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Mini-review

Gut microbiota: A double-edged sword in immune checkpoint blockade immunotherapy against tumors

Juanjuan Wang [a,b,c,1], Ningning Zhu [a,b,c,1], Xiaomin Su [a,b,c], Rongcun Yang [a,b,c,*]

[a] Translational Medicine Institute, Affiliated Tianjin Union Medical Center of Nankai University, Nankai University, Tianjin, 300071, China
[b] Department of Immunology, Nankai University School of Medicine, Nankai University, Tianjin, 300071, China
[c] State Key Laboratory of Medicinal Chemical Biology, Nankai University, Tianjin, 300071, China

A B S T R A C T

Tumor cells can evade immune surveillance by expressing immune checkpoint molecule ligands, resulting in effective immune cell inactivation. Immune checkpoint blockades (ICBs) have dramatically improved survival of patients with multiple types of cancers. However, responses to ICB immunotherapy are heterogeneous with lower patient response rates. The advances have established that the gut microbiota can be as a promising target to overcome resistance to ICB immunotherapy. Furthermore, some bacterial species have shown to promote improved responses to ICBs. However, gut microbiota is critical in maintaining gut and systemic immune homeostasis. It not only promotes differentiation and function of immunosuppressive immune cells but also inhibits inflammatory cells via gut microbiota derived products such as short chain fatty acids (SCFAs), tryptophan (Trp) and bile acid (BA) metabolites, which play an important role in tumor immunity. Since the gut microbiota can either inhibit or enhance immune against tumor, it should be a double-edged sword in ICBs against tumor. In this review, we discuss the effects of gut microbiota on immune cells and also tumor cells, especially enhances of gut microbiota on ICB immunotherapy. These discussions can hopefully promote the development of ICB immunotherapy.

1. Introduction

Gut microbiota, which consists of bacteria and other microbes such as viruses and fungi has a key role in both the development and function of the gut and systemic immune system [1]. It affects the regulation of metabolism, inflammation, hematopoiesis and immunity [2,3]. The products generated by gut microbiota such as short chain fatty acids (SCFAs), tryptophan (Trp) and bile acid (BA) metabolites not only impact genetic and epigenetic modification but also affect the metabolism on the immune cells such as immunosuppressive and inflammatory cells to maintain gut and systemic homeostasis. The alternation of gut microbiota/metabolites can lead to many diseases such as cancers [4,5].

Tumor cells can evade immune surveillance by expressing checkpoint molecule ligands such as programmed death ligand 1 (PD-L1), which can bind to programmed cell death protein 1 (PD-1) on immune effective cells such as T cells to cause T cell inactivation. Cytotoxic T lymphocyte (CTL)-associated antigen 4 (CTLA-4) is another immune checkpoint molecule for T cells that can lead to T-cell inactivation when bound to ligands [6]. One of the major breakthroughs in cancer immunotherapy is to block these immune checkpoint molecules on tumor-reactive T cells. The development of CTLA-4 and PD-1 immunosuppressive antibodies has triggers to search for more effective therapeutic strategies [7]. NKG2A, as a novel immune checkpoint, which is expressed on both natural killer (NK) and $CD8^+$ T cells, is also effective in immunotherapy against tumor after blocking interaction with its ligand HLA-E in the tumors [8,9]. Indeed, immune checkpoint blockade (ICB) immunotherapy has shown to dramatically improve survival of patients with multiple types of cancers [10–12]. ICBs not only unleash immune brake responses but also effectively inhibit tumor immune escape by targeting checkpoint molecules such as PD-1. However, the responses to ICB immunotherapy are heterogeneous, with lower response rates in the patients with tumor (only 10–30 %) [13,14].

Gut microbiota has attracted much interest over the past decade owing to the potential to modulate anti-tumor immunity [12], and emerged as a tumor extrinsic predictive biomarker of ICB responses [15]. The association between gut microbiota composition and responses to anti-PD-1 has been well established in the patients with cancer [15]. Although the precise composition of the most beneficial microbiota has not been fully defined for ICB immunotherapies [15], growing evidence supports a role for the gut microbiota in shaping anti-tumor immune responses [12,16]. Indeed, the gut microbiota plays

* Corresponding author. Department of Immunology, Nankai University School of Medicine, Nankai University, Tianjin, 300071, China.
E-mail address: ryang@nankai.edu.cn (R. Yang).
[1] These authors contributed equally to this work.

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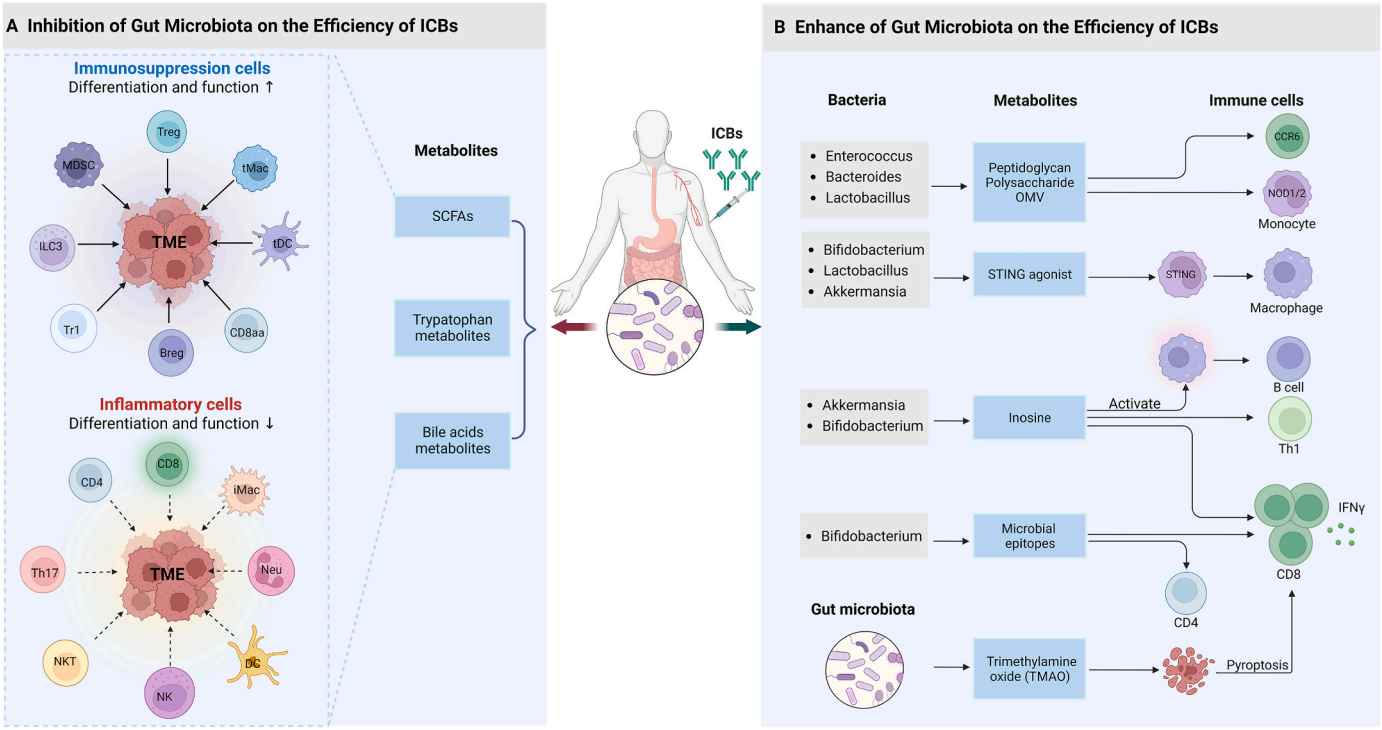

