Interferon regulatory factors orchestrate CD8+ T cell function (Review)

FA-XI WANG[1*], CHUN-LIANG YANG[2*], SHAN-JIE RONG[3], QI-JIE CHEN[3], XIONG-TAO YUE[3] and FEI SUN[2,3]

[1]Department of Ophthalmology, Institute of Translational Medicine, Renmin Hospital of Wuhan University, Wuhan, Hubei 430060, P.R. China; [2]Diabetes Research Center, Qatar Biomedical Research Institute, Hamad Bin Khalifa University, Education City, P.O. Box 34110, Doha, Qatar; [3]The Center for Biomedical Research, National Health Commission Key Laboratory of Respiratory Diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China

Received May 15, 2026; Accepted August 12, 2026

DOI: 10.3892/ijmm.2026.5982

Abstract. The fate of CD8+ T cells is dictated by epigenetic remodeling, metabolic rewiring and most critically, the transcriptional reprogramming that integrates diverse extracellular signaling pathways. Transcription factors (TFs) predetermine cell differentiation state and lineage-specifying hub TFs are decisive for CD8+ T cell functional maturation. The present study aimed to summarize the indispensable roles of interferon regulatory factors (IRFs) in CD8+ T cell biology from early thymic development to the acquisition of distinct functional states. Alone or together with other TFs, IRFs are involved in the regulation of CD8+ T cell commitment, effector differentiation, memory maintenance and terminal exhaustion. In clinical practice, IRF family members hold potential as prognostic biomarkers and valuable therapeutic targets in CD8+ T cell-associated immune disorders, such as tumors, transplant rejection, infection and autoinflammatory diseases.

Contents

1. Introduction
2. IRF1 and IRF2 counter-regulate CD8+ T cell development and maintenance
3. Type 1 IFN signaling and IRF3, 7 and 9 modulate CD8+ T cell function
4. IRF8 in CD8+ T cell functional control
5. IRF4 acts as a master regulator of CD8+ T cell function
6. Conclusion

Correspondence to: Professor Fa-Xi Wang, Department of Ophthalmology, Institute of Translational Medicine, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuhan, Hubei 430060, P.R. China
E-mail: faxiwang@163.com

Professor Fei Sun, Diabetes Research Center, Qatar Biomedical Research Institute, Hamad Bin Khalifa University, Education City, P.O. Box 34110, Doha, Qatar
E-mail: phil_sunfei@163.com

*Contributed equally

Key words: interferon regulatory factor, CD8+ T cell, cooperative binding, transcriptional regulation

1. Introduction

CD8+ T cells, arising from thymic selection, are key components of the adaptive immune system (1,2). In the classical scenario, naïve CD8+ T cells encounter self or foreign antigens derived from tumors or invaded pathogens and undergo clonal expansion and functional maturation, giving rise to a heterogeneous effector population. These effector CD8+ T cells consist of cytotoxic T lymphocytes (CTLs) that form immune synapses with target cells to locally release perforins, granzymes and cytokines for focal killing. From the developmental perspective, three effector subpopulations with distinct fates are discerned: Short-lived effector cells [killer cell lectin-like receptor G1 (KLRG)+ CD127-), which are terminally differentiated and undergo apoptosis following the clearance of antigen; memory precursor effector cells (MPECs, KLRG- CD127+), which develop into memory T cells; and rare long-lived effector cells (KLRG+ CD127+) which display the hybrid phenotype (3). Memory T cell subsets, including effector memory T cells that patrol peripheral circulation and non-lymphoid tissue, central memory T cells that recirculate through lymphoid organs due to the high expression of CCR7 and CD62L and tissue-resident memory T cells (TRMs) that have established stable tissue residency, are primarily derived from MPECs and constitute coordinated layers of CD8+ T cell-mediated immune response (3-5).

In a manner analogous to CD4+ helper T cells, effector CD8+ T cells can be polarized by specific cytokine milieus into context-dependent functional subsets, although such classification is not widely accepted due to lack of stable lineage-defining transcription factors and limited evidence for stable, heritable polarization of CD8+ T cells *in vivo*. Type 1 CD8+ T (Tc1) cells, defined by (T-box transcription factor

expressed in T cells (T-bet) expression and IFN-γ production, are induced by IL-12 and type I IFN signaling to combat intracellular pathogens and tumors (6,7). Tc17 cells, characterized by retinoic acid-related orphan receptor γt (RORγt) expression and secretion of IL-17 and IL-22, differentiate in the presence of TGF-β and pro-inflammatory cytokines such as IL-6 or IL-21 to mediate mucosal immunity and autoimmune reactions (8,9). Tc22 cells, identified as IL-22 producers, are implicated in skin homeostasis and enriched in the tumor microenvironment (10,11). Regulatory $CD8^+$ T cells ($CD8^+$ Tregs), which suppress immune responses via cytolysis or IL-10, are typically induced by suboptimal antigen exposure under tolerogenic conditions (12,13). By contrast, antigen stimulation with insufficient costimulatory signals induces $CD8^+$ T cell anergy (14), whereas chronic antigen exposure drives T cell exhaustion (15,16), establishing a hierarchy comprised of stem-like progenitor exhausted cells, their intermediate descendants that are still sensitive to immune checkpoint blockade, and the terminally exhausted population which has lost effector functions irreversibly (17,18).

With the advent of single-cell and muti-omic technologies, knowledge on $CD8^+$ T cell plasticity has deepened. To meet the increasing demand of modern immunology on the functional heterogeneity of T cells, a modular nomenclature system is used to delineate their lineage, function, migratory capacity, differentiation state and antigen presence state (19). Moreover, progress has been made regarding the epigenetic, transcriptional and metabolic regulation of $CD8^+$ T cell function (20). Understanding the molecular switches and signaling pathways essential for $CD8^+$ T cell fate decision, effector competency and functional persistence is of key for translational purposes, such as manipulating $CD8^+$ T cells for optimal anti-viral and anti-tumor response, or to circumvent the occurrence and decrease the intensity of autoinflammatory diseases. For example, by unraveling molecular machinery modulating the functionality, infiltration and robustness of chimeric antigen receptor (CAR)-T cells (21,22), the application of artificially engineered $CD8^+$ T cells has been extended from blood malignancy to solid tumors and autoimmune disorders (21,23,24).

IFN regulatory factors (IRFs), known for their role in mediating IFN signaling and the transcription of IFN-stimulated genes (ISGs), serve a critical part in metabolic and immune regulation (25,26). IRFs contain a highly conserved N-terminus DNA-binding domain that recognizes IFN-stimulated response elements (5'-AAN NGA AA-3') within the promoters of target genes (27), and the IRF-associated domain at the C-terminus (28). Based on the biological relevance, IRFs could be subdivided into several functional groups: IRF3/7/9 integrate various nucleic acid sensing pathways to facilitate the production of type 1 IFNs (29-31); IRF1 lies downstream of IFN stimulation along with its natural antagonist IRF2 (32); IRF4/5/8 respond to T/B cell receptor (CR) and cytokine stimulation (33-35). A recent study identified an intrinsic T lymphokine-activated killer cell-originated protein kinase (TOPK)-IRF5 axis in $CD8^+$T cells that suppresses anti-tumor immunity (36). IRF6 mutations cause Van der Woude syndrome, popliteal pterygium syndrome and non-syndromic orofacial cleft type 6 (37,38). Aberrant IRF signaling is associated with immune abnormalities (26,32), ranging from classical autoimmune diseases such as inflammatory bowel disease and type 1 diabetes to human autosomal dominant combined immunodeficiency (39,40), which stems from multimorphic IRF4 T95R mutation.

