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The microbiome–immunity axis in lung transplantation: Ecological insights and clinical implications

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Abstract

Lung transplantation (LTx) is the definitive therapeutic option for patients with end-stage lung disease. Improving long-term survival remains a central focus of clinical research in LTx, particularly because post-transplant infection, acute and chronic rejection, and chronic lung allograft dysfunction continue to limit graft survival. However, the prognosis of LTx recipients depends not only on surgical technique but also on pulmonary microbial ecology and immunosuppressive strategies. In recent years, advances in LTx research have increased interest in the post-LTx pulmonary microbial ecosystem, especially its dynamic remodeling and multifaceted interactions with the host immune system, which play critical roles in infection, rejection, and long-term prognosis. Previous studies have shown that LTx-induced changes in microbial community structure affect the stability of the pulmonary environment and are closely associated with immune rejection, thereby representing key determinants of graft survival. Mechanistically, microbial dysbiosis may influence innate immune activation, macrophage polarization, regulatory T cells and T helper 17 cells balance, microbial metabolites, and gut–lung axis-mediated systemic inflammation. However, the underlying mechanisms of microbial ecology and immune regulation remain unclear, hindering the development of precision therapies and personalized management strategies. This review summarizes post-LTx pulmonary microbial community dynamics, immune responses, and bidirectional regulatory mechanisms between the immune system and microbiota, and discusses their impact on graft function, with implications for immune management and microbial ecological regulation strategies. Recent advances in multi-omics analysis, microbiome-related biomarkers, artificial intelligence-assisted analysis, non-invasive monitoring, and methodological standardization may further support precision management in LTx recipients.

Keywords: Lung transplantation; Microbial ecology; Immune mechanisms; Graft rejection; Pulmonary microbiome; Immune regulation

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1. Introduction

Lung transplantation (LTx) is a definitive therapeutic option for patients with end-stage lung diseases.[1] The indications for LTx encompass various pulmonary diseases,

predominantly including chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, pulmonary arterial hypertension, and cystic fibrosis (CF).[2,3] Despite the availability of numerous therapeutic interventions, such as smoking cessation, bronchodilators, oxygen therapy, and pulmonary rehabilitation, patients with end-stage lung disease still face severe respiratory failure and a decline in quality of life. LTx offers a critical survival benefit and significantly improves their quality of life.[4–6] However, despite advances in surgical techniques, perioperative care, antimicrobial prophylaxis, and immunosuppressive therapy, long-term outcomes after LTx remain suboptimal. Chronic lung allograft dysfunction (CLAD), recurrent post-transplant infections, acute and chronic rejection, and complications associated with lifelong immunosuppression remain major causes of morbidity, mortality, and graft failure. These persistent clinical challenges highlight the need to identify modifiable biological mechanisms that link microbial injury, immune dysregulation, and progressive allograft remodeling.

As a unique internal organ directly exposed to the external environment, the lung harbors a complex and dynamic microbial ecosystem.[7] This ecosystem not only modulates local immune responses after LTx but also plays a pivotal role in systemic immune regulation. After LTx, the airway microbial community undergoes marked ecological remodeling, characterized by reduced microbial diversity, restructuring of community composition, enrichment of potentially pro-inflammatory taxa, and loss of protective commensal bacteria.[8] In bronchoalveolar lavage fluid (BALF) from LTx recipients, increased abundances of pro-inflammatory bacteria, such as *Pseudomonas aeruginosa*, Enterobacteriaceae, and Staphylococcaceae, have been observed.[8,9] In contrast, commensal bacterial taxa with potential protective roles, including Prevotellaceae, Veillonellaceae, and Streptococcaceae, are often reduced, further disrupting microbial homeostasis and weakening host defense mechanisms.[10] These shifts in microbial community composition reflect profound changes in the immune and metabolic milieu of the transplanted lungs. The preferential expansion of pro-inflammatory microbial communities may enhance local inflammatory responses, promote pulmonary fibrosis and airway remodeling, and accelerate the development of chronic rejection.[11,12] Nevertheless, whether microbial dysbiosis directly drives allograft injury or primarily reflects the effects of antibiotics, immunosuppression, impaired mucociliary clearance, aspiration, and pre-existing airway disease remains incompletely understood.

The airway microbial community in LTx recipients presents different "lung types," some of which are associated with airway remodeling, inflammatory states, and immune dysregulation.[13,14] Major complications following LTx, such as primary graft dysfunction, acute and chronic rejection, and infections, are closely related to abnormal immune cell function. Maintaining a balance between immune tolerance and rejection is crucial for prolonging graft survival.[15,16] The pulmonary microbial community also contributes to post-LTx rejection. Studies have found that bacterial products present in the donor lung airways can activate Toll-like receptor 2, which subsequently induces the proliferation of $CD8^+$ T cells and antigen-presenting cells, thereby promoting acute cellular rejection.[17] Beyond Toll-like receptor signaling, microbial dysbiosis may influence immune-metabolic pathways, macrophage polarization, neutrophilic inflammation, antigen presentation, and the balance between regulatory T (Treg) cells and T helper 17 (Th17) cells. These mechanisms may provide biological links between altered microbial ecology, persistent alloimmune activation, fibrotic remodeling, and CLAD progression.

In patients with CLAD, bacterial diversity in lung tissue is significantly lower than that observed at the time of primary transplantation. Specific genera, such as *Aerococcus* and *Croceibacter*, are significantly enriched during chronic dysfunction. The composition of immune cells also varies, with increased $CD8^+$ T cells, suggesting that alterations in microbial communities may drive or reflect immune activation states.[18] While alterations in the lung microbiota directly influence local immune responses, emerging evidence highlights that the pulmonary microenvironment is also shaped by distant microbial reservoirs, particularly the gut. The gut–lung axis, a bidirectional communication pathway, regulates pulmonary immune responses through microbes and their metabolites, affecting immune tolerance and rejection after LTx. For example, reduced diversity of gut microbiota is associated with enhanced pulmonary inflammatory responses. Conversely, metabolites such as short-chain fatty acids (SCFAs) produced by gut microbes possess immune regulatory functions that can promote immune tolerance and reduce rejection responses.[19] In addition to SCFAs, tryptophan-derived metabolites and bile acid derivatives may regulate systemic inflammation, epithelial barrier integrity, oxidative stress, and T-cell differentiation after transplantation. Gut microbiota dysbiosis can also lead to immune disorders and systemic inflammatory responses, which in turn exacerbate pulmonary pathological changes.[20,21] Therefore, maintaining gut microecology is of great significance for immune homeostasis in LTx patients.

