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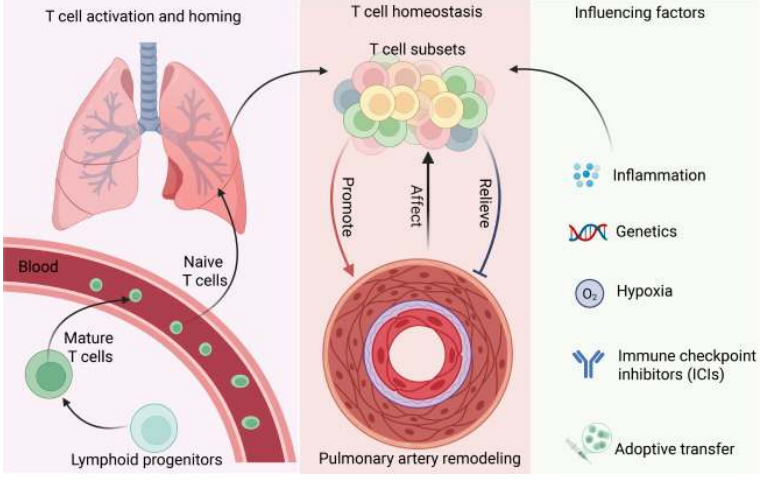
T cells in pulmonary hypertension: protective or pathogenic?

Muhua He[1], Junting Zhang[1], Xiao-Wei Nie[2] ✉, and Jin-Song Bian[1] ✉

[1] *Department of Pharmacology, Joint Laboratory of Guangdong-Hong Kong Universities for Vascular Homeostasis and Diseases, SUSTech Homeostatic Medicine Institute, School of Medicine, Southern University of Science and Technology, Shenzhen, 518055, China*
[2] *Department of Human Cell Biology and Genetics, School of Medicine, Southern University of Science and Technology, Shenzhen, 518055, China*

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ABSTRACT: Pulmonary hypertension (PH) is a complex and progressive syndrome characterized by vascular remodeling, inflammation, and immune imbalance. Although T cell dysregulation is increasingly recognized in PH, their precise role remains controversial. Pathogenic subsets, such as T helper 17 cells (Th17), promote vascular inflammation and smooth muscle proliferation through cytokines including IL-17 and IFN-γ, whereas regulatory T cells (Tregs) counteract these processes by suppressing excessive immune responses and maintaining endothelial stability. In PH, T cell homeostasis is largely shaped by signals from macrophages, dendritic cells, vascular cells and so on. Yet they are not bystanders: once activated, T cells engage in cytokine release and intercellular interactions. Importantly, their activation may represent a secondary consequence of disease, a primary trigger of vascular injury, or a protective mechanism depending on the context. This review integrates current evidence to describe the multifaceted roles of T cells in PH, evaluate their therapeutic potential, and clarify their diverse functions as pathogenic amplifiers or protective regulators in disease progression.



KEYWORDS: pulmonary hypertension, T cells, vascular remodeling, homeostasis, cell interaction

1 Introduction

Pulmonary hypertension (PH) is a multifaceted syndrome characterized by a mean pulmonary arterial pressure (mPAP) greater than 20 mmHg, progressive elevation of pulmonary arterial pressure, vascular remodeling, and right heart failure[1]. Pulmonary arterial hypertension (PAH), a severe subtype of PH, is associated with a 3-year mortality rate of 55% in high-risk patients[2], and survival drops to about 25% at five years for those with PH secondary to combined pulmonary fibrosis and emphysema[3]. Pathologically, PH involves not only vascular changes but also prominent perivascular infiltration of immune cells including macrophages, mast cells, B and T lymphocytes, and dendritic cells[4]. Current treatments, centered on vasodilators such as prostacyclin analogs, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and soluble guanylate cyclase stimulators, offer symptom relief but do not reverse vascular remodeling, fail to correct immune dysregulation, and have not convincingly improved long-term survival[5,6]. Therefore, there is an urgent need for innovative biological insights and therapeutic strategies capable of reversing disease progression.

Notably, T cells are emerging as compelling therapeutic targets in PH, as they can be modulated through adoptive transfer or targeted inhibition. This underscores the importance of defining how specific T cell subsets drive or curb vascular remodeling and immune dysregulation in PH. In this review, we synthesize emerging evidence on the roles of T cells in PH, focusing on their dysregulated phenotypes, activation mechanisms, cellular crosstalk, and therapeutic implications across diverse PH subtypes.

2 Abnormal T cell homeostasis in PH

T cell homeostasis is pervasive across PH subtypes, though the same T cell populations can exert distinct pathogenic roles depending on the disease context (Table 1). T cells are critical for defending against pathogens, but their dysregulation can drive

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✉Address correspondence to Xiao-Wei Nie, niexw@sustech.edu.cn; Jin-Song Bian, bianjs@sustech.edu.cn

Table 1 Abnormal T cell homeostasis in pulmonary hypertension (PH).

PH types	T cell subsets	$CD4^+/CD8^+$	Abnormal Changes	Mechanistic implications	Refs
SSc-PAH	Th17	$CD4^+$	Elevated	IL-17A promotes vascular inflammation and fibrosis	[8]
	Tph	$CD4^+$	Elevated	Enhance B cell activation and autoantibody production	[8]
	Tregs	$CD4^+$	Reduced	Loss of immune tolerance, enhanced vascular autoimmunity	[15]
SLE-PAH	Th17	$CD4^+$	Elevated	Drives endothelial inflammation	[15]
	Tregs	$CD4^+$	Reduced	IL-6–mediated depletion enhances immune activation	[14]
iPAH	Th17	$CD4^+$	Elevated	Promote pulmonary vascular remodeling via IL-17 signaling	[22]
	Tregs	$CD4^+$	Reduced	Impaired suppression of effector T cells, facilitating inflammation	[18, 19]
	$CD8^+$ TEMRA	$CD8^+$	Elevated	Cytotoxic attack on endothelium, promoting apoptosis	[20, 21]
hPAH	Tregs	$CD4^+$	Reduced	Shared Tregs deficiency with iPAH suggests genetic susceptibility	[19]
CHD-PAH	Th17	$CD4^+$	Elevated	Linked to disease severity and hemodynamic burden	[21]
	Tregs	$CD4^+$	Reduced	Loss of protective regulation in congenital lesions	[21]
HIV-PAH	$CD8^+$ T cells	$CD8^+$	Elevated	Persistent activation contributes to vascular injury	[24]
	$CD4^+$ T cells	$CD4^+$	Reduced	HIV-mediated depletion impairs immune regulation	[24]
PH-LHD	Tregs	$CD4^+$	Functional impairment	Dysfunctional Tregs (NLRC3-deficient) promote IL-18/RTK signaling–driven remodeling	[26]
HPH	Th17	$CD4^+$	Elevated	HIF-1α–driven Th17 expansion enhances perivascular inflammation	[28]
	Tregs	$CD4^+$	Reduced	Insufficient suppression of hypoxia-induced inflammation	[29]
	Tfh	$CD4^+$	Elevated	IL-21 production promotes M2 macrophage polarization and remodeling	[31]
CTEPH	$CCR6^+CD4^+$ T cells	$CD4^+$	Elevated	Support persistent inflammation within organized thrombi	[32]
	$CD8^+$ T cells	$CD8^+$	Elevated	Cytotoxic infiltration in pulmonary vasculature	[33, 34]
	$CD4^+$ T cells	$CD4^+$	Elevated	Interact with macrophages/myofibroblasts, sustaining chronic inflammation	[33, 34]

PAH: pulmonary arterial hypertension; $CD4^+$: cluster of differentiation 4^+; $CD8^+$: cluster of differentiation 8^+; SSc: systemic sclerosis; SLE: systemic lupus erythematosus; CHD-PAH: congenital heart disease–associated PAH; HIV-PAH: Human immunodeficiency virus-associated PAH; iPAH: idiopathic PAH; hPAH: heritable PAH; PH-LHD: PH associated with left heart disease; HPH: hypoxia-induced PH; CTEPH: chronic thromboembolic PH; Th17: T helper 17 cells; Tregs: regulatory T cells; Tph: peripheral helper T cells; $CD8^+$ TEMRA: $CD8^+$ terminally differentiated effector memory T cells; Tfh: T follicular helper cells; CCR6: C-C chemokine receptor type 6.

autoimmune pathology by targeting self-tissues[7]. In autoimmune disease–associated PAH, imbalances in T cell subsets, particularly between T helper 17 cells (Th17) and regulatory T cells (Tregs), often precede pulmonary vascular remodeling and position T cells as central drivers of PAH onset in connective tissue diseases (CTDs) such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren's syndrome (SS)[8-11].

