

Review

T cell-intrinsic PRR signaling in immunity and pathology

Yixuan Shi^{1,†}, Meng Wang^{1,†}, Baodi Dai¹, Xinliang Lu^{2,*}, and Sirui Li^{1,*}

¹Shanghai Institute of Biochemistry and Cell Biology, Center for Excellence in Molecular Cell Science, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai 200031, China, and ²Department of Hepatobiliary and Pancreatic Surgery, Zhejiang Provincial Key Laboratory of Pancreatic Disease, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310006, China

[†]These authors contributed equally to this work.

*Correspondence address. Tel: +86-21-54921251; E-mail: sirui.li@sibcb.ac.cn (S.L.) / Tel: +86-18758213098; E-mail: xllu@zju.edu.cn (X.L.)

Received 30 July 2025 Accepted 10 November 2025 Published 19 December 2025

Abstract

The immune system orchestrates a delicate balance between robust defense against pathogens and restraint to prevent tissue damage, with T cells serving as central mediators of adaptive immunity. The canonical pathway for T-cell activation hinges on the precise recognition of peptide antigens presented by major histocompatibility complex (MHC) molecules via the T-cell receptor (TCR), which is complemented by essential co-stimulatory signals. However, this model alone cannot fully explain the nuanced contextualization of immune responses, particularly how T cells integrate signals related to the nature of the threat. Pattern recognition receptors (PRRs), which are traditionally studied in innate immune cells, are recognized as critical regulators of T cell function, challenging the conventional dichotomy between innate and adaptive immunity. T cell-intrinsic PRR signaling integrates endogenous danger signals and microbes to modulate critical processes, including cytokine production, proliferation, and polarization, thereby shaping immune responses and disease outcomes in contexts ranging from viral infections to chronic inflammation and cancer. However, the molecular mechanisms underlying PRR-mediated T cell regulation and their contributions to immune homeostasis or pathology remain incompletely understood. This study investigates the role of T cell-intrinsic PRR signaling in shaping immune responses and its implications for disease. By elucidating key signaling pathways and their impact on T cell function, we aim to offer novel insights into the complex regulation of T cell-mediated immunity and uncover an underappreciated paradigm for immune-related disorders, providing new insights into the pathogenesis of inflammatory and neoplastic diseases.

Key words pattern recognition receptors, T cell, pathology

Introduction

Pattern recognition receptors (PRRs), a class of evolutionarily conserved biomolecules, are understood to be expressed across all cell types. However, their initial discovery and research focused on innate immunity, which is considered an important line of defense against infection [1,2]. The body's initial perception of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) is mediated by PRRs, which include families such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), C-type lectin receptors (CLRs), and AIM2-like receptors (ALRs) [3–8].

Recently, accumulating evidence has revealed significant limitations in this traditional, innate-centric understanding of PRR biology [9–11]. First, the cellular distribution of PRRs has historically been underestimated. However, a long-standing dogma holds that PRR

expression is largely confined to innate immune cells, such as macrophages, dendritic cells, and neutrophils [3–5]. Importantly, the advent of sophisticated high-throughput technologies has unequivocally demonstrated functional PRR expression within human and mouse T lymphocytes [12,13]. Consequently, the direct function of PRRs, particularly their intrinsic functions within T lymphocytes, has emerged as a major focus of contemporary research [14–16]. Despite this growing interest, our understanding of how PRRs directly influence T-cell development, differentiation, and effector functions remains remarkably limited, with fundamental mechanistic insights still lacking. Second, the downstream signalosomes of PRR engagement were oversimplified. The canonical view emphasized the activation of the NF- κ B, MAPK, and interferon pathways, which primarily drive pro-inflammatory cytokine production [17,18]. However, recent discoveries highlight

mediate pyroptosis [24,25]. The RLR family comprises retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2), which function as essential cytosolic sensors of viral RNA across mammalian cell types [7,26,27]. These receptors recognize ssRNA/dsRNA, orchestrating antiviral immunity through the induction of type I interferons (IFNs) and pro-inflammatory cytokines during viral or bacterial RNA exposure [7,26,27]. CLRs are transmembrane or endosomally localized sensors analogous to TLRs that detect extracellularly and endocytose PAMPs through carbohydrate recognition domains [3,5]. In fact, CLR engagement critically contributes to antimicrobial defense through specialized effector mechanisms. The ALR family, including the prototypical member AIM2 and its homologs (e.g., IFI16, p204), functions as specialized cytosolic DNA sensors that trigger inflammasome assembly or interferon responses to preserve cellular integrity [28,29].

Mechanisms Regulating PRRs Expression

Precise regulation of innate inflammatory responses by balancing activation with restraint is essential for effective pathogen clearance while maintaining self-tolerance. Emerging evidence positions epigenetic modifications as master regulators of this equilibrium, dynamically controlling PRR expression and downstream signaling [30]. It has been reported that DNA methylation directly upregulates TLR9 expression and amplifies its signaling cascade (NF-κB activation, IRAK2 induction, and IL-8 production) during immune challenges [31]. Furthermore, histone methylation mediated by the methyltransferase SETDB1 suppresses endogenous retroviral elements (ERVs), and SETDB1 deficiency triggers ERV activation, potentially activating cytosolic RNA sensors through aberrant nucleic acid exposure [32]. Moreover, cellular state transitions and cytokine milieus (e.g., IL-12 signaling) provide additional layers of PRR regulation, enabling context-dependent tuning of the

innate immune response.

PRRs Expression and Regulation in T Cells

Under various pathophysiological conditions, from steady-state homeostasis to infection, inflammation, or malignancy, the molecular signatures and cellular composition of tissue microenvironments undergo substantial remodeling across different anatomical sites. This dynamic heterogeneity extends fundamentally to the spatiotemporal regulation of PRRs expression, resulting in cell-type- and context-dependent variations in innate sensing capabilities. A growing body of evidence underscores their indispensable role in preserving tissue homeostasis by integrating danger signals, regulating cell survival, and fine-tuning immune activation thresholds [16,33,34]. Emerging evidence reveals that PRRs expressed intrinsically by T cells (including TLRs, NLRs, RLRs, CLRs, and ALRs) can directly sense diverse molecular patterns within the disease microenvironment, ranging from microbial components and tumor neoantigens to self-antigens [35–38]. The expression pattern of T cell -intrinsic PRRs ensures that T cell subsets receive contextual signals, as illustrated in Figures 2 and 3. How the precise spatial, temporal, and subset-specific expression patterns of these PRRs orchestrate immune responses and determine the balance between protection and pathology remains unclear.