From a translational perspective, microbiome research in LTx is increasingly moving from descriptive community

profiling toward integrated biomarker discovery and precision monitoring. Multi-omics approaches combining metagenomics, metabolomics, host transcriptomics, immune phenotyping, donor-derived cell-free DNA, and exosomal biomarkers may improve risk stratification for infection, rejection, and CLAD. Meanwhile, artificial intelligence-assisted analysis, biomedical sensing systems, and non-invasive respiratory monitoring technologies may complement microbiome-informed strategies for individualized post-transplant management. Nevertheless, several barriers limit clinical translation, including contamination from low-biomass samples, heterogeneous sampling protocols, inconsistent sequencing and bioinformatic pipelines, small cohort sizes, limited causal inference, and a lack of robust interventional trials.

Taken together, these findings suggest that the microbial ecosystem and immune mechanisms in LTx recipients exhibit complex and dynamic interactions. Alterations in the pulmonary microbiome not only influence local immune responses but also play an important regulatory role in systemic immunity through the gut–lung axis. The functions of immune cells and their interactions with the microbiota are key determinants of transplant success. Against this backdrop, this review aims to summarize current evidence on microbial ecology, immune mechanisms, and microbiome–immune interactions in LTx, with particular emphasis on microbial dysbiosis, CLAD, post-transplant infection, gut–lung crosstalk, multi-omics approaches, microbiome-related biomarkers, and future clinical translation.

2. Methods

This review was conducted as a structured narrative review. Relevant studies were primarily sourced from PubMed, Web of Science, and Scopus. The core search terms included LTx, pulmonary microbiome, microbial ecology, immune regulation, graft rejection, and CLAD.

Additional literature was obtained via cross-referencing from eligible published articles. We prioritized peer-reviewed English papers published in the past five years, and pivotal landmark studies were incorporated to supplement the core mechanistic and clinical background.

3. Dynamic changes in microbial ecology after lung transplantation

3.1. Composition of the pulmonary microbiome and alterations before and after lung transplantation

The pulmonary microbial community primarily comprises bacteria, viruses, and fungi, which establish a stable and diverse ecosystem in healthy lungs and contribute to pulmonary immune homeostasis and barrier function. In healthy individuals, the microbial community exhibits high species diversity and balanced microbial populations, thereby ensuring environmental stability. Studies indicate that microbial diversity in patients before transplantation may be markedly reduced and resembles that of the oropharyngeal microbiome. Post-LTx, the sputum microbial community gradually aligns with that found in the BALF.[22] Significant differences in microbial community composition exist across different sampling sites, with distinct dominant genera: lung tissue is enriched with *Pseudomonas* and Pseudomonadaceae, BALF with Enterobacteriaceae and Propionibacteriaceae, and oropharyngeal samples are abundant in *Streptococcus* and Propionibacteriaceae. Time-series analysis revealed a significant temporal change in the similarity of upper and lower respiratory tract microbial communities. Dissimilarity was greatest pre-LTx and rapidly converged within seven days after LTx, reaching its minimum at six months post-LTx.[23] When microbial diversity is low, the similarity between the upper and lower respiratory tracts increases significantly, particularly during the early post-operative period, when the microbial community is dominated by a single genus, such as *Pseudomonas*, *Staphylococcus*, and *Stenotrophomonas*. In the early post-operative period (within seven days), both the upper and lower respiratory tracts showed enrichment of Gram-positive bacteria, including *Corynebacterium* and *Staphylococcus*. These bacteria gradually decrease in abundance, while bacteria generally found in healthy populations, such as *Prevotella* and *Fusobacterium*, become dominant at six months post-LTx. This shift indicates a trend toward stabilization of respiratory microbial ecology over time. Thus, the similarity between upper and lower respiratory tract microbial communities is closely associated with reduced microbial diversity and the dominance of certain genera, reflecting dynamic changes in the microbial community after LTx.

3.2. The relationship between microbial dysbiosis and pulmonary infection

Following LTx, the structure of the pulmonary microbial community undergoes significant changes, characterized by a marked decrease in diversity and a reorganization of dominant microbial communities. Under normal circumstances, the healthy lung harbors a diverse symbiotic microbial community that maintains the stability of the pulmonary micro-ecosystem and participates in local immune regulation and maintenance of barrier function. However, after LTx, this community may shift from a diverse commensal-dominated profile toward a pathogen-enriched state, with increased abundances of potential

pathogens, such as *P. aeruginosa* and *Staphylococcus aureus*. This dysbiosis disrupts the pulmonary micro-ecological environment, impairs local immune function, and increases the risk of infection. Early after LTx, the composition of the pulmonary microbial community in recipients undergoes profound alterations, characterized by decreased microbial diversity, reduced numbers of normal symbiotic bacteria, and an increased proportion of potential pathogens, such as *P. aeruginosa* and non-tuberculous mycobacteria (Figure 1).[7] This dysbiosis weakens competitive inhibition against pathogens, making it easier for pathogenic bacteria to colonize and cause infections. Research shows that the decline in airway bacterial diversity in LTx recipients is correlated with bronchial inflammation and increased infection risk. The loss of microbial diversity destabilizes the microecosystem and reduces the host's ability to resist foreign pathogens.[7] In addition, structural changes in the pulmonary microenvironment, such as abnormal mucus secretion, also promote pathogenic bacteria to form biofilms, enhancing their drug resistance and immune evasion capabilities.[24] Reduced flora diversity and increased dominant pathogenic bacteria weaken the pulmonary defense barrier and immune defense, increasing the risk of infection and potentially exacerbating alloimmune injury and rejection responses. Therefore, maintaining the balance within the pulmonary microbial community is crucial for preventing infections and reducing the risk of rejection.