Recent profiling of peripheral T cell subsets in SSc-PAH has revealed marked expansions of pathogenic Th17 and T peripheral helper cells (Tph)[8], which align with elevated IL-17A levels in SSc-PAH patients compared to non-PAH SSc individuals, correlating directly with PAH prevalence in SSc cohorts[12]. Whereas SSc is the leading cause of CTD-PAH in Europe and North America, SLE-associated PAH is more common in Asia[13]. In the highly inflammatory SLE-PAH subgroup, loss of Tregs, likely due to IL-6–induced exhaustion, results in the lowest Treg levels among CTD-PAH types, further exacerbating the Th17/Treg imbalance that drives vascular inflammation, remodeling, and disease severity[14,15]. High-dose glucocorticoids and immunosuppressants can quickly control CTD and ameliorate CTD-PAH, with SLE-PAH patients generally responding better than those with SSc-PAH[16,17]. Therefore, early treatment aimed at restoring T cell homeostasis prevent further progression of CTD-PAH.

Treg dysfunction is also observed in idiopathic (iPAH) and heritable PAH (hPAH), where Tregs are both reduced and less suppressive[18,19]. In iPAH, Treg loss coincides with expansion Th17 and accumulation of $CD8^+$ terminally differentiated effector memory T cells ($CD8^+$ TEMRA), which infiltrate pulmonary vessels and drive endothelial apoptosis and remodeling[20-22]. This Treg defect is also seen in hPAH, indicating a genetic basis for immune imbalance[19]. In congenital heart disease-associated PAH (CHD-PAH), the blood ratio of Tregs to Th17 correlates with right heart hemodynamic severity[23]. Human immunodeficiency virus-associated PAH (HIV-PAH) features chronic immune activation with alveolar macrophage–driven T cell activation leading to $CD4^+$ depletion and influx of activated $CD8^+$ T cells into pulmonary vessels[24].

Research on Group 2 PH, associated with left heart disease (PH-LHD), has traditionally concentrated on hemodynamic alterations[25]. However, a recent study showed that NLRC3-deficient Tregs exhibit active IL-18 signaling, which activates endothelial receptor tyrosine kinase pathways and promotes pulmonary arterial remodeling[26]. Evidence also links T cell dysregulation to vascular remodeling in Group 3 hypoxia-induced PH (HPH) and Group 4 chronic thromboembolic PH (CTEPH)[27]. In HPH, prolonged hypoxia activates HIF-1α pathways in vascular cells, expanding Th17 and promoting Treg insufficiency and

perivascular T cell accumulation in both animal models and patient samples[28-30]. T follicular helper cells (Tfh) have been highlighted for their role in promoting M2 macrophage polarization and vascular remodeling through IL-21 in chronic hypoxia models[31]. In CTEPH, elevated CTLA-4 expression and reduced production of key cytokines (TNF-α, IFN-γ, GM-CSF, IL-4) reflect an immunosuppressed state, as confirmed by flow cytometry and single-cell RNA sequencing, showing T cell clustering with macrophages and myofibroblasts, contributing to ongoing inflammation and vascular remodeling[32-34].

3 Mechanisms for T cell activation in PH

T cell activation plays an important role in the immunopathogenesis of PH, involving coordinated processes of development, migration, antigen recognition, and functional polarization (Fig. 1). Naïve T cells originate from bone marrow hematopoietic stem cells, mature in the thymus through positive selection (cortex) and negative selection (medulla), and exit circulation via sphingosine-1-phosphate receptor 1 ($S1P_1$) signaling after achieving functional competence[35-40]. In PH, circulating naïve $CD4^+$ and $CD8^+$ T cells are primed in mediastinal lymph nodes draining the lungs or in tertiary lymphoid structures (TLOs) at disease sites. For instance, in a Schistosoma-induced mouse model of PH, $CD4^+$ T cells migrate from mediastinal lymph nodes to lung parenchyma following antigen embolization[41]. Similarly, lung biopsies from iPAH patients reveal perivascular TLOs containing T cell zones populated by dendritic cells (DCs) and macrophages[42].

Antigen-presenting cells (APCs), particularly dendritic cells (DCs), play a critical role in T cell activation in PH. DCs present exogenous antigens to $CD4^+$ T cells via MHC II and cross-present to $CD8^+$ T cells via MHC I[43,44]. PAH patients exhibit significant accumulation of DCs and macrophages in lung tissue, with DCs serving as critical activators of naïve T cells[45,46]. In PH, serum IgG autoantibodies target vascular structural proteins in endothelial cells (e.g., lamin A/C, β-tubulin), smooth muscle cells (e.g., α-enolase, STIP1), and fibroblasts (e.g., vimentin, tropomyosin 1, HSP27/70)[47-49]. These antigens are captured by B cells, processed, and presented via MHC II to $CD4^+$ T cells[50]. B cells internalize antigens through BCR, receive CD40-CD40L co-stimulation and cytokines (IL-4, IL-21) from T cells, and differentiate into IgG-secreting plasma cells[50]. However, the specific peptide epitopes presented by MHC molecules to T cells in PH remain unidentified.

Emerging evidence suggests T cells in PH may be activated by similar antigens as B cells. Hypoxia-induced vascular injury releases damage-associated molecular patterns (DAMPs) such as mitochondrial DNA and heat shock proteins, which function as "neo-antigens" when processed by DCs, triggering pro-inflammatory T cell responses[51,52]. Notably, hypoxic exposure specifically increases the cDC2 subset in murine lungs, and selective cDC2 depletion not cDC1 prevents HPH, highlighting the critical role of this DC subset in PH pathogenesis.[53].

