FCER1G: A multifunctional regulator in the immune microenvironment (Review)

YUYU ZHANG[1-4], JINGLAN WANG[2-5], WENTING HE[1-5] and TAO LIU[1-5]

[1]The Second Hospital and Clinical Medical School, Lanzhou University, Lanzhou, Gansu 730030, P.R. China; [2]Gansu Provincial Key Laboratory of Environmental Oncology, Lanzhou, Gansu 730030, P.R. China; [3]Digestive System Tumor Prevention and Treatment, and Translational Medicine Engineering Innovation Center of Lanzhou University, Lanzhou, Gansu 730030, P.R. China; [4]Digestive System Tumor Translational Medicine Engineering Research Center of Gansu Province, Lanzhou, Gansu 730030, P.R. China; [5]School of Basic Medical Sciences, Lanzhou University, Lanzhou, Gansu 730000, P.R. China

Received November 4, 2025; Accepted January 30, 2026

DOI: 10.3892/etm.2026.13141

Abstract. The Fc fragment of IgE receptor 1G (*FCER1G*) gene encodes the Fc receptor common γ chain (FcRγ), a crucial adaptor protein in immune signaling. As the core subunit for multiple immune receptors, including high-affinity immunoglobulin E receptor, Fc fragment of IgG receptor and C-type lectin receptors, it regulates both innate and adaptive immune responses through its intracellular immunoreceptor tyrosine-based activation motif. Downstream effector functions include antibody-dependent cytotoxicity, phagocytosis and inflammatory cytokine production. Emerging evidence implicates *FCER1G* in diverse pathological conditions. In inflammatory diseases, epigenetic mechanisms strictly regulate its expression, driving inflammation by influencing immune cell polarization. In the context of cancer, it induces tumor progression by remodeling the immune microenvironment, inducing angiogenesis and enabling platelet-mediated metastasis. Notably, its prognostic value varies according to tissue origin. Although no current drugs directly target *FCER1G*, established agents such as aspirin may indirectly modulate its signaling. The present review aimed to summarize the current knowledge on the molecular structure, immune functions and regulatory mechanisms of *FCER1G* in inflammation and carcinogenesis, establishing a rationale for its potential use as a prognostic biomarker and therapeutic target.

Correspondence to: Professor Tao Liu or Professor Wenting He, The Second Hospital and Clinical Medical School, Lanzhou University, 82 Cuiyingmen, Chengguan, Lanzhou, Gansu 730030, P.R. China
E-mail: liut@lzu.edu.cn
E-mail: hewt@lzu.edu.cn

Key words: Fc fragment of IgE receptor Ig, Fc receptor γ chain, immunoreceptor tyrosine-based activation motif, tumor immune microenvironment, immunotherapy

Contents

1. Introduction

The Fc fragment of IgE receptor 1G (*FCER1G*) gene, mapping to chromosome 1q23.3, encodes the immunoglobulin Fc receptor common γ chain (FcRγ), an integral signaling adaptor in innate and adaptive immunity (1). Initially identified as the third subunit of the high-affinity IgE receptor complex (also known as FcεRIγ), FcRγ is currently recognized as a universal submit for multiple immunoreceptors. It severs as an essential signaling partner for Fc fragment of IgG receptor (FcγRI) (CD64), FcγRIII (CD16) and FcαRI (CD89), as well as for partner recognition receptors, including Dectin-1, Dectin-2 and the natural killer (NK) cell receptor NKp46 (2,3). Via its highly conserved intracellular immunoreceptor tyrosine-based activation motif (ITAM), FcRγ orchestrates canonical immune processes, including antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent phagocytosis (ADCP), antifungal defense and inflammatory modulation (4,5).

Accumulating evidence has established *FCER1G* as a central regulator linking immune signaling to disease pathogenesis. In inflammatory diseases, its expression is tightly controlled by epigenetic mechanisms. Functionally, the protein displays distinct context-dependent effects: It can exacerbate vascular inflammation by polarizing immune cells toward a pro inflammatory phenotype, while it also regulates

inflammatory intensity and promotes pathogen clearance during infection (6). This bidirectional regulation parallels mechanisms underlying tumor immune evasion, offering clues to its role in the tumor microenvironment (TME).

In oncology, *FCER1G* exhibits remarkable tissue-specific heterogeneity. Pan-cancer analyses show that its expression is elevated across numerous malignancies, primarily within monocyte and macrophage populations in the TME, and correlates strongly with immune checkpoint genes (1). In solid tumors such as renal cell carcinoma and gastric cancer, high *FCER1G* expression predicts poor prognosis by fostering an immunosuppressive microenvironment (7,8). Conversely, in hematologic malignancies such as multiple myeloma (MM) and in endometrial carcinoma, it may play a protective role (9,10). Mechanistically, *FCER1G* drives tumor progression by modulating immune suppression, promoting angiogenesis and regulating metastasis-related factors. It also influences the efficacy of antibody-based therapies through its role in antibody-dependent ADCC and ADCP.

Although no current drugs directly target *FCER1G*, several approved agents, such as kinase inhibitors, can indirectly modulate its activity by influencing upstream or downstream signaling nodes or altered ligand-receptor interactions, providing potential therapeutic opportunities (11). In summary, elucidating the mechanisms by which *FCER1G* governs inflammatory and oncogenic processes will deepen the current understanding of immune adaptor signaling in disease, and support the development of *FCER1G*-based biomarkers and targeted immunotherapies.

2. Molecular structure of *FCER1G*

The FcRγ protein encoded by *FCER1G* is a core component of the FcεRI complex (Fig. 1A). FcεRI exists as either a tetramer ($\alpha\beta\gamma_2$) or a trimer ($\alpha\gamma_2$). The FcεRIα chain contains two extracellular Ig-like domains that bind individual IgE molecules, thereby mediating IgE recognition (2). The FcεRIβ chain facilitates the maturation and trafficking of FcεRIα, and stabilizes the FcεRI complex on the cell surface (12). FcRγ is a small protein with a molecular weight of 15-20 kDa. Its extracellular domain is remarkably short, contains a conserved cysteine residue (Cys25) and forms homodimers via disulfide bonds, thereby constituting the essential signaling subunit of FcεRI (Fig. 1B) (2,13).

In addition to FcεRI, FcRγ also serves as an indispensable signaling adaptor for various Ig Fc receptors. These include the high-affinity IgG receptor FcγRI, involved in ADCP and ADCC, the low-affinity IgG receptor FcγRIII, which mediates ADCC in NK cells, and the IgA receptor FcαRI, a key regulator of neutrophil inflammatory responses. FcRγ further associates with pattern recognition receptors (PRRs) such as Dectin-1 and Dectin-2, as well as with the NK cell-activating receptor NKp46, playing a vital role in innate immune recognition.

3. Immunological function and signaling mechanisms of *FCER1G*

FcRγ is a crucial signaling adaptor protein within the immune system. It lacks intrinsic ligand-binding capacity, with its function entirely dependent upon a highly conserved ITAM within its intracellular domain. As a universal signaling subunit for multiple Ig Fc receptors (such as FcεRI and FcγR) and PRRs [such as C-type lectin receptors (CLRs)], FcRγ initiates downstream signaling cascades via its ITAM, thereby participating in regulating core immune processes, including allergic reactions, anti-infective immunity, and ADCC. Crucially, the biological effects of FcRγ are not uniform but exhibit distinct cell-type specificity. This specificity arises from its association with different receptors and the inherent differences in cellular signaling networks, enabling the same FcRγ-ITAM module to be programmed in diverse immune cells to execute differentiated functional programs.

Signal transduction and functional programming of FcRγ in different immune cells

Mast cells and basophils: FcεRI-mediated immediate hypersensitivity reactions. On the surfaces of mast cells and basophils, FcRγ constitutes the core component of the high-affinity IgE receptor FcεRI, forming a tetrameric ($\alpha\beta\gamma_2$) complex (14). Upon cross-linking of the receptor by an allergen-IgE complex, the ITAM of FcRγ rapidly recruits spleen tyrosine kinase (SYK), subsequently phosphorylating it. SYK-activated phospholipase Cγ (PLCγ) hydrolyses phosphatidylinositol bisphosphate to generate inositol trisphosphate (IP_3) and diacylglycerol (14,15). IP_3 subsequently induces intracellular calcium mobilization and extracellular calcium influx, triggering the rapid degranulation of stored mediators such as histamine and tryptamine, which are hallmarks of immediate-type allergic reactions (Fig. 2) (14,15). Knockout of the FCER1G gene prevents IgE-induced mast cell activation and allergic responses in mice (16). This research indicated that FcRγ protein stability is critical for its signaling function (16). For instance, the deubiquitinating enzyme USP5 stabilizes FcRγ by specifically removing K48-linked ubiquitin chains, thereby significantly enhancing IgE-induced mast cell activation and allergic inflammation, while inhibiting USP5 attenuates this process (17). This reveals that targeting FcRγ protein stability represents a novel pathway for regulating allergic responses.

Dendritic cells (DCs): Multireceptor-mediated antigen uptake and immune regulation. The function of FcRγ in DCs exhibits greater diversity and regulatory capacity than in mast cells and basophils, contingent upon the reprogramming of signals from the bound receptor complex FcεRI. The FcεRI expressed by DCs typically adopts a trimeric structure lacking the β chain ($\alpha\gamma_2$) (14). This structural difference leads to functional reprogramming, shifting from rapid effector responses towards antigen capture and presentation. In allergic diseases such as atopic dermatitis (AD), upregulation of FcεRI on cutaneous DCs enables efficient internalization of allergens upon IgE binding. These DCs then migrate to lymph nodes, primarily initiating T helper (Th)2-type immune responses, which is an important mechanism in conditions such as AD (14).