The roles of IRFs in dendritic cells (DCs), macrophages, B cells, $CD4^+$ T cells and other immune cell types have been reported (35,41-43). Specifically, IRF1 serves a key role in both innate and adaptive immune responses through governing the expression of multiple anti-viral and immune-regulatory genes, thereby regulating cell proliferation, differentiation and apoptosis (44). By contrast, IRF2 serves as a natural antagonist of IRF1, suppressing the genes governed by IRF1 and working as a rheostat to safeguard immune homeostasis (45). IRF3 is activated upon recognition of pathogen-associated molecular patterns, especially double-stranded RNA, to initiate the production of type I IFNs (46), while IRF7 amplifies the IFN signal through an IFN feedback loop (47). Although in a traditional view, IRF8 is required for the development of type 1 conventional DC (cDC1) to activate $CD8^+$ T cells (48) and IRF4 acts as a master transcription factor of $CD4^+$ T cell-priming cDC2 (49), lung resident IRF4-dependent $CD11b^+$ $CD24^{hi}$ DCs are key for the formation of memory $CD8^+$ T cells and TRMs during influenza A virus (IAV) infection (50). DC-specific IRF4 knockout (KO) mice demonstrate increased lung pathology upon challenge with heterosubtypic IAV, coupled with defective expansion of IFN-γ^+ $CD8^+$ T cells (50). Previous studies have reviewed the extrinsic regulatory effect of IRFs in cell types that exert an indirect impact on $CD8^+$ T cells (51-53). The present review, however, aimed to summarize the intrinsic roles of IRFs in $CD8^+$ T cell functional regulation.

2. IRF1 and IRF2 counter-regulate $CD8^+$ T cell development and maintenance

The requirement for IRF1 in $CD8^+$ T cell development is evidenced by the fact thatIRF1 deficient mice harbor a decreased number of mature $CD8^+$ T cells in both thymus and peripheral lymphoid organs (54). Deficits in other lymphoid cells, including natural killer (NK) cells, NKT cells and intestinal intraepithelial lymphocytes (IELs), are also observed inIRF1 KO mice and the recovery of all these lymphocyte subsets could be accomplished through IL-15 administration (55,56). Reintroduction of BCL2 into thymocytes rescues the defect of $CD8^+$ T cells, implying differential regulatory effects of IRF1 on distinct lymphocyte populations (57). The paucity of $CD8^+$ T cells inIRF1 KO mice is partially ascribed to the capability of IRF1 to directly bind the promoter regions of transporter associated with antigen processing 1 (TAP1) and low molecular mass polypetide 2 (LMP2), the upregulation of which is central for the antigen presentation process and the development and maintenance of $CD8^+$ T cells (58). However, another study argues that the $CD8^+$ T cell-intrinsic effect of IRF1 rather than the extrinsic impact on the thymic microenvironment is responsible for impaired $CD8^+$ T cell commitment inIRF1 KO mice (57). Despite decreased expression of TAP1, LMP2 and major histocompatibility complex (MHC)-I in IRF1 KO thymic stromal cells, they are capable of supporting $CD8^+$ T cell development *in vivo* bone marrow transplantation and *in vitro* cell re-aggregation models (54,57). By contrast, TCR stimulation induces IRF1 expression in

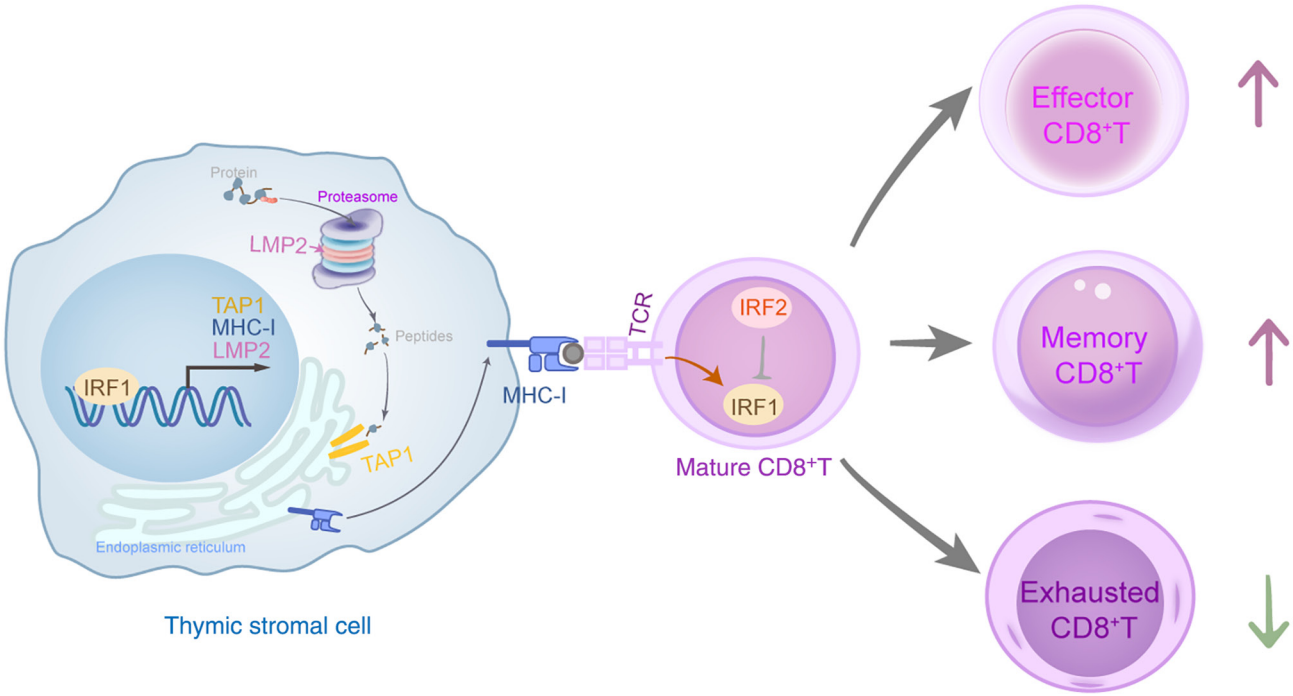


Figure 1. IRF1 and IRF2 counter-regulate CD8+ T cell development and maintenance. IRF1 enhances the antigen-presenting capacity of thymic stromal cells by promoting the expression of key components of the antigen processing and presentation machinery, LMP2, MHC-I and TAP1, which are key for peptide loading and surface presentation of antigens to CD8+ T cells. IRF1 also potentiates TCR signaling in mature CD8+ T cells. While IRF1 promotes the effector activity and memory maintenance of CD8+ T cells, it prevents the exhaustion program. As a natural antagonist, IRF2 suppresses IRF1 functions. IRF, IFN regulatory factor; TCR, T cell receptor; LMP, low molecular mass polypetide; MHC, major histocompatibility complex; TAP, transporter associated with antigen processing.

mature CD8+ T cells and IRF1 KO thymocytes demonstrate abrogated TCR signal transduction, thereby impairing both positive and negative selection processes (54). IRF1 is also key for the maintenance of memory-like T cell transcription factor 1 (TCF1)+ CD8+ T cells, which sustain T cell response in cancer and chronic infection by self-renewal and generating terminally differentiated T cells (59). Opposed to type 1 IFN signaling that couples the effector differentiation and cell division, IL-27 enhances the proliferative capacity of TCF1+ CD8+ T cells through the STAT1-IRF1 axis while impeding the terminal differentiation program (59).