Naïve T cells require inflammatory cytokines as a "third signal" for differentiation following TCR activation[54]. Key polarization pathways include: IL-6/TGF-β driving Th17[55]; TGF-β/IL-2 maintaining Tregs[56,57]; IL-21 promoting Tph[58]; IL-15 expands $CD8^+$ TEMRA[59]; IL-6/IL-21 polarize Tfh[60]; and IL-12 drives Th1 responses[61]. Importantly, T cell activation in PH is largely shaped by the vascular microenvironment, in part because T cells require a "third signal" from inflammatory cytokines to fully polarize. For instance, experimental periodontitis alone does not induce PH in mice, but when combined with pre-existing hypoxia-induced PH, it

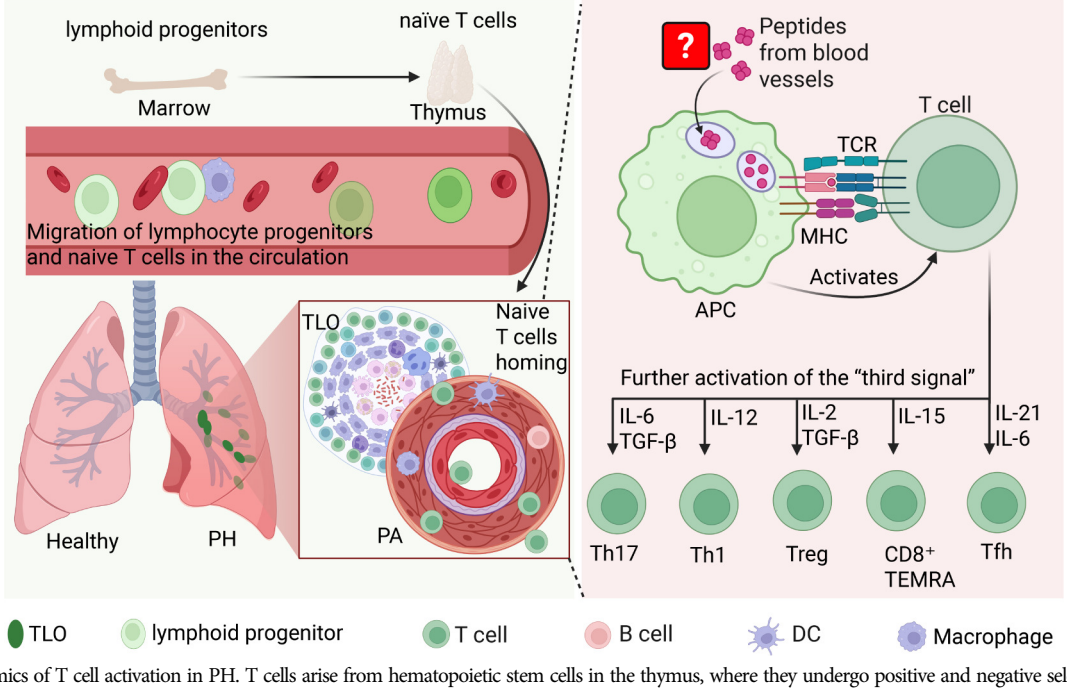


Figure 1 Dynamics of T cell activation in PH. T cells arise from hematopoietic stem cells in the thymus, where they undergo positive and negative selection to become mature $CD4^+$ or $CD8^+$ single-positive cells before exiting under the guidance of $S1P_1$. These circulating naïve T cells are then primed in lung-draining lymph nodes and tertiary lymphoid (TLO) structures by dendritic cells, macrophages, and B cells that present vascular self-antigen peptides via MHC and activate them through TCR engagement and co-stimulatory signals. Once activated, they receive a cytokine "third signal" that directs their polarization—IL-6/TGF-β for Th17, TGF-β/IL-2 for Treg, IL-21 for Tph, IL-6/IL-21 for Tfh, IL-12 for Th1, and IL-15 for $CD8^+$ TEMRA—thus creating a complex, dynamically regulated effector environment that drives inflammatory pulmonary arterial remodeling.

exacerbates right ventricular pressure, vascular remodeling, and inflammation. This effect is mediated by lung infiltration of IFN-γ$^+$ T cells and can be mitigated by cervical lymph node removal or IFN-γ neutralization, highlighting the environment-dependent, immune-driven nature of T cell activation in PH[62].

4 Interactions and effector mechanisms of T cells with other cells in PH

Activated T cells, imprinted with chemokine receptors during clonal expansion in lymphoid tissues, migrate to the pulmonary vasculature and interact with vascular cells under cytokine guidance, infiltrating the vessel wall to drive vascular remodeling in PH[63,64]. Though the activation is largely shaped by external programs, they are not bystanders: through cytokine release and cell-cell interactions, they actively modulate vascular cells and immune populations, driving or restraining remodeling (Fig. 2).

4.1 Endothelial cells

Pulmonary vascular endothelial cell (EC) injury, such as that induced by monocrotaline (MCT), triggers CD4$^+$ T cell infiltration, contributing to vascular remodeling[64]. Paradoxically, depletion of Tregs in immunocompetent models increases susceptibility to PH. Tregs protect endothelial integrity by enhancing IL-10 to suppress apoptosis and inflammation, and by upregulating BMPR2 expression[65]. Immune reconstitution via Treg supplementation can mitigate endothelial injury and prevent PH development[65].

Conversely, ECs modulate T cell function. Pulmonary arterial ECs in PH patients upregulate adhesion molecules (ICAM-1, VCAM-1, E-selectin) and secrete chemokines such as CCL2 and CX3CL1, promoting T cell recruitment and activation[46,66]. Under inflammatory conditions, EC-derived IL-6 activates STAT3 in T cells, driving differentiation into Th17[67]. This bidirectional crosstalk establishes a self-reinforcing loop that sustains PH progression.

4.2 Fibroblasts and smooth muscle cells

Pro-inflammatory T cell subsets, notably Th1 and Th17, secrete IFN-γ and IL-17, stimulating fibroblast proliferation and extracellular matrix deposition, contributing to adventitial fibrosis[68,69]. Shi et al. also found that Th17-derived IL-17A directly stimulates PASMC proliferation and migration in a dose- and time-dependent manner, engaging p38 MAPK signaling and upregulating IL-6 and ICAM-1 expression on PASMCs[70].

Adventitial fibroblasts in PH express high levels of CCL2 and CXCL10, and CXCL10 plays a central role in directing CD4$^+$ and CD8$^+$ T cells to sites of inflammation or injury and promoting their activation[71,72]. In addition, CXCL10 is involved in polarization of T cells to a pro-inflammatory Th1/CD8$^+$ T cell phenotype, thereby enhancing the production of IFN-γ and other inflammatory mediators[73].

4.3 Immune cells

Tregs suppress the proliferation of immune cells, including CD4$^+$ and CD8$^+$ T cells, natural killer (NK) cells, and antigen-presenting