For CLRs lacking intracellular signaling domains, such as Dectin-2, FcRγ serves as an indispensable signaling partner. Upon recognizing fungal α-mannan, Dectin-2 activates SYK via the ITAM of FcRγ (18,19). This subsequently activates the NF-κB pathway through the CARD9-BCL10-MALT1

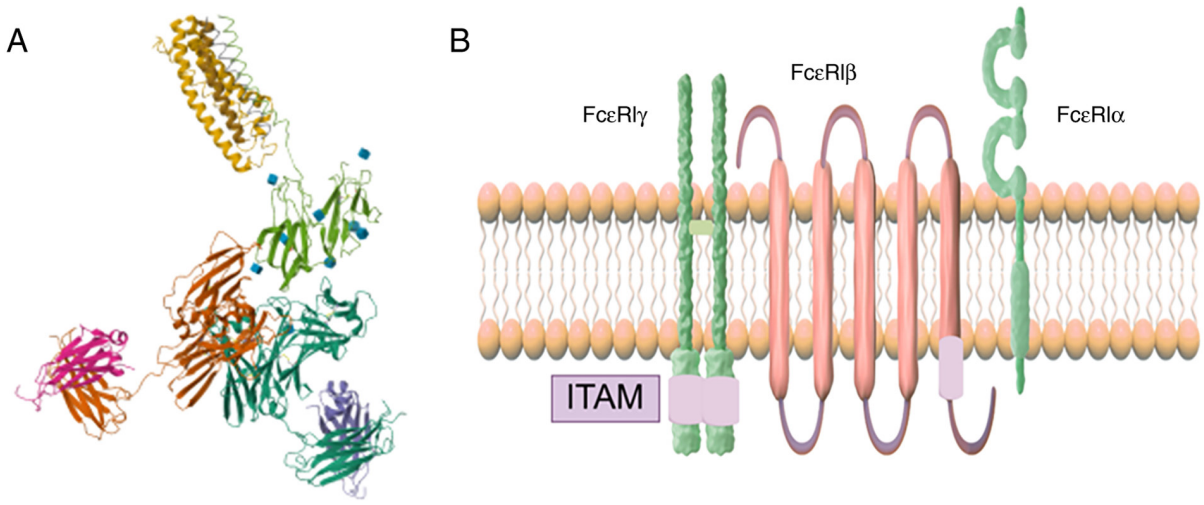

Figure 1. Protein structure of FCER1G and FcεRI schematic structure. (A) Protein structure of *FCER1G* [source: GeneCards database (https://www.genecards.org/)]. In the figure, blackish-brown represents the FcRγ subunit; bronze-gold represents the FcεRIβ subunit; green represents the FcεRIα subunit; brown represents the immunoglobulin heavy constant epsilon; and pink and bluish-purple represent the immunoglobulin kappa region. (B) Structural diagram of the FcεRI receptor. The FcεRIα chain binds individual IgE molecules, thereby mediating for IgE recognition. The FcεRIβ chain facilitates the maturation and trafficking of FcεRIα and stabilizes the FcεRI complex on the cell surface. FcRγ contains an ITAM motif; two molecules of FcRγ assemble with FcεRIα and FcεRIβ chains to form a complete tetrameric high-affinity IgE receptor. The figure was drawn with FigDraw2.0 (supplied by Hangzhou Sifei Technology Co., Ltd.). FCER1G, Fc fragment of IgE receptor 1G; FcεRI, Fc ε receptor I; ITAM, immunoreceptor tyrosine-based activation motif.

junction complex, driving cytokine production (including IL-6 and IL-23) and promoting Th17 differentiation (Fig. 2) (18,19). This is a critical component of antifungal immunity.

Previous research indicates that FcRγ also exerts negative regulatory effects on DCs. For instance, upon binding to Dectin-1 bearing a semi-ITAM, it may attenuate signal output by recruiting phosphatases such as SHP-1 and PTEN (16). This finely tunes DC maturation and cytokine production, preventing excessive inflammation (Fig. 2). This demonstrates that FcRγ in DCs functions not only as a transmitter of activation signals but also as a precise regulator of immune responses.

NK cells: CD16A (FcγRIIIA) signaling and antibody-dependent cytotoxicity. Within NK cells, FcRγ primarily functions as the signal-adaptor subunit for the low-affinity IgG receptor CD16A (FcγRIIIa). Their binding is essential for the stable expression and functional activity of this receptor on the cell surface. Upon NK cell recognition of tumor cells coated with antibodies (namely therapeutic monoclonal antibodies) via CD16A, phosphorylation of the ITAM recruits and activates SYK. Signaling in NK cells predominantly activates the SYK/PI3K-δ/MAPK axis (20). This pathway drives cytoskeletal reorganization as well as polarization and release of cytotoxic granules-a process involving the directed trafficking of perforin- and granzyme-containing vesicles toward the immune synapse - and promotes IFN-γ production, thereby efficiently executing ADCC (Fig. 2) (20). This constitutes a key mechanism underpinning the efficacy of numerous antibody therapeutics. This study indicates that de-fucosylated antibodies, by enhancing CD16A binding, significantly amplify downstream signaling through SYK/PI3K/MAPK and other pathways, thereby enhancing ADCC efficiency (4). Consequently, the functional state of *FCER1G* directly influences the efficacy of monoclonal antibody-based tumor immunotherapies.

Macrophages: Integrated signaling regulates phagocytosis, polarization and inflammatory balance. The function of FcRγ in macrophages integrates effector and regulatory roles, reflecting their immunological multifunctionality. As a signal-transducing subunit of receptors such as FcγRI (CD64), FcγRγ plays a pivotal role in mediating ADCP. Following immune complex cross-linking of FcγR, SYK activated by FcRγ-ITAM synergistically initiates multiple downstream pathways, including PLCγ, PI3K and MAPK (5). These collectively regulate actin remodeling, phagosome maturation and reactive oxygen species production, which is essential for phagocytosis, thereby efficiently eliminating antibody-coated targets (Fig. 2) (5).

Regarding bidirectional regulation of inflammatory phenotype and function, FcRγ signaling serves as a pivotal node in modulating macrophage polarization and inflammatory homeostasis. For instance, in atherosclerosis models, immune complexes activate FcγR to drive macrophage polarization towards a pro-inflammatory M1-like phenotype (21). This activates the NF-κB pathway, and leads to substantial release of inflammatory mediators such as TNF-α and IL-6, exacerbating plaque instability and vascular inflammation (21). Conversely, *FCER1G* deficiency predisposes macrophages towards an anti-inflammatory M2-like phenotype, mitigating disease progression (21). This demonstrates the pivotal role of FcRγ in determining macrophage functional output.

Other cell types and functions. FcRγ also participates in other immune processes, such as acting as a co-signaling chain for the collagen receptor GPVI in platelets to mediate thrombosis, and stabilizing cell surface receptors in type 3 innate lymphoid cells (ILC3s) to promote IL-22 production to combat infections (22,23). Its extensive involvement further underscores its importance as a universal ITAM-binding adaptor protein. FcRγ also functions as a signaling partner for myeloid receptors such as OSCAR and TREM-1, playing

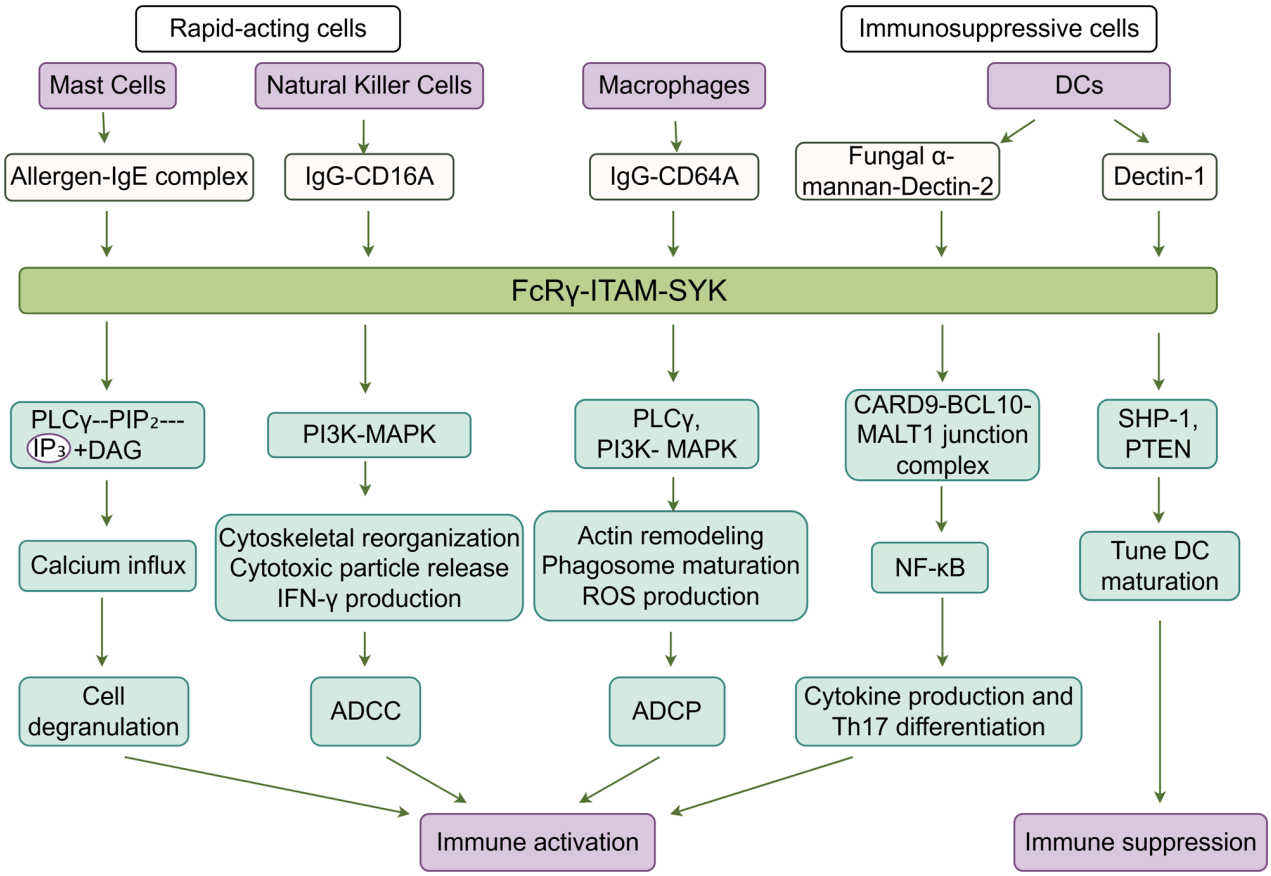

Figure 2. Divergent intracellular signaling and functional mechanism mediated by FcRγ in different innate immune cells. Upon engagement of distinct ligand-receptor complexes (allergen-IgE complex, fungal α-mannan-Dectin-2, IgG-CD16A, IgG-CD64A), signaling is initiated via the associated FcRγ subunit, and phosphorylation of its ITAM recruits and activates SYK. This common initiating module then diverges into cell-type-specific downstream pathways, leading to distinct functional outputs in mast cells, natural killer cells, DCs and macrophages. The figure was drawn with FigDraw2.0 (supplied by Hangzhou Sifei Technology Co., Ltd.). FcR, Fc receptor; ITAM, immunoreceptor tyrosine-based activation motif; SYK, spleen tyrosine kinase; PLCγ, phospholipase Cγ; PIP_2, phosphatidylinositol bisphosphate; IP_3, inositol trisphosphate; DAG, diacylglycerol; DC, dendritic cell; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent phagocytosis; Th, T helper; ROS, reactive oxygen species.

roles in several processes such as osteoclast differentiation and inflammatory amplification (24,25).