TLRs

Expression profiling revealed substantial heterogeneity in the TLR repertoire across mouse and human T lymphocyte subsets, suggesting subset-specific roles in modulating adaptive immune responses (Figures 2 and 3). Caramalho *et al.* [39] systematically profiled TLR expression in resting Treg and conventional T (Tconv) cells from C57BL/6 mice, revealing subset-specific compartmentalization of innate sensors. While both subsets express TLR2 and TLR6, TLR4 and TLR5 are selectively enriched in Tregs. Notably,

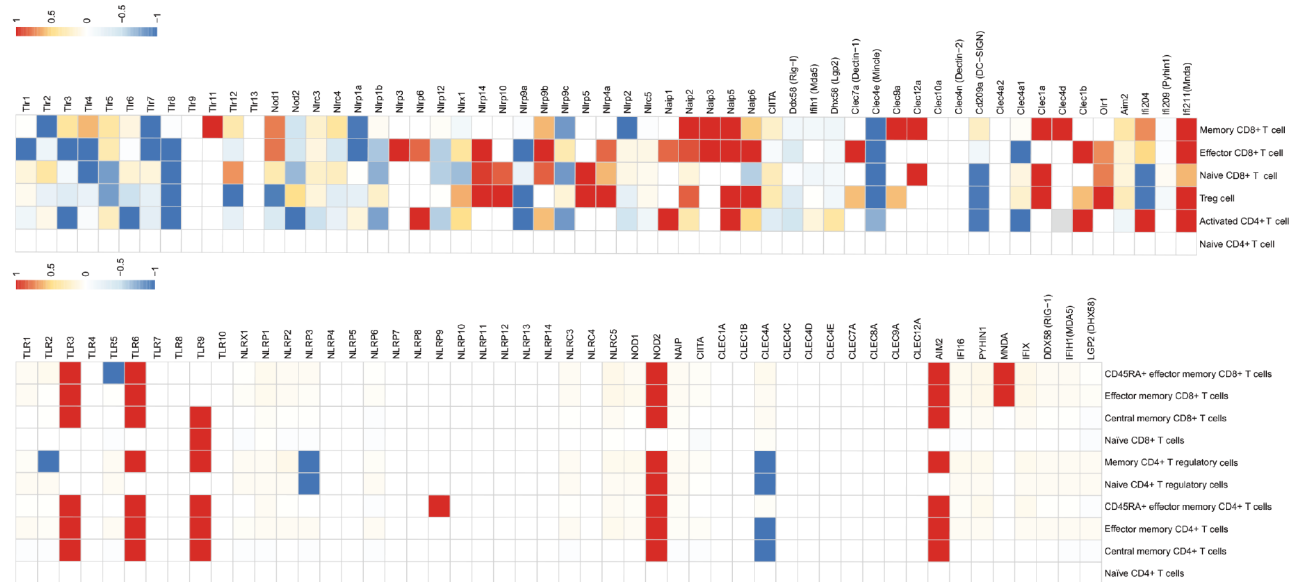


Figure 2. Relative levels of mouse and human PRR transcripts in T cells Heatmap showing the log10-transformed fold change (FC) in transcript abundance for representative PRR genes across mouse (upper panel) and human (lower panel) T-cell subsets. Data sources: Mouse data were obtained from the ImmGen database (<https://www.immgen.org/>), and human data were obtained from the Expression Atlas at EMBL-EBI (<https://www.ebi.ac.uk>). For the normalization of each gene, the TPM values in the indicated subsets were divided by the median TPM in naïve CD4⁺ T cells of the same species to obtain the FC; the FC values were then log10-transformed. TPM: transcripts per million.

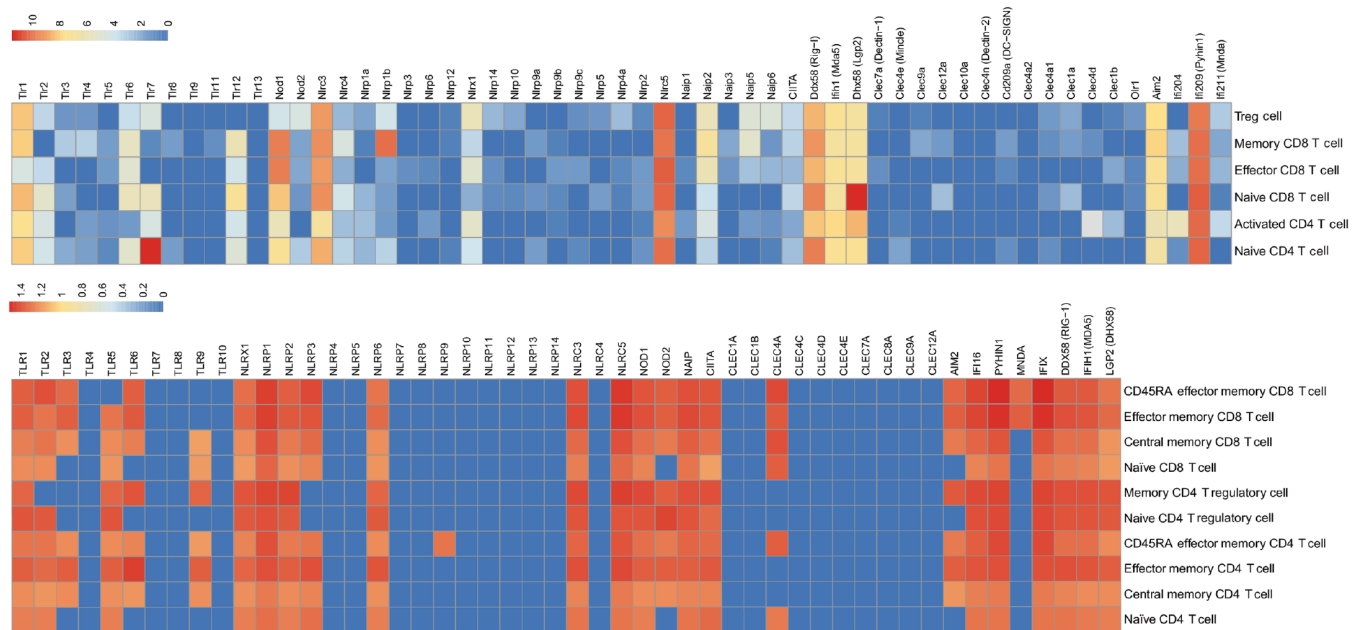


Figure 3. Expressions of mouse and human PRRs in T cells Heatmap showing the log₂-transformed TPM expression levels of PRR genes in T-cell subsets from mice (upper panel) and humans (lower panel). Data sources: Mouse data were obtained from the ImmGen database (<https://www.immgen.org/>), and human data were obtained from the Expression Atlas at EMBL-EBI (<https://www.ebi.ac.uk>). Data processing: For each gene, the TPM values were log₂-transformed prior to visualization. TPM: transcripts per million.

TLR3 and TLR9 transcripts are undetectable across CD4⁺ T cell subsets under steady-state conditions. Upon activation, however, CD4⁺ T cells dynamically upregulate TLR3, TLR5, and TLR9, while downregulating TLR2 and TLR4 [40]. This state-dependent reprogramming highlights the plasticity of TLR expression during immune engagement. Functionally, TLR2 serves as a key regulator of Treg biology. Its constitutively high expression in murine Tregs enables microenvironmental sensing, where ligand engagement triggers metabolic reprogramming (enhanced glycolysis) and proliferation but paradoxically impairs their immunosuppressive capacity [41]. Mechanistically, Lal *et al.* [42] demonstrated that peptidoglycan-induced TLR2 activation engages the MyD88-IRF1 axis. Nuclear IRF1 then binds to conserved response elements within Foxp3 regulatory regions (promoters, introns, and enhancers), directly repressing Foxp3 transcription and destabilizing Treg function. Collectively, these studies establish that TLR expression is dynamically regulated across T cell subsets and activation states, with profound functional consequences for adaptive immunity.