The role of IRF1 in CD8+ T cell-mediated anti-infection response is an issue of debate. IRF1 deficiency inhibits CD8+ T cell proliferation, the production of IFN-γ and the surface expression of chemokine receptor CXCR3, which is key for the recruitment of CD8+ T cells into the brain, thereby ameliorating the immunopathological damage to the brain associated with malaria (60). In the case of inoculation of replication-defective adenovirus, IRF1 whole-body KO ($Irf1^{-/-}$) mice demonstrate initially reduced NK, CD8+ T, and NKT cell numbers in both spleen and liver, which recover over time (61). Although IRF1 is hypothesized to promote IFN-γ production in CD8+ T cells, adenovirus-afflicted $IRF1^{-/-}$ mice show higher levels of IFN-γ and IL-18 and lower levels of myeloid-derived IL-12 (62). As a result, the temporary decrease in CD8+ T cells and the elevated expression of IFN-γ delay adenovirus eradication, pointing to the existence of compensatory mechanisms to support CD8+ T cell effector function under IRF1 deficiency (62). IRF1 ablation also brings about paradoxically diminished CD8+ T cells in naïve mice, yet a marked expansion of West Nile virus (WNV)-specific cytolytic CD8+ T cells upon infection to restrain the WNV spread (63). Therefore, the function of IRF1 in infectious disease might be heavily context-dependent, and more evidence is required to clarify this issue. Such context-dependence extends beyond infectious models. For example, in major depressive disorders, bioinformatic analyses reveal notable upregulation of the IRF1 transcriptional pathway within the peripheral immune cell transcriptome, suggesting its involvement in the sterile inflammatory response (57,64).

IRF2 is a natural antagonist of IRF1 (Fig. 1) (45,65-67). IRF1/IRF2 binding activity is weakly induced in MHC class I-restricted double-positive thymocytes but not in MHC class II-restricted models (57,68). IRF2 deficient mice exhibit decreased bone marrow hematopoiesis, B cell lymphopoiesis and high mortality rate following lymphocytic choriomeningitis virus (LCMV) infection, potentially due to the hyperactivation of proinflammatory CD8+ T cells (44). Mice lacking Irf2 develop spontaneous inflammatory skin disease with CD8+ T cells hyperresponsive to antigen stimulation and expressing IFN-stimulated genes (69), highlighting the repressive role of IRF2 in CD8+ T cell activation (70) and the homeostatic maintenance of the IFN system under physiological conditions (71). However, a unique function of IRF2 in IEL development is also reported. CD8αα+ IELs bearing TCRαβ or TCRγδ, but not CD8αβ+ IELs, are severely decreased in IRF2 deficient mice and the residual CD8αα+ TCRαβ+ IELs are functionally immature with low T-bet expression The requirement for IRF2 in IEL development is independent of IL-15, as the $IRF2^{-/-}$ $IL15^{-/-}$ double KO mice display more severe IEL defects than IL-15 single-deficient mice (72). Acute and transient IFN

signaling may upregulate IRF1 to transcribe proinflammatory genes, while sustained IFN signaling in conditions such as tumor and chronic infection induces IRF2 upregulation to terminate IRF1 signaling and initiate immune suppressive programs. CD8+ T cell-specific deletion of IRF2 prevents T cell exhaustion and enables sustained effector functions that enhance responsiveness to immune checkpoint blockade and adoptive cell therapy (Fig. 1) (65,73,74).

Modulatory effects of IRF1 and IRF2 may be indirect. For example, IRF1 binds to the promoter region of Cxcl10 and enhances its expression in hepatocellular carcinoma, leading to the enhanced infiltration of CD8+ T cells within the tumor microenvironment, while the transcriptional activity of IRF1 is antagonized by IRF2 (75). In skin cutaneous melanoma, expression of IRF1 is controlled by four CpG sites (cg00255919, cg21138405, cg15375424 and cg27587780) within the Irf1 gene locus, and the expression of IRF1 is positively associated with the extent of CD8+ T infiltration in the tumor microenvironment (76). However, the association between IRF1 and CD8+ T cell states is reversed in autoimmune contexts. In systemic lupus erythematosus, IRF1 expression is downregulated in peripheral central memory CD8+ T cells during active disease, and its restoration is associated with remission, highlighting its dynamic and disease phase-specific role in immune homeostasis (77). IRF1 is also key for hepatic production of the IL-15/IL-15Rα complex, as Irf1 KO reduces the expression of IL-15 and IL-15Rα in hepatocytes, resulting in poor recruitment of NK, NKT and CD8+ T cells, and alleviates liver damage in the ischemia/reperfusion model (61).

IRF1 and IRF2 serve as opposing regulatory pairs to keep CD8+ T cell activation in check, reflected by the seemingly contradictory effects of IRF1/2 in anti-infection vs. anti-tumor responses. IRF1 upregulation or IRF2 ablation bolsters CD8+ T cell effector program but prevents CD8+ T cell exhaustion, offering therapeutic benefits in tumor eradication. However, compared with tumors, which are often hypo-immunogenic and immune evasive, virulent pathogens cause acute damage to the human body by inducing overactive immunopathological reactions that may be otherwise life-threatening in situations such as coronavirus disease 2019 infection (78). Meanwhile, chronic infection, such as those elicited by hepatitis B virus, induce CD8+ T cell exhaustion to allow pathogen persistence (79). Thus, IRF1/2 targeting strategies should be cautiously applied in infectious disease to balance the pathogen-killing and self-destructive effects of CD8+ T cells, based on understanding of specific pathogen type, the host immune status and the dynamic nature of host-pathogen interplay.

3. Type 1 IFN signaling and IRF3, 7 and 9 modulate CD8+ T cell function

IRF3, IRF7 and IRF9 are critical IRF members involved in anti-viral response and the production of type 1 IFN through integrating diverse nucleic acid sensing pathways (30,80-83). Plasmacytoid DCs (pDCs) are the predominant producers of type 1 IFN, which promotes the proliferation of autoreactive CD8+ T cells and upregulates the expression of very late antigen-4/Lymphocyte function-associated antigen 1 (LFA1) on activated CD8+ T cells to facilitate their tissue infiltration (84). In skin, type 1 IFN is mainly produced by mononuclear phagocytes and is restrained by Tregs. Overproduction of type 1 IFN facilitates CD8+ T cell accumulation in the skin lesion, while type 1 IFN signaling blockade or CD8+ T cell depletion mitigates psoriasiform skin inflammation (85). In a murine model of lymphocytic choriomeningitis virus infection, type 1 IFN triggers the expression of inhibitory NK cell receptor ligands on T cells, protecting them from NK-mediated elimination and conferring prolonged anti-viral T cell immunity (86). In the diet-induced obesity model, upregulated IFNα in the liver causes the accumulation and activation of CD8+ T cells, associated with inflammation-associated insulin insensitivity and glucose dysregulation (87). IFNαR1$^{-/-}$ and CD8+ T cell-specific IFNαR1$^{-/-}$ chimeric mice and IFNαR1 inhibitors all suppress the type 1 IFN-CD8+ T cell axis, thereby improving the metabolic parameters of non-alcoholic fatty liver disease (87). Type 1 IFN is an antiproliferative cytokine hindering the expansion of CD8+ T cells, which inhibits the CD8+ T cell-mediated anti-infection response *in vivo* (88). The early presence of type 1 IFN (IFN-I) permits CD8+ T cell infiltration and activation; however, sustained IFN-I signaling impair CD8+ T cell function, and its decrease is therefore key for the expansion of full functional effector cells (Fig. 2) (89-91). This calibration of the type I IFN response is exemplified by its integration with cellular oxygen-sensing pathways. Environmental oxygen tension, sensed via the prolyl hydroxylase domain-containing protein 2-Hypoxia inducible factor 1-alpha (HIF1α) axis, directly modulates the activity of IRF3 and IRF7, thereby dictating the magnitude of IFN production and CD8+ T cell responses in a context-dependent manner (92).