3.3. Factors influencing microbial community reconstruction and its clinical implications

The reconstruction of microbial communities following LTx is a complex process influenced by multiple factors. These factors can be organized into six major categories: donor-related factors, recipient-related factors, surgical and perioperative factors, immunosuppressive therapy, antibiotic exposure, and hospital or environmental factors.

3.3.1. Donor-related factors

The source of the donor lung plays an important role in shaping the initial microbial community. Studies have shown that the types and abundance of microorganisms present in the donor lung directly influence the composition of the pulmonary microbiota in the early post-LTx period. Donor airway colonization, aspiration before organ procurement, antimicrobial exposure, and organ preservation conditions may all contribute to the initial microbial burden of the graft.

3.3.2. Recipient-related factors

Over the long term, recipient-related factors, including environmental exposures and underlying lung disease, have a greater impact on microbial community structure.[25] The recipient's primary disease, such as CF or idiopathic pulmonary fibrosis, significantly affects the diversity and stability of lung microbiota. For example, CF recipients tend to have a lower pulmonary microbial burden post-LTx, with a reduced presence of classical CF-associated microbial taxa, which has been associated with an increased risk of CLAD.[26]

3.3.3. Surgical and perioperative factors

Surgical and perioperative factors may also influence microbial reconstruction after LTx. Airway instrumentation, mechanical ventilation, ischemia-reperfusion injury, primary graft dysfunction, and repeated bronchoscopy can disturb the airway microenvironment and affect microbial succession. These factors may impair epithelial barrier integrity, alter mucus clearance, and create conditions that favor colonization by opportunistic pathogens.

3.3.4. Immunosuppressive therapy

Immunosuppressants are one of the key factors affecting the reconstruction of the pulmonary microbial community. Immunosuppressants not only suppress the host immune response and reduce the risk of rejection but also weaken the host's immune defense against pathogens, rendering patients more susceptible to infections.[27] In addition, immunosuppression may alter immune–microbial interactions, thereby contributing to microecological imbalance and impaired graft tolerance.

3.3.5. Antibiotic exposure

Antibiotic therapy is widely applied in LTx recipients, but its effect on the pulmonary microbial community is dual-sided. Antibiotics can inhibit pathogenic bacteria and reduce infection risk; however, broad-spectrum antibiotics may disrupt normal flora, leading to microecological imbalance and promoting the emergence of drug-resistant strains.[28] Prolonged or repeated antibiotic exposure may further reduce microbial diversity, impair colonization resistance, and create ecological niches for opportunistic pathogens.

3.3.6. Hospital and environmental factors

Hospital and environmental factors significantly affect the reconstruction of pulmonary microbial ecology. These factors include hospital-associated pathogens, aerosolized microbes, intensive care exposure, environmental microbial reservoirs, and the post-transplant living environment.[29,30] These environmental pressures may influence microbial acquisition and ecological succession within the transplanted lung. They may also interact

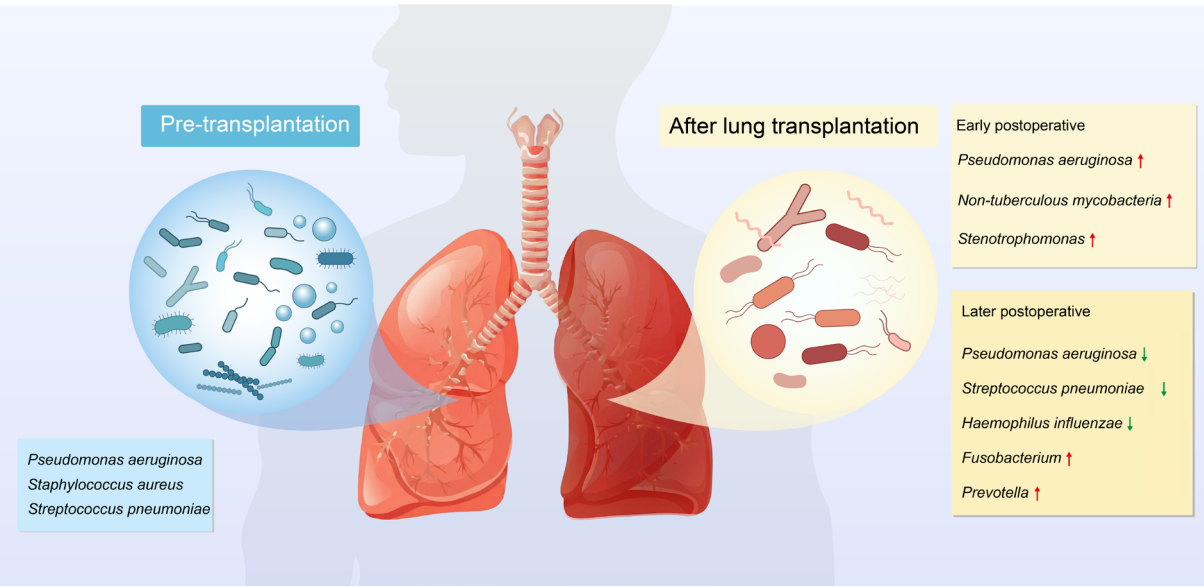

Figure 1. Pulmonary microbial remodeling before and after lung transplantation. After lung transplantation, the airway microbiota undergoes dynamic remodeling, with reduced microbial diversity and enrichment of potentially pathogenic taxa in the early postoperative stage, followed by partial recovery of microbial diversity in the later stage. These changes may influence pulmonary immune homeostasis, infection risk, and long-term graft outcomes. Upward and downward arrows indicate increased and decreased relative abundance, respectively. Image created originally by the author.

with donor-, recipient-, surgical-, immunosuppressive-, and antibiotic-related factors, jointly shaping post-LTx microbial dynamics.

Thus, reconstitution of the pulmonary microbiota after LTx results from the interplay of multiple factors, including donor characteristics, recipient disease background, immunosuppressants, antibiotic exposure, surgery-related factors, and post-LTx environment (Figure 2).[31] A better understanding of how these factors shape microbial ecology will facilitate the development of individualized management strategies and ultimately improve outcomes in LTx recipients.