NLRs

In addition to TLRs, NLRs have emerged as critical regulators of T cell function. As predominantly intracellular sensors, NLRs detect cytosolic PAMPs and DAMPs generated during cellular stress. NLR family members exhibit remarkable functional specialization in T lymphocytes, governing diverse immunological processes beyond classical inflammasome activation. For example, NLRC5 enhances CD8⁺ T cell recognition by upregulating MHC-I expression in antigen-presenting cells [43,44]. NLRX1 (NOD5) localizes to mitochondrial matrices and regulates immunometabolism. During HIV-1 infection, NLRX1 promotes OXPHOS and glycolysis in CD4⁺ T cells, facilitating viral replication [45,46]. Moreover, NLRX1 deficiency exacerbates DSS-induced colitis with enhanced Th1/Th17 responses. Importantly, NLRC3/NLRP11 also attenuate Th1/

Th17 differentiation, with NLRC3 deficiency resulting in context-dependent outcomes: improved viral control but worsened EAE and tuberculosis pathology [47,48]. Notably, in CD4⁺ T cells, NLRP3 promotes Th2/Treg differentiation and reprograms tumor-infiltrating Th17 cells via AMPK suppression-enhanced glycolysis and Foxp3 demethylation [49,48]. Critically, the inflammasome-independent functions of most NLRs in T cell biology remain poorly characterized—a significant knowledge gap with therapeutic implications.

RLRs

Emerging evidence reveals complex RLR expression patterns and functions specifically within T lymphocytes. Comparative analyses revealed species- and subset-specific heterogeneity in RLR expression between murine and human T cells (Figures 2, 3). Functionally, LGP2 enhances antiviral CD8⁺ T cell responses by promoting antigen-specific expansion and effector differentiation [50]. Strikingly, however, RIG-I exhibits context-dependent duality: while it is canonically antiviral, it paradoxically functions as an intrinsic checkpoint in tumor-infiltrating CD8⁺ T cells, suppressing effector functions and limiting antitumor immunity [51,52]. This functional antagonism underscores the nuanced regulation of T cell responses by cytosolic RNA sensors.

CLRs

In T cell biology, CLRs primarily exert indirect regulatory functions. By recognizing pathogen glycans, CLRs on antigen-presenting cells augment antigen processing and presentation, orchestrate tailored helper T cell differentiation and collaboratively shape pathogen-specific adaptive immunity [53]. This modulation is amplified through crosstalk with other PRRs and cytokine receptors (e.g., IFNAR), enhancing Th cell response diversity against evolving pathogens. Importantly, the CLR member Dectin-1 exemplifies functional specialization: upon fungal β -glucan recognition, it

triggers synergistic signaling cascades that polarize potent Th1/Th17 responses essential for antifungal immunity [54–57].

ALRs

Emerging evidence reveals that T lymphocytes intrinsically express functional ALRs, enabling direct perception of DNA threats independent of professional antigen-presenting cells [58], which has been traditionally studied in innate immune cells. Their context-dependent outcomes hinge on T cell subset specificity, microenvironmental cues, or cross-talk with TCR/co-inhibitory signals.

How PRRs Regulate T Cell Function

This intrinsic sensing capacity of PRRs endows T cells with the remarkable ability to detect nuanced shifts within complex milieus, such as inflammation, autoimmunity and the tumor microenvironment. The engagement of these receptors profoundly influences critical T cell processes, such as activation thresholds, tissue infiltration, clonal expansion, differentiation, and effector function execution. Ultimately, these intrinsic PRR signals act as pivotal regulators, shaping the spectrum of anti-tumor immune responses, from potent effector activity that drives tumor clearance to dysfunctional states that facilitate immune evasion.

$\alpha\beta$ T cells

Conventional $\alpha\beta$ T cells, Th1, Th2, Th17, Tfh, Treg and CD8⁺ T cells, require antigen-presenting cells (APCs), such as dendritic cells (DCs), for MHC-dependent activation. Within this paradigm, PRRs serve as critical molecular interpreters, detecting microbial threats to license DC maturation and instruct T cell differentiation. However, emerging evidence reveals that PRRs directly regulate T cell function through non-canonical, APC-independent pathways, a paradigm shift in adaptive immunity. PRRs regulate CD8⁺ T-cell fitness. Abigail *et al.* [59] revealed that TCR signaling upregulates MAVS expression, enhancing mitochondrial biogenesis to increase metabolic flexibility, activate proliferation, and enhance effector function. PRRs not only provide co-stimulatory signals at the early stage of T-cell activation but also play a central role in subsequent fate determination and functional maintenance. cGAS-STING activation preserves stem-like properties, amplifying anti-tumor/infectious immunity [36,60]. Moreover, PRRs dynamically reshape T cell metabolism, resulting in pathological consequences. A study by Clinical Rheumatology in 2024 revealed that TLR2 activation in CD4⁺ T cells increases glycolysis and TNF- α /ROS overproduction, thereby promoting the disease development of rheumatoid arthritis in patients [56]. NLRP3 activation in tumoral Th17 cells promotes Treg differentiation in an inflammasome-independent manner [48]. Specifically, NLRP3 suppresses AMPK to increase glycolysis, resulting in Foxp3 demethylation and Treg-mediated immune evasion. Similarly, Aim2 activation promotes Treg metabolic rewiring and enhances immunosuppressive function in an inflammasome-independent manner, thereby inhibiting the autoimmune response [16].

Innate-like T cells

Innate-like T cells, including $\gamma\delta$ T cells, NKT cells, and mucosa-associated lymphoid tissue (MAIT) cells, constitute a functionally specialized frontier in immune surveillance and rapid pathogen response. These cells express evolutionarily conserved receptors enabling immediate reactivity at barrier sites and inflamed tissues. For NKT and MAIT cells, DCs serve as essential intermediaries. NKT

activation requires DC-presented lipid antigens via CD1d molecules upon PRR engagement [61]. Moreover, MAIT activation depends on DC-mediated bacterial metabolite presentation through MR1 [61]. DCs further amplify $\gamma\delta$ T cell responses through cytokine secretion (e.g., type I IFNs) and co-stimulatory signals, enhancing proliferation and IFN- γ production [62–64]. In contrast to NKT/MAIT cells, $\gamma\delta$ T cells exhibit DC-independent antigen recognition, directly recognizing antigenic ligands such as phosphate antigens, stress molecules, lipids, or metabolites without the assistance of MHCs. There is sufficient evidence that the co-stimulation of receptors such as TLR2/6, TLR5 and TLR3 expressed by $\gamma\delta$ T cells and TCR can promote the expression of CD69, the production of cytokines/chemokines or granzyme B, and the degranulation and proliferation of $\gamma\delta$ T cell surface activation markers [63,65,66]. Therefore, PRRs are important for the activation of intrinsic T cells. The direct activation of $\gamma\delta$ T cells by TLRs may provide new ideas for immunotherapy targeting $\gamma\delta$ T cells.

PRRs in T Cells Regulate Disease Outcome

PRRs, as important components of innate immune receptors, are encoded by a limited number of germline genes whose expression has passed through generations, indicating significant evolutionary conservation and indicating that such receptors are extremely important for the host. This conserved evolutionary mechanism endows PRRs with the ability to rapidly non-specifically recognize pathogens. However, in response to the diversity of ligands, PRRs have also shown a tendency toward adaptive evolution. This positive evolution enhances the ability of PRRs to recognize ligands or drives the diversity of PRR alleles (such as the 248S>N polymorphism in human TLR1). This positive evolution enhances the breadth of pathogen resistance at the population level. In recent years, research on PRRs in T cells has significantly improved our understanding of innate and adaptive immune responses (Figure 4) and has provided new therapeutic strategies to combat tumors, autoimmune diseases, infections, and transplant immunity [67–69].