Bovine viral diarrhea virus infection of bovine CD8+ T cells activates the PI3K-AKT signaling pathway to enhance the *de novo* lipid biosynthesis supporting viral replication. Inhibition of fatty acid synthase activates retinoid acid-inducible gene 1 and melanoma differentiation-associated protein 5, triggering the TANK binding kinase-IRF3 axis and the production of type 1 IFN (93). IRF3 deficient CD8+ T cells also manifest higher expression levels of IL-17A and IL-23 receptor, in the presence or absence of the stimulatory nucleic acid mimic polyinosinic–polycytidylic acid, the phenotype of which is further corroborated by adoptively transferring IRF3-KO OT-I CD8+ T cells. Mechanistically, via the IRF interaction domain, IRF3 interacts with cytoplasmic RORγt and prevents it from binding and transactivating the Il-17 promoter. Thus, IRF3 serves as a rheostat for the Tc17 program (94). Activation of the MyD88-IRF7 pathway in pDCs determines the production of type 1 IFN and induction of CD8+ T cell response (47). Additionally, the intrinsic regulatory effect of IRF7 is exemplified by microRNA (miR)-155, which is upregulated in effector and effector memory CD8+ T cells but downregulated in naïve and central memory CD8+ T cells. miR-155 deficient CD8+ T cells exhibit heightened type 1 IFN signaling and are more susceptible to the antiproliferative effect of IFN, which is rescued by inhibition of STAT1 or IRF7 (88). By contrast, IRF9 extrinsically prevents CD8+ T cell exhaustion in mice acutely infected with LCMV-Armstrong strain. IRF9 deficiency impairs the production of type 1 IFN from DCs, leading to unchecked LCMV replication and antigen exposure that causes CD8+ T cell exhaustion and chronic infection (95).

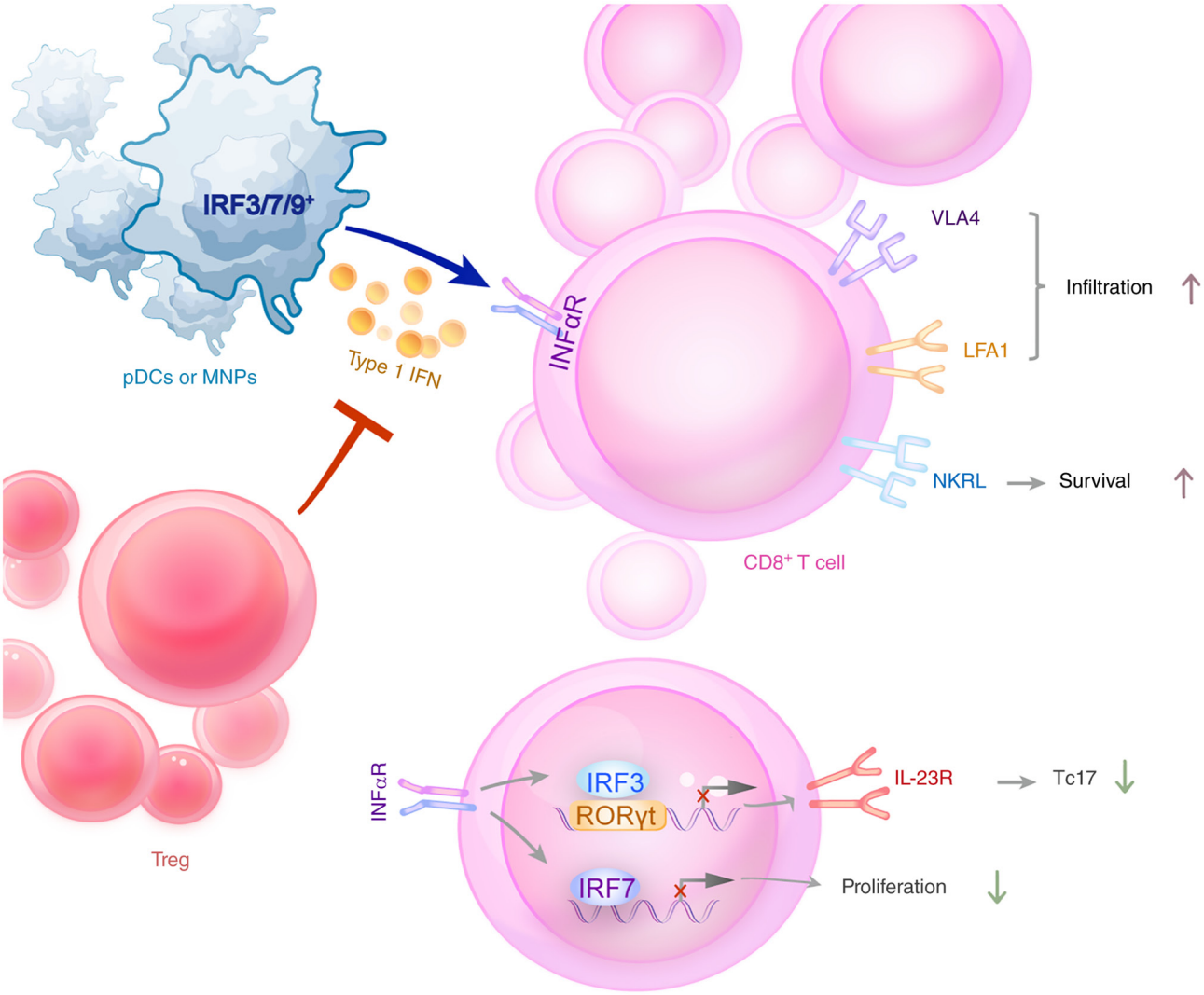


Figure 2. Type 1 IFN signaling and IRF3, 7 and 9 modulate CD8+ T cell function. pDCs and MNPs are the major source of type 1 IFN, while Tregs suppress their production and release. Type 1 IFN promotes the infiltration and survival of CD8+ T cells by upregulating adhesion molecules (VLA4, LFA1) and inhibitory NKRL that confer resistance to NK-mediated killing. IRF3 restrains the Tc17 program by blocking the binding of RORγt to the IL-17 promoter, and IRF7 impairs CD8+ T cell proliferation. IRF, IFN regulatory factor; pDC, plasmacytoid DC; MNP, mononuclear phagocyte; VLA, very late antigen; LFA, lymphocyte function-associated antigen; NKRL, natural killer receptor ligand; ROR, retinoid-related orphan receptor; Treg, regulatory T cell; Tc17, type 17 CD8+ T cells; IL-23R, IL-23 receptor.