Fig. 1. Gut microbiota, a double-edged sword in immune checkpoint blockade (ICB) immunotherapy against tumor. A. Gut microbiota derived metabolites such as short chain fatty acids (SCFAs), tryptophan (Trp) and bile acid (BA) metabolites inhibit the differentiation and function of inflammatory cells and promote the immunosuppressive cells, which potentially promote the tumor growth. These immune cells include inflammatory cells such as NK cells, CD4 cells, CD8 T cells inflammatory macrophages (iMACs), dendritic cells (DC), neutrophils (Neu), Th17 cells and NKT cells, and immunosuppressive cells such as regulatory T cells (Tregs), T regulatory 1 cells (Tr1), regulatory B cells (Bregs), tolerant macrophages (tMACs), tolerant dendritic cells (tDCs), MDSCs, innate lymphocyte 3 (ILC3) and CD8aa T cells. B. The metabolites from gut microbiota enhance ICB immunotherapy, which potentially inhibits tumor growth. Gut microbiota bacteria such as *Enterococcus*, *Bacteroides* and *Lactobacillus* derived peptidoglycan (PGN), polysaccharide (PSA) and outer membrane vesicle (OMV) can enhance the functions of monocytes/macrophages; *Bifidobacterium*, *Lactobacillus* and *Akkermansia* derived stimulator of interferon gene (SING) agonist also promotes the functions of monocytes/macrophages; *Akkermansia*, and *Bifidobacterium* derived inosine promotes the functions of monocyte/macrophages, Th1 and CD8 T cells; Trimethylamine oxide (TMAO) from gut microbiota enhances activity of CD8 T cells; Microbial epitopes from *Bifidobacterium* can induce specific responses of CD4 and CD8 T cells against tumors. TME, tumor micro-environments.

an important role in the ICB response in preclinical and clinical studies [17,18]. Thus, administration of gut microbiota provides a novel insight for improving the antitumor response and expanding ICB efficacy. However, gut microbiota is critical in maintaining the homeostasis of gut and systemic immune through promoting immunosuppressive cells and inhibiting inflammatory cells. Thus, gut microbiota is a double-ad ged sword in ICB immunotherapy against tumor (Fig. 1). The functions of the gut microbiota in modulating local and systemic immune responses have caused the emergence of studies on the effects of the cancer-immune system and ICB therapeutic responses [13]. The reason why responses to ICBs are regulated by gut microbiota, requires insight into the intrinsic link among gut microbiome, cancer and anti-tumor immunity of the host. In this review, we discussed the effects of gut microbiota on the immune cells and tumor cells, especially enhances of gut microbiota on ICB immunotherapy.

2. ICB immunotherapy against tumors

ICB immunotherapy against tumor mainly depends on immune effective cells such as CD8 and NK cells. These CD8 and NK cells can induce cytolysis of cancer cells through perforins/granzymes. They also express TNF-related apoptosis-inducing ligand (TRAIL) and FAS ligand (FASL) to bind to death receptor (DR) and FAS, inducing apoptosis of tumor cells. Notably, the functions of CD8 and NK cells can be regulated by co-signaling molecules such as checkpoint molecules. For example, $CD8^+$ T cells to become effector T cells require T cell receptor (TCR) activation and CD28 co-activation. However, this process is negatively regulated by CTLA-4 by competing with CD28 for the ligands CD80 and CD86. PD-1, another regulatory molecule, can bind to its ligands, PD-L1 (also named B7-1; CD 274) and PD-L2 (B7-DC; CD273) in other cells such as tumor cells to transmit signals to inhibit TCR signaling in $CD8^+$ T cells. These CTLA-4 and PD-1 immune checkpoint molecules can compel tumor-killing $CD8^+$ T cells into inactive states [19]. ICB as an immunotherapeutic method is to bind and block the function of these molecules through antibodies or small molecules, thereby reducing tumor-induced $CD8^+$ T cell exhaustion and restoring anticancer immunity [20]. The most widely used ICBs against tumors are blocking antibodies targeted to immune checkpoint molecules such as CTLA-4, PD-1, and PD-L1.

2.1. $CD8^+$ T cells in ICBs

$CD8^+$ T cells are the critical immune cells to kill cancer cells which present major histocompatibility complex (MHC) class I molecules through the release of cytolytic factors and induction of apoptosis in tumor cells. Many co-signaling molecules in CD8 can be acted as checkpoint molecules such as CD28, CTLA-4, PD-1(CD279, PDCD1), PD-2 (PDCD1LG2), Tim3, 2B4, TIGHT, TLT-2 (TREML2), NKP30 (NCR3), BTLA, PSGL-1(SELPLG), NKG2A (KLRC1) and CD94 (KLRD1) (Fig. 2A) [21–24]. In ICB immunotherapy against cancers, most often targeting molecules are CTLA-4 and PD-1 expressed on the surface of $CD8^+$ T cells. Two ligands for PD-1, PD-L1 is usually expressed in the tumors such as gastric cancers, leukemia, melanomas, non-small cell lung cancer, renal cell carcinoma, and other cancers, whereas another ligand PD-L2 is