Tumors

Within the tumoral complex milieu, PRRs emerge as master regulators whose context-dependent signaling cascades critically shape anti-tumor immunity. PRRs (including TLRs, NLRs, RLRs, and cGAS-STING) exhibit broad expression across diverse malig-

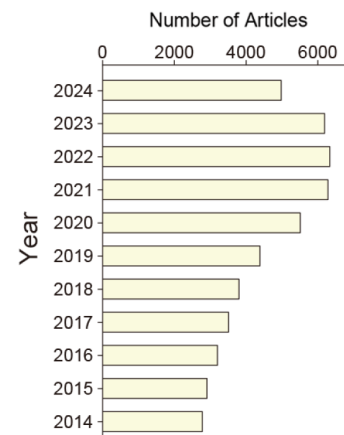


Figure 4. T cell intrinsic PRRs signaling The number of articles retrieved from Google Scholar with the key words “T-cell-intrinsic PRRs signaling”.

nancies, from colorectal and lung carcinomas to breast cancer, gastric adenocarcinoma, and melanoma. Tumor cell-intrinsic PRR activation drives a pathogenic feed-forward loop including massive secretion of pro-inflammatory cytokines, chemokine networks recruiting immunosuppressive cells, angiogenic factors promoting vascularization and metabolite reprogramming agents [70]. Tumor-associated RIG-I was reported to physically sequester STAT5, blocking its phosphorylation/nuclear translocation and suppressing cytotoxic gene programs in CD8⁺ T cells [51]. Critically, chronic PRR stimulation orchestrates T-cell exhaustion through multi-layered mechanisms. TLR4-MyD88 signaling in T cell induces the nuclear translocation of NF- κ B, mitochondrial dysfunction and ROS accumulation [71]. ROS-dependent upregulation of PD-1, TOX, and other inhibitory receptors on tumor-infiltrating lymphocytes (TILs) has been reported [71]. While cytosolic DNA sensing typically promotes anti-tumor immunity, chronic activation induces CD8⁺ T cell apoptosis [72]. NLRP3 inflammasome activation in Th17 cells suppresses AMPK, skewing differentiation toward immunosuppressive Tregs [48].

Despite their pro-tumor roles, compelling evidence reveals context-dependent anti-tumor functions of PRR pathways. pDC TLR9 ligation triggers CXCL10 release, thereby recruiting CXCR3⁺CD8⁺ T cells to tumors [73]. In T cell-intrinsic mechanisms, cGAMP-STING activation induces IRF-3 phosphorylation and IFN-I secretion, promoting Th1 differentiation. cGAMP also induces mTOR activation, which promotes Th9 commitment (IL-9⁺) and tumor suppression. In CD8⁺ T cells, STING activation has been reported to be important for maintaining T cell stemness [36].

Collectively, this duality positions PRRs as central arbiters of tumor immunity. Their effects depend on the tissue context, activation duration, spatial localization, ligand source or metabolic constraints (e.g., hypoxia/nutrient stress).

Autoimmune diseases

Autoimmune diseases represent a spectrum of debilitating conditions characterized by the breakdown of self-tolerance, wherein the immune system erroneously targets host tissues [71]. This pathological self-reactivity arises from complex interactions between genetic susceptibility, environmental triggers, and dysregulated immune pathways. Central to this dysregulation is the paradoxical role of PRRs, which typically orchestrate protective immune responses, and their inappropriate or sustained activation generates pathogenic inflammation that disrupts peripheral tolerance mechanisms. The inflammatory milieu promotes the maturation of autoreactive lymphocytes and alters the balance between effector and regulatory immune cells. Notably, engagement of endosomal TLR7/TLR9 by self-nucleic acids triggers massive production of IFNs, particularly IFN- α -autoreactive T cells, which are then activated through the JAK-STAT signaling upon binding to the IFNAR receptor, establishing a pivotal feedback loop in systemic lupus erythematosus (SLE) pathogenesis [74–77]. TLR2 expression on CD4⁺ T cells serves as a potent co-stimulatory signal that bypasses conventional activation checkpoints. In rheumatoid arthritis (RA), TLR2 ligation drives pathogenic T-cell hyperactivation, enhances TNF- α secretion, and stimulates ROS production, collectively exacerbating synovial inflammation and joint destruction [78]. This T cell-intrinsic PRR functionality blurs traditional boundaries between innate and adaptive immunity, positioning PRRs as direct modulators of autoreactive responses.

Infection

As pivotal executors of adaptive immunity, CD8⁺ T cells provide critical protection against intracellular pathogens, including viruses, bacteria, and fungi, through direct cytolytic activity and cytokine-mediated pathogen containment. Their efficacy hinges on precise activation by innate immune signals, particularly those initiated by PRRs that bridge early pathogen detection to T-cell functional specialization [79]. RIG-I activation promotes cross-presentation of viral antigens by DCs to naïve CD8⁺ T cells, clonal expansion and effector differentiation of virus-specific CD8⁺ T cells, as well as transcriptional reprogramming favoring granzyme B and perforin upregulation [80–82]. While positive selection of PRR variants (e.g., TLR1 S248N) broadens antimicrobial recognition at the population level, certain polymorphisms can tilt the balance toward pathological inflammation. The TLR4 D299G polymorphism, which is associated with increased susceptibility to sepsis, highlights this risk: altered LPS responsiveness may simultaneously impair microbial clearance and promote sterile inflammation through DAMP sensing [83]. Such genetic variations resulting in hyperresponsive PRR alleles may compromise tolerance mechanisms.

Transplant immunity

Graft-versus-host disease (GvHD) is one of the unmet challenges in allogeneic transplantation. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains a cornerstone therapy for hematologic malignancies, yet GvHD persists as a life-threatening complication affecting 30–50% of recipients. This condition arises when donor T cells recognize host tissues as foreign, triggering inflammatory cascades that damage the skin, gut, and liver. While traditional models focus on TCR-MHC mismatches, emerging evidence implicates innate immune pathways, particularly T cell-intrinsic PRRs, as critical amplifiers of alloreactivity. Importantly, PRR-driven inflammasome assembly in alloreactive T cells significantly contributes to GvHD pathogenesis [84]. RNA sequencing of GvHD T cells demonstrated significant upregulation of NLR sensors, including NLRP1, NLRP3, and NLRP12, as well as the DNA-sensing adaptors Pyrin and IFI204. This finding suggests transcriptional priming for inflammasome assembly. Furthermore, detection of ASC specks in FLICA⁺ T cells confirmed functional inflammasome oligomerization, the definitive hallmark of inflammasome activation. Moreover, a prominent ~33 kDa protein band corresponding to active caspase-1 within inflammasome complexes of donor T cells was detected, indicating that proteolytic maturation is critical for IL-1 β /IL-18 processing. The discovery of functional inflammasomes in T cells challenges the basic view of transplant immunology, establishing T cell-intrinsic inflammasomes as fundamental drivers of transplant immunopathology. More questions await further study, including the specific DAMPs (e.g., mtDNA, ATP) that trigger T cell inflammasomes in GvHD target organs, the possibility of the application of NLRP3 polymorphisms for personalized GvHD risk stratification, and the potential immunosuppressants (calcineurin inhibitors) that intersect with this pathway.