4. IRF8 in CD8+ T cell functional control

IRF8 indirectly impacts CD8+ T cell function in tumor development (96,97). In estrogen receptor-negative breast cancer, tumoral expression of IRF8 is positively associated with effector CD8+ T cell infiltration (98). IRF8 suppresses p53 expression to maintain the sensitivity of tumor cells to intrinsic ferroptosis triggered by tumor-reactive CTLs. IRF8-KO tumor cells acquire resistance to ferroptosis and grow faster in immune-competent mice. In patients with cancer, nivolumab (anti-PD-1 antibody) responders have higher IRF8 expression in their tumor cells as compared with non-responders, which implies IRF8 is a useful biomarker of cancer immunotherapy (99). IRF8 and IRF4 suppress the expression of inflammasome-associated genes in cDC1s and cDC2s, respectively, to prevent pyroptotic cell death and preserve their ability to prime both CD4+ and CD8+ T cells (100). IRF8 is key for the expansion of monocyte-derived tumor-associated macrophages (TAMs) and the activation of tumor cDC1s. While cDC1s prime CTLs in tumor-draining lymph nodes, TAMs enriched for IRF8 promote exhaustion of tumor-reactive CTLs and facilitate tumor growth (101), indicating a complex role of IRF8 in tumorigenesis.

Regarding the direct effect of IRF8 in CD8+ T cells, TCR/co-stimulation signals along with γc-cytokines converge on the upregulation of IRF8 to mediate the transition of naive CD8+ T cells into effector cells in graft vs. host disease mice, identifying IRF8 a key transcription factor in driving CD8+ T cell effector differentiation (34). Additionally, IRF8 serves as a potential intrinsic factor constraining effector to memory phenotype transition (102). Conditional ablation of IRF8 in T cells increases the frequency of virus-specific MPECs in herpes simplex virus 1 (HSV-1) induced eye infection, thereby promoting HSV-1-specific CD8+ T cell expansion and corneal inflammatory infiltration (102). These immunological changes facilitate the elimination of viruses residing

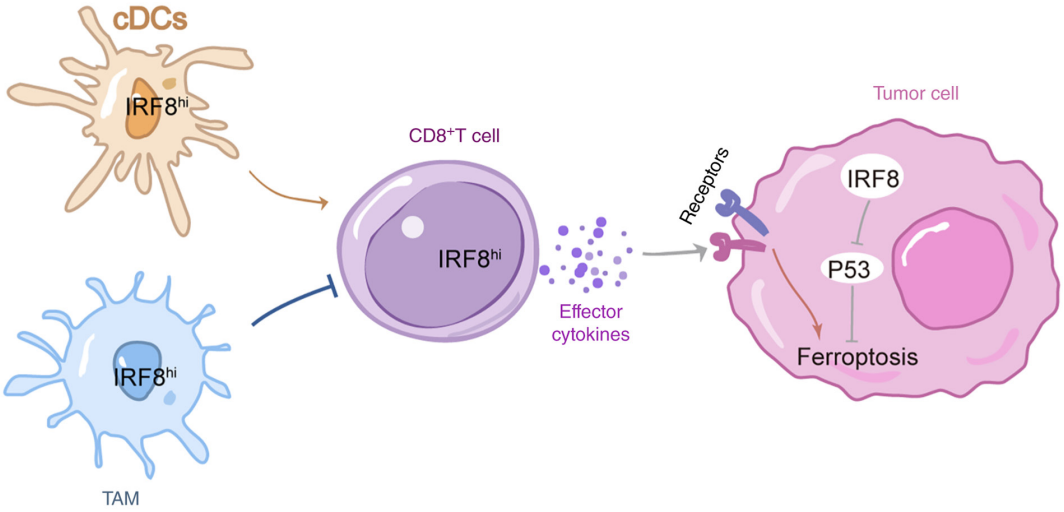


Figure 3. IRF8 in CD8+ T cell functional control. IRF8-expressing type 1 cDCs prime the activation of CTLs in tumor-draining lymph nodes. IRF8-expressing TAMs induce the exhaustion of CTLs. Intrinsic expression of IRF8 in CD8+ T cells solidifies the effector program, which may be crucial for anti-tumor response considering its role in sensitizing tumor cells to the ferroptosis pathway. IRF, IFN regulatory factor; cDC, conventional dendritic cell; CTL, cytotoxic T lymphocyte; TAM, tumor-associated macrophage.

within the trigeminal ganglion but risk ocular inflammation and limbitis (102). Thus, similarly to T-bet and emesodermin (Eomes), well-established drivers of the effector CD8+ T cell program (7,103,104), IRF8 is a hub transcription factor facilitating the same program (Fig. 3).

5. IRF4 acts as a master regulator of CD8+ T cell function

IRF4 promotes CD8+ T cell effector differentiation. At the molecular level, IRF4 can be transiently upregulated by TCR signaling through mTOR (105-107), and the varied strength of TCR signaling dictates the graded expression of IRF4 (108). Strong TCR signals trigger rapid IRF4 induction, while weak TCR elicits delayed IRF4 induction. Tyrosine kinase IL-2 inducible T-cell kinase (ITK) regulates the rate of TCR signaling, which affects the kinetics of nuclear factor of activated T cells 1 (NFAT1). The delayed nuclear translocation, rather than reduced signal strength (magnitude), of NFAT1 contributes to downregulating IRF4 levels within CD8+ T cells (109). ITK-deficient T cells display downregulated expression of gut-homing receptors and possess impaired migratory capacity toward the intestinal mucosa. Such defects are rectified by reconstitution of IRF4, corroborating its role as a key downstream of ITK (110). Thymic IRF4 is preferentially highly expressed in CD4+ single positive (SP) cells, rather than CD8+ SP cells (109). Mechanistic study reveals that ectopically upregulated IRF4 binds to the distal promoter region of Runx3 to suppress its transcription, leading to impaired generation and maturation of CD8+ SP thymocytes (111).

IRF4 is key for the early thymic development of CD8+ T cells and to sustain the expansion and effector differentiation of mature CD8+ T cells by upregulating the expression levels of B lymphocyte-induced maturation protein 1 (Blimp1) and T-bet while inhibiting genes related to cell cycle arrest and apoptosis (112). IRF4 deficiency in CD8+ T cells impedes antiviral CD8+ T cell response and viral clearance (105). On the other hand, B6. Recombination activating gene $1^{-/-}$ mice that receive adoptive transfer of CD8+ T cells from Cd4-Cre recombinase; $Irf4^{fl/fl}$ mice (T cell-specific Irf4 ablation) accepted the BALB/c skin transplants. When compared to their wild-type counterparts, IRF4 deficient CD8+ T cells exhibit a low capacity to differentiate into $CD127^{-}$ $KLRG1^{+}$ terminal effector cells, produce fewer effector cytokines and cytotoxic molecules (IL-2, IFN-γ, TNF-α, granzyme A and granzyme B) and are defective in proliferative capacity (112). Inhibitor of DNA binding 2 (ID2) and T-bet, key for the terminal effector program, are decreased in IRF4 deficient cells, while TCF1, essential for naïve and memory program, is elevated by IRF4 deficiency (112). Moreover, during acute *Listeria monocytogenes* infection, IRF4-deficient mice generate less antigen-specific effector CD8+ T cells and are unable to clear the infection. Such functional incompetency is rescued by forced IRF4 expression or transfer of IRF4-replete CD8+ T cells (113). Nuclear receptor subfamily 4, group A, member 1 (NR4A1) serves as a negative regulator of IRF4 via transcriptional suppression. Nr4a1-deficient mice demonstrate elevated expression of IRF4, resulting in enhanced expansion, differentiation and effector function of CD8+ T cells accompanied by improved clearance of *L. monocytogenes* (114). IRF4 also promotes the expression of key molecules involved in aerobic glycolysis and is key for the clonal expansion and maintenance of antigen-specific effector CD8+ T cells (106). Stimulation with toll-like receptor (TLR)7 ligand induces upregulation of IRF4 in αCD3 primed CD8+ T cells, bolstering glucose uptake and glycolytic metabolism to support the effector function of CD8+ T cells (115). Therefore, IRF4 is essential for the effector differentiation of CD8+ T cells (Fig. 4) (116). In lung adenocarcinoma (LUAD), IRF4 expression is higher in tumor than in normal tissue, serving as a favorable prognostic biomarker. High IRF4 expression is positively associated with better survival of patients with LUAD, more immune infiltration of CD8+ T cells and the upregulation of PD-1/PD-L1 that predicts positive response to immunotherapy (117).