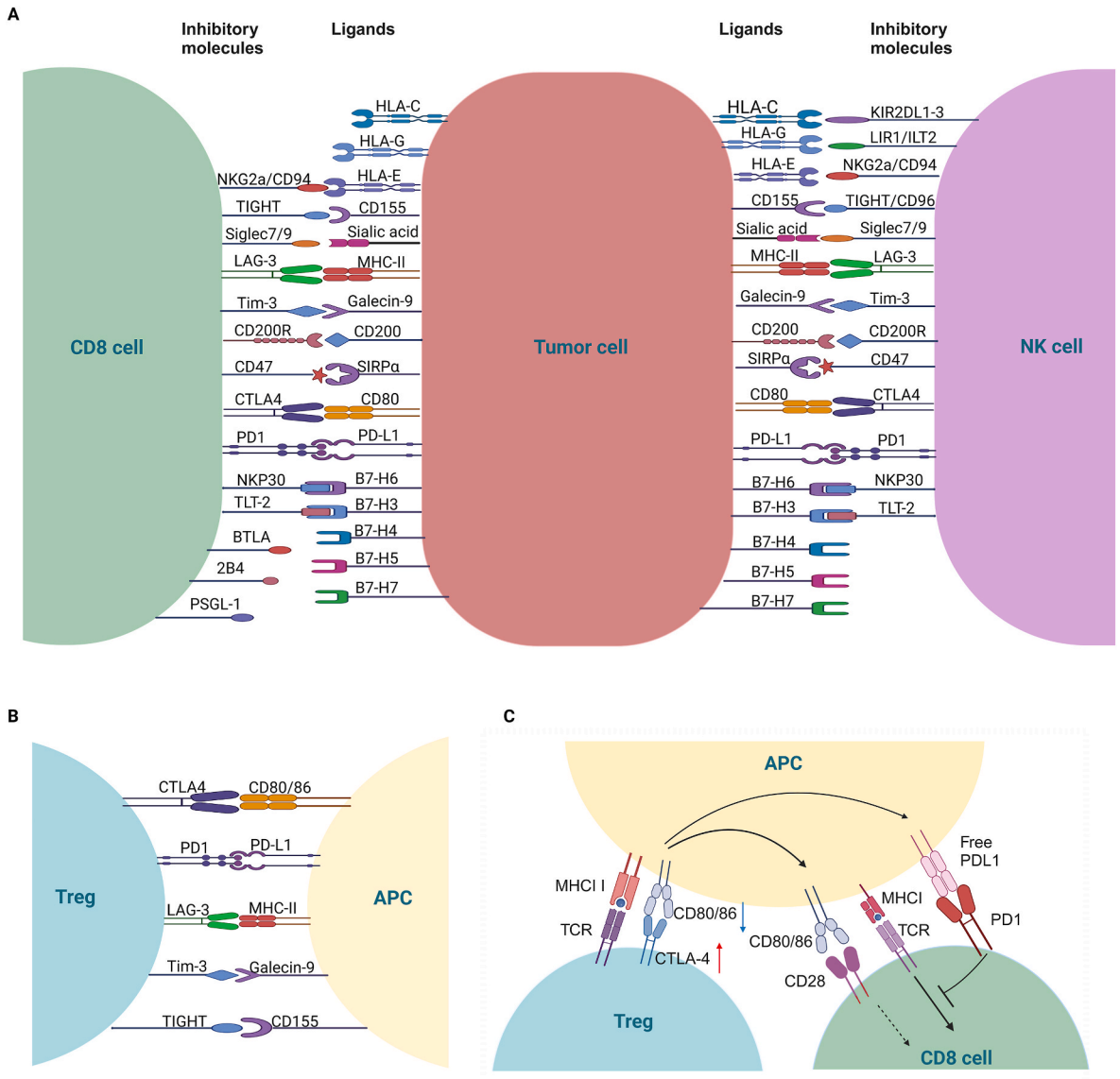

Fig. 2. Potential immune checkpoint molecules in immune cells and tumor cells. A. Potential checkpoint molecules in CD8 and NK cells, and their ligands on tumor cells. B. Checkpoint molecules in Tregs and their ligands on antigen-presenting cells such as macrophages and tumor cells. C. Regulation of Tregs in the effective CD8 T cells through immune checkpoint molecules. CTLA4 highly expressed on Tregs binds to CD80/86 on antigen-presenting cells (APCs) to reduce CD80/86 expression in APCs through *trans*-endocytosis, which finally inhibit the activation of T cells by APCs. Tregs, regulatory T cells; APC, antigen-presenting cells; TCR, T cell receptor; MHC, major histocompatibility complex.

expressed in antigen presenting cells (APCs) and also less expressed in tumor cells as compared to PD-L1 [25]. PD-1 and PD-L1 have close association with the progression of human cancers, and also are as the biomarkers for cancer therapy [26–28]. ICB immunotherapy based on PD-1 in the $CD8^+$ T cells can not only stop immune brake responses but also effectively suppress tumor immune escape. This ICB immunotherapy has shown to dramatically improve survival of patients with multiple types of cancers [10–12].

Importantly, the function and activity of $CD8^+$ T cells can be regulated by other multiple immune cells. These $CD8^+$ T cells have positive cross-talking with natural killer (NK) cells, antitumor macrophage type 1 (Mac 1) cells, $CD4^+$ T cells, and dendritic cells (DCs), whereas there has a negative cross-talking in $CD8^+$ T cells with regulatory T cells (Tregs), myeloid derived suppressive cells (MDSCs) and M2-like Macs [29].

2.2. NK cells in ICBs

NK cells are innate lymphocytes with antigen-independent cytotoxic activity. These cells can be identified by the expression of CD56 and the absence of T cell receptor (TCR) and CD3 [30]. There also exist multiple co-stimulatory and co-inhibitory molecules on the surface of NK cells. Notably, tumor microenvironment (TME) can promote the expression of immune co-inhibitory molecules such as killer immunoglobulin-like receptors (KIRs), NKG2A, PD-1, T-cell immunoglobulin domain and mucin domain-3(Tim-3), and T cell immune-receptor with Ig and immune-receptor tyrosine-based inhibition motif domains (TIGIT) on the surfaces of NK cells (Fig. 2A) [31–33], which can also be acted as immune checkpoint molecules in NK cells [34,35]. NKG2A, a checkpoint molecule present on both NK cells and also T cells, binds with CD94 to form a heterodimer [8]. The combined treatment of NKG2A by anti-NKG2A with PD-1/PD-L1 antibodies demonstrated the improvement of NK cells-mediated cytotoxic activity and also increased immune response of $CD8^+$ T cells against different tumors as compared to

Table 1
Gut microbiota species and their metabolites.