Therapeutic Strategies and Challenges Targeting T-cell PRRs

The limitations of the current research lies in the unclear underlying mechanisms

Emerging evidence reveals that PRRs, which are traditionally confined to innate immune cells, are functionally expressed in T

cell subsets, enabling direct pathogen/danger-sensing and fine-tuning of effector functions. This paradigm shift unveils unprecedented opportunities for cell-intrinsic immunomodulation, yet our understanding remains fragmented by critical knowledge barriers. While PRRs offer compelling targets for manipulating T cell responses in autoimmunity, cancer and infection, current strategies face three fundamental limitations. Most PRR research emphasizes innate cell-mediated bystander effects on T cells, neglecting cell-autonomous signaling. More importantly, the unknown PRR expression kinetics across T cell states establish dynamically regulated binding sites. Last but not the least, context-dependent signaling, including ligand availability, the tissue microenvironment, and metabolic states, dictates whether PRR engagement activates or suppresses immunity.

Advanced cutting-edge technologies have developed rapidly in recent years. These technologies could be used to bridge the gap in knowledge concerning T cell PRR function in three critical dimensions: cellular heterogeneity, spatial organization, and regulatory network complexity. Specifically, spatial transcriptomics can be used to reveal the localization of T cell PRR in the tissue microenvironment, thereby establishing spatiotemporally controllable PRR regulation strategies to achieve precise “programming” of T cell immune responses. CRISPR screening can be used to identify co-stimulatory/inhibitory factors that regulate T cell function through PRRs. The combination of these cutting-edge technologies with the study of PRRs in T cell regulation can provide breakthrough therapies for autoimmune diseases, tumors, and infectious diseases.

Reimagining immunotherapy through T cell-intrinsic PRR signaling

Despite transformative advances in checkpoint blockade and CAR-T therapies, durable remission in solid tumors remains elusive. Cancer vaccines represent a promising frontier, yet their efficacy hinges on overcoming fundamental barriers: poor antigen immunogenicity, immunosuppressive microenvironments, and inadequate T cell memory formation. PRRs have emerged as master molecular switches capable of reprogramming antitumor immunity not only through classical innate immune activation but also via direct T cell immunomodulation, positioning them as pivotal targets for rational vaccine design.

PRRs agonists function as vaccine adjuvants by mimicking PAMPs, thereby amplifying innate immune signaling and potentiating adaptive immunity. This mechanistic foundation underpins their established role in modern vaccinology. Advances in understanding PRR-mediated T cell regulation have led to the development of novel paradigms for treating T-cell-related pathologies through tailored immunotherapy [85,86]. The TLR9 agonist CpG-ODN induces Th1-polarized immunity via the IL-12/IFN- γ axis and enhances CD8⁺ T cell cytotoxic function in melanoma trials (NCT03831295). Delivering a chitin-derived C100 adjuvant directly to tumors can enhance the STING-IFNAR signaling pathway and CD8⁺ T cell-dependent anti-tumor immunity [87]. TLR7/8 nanoparticles reprogram TAMs to an immunostimulatory phenotype and augment T-cell priming [88]. A phase I NSCLC study reported doubled objective response rates [89]. Clinically approved TLR agonists—including AS04 (HPV), RC-529 (HBV), and AF03 (influenza)—demonstrate translational success, while CpG-1018 significantly contributes to COVID-19 vaccine efficacy [85,90]. Similarly,

the ability of RIG-I to enhance CD8⁺ T cell function has spurred the development of RIG-I-targeted vaccine platforms [91]. However, PRR-mediated regulation of T cells is considerably complex. The clinical translation of PRR-targeted therapies faces significant challenges, including limited cellular specificity, intricate signaling pleiotropy, and inter-individual variability. PRR responses demonstrate marked cell type dependence and functional divergence, as evidenced by differential signaling outcomes in T cells versus other immune populations—a phenomenon reflecting evolutionary diversification across species. Critically, distinct PRR classes differentially modulate T cell activity (as detailed previously), necessitating precisely calibrated therapeutic interventions. Therefore, comprehensive elucidation of PRR regulatory networks in T cells is imperative. Future efforts must (I) validate PRR-specific functional consequences in T cell subsets, (II) rationally design context-dependent agonists/antagonists, (III) develop advanced delivery systems enabling tissue-specific targeting, and (IV) mitigate systemic hyperinflammation risks (e.g., cytokine storm syndromes) through engineered selectivity.

Clinical translation challenges of T cell-targeted PRR therapeutics

The therapeutic targeting of T cell-intrinsic PRRs represents a promising frontier in immunotherapy but faces significant safety-efficacy barriers impeding clinical translation [92–94]. The five core challenges demand resolution are as follows. First, systemic PRR agonism risks uncontrolled inflammation and autoimmune sequelae due to broad receptor distribution. Second, there is limited efficacy in immunosuppressive microenvironments with low T cell infiltration or high Treg/MDSC presence. Third, PRRs exert context-dependent signaling duality. Therefore, identical PRR engagement can elicit opposing pro-inflammatory or tolerogenic outcomes on the basis of the cellular context. Fourth, precise temporal control is essential, as evidenced by TLR3 agonists requiring administration within 24 h post-radiation for synergistic effects. Fifth, compensatory immunosuppressive pathways frequently emerge during chronic stimulation. Successful clinical implementation hinges on decoding the fundamental logic governing T cell-intrinsic PRR signaling networks—transforming empirical approaches into rationally engineered therapeutics.

Conclusions and Outlook

T cell regulation by PRRs bridges innate-adaptive immunity and uncharted mechanisms. PRRs orchestrate multidimensional control over T cell responses through T cell-intrinsic and antigen-presenting cell-mediated pathways. As important components in T cell activation, DCs serve as “bridge” cells between innate and adaptive immunity, whereas PRRs expressed on DCs act as “bridge” molecules between innate and adaptive immunity. Currently, most studies on the impact of PRRs on T cells still focus on DC-dependent regulatory mechanisms. The activation of PRRs on DCs provides three effective signals for T-cell activation, and owing to the highly conserved evolution of PRRs, the activation of PRRs on DCs resulting in T-cell activation is a key part of the immune response. Recently, T cell-intrinsic PRRs have been shown to constitute a fundamental immunological axis. The expression of PRRs on T cells varies between physiological and pathological states, and the regulation of T cells by PRRs shows tissue specificity. The discovery of functional TLRs, NLRs, RLRs, and ALRs across T cell subsets

(Figures 2 and 3) reveals an evolutionarily conserved layer of contextual intelligence, enabling T cells to autonomously interpret microenvironmental threats from microbial invasion to malignant transformation. Moreover, the influence of PRRs on T cells involves multiple processes, such as T cell metabolic reprogramming, differentiation and polarization, and functional shaping. Nevertheless, the direct regulatory mechanisms by which PRRs affect the ability of T cells to adapt to local inflammatory cues without DC intermediation remain unclear and lack systematic description. Hence, future research should focus on systematically analyzing the direct regulatory effects of PRRs on T cells, elucidating their positive or negative regulatory mechanisms, and mapping the dynamic expression profiles of T cell PRRs. On the basis of these findings, novel therapeutic strategies targeting T cell PRRs could be developed, which could provide extensive application value for the future clinical treatment of autoimmune diseases, infectious diseases, transplants and tumors. The Specificity-safety conundrum of PRRs therapeutic translation consists of three barriers: cellular promiscuity, signaling pleiotropy and temporal paradoxes. By applying technology-enabled solutions of spatial transcriptomics, CRISPR suppressor screens, and logic-gated nanoparticles, the clinical translation of T Cell-Targeted PRR Therapeutics gain promise. T cell-intrinsic PRRs represent master interpreters of the immunological context, functionally integrating danger perception, metabolic adaptation, and effector programming. Their duality, as both guardians of homeostasis and drivers of pathology, stems from spatiotemporal dysregulation rather than inherent pathogenicity. Future therapeutics must embrace circuit-specific immunomodulation: selectively rewiring pathogenic PRR pathways while preserving protective functions.