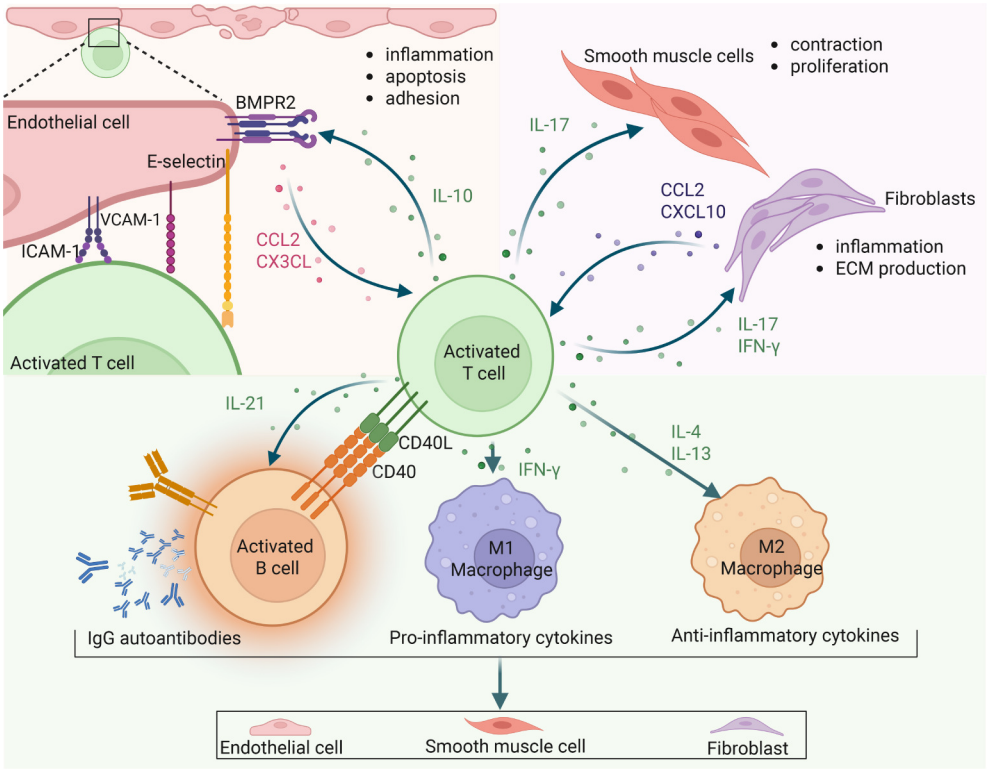


Figure 2 Interactions and effector mechanisms of T cells with other cells in PH. Activated T cells in PH undergo chemokine-driven homing from lung-draining lymphoid tissues to the pulmonary vasculature, where they engage in bidirectional crosstalk with endothelial cells, smooth muscle cells/fibroblasts and other immune populations: endothelial injury promotes ICAM-1/VCAM-1/E-selectin and chemokine (CCL2, CX3CL1) expression to recruit and activate T cells, while Treg counterbalance damage by secreting IL-10 and upregulating BMPR2; conversely, pro-inflammatory Th1/Th17 cells secrete IFN-γ and IL-17 to drive fibroblast proliferation, ECM deposition and PASMC growth via p38 MAPK and IL-6/ICAM-1 induction; adventitial fibroblast-derived CXCL10 further amplifies Th1/CD8$^+$ responses; and CD4$^+$ helper cells support B cell maturation into IgG-secreting plasma cells. Together, these dynamic and self-reinforcing interactions sustain inflammation, vascular remodeling and disease progression in PH.

cells, through the secretion of cytokines such as IL-10 and TGF-β[15,69]. $CD4^+$ T helper cells engage B cells via co-stimulatory molecules such as CD40 ligand (CD40L) and secrete IL-21, promoting B cell activation, proliferation, and differentiation into IgG autoantibodies secreting plasma cells[74].

Th1 secrete IFN-γ, while Th2 produce IL-4 and IL-13[75,76]. In PH, the levels of these cytokines are often abnormally elevated[77,78]. Elevated IFN-γ promotes macrophage activation into the M1 phenotype, leading to increased production of pro-inflammatory cytokines and exacerbating vascular inflammation[79,80]. Meanwhile, elevated IL-4 and IL-13 promote macrophage activation into the M2 phenotype, which, while typically involved in tissue repair, can contribute to chronic inflammation and vascular remodeling in the context of PH[78,81].

5 Immune checkpoint inhibitors induce PH

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy by unleashing anti-tumor immunity through blockade of PD-1/PD-L1 and CTLA-4[82]. However, this therapeutic strategy carries a risk of severe immune-related adverse events, including the emerging cardiotoxicity of PH, which affects about 0.4-0.7% of ICIs-treated patients[83]. Most cases arise during ICI monotherapy, 50% following nivolumab, and present at a median of 77 days, with fatality rates up to 31%[84]. These outcomes suggest that the loss of immune tolerance induced by ICIs promotes pulmonary vascular inflammation and arterial remodeling[85]. Clinicians should remain vigilant for ICI-associated PH, as prompt drug withdrawal and early initiation of PH-specific therapy may reverse disease progression[86].

Although several clinical risk factors have been identified, the underlying immune mechanisms remain unclear. Checkpoint blockade enhances effector T cell activity, impairs regulatory T cell suppression, and skews responses toward Th1/Th17 polarization—features that parallel T cell dysregulation in PH[87,88]. Interestingly, co-administration of anti–PD-1/PD-L1 with VEGF inhibitors appears to modestly reduce vasculitis incidence[89,90]. VEGF promotes arterial remodeling by facilitating $CD3^+/CD4^+$ T cell adhesion and recruitment across the endothelium, whereas VEGF blockade with bevacizumab diminishes perivascular T cell accumulation without affecting their activation[91], highlighting a potential strategy to mitigate ICI-associated vascular toxicity (Fig. 3).

In ICI-induced PH, T cells seem to act as key pathogenic drivers. Yet several fundamental questions remain: Do autoreactive T cells accumulate and activate directly within the pulmonary arterial wall, or do primed T cells in peripheral sites release pro-inflammatory cytokines that secondarily target the pulmonary vasculature? Alternatively, could PD-1/CTLA-4 blockade itself be sufficient to trigger arterial remodeling, analogous to its role in precipitating myocarditis and accelerating atherosclerotic plaque formation[92]?

6 Targeting T cell subsets as a therapeutic strategy in PH

T cell modulation represents a promising therapeutic approach in PH, requiring suppression of pathogenic subsets like Th17 while preserving protective ones such as Tregs (Table 2). In MCT-treated athymic nude rats, medial thickening of small pulmonary arteries, right ventricle (RV) hypertrophy, extensive mast cell infiltration, and severe histopathological changes were significantly exacerbated versus euthymic controls[93]. Unlike immune-competent rats, which develop PAH only under chronic hypoxia with SU5416, athymic rats rapidly show precapillary remodeling, higher mPAP, and strong inflammatory infiltration even in normoxia[94]. Reconstitution with splenic T cells before SU5416 attenuated remodeling and normalized mPAP[94], while adoptive transfer of

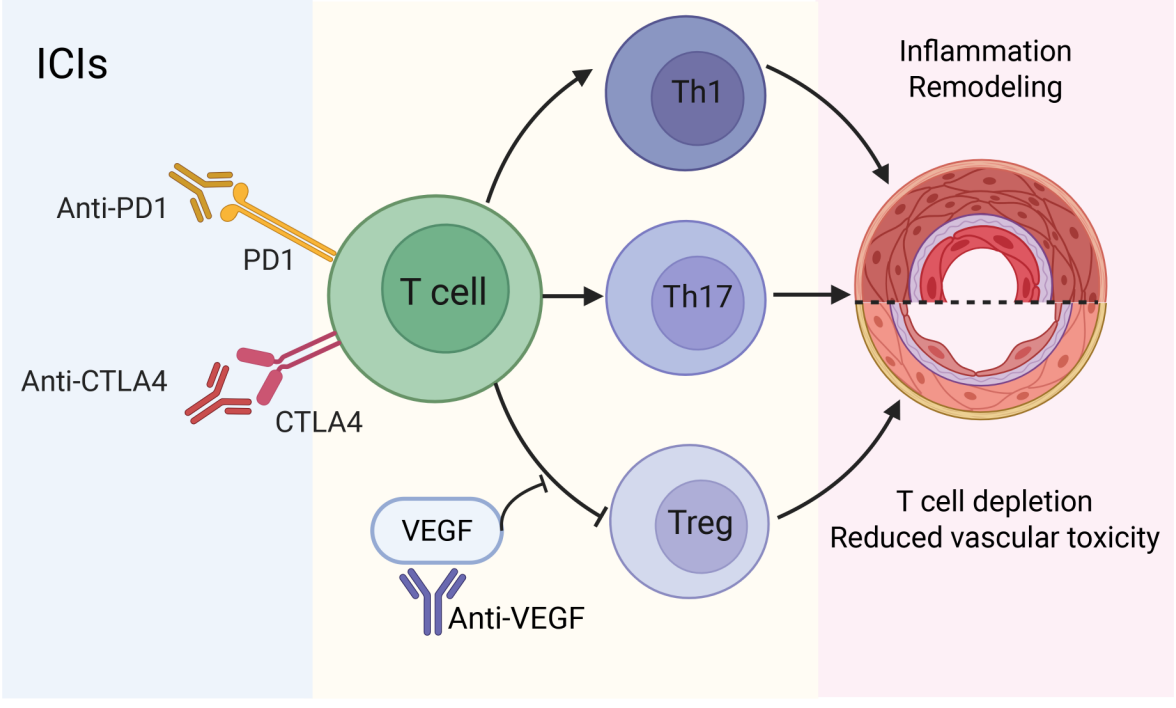


Figure 3 Immune checkpoint inhibitors induce PH. ICIs by blocking the PD-1/PD-L1 and CTLA-4 pathways, disrupt T cell tolerance, leading to Th1/Th17 overactivation and impaired Tregs function, thereby driving pulmonary arterial inflammation and vascular remodeling. VEGF promotes T cell adhesion and recruitment, while its inhibition reduces vascular toxicity, suggesting that combined anti-VEGF therapy may help mitigate ICI-associated PH.