Common mechanisms and differentiation basis of FcRγ signaling. Despite varying functions across different cell types, the molecular mechanisms initiating FcRγ signaling remain highly conserved. Ligand-induced receptor clustering leads to mutual phosphorylation and activation of adjacent Src family kinases, which subsequently phosphorylate two tyrosine residues on the FcRγ-ITAM. The doubly phosphorylated ITAM recruits and activates SYK with high affinity, establishing SYK as the central hub for downstream signal differentiation (13,26).

From SYK, signals diverge into at least three primary pathways, with cells selectively amplifying specific pathways according to their functional predisposition: i) The PLCγ/Ca^{2+} pathway, which drives rapid degranulation responses in effector cells such as mast cells; ii) the PI3K/MAPK pathway, which predominantly governs ADCC/ADCP, cell migration, cell proliferation, and partial cytokine synthesis in NK cells and macrophages; and iii) the CARD9/NF-κB pathway, which predominantly governs transcriptional activation of pro-inflammatory cytokines and chemokines in DCs, macrophages and other cells following pathogen recognition via CLRs.

Therefore, FcRγ functions as a universal signaling molecule, receiving initial signals from upstream receptor clusters via its ITAM module and subsequently diverting these signals through SYK. Its ultimate functional output is co-programmed by the specific receptor it binds to and the downstream signaling network preferences dictated by the host cell type. This characteristic of 'common mechanism, differential programming' provides the molecular basis for understanding how FcRγ serves distinct roles across diverse pathological contexts, including allergy, infection, autoimmunity and even tumorigenesis, while also offering a logical explanation for its paradoxical dual function within the TME.

4. Immunoregulatory role of *FCER1G* in inflammatory diseases

Previous studies have revealed the multifaceted pathological roles of the innate immunity-related *FCER1G* gene. In non-neoplastic diseases, this gene contributes to the pathogenesis of inflammatory disorders such as eczema and AD (27-31).

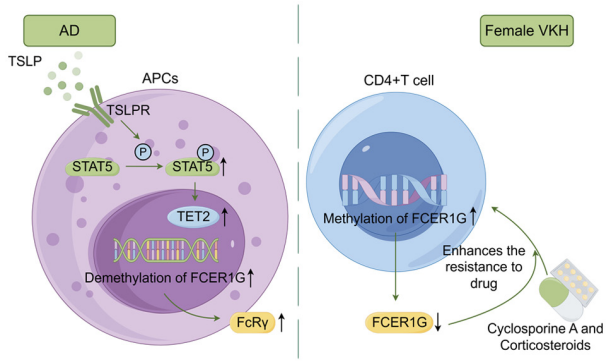

Figure 3. Examples of epigenetic regulation of FCER1G in inflammatory diseases. In AD, the cytokine TSLP induces active demethylation of FCER1G by activating STAT5 and recruiting the demethylase TET2 to the FCER1G promoter region, thereby upregulating FCER1G expression and exacerbating allergic responses. In female patients with Vogt-Koyanagi-Harada disease, hypermethylation of the FCER1G promoter region in $CD4^+$ T cells leads to gene silencing and is associated with glucocorticoid resistance. The figure was drawn with FigDraw2.0 (supplied by Hangzhou Sifei Technology Co., Ltd.). FCER1G, Fc fragment of IgE receptor 1G; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor; AD, atopic dermatitis; TET2, ten-eleven translocation 2; STAT5, signal transducer and activator of transcription 5; APCs, antigen-presenting cells; FcRγ, Fc receptor common γ chain; p, phosphorylation.

Multilayered epigenetic regulation of FCER1G expression. The expression of *FCER1G* undergoes intricate and multilevel epigenetic regulation, forming a crucial molecular basis for its abnormal expression and functional plasticity in disease. In inflammatory conditions, DNA methylation emerges as a central regulatory mechanism controlling its expression, offering a relatively clear framework for understanding its functional regulation (Fig. 3).

Dynamic regulation of DNA methylation/demethylation. DNA methylation constitutes a core epigenetic mechanism in the regulation of *FCER1G* expression. Previous studies have shown a significant inverse correlation between the methylation status of CpG islands in the *FCER1G* promoter region and its expression levels (28,32-35). In patients with AD, monocytes exhibit specific hypomethylation of the *FCER1G* promoter, which directly upregulates its mRNA and protein levels. This consequently causes overexpression of receptors such as FcεRI on antigen-presenting cell (APC) surfaces, exacerbating allergic reactions (28). This causal association has been directly validated by patch methylation combined with luciferase reporter assays (28,36).

In rheumatoid arthritis, *FCER1G* also displays a pattern of high expression associated with hypomethylation (33,34). Similarly, in female patients with Vogt-Koyanagi-Harada disease, hypermethylation of the *FCER1G* promoter in $CD4^+$ T cells silences its expression, enhancing patient resistance to cyclosporine A and corticosteroids (32). This suggests that intervention targeting the methylation status of the *FCER1G* promoter may represent a potential therapeutic sensitization strategy.

Synergistic interaction between key transcription factors and demethylases: The demethylation of *FCER1G* is driven by specific cytokine signals through an active mechanism involving transcription factor-mediated recruitment of DNA demethylases. Within the pathological environment of AD, thymic stromal lymphopoietin (TSLP) produced by epithelial cells serves as the key driver. TSLP activates its receptor, leading to signal transduction and the phosphorylation of signal transducer and activator of transcription 5 (STAT5) (29,37). Activated phosphorylated (p)-STAT5, acting as a transcription factor, is recruited to the FCER1G promoter region, simultaneously recruiting the DNA demethylase ten-eleven-translocation 2 (TET2), which catalyzes the conversion of 5-methylcytosine to 5-hydroxymethylcytosine, thereby initiating an active demethylation program that relieves the transcriptional repression of *FCER1G* (29,37). This TSLP/p-STAT5/TET2 axis forms a coherent epigenetic reprogramming pathway, explaining the epigenetic basis for the sustained high expression of *FCER1G* in AD.

Regulation through chromatin plasticity by transcription factors. In addition to the aforementioned core mechanisms, the regulation of chromatin plasticity by specific transcription factors also contributes to the control of *FCER1G* expression. For instance, in hematopoietic stem cells (HSCs), the transcription factor Bcl11a directly represses *FCER1G* transcription by suppressing chromatin accessibility at its promoter region, a process that is critical for maintaining HSC quiescence (38). This mechanism illustrates how transcription factors can precisely control *FCER1G* expression at the epigenetic level by modifying chromatin architecture.

The aforementioned complex epigenetic regulatory mechanisms determine that *FCER1G* expression exhibits a high degree of microenvironmental dependency and dynamic plasticity. This characteristic enables it to perform differentiated roles across distinct pathological contexts, where both its expression levels and functional outputs (pro-inflammatory or anti-inflammatory) must be interpreted within specific diseases (39-41).

Context-dependent regulation of FcRγ in anti-infection immunity. In anti-infection immunity, the FcRγ exhibits a dual function, with its presence or absence influencing pathogen clearance and host prognosis differently across various infection models, thus profoundly demonstrating its context-dependent nature. In a chronic lymphocytic choroid plexus meningitis virus infection model, FcRγ expressed in NK cells delays pathogen clearance by suppressing virus-specific $CD8^+$ T-cell responses (6). In addition, deletion of FcRγ significantly reduces mortality in mouse models of sepsis induced by lipopolysaccharide or *Escherichia coli*, which is characterized by lower serum levels of TNF-α, IL-6 and IL-10 (39). These models suggest that, under certain circumstances, FcRγ-mediated signaling may prove detrimental to infection control or host survival by promoting excessive inflammation or suppressing adaptive immunity. However, in other infection models, FcRγ plays an indispensable role in defensive mechanisms. Conversely, the absence of FcRγ in ILC3s impairs JAK-STAT pathway activation and reduces IL-22 and IL-17A secretion, thereby increasing mortality during fungal infection (22). Similarly, during *Pneumocystis* pneumonia, FcRγ deficiency decreases the production of inflammatory cytokines (TNF-α, IL-6 and IL-1β) but compromises pathogen clearance efficiency (40). This indicates that FcRγ-mediated immune responses are essential for the effective clearance of the aforementioned pathogens.

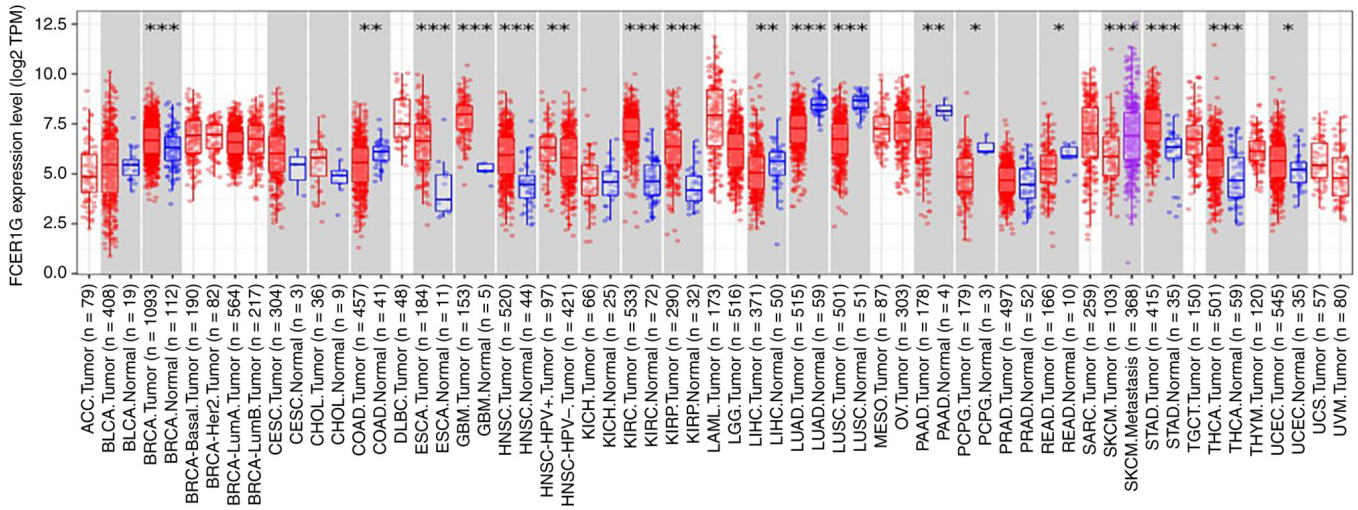

Figure 4. Expression of *FCER1G* across 33 cancer tissue types and 21 paired normal tissues based on the TIMER2.0 database (*P<0.05, **P<0.01 and ***P<0.001). The figure was from the TIMER2.0 database (https://compbio.cn/timer2/). FCER1G, Fc fragment of IgE receptor 1G; TPM, transcripts per million. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, Kidney Renal Papillary Cell Carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAP, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma.

