S-adenosylmethionine (SAM), due to the reduced SAM synthase (Mat2a) expression affected by intestinal microbiota (Jabs et al. 2020). Since NSPs have an impact on intestinal microbiota, it is possible that the mediators among NSPs, intestinal microbiota and cancer during the epitranscriptomic modifications will be the methyl donor substances. Hence, we will focus on these substances in the following sections.

Changes of intestinal microbiota affect the supply of methyl donors

In recent years, epigenetic/epitranscriptomic modifications have been recognized to play an important role in the initiation and progression of colon cancer, and the alteration of methylation is believed to be associated with the cancer risk (Guo et al. 2018). At the same time, the consumption of NSPs lowered the cancer risk and exhibited cancer improvement associated with the altered intestinal microbiota, indicating that intestinal microbiota and methylation are connected. Actually, methyl donor substances can be generated by intestinal microbiota, and the alteration of intestinal microbiota can affect the supply of methyl donors.

One-carbon metabolism pathway and methyl donors

One-carbon metabolism is a common biochemical pathway through which methyl groups (CH_3) are generated.

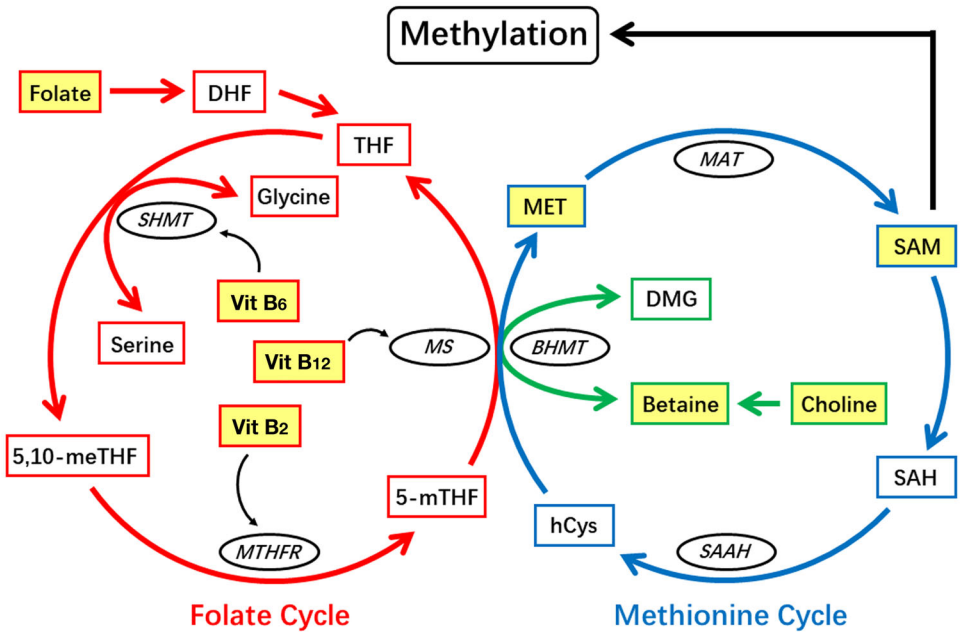

Figure 1. Folate and methionine cycle in the one-carbon metabolism pathway (Anderson, Sant, and Dolinoy 2012; Mentch and Locasale 2016; Friso et al. 2017). In the folate cycle, folate is first reduced to dihydrofolate (DHF) and subsequently to tetrahydrofolate (THF). Catalyzed by serine hydroxymethyltransferase (SHMT), which contains vitamin B_6 (Vit B_6) as its coenzyme, a methyl group is transferred from THF to generate 5, 10-methyleneTHF (5, 10-meTHF). The 5, 10-meTHF is further converted to 5-methylTHF (5-mTHF) with the irreversible catalysis of a vitamin B_2 (Vit B_2)-containing enzyme, methylenetetrahydrofolate reductase (MTHFR). With the aid of methionine synthase (MS), which contains a vitamin B_{12} (Vit B_{12}) co-factor, homocysteine (hCys) accepts the methyl group from 5-mTHF, and methionine (MET) is produced. The MET will then participate in the methionine cycle. The 5-mTHF is thereby converted to THF and completes the folate cycle; In the methionine cycle, S-adenosylmethionine (SAM), the universal methyl donor for all methylation, is produced from MET by methionine adenosyltransferase (MAT). After donating a methyl group, SAM is converted to S-adenosylhomocysteine (SAH), and SAH is further converted to homocysteine (hCys) with the catalysis of S-adenosylhomocysteine hydrolase (SAHH). To complete the cycle, hCys can be remethylated to regenerate MET by accepting methyl groups donated from 5-mTHF catalyzed by MS or from choline and/or betaine catalyzed by betaine-homocysteine S-methyltransferase (BHMT). Overall, methyl groups were generated via the folate cycle (red) and/or generated by betaine metabolism (green) and transferred to the methionine cycle (blue) to produce MET and then SAM.

The methyl groups are then utilized for the biological methylation of proteins, phospholipids and nucleic acids, including DNA and RNA, which is one of the main epigenetics characteristics of the mammalian genome (Friso et al. 2017).