SCFAs	Bacterial species	References
Acetate (C2)	*Akkermansia muciniphila, Bacteroides* spp., *Bifidobacterium* spp., *Blautia hydrogenotrophica, Clostridium* spp., *Prevotella* spp., *Ruminococcus* spp., *Streptococcus* spp.,	[50–52]
Popionate (C3)	*Akkermansia muciniphila, Bacteroides* spp., *Clostridium* spp., *Clostridiales bacterium. Coproccus catus, Coprococcus catus, Clostridium* spp., *Dialister* spp., *Eubacterium halli, Eubacterium* spp., *Firmicutes, Megasphaera elsdenii, Phascolarctobacterium succinatutens, Roseburia* spp., *Roseburia inulinivorans, Ruminucocus* spp., *Roseburia inulinivorans, Ruminococcus obeum, Salmonella* spp., *Veillonella* spp.,	[51,53,54]
Butyrate (C4)	*Anaerostipes* spp., *Costridium symbiosum, Coprococcus catus, Clostridiales bacterium, Coprococcus comes, Coprococcu* spp., *Coprococcus eutactus. Eubacterium hallii, Eubacterium hallii, Eubacterium rectale, Faecalibacterium prausnitzii, Faecalibacterium prasnitzii, Roseburia* spp., *Roseburia intestinalis, Roseburia insulinivorans,*	[51,53,55,56]
Trp metabolites		
Indole	*Bacteroides ovatus, Clostridium limosum, Escheichia coli, Enterococcus faecalis*	[57]
Indole-3 acid-acetic (IAA)	*Bifidobacterium* spp., *Clostridium bartlettii Clostridium sporogenes*	[58–60]
Indole-3-propionic acid (IPA)	*Bifidobacterium* spp., *Clostridium sporogenes Clostridium bartlettii, Peptostreptococcus* spp.,	[58–60]
Indoleacrylic acid (IA)	*Peptostreptococcus* spp.	[61]
Skatole	*Bacteroides* spp., *Clostridium* spp.,	[60,62]
Indole-3-adehyde (IA1d)	*Lactobacillus acidophilus, Lactobacillus murinus, Lactobacillus reuteri, Lactobacillus johnsonii*	[63]
Ttryptamine	*Clostridium sporogenes, Ruminococcus gnavus*	[64]
3-hydroxyanthranilic acid (3-HAA)	*Bacillus, Burkholderia, Pseudomonas, Shewanella, Stenotrophomonas, Xanthomonas*	[65]
Bile acids (BAs)		
Conjugated BAs	*Actinobacteria, Bacteriodetes, Bacterorides vulgatus, Clostridium bolteae, Clostridium scindens Firmicutes, Hungatella hathewayi, Holdemania filiformis, Lactobacillus ruminis*	[66–68]
Deconjugated BAs	*Bacteroides* spp., *Bifidobacterium* spp., *Clostridium* spp., *Enterococcus* spp., *Lactobacillus* spp.,	[69–72]
Secondary BAs (DCA, LCA)	*Blautia producta, C. hylemonae, Clostridium scindens, C. scindens, Clostridium clusters* XIVa, IV, XI, *C. perfringens, Eggerthella lenta,*	[73,74]
3-oxoLCA and isoLCA	*Adlercreutzia. Bifidobacterium, Collinsella, Clostridium, Enterocloster, Eggerthella, Gordonibacter, Mediterraneibacte, Monoglobus, Phocea, Peptoniphilus, Raoultibacter,*	[75]
Ursodeoxycholic acid (UDCA)	*Clostridium baratii, Clostridium absonum, Collinsella aerofaciens, Ruminococcus gnavus, Stenotrophomonas maltophilia*	[76–78]

PD-1/PD-L1 blockade alone [36]. Notably, the blockade of NKG2A could not only stimulate $CD8^+$ T cells-dependent anti-tumor immunity [9], but also mediate evasion of circulating tumor cells by NK cells [37]. In addition, NKG2A-blocking also improved clinical responses to cancer vaccines [9,38]. Other immune checkpoint molecules such as TIM-3, were also investigated as therapeutic targets in acute myeloid leukemia (AML) and high risk myelodysplastic syndromes (HR-MDS) [39,40].

Notably, the function and activity of NK cells are also regulated by DCs, Macs, MDSCs, Th1 and Treg cells. The NK cells in tumor tissues engage in contact-dependent and independent interactions with other immune cells such as Tregs, M2-like Macs and MDSCs, that ultimately inhibit their anticancer activity [41].

2.3. Other immune cells in ICBs

Immune checkpoint molecules not only express in CD8 and NK cells. Other immune cells such as Tregs, Macs, DCs, MDSCs, neutrophils, B cells, innate lymphocytes and CD4 T cells also widely express these immune molecules to affect the efficacy of ICB immunotherapy [31–33]. Multiple co-signaling molecules in Macs can be acted as checkpoint blocking molecules such as B7–H1 (PD-L1/CD274), galecin-9, CD155 (Fig. 2B) [21–24]. Expression of PD-L1 in Macs could further enhances their immunosuppressive roles to indirectly affect the efficacy of ICBs against tumors [42]. Tumor-infiltrating MDSCs also expressed higher levels of immune checkpoint molecules such as PD-L1 in different cancers including colon, ovarian, and bladder cancer [43]. Notably, Tregs, which express high levels of cell surface molecules such as CTLA-4, PD-1, LAG3, Tim3 and TIGIT (Fig. 2B) [44], which are associated with T-cell activation, can compel effective $CD8^+$ T cells to a hypo-responsive state known as anergy through the immune checkpoint molecules. CTLA-4, which is highly expressed on Tregs, binds to CD80/86 on antigen-presenting cells (APCs), reducing CD80/86 expression by APCs through *trans*-endocytosis to inhibit the activation of T cells by APCs (Fig. 2C) [44–46]. Tregs-mediated reduction of CD80 may also accentuate PD-L1-mediated inhibition of activated T cells, as described by the $PD\text{-}L1^+$APCs co-cultured with Tregs (Fig. 2C) [45]. In addition, siglecs (sialic acid-binding immunoglobulin-like lectins), as type-1 immunoglobulin-like transmembrane immune cell receptors could bind a wide range of sialic acids ligands in tumor [47,48]. There at least are nine CD33-related siglecs in humans, which are mostly expressed by mature innate immune cells such as neutrophils, eosinophils, monocytes, Macs, NK cells, DCs, and mast cells.

3. Effects of gut microbiota on immune cells

3.1. Gut microbiota and metabolites

Gut microbiota can affect innate and adaptive immunity in the mucosa, lamina propria, Peyer's patches, and mesenteric lymph nodes, inducing systemic immune dysregulation. Especially, SCFAs, Trp and BA metabolites from gut microbiota exert a key role in maintaining gut and systemic homeostasis through suppressing the inflammatory immune cells and enhancing the differentiation and function of immunosuppressive cells [49] (Fig. 1). So far, some gut bacteria, which can produce the metabolites, have been identified (Table 1).