Funding

This work was supported by the grants from the National Natural Science Foundation of China (No. 82573507), the Strategic Priority Research Program of the Chinese Academy of Science (No. XDB0990303), and the Shanghai Pujiang Program (No. 24PJ139).

Conflict of Interest

The authors declare that they have no conflict of interest.

References

- Oh SH, Choi YK, Lee SJ. Pattern recognition receptors and inflammasome: now and beyond. *Molecules Cells* 2025, 48: 100239
- Chen R, Zou J, Chen J, Zhong X, Kang R, Tang D. Pattern recognition receptors: Function, regulation and therapeutic potential. *Sig Transduct Target Ther* 2025, 10: 216–269
- Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. *Cell* 2006, 124: 783–801
- Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell* 2010, 140: 805–820
- Wu J, Chen ZJ. Innate immune sensing and signaling of cytosolic nucleic acids. *Annu Rev Immunol* 2014, 32: 461–488
- Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. *Immunity* 2011, 34: 637–650
- Kawai T, Takahashi K, Sato S, Coban C, Kumar H, Kato H, Ishii KJ, *et al.* IPS-1, an adaptor triggering RIG-I- and Mda5-mediated type I interferon induction. *Nat Immunol* 2005, 6: 981–988
- Inohara N, Koseki T, del Peso L, Hu Y, Yee C, Chen S, Carrio R, *et al.* Nod1, an Apaf-1-like activator of caspase-9 and nuclear factor- κ B. *J Biol Chem* 1999, 274: 14560–14567
- Kawai T, Ikegawa M, Ori D, Akira S. Decoding Toll-like receptors: recent insights and perspectives in innate immunity. *Immunity* 2024, 57: 649–673
- Liston A, Masters SL. Homeostasis-altering molecular processes as mechanisms of inflammasome activation. *Nat Rev Immunol* 2017, 17: 208–214
- Kufer TA, Sansonetti PJ. NLR functions beyond pathogen recognition. *Nat Immunol* 2011, 12: 121–128
- Murphy DM, Mills KHG, Basdeo SA. The effects of trained innate immunity on T cell responses, clinical implications and knowledge gaps for future research. *Front Immunol* 2021, 12: 706583
- Carroll SL, Pasare C, Barton GM. Control of adaptive immunity by pattern recognition receptors. *Immunity* 2024, 57: 632–648
- Li Y, Wang Z, Hou Y, Liu X, Hong J, Shi X, Huang X, *et al.* Novel TLR7/8 agonists promote activation of HIV-1 latent reservoirs and human T and NK cells. *Front Microbiol* 2023, 14: 1033448
- Reynolds JM, Pappu BP, Peng J, Martinez GJ, Zhang Y, Chung Y, Ma L, *et al.* Toll-like receptor 2 signaling in CD4⁺ T Lymphocytes promotes T Helper 17 responses and regulates the pathogenesis of autoimmune disease. *Immunity* 2010, 32: 692–702
- Chou WC, Guo Z, Guo H, Chen L, Zhang G, Liang K, Xie L, *et al.* AIM2 in regulatory T cells restrains autoimmune diseases. *Nature* 2021, 591: 300–305
- Yao Y, Chen S, Cao M, Fan X, Yang T, Huang Y, Song X, *et al.* Antigen-specific CD8⁺ T cell feedback activates NLRP3 inflammasome in antigen-presenting cells through perforin. *Nat Commun* 2017, 8: 15402
- Thomas G, Micci L, Yang W, Katakowski J, Oderup C, Sundar P, Wang X, *et al.* Intra-Tumoral activation of endosomal TLR pathways reveals a distinct role for TLR3 agonist dependent Type-1 interferons in shaping the tumor immune microenvironment. *Front Oncol* 2021, 11: 711673
- Marakalala MJ. Dectin-1-Syk-CARD9 signaling pathway in TB immunity. *Front Immunol* 2018, 9: 225
- Man SM, Jenkins BJ. Context-dependent functions of pattern recognition receptors in cancer. *Nat Rev Cancer* 2022, 22: 397–413
- Wang Z, Gu Y, Liu Y, Wang Z, Chen X, Wang H, Zhang W, *et al.* Phosphorylated Toll-like receptor 3 nuclear translocation in cancer cell promotes metastasis and chemoresistance. *Sig Transduct Target Ther* 2025, 10: 225
- Yang Z, Ji S, Liu L, Liu S, Wang B, Ma Y, Cao X. Promotion of TLR7-MyD88-dependent inflammation and autoimmunity in mice through stem-loop changes in Lnc-Atg16l1. *Nat Commun* 2024, 15: 10224
- Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol* 2010, 11: 373–384
- Bauernfeind FG, Horvath G, Stutz A, Alnemri ES, MacDonald K, Speert D, Fernandes-Alnemri T, *et al.* Cutting edge: NF- κ B activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. *J Immunol* 2009, 183: 787–791
- Hu Z, Chai J. Assembly and architecture of NLR resistosomes and inflammasomes. *Annu Rev Biophys* 2023, 52: 207–228
- Goubau D, Schlee M, Deddouch S, Pruijssers AJ, Zillinger T, Goldeck M, Schuberth C, *et al.* Antiviral immunity via RIG-I-mediated recognition of RNA bearing 5'-diphosphates. *Nature* 2014, 514: 372–375
- Yoneyama M, Kikuchi M, Natsukawa T, Shinobu N, Imaizumi T, Miyagishi M, Taira K, *et al.* The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. *Nat Immunol* 2004, 5: 730–737
- Hornung V, Ablasser A, Charrel-Dennis M, Bauernfeind F, Horvath G, Caffrey DR, Latz E, *et al.* AIM2 recognizes cytosolic dsDNA and forms a