Table 2 Targeting T cell subsets as a therapeutic strategy in PH.

Drug/Intervention	T cell Target (s)	Mechanism	Refs
Treg infusion	Restores Tregs	Suppresses inflammation, prevents remodeling/RV hypertrophy.	[95]
Splenic T-cell reconstitution	Broad T cells	Restores immune balance, reduces remodeling, normalizes mPAP.	[94]
FTY720 (S1P modulator)	Traps T cells in lymph nodes	Lowers circulating T cells, but no effect on lung $CD4^+$ T cells or PH.	[96]
Abatacept (CTLA4-Ig)	Effector T cells	Blocks CD28 co-stimulation, reduces T cell activation and inflammation.	[97]
Tocilizumab (anti–IL-6R)	Th17	Inhibits IL-6/IL-6R signaling, reduces Th17, safe in PAH but no PVR benefit.	[102]
SR1001 (Th17 inhibitor)	Th17	Blocks Th17 differentiation/IL-17A, alleviates hypoxia-induced PH.	[28]

RV: right ventricle; mPAP: mean pulmonary arterial pressure; Treg: regulatory T cell; Th17: T helper 17 cell; S1P: sphingosine-1-phosphate; CTLA4: cytotoxic T lymphocyte–associated protein 4; IL-6R: interleukin-6 receptor; IL-17A: interleukin-17A; PVR: pulmonary vascular resistance.

Tregs protected against hypoxia-induced PH through anti-inflammatory effects[95].

Pharmacologic studies confirm the role of T cells in PH. FTY720, an S1P receptor modulator that traps lymphocytes in lymphoid organs[96], reduced circulating T cells and increased lymph node T cells in Schistosoma-induced PH mice, but did not change lung effector/memory $CD4^+$ T cells or improve disease[41]. In contrast, selective inhibition of T cell activation may be effective. Abatacept (CTLA4-Ig) blocks CD28 co-stimulation and reduces T cell proliferation, inflammation, and vascular remodeling in a model of pulmonary fibrosis[97]. Abatacept may hold therapeutic potential for PH associated with pulmonary fibrosis and possibly other PH subtypes.

Among pathogenic subsets, Th17 cells are particularly implicated in PH pathogenesis. Their activation is primarily driven by elevated interleukin-6 (IL-6) levels[98,99], which are consistently increased in the lungs of PH patients[100]. Hashimoto-Kataoka et al. demonstrated that three days of chronic hypoxia significantly increased pulmonary Th17 numbers, an effect abrogated by anti–IL-6 receptor antibody treatment[101]. Tocilizumab, an IL-6 receptor antagonist, has been proven safe and effective and is primarily used to treat RA[102], while also demonstrating therapeutic potential for SSc–associated interstitial lung disease (SSc-ILD)[103]. Moreover, pharmacologic inhibition of Th17 differentiation with SR1001 alleviated pulmonary vascular remodeling and reduced pulmonary pressures in chronically hypoxic mice[28]. Mechanistically, Th17 cells secrete IL-17A[104], which promotes smooth muscle cell migration and thereby accelerates vascular remodeling[28]. These findings suggest that future drug development in PH could focus on selectively inhibiting pathogenic T cell subsets like Th17 while preserving or enhancing protective Tregs to effectively modulate vascular remodeling and inflammation.

7 Challenges and perspectives

Although progress has been made in understanding the biology of T cells in PH, key questions remain. Do pathogenic subsets directly cause EC injury, or do they mainly amplify inflammation through interactions with macrophages, fibroblasts, and dendritic cells? Can restoring Treg function in late disease, rather than early stages, reverse established vascular remodeling? How antigen-specific responses from self-antigens or damage signals shape T cell behavior in PH remains unclear. Addressing these questions is critical to clarify whether T cells act as pathogenic or protective players in disease progression.

Preclinical studies support T cell targeted strategies (e.g., IL-6/IL-17 blockade, Treg transfer), but disease heterogeneity, compensatory immune circuits, and the timing of intervention limit clinical translation. Future breakthroughs may depend on biomarker-guided patient stratification to identify T cell features for personalized therapy, combination treatments targeting multiple inflammatory axes, and strategies to restore immune balance without compromising protective immunity. These insights may ultimately shift treatment from symptomatic care to precise immune modulation, with the potential to change outcomes for patients with PH.

8 Conclusions

In summary, T cells have emerged as central immune mediators in the pathogenesis of PH, orchestrating vascular inflammation, EC dysfunction, and maladaptive remodeling through diverse mechanisms. Pathogenic subsets promote disease progression via proinflammatory cytokine secretion and direct cytotoxicity, whereas Tregs exert protective effects by suppressing immune activation and preserving vascular integrity. The imbalance between these subsets, particularly Th17/Treg dysregulation, represents a hallmark of PH across etiologies. Although shaped by external cues, T cells are not bystanders; through cytokines and cell interactions, they actively regulate vascular and immune cells.

Ultimately, a comprehensive understanding of T cell biology in PH requires multidisciplinary efforts to unravel their dynamic roles in vascular injury, immune regulation, and tissue repair. Such advances may redefine PH not merely as a vascular disorder but as a disease with immunological underpinnings, paving the way for novel therapies that improve survival and quality of life.

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Data available statement

N/A

Author contribution

M.H. and J.Z. drafted the manuscript and visualized the figures and tables. X.W.N and J.S.B. revised the manuscript and provided funding. All authors approved the final manuscript.

Ethics approval and consent

N/A

Consent for publication

All authors agree to publish.

Conflicts of interest

Jin-Song Bian holds the position of Associate Editor of *Oral Science and Homeostatic Medicine*, but he was not involved in peer review or editorial decisions for this manuscript. The other authors declare no conflicts of interest.

References

[1] Mocumbi, A.; Humbert, M.; Saxena, A.; et al. Pulmonary hypertension. *Nat. Rev. Dis. Primers* **2024**, *10*, 1.

[2] Chang, K. Y.; Duval, S.; Badesch, D. B.; et al. Mortality in pulmonary arterial hypertension in the modern era: Early insights from the pulmonary hypertension association registry. *J. Am. Heart Assoc.*, **2022**,*11(9)*:e024969.

[3] Cottin, V.; Nunes, H.; Brillet, P. Y.; et al. Combined pulmonary fibrosis and emphysema: A distinct underrecognised entity. *Eur. Respir. J.* **2005**, *26*, 586–593.

[4] Humbert, M.; Guignabert, C.; Bonnet, S.; et al. Pathology and pathobiology of pulmonary hypertension: State of the art and research perspectives. *Eur. Respir. J.* **2019**, *53*, 1801887.

[5] Sharma, M.; Paudyal, V.; Syed, S. K.; et al. Management of pulmonary arterial hypertension: Current strategies and future prospects. *Life* **2025**, *15*, 430.

[6] Delcroix, M.; Howard, L. Pulmonary arterial hypertension: The burden of disease and impact on quality of life. *Eur. Respir. Rev.* **2015**, *24*, 621–629.