Two major components including the folate cycle and the methionine cycle are involved in this pathway (Figure 1), resulting in the transfer of methyl groups to the acceptor substrates (Mentch and Locasale 2016). Those substances in these two cycles that donated the methyl groups are called methyl donors. Among them, SAM is the most direct and universal methyl donor for all of the biological methylation described above. Other common methyl donors are methionine (MET), choline, betaine, and folate. Additionally, vitamins B_2, B_6, and B_{12} are also important since they are the coenzymes of some key enzymes involved in the methyl group transfer in one-carbon metabolism. All of these methyl donors mentioned can be obtained in diets while they can also be biosynthesized in prokaryotes such as bacteria. Furthermore, their metabolism can be affected by intestinal bacteria. There must be some relationship between intestine microflora and methyl donors.

Intestinal microflora and methyl donors

Massive works have indicated that the intestinal microflora might be considered as important mediators of the epigenome. They may alter the epigenome through intestinal microbial metabolites. Methylation, as one of the characteristics of epigenetics, is also closely related to the microbial metabolites (Majnik and Lane 2015). Human and animal studies revealed that dietary components can affect the colonization of commensal bacteria and change the microbial structure (Li et al. 2019). In this process, some epigenetic-active metabolites produced by gut bacteria such as methyl donor substances including folate and choline will be changed, resulting in alterations of methylation. Herein, we will focus on the association of intestinal microflora alterations and those methyl donors generated in the one-carbon metabolism pathway.

Intestinal microflora alteration and MET or SAM

MET, an essential amino acid of humans, is one of the less abundant amino acids in proteins in all organisms, including the bacteria. Still, it serves as a substrate of MAT and is converted to SAM, the prime carrier of methyl groups.

Biosynthetic pathways of MET could be found in almost all species of bacteria. Moreover, SAM could also be produced by *E. coli* (Chen et al. 2016). Furthermore, studies have also reported that strains of lactic acid bacteria (LAB), including those bacteria in the genus of *Enterococcus* and *Bacillus*, had an ability to produce a large amount of SAM in vitro (Park et al. 2014). These findings indicate commensal bacteria, such as *E. coli* and some other LAB mentioned, were capable of producing MET and even SAM in the hosts' intestine. The influence of MET biosynthesis

could also have occurred due to the interactions among the bacteria. In an in vitro assay, *Ruminococccus gnavus* ATCC 29149 and *R. bromii* L2-63 were cocultured in a medium with resistant starch as the sole carbon source, and a decrease of vitamin B_{12}-dependent methionine biosynthesis was obtained compared to the *R. bromii* mono-culture (Crost et al. 2018). A recent study using an in vivo rodent model demonstrated that supplementation with *Lactobacillus reuteri* DSM 17938 altered the composition of the intestinal microbiota and increased the level of several methionine derivatives, including SAM (Liu, Tian et al. 2019). Based on the results in previous studies, it can be concluded that the alteration of intestinal microflora affected the supply of MET and/or SAM.

Intestinal microflora alteration and B-vitamins

Folate is a water-soluble B-vitamin available from various foods or as a supplement. The main absorption occurs in the small intestine, but it can also be absorbed in the large intestine. It is the most extensively studied micronutrient due to its influence on epidemiological methylation in rodents and humans (Anderson, Sant, and Dolinoy 2012). It donates a methyl group to MET via the folate cycle and further increases SAM. Vitamin B_{12}, or cobalamins, is also a water-soluble B-vitamin that is critical for one-carbon metabolism, and it creates methyl groups. It acts as a co-factor of MS, and therefore becomes a connection between the folate and methionine cycle. Vitamin B_6 and B_2 are also water-soluble and serve as coenzymes of SHMT and MTHFR, respectively. They assist the transfer of methyl groups in the folate cycle of the one-carbon metabolism pathway.

A recent study compared the stool microbiome profile of children and adults. According to their results, diverse intestinal microbial structures were found, accompanied by different predicted functional metagenome profiles. In children, genes on the riboflavin (vitamin B_2), pyridoxine (vitamin B_6) and folate (vitamin B_9) biosynthesis pathways were activated. In contrast, genes on the thiamin (vitamin B_1) and pantothenic (vitamin B_5) biosynthesis pathways were activated in adults (Radjabzadeh et al. 2020).

Moreover, B-vitamin biosynthesis should be the outcome of co-operations among intestinal microbes (Magnúsdóttir et al. 2015). Therefore, it seems that various microbial structures will lead to different types of B-vitamin production, and the alterations of certain bacteria will affect the content of B-vitamins, including folate (methyl donor), vitamin B_{12}, B_6 and B_2. Actually, increased *Bifidobacteria* was found to be associated with adequate folate and vitamin B_{12} in people with low-grade inflammation (Valentini et al. 2015). Some specific bacteria did have the ability to produce folate, such as *Bifidobacteria* and *Lactobacilli*. Several folate-producing strains were selected within the genus *Bifidobacterium* in an in vitro study. The results demonstrated that most of the bacteria belonged to the species *B. adolescentis* and *B. pseudocatenulatum* that could produce folate and release it into the medium. Further evaluation of plasma folate was achieved in an animal assay to confirm this vitamin was produced and absorbed (Rossi, Amaretti, and Raimondi 2011).

Another assay indicated that all strains of human-residential *Bifidobacteria* (HRB) had the ability to produce folate in vitro. In contrast, most strains of non-HRB, except the *B. thermophilum* and *B. longum* ssp. suis strains, did not (Sugahara et al. 2015). Different from the *Bifidobacteria*, only *Lactobacillus plantarum* was capable of producing folate in vitro. Nevertheless, it should be tested in animal trials to validate its ability of in vivo production of folate (Rossi, Amaretti, and Raimondi 2011). Lately, based on the analysis of bioinformatics, a report concluded that bacterial folate synthesis genes were common in 512 gastrointestinal (GI) reference genomes, of which 13% contained all of the genes required for complete de novo synthesis of folate and an additional 39% contained genes for folate synthesis in the presence of *p*-aminobenzoic acid (pABA) (Engevik et al. 2019). For vitamin B_{12}, certain strains of LAB can produce this complex vitamin (LeBlanc et al. 2013).