3.2. Effects of gut microbiota on immune cells

Gut microbiota and its metabolites not only affect effective immune cells CD8, NK cells, but also other immune cells such as Tregs, T helper (Th)1, Th2, Macs and DCs. These gut microbial metabolites can promote the differentiation and function of immune suppressive cells, and inhibit inflammatory cells through SCFA receptors such as G-protein coupled receptor (GPR)43, GPR41 (also known as free fatty acid receptor (FFAR3)) and GPR109a (also called hydroxycarboxylic acid receptor 2 (HCA2)), Trp metabolite receptors such as aryl hydrocarbon receptor (AhR), and BA metabolite receptors such as farnesoid X receptor (FXR), vitamin D receptor (VDR), liver-X-receptor (LXR), pregnane X receptor (PXR), constitutive androstane receptor (CAR), retinoid related orphan receptor (RORγt), and cell membrane receptors such as G-protein BA receptor 1 (GPBAR1) known as Takeda G protein-coupled receptor 5 (TGR5) [49].

3.2.1. Regulatory T cells

Trp metabolites from gut microbiota promoted differentiation and function of Tregs through AhR-ligand-Treg axis [79,80]. These Trp metabolites induced the expression of foxp3 gene to promote he differentiation of Tregs and suppressed retineic-acid-receptor-related orphan nuclear receptor gamma (RORγ), which controled differentiation of pro-inflammatory Th17 cells. Kynurenine (Kyn) in Trp metabolite pathway of gut microbiota also enhanced differentiation of Tregs through the activation of AhR [81–83]. Foxp3$^+$Tregs promoted by Kyn metabolites were through direct transactivation and the induction of epigenetic modifications, which controled foxp3 transcription [84–86]. 3-HAA in Kyn pathway also promoted the generation of foxp3$^+$Treg cells via a nuclear coactivator 7 (NCOA7)-dependent pathway [87]. In addition, Trp metabolites also supported the differentiation of Tr1 cells, another regulatory T cells through their receptor AhR [88]. The AhR could act in synergy with c-Maf to promote the development of Tr1 cells during Tr1 cell differentiation [89]. AhR activation also initiated the differentiation of mucosal-homing Tim3$^+$Lag3$^+$Tr1 cells [90]. In addition, the differentiation and function of Treg cells could also be regulated by BA metabolites [91]. The metabolites such as isoalloLCA [92–94] increased the differentiation of Tregs through promoting mitochondrial reactive oxygen species (mitoROS), leading to increased expression of foxp3 [92]. Nuclear receptor subfamily 4 group A member 1 (NR4A1) was also required for the effect of isoalloLCA on Treg cells [95]. The binding of NR4A1 at the foxp3 locus was promoted by isoalloLCA, leading to enhanced foxp3 gene transcription [96]. 3-OxoLCA, another BA metabolite also inhibited the differentiation of Th17 cells by transcription factor retinoid-related orphan receptor-γt (RORγt) [97]. The transcriptional and post-transcriptional regulation of RORγt and foxp3 also affected Th17/Treg balance. Foxp3 expression was also induced by BA metabolite isoDCA by reducing DC immune-stimulatory properties [93]. Notably, in Treg cell polarization condition, gut microbial metabolites SCFAs also promoted the conversion of naïve T cells toward Tregs [98]. Indeed, there had an increased number of extra-thymic foxp3$^+$Tregs in mice provided with SCFAs [99]. Butyrate might upregulate the histone H3 acetylation of foxp3 to promote the differentiation of Tregs [99]. DCs, after exposed to butyrate, could facilitate the differentiation of naïve T cells into foxp3$^+$Tregs, and meanwhile also inhibit interferon (IFN)-γ-producing cells through inducing indoleamine 2,3-dioxygenase 1 (IDO1) and aldehyde dehydrogenase 1A2 (Aldh1A2) [100]. Notably, IL-10 production in T cell, including Th1, Th17 and Treg cells was also promoted by SCFAs [101].

3.2.2. Macrophages

Gut microbial metabolites also have widely effects on the function and differentiation of Macs. Trp metabolites were very important in regulating the function of Macs through receptor AhR [102]. *In vitro* studies showed that Trp metabolites could mediate suppression on inflammatory responses through suppressing histamine production in the Macs [103]. 3-HAA, a Trp metabolite also inhibited LPS mediated PI3K (phosphatidylinositol 3 kinase)/Akt (protein kinase B)/mTOR (mammalian target of rapamycin) and NF-κB (nuclear factor κ gene binding) signaling pathways to reduce inflammatory cytokine production in the Macs [104]. BA metabolites also were essential to maintain tolerant phenotypes of the Macs via BA receptors TGR5 (GPBAR1) [105–107]. Notably, Macs treated with butyrate also inhibited lipopolysaccharide (LPS)-induced inflammatory mediators, including nitric oxide (NO), IL-6 and IL-12. The inflammatory signaling pathway mediated by NLRP3 (NOD-like receptor thermal protein domain associated protein 3) was regulated by butyrate to inhibit the activation of the Macs [108]. Importantly, butyrate could reprogram Mac metabolism toward oxidative phosphorylation, leading to an anti-inflammatory tolerant phenotype [109].

3.2.3. Dendritic cells

Gut microbiota derived Trp metabolites mediated activation of AhR could induce tolerant phenotype in DCs, which promoted the generation and expansion of Tregs. BA metabolite DCA also suppressed BA receptor TGR5, which mediated suppression through inhibiting NF-κB by TGR5–cAMP–PKA (protein kinase A) signaling [110]. The secondary BA derivative isoDCA limited FXR activity in DCs and conferred upon them an anti-inflammatory phenotype [93]. The DC maturation and the inflammatory cytokine production could be inhibited by activation of BA receptor VDR [111]. In addition, the activation of bone marrow derived DCs (BMDCs) might be inhibited by butyrate and propionate via inhibiting LPS-induced expression of CD40 and production of IL-6 and IL-12p40 [112].

3.2.4. CD8$^+$ T cells

The expression of PD-1 in CD8$^+$ T cells could be upregulated through Trp metabolites Kyn, which interacted with the ligand-activated transcription factor AhR [113]. Metabolite 3-HAA of Kyn caused immune suppression by inducing apoptosis in T-cells through glutathione depletion [114]. Notably, BA metabolites also disrupted intracellular calcium homeostasis, which was essential for (nuclear factor of activated T cells) NFAT signaling and T cells activation [115]. The immune-metabolism in CD8$^+$ T cells could be reshaped by 24-Norursodeoxycholic acid (NorUDCA) to alleviate hepatic inflammation [116]. The proportion of infiltrated CD8$^+$PD-1$^+$ T cells were positively correlated with the abundance of *Akkermansia* in colorectal cancer [117]. In addition, butyrate and propionate also regulated CD8$^+$ T cell activation via the inhibition of IL-12 secretion from DCs.