[7] Seiringer, P.; Garzorz-Stark, N.; Eyerich, K. T-cell–mediated autoimmunity: Mechanisms and future directions. *J. Invest. Dermatol.* **2022**, *142*, 804–810.

[8] Papadimitriou, T. I.; Lemmers, J. M. J.; van Caam, A. P. M.; et al. Systemic sclerosis-associated pulmonary arterial hypertension is characterized by a distinct peripheral T helper cell profile. *Rheumatology* **2024**, *63*, 2525–2534.

[9] Suárez-Fueyo, A.; Bradley, S. J.; Tsokos, G. C. T cells in systemic lupus erythematosus. *Curr. Opin. Immunol.* **2016**, *43*, 32–38.

[10] Shaw, M.; Collins, B. F.; Ho, L. A.; et al. Rheumatoid arthritis-associated lung disease. *Eur. Respir. Rev.* **2015**, *24*, 1–16.

[11] Coppi, F.; Cavalletti, A.; Pagnoni, G.; et al. Pulmonary hypertension in patients with Sjögren's syndrome: Gender differences in cardiovascular risk factors and instrumental data. *Int. J. Cardiol.* **2025**, *428*, 133131.

[12] Seki, N.; Tsujimoto, H.; Tanemura, S.; et al. Th17/IL-17A axis is critical for pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc): SSc patients with high levels of serum IL-17A exhibit reduced lung functions and increased prevalence of PAH. *Cytokine* **2024**, *176*, 156534.

[13] Khangoora, V.; Bernstein, E. J.; King, C. S.; et al. Connective tissue disease-associated pulmonary hypertension: A comprehensive review. *Pulm. Circ.* **2023**, *13*, e12276.

[14] Li, Y.; Qian, J.; Deng, X.; et al. pos1010 deciphering the transcriptomic landscape of systemic lupus erythematosus-associated pulmonary arterial hypertension. *Ann. Rheum. Dis.* **2025**, *84*, 1119.

[15] Gaowa, S. R.; Zhou, W. Y.; Yu, L. L.; et al. Effect of Th17 and Treg axis disorder on outcomes of pulmonary arterial hypertension in connective tissue diseases. *Mediat. Inflamm.* **2014**, *2014*, 247372.

[16] Thoreau, B.; Mouthon, L. Pulmonary arterial hypertension associated with connective tissue diseases (CTD-PAH): Recent and advanced data. *Autoimmun. Rev.* **2024**, *23*, 103506.

[17] Condliffe, R.; Kiely, D. G.; Peacock, A. J.; et al. Connective tissue disease–associated pulmonary arterial hypertension in the modern treatment era. *Am. J. Respir. Crit. Care Med.* **2009**, *179*, 151–157.

[18] Tian, W.; Jiang, S. Y.; Jiang, X. G.; et al. The role of regulatory T cells in pulmonary arterial hypertension. *Front. Immunol.* **2021**, *12*, 684657.

[19] Huertas, A.; Phan, C.; Bordenave, J.; et al. Regulatory T cell dysfunction in idiopathic, heritable and connective tissue-associated pulmonary arterial hypertension. *Chest* **2016**, *149*, 1482–1493.

[20] Li, C.; Liu, P. P.; Song, R.; et al. Immune cells and autoantibodies in pulmonary arterial hypertension. *acta Biochim biophys sin* **2017**, *49*, 1047–1057.

[21] Tomaszewski, M.; Bębnowska, D.; Hrynkiewicz, R.; et al. Role of the immune system elements in pulmonary arterial hypertension. *J. Clin. Med.* **2021**, *10*, 3757.

[22] Chen, C. N.; Hajji, N.; Yeh, F. C.; et al. Restoration of $Foxp3^+$ regulatory T cells by HDAC-dependent epigenetic modulation plays a pivotal role in resolving pulmonary arterial hypertension pathology. *Am. J. Respir. Crit. Care Med.* **2023**, *208*, 879–895.

[23] Wang, Z. X.; Li, L.; Lyu, Y. X.; et al. Correlation between T-lymphocyte subsets and hemodynamics in patients with congenital heart disease-associated pulmonary arterial hypertension. *Medicine* **2025**, *104*, e41834.

[24] Dominick, L.; Midgley, N.; Swart, L. M.; et al. HIV-related cardiovascular diseases: The search for a unifying hypothesis. *Am. J. Physiol. Heart Circ. Physiol.* **2020**, *318*, H731–H746.

[25] Maron, B. A.; Bortman, G.; De Marco, T.; et al. Pulmonary hypertension associated with left heart disease. *Eur. Respir. J.* **2024**, *64*, 2401344.

[26] Zhakeer, G.; Zeng, Y. X.; Guangxi, E.; et al. T_{reg}Cells attenuate pulmonary venous remodeling in pH-LHD *via* NLRC3 signaling. *Circ. Res.* **2025**, *136(10)*:e113-e128.

[27] Ye, Y.; Xu, Q. Y.; Wuren, T. Inflammation and immunity in the pathogenesis of hypoxic pulmonary hypertension. *Front. Immunol.* **2023**, *14*, 1162556.

[28] Maston, L. D.; Jones, D. T.; Giermakowska, W.; et al. Central role of T helper 17 cells in chronic hypoxia-induced pulmonary hypertension. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2017**, *312*, L609–L624.

[29] Lantz, B. J.; Moriwaki, M.; Oyebamiji, O. M.; et al. Chronic hypoxia disrupts T regulatory cell phenotype contributing to the emergence of exTreg-TH17 cells. *Front. Physiol.* **2024**, *14*, 1304732.

[30] Hu, Y. J.; Chi, L.; Kuebler, W. M.; et al. Perivascular inflammation in pulmonary arterial hypertension. *Cells* **2020**, *9*, 2338.

[31] Li, C.; Liu, P. P.; Zhu, H.; et al. T follicular helper cell is essential for M2 macrophage polarization and pulmonary vascular remodeling in hypoxia-induced pulmonary hypertension. *Respir. Res.* **2024**, *25*, 428.

[32] van Uden, D.; Koudstaal, T.; van Hulst, J. A. C.; et al. Evidence for a role of CCR6+ T cells in chronic thromboembolic pulmonary hypertension. *Front. Immunol.* **2022**, *13*, 861450.

[33] VAN UDEN D. Adaptive immunity in different pulmonary hypertension subgroups [M]. Rotterdam, 2023.

[34] Viswanathan, G.; Kirshner, H. F.; Nazo, N.; et al. Single-cell analysis reveals distinct immune and smooth muscle cell populations that contribute to chronic thromboembolic pulmonary hypertension. *Am. J. Respir. Crit. Care Med.* **2023**, *207*, 1358–1375.

[35] Lai, A. Y.; Kondo, M. T and B lymphocyte differentiation from hematopoietic stem cell. *Semin. Immunol.* **2008**, *20*, 207–212.

[36] Klein, L.; Kyewski, B.; Allen, P. M.; et al. Positive and negative selection of the T cell repertoire: What thymocytes see (and don't see). *Nat. Rev. Immunol.* **2014**, *14*, 377–391.

[37] Punt, J. A.; Suzuki, H.; Granger, L. G.; et al. Lineage commitment in the thymus: Only the most differentiated (TCRhibcl-2hi) subset of $CD4^+CD8^+$Thymocytes has selectively terminated CD4 or CD8 synthesis. *J. Exp. Med.* **1996**, *184*, 2091–2100.

[38] McDonald, B. D.; Bunker, J. J.; Erickson, S. A.; et al. Crossreactive αβ T cell receptors are the predominant targets of thymocyte negative selection. *Immunity* **2015**, *43*, 859–869.

