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Mushroom Polysaccharides as Natural Modulators of IL-17: Implications for Gut Microbiota, Autoimmune Diseases and Cancer Therapy

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ABSTRACT

Interleukin-17 (IL-17, also known as IL-17A) is a member of the pro-inflammatory cytokine family that plays a pivotal role in immune defense, inflammatory responses, and tissue homeostasis. It contributes to host protection, autoimmune diseases, and cancer progression. Recent studies have highlighted the critical role of gut microbiota in immune regulation and tumor progression. Alterations in its composition can disrupt protective mechanisms, increase infection risk, and elevate the likelihood of metabolic and immune-related diseases. Mushroom polysaccharides are biological macromolecules extracted from the fruiting bodies, mycelia, or fermentation broth of mushrooms. These compounds achieve anti-tumor, anti-inflammatory, anti-oxidative, and immune-regulatory effects by modulating gut microbiota, increasing short-chain fatty acid production, enhancing intestinal mucosal barrier function, regulating lipid metabolism, and activating specific signaling pathways. Mushroom polysaccharides have been shown to regulate IL-17 both directly through key signaling pathways and indirectly by modulating gut microbiota, thereby influencing immune-related diseases and tumor progression. Therefore, mushroom polysaccharides, acting as natural regulators of IL-17, possess extensive application potentials in cancer therapy and immune disease management.

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1. Background

Interleukin-17 (IL-17, also named IL-17A), is a family of pro-inflammatory cytokines comprising six members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F[1, 2]. IL-17A and IL-17F are the most thoroughly studied members of the IL-17 family, displaying both structural and functional similarities[3]. These cytokines exert their effects through five IL-17 receptors (IL-17Rs): IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE[4, 5]. IL-17RA is the most extensively studied member of the IL-17 receptor family. It forms heterodimeric receptor complexes with IL-17RC to mediate the signaling of IL-17A and IL-17F. Additionally, IL-17RA pairs with IL-17RB and IL-17RE, facilitating the signaling of IL-17E (also known as IL-25) and IL-17C, respectively. As a shared receptor subunit, IL-17RA plays a central role in various IL-17-mediated pathways, influencing inflammation, immune regulation, and tissue homeostasis[6-9]. IL-17A is primarily secreted by CD4+ T helper 17 (Th17) cells, characterized by expression of retinoic acid receptor-related orphan receptor gamma ($ROR_\gamma t$) and polarized by transforming growth factor beta (TGF-β), IL-6, IL-21, and IL-23. IL-17A is also produced by a variety of innate immune cells, including CD8 + T cells, γδ T cells, mucosal-associated invariant T (MAIT) cells, innate lymphoid cells (ILCs), natural killer (NK) cells, and Paneth cells[10-14]. The IL-17 family plays a pivotal role in immune defense, inflammatory responses, and tis-

sue homeostasis, contributing to host protection, autoimmune diseases, and cancer progression[15-17].

Mushrooms are rich sources of bioactive compounds, including polysaccharides, phenolic compounds, terpenoids, flavonoids, sterols, and lectins. These compounds possess a wide range of pharmacological properties, such as anti-cancer, anti-inflammatory, immunomodulatory, antioxidant, anti-obesity, antibacterial, and antiviral activities[18, 19]. Mushroom polysaccharides are a kind of biological macromolecules extracted from the fruiting bodies, mycelia or fermentation broth of mushrooms. They can achieve the effects of anti-tumor, anti-inflammatory, anti-oxidative and immune regulation by regulating the intestinal microbiota, increasing the production of short-chain fatty acids (SCFAs), improving the intestinal mucosal barrier, regulating lipid metabolism, and activating specific signaling pathways[20]. Recent studies have suggested that the mechanisms underlying the anti-cancer and immunomodulatory effects of mushroom polysaccharides may involve the following processes: (1) regulating the Th1/Th17 immune balance and inhibiting IL-17-mediated inflammation[21]; (2) activating immune cells such as T cells, macrophages, and NK cells through signaling pathways including NF-κB, JAK/STAT, and MAPK[22]; and (3) modulating gut microbiota to promote the production of SCFAs and thereby enhancing host immune function. Therefore, mushroom polysaccharides, acting as natural regulators of IL-17, possess extensive application potentials in various fields of biomedical research and therapeutic development[23].