- caspase-1-activating inflammasome with ASC. *Nature* 2009, 458: 514–518
29. Bowie AG, Unterholzner L. Viral evasion and subversion of pattern-recognition receptor signalling. *Nat Rev Immunol* 2008, 8: 911–922
30. Liu J, Qian C, Cao X. Post-translational modification control of innate immunity. *Immunity* 2016, 45: 15–30
31. Füri I, Sipos F, Spisák S, Kiszner G, Wichmann B, Schöller A, Tulassay Z, *et al.* Association of Self-DNA mediated TLR9-Related gene, DNA methyltransferase, and cytokeratin protein expression alterations in HT29-Cells to DNA fragment length and methylation status. *Sci World J* 2013, 2013(1): 293296
32. Lyu Y, Kim SJ, Humphrey ES, Nayak R, Guan Y, Liang Q, Kim KH, *et al.* Stem cell activity-coupled suppression of endogenous retrovirus governs adult tissue regeneration. *Cell* 2024, 187: 7414–7432.e26
33. Padovan E, Landmann RM, De Libero G. How pattern recognition receptor triggering influences T cell responses: a new look into the system. *Trends Immunol* 2007, 28: 308–314
34. Shaw PJ, Lamkanfi M, Kanneganti TD. NOD-like receptor (NLR) signaling beyond the inflammasome. *Eur J Immunol* 2010, 40: 624–627
35. Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. *Nat Immunol* 2015, 16: 343–353
36. Li W, Lu L, Lu J, Wang X, Yang C, Jin J, Wu L, *et al.* cGAS-STING-mediated DNA sensing maintains CD8⁺ T cell stemness and promotes antitumor T cell therapy. *Sci Transl Med* 2020, 12: 9013
37. Speakman EA, Dambuza IM, Salazar F, Brown GD. T cell antifungal immunity and the role of C-Type lectin receptors. *Trends Immunol* 2020, 41: 61–76
38. Vobořil M, Brabec T, Dobeř J, Šplíchalová I, Březina J, Čepková A, Dobeřová M, *et al.* Toll-like receptor signaling in thymic epithelium controls monocyte-derived dendritic cell recruitment and Treg generation. *Nat Commun* 2020, 11: 2361
39. Caramalho I, Lopes-Carvalho T, Ostler D, Zelenay S, Haury M, Demengeot J. Regulatory T cells selectively express toll-like receptors and are activated by lipopolysaccharide. *J Exp Med* 2003, 197: 403–411
40. Gelman AE, Zhang J, Choi Y, Turka LA. Toll-Like receptor ligands directly promote activated CD4⁺ T cell survival. *J Immunol* 2004, 172: 6065–6073
41. Gerriets VA, Kishton RJ, Johnson MO, Cohen S, Siska PJ, Nichols AG, Warmoes MO, *et al.* Foxp3 and Toll-like receptor signaling balance Treg cell anabolic metabolism for suppression. *Nat Immunol* 2016, 17: 1459–1466
42. Lal G, Yin N, Xu J, Lin M, Schroppel S, Ding Y, Marie I, *et al.* Distinct inflammatory signals have physiologically divergent effects on epigenetic regulation of foxp3 expression and treg function. *Am J Transplant* 2011, 11: 203–214
43. Meissner TB, Liu YJ, Lee KH, Li A, Biswas A, van Eggermond MCJA, van den Elsen PJ, *et al.* NLRC5 cooperates with the RFX transcription factor complex to induce MHC class I gene expression. *J Immunol* 2012, 188: 4951–4958
44. Kobayashi KS, van den Elsen PJ. NLRC5: a key regulator of MHC class I-dependent immune responses. *Nat Rev Immunol* 2012, 12: 813–820
45. Bi PY, Killackey SA, Schweizer L, Girardin SE. NLRX1: versatile functions of a mitochondrial NLR protein that controls mitophagy. *BioMed J* 2024, 47: 100635
46. Guo H, Wang Q, Ghneim K, Wang L, Rampanelli E, Holley-Guthrie E, Cheng L, *et al.* Multi-omics analyses reveal that HIV-1 alters CD4⁺ T cell immunometabolism to fuel virus replication. *Nat Immunol* 2021, 22: 423–433
47. Leber A, Hontecillas R, Tubau-Juni N, Zoccoli-Rodriguez V, Hulver M, McMillan R, Eden K, *et al.* NLRX1 regulates effector and metabolic functions of CD4⁺ T cells. *J Immunol* 2017, 198: 2260–2268
48. Accogli T, Hibos C, Milian L, Geindreau M, Richard C, Humblin E, Mary R, *et al.* The intrinsic expression of NLRP3 in Th17 cells promotes their protumor activity and conversion into Tregs. *Cell Mol Immunol* 2025, 22: 541–556
49. Bruchard M, Rebé C, Derangère V, Togbé D, Ryffel B, Boidot R, Humblin E, *et al.* The receptor NLRP3 is a transcriptional regulator of TH2 differentiation. *Nat Immunol* 2015, 16: 859–870
50. Suthar MS, Ramos HJ, Brassil MM, Netland J, Chappell CP, Blahnik G, McMillan A, *et al.* The RIG-I-like receptor LGP2 controls CD8⁺ T cell survival and fitness. *Immunity* 2012, 37: 235–248
51. Jiang X, Lin J, Shangguan C, Wang X, Xiang B, Chen J, Guo H, *et al.* Intrinsic RIG-I restrains STAT5 activation to modulate antitumor activity of CD8⁺ T cells. *J Clin Invest* 2023, 133: e160790
52. Duan X, Hu J, Zhang Y, Zhao X, Yang M, Sun T, Liu S, *et al.* RIG-I is an intracellular checkpoint that limits CD8⁺ T-cell antitumour immunity. *EMBO Mol Med* 2024, 16: 3005–3025
53. Geijtenbeek TBH, Gringhuis SI. C-type lectin receptors in the control of T helper cell differentiation. *Nat Rev Immunol* 2016, 16: 433–448
54. Agrawal S, Gupta S, Agrawal A, Wang FS. Human dendritic cells activated via dectin-1 are efficient at priming Th17, cytotoxic CD8 T and B cell responses. *PLoS One* 2010, 5: e13418
55. Daley D, Mani VR, Mohan N, Akkad N, Ochi A, Heindel DW, Lee KB, *et al.* Dectin 1 activation on macrophages by galectin 9 promotes pancreatic carcinoma and peritumoral immune tolerance. *Nat Med* 2017, 23: 556–567
56. Gringhuis SI, Kaptein TM, Remmerswaal EBM, Drewniak A, Wevers BA, Theelen B, D’Haens GRAM, *et al.* Fungal sensing by dectin-1 directs the non-pathogenic polarization of TH17 cells through balanced type I IFN responses in human DCs. *Nat Immunol* 2022, 23: 1735–1748
57. Gringhuis SI, den Dunnen J, Litjens M, van der Vlist M, Wevers B, Bruijns SCM, Geijtenbeek TBH. Dectin-1 directs T helper cell differentiation by controlling noncanonical NF- κ B activation through Raf-1 and Syk. *Nat Immunol* 2009, 10: 203–213
58. Brüser C, Keller-Findeisen J, Jakobs S. The TFAM-to-mtDNA ratio defines inner-cellular nucleoid populations with distinct activity levels. *Cell Rep* 2021, 37: 110000
59. Vanderheiden A, Valenzuela RA, Verkerke H, Jin F, Price M, Boss JM, Grakoui A, *et al.* Cell-intrinsic MAVS promotes antigen specific CD8⁺ T cell proliferation and mitochondrial metabolism. *J Immunol* 2021, 206: 10307
60. Kwon J, Bakhoun SF. The cytosolic DNA-Sensing cGAS-STING pathway in cancer. *Cancer Discov* 2020, 10: 26–39
61. Ruf B, Greten TF, Korangy F. Innate lymphoid cells and innate-like T cells in cancer—at the crossroads of innate and adaptive immunity. *Nat Rev Cancer* 2023, 23: 351–371
62. Serrano R, Wesch D, Kabelitz D. Activation of human $\gamma\delta$ T cells: modulation by Toll-Like receptor 8 ligands and role of monocytes. *Cells* 2020, 9: 713
63. Wesch D, Peters C, Oberg HH, Pietschmann K, Kabelitz D. Modulation of $\gamma\delta$ T cell responses by TLR ligands. *Cell Mol Life Sci* 2011, 68: 2357–2370
64. Kunzmann V, Kretzschmar E, Herrmann T, Wilhelm M. Polyinosinic-polycytidylic acid-mediated stimulation of human $\gamma\delta$ T cells via CD11c⁺ dendritic cell-derived type I interferons. *Immunology* 2004, 112: 369–377
65. Wesch D, Beetz S, Oberg HH, Marget M, Krengel K, Kabelitz D. Direct costimulatory effect of TLR3 ligand poly(I:C) on human $\gamma\delta$ T lymphocytes. *J Immunol* 2006, 176: 1348–1354
66. Pietschmann K, Beetz S, Welte S, Martens I, Gruen J, Oberg HH, Wesch D, *et al.* Toll-like receptor expression and function in subsets of human $\gamma\delta$ T lymphocytes. *Scand J Immunol* 2009, 70: 245–255
67. Ngou BPM, Wyler M, Schmid MW, Kadota Y, Shirasu K. Evolutionary trajectory of pattern recognition receptors in plants. *Nat Commun* 2024,