These works all support the fact that specific intestinal bacteria have an ability to produce folate, one of the methyl donors, both in vitro and in vivo. In addition, co-factors of key enzymes of the folate cycle in one-carbon metabolism, including vitamin B_{12}, B_6 and B_2, were also produced via intestinal microbiota. Hence, alteration of the intestinal microbiota structure, either by the health status or by dietary interventions, would ultimately affect the supply of folate as well as other B-vitamins involved in the folate cycle.

Intestinal microflora alterations and choline and betaine

Choline is an important chemical participating in many biologic reactions. For one thing, it is the precursor of trimethylamine (TMA). It can be oxidized to trimethylamine oxide (TMAO) by flavin-containing monooxygenase 3 (FMO3), increasing the risk of cardiovascular disease. For another thing, it is the precursor of betaine. It can provide methyl groups for remethylation of hCys to generate dimethylglycine (DMG) and MET (Smallwood, Allayee, and Bennett 2016) (Figure 2).

Gut commensals such as *E. coli*, are able to produce choline in vivo by hydrolyzing phosphatidylcholine to release choline (Wright 2019). Therefore, when the composition of the intestinal microbiota alters, the choline levels will also be changed. Especially, the microbiota can affect the destination of choline metabolism, making it a supply of methyl donors or a substance harmful to the cardiovascular system. TMA-lyase (cutC) is essential for the conversion of choline to TMA. The "cut" gene cluster including the genes encoding cutC was discovered in sulfate-reducing bacteria (Krishnan, Alden, and Lee 2015). Hence, reducing the abundance of these sulfate-reducing bacteria could be a strategy to avoid TMA and TMAO formation and potentially promote choline metabolism to another destination. In fact, changes in the composition of the intestinal microbiota through dietary interventions will be accompanied by changes in the functional genome involved in the choline utilization pathway (Li, Tian et al. 2019). For instance, nopal cladode consumption modified the intestinal microbiota composition and generated a high serum level of betaine (Moran-Ramos et al. 2017). It should be noted that betaine can be metabolized

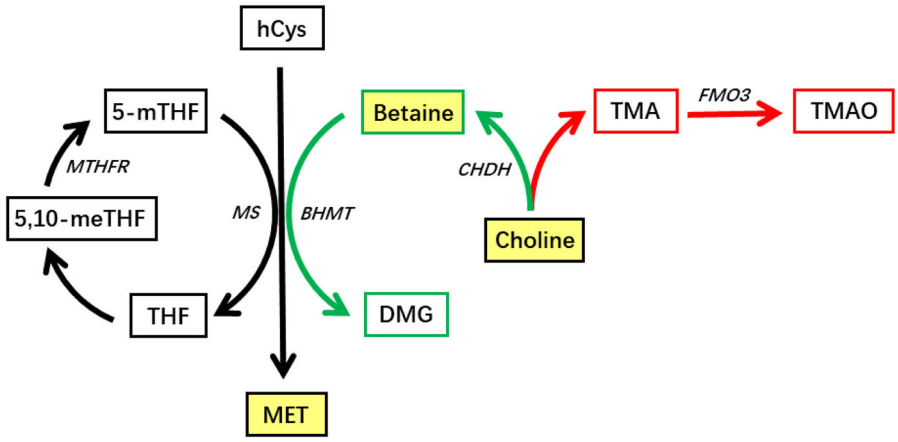

Figure 2. Two branches in choline metabolism (Smallwood, Allayee, and Bennett 2016). THF: tetrahydrofolate; 5, 10-meTHF: 5, 10-methyleneTHF; 5-mTHF: 5-methylTHF; hCys: homocysteine; MET: methionine; DMG: dimethylglycine; TMA: trimethylamine; TMAO: trimethylamine oxide; MTHFR: methylenetetrahydrofolate reductase MS: methionine synthase; BHMT: betaine-homocysteine S-methyltransferase; CHDH: choline dehydrogenase; FMO3: flavin-containing monooxygenase 3. Choline metabolism has two destinations, one is conversion to TMA, then to TMAO (red) and the other one is conversion to betaine and further to DMG (green). The latter pathway provides methyl groups and participates in one-carbon metabolism (black).

into betainized compounds via intestinal bacteria, including proline betaine (Koistinen et al. 2019). Nevertheless, these betainized compounds can also provide methyl groups in the presence of other gut bacteria. Human intestinal isolate *Eubacterium limosum* ATCC 8486 is reported to carry MtpB, a member of the trimethylamine methyltransferase (MttB) superfamily. MtpB catalyzes the anoxic demethylation of proline betaine, generating methyl groups and participating in THF methylation (Picking et al. 2019), which thereby enters the folate cycle.

These studies illustrate that the intestinal microbiota have a very close relationship with choline and betaine production and metabolism. Therefore, alteration of the microbiota could affect the supply of methyl donors, including choline and betaine.