3.3.7. Prognostic Implications of microbial reconstruction

Microbial communities exhibit diverse characteristics, which are tightly linked to the recovery status of LTx recipients. A microbial community structure associated with favorable recovery after LTx is typically characterized by high diversity and the dominance of commensal bacteria. Greater microbial diversity contributes to ecosystem stability and function, thereby supporting graft stability and the restoration of normal lung function. Representative commensal taxa include *Bacteroides* spp. and *Lactobacillus* spp., which exert anti-inflammatory effects and modulate host immune responses, helping to maintain pulmonary barrier integrity. For example, *Lactobacillus* species are known for their immunomodulatory properties, as they can suppress inflammatory responses and promote immune tolerance by producing metabolites such as lactic acid. In addition, commensal bacteria limit pathogen colonization and overgrowth through competitive exclusion, thereby reducing the risk of pulmonary infection and contributing to a lower incidence of CLAD. The composition of the pulmonary microbiota in LTx recipients is influenced by environmental exposure and immune status, and a stable commensal-dominated microbial community helps preserve immune homeostasis in the transplanted lung and attenuate immune-mediated rejection.[32] Therefore, maintaining or restoring a diverse microbiota enriched with commensal taxa such as *Bacteroides* spp. and *Lactobacillus* spp. is critical for promoting post-LTx lung function recovery and preventing CLAD. In contrast, pulmonary dysbiosis after LTx is commonly marked by the persistent dominance of pathogenic bacteria, including *P. aeruginosa* and *S. aureus*. Overgrowth of these pathogens can drive chronic inflammatory responses, disrupt lung tissue architecture, promote fibrosis, and accelerate the onset and progression of CLAD. *P. aeruginosa,* a frequent pathogen in LTx recipients, can evade host immune defenses through multiple mechanisms, form biofilms,

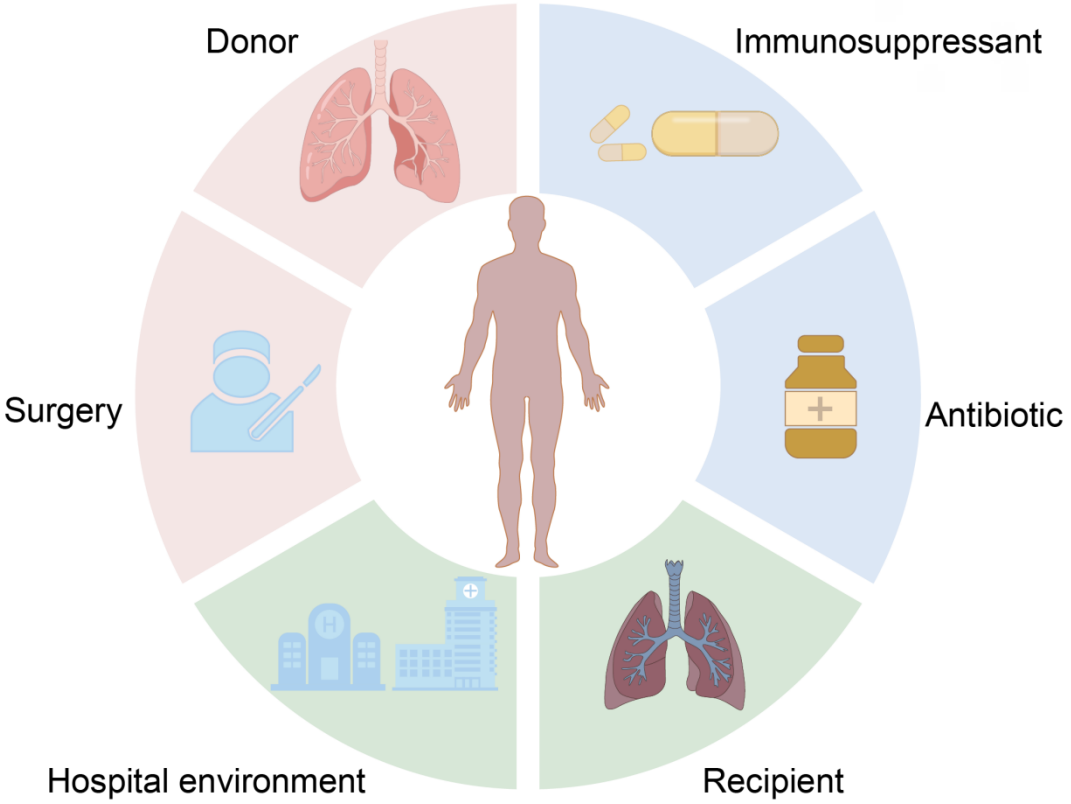

Figure 2. Factors influencing microbial community reconstruction after lung transplantation. Post-lung transplantation microbial reconstruction is shaped by multiple interacting factors, including donor-derived microbiota, recipient disease background and immune status, surgical and perioperative factors, immunosuppressive therapy, antibiotic exposure, and the hospital environment. These factors jointly influence microbial diversity, pathogen colonization, immune homeostasis, and long-term graft outcomes. Image created originally by the author.

and develop antimicrobial resistance, leading to recurrent inflammation and progressive decline in lung function.[33,34] *S. aureus* may also cause severe infections and induce immune cell infiltration and tissue injury.

4. Immune mechanisms and their regulation in lung transplantation

4.1. Immunological basis of graft rejection

The primary immune-related issue following LTx is allograft rejection, which mainly comprises acute and chronic rejection. Acute rejection is primarily driven by T cell-mediated immune responses, representing an adaptive immune response targeting alloantigens. T cells recognize donor human leukocyte antigens and non-human leukocyte antigens, become activated, and produce abundant cytokines and chemokines. This process promotes the recruitment and migration of immune cells to the allograft site, exacerbating tissue inflammation and injury (Figure 3A).[35,36] During acute rejection, there is a marked increase in the number of $CD4^+$ and $CD8^+$ T cells, and the activation of antigen-presenting cells, particularly dendritic cells, plays a pivotal role in driving T-cell activation.[15,36] Additionally, B cells also play important roles in both acute and chronic rejection, directly mediating humoral immune rejection by producing donor-specific antibodies, activating T cells, and forming lymphoid structures within the graft, thereby creating a local immune center.[37] Chronic rejection is clinically manifested as airway fibrosis and vascular lesions, particularly CLAD, which includes bronchiolitis obliterans syndrome and restrictive allograft syndrome. The immune mechanisms of chronic rejection are more complex, involving interactions between immune cells and non-immune cells (such as