2. The Role of IL-17 in Immune Diseases and Cancer

Among the IL-17 family members, IL-17A plays a pivotal role in human health and disease. It is predominantly implicated in inflammatory and immune-mediated disorders such as psoriasis, psoriatic arthritis (PsA), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), and inflammatory bowel disease (IBD)[15-17]. Moreover, emerging evidence underscores its dual roles in cancer, particularly colorectal cancer (CRC), lung cancer, and prostate cancer, where it can either promote tumorigenesis or enhance anti-tumor immunity depending on the specific context[24].

IL-17 is a major regulator of pro-inflammatory pathways, activating NF-κB, JNK, chemokines, and other inflammatory cytokines[25]. It plays a complex role in tumor biology, contributing to cancer progression through multiple mechanisms: enhancing cell proliferation by regulating the cell cycle and growth signaling pathways (e.g., activation of NF-κB, JNK, and STAT3); suppressing apoptosis and autophagy by inhibiting pro-apoptotic signals (e.g., downregulation of Bax and upregulation of Bcl-2); recruiting and polarizing inflammatory cells via regulation of immune cell infiltration (e.g., recruitment of neutrophils, Th17 cells, and macrophages through chemokine signaling); influencing metabolic processes such as glycolysis and oxidative phosphorylation; stimulating angiogenesis and epithelial-mesenchymal transition (EMT) by upregulating VEGF, HIF-1α, and TGF-β, which leads to vascular formation and enhanced tumor invasiveness; and upregulating matrix metalloproteinases (MMPs) and programmed cell death ligand 1 (PD-L1) expression[25-27].

In non-small cell lung cancer (NSCLC), IL-17 accelerates disease progression by activating NF-κB, regulating autophagy, and promoting M2 macrophage-mediated immune suppression. Inhibiting IL-17 signaling may disrupt the tumor microenvironment and enhance anti-tumor immune responses[28]. Recent studies also indicate that IL-17 contributes to digestive tract cancer progression by activating SPP1+ macrophages, which drive tumor angiogenesis, immune suppression, and CXCL1/5/8-mediated inflammation through the TRAF3IP2 signaling pathway[29]. Studies in specific tumor models further support the tumor-promoting effects of IL-17. IL-17 promotes cell migration and invasion by upregulating MTA1 expression in HeLa and DU-145 cells, with a positive correlation between IL-17 levels and MTA1 expression in tissue samples[30]. A recent study demonstrated that Oct4 transcriptionally activates IL-17A, which subsequently regulates the p38 signaling pathway, induces M2 macrophage polarization, and enhances tumor proliferation, migration, and invasion, thereby facilitating cervical cancer metastasis[31].

At the signaling level, NF-κB activator 1 (Act1) contains a SEFIR domain that enables its interaction with IL-17RA/RC via SEFIR-SEFIR interactions, thereby activating IL-17-dependent signaling pathway[25, 32]. Research has shown that IL-17 and TNF-α independently induce PD-L1 expression through the NF-κB pathway, with distinct signaling dependencies in different tumor cell types, for example, through activating ERK1/2 in HCT116 colon cancer cells

and AKT in LNCaP prostate cancer cells[26]. Recent findings indicate that IL-17 promotes PD-L1 gene transcription in NSCLC cells through TRIM31-dependent K63-linked polyubiquitination of MEF2C, enhancing immune evasion and tumor progression[33].