The dual outcomes of FcRγ during infection (beneficial or detrimental) are likely determined by two major factors. On the one hand, the type of pathogen and the nature of the infection are critical. For intracellular chronic viruses (such as lymphocytic choriomeningitis virus) or systemic bacterial toxins (sepsis), excessive inflammation or inappropriate immune regulation may lead to immunopathology or tissue damage, where FcRγ activity often contributes to detrimental outcomes. Conversely, combating certain fungi and opportunistic pathogens (such as *Pneumocystis*) necessitates FcRγ-dependent rapid initiation of innate immune effector programs in specific cells (namely ILC3s), where its function is beneficial. On the other hand, maybe the dominant immune cells and effector mechanisms govern the response. FcRγ's function is entirely dependent on its cellular environment. In NK cells, it may modulate immune crosstalk, occasionally suppressing T cell function, whereas, in ILC3s, it directly stimulates antimicrobial cytokine production. Thus, the cell type dictates whether FcRγ-mediated signaling leads to inhibitory regulation or effector activation.

In summary, the presence of FcRγ is not inherently positive or negative in infectious immunity. Instead, its value depends on the immune equilibrium set by the specific infection microenvironment. FcRγ dynamically modulates the intensity and quality of immune responses by influencing two critical balances: i) Pro-inflammation vs. anti-inflammation and ii) immune activation vs. suppression. This capacity for flexible role-switching in response to microenvironmental signals and precise regulation of immune balance bears striking similarity to the functional plasticity of immune checkpoint molecules within the TME, and provides a core logical framework for understanding the complex role of *FCER1G* in tumor immunity.

5. Expression of *FCER1G* in tumors

Pan-cancer expression profile and characteristics associated with the immune microenvironment. Pan-cancer analysis based on the TIMER 2.0 database (https://compbio.cn/timer2/) shows that FCER1G is significantly upregulated in 9 types of malignant tumor compared with normal tissues (Fig. 4). These include esophageal carcinoma, glioblastoma multiforme (GBM), head and neck squamous cell carcinoma, kidney clear cell carcinoma, kidney papillary cell carcinoma, stomach adenocarcinoma (STAD) and thyroid carcinoma. Gene enrichment analyses further reveal that FCER1G is predominantly involved in cell proliferation-related pathways across multiple tumor types, particularly STAD, TGCT, acute myeloid leukemia and GBM (P<0.05, false discovery rate <0.25) (41). Furthermore, FCER1G expression positively correlates with >50% of immune checkpoint genes, suggesting that it functions as a hub regulator within the tumor immunoregulatory network (41). Single-cell transcriptomic data from the TISCH database indicate that FCER1G is preferentially expressed in monocyte/macrophage populations within the TME across ~85% of the tumors analyzed, thus providing cellular-level evidence for its involvement in TME remodeling.

Dual nature of tissue-specific expression patterns and prognostic value

FCER1G expression correlates with poor prognosis in tumors. Comprehensive analysis indicates that *FCER1G* is

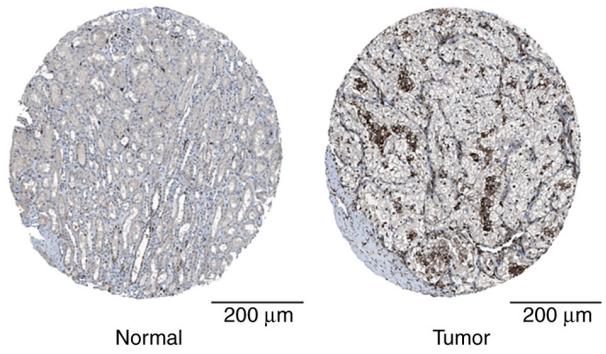

Figure 5. *FCER1G* protein is highly expressed in ccRCC tissues. Immunohistochemical staining from the Human Protein Atlas database revealed significantly elevated FCER1G expression in ccRCC tissue compared with that in normal renal tissue (increased staining intensity and proportion of positive cells). The normal kidney sample corresponds to a 16-year-old male donor (sample ID, 1,767; staining, medium; intensity, low; quantity of FCER1G-positive cells <25%; location of FCER1G protein, nuclear), while the renal cancer sample corresponds to a 70-year-old female patient with ccRCC (sample ID, 1,498; staining, medium; intensity, medium; quantity of FCER1G-positive cells >75%; location of FCER1G protein, nuclear). This figure is from the public database HPA (Human Protein Atlas), for which patient consent for publication is not required in accordance with the database's usage guidelines (https://www.proteinatlas.org/). Scale bar, 200 μm. FCER1G, Fc fragment of IgE receptor 1G; ccRCC, clear cell renal cell carcinoma.

highly expressed in multiple solid tumors, including clear cell renal cell carcinoma (ccRCC) (presented as KIRC in Fig. 4), esophageal squamous cell carcinoma (ESCC) (included within the esophageal cancer group when presented in Fig. 4) and STAD (7,8,42) (Fig. 4). Its expression is predominantly enriched in myeloid immune cells, where it promotes the formation of an immunosuppressive microenvironment, thereby contributing to poor prognosis.

Data from the Human Protein Atlas (HPA) show markedly stronger immunohistochemical staining of *FCER1G* in renal carcinoma tissues than in adjacent normal tissues (Fig. 5). According to Wang *et al* (7), analysis of the ONCOMINE database and three validation datasets identified significantly elevated *FCER1G* expression in ccRCC, where high expression correlated with reduced overall survival (OS). Similarly, Dong *et al* (43) observed that, in ccRCC, *FCER1G* expression exhibited a strong correlation with *CD68* and co-localization with macrophages. Their concurrent overexpression portends an unfavorable prognosis. Joint assessment of *FCER1G* and *CD68* expression levels can optimize prognostic stratification models for patients. Furthermore, gene set enrichment analysis revealed that high *FCER1G* expression is associated with suppression of T-cell activation and proliferation (43). *FCER1G* shows moderate diagnostic accuracy (area under the curve, 0.74) in distinguishing localized (stage I/II) from advanced (stage III/IV) ccRCC, and functions as an independent prognostic biomarker (44).

In ESCC, *FCER1G* is predominantly enriched within the tumor stroma. Double immunofluorescence staining clearly demonstrates that *FCER1G*-positive cells highly co-express the M2 macrophage marker *CD163*, meaning that the majority of infiltrating M2 macrophages simultaneously express *FCER1G* (42). The infiltration density of these *FCER1G*$^+$ M2 macrophages correlates directly with worse prognosis, and *FCER1G* itself constitutes an independent risk factor affecting patients' OS (42). In STAD, analyses from multiple transcriptomic cohorts (The Cancer Genome Atlas, GSE13195 and GSE15459) consistently showed higher *FCER1G* expression in tumor tissues than in adjacent normal tissues (8,41,45). Its overexpression is linked to poorer OS and increased infiltration of M2 macrophages (8). Furthermore, *FCER1G* expression progressively increases with advancing tumor stage, suggesting a dynamic upregulation trend during tumor progression. This finding, similar to that observed for ESCC, suggests that *FCER1G* may be primarily expressed in M2-type tumor-associated macrophages (TAMs) within STAD and participate in shaping the immunosuppressive microenvironment.

Additionally, in gliomas, diffuse large B-cell lymphoma, bladder cancer and papillary thyroid carcinoma, *FCER1G* acts as a progression-associated gene, where high expression of *FCER1G* correlates with aggressive tumor behavior, poor prognosis and distinct immune infiltration patterns (11,46-51). In osteosarcoma, a dual-gene risk model incorporating *FCER1G* and SPI1, developed based on Cox regression analysis, holds independent prognostic significance. Patients in the low-expression group for this signature exhibit an immunosuppressive microenvironment, worse clinical outcomes and a higher risk of metastasis, highlighting the potential of *FCER1G* as a prognostic biomarker and immunotherapeutic target (52). It is noteworthy that bioinformatics analysis suggests that *FCER1G* may be a hypermethylated gene in osteosarcoma, offering a potential epigenetic hypothesis to explain its low expression in this tumor type. However, the precise regulatory mechanisms require experimental validation (35).

In summary, *FCER1G* is highly expressed in multiple solid tumors, including ccRCC, ESCC, STAD and glioma. By promoting M2 macrophage infiltration and shaping an immunosuppressive TME, it contributes to tumor progression and serves as a consistent indicator of poor prognosis across various cancer types (Table I).

FCER1G correlates with favorable patient prognosis. In contrast to its generally pro-tumor pattern, *FCER1G* displays a protective role in certain malignancies, where high expression is associated with prolonged survival and enhanced immune activation. In MM, analyses of several datasets (including GSE39754, GSE5900 and GSE2113) reveal a progressive decline in *FCER1G* expression with disease advancement (9,53). Multivariate Cox regression analysis identifies high *FCER1G* expression as an independent predictor of both event-free survival and OS, establishing it as a favorable prognostic biomarker in MM (9). Furthermore, *FCER1G* overexpression correlates with NK cell-mediated cytotoxic pathways (9). Notably, previous research has identified a functionally distinct FcεRIγ$^-$ NK cell subset (termed g-NK cells) (54). Compared to conventional NK cells, these cells exhibit enhanced ADCC following CD16 cross-linking and significantly amplify the efficacy of monoclonal antibodies such as daratumumab in preclinical models (54). This offers a novel perspective on the association between *FCER1G* expression in MM, NK cell function and favorable prognosis. Similarly, in uterine corpus endometrial carcinoma (UCEC), high *FCER1G* expression predicts improved prognosis,

Table I. Expression patterns, cellular types, prognostic correlations and immune microenvironment characteristics of FCER1G in different tumors.