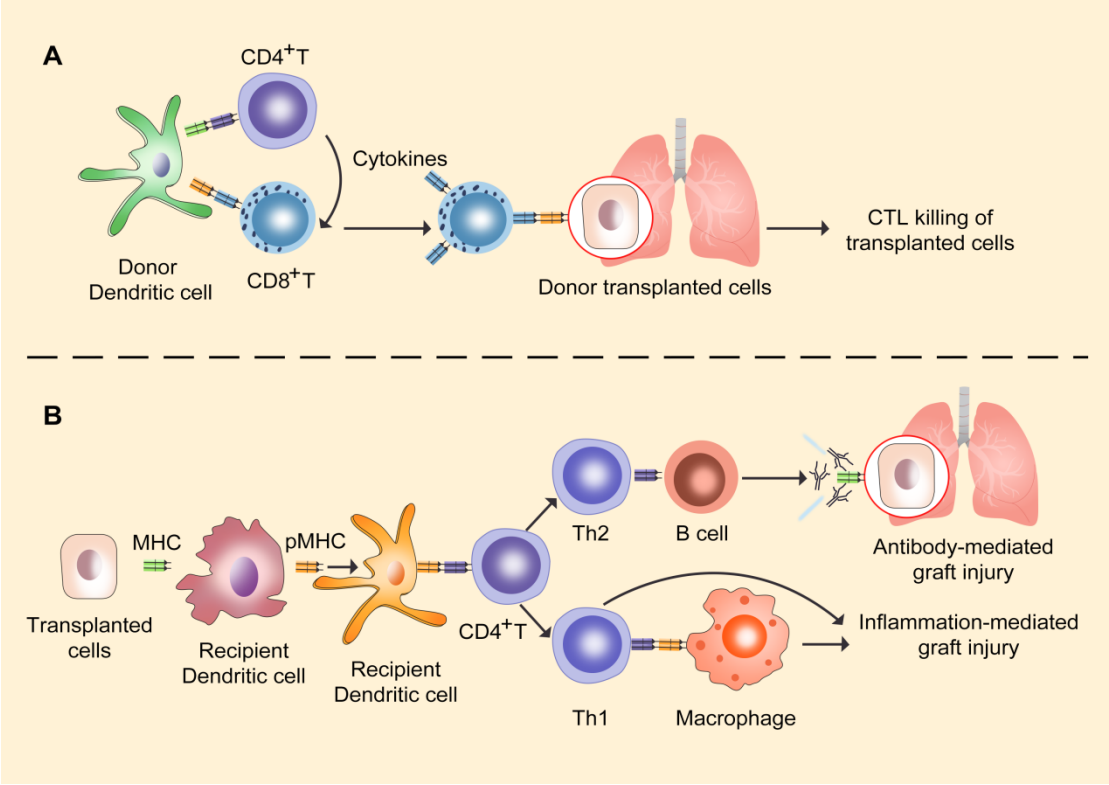

Figure 3. Immune mechanisms of graft rejection after lung transplantation. (A) In the direct allorecognition pathway, donor antigen-presenting cells activate recipient CD4+ and CD8+ T cells, leading to cytokine production and cytotoxic T lymphocyte-mediated injury of transplanted cells. (B) In the indirect allorecognition pathway, recipient antigen-presenting cells process donor antigens and activate CD4+ T cells, promoting Th1/Th2 responses, B-cell activation, antibody-mediated graft injury, macrophage recruitment, and inflammation-mediated tissue damage. Image created originally by the author. Abbreviations: CTL: Cytotoxic T lymphocyte; MHC: Major histocompatibility complex; Th: Helper T cells.

epithelial cells and fibroblasts). Chronic inflammatory stimulation promotes epithelial-mesenchymal transition, fibrosis, and vascular remodeling.[38,39] Furthermore, endogenous danger signals released during allograft injury activate innate immune pathways, inducing immune cell infiltration and inflammatory responses, which further drive the development of chronic rejection.[40,41] In addition to adaptive alloimmune responses, immune-metabolic remodeling, macrophage polarization, neutrophil-dominated inflammation, and an imbalance between Treg cells and Th17 cells may contribute to persistent inflammation, impaired immune tolerance, and CLAD progression. Exosomes released during allograft injury carry lung-related autoantigens, co-stimulatory molecules, and major histocompatibility complex class II molecules, promoting the immune system's recognition of self-antigens, enhancing autoimmune responses, and accelerating the development of chronic rejection (Figure 3B).[35,42,43]

4.2. The role and challenges of immunosuppressive therapy

Immunosuppressive therapy is the primary method for preventing rejection in LTx, aiming to suppress the recipient's immune system response against the graft, thereby improving graft survival and the patient's long-term prognosis. Calcineurin inhibitors (such as cyclosporine A and tacrolimus), corticosteroids, and antimetabolites (such as mycophenolate mofetil [MMF]) are commonly used drugs (Table 1).[7] Calcineurin inhibitors are associated with significant adverse effects, including nephrotoxicity, which manifests as tubulointerstitial injury and progressive decline in renal function. They can also cause hyperglycemia, hypertension, and neurological complications such as headache, tremor, and seizures. Nephrotoxicity is one of the major factors limiting the long-term use of Calcineurin inhibitors, and dose adjustment or modification of immunosuppressive regimens is often required in patients with impaired renal

Table 1. Common immunosuppressants used in lung transplantation

Category	Representative drug	Action	Pharmacological action	Adverse reactions
IL-2 receptor antagonists	Basiliximab	Immunosuppressive effect	Specifically binds to the α chain of IL-2 receptor, blocking the transmission of T-cell proliferation signals	Rare, occasional allergic reactions
Corticosteroids	Prednisone	Immunosuppressive maintenance therapy	Block NF-AT signal transduction, inhibits T-cell activation	Hyperglycemia, hypertension, osteoporosis, avascular necrosis of the femoral head, fluid retention, Cushing's syndrome, infection, slow wound healing
Calcineurin inhibitors	Tacrolimus	Immunosuppressive maintenance therapy	Inhibits NF-AT activity, blocks cytokine transcription, and inhibits T cells and macrophages from secreting cytokines	Renal toxicity, electrolyte disorders, neurotoxicity, hyperglycemia, hypertension
Antiproliferative agents	Mycophenolate mofetil	Immunosuppressive maintenance therapy	Inhibits inosine monophosphate dehydrogenase, thereby blocking guanosine nucleotide synthesis and suppressing lymphocyte proliferation	Nausea, vomiting, diarrhea, abdominal pain, leukopenia, thrombocytopenia, anemia