- 15: 308
68. Jin X, Wang W, Zhao X, Jiang W, Shao Q, Chen Z, Huang C. The battle between the innate immune cGAS-STING signaling pathway and human herpesvirus infection. *Front Immunol* 2023, 14: 1235590
69. Areal H, Abrantes J, Esteves PJ. Signatures of positive selection in Toll-like receptor (TLR) genes in mammals. *BMC Evol Biol* 2011, 11: 368
70. Li D, Wu M. Pattern recognition receptors in health and diseases. *Sig Transduct Target Ther* 2021, 6: 291
71. Fang L, Liu K, Liu C, Wang X, Ma W, Xu W, Wu J, *et al.* Tumor accomplice: T cell exhaustion induced by chronic inflammation. *Front Immunol* 2022, 13: 979116
72. Wu J, Dobbs N, Yang K, Yan N. Interferon-independent activities of mammalian STING mediate antiviral response and tumor immune evasion. *Immunity* 2020, 53: 115–126.e5
73. Limagne E, Nuttin L, Thibaudin M, Jacquin E, Aucagne R, Bon M, Revy S, *et al.* MEK inhibition overcomes chemoimmunotherapy resistance by inducing CXCL10 in cancer cells. *Cancer Cell* 2022, 40: 136–152.e12
74. Wolf SJ, Theros J, Reed TJ, Liu J, Grigorova IL, Martínez-Colón G, Jacob CO, *et al.* TLR7-mediated lupus nephritis is independent of type I IFN signaling. *J Immunol* 2018, 201: 393–405
75. Marshak-Rothstein A. Toll-like receptors in systemic autoimmune disease. *Nat Rev Immunol* 2006, 6: 823–835
76. Gong L, Wang Y, Zhou LL, Bai X, Wu S, Zhu F, Zhu YF. Activation of toll-like receptor-7 exacerbates lupus nephritis by modulating regulatory T cells. *Am J Nephrol* 2014, 40: 325–344
77. Deane JA, Bolland S. Nucleic Acid-Sensing TLRs as modifiers of autoimmunity. *J Immunol* 2006, 177: 6573–6578
78. Lin Q, Zhang C, Huang H, Bai Z, Liu J, Zhang Y, Li X, *et al.* TLR2 reprograms glucose metabolism in CD4+ T cells of rheumatoid arthritis patients to mediate cell hyperactivation and TNF- α secretion. *Clin Rheumatol* 2024, 43: 3537–3549
79. Lazear HM, Pinto AK, Ramos HJ, Vick SC, Shrestha B, Suthar MS, Gale Jr. M, *et al.* Pattern recognition receptor MDA5 modulates CD8+ T cell-dependent clearance of west nile virus from the central nervous system. *J Virol* 2013, 87: 11401–11415
80. Liu Y, Olganier D, Lin R. Host and viral modulation of RIG-I-Mediated antiviral immunity. *Front Immunol* 2017, 3: 7
81. Chan YK, Gack MU. RIG-I-like receptor regulation in virus infection and immunity. *Curr Opin Virol* 2015, 12: 7–14
82. Onomoto K, Onoguchi K, Yoneyama M. Regulation of RIG-I-like receptor-mediated signaling: interaction between host and viral factors. *Cell Mol Immunol* 2021, 18: 539–555
83. Hold GL, Berry S, Saunders KA, Drew J, Mayer C, Brookes H, Gay NJ, *et al.* The TLR4 D299G and T399I SNPs are constitutively active to up-regulate expression of Trif-dependent genes. *PLoS ONE* 2014, 9: e111460
84. Talley S, Rademacher DJ, Campbell EM. Inflammasome activation occurs in CD4+ and CD8+ T cells during graft-versus-host disease. *Cell Death Dis* 2023, 14: 632
85. Coffman RL, Sher A, Seder RA. Vaccine adjuvants: putting innate immunity to work. *Immunity* 2010, 33: 492–503
86. Bendelac A, Medzhitov R. Adjuvants of immunity. *J Exp Med* 2002, 195: F19–F23
87. Turley JL, Ward RW, Huete-Carrasco J, Muñoz-Wolf N, Roche K, Jin L, Bowie A, *et al.* Intratumoral delivery of the chitin-derived C100 adjuvant promotes robust STING, IFNAR, and CD8+ T cell-dependent anti-tumor immunity. *Cell Rep Med* 2024, 5: 101560
88. Rodell CB, Arlauckas SP, Cuccarese MF, Garriss CS, Li R, Ahmed MS, Kohler RH, *et al.* TLR7/8-agonist-loaded nanoparticles promote the polarization of tumour-associated macrophages to enhance cancer immunotherapy. *Nat Biomed Eng* 2018, 2: 578–588
89. VanderWalde A, Bellasea SL, Kendra KL, Khushalani NI, Campbell KM, Scumpia PO, Kuklinski LF, *et al.* Ipilimumab with or without nivolumab in PD-1 or PD-L1 blockade refractory metastatic melanoma: a randomized phase 2 trial. *Nat Med* 2023, 29: 2278–2285
90. Yang JX, Tseng JC, Yu GY, Luo Y, Huang CYF, Hong YR, Chuang TH. Recent advances in the development of toll-like receptor agonist-based vaccine adjuvants for infectious diseases. *Pharmaceutics* 2022, 14: 423
91. Martínez-Gil L, Goff PH, Hai R, García-Sastre A, Shaw ML, Palese P. A sendai virus-derived RNA agonist of RIG-I as a virus vaccine adjuvant. *J Virol* 2013, 87: 1290–1300
92. Goutagny N, Estornes Y, Hasan U, Lebecque S, Caux C. Targeting pattern recognition receptors in cancer immunotherapy. *Targ Oncol* 2012, 7: 29–54
93. Jeon D, Hill E, McNeel DG. Toll-like receptor agonists as cancer vaccine adjuvants. *Hum Vaccines ImmunoTher* 2024, 20: 2297453
94. Decout A, Katz JD, Venkatraman S, Ablasser A. The cGAS-STING pathway as a therapeutic target in inflammatory diseases. *Nat Rev Immunol* 2021, 21: 548–569