Tc1 and Tc17 are distinct CD8+ T cell effector subsets, the latter of which shows decreased cytotoxic activity (118-120).

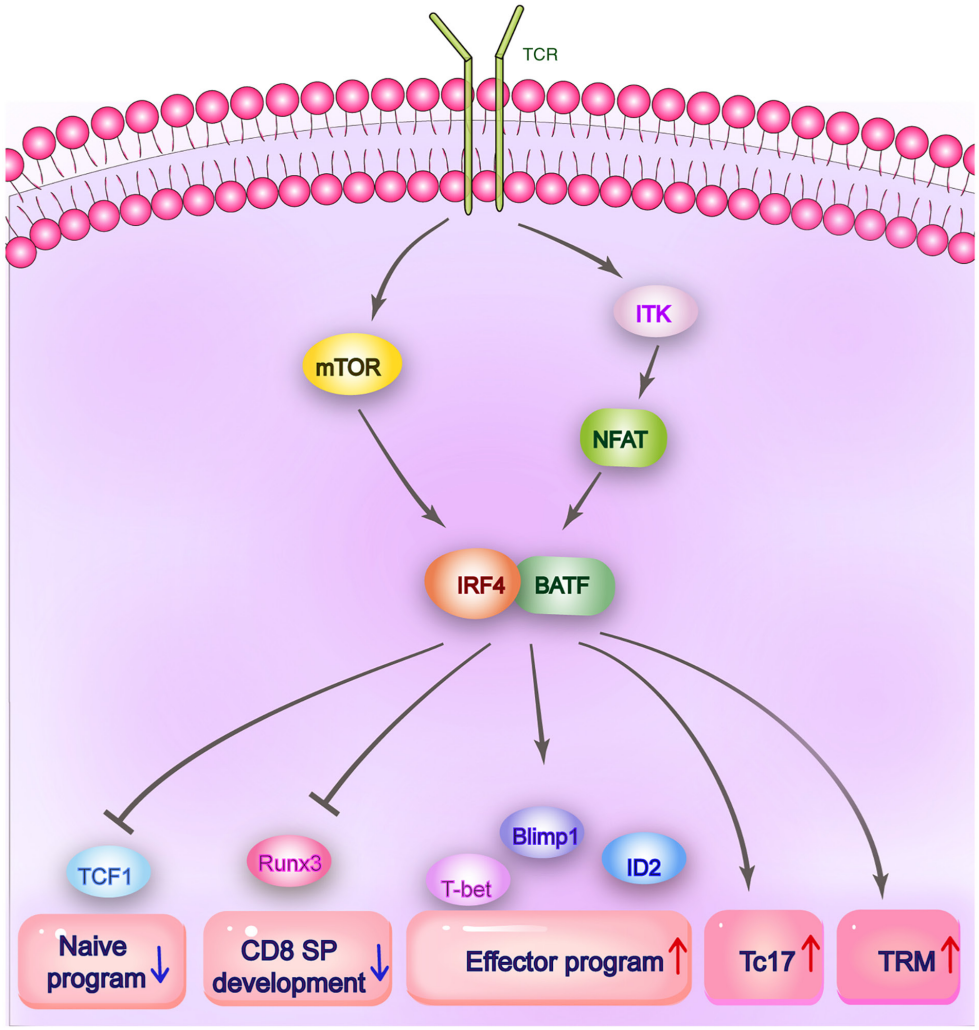


Figure 4. IRF4 serves as a master regulator of CD8$^+$ T cell function. TCR signaling activates the mTOR and ITK pathways, leading to the upregulation of IRF4. IRF4 suppresses TCF1 and RUNX3 to block the naïve program and CD8 SP maturation, respectively, and facilitates effector CD8$^+$ T cell program via inducing Blimp1, T-bet and ID2. Moreover, IRF4 is required for the formation of Tc17 and TRM. IRF, IFN regulatory factor; TCR, T cell receptor; TCF, T cell factor; SP, single positive; Blimp, B lymphocyte-induced maturation protein; T-bet, T-box transcription factor expressed in T cells; ID, inhibitor of DNA binding; BATF, basic leucine zipper transcription ATF-like; ITK, IL-2 inducible T-cell kinase; Tc17, type 17 CD8$^+$ T cells; TRM, tissue-resident memory T cells.

CTLA4 upregulates IRF4, RORγt and IL-17A, thus promoting Tc17 differentiation and impeding the clearance of infection (121). IL-17-producing Tc17 cells are required for experimental allergic encephalomyelitis (EAE) development and IRF4-deficient mice cannot generate Tc17 and Th17 cells. While the adoptive transfer of either wild-type (WT) CD8$^+$ T cells or a small number of WT CD4$^+$ T cells fails to evoke EAE following antigen immunization, co-transfer of CD4$^+$ and CD8$^+$ T cells induces severe EAE. Additionally, Tc17 cells are enriched in the cerebrospinal fluid of patients with early-stage multiple sclerosis (MS), supporting the key role of Tc17 in promoting Th17 pathogenicity (122). Fingolimod, recognized as an immunomodulatory agent preventing the egress of lymphocytes from lymph nodes, decreases the expression of IRF4 in peripheral blood mononuclear cells of patients with relapsing MS. This causes a marked decrease in the frequency of IFN-γ$^+$ CD8$^+$ T cell and IL17$^+$ CD8$^+$ T cell subsets and IFN-γ$^+$ IL17$^+$ co-producing CD8$^+$ T cells in patients with MS (123). Therefore, IRF4 inhibition is a viable strategy for fighting against autoinflammatory disease characterized by type 17 responses.

IRF4 in CD8$^+$ T cell memory maintenance. IRF4 deficient CD8$^+$ T cells exhibit higher expression of PTEN, resulting in a hypo-activated AKT pathway and impaired homeostatic proliferation of naïve CD8$^+$ T cells. Nonetheless, memory-like IRF4$^{-/-}$ CD8$^+$ T cells expand similarly to their WT counterparts, suggesting a key role of IRF4 in memory-like CD8$^+$ T cell maintenance (124). Whole body KO cannot distinguish T cell-intrinsic effects from indirect effects of other cell types. To overcome this limitation and exclude the potential influence of IRF4 on CD8$^+$ T cell activation, proliferation, effector differentiation and memory formation, tamoxifen-inducible IRF4 KO mice have been infected with ovalbumin-expressing recombinant listeria followed by inducible IRF4 KO. Following pathogen clearance, IRF4 was deleted to explore its role in memory cell maintenance. The survival of memory CD8$^+$ T cells remains intact, however, the expansion and acquisition of effector function are compromised during the recall responses (102). By contrast, CD8$^+$ tissue-resident memory T cells (TRMs) express a higher level of IRF4, and both constitutive and inducible IRF4 ablation diminishes the TRM population, implying a role of IRF4 in TRM maintenance (Fig. 4) (125).