Abbreviations: IL-2: Interleukin 2; NF-AT: Nuclear factor of activated T-cells.

function.[44] Clinically, tacrolimus has become the preferred immunosuppression in LTx recipients because of its superior immunosuppressive efficacy and lower incidence of acute rejection.[45]

Glucocorticoids are widely used as key agents for both induction and maintenance immunosuppression, particularly in the early postoperative period. Their rapid and potent anti-inflammatory effects help attenuate acute rejection.[46] Studies have shown that glucocorticoids significantly improve early outcomes after LTx; however, long-term use is associated with substantial adverse effects. These include hyperglycemia, osteoporosis, increased susceptibility to infection, and metabolic disturbances. Prolonged or high-dose glucocorticoid therapy markedly increases the risk of steroid-induced osteoporosis and infections, which are major contributors to impaired long-term quality of life.[47]

Mycophenolate mofetil is widely incorporated into immunosuppressive regimens for LTx recipients because of its favorable tolerability and relatively low risk of bone marrow suppression. Evidence indicates that combination therapy with MMF and tacrolimus effectively reduces the incidence of acute rejection while maintaining an acceptable safety profile.[48] Nevertheless, MMF is still associated with adverse effects, including gastrointestinal symptoms such as diarrhea and nausea, bone marrow suppression (e.g., leukopenia), and an increased risk of infection, particularly in patients receiving high doses or those with compromised immune function.[49]

These drugs effectively suppress the activation and proliferation of immune cells, thereby reducing the incidence of acute and chronic rejection and improving graft survival rates. However, immunosuppression is associated with significant adverse effects, notably an elevated risk of infection, a higher incidence of malignancy, and drug-related toxicities.[50] LTx recipients require more potent immunosuppression, thereby increasing the risk of infection. Moreover, immunosuppressants disturb the microbial homeostasis, leading to microecological imbalances that further compromise immune responses and graft tolerance.[51–53] Consequently, personalized optimization of immunosuppressive strategies has emerged as a central focus of contemporary research, with the dual objective of effectively preventing allograft rejection while minimizing treatment-related adverse effects.[54] Novel immunomodulatory strategies, such as cellular immunotherapy (e.g., Treg cell therapy), photodynamic therapy, and exosome-mediated regulation, are also being increasingly investigated for application in LTx to achieve more precise immune regulation.[55] However, these emerging strategies remain largely experimental or early-stage in the context of LTx, and their safety, durability, optimal timing, and compatibility with conventional immunosuppression require further validation.

4.3. Interaction between the immune system and microbial communities

A close bidirectional regulatory relationship exists between the pulmonary and systemic microbiota and the immune system, which is critical for maintaining host homeostasis. The pulmonary microbiota modulates immune cell activity, cytokine secretion, and barrier function through metabolites such as SCFAs, thereby promoting immune tolerance and maintaining immune homeostasis.[56] Beyond SCFAs, other microbial metabolites, including tryptophan-derived metabolites and bile acid derivatives, may also influence epithelial barrier integrity, oxidative stress, macrophage function, and T-cell differentiation. In LTx recipients, respiratory viral infections can induce the release of exosomes carrying lung-associated autoantigens and viral antigens, thereby activating immune responses and promoting the development of chronic rejection. The gut microbial community interacts with the pulmonary immune environment through the "gut–lung axis," regulating pulmonary inflammation and immune tolerance.[57] Metabolites produced by gut microbes, such as SCFAs, can affect pulmonary immune cells via systemic circulation, thereby modulating inflammatory responses.[58]

Conversely, the immune system also modulates the composition and function of microbial communities, creating a dynamic balance. Immune cells maintain microecological balance by secreting antimicrobial peptides and regulating mucosal barriers and immune tolerance mechanisms.[56,59] When immune deficiency or abnormal immune regulation occurs, microbial community imbalances can easily lead to infections, inflammation, and rejection responses.[60] Dysfunctional innate immune responses, particularly in macrophages and dendritic cells, compromise local defense and increase susceptibility to infection. Alveolar macrophages maintain pulmonary homeostasis by regulating inflammatory responses and tissue repair, with an appropriate balance of M1/M2 macrophage polarization being important for limiting excessive inflammation while supporting tissue repair.[61] Additionally, the balance between Th17 and Treg cells may modulate pulmonary inflammation, infection susceptibility, and alloimmune responses.[8] The interaction between microbial communities and the immune system forms a complex bidirectional regulatory network. Understanding this network is essential for elucidating the mechanisms of LTx rejection and infection, and for providing a theoretical basis and novel strategies for microbial ecological interventions and immunomodulatory therapy.[52,62,63]

5. Clinical significance and future translational perspectives of microbial ecology and immune mechanisms in lung transplantation

5.1. Microbiome-based interventions and their clinical limitations

Immunosuppressants compromise intestinal barrier function, thereby increasing intestinal permeability. Disruption of the intestinal barrier allows bacteria and their metabolites to more readily traverse the intestinal mucosa and enter the systemic circulation, thereby exacerbating systemic inflammatory responses.[64,65] Additionally, there is a general decline in gut microbial diversity, especially beneficial bacteria such as Muribaculaceae and *Lactobacillus*, while pathogenic or opportunistic pathogens proliferate extensively, further destabilizing the intestinal microecological balance.[66] This microecological imbalance affects the pulmonary immune environment through the gut–lung axis, exacerbating pulmonary inflammatory responses and increasing the risk of pulmonary infections. Beyond SCFAs, gut-derived metabolites such as tryptophan metabolites and bile acid derivatives may also regulate systemic immunity by influencing epithelial barrier integrity, macrophage activation, dendritic cell function, and T-cell differentiation. Therefore, the gut–lung axis may represent an important mechanistic link between intestinal dysbiosis, systemic inflammation, pulmonary immune activation, and post-transplant complications.[67] Targeted regulation of microbial ecology in LTx recipients, including probiotics, fecal microbiota transplantation, and targeted antibiotic therapy, has attracted increasing attention as a potential adjunctive strategy. However, these approaches remain investigational in the context of LTx, and their clinical efficacy, optimal timing, safety, and long-term impact on rejection and graft survival have not been fully established.