Despite its tumor-promoting roles, IL-17 can also exert anti-tumor effects in certain contexts. For instance, in colorectal cancer (CRC), IL-17 can both promote inflammation and directly interact with regulatory T cells (Tregs). One study suggests that IL-17 enhances Treg maturation and function, forming a negative feedback loop that regulates inflammation and inhibits tumor progression[34]. Some studies highlight that IL-17 signaling not only promotes inflammation but also modulates immune cell composition within the tumor microenvironment (TME). In some cancers, IL-17A enhances immunosuppressive pathways by increasing PD-L1 expression, while in others, it supports anti-tumor immunity by enhancing immune cell infiltration[35]. The dual functions suggest that IL-17-targeted therapies should be tailored based on the specific tumor type, immune landscape, and patient profile to maximize therapeutic benefits while minimizing potential adverse effects.

3. Gut Microbiota Modulates IL-17 Production and Immune Homeostasis

Recent studies indicate that changes in gut microbiota composition can disrupt protective mechanisms, increase infection risk, and elevate the risk of metabolic and immune-related diseases[36]. The gut microbiota plays a crucial role in modulating responses to immune checkpoint inhibitors (ICIs) in cancer. Emerging evidence suggests that microbial composition influences both the efficacy and toxicity of cancer treatments, while dietary interventions may enhance immunotherapy outcomes by shaping tumor immune surveillance. In NSCLC patients, gut microbiota composition significantly affects anti-PD-1 therapy outcomes[37]. Long progression-free survival (PFS) is associated with enrichment of *Alistipes shahii* and *Barnesiella visceriola*, while short PFS correlates with increased *Streptococcus salivarius*, *Streptococcus vestibularis*, and *Bifidobacterium breve*[38].

Specific probiotic species, such as *Bifidobacterium*, enhances ICI efficacy by modulating gut microbiota, promoting dendritic cell (DC) activation, and priming tumor-specific $CD8^+$ T cells, thereby strengthening antitumor immunity and synergizing with anti-PD-L1 therapy[39, 40]. *Lactobacillus rhamnosus* Probio-M9 improves anti-PD-1 therapy outcomes by enhancing beneficial bacteria, inhibiting harmful ones, restoring antibiotic-disrupted microbiota, and modulating immune-related metabolic pathways, thus promoting an improved antitumor immune response [41].

Akkermansia muciniphila (AKK) has been positively correlated with improved responses to anti-PD-1/PD-L1 therapy, with patients harboring AKK exhibiting better treatment outcomes[42]. The NEOSTAR trial further supported this link. Neoadjuvant ipilimumab + nivolumab (IpiNivo) and nivolumab + chemotherapy (Nivo+CT) improved major pathologic response (MPR) rates in operable NSCLC, with both groups showing *Akkermansia* muciniphila-enriched microbiota at baseline[43].

The interplay between IL-17 and gut microbiota is critical for maintaining intestinal immune homeostasis. IL-17 plays a fundamental role in preserving the balance of intestinal flora by stimulating antimicrobial peptide (AMP) production, thereby strengthening the intestinal barrier. This protective mechanism is particularly important in inflammatory conditions such as ileitis[44]. In a study involving mice with ileitis, IL-17 receptor deficiency in Paneth cells compromised antibacterial defense in the ileum, leading to reduced alpha-defensin production and pronounced microbiota dysbiosis[45]. Recent studies indicate that commensal gut microbiota also regulate IL-17 production and function, influencing immune homeostasis[44]. IL-17 signaling in gut epithelial cells is crucial for preventing microbial dysbiosis. Impaired IL-17RA signaling increases systemic IL-17 levels through compensatory mechanisms, which can influence the tumor microenvironment and potentially promote tumor growth[46]. These findings highlight why single-target inhibition of IL-17 or IL-17RA may have limited clinical efficacy and support the need for combination strategies targeting both antimicrobial therapy and IL-17 signaling.