Tumor	*FCER1G* expression	Prognosis	Primary cell types expressing *FCER1G*	Key associated immune cells/ pathways
ccRCC	Upregulated	Poor	Tumor-associated macrophages	Co-expressed with CD68, associated with suppression of T-cell activation
ESCC	Upregulated	Poor	M2 macrophages	Positively correlated with $CD163^+$ M2 macrophage infiltration
STAD	Upregulated	Poor	Hematopoietic immune cells (such as macrophages)	Associated with enhanced M2 macrophage infiltration
MM	Downregulated	Favorable	NK and other effector immune cells	Associated with NK cell-mediated cytotoxicity pathway
UCEC	Downregulated	Favorable	Multiple immune cells (including B, $CD8^+$ T and dendritic cells)	Associated with increased infiltration of B, $CD8^+$ T and other cells

FCER1G, Fc fragment of IgE receptor 1G; ccRCC, clear cell renal cell carcinoma; ESCC, esophageal squamous cell carcinoma; STAD, stomach adenocarcinoma; MM, multiple myeloma; UCEC, uterine corpus endometrial carcinoma; NK, natural killer.

and correlates with increased infiltration of immune cells, including B cells, $CD8^+$ T cells and DCs (Table I) (10).

In lung adenocarcinoma (LUAD), *FCER1G* expression exhibits stage-specific dynamics, being downregulated in early stages and restored at advanced stages (55). Network analyses further indicate that *FCER1G* consistently functions as an immune regulatory hub throughout LUAD progression, and that its functional loss impairs antitumor immune activity (55).

Overall, the prognostic significance of *FCER1G* shows clear tumor-type specificity.

In malignancies such as MM and UCEC, as well as in specific stages of LUAD, elevated FCER1G expression is not associated with tumor promotion. Instead, it may exert a protective effect by sustaining or activating antitumor immune responses, ultimately predicting more favorable clinical outcomes (Table I).

Contradictory prognostic value of FCER1G arises from heterogeneity in the TME. In summary, the prognostic value of *FCER1G* exhibits marked inconsistencies, fundamentally stemming from the cellular types expressing *FCER1G*, which determine the nature of the specific, coordinated immune processes in which it participates (Fig. 6).

Regarding its expression in immunosuppressive myeloid cells (pro-tumor function), in solid tumors such as ccRCC and ESCC, *FCER1G* is primarily expressed in M2-type TAMs. These cells shape an immunosuppressive TME by secreting immunosuppressive factors (such as IL-10 and TGF-β), depleting T cells and promoting angiogenesis. This drives tumor progression and immune evasion, leading to poor prognosis (42,43). Regarding its expression in cytotoxic cells or APCs (antitumor function), in tumors such as MM and UCEC, high expression of *FCER1G* correlates with the active state of effector cells or APCs, including DC, and NK, cytotoxic T and B cells. In this context, *FCER1G* functions as a signaling adaptor for activation receptors (CD16A) on these cells, participating in the initiation of antitumor immune responses such as ADCC and T-cell activation, thereby correlating with favorable prognosis (9,10,41).

Therefore, assessing the clinical relevance of *FCER1G* necessitates moving beyond mere expression levels to deeply analyze its cellular localization and the associated functional state of the overall immune microenvironment. This cellular context determinism lies at the core of understanding its complexity as a biomarker.

Core mechanisms driving tumor progression and immune remodeling

Regulation of immune microenvironment structure and function. *FCER1G* exhibits distinct immunoregulatory patterns across different tumor types. In STAD, its expression correlates positively with the infiltration of M1/M2 macrophages, quiescent mast cells and DCs, but negatively with plasma and $CD8^+$ T cells (45). This opposing infiltration pattern indicates that *FCER1G* may facilitate tumor progression by reshaping an immunosuppressive immune microenvironment. In glioma, *FCER1G* expression is strongly associated with the infiltration of T cells, macrophages and B cells, further implicating it in disease progression and immune landscape remodeling (47). Notably, previous single-cell RNA sequencing studies have identified a tumor-specific, innate-like cytotoxic T-cell subset characterized by $FCER1G^+$ $\alpha\beta TCR^+$ cells (56,57). *FCER1G* serves as a definitive lineage marker for this population. Unlike conventional tumor-reactive T cells, these cells recognize unmutated self-antigens presented by MHC-I molecules rather than tumor-derived neoantigens. Their intratumoral activation and effector functions depend strictly on the IL-15 signaling axis, underscoring a unique *FCER1G*-mediated mechanism of cytotoxic immune regulation within the TME (56,57).

This identification implies that *FCER1G* is not merely a participant in immunosuppression but also acts as a phenotypic identity tag for specific antitumor immune cell subsets, highlighting its multifaceted roles within the TME. Collectively, the evidence suggests that *FCER1G* possesses dual regulatory properties. It can promote immunosuppressive phenotypes in

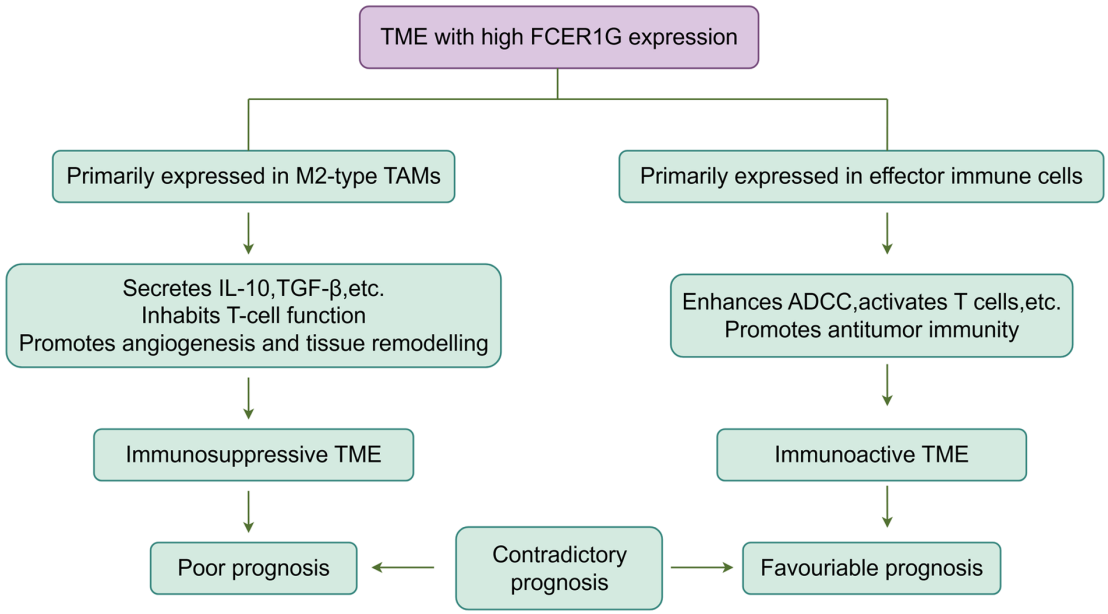

Figure 6. Schematic diagram of the cytological basis for *FCER1G* prognostic paradox. The dual prognostic value of *FCER1G* is clearly demonstrated to depend on the cellular context in which it is expressed. Left pathway: When *FCER1G* is highly expressed in M2 TAMs, it promotes an immunosuppressive microenvironment, leading to poor prognosis. Right pathway: When *FCER1G* is highly expressed in effector immune cells such as natural killer cells, it enhances the antitumor immune response, which is associated with favorable prognosis. The figure was drawn with FigDraw2.0 (supplied by Hangzhou Sifei Technology Co., Ltd.). FCER1G, Fc fragment of IgE receptor 1G; TME, tumor microenvironment; TAMs, tumor-associated macrophages; ADCC, antibody-dependent cellular cytotoxicity.

certain contexts while also functioning as a key regulatory node for antitumor responses in distinct immune populations. Dysregulation of its expression or signaling may therefore disrupt immune homeostasis and drive the pathological remodeling of the TME.

Supporting its functional relevance, analyses of the Gene Expression Profiling Interactive Analysis and HPA databases showed that *FCER1G* expression is significantly higher in PAAD tissues than in normal tissues at both the mRNA and protein levels. In animal models, FcRγ-deficient [*FCER1G*$^{-/-}$, FcRγ knockout (KO)] mice bearing pancreatic ductal adenocarcinoma exhibit reduced tumor growth and attenuated desmoplasia, accompanied by a complete loss of FcγRI/III expression within tumors (58). These findings indicate that *FCER1G* likely modulates the TME and drives malignant progression through the regulation of Fc receptor-mediated signaling pathways.

Promotion of angiogenesis. Andreu *et al* (59), using an HPV16^{+}/FcRγ$^{-/-}$ mouse model, revealed a key role for FcRγ in tumorigenesis. Compared with wild-type (WT) mice, FcRγ KO mice showed a lower incidence of SCC. This effect was associated with inhibited angiogenesis and decreased expression of major oncogenic factors, including vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) (59). Further experiments demonstrated that mast cells and macrophages promote endothelial cell migration via FcRγ-dependent pathways, thereby enhancing the *in vivo* tumorigenicity of the PDSC5 SCC cell line (59). Collectively, these findings indicate that FcRγ promotes tumor angiogenesis by mediating interactions between immune and stromal cells within the TME.

Promotion of tumor metastasis. The expression status of *FCER1G* is frequently implicated in tumor metastasis, although its effects vary among cancer types. In hepatocellular carcinoma (HCC), *FCER1G* shows a downregulated trend, and its low expression is associated with the activation of apoptotic and ferroptotic pathways (60). Previous *in vitro* experiments have shown that silencing FCER1G enhances the proliferation and migration of HCC cells by upregulating Snail1, TWIST1 and N-cadherin while suppressing E-cadherin expression (60). These results suggest that *FCER1G* may restrain HCC invasiveness by modulating epithelial-mesenchymal transition (EMT) processes.