Methyl donor supply and methylation

Methylation refers any chemical reaction that introduces a methyl group into a substance. In biological systems, methylation is catalyzed by specific enzymes such as methyltransferases. As mentioned above, SAM is the most universal methyl donor, while other common methyl donors include MET, choline, betaine and folate. Methylation is commonly found among nucleotides, including DNA and RNA (Mosca, Leheup, and Dreumont 2019). The supply of methyl donors affects the methylation and consequently affects health (Shorter, Felder, and Vrana 2015).

The biochemical mechanism of DNA methylation has been comprehensively studied. Multiple researchers have reported an association of the methyl donor supply with methylation alterations. Pogribny et al. (2008) concluded that long-term administration of diets lacking methyl donors resulted in alterations of global DNA methylation in the brain; Geng et al. (2015) confirmed that the folate supply (folate deficiency) was able to change the methylation patterns of the genome; Wang, Zhang et al. (2014) proved that betaine supplementation elevated genomic methylation in mice fed a high-fat diet. These results indicate that methyl donor status could influence the gene expression of methyltransferase and global DNA methylation as well.

As another type of nucleic acid methylation, RNA methylation is an important event in RNA modification. Observations of the methyl donor supply and transfer RNA (tRNA) methylation originated in the late 1970s (Lapeyre and Becker 1979; Phizicky and Hopper 2015). It was reported that rats fed methyl groups (methionine, folate, and choline)-deficient diets developed hypomethylation of hepatic tRNAs (Christman et al. 1993). In addition, methionine deprivation altered the activity of tRNA methyltransferase in vitro (Tisdale 1980). Actually, RNA methyltransferases, either recombinant or naturally existing methyltransferase like 3/methyltransferase like 14 (METTL3/METTL14), which is responsible for N^6-methyladensosine (m^6A) formation, were reported to utilize SAM as the methyl donor (Liu et al. 2014). Therefore, similar to DNA methylation, the supply of methyl donors could affect RNA methylation, probably due to the influence of methyl donors on methyltransferase activity.

Nevertheless, it is still necessary to further evaluate the influence of methyl donors that are biosynthesized or metabolized by intestinal microbiota on RNA methylation because RNA methylation is related to lots of diseases including cancer (Sun, Wu, and Ming 2019).

RNA methylation, especially for the m^6A, is closely related to human cancer

In recent decades, the availability of new technology and understanding have revealed linkages between RNA methylation and disease. Methylation of RNA occurs at a variety of atoms, nucleotides, sequences and tertiary structures, and is involved in different RNA species, including tRNA, rRNA, mRNA, tmRNA, snRNA, snoRNA, miRNA, and viral RNA. RNA methylation also strongly related to other post-transcriptional modifications. More than 150 types of post-transcriptional modifications were identified in RNAs including m^6A, N^1-methyladenosine (m^1A), 5-methylcytosine (m^5C) (Sun, Wu, and Ming 2019).

Among all of the RNA modifications, m^6A, methylated at the N^6 position of adenosine, is the most prevalent internal modification on eukaryotic mRNA, accounting for approximately 50% of total methylated ribonucleotides (He et al. 2019; Yue, Liu, and He 2015). It contains methyltransferase complexes ("writers"), demethylases ("erasers") and proteins that recognize and bind to m^6A-modified RNAs, leading to different destinies of them such as translation or degradation ("readers") (He et al. 2019). It is involved in various aspects of RNA metabolism, including pre-mRNA splicing, 3′-end processing, nuclear export, translation regulation, mRNA decay and noncoding RNA (ncRNA) processing (Sun, Wu, and Ming 2019). Studies have discovered that m^6A modifications in RNA play a crucial role in many physiological processes, including circadian rhythms (Wang et al. 2015), spermatogenesis (Lin et al. 2017), embryogenesis (Qi et al. 2016), heat shock responses (Yu, Li, et al. 2018), DNA damage response (Robinson et al. 2019), pluripotency and reprogramming (Aguilo and Walsh 2017). Therefore, it is reasonable that m^6A modification of RNA is involved in the pathogenesis of tumors. Herein, we review recent studies of m^6A modification in cancer-related genes and pro-carcinogenic inflammatory cytokine genes.

m^6A modified cancer-related genes

m^6A methylation of cancer-related genes affected the progression of multiple cancers (Table 2).

On one hand, m^6A methylation inhibits tumor progression by modifying the cancer-related genes. The reduction of m^6A methylation by down-regulating the "writers" or up-regulating the "erasers" may stimulate the tumor development and progression. It is reported that the reduced m^6A methylation of a disintegrin and metallopeptidase domain 19 (ADAM19), ephrin type-A receptor 3 (EPHA3) and Kruppel-like factor 4 (KLF4) mediated by methyltransferase-like protein 3/14 (METTL3/14) knockout, ultimately led to their upregulation and further tumorigenesis in glioblastoma stem cells (GSC) (Cui et al. 2017). Similarly, lower METTL3 expression or METTL14 mutation could reduce the m^6A methylation and lead to the endometrial cancer cell growth by activating the protein kinase (AKT) signaling (Liu, Eckert, et al. 2018). Fat mass and obesity-associated protein (FTO) mediated m^6A demethylation in the 3'-UTR of tumor suppressor BCL2/adenovirus E1B 19 kDa-interacting protein 3 (BNIP3) and induced its degradation (Niu et al. 2019). FTO also repressed the m^6A methylation of β-catenin and led to chemo-radiotherapy resistance of cervical cancer (Zhou et al. 2018), and decreased the m^6A level to increase the mRNA stability of oncogene *Usp7* in lung cancer. However, modulation of those specific m^6A components including recovery of "writers" and inhibition of "erasers" to maintain the methylated RNA level could suppress the cancer growth. For example, METTL14 suppressed the metastatic potential of hepatocellular carcinoma by modulating the m^6A level of primary MicroRNA 126 (pri-miR126) (Ma et al. 2017). Inhibition of the FTO suppressed GSC growth and self-renewal (Cui et al. 2017), and also caused repression of acute myeloid leukemia (AML) due to the reduction of myelocytomatosis oncogene (MYC) and CCAAT/enhancer binding protein alpha (CEBPA) transcripts by increasing m^6A methylated level (Su et al. 2018). Additionally, some m^6A "readers" such as YTH N^6-methyladenosine RNA binding protein 1 (YTHDF1) recognized the methylated mRNA of a tumor suppressor histidine triad nucleotide binding protein 2 (HINT2) and promoted its translation and inhibited the ocular melanoma progression (Jia et al. 2019).