Dysbiosis, characterized by reduced microbial diversity and an imbalance between pathogenic and beneficial bacteria, leads to abnormal production of metabolites such as SCFAs, bile acids, and amino acid derivatives. These metabolites promote tumorigenesis by modulating immune responses, highlighting their potential as biomarkers for early diagnosis and precision treatment of gastrointestinal cancers[47]. Moreover, gut microbiota dysbiosis disrupts the gut-liver axis, facilitating the progression from metabolic-associated fatty liver disease (MAFLD) to hepatocel-

lular carcinoma (HCC), which are new avenues for biomarker discovery and therapeutic intervention[48]. However, clinical translation remains challenging.

Specific probiotics, such as *Limosilactobacillus reuteri* ZY15, has been shown to alleviate intestinal barrier damage and inflammation by enhancing antioxidant capacity, upregulating intestinal barrier proteins, and suppressing inflammatory cytokines through inhibition of the AKT/mTOR/HIF-1α/RORγt/IL-17 signaling pathway, thereby modulating gut microbiota composition[49]. The polymeric immunoglobulin receptor (pIgR) regulates the IL-17 signaling pathway and the secretion of the antimicrobial peptide Reg3b via STAT3-dependent mechanisms. This regulation helps maintain gut microbiota balance, protect intestinal barrier integrity, and inhibit liver inflammation. In contrast, pIgR deficiency leads to gut dysbiosis, reduced Reg3b expression, and exacerbated LPS-mediated liver damage, suggesting that targeting the pIgR/STAT3/IL-17 axis could be a promising approach for diagnosing and treating autoimmune hepatitis (AIH)[50].

4. Mushroom Polysaccharides and Their Bioactivity in IL-17 Modulation

The effects of mushroom polysaccharides on IL-17 in tumors and the immune system are summarized in Table 1. Mushroom polysaccharides are a class of complex carbohydrates derived from various edible and medicinal mushrooms, demonstrating extensive biological activities such as immune modulation, anti-tumor effects, anti-inflammatory responses, antioxidant properties, and regulation of gut microbiota[51]. Based on their structural composition, these polysaccharides can be classified into two main categories: homoglycans and heteroglycans. Heteroglycans comprise two or more different types of monosaccharide residues, while homoglycans consist solely of one type of monosaccharide residue[51]. By interacting with various immune cells and signaling pathways, mushroom polysaccharides modulate the tumor microenvironment, regulate cytokine production, and influence processes such as cell proliferation and angiogenesis, thereby enhancing antitumor immunity and supporting conventional cancer therapies[52, 53].

Different mushroom polysaccharides exert immunomodulatory effects through distinct pathways. *Cordyceps sinensis* polysaccharides (CSP) enhance microbial metabolism of butyrate, inhibit histone deacetylases (HDAC), increase histone H3 acetylation, and ultimately upregulate Foxp3 expression, thereby promoting Treg cell function and suppressing IL-17-mediated inflammatory responses[54]. *Ganoderma atrum* polysaccharides (PSG) significantly downregulate MyD88 while increasing IL-10 and TGF-β3 levels, thereby enhancing anti-inflammatory responses[54]. The combined use of different bioactive polysaccharides may potentiate immune regulation. Co-administration of CSP and PSG (CFP) has been shown to restore cytokine balance, regulate the Foxp3/RORγt ratio associated with Th17/Treg equilibrium, downregulate TLR-mediated inflammatory signaling, and promote secretory immunoglobulin A (sIgA) secretion[54]. These findings provide novel scientific insights into immune homeostasis regulation and the development of natural immunomodulatory agents. Alkali-extracted polysaccharide (PEAP) from *Pleurotus eous* enhances macrophage activation, promotes the secretion of various cytokines including IL-17, TNF-α, IL-4, IL-12, and IFN-γ, and stimulates immune responses[55]. *Lignosus rhinocerus* (syn. *Polyporus rhinocerus)* polysaccharides exhibit significant immunomodulatory effects, specifically by enhancing IL-17-mediated neutrophil activation and concurrently inhibiting VEGF to restrict tumor angiogenesis. These results indicate the potential of these polysaccharides in augmenting cancer immunity and modulating the tumor microenvironment[56]. This suggests that the extract may modulate immune responses and exert anti-inflammatory effects, thereby regulating IL-17 expression.