In malignant melanoma (MEL), the role of FcRγ exhibits a more intricate profile, characterized by context-dependent effects. On the one hand, lung metastasis can be suppressed by treatment with the monoclonal antibody TA99 or intravenous Ig (IVIG) (61,62). This antimetastatic effect depends entirely on FcRγ, as it is abolished in FcRγ KO mice, indicating that ADCC serves as a key mechanism. On the other hand, FcRγ deficiency itself exerts dual and opposing effects on metastasis (Fig. 7). Specifically, the absence of FcRγ enhances platelet adhesion to circulating tumor cells, and stimulates platelets to release the chemokines C-X-C motif chemokine ligand (CXCL)5 and CXCL7. This cascade promotes neutrophil recruitment to lung tissue and creates a pro-transfer microenvironment that accelerates lung metastasis without affecting primary tumor growth (3).

Furthermore, FcRγ KO impairs CD244-mediated inhibitory signaling during NK cell development, leading to diminished NK cell function (63). This defect can be reversed by treatment with IL-2 or IL-15, which upregulates activation receptors [natural killer cell group 2 (NKG2)D and DNAX accessory molecule-1] and downregulates inhibitory receptors (LY49 and NKG2A), thereby restoring NK cell cytotoxicity and suppressing metastasis (63). Therefore, therapeutic strategies aimed at modulating

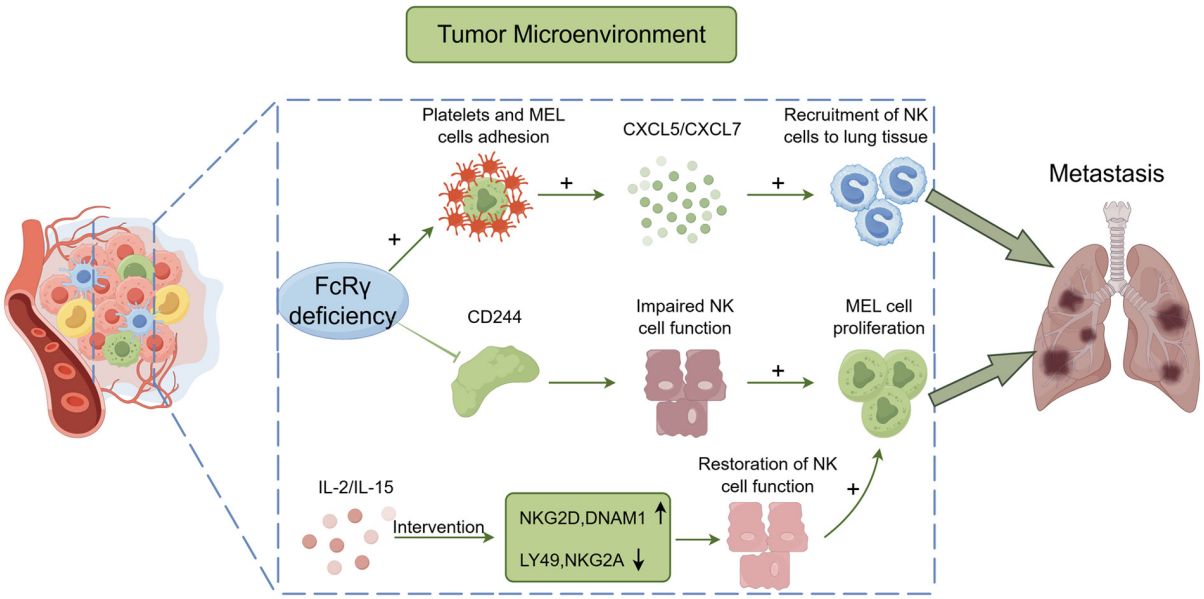

Figure 7. Two mechanisms by which FcRγ deficiency promotes tumor lung metastasis in MEL: i) Enhances adhesion between platelets and circulating tumor cells, inducing platelets to release chemokines CXCL5/7 to recruit neutrophils and establish a pre-metastatic microenvironment; and ii) reduces the expression of CD244, a key maturation molecule for NK cells, thereby impairing NK cell function. The figure was drawn with FigDraw2.0 (supplied by Hangzhou Sifei Technology Co., Ltd.). MEL, malignant melanoma; NK, natural killer; FcRγ, Fc receptor common γ chain; CXCL, C-X-C motif chemokine ligand; NKG2, natural killer cell group 2; LY49, Lymphocyte Antigen 49 Complex; DNAM-1, DNAX Accessory Molecule-1.

FcRγ signaling must carefully balance the benefits of enhancing antibody-dependent tumor clearance against the potential risk of facilitating metastatic dissemination.

FcRγ-dependent therapeutic responses and resistance mechanisms

Essential role of the FcγRI/III signaling pathway. FcRγ serves as a critical molecular determinant for the efficacy of multiple antibody-based therapies. In colorectal cancer (CRC), *FCER1G* expression is paradoxically higher in adjacent non-tumorous tissues than in tumor tissues (64). Within this setting, IVIG treatment fails to produce antitumor effects in FcRγ KO mice. Mechanistically, the therapeutic activity of IVIG depends on FcγRI/III signaling, which drives the reprogramming of TAMs from an M2-like, pro-tumor state toward an M1-like, antitumor phenotype (64).

In adult T-cell leukemia/lymphoma (ATL) models, anti-CD2 monoclonal antibody MEDI-507 and anti-CD25 monoclonal antibodies significantly suppress tumor progression and prolong survival, with their efficacy strictly dependent on FcRγ (65,66). Specifically, polymorphonuclear leukocytes and monocytes eliminate $CD2^+/CD25^+$ tumor cells through FcγRIII-mediated ADCC (65,66). The absence of FcRγ disrupts this pathway, resulting in therapeutic resistance despite normal antibody pharmacokinetics.

It is noteworthy that not all antibody therapies rely on FcγR signaling. In anaplastic large-cell lymphoma (ALCL), the anti-CD30 monoclonal antibody HeFi-1 suppresses tumor growth primarily by inducing G_1-phase cell-cycle arrest, thereby exerting its antitumor effect independently of FcγRIII expression (67).

In general, these findings underscore a crucial principle: For a broad range of antibody therapies targeting tumors such as CRC and ATL, the FcγRI/III signaling pathway represents an indispensable axis for antitumor efficacy. This pathway mediates the key effector functions of myeloid cells, including macrophages and neutrophils, in achieving therapeutic success.

Impact of drug intervention on the prognostic value of FCER1G. The prognostic importance of *FCER1G* in ccRCC appears to be treatment specific. It shows strong prognostic value in patients treated with the anti-PD-1 antibody nivolumab, but not in those receiving the mTOR inhibitor everolimus (43). This treatment-specific difference may reflect the regulatory role of *FCER1G* in modulating responses to immune checkpoint inhibitors such as nivolumab, whereas its association with mTOR pathway-targeted therapies appears to be relatively weak (41). Furthermore, pharmacological interventions can dynamically influence the immunoregulatory activity of FcRγ. For instance, peripheral blood NK cells from lung transplant recipients treated with rapamycin (an mTOR inhibitor) exhibit markedly reduced FcRγ expression. This observation suggests that drug-induced modulation of FcRγ may indirectly affect immune homeostasis and therapeutic outcomes (68).

6. Existing drugs indirectly regulating *FCER1G*-related pathways

Despite the pivotal role of *FCER1G* in multiple tumor immune microenvironments, no clinical drugs directly targeting this molecule currently exist. Through an integrated analysis of the DrugBank website and the DGIdb database, four classes of drugs have been identified that indirectly influence *FCER1G*-related pathways by regulating upstream and downstream signaling molecules (Table II). These include aspirin, benzylpenicilloyl polylysine, omalizumab and fostamatinib. For instance, omalizumab functions as an IgE monoclonal antibody. By blocking the binding of IgE to its high-affinity receptor FcεRI, it is widely employed in treating asthma and chronic spontaneous urticaria.

Table II. Candidate drugs that may indirectly modulate the FCER1G-associated signaling pathway.

Potential drugs	Drug category	Status	Primary mechanism of action	Target
Aspirin	Nonsteroidal anti-inflammatory drug	Approved	Non-selective COX inhibitor	COX
Benzylpenicilloyl polylysine	Diagnostic reagent	Approved	FCER1A agonist	FCER1A
Omalizumab	Monoclonal antibody	Approved	IgE inhibitor	IgE
Fostamatinib	Small-molecule inhibitor	Approved	SYK inhibitor	SYK

FCER1G, Fc fragment of IgE receptor 1G; COX, cyclooxygenase; SYK, spleen tyrosine kinase.

Similarly, fostamatinib, as a SYK inhibitor, targets SYK, the core downstream signaling molecule of FcRγ. Although these drugs do not directly target *FCER1G*, their mechanisms of action demonstrate that intervention in pathways upstream (ligand-receptor binding) or downstream (ITAM signaling) of *FCER1G* can produce distinct biological effects.

Although existing pharmacological agents offer valuable insights into modulating the ITAM-SYK pathway activated by FCRγ, directly targeting *FCER1G* for cancer therapy remains considerably challenging. Therefore, a more feasible current approach may be to leverage *FCER1G* not as a direct therapeutic target, but as a key interpretative factor for understanding tumor immune microenvironment heterogeneity and as a biomarker for patient stratification. For instance, evaluating *FCER1G* expression and its associated immune cell infiltration patterns could help identify patients most likely to benefit from antibody therapies or immune checkpoint inhibitors that rely on FcγR effects. Future research should elucidate the precise molecular switches determining whether *FCER1G* function shifts towards a pro-tumor or antitumor role across different tumor types. This is a prerequisite for its safe translation into an effective therapeutic target.

7. Conclusion and outlook

As a core signaling adaptor, *FCER1G* mediates activation signals for multiple immune receptors through its ITAM, playing an indispensable role in both innate and adaptive immune responses. The present review systematically summarizes the multidimensional functions of *FCER1G*, spanning fundamental immune regulation to its involvement in disease pathogenesis. Beyond its classical roles in allergic reactions and anti-infection immunity, *FCER1G* shows profound pathological importance in inflammatory diseases and tumors.

In inflammation, *FCER1G* expression is finely regulated by epigenetic mechanisms. Acting as a sensor of the immune microenvironment, it dynamically modulates the magnitude and outcome of inflammatory responses by influencing the polarization of immune cells such as macrophages. Its functional plasticity provides essential clues to its behavior within the more complex TME.