On the other hand, m^6A modification promotes tumor progression. The m^6A "writer" METTL14 increased the m^6A methylation of myeloblastosis oncogene (MYB) and MYC, and promoted the AML (Weng et al. 2018). METTL3 up-regulated the expression of oncoprotein hepatitis B X-interacting protein (HBXIP) by promoting its m^6A modification in breast cancer cells (Cai et al. 2018). In bladder cancer, METTL3 m^6A modified AF4/FMR2 family member 4 (AFF4), inhibitor of nuclear factor kappa B kinase subunit beta (IKBKB), RELA proto-oncogene, nuclear factor kappa B subunit (RELA), MYC (Cheng et al. 2019), as well as the 3′-UTR of CUB domain containing protein 1 (CDCP1) (Yang et al. 2019), promoting the translation of these oncogenes. METTL3 together with YTH domain containing 1 (YTHDC1) also elevated the m^6A level of circle NOP2/Sun RNA methyltransferase 2 (circNSUN2) to promote CRC patients with liver metastasis (Chen et al. 2018). In GC, the level of m^6A methylated heparin binding growth factor (HDGF) was significantly increased, and further promoted the cancer growth mediated by METTL3 (Wang, Chen et al. 2019). The m^6A modification regulated by another "writer" WT1 associated protein (WTAP) suppressed sulfotransferase family 1E member 1 (EST1) expression and accelerated hepatocellular carcinoma (HCC) progression (Chen, Peng et al. 2019). Increased frizzled homolog 10 (FZD10) m^6A modification was mediated by downregulating FTO and human AlkB homolog H5 (ALKBH5), and resulted in the poly (ADP-ribose) polymerase inhibitors (PARPi) resistance in epithelial ovarian cancer cells which made the therapy more difficult (Fukumoto et al. 2019). In this sense, lower the m^6A level of certain genes could suppress the tumor growth. For example, knockdown of METTL3 substantially abolished the m^6A modification of suppressor of cytokine signaling 2 (SOCS2) and augmented its expression in HCC (Chen et al. 2018). The silencing of METTL3 also reduced the m^6A level of methylated lymphoid enhancer binding factor 1 (LEF1) and inhibited the osteosarcoma (Miao et al. 2019). Demethylation of WNT inhibitory factor 1 (WIF1) RNA methylation by ALKBH5 was able to suppress pancreatic cancer by mediating Wnt signaling (Tang et al. 2020).

In summary, m^6A RNA methylation plays an important role in tumor initiation and progression, and the tumorigenesis could be suppressed by modulating m^6A methylation of those cancer-related genes.

m^6A modified the pro-carcinogenic inflammatory cytokine genes

Strong evidence has been proposed that inflammation and tumorigenesis was closely connected (Zitvogel, Petrocola, & Kroemer, 2017). Metabolic dysregulation such as obesity,

Table 2. Information about the relationship between cancer-related genes and m^{6}A components.