Existing studies indicate that regulating gut microbial communities through the gut–lung axis can significantly impact pulmonary microbial communities and immune environments. Probiotics and high-fiber diets may promote the production of SCFAs, thereby modulating immune responses and alleviating pulmonary inflammation (Figure 4).[68–70] For example, studies in murine models have demonstrated that sirolimus reduces gut barrier thickness and increases intestinal permeability, concurrent with elevated plasma levels of proinflammatory mediators. These findings suggest that immunosuppressive therapy may promote gut microbiota dysbiosis and barrier dysfunction,

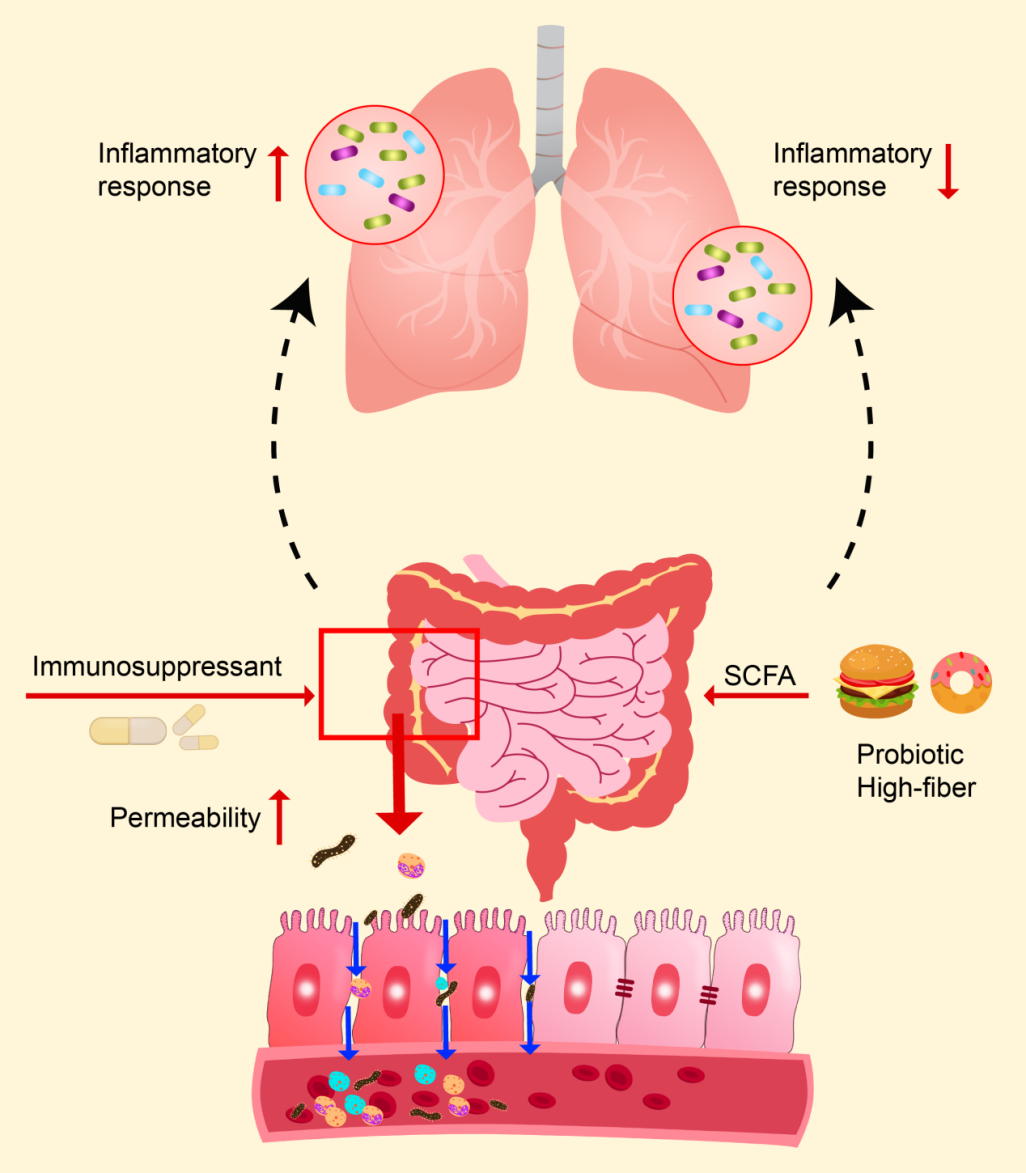

Figure 4. Role of the gut–lung axis in immune regulation after lung transplantation. Immunosuppressive therapy may disrupt gut barrier integrity and increase intestinal permeability, allowing microbial products and metabolites to enter systemic circulation and promote inflammatory responses. Conversely, probiotics and high-fiber diets may increase the production of short-chain fatty acids (SCFAs), which can help regulate pulmonary inflammation and support immune homeostasis through the gut–lung axis. Image created originally by the author.

thereby contributing to systemic inflammation.[71] Fecal microbiota transplantation has shown potential in other organ transplantation fields for improving microbial diversity and immune homeostasis. However, evidence supporting fecal microbiota transplantation in LTx recipients remains extremely limited, and important safety concerns must be considered, including transmission of multidrug-resistant organisms, variability in donor screening, risk of infection, and the uncertain effects on alloimmune responses. Therefore, although fecal microbiota transplantation may represent a potential strategy for restoring ecological balance, its use in LTx should be evaluated in carefully designed clinical trials.[72] Targeted antibiotic therapy should be tailored based on individual microbial profiles to minimize microecological damage caused by non-specific antibacterial treatment.