FCER1G is highly expressed in several malignancies, including ccRCC, STAD and GBM, and correlates positively with immune checkpoint molecules such as PD-L1, suggesting its role as a central immune regulatory hub. Its tumor-promoting mechanisms are multifaceted, manifested in the formation of an immunosuppressive milieu through M2 macrophage recruitment and limited $CD8^+$ T-cell infiltration (as in STAD). *FCER1G* also mediates signaling crosstalk between FcγR and EMT pathways, thus shaping tumor-immune interactions. Beyond immunity, it participates in various non-immune regulatory processes, including angiogenesis (via VEGF/MMP-9 in SCC), platelet-mediated metastasis (via CXCL5/CXCL7 in MEL) and cell-cycle progression (in ALCL).

Clinically, the impact of *FCER1G* is context dependent. High expression predicts favorable prognosis in MM and UCEC, but correlates with poor outcomes in ccRCC and STAD, underscoring its tissue-specific prognostic importance. Furthermore, antibody therapies that rely on FcRγ show pronounced therapeutic efficacy in ATL and MEL models. Although several drugs targeting *FCER1G*-related pathways have been identified, such as aspirin and penicillanoyl polylysine (11), their translational value in oncology remains to be thoroughly investigated.

Despite substantial progress has been achieved in *FCER1G* research, several critical directions demand further investigation. Future studies should first prioritize elucidating the cross-cancer synergistic mechanisms between *FCER1G* and immune checkpoints (such as PD-1/PD-L1) as well as other immunoregulatory molecules, providing a conceptual basis for rationally designed combination therapies. Particular attention should be given to elucidating the molecular mechanisms underlying *FCER1G*'s dual roles in promoting or suppressing tumor progression across distinct microenvironmental contexts. Additionally, clinical translation faces notable challenges, especially concerning the dose-dependent toxicity and limited tissue selectivity of existing *FCER1G*-related drugs (such as aspirin and penicillanoyl polylysine). Thus, well-designed, multicenter clinical trials are urgently needed to validate therapeutic efficacy and safety profiles of interventions targeting *FCER1G* or its associated pathways (FcγR and SYK) in both solid tumors and hematological malignancies.

Furthermore, optimizing therapeutic strategies through tissue-targeted drug delivery represents a promising avenue. Developing delivery systems capable of specifically targeting *FCER1G*-expressing immune subsets or tumor-associated stromal cells could improve treatment precision. Such strategies may also help minimize off-target effects and mitigate potential pro-metastatic risks such as unintended platelet activation, which can arise from the broad distribution of FcγRs.

In summary, as a multifunctional molecule with both fundamental immunological importance and translational potential, *FCER1G* represents a promising target for next-generation cancer immunotherapy. Continuous elucidation of its

complex regulatory networks and development of innovative therapeutic strategies are expected to further expand its clinical value and ultimately improve patient outcomes.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Science and Technology Program of Gansu Province (grant no. 23JRRA1015).

Availability of data and materials

Not applicable.

Authors' contributions

YZ and JW wrote the original draft. JW, WH and TL conceptualized the topic, reviewed and edited the review. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zhang X, Cai J, Song F and ang Z: Prognostic and immunological role of FCER1G in pan-cancer. Pathol Res Pract 240: 154174, 2022.
2. Deng M, Du S, Hou H and Xiao J: Structural insights into the high-affinity IgE receptor FcεRI complex. Nature 633: 952-959, 2024.
3. Wang Y, Tian W, Li R, Zhou D, Ding K, Feng S, Ge Y, Luo Y, Chen Z and Hou H: Platelet FcRγ inhibits tumor metastasis by preventing the colonization of circulating tumor cells. Eur J Pharmacol 990: 177286, 2025.
4. Wang W, Erbe AK, Hank JA, Morris ZS and Sondel PM: NK cell-mediated antibody-dependent cellular cytotoxicity in cancer immunotherapy. Front Immunol 6: 368, 2015.
5. Vallières F and Girard D: Mechanism involved in interleukin-21-induced phagocytosis in human monocytes and macrophages. Clin Exp Immunol 187: 294-303, 2017.
6. Duhan V, Hamdan TA, Xu HC, Shinde P, Bhat H, Li F, Al-Matary Y, Häussinger D, Bezgovsek J, Friedrich SK, *et al*: NK cell-intrinsic FcεRIγ limits CD8+ T-cell expansion and thereby turns an acute into a chronic viral infection. PLoS Pathog 15: e1007797, 2019.
7. Wang L, Lin Y, Yuan Y, Liu F and Sun K: Identification of TYROBP and FCER1G as Key genes with prognostic value in clear cell renal cell carcinoma by bioinformatics analysis. Biochem Genet 59: 1278-1294, 2021.
8. Liu R, Liu J, Cao Q, Chu Y, Chi H, Zhang J, Fu J, Zhang T, Fan L, Liang C, *et al*: Identification of crucial genes through WGCNA in the progression of gastric cancer. J Cancer 15: 3284-3296, 2024.
9. Fu L, Cheng Z, Dong F, Quan L, Cui L, Liu Y, Zeng T, Huang W, Chen J, Pang Y, *et al*: Enhanced expression of FCER1G predicts positive prognosis in multiple myeloma. J Cancer 11: 1182-1194, 2020.
10. Chen Q, Wang S and Lang JH: Development and validation of nomogram with tumor microenvironment-related genes and clinical factors for predicting overall survival of endometrial cancer. J Cancer 12: 3530-3538, 2021.
11. Jiang H, He Y, Lan X and Xie X: Identification and validation of potential common biomarkers for papillary thyroid carcinoma and Hashimoto's thyroiditis through bioinformatics analysis and machine learning. Sci Rep 14: 15578, 2024.
12. Kraft S and Kinet JP: New developments in FcepsilonRI regulation, function and inhibition. Nat Rev Immunol 7: 365-378, 2007.
13. Hamerman JA, Ni M, Killebrew JR, Chu CL and Lowell CA: The expanding roles of ITAM adapters FcRgamma and DAP12 in myeloid cells. Immunol Rev 232: 42-58, 2009.
14. Novak N: New insights into the mechanism and management of allergic diseases: atopic dermatitis. Allergy 64: 265-275, 2009.
15. Lieberman P and Garvey LH: Mast cells and anaphylaxis. Curr Allergy Asthma Rep 16: 20, 2016.
16. Pan YG, Yu YL, Lin CC, Lanier LL and Chu CL: FcεRI γ-Chain negatively modulates dectin-1 responses in dendritic cells. Front Immunol 8: 1424, 2017.
17. Zhou ZW, Xu XT, Liang QN, Zhou YM, Hu WZ, Liu S, Jiao YX, Zhang SC, Ji K and Chen JJ: USP5 deubiquitylates and stabilizes FcεRIγ to enhance IgE-induced mast cell activation and allergic inflammation. Sci Signal 18: eadr3411, 2025.
18. Saijo S, Ikeda S, Yamabe K, Kakuta S, Ishigame H, Akitsu A, Fujikado N, Kusaka T, Kubo S, Chung SH, *et al*: Dectin-2 recognition of alpha-mannans and induction of Th17 cell differentiation is essential for host defense against Candida albicans. Immunity 32: 681-691, 2010.
19. Walsh NM, Wuthrich M, Wang H, Klein B and Hull CM: Characterization of C-type lectins reveals an unexpectedly limited interaction between Cryptococcus neoformans spores and Dectin-1. PLoS One 12: e0173866, 2017.
20. Liu SD and Lowe JB: Implications of understanding the signaling, cellular, and cytotoxic mechanisms afforded by afucosylated antibodies. Oncoimmunology 4: e1009288, 2015.
21. Mallavia B, Oguiza A, Lopez-Franco O, Recio C, Ortiz-Muñoz G, Lazaro I, Lopez-Parra V, Egido J and Gomez-Guerrero C: Gene deficiency in activating Fcγ Receptors influences the macrophage phenotypic balance and reduces atherosclerosis in mice. PLoS One 8: e66754, 2013.
22. Huang C, Zhu W, Li Q, Lei Y, Chen X, Liu S, Chen D, Zhong L, Gao F, Fu S, *et al*: Antibody Fc-receptor FcεR1γ stabilizes cell surface receptors in group 3 innate lymphoid cells and promotes anti-infection immunity. Nat Commun 15: 5981, 2024.
23. Oishi S, Tsukiji N, Otake S, Oishi N, Sasaki T, Shirai T, Yoshikawa Y, Takano K, Shinmori H, Inukai T, *et al*: Heme activates platelets and exacerbates rhabdomyolysis-induced acute kidney injury via CLEC-2 and GPVI/FcRγ. Blood Adv 5: 2017-2026, 2021.
24. Barrow AD, Raynal N, Andersen TL, Slatter DA, Bihan D, Pugh N, Cella M, Kim T, Rho J, Negishi-Koga T, *et al*: OSCAR is a collagen receptor that costimulates osteoclastogenesis in DAP12-deficient humans and mice. J Clin Invest 121: 3505-3516, 2011.
25. Yabe R, Chung SH, Murayama MA, Kubo S, Shimizu K, Akahori Y, Maruhashi T, Seno A, Kaifu T, Saijo S and Iwakura Y: TARM1 contributes to development of arthritis by activating dendritic cells through recognition of collagens. Nat Commun 12: 94, 2021.
26. Bashore FM, Katis VL, Du Y, Sikdar A, Wang D, Bradshaw WJ, Rygiel KA, Leisner TM, Chalk R, Mishra S, *et al*: Characterization of covalent inhibitors that disrupt the interaction between the tandem SH2 domains of SYK and FCER1G phospho-ITAM. PLoS One 19: e0293548, 2024.
27. Han S, Lan Q, Park AK, Lee KM, Park SK, Ahn HS, Shin HY, Kang HJ, Koo HH, Seo JJ, *et al*: Polymorphisms in innate immunity genes and risk of childhood leukemia. Hum Immunol 71: 727-730, 2010.
28. Liang Y, Wang P, Zhao M, Liang G, Yin H, Zhang G, Wen H and Lu Q: Demethylation of the FCER1G promoter leads to FcεRI overexpression on monocytes of patients with atopic dermatitis. Allergy 67: 424-430, 2012.
29. Liang Y, Yu B, Chen J, Wu H, Xu Y, Yang B and Lu Q: Thymic stromal lymphopoietin epigenetically upregulates Fc receptor γ subunit-related receptors on antigen-presenting cells and induces T(H)2/T(H)17 polarization through dectin-2. J Allergy Clin Immunol 144: 1025-1035.e7, 2019.