Cancer type	Component	Function	Related genes	Mechanism	Reference
AML	METTL14	Promote	MYB, MYC	METTL14 regulates MYB and MYC mRNA through m^{6}A methylation	Weng et al. 2018
	FTO	Promote	MYC, CEBPA	FTO is associated with MYC and CEBPA. Inhibition of FTO leads to stability reduction of MYC and CEBPA by increasing the m^{6}A methylated level	Su et al. 2018
Bladder cancer	METTL3	Promote	AFF4, NF-κB (IKBKB, RELA), MYC	METTL3 and METTL3-mediated m^{6}A modification overexpress in cancer. The modification targets AFF4, NF-κB (IKBKB, RELA), and MYC directly.	Cheng et al. 2019
	METTL3 YTHDF1 ALKBH5	Promote Promote Suppress	CDCP1	METTL3 and m^{6}A reader YTHDF1 preferentially recognize m^{6}A residues on CPCP1 3′-UTR and promote oncogene CDCP1 translation; demethylases ALKBH5 also mediates the m^{6}A of CDCP1.	Yang et al. 2019
Breast cancer	FTO	Promote	BNIP3	FTO mediates m^{6}A demethylation in the 3′-UTR of tumor suppressor BNIP3 mRNA and induces its degradation.	Niu et al. 2019
Breast cancer	METTL3	Promote	HBXIP, let-7g	METTL3 promotes the expression of HBXIP through m^{6}A modification, further inhibits the tumor suppressor let-7g	Cai et al. 2018
Cervical cancer	FTO	Promote	β-catenin	FTO repressed the m^{6}A methylation of β-catenin leading to chemo-radiotherapy resistance of cancer	Zhou et al. 2018
CRC	METTL3	Promote	SOX2, IGF2BP2	METTL3 methylates SOX2 transcripts, making it can be recognized by IGF2BP2 to prevent SOX2 mRNA degradation and promote CRC	Li, Hu et al. 2019
CRC	METTL3 YTHDC1	Promote Promote	circNSUN2	YTHDC1 and METTL3 relate to cytoplasmic export of circNSUN2. m^{6}A methylation levels are elevated, and CRC cells invasion activity is promoted. m^{6}A modification of circNSUN2 modulates cytoplasmic export and stabilizes HMGA2 to promote liver metastasis	Chen, Chen et al. 2019
Endometrial cancer	METTL3 METTL14	Suppress Suppress	PHLPP2, mTORC2	METLL14 mutation or reduced METTL3 expression probably reduces m^{6}A methylation leading to tumor growth. The decreased methylation leads to AKT signaling activation (downregulation of negative AKT regulator PHLPP2 and upregulation of positive AKT regulator mTORC2)	Liu, Eckert, et al. 2018
GC	METTL3	Promote	HDGF, GLUT4, ENO2	METTL 3 increases m^{6}A methylation, and stimulates HDGF mRNA, further activates GLUT4 and ENO2 expression	Wang, Chen et al. 2019
GSC	METTL3 METTL14 FTO	Suppress Suppress Promote	ADAM19, EPH3, KLF4	Knockdown of METTL3 or METTL14 promotes GSC, probably by alteration of mRNA m^{6}A enrichment, upregulation of oncogene ADAM19, EPHA3 and KLF4; overexpression of METTL3 or inhibition of the RNA demethylase FTO suppresses GSC growth and self-renewal.	Cui et al. 2017
HCC	METTL3	Promote	SOCS2	Knockdown of METTL3 substantially abolishes SOCS2 mRNA m^{6}A modification and augments SOCS2 mRNA expression	Chen et al. 2018
	METTL14	Suppress	DGCR8, miR-126	METTL14 interacts with DGCR8, positively modulates the primary microRNA 126	Ma et al. 2017
	WTAP	Promote	ETS1	The m^{6}A modification regulated by WTAP leads to the suppression of ETS1, a gene which could inhibit the progression of HCC	Chen, Peng et al. 2019
Lung cancer	FTO	Promote	USP7	FTO decreases the m^{6}A level and increases mRNA stability of USP7	Li, Han et al. 2019
Ovarian cancer	FTO ALKBH5	Suppress Suppress	FZD10, PARPi	Downregulation of FTO and ALKBH5 is sufficient to increase FZD10 mRNA m^{6}A modification, contributing to PARPi resistance by upregulating the Wnt/β-catenin pathway in BRCA-mutated EOC cells	Fukumoto et al. 2019
Ocular melanoma	YTHDF1	Suppress	HINT2	The RNA methylation inhibits the cancer progression. YTHDF1 promotes the translation of methylated HINT2 mRNA, a tumor suppressor in ocular melanoma	Jia et al. 2019
Osteosarcoma	METTL3	Promote	LEF1	The m^{6}A level was upregulated in cancer. METTL3 silencing decreases the m^{6}A methylation and total mRNA level of LEF1 and further inhibits the activity of Wnt/β-catenin signaling pathway	Miao et al. 2019
Pancreatic cancer	ALKBH5	Suppress	WIF1	ALKBH5 reduces WIF1 RNA methylation and mediates Wnt signaling to suppress the cancer	Tang et al. 2020

AML: acute myeloid leukemia; GC: gastric cancer; GSC: glioblastoma stem cell; HCC: hepatocellular carcinoma; CRC: colorectal cancer; RCC: renal cell carcinoma.

Table 3. Information about the relationship between cancer-related inflammatory cytokine genes and m^{6}A components.

Cells	Component	Function	Cytokines	Mechanism	Reference
Endothelial cell	METTL14	Promote	FOXO1	METTL14 directly binds to FOXO1 mRNA, increases its m^{6}A modification, and enhances its translation; METTL14 knockdown significantly decreases TNF-α-induced FOXO1 expression.	Jian et al. 2020
Hepatocellular carcinoma	YTHDF2	Suppress	IL11	YTHDF2 processes the decay of m^{6}A-containing IL-11, and IL11 is responsible for the inflammation-mediated malignancy and disruption of vascular normalization.	Hou et al. 2019
HK2 cell line	FTO	Suppress	PPAR-α	Downregulation of FTO increases the m^{6}A methylation of PPAR-α, which ultimately leads to activation of NLRP3 inflammasomes and NF-κB-driven renal inflammation in the kidney	Yu et al. 2021
IPEC-J2 cell	METTL3	Promote	TRAF6	Depletion of METTL3 decreases the m^{6}A level of TRAF6, and reduces its expression, leading to the suppression of inflammatory signaling pathway	Zong et al. 2019
HTC (Mouse)	YTHDF2	Suppress	STAT1	YTHDF2 recognizes m^{6}A-modified transcripts that related to inflammatory cytokines such as STAT1 and promotes their degradation	Mapperley et al. 2021
THP-1 cell HEK 293 T cells PBMCs	YTHDF2	Suppress	KDM6B	m^{6}A-modified KDM6B is degraded mediated by YTHDF2. YTHDF2 deficiency stabilizes KDM6B to promote H3K27me3 demethylation of multiple proinflammatory cytokines and subsequently enhances their transcription.	Wu et al. 2020