3.2.5. NK cells

NK cells act as powerful effectors of innate immunity, which constitute a first line of defense against cancers. These cells express an array of receptors which are used to eliminate tumor cells. The activity of NK cells could be suppressed by Trp metabolite Kyn [118] to lead to cell death via ROS pathway [119]. Kyn also prevented cytokine-mediated up-regulation of the receptors, which were responsible for the induction of NK-cell-mediated killing [120].

3.2.6. Th1 and Th2 cells

Antigen-specific Th1 responses could be inhibited by oral tryptophan supplementation at sub-toxic concentrations [121]. In the presence of BA metabolites, the xenobiotic transporter Mdr1 was upregulated in CD4$^+$ T effector cells to maintain homeostasis in the ileum [122]. The activation of primary human and mouse CD4$^+$ Th1 cells was inhibited by unconjugated BA metabolite LCA through a VDR-dependent mechanism, causing decreased TNFα and IFNγ [123]. A shift from the Th1 to the Th2 phenotype was promoted by VDR activation through increased transcription factors c-Maf and GATA-3 [124]. BA transcription factor PXR activation in both mouse and human T cells also inhibited T cell proliferation in vitro. Additionally, DCs treated with SCFA propionate exhibited the impaired ability to initiate Th2 effector function in mice [2], which were characterized by decreased expression of CD40, programmed cell death lignad2 (PD-L2) and CD86.

3.2.7. Other immune cells

Gut microbial metabolites also affect other immune cells such as IL-17-producing T helper [75,92,97,125], regulatory B (Breg) cells [126,127], B cells, myeloid-derived suppressor cells (MDSCs) [128], innate lymphoid cells [129–131], neutrophils [132], CD4$^+$CD8αα$^+$ intestinal intraepithelial lymphocytes (IELs) [133] and NKT cells. NKT cells are an unusual population of T cells, which can recognize lipids presented by CD1d, a non-classical class-I-like molecule. BA receptor FXR in NKT cells could result in a profound suppression on the osteopontin, a potent inflammatory mediator, along with IFN-γ and IL-1β [134].

4. Enhancement of ICB efficacy by gut microbiota

The efficacy of immunotherapy against tumor is associated to the

composition of intestinal bacteria [135]. In 2015, the first report showed the relationship between gut microbiota and ICB responses in mouse models [136]. So far, studies have already found that gut microbiota can stimulate antitumor immune responses by modulating immune cells such as Th1 [137], $CD8^+$ T cells [138], and tumor-associated myeloid cells [139]. Some bacteria such as *Bifidobacterium pseudolongum (B. pseudolongum), Akkermansia muciniphila (A. muciniphila), Bacteroides fragilis, Clostridiales* strains, *Eleven* strains and *Lactobacillus* species significantly enhanced efficacy of ICBs in the cancer [140–142]. Importantly, some metabolites from the gut microbiota, which can enhance ICB immunotherapy, have been identified (Fig. 1).

4.1. Gut microbiota

4.1.1. Bifidobacterium

Bifidobacterium could promote responses to ICB immunotherapy [140], and alter the functional capacity of DCs to induce $CD8^+$T cell proliferation and IFNγ production [136,142]. This bacterium also enhanced Th1 differentiation and antitumor immune responses to improve ICB efficacy through the gut microbial derived inosine [140]. Bifidobacterium also modulated the functional metabolism of Tregs in the context of ICBs [143]. Bifidobacterium adolescentis (B. adolescentis) induced decorin+ Macs via TLR2 to suppress colorectal carcinogenesis [144]. These bacteria indeed enhanced the effect of anti-PD-1 mAb by secreting the metabolite maurate, inhibiting PD-1 expression, and activating natural killer cells to mediate tumor destruction via perforin and IFN-γ in a mouse model of melanoma [145]. The administration of *Bifidobacterium* restored the antitumor efficacy of PD-L1 blockade by promoting DC maturation and $CD8^+$ T cell accumulation in the TME [136]. *B. bifidum* strains synergized with ICBs to reduce tumor burden in mice [146]. Thus, *Bifidobacterium* was effective in promoting ICB immunotherapy against tumors. ***Akkermansia.*** Routy et al. found that the responses of patients with lung or kidney tumor to PD-1 monoclonal antibody was associated to an abundance of *Akkermansia muciniphila (A. muciniphila)* [147]. Notably, cdAMP-producing *A. muciniphila* or transferring fecal microbiota from ICB responders could improve the antitumor responses and ICB efficacy [148]. Oral administration with *A. muciniphila* in fecal microbiota transplantation (FMT) non-responsive mice recovered anti-PD-1 responses by $CCR9^+CXCR3^+CD4^+$ T lymphocyte recruitment into tumor [147]. *A. muciniphila* and *Bifidobacterium pseudolongum* (*B. pseudolongum)*-derived inosine modulated the response to ICB immunotherapy [140]. *A. muciniphila*, *B.* spp. and *L. rhamnosus* also activated stimulator of interferon genes (STING)-interferon pathways to slow tumor progression and enhance responses to ICBs [148,149]. ***Bacteroides***. Supplementation with *Bacteroides fragilis* (*B. fragilis*) could augment anti-CTLA-4 therapeutic efficacy [18] by triggering DC maturation and stimulating IL-12-dependent Th1 cell immune responses [150]. *B. fragilis* also induced macrophage polarization to M1 and upregulated CD80 and CD86 expression on the cell, which could promote innate immunity [151]. ***Clostridiales.*** Clostridiales strains might mediate effective anti-cancer immune response against solid tumors [152]. They promoted antigen presentation to improve effector $CD4^+$ T cell and $CD8^+$ T cell function, and to ameliorate the antitumor efficacy of ICBs [142]. ***Eleven***. *Eleven* strains combined with ICBs robustly induced IFN γ^+CD8^+T cells to inhibit tumor growth [150]. ***Lactobacillus***. *L. plantarum* effectively increased expression of the natural cytotoxic receptor protein and promoted NK cell activation to trigger innate immunity [153]. *L. johnsonii* derived inosine also modulated response to ICB immunotherapy [140]. ***Faecalibacterium.*** *Faecalibacterium prausnitzii* and other members of *Ruminococcaceae* family were associated with the responses in patients receiving ICBs [142,154]. These bacteria increased $CD4^+$T cell proportion and also reduced Treg cell proportion in peripheral blood [155]. ***Enterococcus.*** *Enterococcus* species could promote responsiveness to ICBs. This might be derived from peptidoglycan re-modelling capabilities [156]. Interestingly, the translocated *Enterococcus hirae* could induce the polarization of immune cells in secondary lymphoid organs towards a Th1phenotype in mouse models [137,157]. **Others.** *Ruminococcaceae* and *Collinsella aerofaciens* also promoted the responses to anti-PD-1 immunotherapy in the patients with melanoma [142,158].