Compared with empirical broad-spectrum antibiotic exposure, microbiome-guided antimicrobial strategies may help preserve commensal microbial communities, reduce antimicrobial resistance, and limit recurrent infection. However, standardized sampling methods, sequencing platforms, bioinformatic pipelines, and clinically validated microbial thresholds are still lacking, which currently limits the routine implementation of microbiome-guided therapy. Future microbiome-based interventions should therefore be integrated with immune monitoring, antimicrobial stewardship, and individualized immunosuppressive management rather than being viewed as stand-alone therapies.[73]

5.2. Emerging artificial intelligence-assisted and biomedical monitoring strategies for post-lung transplantation precision medicine

In addition to microbiome- and immune-based biomarkers, emerging artificial intelligence (AI)-assisted analytical strategies and biomedical monitoring technologies may provide complementary tools for precision management after LTx. AI-based models can integrate heterogeneous data, including pulmonary function trajectories, imaging features, microbiome profiles, metabolomic signatures, inflammatory markers, donor-derived cell-free DNA, and wearable sensor outputs, to support individualized prediction of infection, rejection, and CLAD progression.[23]

Recent advances in AI-assisted biomedical monitoring, thermographic sensing, and air-coupled ultrasound systems highlight the broader potential of non-invasive, data-driven monitoring platforms.[74] Although these technologies have not yet been specifically validated in LTx recipients, they may complement conventional spirometry, bronchoscopy, imaging, and molecular biomarkers by enabling repeated or continuous assessment of respiratory function and early physiological deterioration. Future studies should evaluate their diagnostic accuracy, reproducibility, integration with microbiome–immune biomarkers, and ability to improve clinically meaningful outcomes.

5.3. Challenges and standardization in microbiome research for clinical translation

Despite growing evidence linking microbial dysbiosis with infection, rejection, and CLAD after LTx, clinical translation remains limited by methodological heterogeneity. Major sources of variability include differences in sample type (BALF, sputum, oropharyngeal swabs, and lung tissue); sampling timing; storage conditions; DNA extraction methods; sequencing platforms; and bioinformatic pipelines.[75]

This issue is particularly important in lung microbiome studies because respiratory samples often contain low microbial biomass and are highly susceptible to contamination from reagents, instruments, sequencing procedures, and the clinical environment.[61] In addition, differences between 16S rRNA sequencing and shotgun metagenomics may affect taxonomic resolution, functional interpretation, and reproducibility of microbial signatures associated with infection, rejection, or CLAD.

To improve comparability and clinical applicability, future studies should adopt standardized protocols for sample collection, contamination control, sequencing, data processing, and reporting of antibiotic exposure, immunosuppressive regimens, sampling time points, and clinical phenotypes.[76] Longitudinal multi-center studies integrating microbiome, immune, metabolic, imaging, and clinical data are needed to determine whether specific microbial patterns precede clinical deterioration or merely reflect established allograft injury. Only through methodological standardization and multi-omics integration can microbiome research move from descriptive association toward clinically actionable precision medicine in LTx.

6. Conclusion

The long-term success of LTx depends not only on advances in surgical techniques and immunosuppressive regimens, but also on the dynamic interplay between the host immune system and microbial ecology. Following transplantation, the pulmonary microbiome typically exhibits reduced diversity and compositional shifts, which may disrupt immune homeostasis and contribute to both allograft rejection and heightened susceptibility to infection. Specific microbial communities have been shown to trigger immune activation, and persistent dysbiosis is strongly associated with CLAD.[77] However, whether microbial dysbiosis directly drives CLAD progression or mainly reflects ongoing allograft injury remains to be further clarified.

Concurrently, the gut–lung axis plays a vital role in immune regulation, in which metabolites from gut bacteria, such as SCFAs, contribute to allograft acceptance and mitigate rejection. In addition to SCFAs, tryptophan metabolites and bile acid derivatives may also participate in systemic immune regulation by influencing epithelial barrier integrity, macrophage activation, and T-cell differentiation. However, conventional immunosuppressive regimens, while effective in curbing rejection, often exacerbate microbial imbalance, thereby increasing infection risk and potentially undermining graft outcomes.

Despite considerable progress in monitoring microbial ecology, the standardized detection and application of microbiota in LTx still face several challenges. Firstly, a major barrier is the absence of standardized protocols for sample collection, processing, and analysis, which introduces significant variability in microbiome data and hinders the validation of reliable microbial biomarkers. Secondly, the implementation of dual regulation strategies for immunity and microbiota must account for individual differences and dynamic changes among patients, particularly within the complex context of immunosuppressant use and antibiotic exposure, where ecological regulation efficacy may vary.[73]

In the future, integrating microbiomics and immunology research will facilitate the development of precise immune intervention strategies based on ecological regulation, such as probiotics, fecal microbiota transplantation, and personalized antibiotic applications. Nevertheless, these microbiome-based interventions remain investigational in LTx recipients, and their safety, optimal timing, long-term efficacy, and effects on rejection and graft survival require validation in well-designed clinical studies. These approaches offer new perspectives and therapeutic options for improving long-term graft survival and patient prognosis. Additionally, the discovery of biomarkers and the development of novel therapeutic methods, such as microbiome-based biofeedback regulation and drug design targeting microbial metabolic pathways, are expected to propel the advancement of precision medicine in LTx. Future integration of standardized microbial profiling, multi-omics analysis, immune monitoring, and AI-assisted non-invasive monitoring may further support individualized risk prediction and precision management after LTx.

In summary, the bidirectional regulation between the pulmonary microbiota and the immune system after LTx is a key determinant of transplant success. Although substantial progress has been made in elucidating the mechanisms underlying microbiota-immune interactions, translating these findings into clinical practice remains challenging and requires close multidisciplinary collaboration. In the future, integrating standardized microbial profiling techniques, individualized immunomodulatory strategies, and the development of novel microbiota-based therapies may enable the field of LTx to move from empirical treatment toward precision medicine, ultimately improving clinical outcomes and quality of life for transplant recipients. This transition is not only a critical requirement for advancing LTx practice but also an important direction for the broader development of translational medicine.

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Conflict of interest

The authors declare that they have no competing interests.

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