[39] Bankovich, A. J.; Shiow, L. R.; Cyster, J. G. CD69 suppresses sphingosine 1-phosophate receptor-1 ($S1P_1$) function through interaction with membrane helix 4. *J. Biol. Chem.* **2010**, *285*, 22328–22337.

[40] Saba, J. D. The low down on sphingosine-1-phosphate lyase as a regulator of thymic egress. *J. Immunol. Sci.* **2017**, *1*, 1–8.

[41] Fonseca Balladares, D. C.; Kumar, R.; Mickael, C.; et al. Intrapulmonary T cells are sufficient for *Schistosoma*-induced pulmonary hypertension. *A31. IMMUNE CELL MOLECULAR ACTIVATION SWITCH IN LUNG INJURY AND INFLAMMATION*. American Thoracic Society, **2024**: A1306-A1306.

[42] Perros, F.; Dorfmüller, P.; Montani, D.; et al. Pulmonary lymphoid *Neogenesis* in idiopathic pulmonary arterial hypertension. *Am. J. Respir. Crit. Care Med.* **2012**, *185*, 311–321.

[43] ten Broeke, T.; Wubbolts, R.; Stoorvogel, W. MHC class II antigen presentation by dendritic cells regulated through endosomal sorting. *Cold Spring Harb. Perspect. Biol.* **2013**, *5*, a016873.

[44] Embgenbroich, M.; Burgdorf, S. Current concepts of antigen cross-presentation. *Front. Immunol.* **2018**, *9*, 1643.

[45] van Uden, D.; Boomars, K.; Kool, M. Dendritic cell subsets and effector function in idiopathic and connective tissue disease-associated pulmonary arterial hypertension. *Front. Immunol.* **2019**, *10*, 11.

[46] Pullamsetti, S. S.; Savai, R.; Janssen, W.; et al. Inflammation, immunological reaction and role of infection in pulmonary hypertension. *Clin. Microbiol. Infect.* **2011**, *17*, 7–14.

[47] Dib, H.; Tamby, M. C.; Bussone, G.; et al. Targets of anti-endothelial cell antibodies in pulmonary hypertension and *Scleroderma*. *Eur. Respir. J.* **2012**, *39*, 1405–1414.

[48] Bussone, G.; Tamby, M. C.; Calzas, C.; et al. IgG from patients with pulmonary arterial hypertension and/or systemic sclerosis binds to vascular smooth muscle cells and induces cell contraction. *Ann. Rheum. Dis.* **2012**, *71*, 596–605.

[49] Terrier, B.; Tamby, M. C.; Camoin, L.; et al. Identification of target antigens of antifibroblast antibodies in pulmonary arterial hypertension. *Am. J. Respir. Crit. Care Med.* **2008**, *177*, 1128–1134.

[50] McShane, A. N.; Malinova, D. The ins and outs of antigen uptake in B cells. *Front. Immunol.* **2022**, *13*, 892169.

[51] Gallo, P. M.; Gallucci, S. The dendritic cell response to classic, emerging, and homeostatic danger signals. *Implications for autoimmunity. Front. Immunol.* **2013**, *4*, 138.

[52] Rahman, M.; Steuer, J.; Gillgren, P.; et al. Induction of dendritic cell–mediated activation of T cells from atherosclerotic plaques by human heat shock protein 60. *J. Am. Heart Assoc.* **2017**, *6*, e006778.

[53] Mickael, C.; Sanders, L. A.; Lee, M. H.; et al. Classical dendritic cells contribute to hypoxia-induced pulmonary hypertension. *FASEB J.* **2024**, *38*, e70015.

[54] Curtsinger, J. M.; Schmidt, C. S.; Mondino, A.; et al. Inflammatory cytokines provide a third signal for activation of naive $CD4^+$ and $CD8^+$ T cells. *J. Immunol.* **1999**, *162*, 3256–3262.

[55] Hwang, E. S. Transcriptional regulation of T helper 17 cell differentiation. *Yonsei Med. J.* **2010**, *51*, 484.

[56] Mahmud, S. A.; Manlove, L. S.; Farrar, M. A. Interleukin-2 and STAT5 in regulatory T cell development and function. *JAKSTAT* **2013**, *2*, e23154.

[57] Zheng, S. G.; Wang, J. H.; Wang, P.; et al. IL-2 is essential for TGF-β to convert naive $CD4^+CD25^-$cells to $CD25^+Foxp3+$ regulatory T cells and for expansion of these cells. *J. Immunol.* **2007**, *178*, 2018–2027.

[58] Bocharnikov, A. V.; Keegan, J.; Wacleche, V. S.; et al. PD-1hiCXCR5–T peripheral helper cells promote B cell responses in lupus *via* MAF and IL-21. *JCI Insight* **2019**, *4*, e130062.

[59] Setoguchi, R. IL-15 boosts the function and migration of human terminally differentiated $CD8^+$ T cells by inducing a unique gene signature. *Int. Immunol.* **2016**, *28*, 293–305.

[60] Choi, J.; Crotty, S.; Choi, Y. S. Cytokines in follicular helper T cell biology in physiologic and pathologic conditions. *Immune Netw.* **2024**, *24*, e8.

[61] Zhou, W. S.; Zhang, F.; Aune, T. M. Either IL-2 or IL-12 is sufficient to direct Th1 differentiation by nonobese diabetic T cells. *J. Immunol.* **2003**, *170*, 735–740.

[62] Meng, X. Q.; Du, L. J.; Xu, S.; et al. Periodontitis exacerbates pulmonary hypertension by promoting IFNγ+ T cell infiltration in mice. *Int. J. Oral Sci.* **2024**, *16*, 27.

[63] Wardlaw, A. J.; Guillen, C.; Morgan, A. Mechanisms of T cell migration to the lung. *Clin. Exp. Allergy* **2005**, *35*, 4–7.

[64] Cuttica, M. J.; Langenickel, T.; Noguchi, A.; et al. Perivascular T-cell infiltration leads to sustained pulmonary artery remodeling after endothelial cell damage. *Am. J. Respir. Cell Mol. Biol.* **2011**, *45*, 62–71.

[65] Tamosiuniene, R.; Tian, W.; Dhillon, G.; et al. Regulatory T cells limit vascular endothelial injury and prevent pulmonary hypertension. *Circ. Res.* **2011**, *109*, 867–879.

[66] Kuebler, W. M.; Bonnet, S.; Tabuchi, A. Inflammation and autoimmunity in pulmonary hypertension: Is there a role for endothelial adhesion molecules? (2017 Grover Conference Series). *Pulm. Circ*. **2018**, *8*, 2045893218757596.

[67] Taflin, C.; Favier, B.; Baudhuin, J.; et al. Human endothelial cells generate Th17 and regulatory T cells under inflammatory conditions. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 2891–2896.

[68] Zhang, H.; Li, M.; Hu, C.-J.; et al. Fibroblasts in pulmonary hypertension: Roles and molecular mechanisms. *Cells* **2024**, *13*, 914.

[69] Plecitá-Hlavatá, L.; Brázdová, A.; Křivonosková, M.; et al. Microenvironmental regulation of T-cells in pulmonary hypertension. *Front. Immunol.* **2023**, *14*, 1223122.

[70] Shi, T. Y.; Wen, X. H.; Meng, J.; et al. Effect of IL-17 on pulmonary artery smooth muscle cells and connective tissue disease-associated pulmonary arterial hypertension. *Immun. Inflamm. Dis.* **2024**, *12*, e1243.

[71] Mamazhakypov, A.; Viswanathan, G.; Lawrie, A.; et al. The role of chemokines and chemokine receptors in pulmonary arterial hypertension. *Br. J. Pharmacol.* **2021**, *178*, 72–89.