The influence of IRF4 on TRM maintenance may be due to the unique tissue microenvironment and the signaling context. The strength and duration of TCR signaling determines effector differentiation vs. memory formation. Strong and sustained TCR signals, which facilitate IRF4 expression, typically drive effector differentiation, while weaker and short-term signals favor memory formation (126,127). IRF4 typically works in concert with other transcription factors, such as T-bet and Eomes, to regulate CD8+ T cell fate decision. The relative abundance and activity of these co-factors may affect the expression level and regulatory effects of IRF4. Compared with conventional lymph organ residing memory CD8+ T cells, TRMs would receive more potent TCR signals and different panels of cytokine stimulation (128,129). These signals impart TRMs with a hybrid memory, effector phenotype and dependence on IRF4 function.

IRF4-basic leucine zipper transcription ATF-like (BATF) complex and the cooperative transcription in CD8+ T cells. The cooperative binding of different transcription factors is commonly observed in immune cell functional regulation: For example, STAT1, STAT2, and IRF9 assemble into a tripartite complex (ISGF3) to transcribe downstream ISGs (130-132). While NFAT, together with activator protein 1 (AP-1), promotes T cell effector responses, NFAT alone induces T cell exhaustion (133). Due to the presence of a carboxy-terminal auto-inhibitory domain, IRF4 binds DNA weakly. Cooperative binding to the composite elements, such as E26 transformation-specific (ETS)-IRF composite elements (5'-GGA Ann GAA A-3') recognized by IRF4/PU.1 (an ETS transcription factor) in B cells, greatly enhances the binding affinity to DNA (134). In T cells, BATF, a member of the JUN family, complexes with IRF4 to bind to AP-1-IRF4 composite (5'-TGA nTC A/GA AA-3') motifs denoted as AP-1-IRF composite elements (Fig. 5). IRF4 binding and IRF4-dependent transcription are compromised in T cells deficient in BATF (135). Similarly, through genome-scale profiling, a core network of transcription factors including IRF4, RUNX3 (136,137), and T-bet have been shown to cooperate with BATF to cause chromatin reorganization and changes in gene expression pattern (136). BATF and IRF4, but not BATF alone, are sufficient to shape the effector CD8+ T cell program, which is reinforced by the presence of RUNX3 and T-bet (136,138). BATF forms a complex with IRF4 to counter T cell exhaustion, which bolsters the survival and expansion of tumor-infiltrating CAR-T cells, increases the production of effector cytokines, decreases the expression of inhibitory receptors and supports the generation of long-lived memory T cells that control tumor recurrence. However, these effects are diminished when CD8+ CAR-T cells are introduced with a BATF variant that is unable to interact with IRF4 (138). CD4+ T cells provide allow CD8+ T cells to sustain their effector response. CD4+ T cell-derived cytokine IL-21 induces potent and persistent high expression of BATF, which cooperates with IRF4 to preserve Blimp-1 expression and expression of effector genes to constrain chronic viral infection (139). The absence of either IRF4 or BATF in CD8+ T cells results in decreased CD8+ T cell effector function, limited immunopathology and viral persistence (140).

BATF family members (BATF, BATF2, BATF3) form heterotrimers with JUNB and either IRF4 or IRF8. While BATF-JUNB heterodimers exhibit binding preferences comparable with both TGA C/GTC A and CRE (TGA CGT CA) motifs, the incorporation of IRF4 or IRF8 into the complex shifts the binding preference away from CRE in favor of TGA C/GTC A across all BATF-JUNB combinations (141). The BATF-JUN-IRF4 trimer binds and promotes the early expression of genes encoding lineage-specific transcription factors (T-bet and Blimp1) and cytokine receptors yet paradoxically suppresses the expression of effector molecules (IFN-γ and granzyme B). This dual activity avoids irreversible commitment to an effector fate until a critical threshold of downstream transcriptional activity has been achieved (142). Therefore, the cooperative IRF4-BATF interaction forms a unique immune-regulatory network necessary for CD8+ T cell function (143) (Fig. 5).

6. Conclusion

Alone or together with other partners, IRF family members serve as multifaceted transcription factors regulating CD8+ T cell biology. In common, nearly all IRFs pull CD8+ T cells away from the naïve state and favor the effector program by inducing Blimp1, T-bet or ID2. Nonetheless, combined and antagonistic actions exist between IRF members pertaining to the regulation of particular CD8+ T cell functional aspects. For thymic CD8+ T cell development and maturation, IRF1 is required due to its ability to stimulate TCR signaling and enhance the expression of antigen-presenting molecules (TAP1, LMP2, MHC-I) in thymic stromal cells. By contrast, IRF4 impedes CD8+ SP cell development by suppressing RUNX3 and IRF2 is critical for the generation of CD8+αα+ IELs. IRF1 promotes the expansion of memory-like CD8+ T cells. However, IRF8 hinders the transition from the effector state to the memory state and IRF4 impacts TRM maintenance. IRF4 facilitates the polarization of Tc17 while IRF3 restrains it by sequestering RORγt to prevent binding to the Il-17 promoter region. Finally, although type 1 IFN promotes CD8+ T cell survival and tissue infiltration, persistent stimulation of IFN may cause IRF7-mediated inhibition of CD8+ T cell expansion.

Despite the function of IRF4 in effector CD8+ T cell activation, its downregulation in CAR-T cells does not impair their cytotoxicity but instead achieves long-term persistence and better tumor control through the elevation of CD27 upon repetitive antigen encounter, contradicting the conventional hypothesis (144). Moreover, chronic and strong TCR stimulation drives the upregulation of IRF4, BATF and NFATc1, which together upregulate PD-1 and hinder memory T cell differentiation by suppressing TCF1 (33). These contradictory results suggest the complex and context-dependent roles of IRFs in regulating CD8+ T cell function. Although IRFs such as IRF4 increase glycolytic metabolism in CD8+ T cells and coordinate the epigenetic landscape in B cells (106,145), it is unknown whether extensive crosstalk exists between IRFs, metabolic rewiring and epigenetic remodeling in CD8+ T cell biology. Supporting the potential for such crosstalk, a multi-omics study in non-segmental vitiligo found increased chromatin accessibility at binding motifs for IRF1 and IRF4 in circulating CD8+ T cells and monocytes, which is associated with a pro-inflammatory gene expression signature (146).

IRFs, particularly their DNA-binding domains, are typically considered undruggable due to the flat and featureless