HK2 cell line: human kidney tubular epithelial cell line; IPEC-J2 cell: intestinal porcine epithelial cell line J2 cell; HTC (Mouse): mouse hematopoietic stem cells; THP-1 cells: human myeloid leukemia mononuclear cells; HEK 293 T cells: human embryonic kidney 293 T cells; PBMCs: peripheral blood mononuclear cells.

type 2 diabetes and nonalcoholic fatty liver disease may cause low-grade inflammation (Tilg et al. 2020), which had been considered as pro-carcinogenic factors (Iyengar et al. 2016). These inflammation-related pro-carcinogenic factors can also be regulated by m^{6}A modification. Transcriptome-wide high-throughput m^{6}A sequencing revealed that multiple genes enriched in inflammation-related pathways were m^{6}A modified in human rheumatoid arthritis fibroblast-like synoviocytes cell line MH7A (Jiang et al. 2021). Actually, some studies on the modulation of inflammatory cytokines by m^{6}A modification have been reported in recent years (Table 3). Increased m^{6}A methylation and translation of forkhead box O1 (FOXO1) due to its binding to METTL14, resulted in endothelial inflammation (Jian et al. 2020). Similarly, increased m^{6}A methylation of peroxisome proliferator activated receptor alpha (PPAR-α) due to downregulation of FTO ultimately led to the activation of NLR family pyrin domain containing 3 (NLRP3) inflammasomes and (nuclear factor kappa B) NF-κB-driven renal inflammation in the kidney (Yu et al. 2021). Hence, reduction of the m^{6}A level will sometimes suppressed the inflammation. For example, depletion of METTL3 decreased the m^{6}A methylated TNF receptor associated factor 6 (TRAF6) and led to the suppression of NF-κB and MAPK signaling pathway (Zong et al. 2019).

Differently, m^{6}A "reader" YTH N^6-methyladenosine RNA binding protein 2 (YTHDF2) recognized the m^{6}A methylated genes, and generally suppress the inflammation. It is reported that YTHDF2 recognized m^{6}A-modified inflammatory cytokines transcripts such as signal transducer and activator of transcription 1 (STAT1) and promoted their degradation in hematopoietic stem cells (Mapperley et al. 2021). Besides, m^{6}A-containing interleukin 11 (IL11) can be decayed by YTHDF2, which was responsible for the suppression of inflammation-mediated malignancy and disruption of vascular normalization in HCC (Hou et al. 2019). The mRNA of lysine demethylase 6B (KDM6B) was m^{6}A-modified and also further decayed by YTHDF2, and the enhancement of multiple proinflammatory cytokines were hereby prohibited (Wu et al. 2020).

Additionally, it is also reported that m^{6}A components such as METTL3 (writer) and YTHDF2 (reader) directly regulated the LPS-induced inflammatory response by modulating multiple inflammatory cytokines in human myeloid leukemia mononuclear cells (THP-1) and leukemia cells in mouse macrophage (RAW264.7), respectively (Wang, Yan et al. 2019; Yu et al. 2019).

Therefore, m^{6}A methylation affects the inflammation by modification of inflammatory cytokines as well as by direct regulation of m^{6}A components themselves. Since inflammation is considered as pro-carcinogenic factor, m^{6}A should also play an important role in tumorigenesis by modulating inflammation.

Could the in vivo cancer improvement of some NSPs be attributed to changing m^{6}A methylation through intestinal microbiota?

The role of NSPs in reducing cancer risk is well recognized. Since m^{6}A is also closely related to cancer initiation and progression, could the anti-cancer effect of NSPs be attributed to m^{6}A alteration by affecting the methyl donor substances generating from NSP fermentation by the intestinal microbiota?

We present a schematic diagram to speculate how NSPs ameliorate cancer by altering m^{6}A methylation through affecting the intestinal microbiota and subsequently the methyl donor supply (Figure 3). NSPs escape digestion in the upper GI tract and flow into the large intestine. The intestinal epithelium in the large intestine is covered by