[72] Karin, N. CXCR3 ligands in cancer and autoimmunity, chemoattraction of effector T cells, and beyond. *Front. Immunol.* **2020**, *11*, 976.

[73] Norose, K.; Kikumura, A.; Luster, A. D.; et al. CXCL10 is required to maintain T-cell populations and to control parasite replication during chronic ocular toxoplasmosis. *Invest. Ophthalmol. Vis. Sci.* **2011**, *52*, 389.

[74] Koudstaal, T.; Boomars, K. A.; Kool, M. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: An immunological perspective. *Journal Clin. Med.* **2020**, *9*, 561.

[75] Benson, L. N.; Liu, Y. M.; Deck, K.; et al. IFN-γ contributes to the immune mechanisms of hypertension. *Kidney360* **2022**, *3*, 2164–2173.

[76] Junttila, I. S. Tuning the cytokine responses: An update on interleukin (IL)-4 and IL-13 receptor complexes. *Front. Immunol.* **2018**, *9*, 888.

[77] Kumar, R.; Mickael, C.; Chabon, J.; et al. The causal role of IL-4 and IL-13 in*Schistosoma mansoni*Pulmonary hypertension. *Am. J. Respir. Crit. Care Med.* **2015**, *192*, 998–1008.
[78] Abid, S.; Marcos, E.; Parpaleix, A.; et al. CCR2/CCR5-mediated macrophage–smooth muscle cell crosstalk in pulmonary hypertension. *Eur. Respir. J.* **2019**, *54*, 1802308.
[79] Dousdampanis, P.; Aggeletopoulou, I.; Mouzaki, A. The role of M1/M2 macrophage polarization in the pathogenesis of obesity-related kidney disease and related pathologies. *Front. Immunol.* **2024**, *15*, 1534823.
[80] Zhang, M. Q.; Wang, C. C.; Pang, X. B.; et al. Role of macrophages in pulmonary arterial hypertension. *Front. Immunol.* **2023**, *14*, 1152881.
[81] Scott, T. E.; Lewis, C. V.; Zhu, M. Y.; et al. IL-4 and IL-13 induce equivalent expression of traditional M2 markers and modulation of reactive oxygen species in human macrophages. *Sci. Rep.* **2023**, *13*, 19589.
[82] Pandey, P.; Khan, F.; Qari, H. A.; et al. Revolutionization in cancer therapeutics *via* targeting major immune checkpoints PD-1, PD-L1 and CTLA-4. *Pharmaceuticals* **2022**, *15*, 335.
[83] Palassin, P.; Maria, A. T. J.; Ladhari, C.; et al. Pulmonary hypertension reported with immune checkpoint inhibitors: A pharmacovigilance study. *Cancer Immunol. Immunother.* **2022**, *71*, 3093–3097.
[84] Rapoport, B. L.; Shannon, V. R.; Cooksley, T.; et al. Pulmonary toxicities associated with the use of immune checkpoint inhibitors: An update from the immuno-oncology subgroup of the neutropenia, infection & myelosuppression study group of the multinational association for supportive care in cancer. *Front. Pharmacol.* **2021**, *12*, 743582.
[85] Glick, M.; Baxter, C.; Lopez, D.; et al. Releasing the brakes: A case report of pulmonary arterial hypertension induced by immune checkpoint inhibitor therapy. *Pulm. Circ.* **2020**, *10*, 2045894020960967.
[86] Abdolall, A.; Jabri, A.; Hamade, H.; et al. A case of pembrolizumab induced pulmonary hypertension. *J. Am. Coll. Cardiol.* **2022**, *79*, 3194.
[87] Vuong, J. T.; Stein-Merlob, A. F.; Nayeri, A.; et al. Immune checkpoint therapies and atherosclerosis: Mechanisms and clinical implications JACC state-of-the-art review. *J. Am. Coll. Cardiol.* **2022**, *79*, 577–593.
[88] Zheng, J. X.; Yi, Y. Y.; Tian, T. C.; et al. ICI-induced cardiovascular toxicity: Mechanisms and immune reprogramming therapeutic strategies. *Front. Immunol.* **2025**, *16*, 1550400.
[89] Li, X.; Peng, W. Y.; Wu, J.; et al. Advances in immune checkpoint inhibitors induced-cardiotoxicity. *Front. Immunol.* **2023**, *14*, 1130438.
[90] Watanabe, R.; Zhang, H.; Berry, G.; et al. Immune checkpoint dysfunction in large and medium vessel vasculitis. *Am. J. Physiol. Heart Circ. Physiol.* **2017**, *312*, H1052–H1059.
[91] Zhang, J. S.; Silva, T.; Yarovinsky, T.; et al. VEGF blockade inhibits lymphocyte recruitment and ameliorates immune-mediated vascular remodeling. *Circ. Res.* **2010**, *107*, 408–417.
[92] Huang, S. L.; Kang, Y.; Liu, T.; et al. The role of immune checkpoints PD-1 and CTLA-4 in cardiovascular complications leading to heart failure. *Front. Immunol.* **2025**, *16*, 1561968.
[93] Miyata, M.; Sakuma, F.; Ito, M.; et al. Athymic nude rats develop severe pulmonary hypertension following monocrotaline administration. *Int. Arch. Allergy Immunol.* **2000**, *121*, 246–252.
[94] Taraseviciene-Stewart, L.; Nicolls, M. R.; Kraskauskas, D.; et al. Absence of T cells confers increased pulmonary arterial hypertension and vascular remodeling. *Am. J. Respir. Crit. Care Med.* **2007**, *175*, 1280–1289.
[95] Chu, Y. B.; Xiangli, X. Y.; Xiao, W. Regulatory T cells protect against hypoxia-induced pulmonary arterial hypertension in mice. *Mol. Med. Rep.* **2015**, *11*, 3181–3187.
[96] Zhi, L.; Kim, P.; Thompson, B. D.; et al. FTY720 blocks egress of T cells in part by abrogation of their adhesion on the lymph node sinus. *J Immunol* **2011**, *187*, 2244–2251.
[97] Boleto, G.; Guignabert, C.; Pezet, S.; et al. T-cell costimulation blockade is effective in experimental digestive and lung tissue fibrosis. *Arthritis Res. Ther.* **2018**, *20*, 197.
[98] Kimura, A.; Naka, T.; Kishimoto, T. IL-6-dependent and-independent pathways in the development of interleukin 17-producing T helper cells. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 12099–12104.
[99] Kimura, A.; Kishimoto, T. IL-6: Regulator of treg/Th17 balance. *Eur. J. Immunol.* **2010**, *40*, 1830–1835.
[100] Selimovic, N.; Bergh, C. H.; Andersson, B.; et al. Growth factors and interleukin-6 across the lung circulation in pulmonary hypertension. *Eur. Respir. J.* **2009**, *34*, 662–668.
[101] Hashimoto-Kataoka, T.; Hosen, N.; Sonobe, T.; et al. Interleukin-6/interleukin-21 signaling axis is critical in the pathogenesis of pulmonary arterial hypertension. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112(20)*: E2677-86.
[102] Alten, R. Tocilizumab: A novel humanized anti-interleukin 6 receptor antibody for the treatment of patients with rheumatoid arthritis. *Ther. Adv. Musculoskelet. Dis.* **2011**, *3*, 133–149.
[103] Ghazipura, M.; Macrea, M.; Herman, D.; et al. Tocilizumab in patients with systemic sclerosis–associated interstitial lung disease: A systematic review and meta-analysis. *Ann. Am. Thorac. Soc.* **2024**, *21*, 328–337.
[104] Bettelli, E.; Korn, T.; Oukka, M.; et al. Induction and effector functions of TH17 cells. *Nature* **2008**, *453*, 1051–1057.

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