Many naturally derived polysaccharides can activate macrophages and enhance immune function with low toxicity and side effects. Mushroom polysaccharides have demonstrated significant potential in cancer therapy, specifically by enhancing tumor immunity, inhibiting tumor progression, and augmenting the efficacy of conventional treatments. Exposure of B16 cells to *Tremella fuciformis*-derived polysaccharide (TFP) in mice elicited immune and inflammatory responses through the recruitment of leukocytes, neutrophils, dendritic cells (DCs), and mast cells, promoting the production of cytokines such as TNF-α, IL-6, IL-1β, and IL-1. TFP also activated Th17 lymphocytes to secrete IL-17 and IFN-γ and enhanced tumor immunity via the TNF-α signaling pathway, ultimately resulting in tumor shrinkage[57]. *Sparassis latifolia* extract (polysaccharides) significantly suppresses IL-17 expression and alleviates colorectal cancer (CRC)-associated inflammation. In an AOM-DSS-induced CRC mouse model, IL-17 lev-

Table 1. The regulatory role of mushroom polysaccharides on IL-17 in tumors and immunomodulation.

Name of the mushroom	Type of disease	Antitumor and Immunoregulatory Mechanisms	Effect on IL-17	Related inflammatory factors	Associated pathways	Reference
Sanghuangporus vaninii	Colorectal cancer	Promotes Th1 cell differentiation; enhances IFN-γ and TNF-α production; suppresses Th17-mediated inflammation; modulates gut microbiota composition; inhibits tumor proliferation and migration.	Reducing IL-17 Expression	↑ IFN-γ, ↑ TNF-α, ↓ IL-17, ↓ IL-22, ↓ IL-23	JAK/STAT signaling inhibition	[21]
Tremella fuciformis	Melanoma	Promotes M1 macrophage polarization; enhances NO, IL-6, TNF-α production; induces apoptosis in melanoma cells via macrophage activation.	Potential regulation of IL-17 signaling	↑ IL-6, ↑ TNF-α, ↑ ROS	IL-17 signaling pathway, MAPK and NF-κB signaling pathways	[22]
Cordyceps sinensis	Colon immune dysfunction	Enhances microbial-derived butyrate production; promotes Foxp3 expression via histone H3 acetylation; suppresses IL-17 and IL-21.	Reducing IL-17 expression	↓IL-21, ↑IL-10, ↑TGF-β3,	Foxp3/RORγt balance regulation and SCFAs production	[54]
Pleurotus eous	Immunomodulation	Enhances macrophage activation; promotes cytokine secretion; stimulates immune response via phagocytic activity.	Enhances IL-17 production	↑ IL-4, ↑ IL-12, ↑ TNF-α, ↑ IFN-γ	Macrophage activation, Th17-mediated immune response	[55]
Lignosus rhinocerus	Immunomodulation	Promotes of innate immune response; increases neutrophil recruitment; immune modulation via IL-17, G-CSF and GM-CSF.	Increased IL-17 expression	↑G-CSF, ↑GM-CSF, ↑IL-12, ↓VEGF	Neutrophil recruitment via G-CSF and GM-CSF	[56]
Tremella fuciformis	Melanoma	Promotes Th17 differentiation; increases IFN-γ and TNF-α expression; enhances immune cell infiltration; and activates NF-κB signaling.	Enhances IL-17 production	↑TNF-α, ↑IL-6, ↑IL-1β, ↑IFN-γ, ↑CXCL2, ↑CXCL3	IL-17 pathway, NF-κB signaling, TNF-α signaling	[57]
Sparassis latifolia	Colorectal cancer	Regulation of inflammatory response; inhibition of tumor growth; modulation of ceRNA network; suppression of oxidative stress; enhancement of immune function.	Reducing IL-17 expression	↓IL-1β, ↓IL-2, ↓CXCL8, ↓FN1	PI3K-Akt signaling pathway and IL-4/IL-13/IL-17/IL-18 signaling pathway	[58]