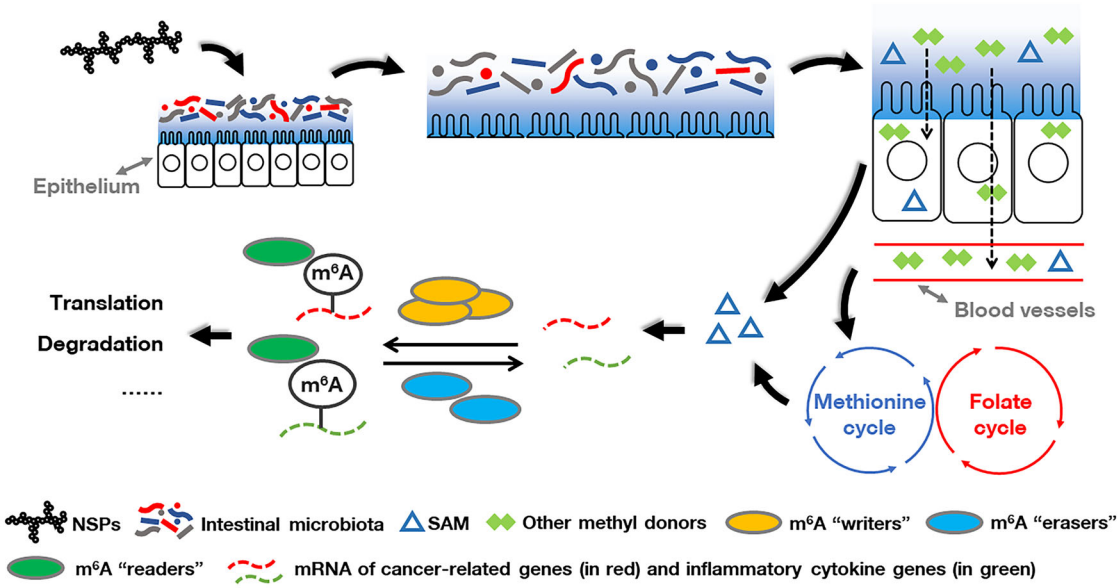

Figure 3. A schematic diagram depicting the relationship of NSPs, intestinal microbiota, methyl donors, oncogenes and RNA methylation. Different colors indicate different types of intestinal bacteria. Blue: bacteria capable of degrading NSPs and producing methyl donor substances; Gray: bacteria capable of producing methyl donor substances; Red: bacteria without the capability to degrade NSPs and produce methyl donor substances.

both outer and inner mucosal layers. Hence, when NSPs in food residue flows into cavities of the large intestine, the direct interaction between NSPs and the intestinal epithelium will be blocked (Lovegrove et al. 2017). However, intestinal bacteria exist in the enteric cavity while some colonize at the outer mucosal layer (Johansson and Hansson 2016), and some of them have the ability to degrade and utilize specific NSPs. Correspondingly, the abundances of those bacteria will be elevated and the microbial structure will be reshaped. In the meantime, specific metabolites, including different amounts of methyl donor substances, will be generated by gut bacteria multiplying in response to the intervention of some NSPs. SAM, one of the methyl donor substances, will be absorbed and transferred via blood flow and further serve as a direct methyl group for m^6A modification of cancer-related genes and pro-carcinogenic inflammatory cytokine genes. Other methyl donor substances will take part in one-carbon metabolism and convert into SAM and affect m^6A methylation.

Even if the NSP-fermenting bacteria produce insufficient methyl donor substances, their other metabolites may also reshape the microbial structure, resulting in the growth of some other gut bacteria due to the cross-feeding effect (Requena, Martínez-Cuesta, and Peláez 2018). These bacteria may also have diverse abilities to generate methyl donor substances. Therefore, the level of m^6A varies with the supply of methyl donors. As a result, epigenetic modifications to different degrees can be applied to mRNA of cancer-related genes (including oncogenes and cancer suppressor genes) and pro-carcinogenic inflammatory cytokine genes, thus improving cancer. Different NSPs have different effects on the structure of intestinal microorganisms, resulting in different supplies of methyl donors and thus different effects on the amounts of m^6A methylated RNA. Therefore, each NSP has distinct effects on tumor improvement.

The contribution of oncogenes to cancer development is mediated mainly through epigenetic priming of cancer-initiating cells, and environmental stimuli may trigger this priming (Vicente-Dueñas et al. 2018). For example, exposure to environmental toxicants (one of the stimuli) reduced global m^6A methylation (Cayir et al. 2019). Since NSPs can increase the abundance of methyl donor-generating gut bacteria, including probiotics such as LAB and *Bifidobacterium*, there is a very definite possibility that NSPs-shaped intestinal microbiota elevates global m^6A methylation and further reduces the cancer risk. As concluded above, the increased m^6A methylation does not always ameliorate cancer because it depends on the cancer types, the target mRNA, as well as the m^6A components such as "readers." As extensive research is rare on the epigenetic impact of NSPs regulating the structure of intestinal microbiota, it is inconclusive whether the mechanism of tumor improvement by bioactive NSPs lies in a decreased methylation level. However, it is probable that NSPs regulate the intestinal microbiota and affect the supply of methyl donors to improve cancers caused by the alteration of m^6A methylation.

So far, there is no direct report of NSPs affecting the m^6A methylation level. It appears to be a promising and insightful research direction to explore the mechanism of NSP intervention in the occurrence and development of different cancers by changing the intestinal microbiota structure and thus the m^6A level. Many NSPs have been found to have anti-cancer effects, and most of which were reported to be mediated by SCFAs generated via NSPs fermentation. However, diet also affected cancer through methylation with the direct mechanism closely related to methyl donor substances (Sapienza and Issa 2016). In addition, m^6A RNA methylation closely related to nutrition, microbiota (Wu et al. 2020) and cancer (He et al. 2019). Given that, it seems some other mediators such as methyl donor substances also play an important role in the m^6A modification of cancer-

related and pro-carcinogenic inflammatory cytokine genes after NSP intervention besides SCFAs.

To make a confirmation, the following questions await to be answered through experimental data. First, are there any differences in the supply of methyl donor substances by NSPs from various sources? Second, will these differences of methyl donor substances changed by different NSPs alter the intestinal microbiota structure in those hosts with cancer? Third, among those bacteria associated with the change of methyl donor substances, which are affected by NSPs from each source? Fourth, is the difference of m^6A methylation caused by structural change of intestinal microbiota due to the changes of methyl donor substances? Fifth, which m^6A components as well as their target RNAs (including RNAs of cancer-related genes and pro-carcinogenic inflammatory cytokine genes) are involved in improving the occurrence and development of cancer after the intervention of NSPs? If all these questions are answered in future research, the cancer amelioration of NSPs by altering m^6A methylation through methyl donor substances generated from intestinal microbiota will be confirmed. More microbial metabolites beneficial to host health besides SCFAs will be discovered and studied, and the industrial application of NSPs may thereby rise to an upper level.

Declaration of competing interest

No potential conflict of interest was reported by the authors.

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