4.2. Gut microbial metabolites

4.2.1. Inosine

Inosine, a purine metabolite of *A. muciniphila* and *B. pseudolongum*, played a critical role in improving the efficacy of ICBs [140]. Colonization of *B. pseudolongum* in intestine enhanced the gut microbiota metabolism to produce inosine and increase the content of inosine in serum [140]. It was previously reported that inosine had immunosuppressive effects [159]. However, more studies have already shown that inosine can reprogram the TME and improve the responses to ICB therapy [140,160]. Inosine, which could improve the efficacy of ICBs, acted on adenosine 2A receptor (A2AR) on T lymphocytes in intestinal cancer, bladder cancer, and melanoma mouse models [140]. As a potent agonist of A2AR, inosine could affect Th1-cell responses and antitumor immunity through A2AR signaling. Inosine could also act as a substitute carbon source for T-cell metabolism in the TME, assisting T-cell proliferation and differentiation to improve sensitivity to ICBs. It might be metabolized into hypoxanthine and phosphorylated ribose (PNP) [160] to enter the central metabolic pathway for ATP and biosynthetic precursors for the glycolytic pathway and the pentose phosphate pathway [160]. In addition, inosine also promoted phyto-hemagglutinin mediated immune responses, increased tumor antigen levels, and strengthened T lymphocyte differentiation and proliferation [160], and also induced B lymphocyte differentiation and antibody production by activating Macs to exert antitumor actions [160]. However, *in vivo* antitumor effects of ICBs combined with inosine required a co-stimulus such as CpG and IL-12 [140]. **Trimethylamine oxide.** The choline or carnitine in foods can be metabolized by the gut microbiota to generate trimethylamine (TMA), and then TMA enters the liver through portal vein circulation. In liver, TAM is catalyzed to produce trimethylamine oxide (TMAO). TMAO was demonstrated to promote $CD8^+$ T cell-mediated anti-tumor immunity via induction of pyroptosis to enhance activity of anti-PD-1 antibodies in mouse models of triple-negative breast cancer [161]. Delivery of TMAO intra-peritoneally reduced tumor growth, which was associated with an immune-stimulatory tumor-associated macrophage phenotype, and activated effector T cell response in the TME [162]. A choline-rich diet or dietary supplementation with choline also enhanced tumor control with an ICBs [161,162]. Stimulator of interferon gene **agonists.** Gut microbiota derived stimulator of interferon gene **(**STING) agonists such as cdAMP was also shown to induce monocytes to produce type I IFN and to skew the polarization of innate immune cells towards an anti-tumorigenic phenotype in the TME [148]. *B.* spp., *A. muciniphila*, and *L. rhamnosus* could activate STING–interferon pathways, slow tumor progression, and enhance responses to ICB immunotherapy against tumors [148,149]. **Peptidoglycan and polysaccharide.** Recognition of gut microbiota-derived peptidoglycan (PGN) in a nucleotide-binding oligomerization domain containing 1 (NOD1)-dependent manner facilitated systemic innate immunity [163] such as that PGN from Enterococcus promoted ICB immunotherapy. *Enterococcus*, which expressed and secreted orthologs NlpC/p60 PGN hydrolase SagA, could promote expression of the innate immune sensor protein NOD2 and augment ICB antitumor efficacy [156]. Polysaccharide (PSA) from *Leuconostoc mesenteroides* strain NTM048 or *Bacteroides fragilis* acted as a stimulant to enhance the mucosal barrier and influence systemic immune responses [164]. Lactobacillus-derived PSA also enhanced ICB therapy [165]. The microbial PSA produced by *L. delbrueckii* could induce $CCR6^+CD8^+$ T cells in mice and humans [165]. **Outer membrane vesicles.** Microbiota-derived outer membrane vesicle (OMVs) can reprogram the TME. These substances have widely been developed

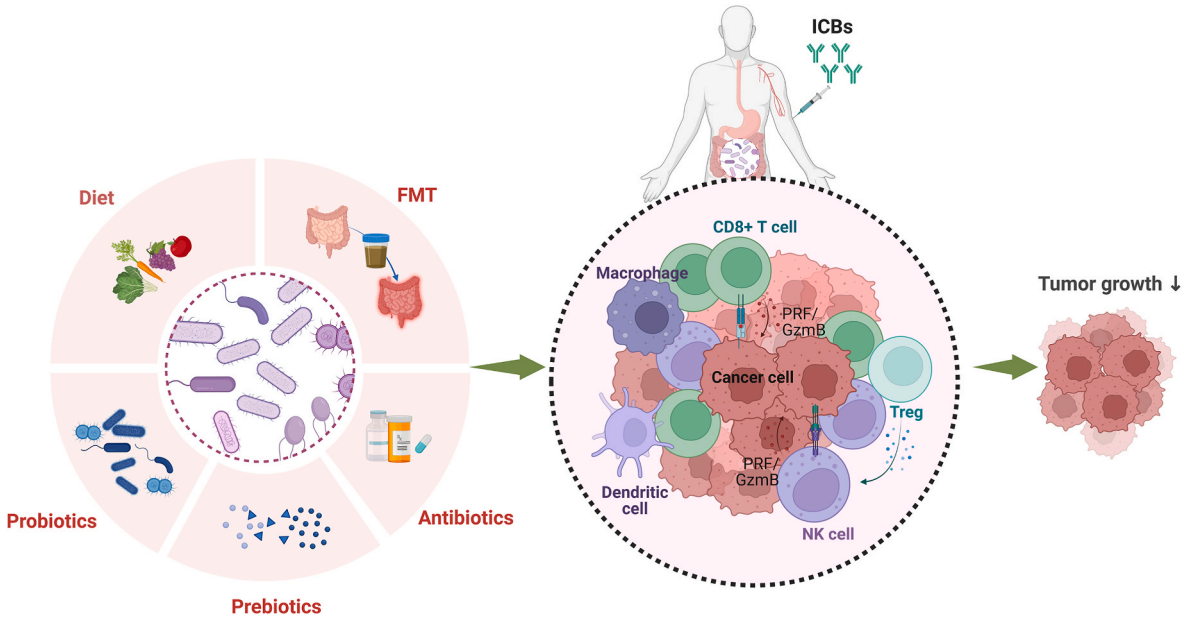

Fig. 3. Intervention of gut microbiota can improve efficacy of ICBs against tumor. Different intervention strategies such as diet, fecal microbiota transplantation (FMT), probiotics and/or bacteria consortia, prebiotics and antibiotics may be used to regulate gut microbiome to improve the efficacy of ICB immunotherapy against cancers. FMT, fecal microbiota transplantation; Macs, Macrophages; Tregs, regulatory T cells; PRF, perforin; GzmB, granzyme B.

into tumor immunotherapeutic reagents such as bacterial vaccines, adjuvants, and drug delivery carriers [166,167]. Microbial peptides. Microbial peptides could activate tumor-infiltrating lymphocytes in glioblastoma [168]. **Others.** Gut microbial metabolites castalagin could alter the gut microbial composition in mice and enhance antitumor activity and anti-PD-1 responses in mice [169]. Anacardic acid could switch the classic activation pathway in the Macs by mitogen-activated protein kinases (MAPKs), which activated innate immunity [170]. It also induced production of a neutrophil extracellular trap, which could promote creation of tumor-infiltrating immune cells [170] such as tumor-infiltrated NK cells and CTLs in breast cancer models. In addition, *B. fragilis* and *B. thetaiotaomicron,* which could produce 3-IAA, were also linked with anti-tumor immunity in patients receiving ICBs [18,171]. Notably, evidence on the implications of SCFAs for the responses to ICBs is conflicting [172–174], which needs to be further investigated.