30. Mahachie John JM, Baurecht H, Rodríguez E, Naumann A, Wagenpfeil S, Klopp N, Mempel M, Novak N, Bieber T, Wichmann HE, *et al*: Analysis of the high affinity IgE receptor genes reveals epistatic effects of FCER1A variants on eczema risk. Allergy 65: 875-882, 2010.
31. Rajaraman P, Brenner AV, Neta G, Pfeiffer R, Wang SS, Yeager M, Thomas G, Fine HA, Linet MS, Rothman N, *et al*: Risk of meningioma and common variation in genes related to innate immunity. Cancer Epidemiol Biomarkers Prev 19: 1356-1361, 2010.
32. Chang R and Yang P: Molecular and Mechanistic Study of Resistance to Glucocorticoid Combined with Cyclosporine A Therapy in Female Patients with Vogt-Koyanagi-Harada Syndrome. The 23rd International Ophthalmology Conference 2023. Haikou, Hainan, China.
33. Podgórska D, Cieśla M and Kolarz B: FCER1G gene hypomethylation in patients with rheumatoid arthritis. J Clin Med 11: 4664, 2022.
34. Yang M, Zheng H, Su Y, Xu K, Yuan Q, Aihaiti Y, Cai Y and Xu P: Bioinformatics analysis identified the Hub Genes, mRNA-miRNA-lncRNA axis, and signaling pathways involved in rheumatoid arthritis pathogenesis. Int J Gen Med 15: 3879-3893, 2022.
35. Zhang K, Gao J and Ni Y: Screening of candidate key genes associated with human osteosarcoma using bioinformatics analysis. Oncol Lett 14: 2887-2893, 2017.
36. Liang Y, Zhao M, Liang G, Yin H and Lu Q: Construction of special reporter to detect DNA methylation regulatory activity in FCER1G gene promoter through patch-methylation. Zhong Nan Da Xue Xue Bao Yi Xue Ban 38: 120-124, 2013 (In Chinese).
37. Liang Y: Molecular Mechanism of STAT5/TET2 Regulating DNA Methylation of FCER1G Promoter in Monocyte and its role in the Pathogenesis of Atopic Dermatitis. Central South University, 2013.
38. Wang J, Zhang L, Cui X, Xu X, Guo R, Li K, Zhang L, Xu B, Jiang C and Yu Y: Bcl11a maintains hematopoietic stem cell function but accelerates inflammation-driven exhaustion during aging. Sci Immunol 10: eadr2041, 2025.
39. Wei ZM, Wang Z, Wan XJ, Li XJ, Li YX, Bai Y, Yang X, Yang Y, Jiao SC and Liu ZF: FcRγ deficiency improves survival in experimental sepsis by down-regulating TLR4 signaling pathway. Immunol Res 67: 77-83, 2019.
40. Kottom TJ, Carmona EM, Schaefbauer K, Stelzig KE, Pellegrino MR, Bindzus M and Limper AH: The importance of Fcγ and C-type lectin receptors in host immune responses during Pneumocystis pneumonia. Infect Immun 93: e0027624, 2025.
41. Yang R, Chen Z, Liang L, Ao S, Zhang J, Chang Z, Wang Z, Zhou Y, Duan X and Deng T: Fc Fragment of IgE Receptor Ig (FCER1G) acts as a key gene involved in cancer immune infiltration and tumour microenvironment. Immunology 168: 302-319, 2023.
42. Peng W, Zhao Y, Yang N, Fang Y, Wu Y, Feng Z, Wu Q and Wang X: Prognostic value of FCER1G expression and M2 macrophage infiltration in esophageal squamous cell carcinoma. Discov Oncol 16: 113, 2025.
43. Dong K, Chen W, Pan X, Wang H, Sun Y, Qian C, Chen W, Wang C, Yang F and Cui X: FCER1G positively relates to macrophage infiltration in clear cell renal cell carcinoma and contributes to unfavorable prognosis by regulating tumor immunity. BMC Cancer 22: 140, 2022.
44. Chen L, Yuan L, Wang Y, Wang G, Zhu Y, Cao R, Qian G, Xie C, Liu X, Xiao Y and Wang X: Co-expression network analysis identified FCER1G in association with progression and prognosis in human clear cell renal cell carcinoma. Int J Biol Sci 13: 1361-1372, 2017.
45. Ding W, Jiang H, Ye N, Zhuang L, Yuan Z, Tan Y, Xue W and Xu X: Identification and analysis of crucial genes in H. Pylori-Associated gastric cancer using an integrated bioinformatics approach. J Oncol 2023: 8538240, 2023.
46. Xu H, Zhang A and Lou M: The role of FCER1G gene in evaluating the prognosis of glioma. Chin J Minim Invasive Neurosurg 26: 363-366, 2021.
47. Xu H, Zhu Q, Tang L, Jiang J, Yuan H, Zhang A and Lou M: Prognostic and predictive value of FCER1G in glioma outcomes and response to immunotherapy. Cancer Cell Int 21: 103, 2021.
48. Tian Z, Meng L, Long X, Diao T, Hu M, Wang M, Liu M and Wang J: Identification and validation of an immune-related gene-based prognostic index for bladder cancer. Am J Transl Res 12: 5188-5204, 2020.
49. Xiang X: Identification, expression and prognostic significance of FCER1G gene related to CD4+ T lymphocyte infiltration in Diffuse Large B-cell Lymphoma. CNKI: Sichuan University, 2023.
50. Li B, Cai Z, Zhang Y, Chen R, Tang S, Kong F, Li W, Ding L, Chen L and Xu H: Biomarkers associated with papillary thyroid carcinoma and Hashimoto's thyroiditis: Bioinformatic analysis and experimental validation. Int Immunopharmacol 143: 113532, 2024.
51. Xiang X, Gao LM, Zhang Y, Tang Y, Zhao S, Liu W, Ye Y and Zhang W: Identification of FCER1G related to Activated Memory CD4(+) T Cells Infiltration by Gene Co-expression Network and Construction of a Risk Prediction Module in Diffuse Large B-Cell Lymphoma. Front Genet 13: 849422, 2022.
52. Li J, Shi H, Yuan Z, Wu Z, Li H, Liu Y, Lu M and Lu M: The role of SPI1-TYROBP-FCER1G network in oncogenesis and prognosis of osteosarcoma, and its association with immune infiltration. BMC Cancer 22: 108, 2022.
53. Qiu X, Zhang JH, Xu Y, Cao YX, Zhang RT, Hu LN and Zhou JH: Identification of FCER1G as a key gene in multiple myeloma based on weighted gene co-expression network analysis. Hematology 28: 2210904, 2023.
54. Bigley AB, Spade S, Agha NH, Biswas S, Tang S, Malik MH, Dai L, Masoumi S, Patiño-Escobar B, Hale M, *et al*: FcεRIγ-negative NK cells persist in vivo and enhance efficacy of therapeutic monoclonal antibodies in multiple myeloma. Blood Adv 5: 3021-3031, 2021.
55. Shukla M and Sarkar RR: Differential cellular communication in tumor immune microenvironment during early and advanced stages of lung adenocarcinoma. Mol Genet Genomics 299: 100, 2024.
56. A Self-reactive Innate-like T-cell program was identified in cancer immunity. Cancer Discov 12: Of11, 2022.
57. Morrish E and Ruland J: Cytotoxic FCER1G(+) innate-like T cells: New potential for tumour immunotherapy. Signal Transduct Target Ther 7: 204, 2022.
58. Gunderson AJ, Kaneda MM, Tsujikawa T, Nguyen AV, Affara NI, Ruffell B, Gorjestani S, Liudahl SM, Truitt M, Olson P, *et al*: Bruton tyrosine kinase-dependent immune cell cross-talk drives pancreas cancer. Cancer Discov 6: 270-285, 2016.
59. Andreu P, Johansson M, Affara NI, Pucci F, Tan T, Junankar S, Korets L, Lam J, Tawfik D, DeNardo DG, *et al*: FcRgamma activation regulates inflammation-associated squamous carcinogenesis. Cancer Cell 17: 121-134, 2010.
60. Kong D, Zhang Y, Jiang L, Long N, Wang C and Qiu M: Comprehensive analysis reveals the tumor suppressor role of macrophage signature gene FCER1G in hepatocellular carcinoma. Sci Rep 15: 3995, 2025.
61. Clynes R, Takechi Y, Moroi Y, Houghton A and Ravetch JV: Fc receptors are required in passive and active immunity to melanoma. Proc Natl Acad Sci USA 95: 652-656, 1998.
62. Domínguez-Soto A, de las Casas-Engel M, Bragado R, Medina-Echeverz J, Aragoneses-Fenoll L, Martín-Gayo E, van Rooijen N, Berraondo P, Toribio ML, Moro MA, *et al*: Intravenous immunoglobulin promotes antitumor responses by modulating macrophage polarization. J Immunol 193: 5181-5189, 2014.
63. Duhan V, Gomez MR, Le TT, Rana S, Chen YE, Balakrishnan D, Kelly G, Johnston RL, Krebs P and Khanna R: FcRγ-dependent NK cell licensing through CD244 promotes antitumour immunity. Cancer Immunol Res 13: 2075-2092, 2025.
64. Chan RH, Chen PC, Yeh YM, Lin BW, Yang KD, Shen MR and Lin PC: The expression quantitative trait loci in immune response genes impact the characteristics and survival of colorectal cancer. Diagnostics (Basel) 12: 315, 2022.
65. Zhang M, Zhang Z, Garmestani K, Goldman CK, Ravetch JV, Brechbiel MW, Carrasquillo JA and Waldmann TA: Activating Fc receptors are required for antitumor efficacy of the antibodies directed toward CD25 in a murine model of adult t-cell leukemia. Cancer Res 64: 5825-5829, 2004.
66. Zhang Z, Zhang M, Ravetch JV, Goldman C and Waldmann TA: Effective therapy for a murine model of adult T-cell leukemia with the humanized anti-CD2 monoclonal antibody, MEDI-507. Blood 102: 284-288, 2003.
67. Zhang M, Yao Z, Zhang Z, Garmestani K, Goldman CK, Ravetch JV, Janik J, Brechbiel MW and Waldmann TA: Effective therapy for a murine model of human anaplastic large-cell lymphoma with the anti-CD30 monoclonal antibody, HeFi-1, does not require activating Fc receptors. Blood 108: 705-710, 2006.
68. Shemesh A, Su Y, Calabrese DR, Chen D, Arakawa-Hoyt J, Roybal KT, Heath JR, Greenland JR and Lanier LL: Diminished cell proliferation promotes natural killer cell adaptive-like phenotype by limiting FcεRIγ expression. J Exp Med 219: e20220551, 2022.