els were markedly elevated in both the cancer group (COL) and the chemotherapy group (COL + Chem), indicating that IL-17 plays a pro-inflammatory and tumor-promoting role in CRC progression. Notably, the administration of Sparassis latifolia extract to the COL + Chem group resulted in a significant reduction in IL-17 levels[58]. *Sanghuangporus vaninii* polysaccharide (SVP-A-1) modulates the tumor microenvironment (TME) by promoting Th1 cell differentiation and inhibiting Th17 cell activation along with its associated inflammatory factors, including IL-17A, IL-22, and IL-23, thereby suppressing the growth and migration of colorectal cancer (CRC)[21]. Other studies have shown that homogeneous polyporus polysaccharide (HPP) promotes M1 macrophage polarization, thereby suppressing bladder cancer cell proliferation and migration while inducing apoptosis[59]. *Tremella fuciformis* polysaccharides (TFPS) indirectly induce melanoma cell apoptosis by promoting M1 macrophage polarization and enhance anti-tumor immunity via the MAPK and NF-κB signaling pathways[22].

Recent evidence underscores the pivotal role of gut microbiota in modulating immune homeostasis and influencing outcomes of cancer therapy. Mushroom polysaccharides possess prebiotic properties that can alter microbial composition, enhance SCFA production, and modulate immune signaling pathways[60, 61]. Mushroom polysaccharides exert both direct effects on the immune system and indirect effects through modulation of the gut microbiota, leading to increased production of SCFAs, particularly butyrate[62]. This enhancement in SCFA production strengthens host immune responses and may contribute to more favorable outcomes in immunotherapy. *Lactarius hatsudake* Tanaka polysaccharides (LHP) undergo fermentation by gut microbiota, leading to the production of SCFAs with a reduction in molecular weight and pH, which can selectively enhance beneficial bacteria while inhibiting harmful ones through modulation of amino acid and lipid metabolism[23]. Recent studies have demonstrated that SCFAs modulate the intestinal immune barrier, which consists of immune factors, immune cells, and gut-associated lymphoid tissues, by binding to cellular receptors and activating signaling pathways that promote cell differentiation and proliferation[63]. Furthermore, emerging evidence indicates that SCFAs, particularly propionate produced by the gut microbiota, can directly modulate γδ T cells and suppress IL-17 production via a histone deacetylase (HDAC)-dependent mechanism[64].

5. Conclusion

Mushroom polysaccharides have emerged as promising natural immunomodulators, particularly in their role as regulators of IL-17 in immune-related diseases and cancer. Their ability to restore the Th1/Th17 balance, inhibit IL-17-mediated inflammation, activate immune cells via key signaling pathways (NF-κB, JAK/STAT, MAPK), and modulate gut microbiota, underscores their broad therapeutic potentials. These bioactive compounds not only exhibit anti-inflammatory and immunoregulatory effects but also contribute to tumor suppression by enhancing immune surveillance, inducing apoptosis, and inhibiting tumor growth and metastasis. Despite these promising findings, challenges remain in standardizing mushroom-derived compounds, identifying specific bioactive molecules, and optimizing dosages for clinical applications. Most current studies focus on whole extracts rather than isolated components, complicating efforts to precisely determine their molecular mechanisms and therapeutic targets. Additionally, variability in bioactive compound concentrations across different mushroom species and extraction methods poses a challenge in ensuring consistent clinical efficacy. Future research should aim to elucidate the structure-activity relationships (SAR) of mushroom polysaccharides, optimize their formulation, and conduct well-designed clinical trials to assess their safety, efficacy, and potential synergies with conventional therapies. By bridging the gap between preclinical studies and clinical applications, mushroom-derived polysaccharides could serve as valuable complementary or adjunctive treatments for IL-17-mediated autoimmune diseases, chronic inflammation, and cancer. Their integration into precision medicine and immunotherapy strategies may open new avenues for innovative and effective therapeutic approaches.

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