5. Negative effects of gut microbiota on ICB efficacy

Since ICB efficacy against tumor is not only related to $CD8^+$ and NK cells but also other multiple immune cells such as Macs and Tregs, the gut microbiota, which can influence the differentiation and function of the immune cells, also affects the ICB outcomes [175]. For example, the administration of antibiotics had a negative effect on the efficacy of anti-PD-1 immunotherapy against tumor, either alone or in combination with anti-CTLA-4 antibodies, causing increased tumor size, reduced antitumor effects and decreased survival in germ-free (GF) mice [147]. The gut microbiota enriched with *Bacteroidales*, which was related to Treg cells and MDSCs, had a reduced cytokine response to anti-PD-1 therapy [142]. Gut microbiota derived SCFAs also blunted the responses with anti-CTLA4 therapy in the patients with melanoma [172]. Bacteroidales could negatively impact the response of the patients with melanoma to ICBs [176]. In addition, gut microbiome also was associated with immune-related adverse events following ICBs [177]. Notably, gut microbiota also directly drove tumorigenesis such as that *Helicobacter pylori* was related to progression to gastric cancer [178], and that Fnucleatum, and Bacteroides fragilis were also mechanistically linked to the development of CRCs [179].

Interestingly, analyses of fecal DNA by 16S and shotgun sequencing have exhibited the differences in the microbiota composition between responder and non-responder patients. The reconstitution of GF mice with patient microbiota also further confirmed a mechanistic link between the composition of gut microbiota and anti-tumor immunity [147]. Thus, gut microbiota should be a promising biomarker to screen suitable candidates for ICB immunotherapy [180].

6. Gut microbiota modulates immunogenicity of tumor cells

The downregulation in tumor immunogenicity is a basic mechanism by which tumor cells can resist T cell killing. The gut microbiota can not only directly enhance the innate immunogenicity of tumor cells to improve ICB responses but also indirectly increase immunogenicity of tumor cells by providing tumor cross-antigens to promote the efficacy of ICBs [150,181,182]. Notably, cross-reactivity between antigens expressed in gut microbes and tumor cells has been found [183]. Memory Th1 recall responses directed against specific bacteria, including *A. muciniphila*, *B. thetaiotaomicron*, *Bacteroides fragilis* and *Enterococcus hirae*, have been associated with improved responses to ICBs in patients with tumor [147,157]. There also existed high similarity between the antigenic epitope tail length tape measure protein 1 (TMP1) in *Enterococcus hirae* and the proteasome subunit beta type-4 (PSMB4) tumor antigen, which could activate $CD8^+$ T cells and improve the efficacy of PD-1 blockade therapy [183]. Interestingly, the antigen epitope SVYRYYGL (SVY) in the *Bifidobacterium breve* was similar to the tumor-expressed antigen epitope SIYRYYGL (SIY) [184]. T cells specific for an epitope expressed by *Bifidobacterium breve* also cross-reacted with a neo-antigen expressed by the B16·SIY melanoma cell line. In addition, gut microbial metabolite inosine also significantly enhanced the ability of tumor cells to present tumor antigens, so that cytotoxic immune cells could easily recognize and kill tumor cells [185].

Notably, HLA-E surface expression may be post-translationally regulated through availability of the conserved leader peptides, the peptide transporter TAP, and proteolytic enzymes, which do not influence RNA expression [186]. However, so far there is absence of report(s) on the regulation of gut microbiota on HLA-E expression. Since HLA-E expression in tumor cells plays an important role in tumor immunotherapy [25], it is necessary to investigate the regulation of gut microbiota on the expression of HLA-E. In addition, MHC class I molecules HLA-A, -B, –C, and -G are expressed with a typical signal sequence for

targeting to the secretory pathway. The signal sequences contain a highly conserved segment that is eventually presented at the cell surface to promote the expression of the HLA-E.

7. Interventions of gut microbiota can improve ICB efficacy

Gut microbial modulation can improve the efficacy of immunotherapy against tumors. Different strategies can be used to regulate the gut microbiome to improve the efficacy of ICB immunotherapy such as diet, FMT, probiotics and/or bacteria consortia, prebiotics and antibiotics (Fig. 3). FMT could change the gut microbiota composition of patients with cancer to improve the efficacy of ICBs such as anti-PD-1 monoclonal antibody [146,152]. Probiotics and/or bacteria consortia containing *Bifidobacteria, Lactobacillus*, *Propionibacterium* and *Streptococcus thermophiles* combined with anti-PD-1 and anti-CTLA-4 antibodies could significantly improve the outcomes of cancer. Prebiotics or antibiotics are capable to facilitate the growth of healthier microorganisms and their metabolites such as inosine, which enhances tumor cell killing efficacy through promoting both effector T lymphocyte.

8. Conclusion and perspectives

Gut microbiota plays a critical role in maintaining gut and system homeostasis through gut microbial metabolites, which can promote immunosuppressive cells and inhibit inflammatory cells. However, the gut microbiota indeed also improve the efficacy of ICB immunotherapy through microbial-derived products such as microbe-associated or pathogen-associated molecular patterns such as lipopolysaccharide (LPS), PGN and nucleic acids, and gut microbial metabolites such as inosine and STING agonist, as well as cross-reactivity between self-antigens and microbial xeno-antigens. Interventions designed to modulate gut microbiota also produce profound effects in improving the effectiveness of ICBs in patients. However, it is necessary to explore the mechanisms of these complex interactions as well as the specific microorganisms which play the crucial role in mediating antitumor responses. Notably, inter-individual microbial heterogeneity may be a major challenge in studying the microbiota across different human populations and the translation of microbial findings into clinical interventions.

CRediT authorship contribution statement

Juanjuan Wang: Investigation. **Ningning Zhu:** Investigation. **Xiaomin Su:** Investigation. **Rongcun Yang:** Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

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