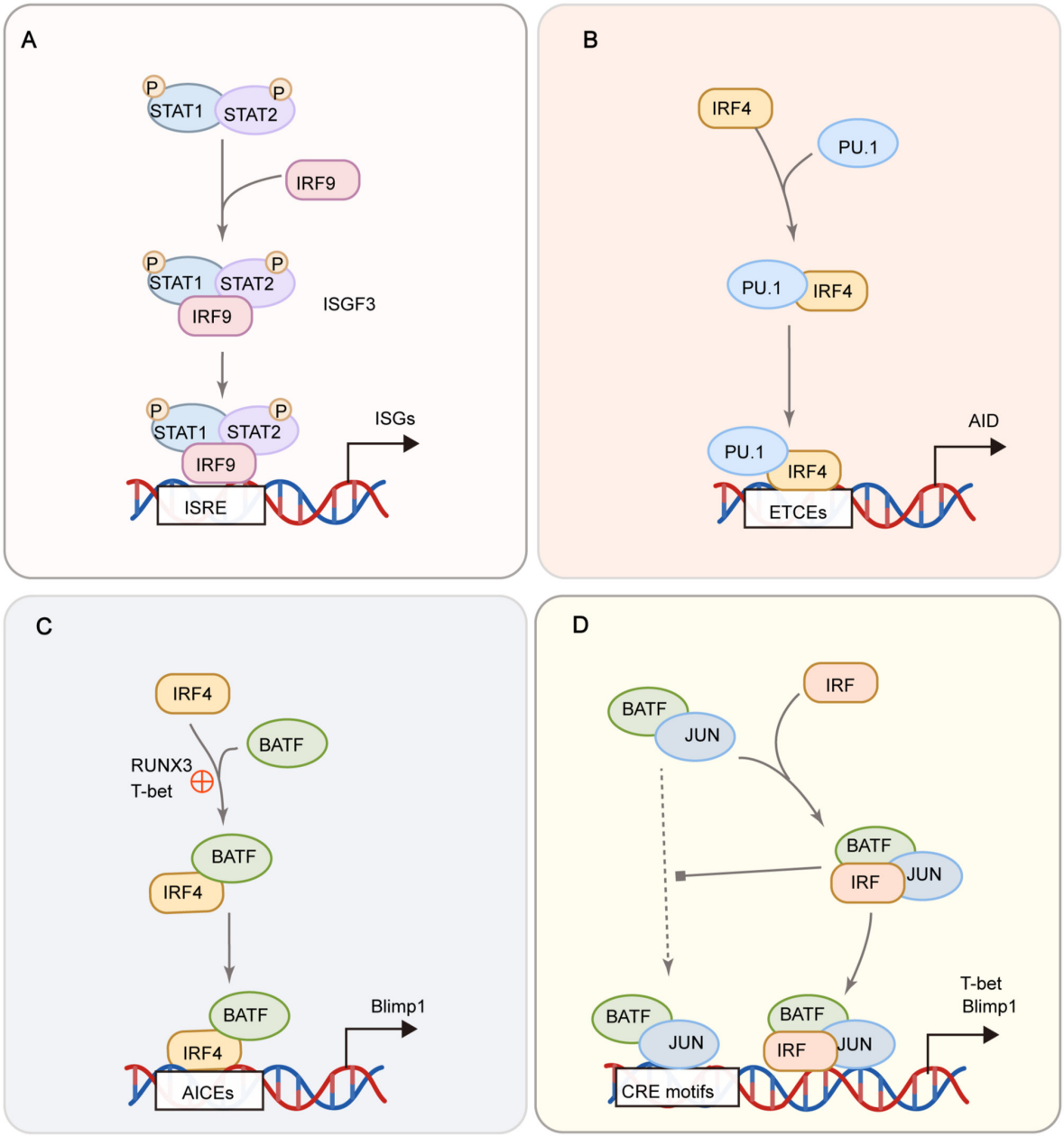


Figure 5. IRF complexes and cooperative transcriptional activity. IRFs complex with transcription factors and bind to the composite cis-regulatory elements. (A) IRF9 forms a heterotrimer with pSTAT1 and pSTAT2 (ISGF3 complex) and promotes the transcription of ISGs by binding ISRE. (B) IRF4 forms a heterodimer with PU.1 and binds ETCEs to transcribe AID. (C) IRF4 forms a heterodimer with BATF and binds AICEs to transcribe Blimp1. (D) BATF-IRF-JUN heterotrimer prevents BATF-JUN from binding the CRE motif, facilitating the transcription of Blimp1 and T-bet. IRF, IFN regulatory factor; p, phosphorylated; ISGF, interferon-stimulated gene factor; ISRE, interferon-stimulated response element; PU.1, purine rich box-1; ETCE, E26 transformation-specific-IRF composite element; AID, activation-induced cytidine deaminase; BATF, basic leucine zipper transcription ATF-like; AICE, activator protein-1-IRF composite element; Blimp, B lymphocyte-induced maturation protein; CRE, cyclic adenosine monophosphate response element; T-bet, T-box transcription factor expressed in T cells.

surface, making it difficult to design small molecules that effectively inhibit their function (147). Despite this challenge, a recent study screened 210,000 compounds and identified two small molecules, IRF1-inhibitor-1 and -2, that effectively inhibit IRF1 transcriptional activity (148). In radiation-induced skin damage models, these inhibitors decrease IRF1 activation and alleviate skin damage (148,149). Imiquimod, widely applied in condyloma acuminate treatment, activates the TLR7-IRF7 pathway and has been increasingly explored in cancer immunotherapy (150,151). Imiquimod boosts antitumor response by enhancing $CD8^+$ T cell effector function, particularly when combined with therapies such as PD-1/PD-L1 blockade (152).

To the best of our knowledge, no small molecules directly binding IRF4 and disrupting its DNA interaction have been reported in clinical trials. However, epigenetic modulation strategies show promise in indirectly suppressing the IRF4-MYC axis, a key pathway for multiple myeloma (MM) survival: Ishiguro *et al* (153) demonstrated that dual inhibition of the histone methyltransferases EZH2 and G9a suppresses MM cell proliferation by downregulating key genes, including IRF4 and MYC. Beyond direct DNA-binding inhibition, complementary strategies are emerging. Genome-wide clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 screens have identified synthetic lethal partners of

IRF4, such as BATF, in certain types of B cell malignancy (154) and inhibitors disrupting IRF protein-protein interactions offer another avenue to modulate IRF activity (155). Advances in drug design platforms, including anti-sense oligonucleotides and targeted protein degradation constructs such as proteolysis-targeting chimeras (PROTACs) and lysosme-targeting chimeras (LYTACs), are expanding the toolbox for IRF-directed therapy beyond conventional small molecules. Notably, a first-in-class IRF4-selective PROTAC degrader has been shown to induce cytotoxicity in MM cells (156). By exploiting these platforms, novel IRF-targeting strategies may be developed. Nonetheless, given IRFs are widely expressed in various cell types (26,157), preclinical studies must evaluate the drug safety issue to minimize potential side effects of IRF inhibition. In this regard, future development should prioritize tissue- or cell-specific targeting strategies that restrict IRF modulation to disease-relevant cells or local microenvironments, thereby circumventing off-target effects and improving therapeutic windows.

In summary, while pharmacological targeting of IRFs presents challenges, strategies are emerging to modulate their activities. The observation that virus-specific $CD8^+$ T cell memory can persist for a decade prompts the question of whether specific IRF-driven transcriptional programs underpin durable immunity (158). As research bridges these mechanistic insights with therapeutic innovation, the IRF family is positioned at the forefront of immunology and translational medicine.

Acknowledgements

Not applicable.

Funding

The present study was supported by Non-communicable Chronic Diseases-National Science and Technology Major Project (grant no. 2024ZD0531400), National Natural Science Foundation of China (grant nos. 82570968, 82200923 and 82570953) and Science and Technology Innovation Special Program of Hubei Province (grant no. 2024CFC001).

Availability of data and materials

Not applicable.

Authors' contributions

FXW conceived the study and wrote the manuscript. SJR, QJC and XTY edited the manuscript. CLY wrote the manuscript and constructed figures. FS conceived the study and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

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. Murphy K and Weaver C: Janeway's immunobiology. Garland Science, 2016.
2. Smith-Garvin JE, Koretzky GA and Jordan MS: T cell activation. Annu Rev Immunol 27: 591-619, 2009.
3. Joshi NS, Cui W, Chandele A, Lee HK, Urso DR, Hagman J, Gapin L and Kaech SM: Inflammation directs memory precursor and short-lived effector CD8(+) T cell fates via the graded expression of T-bet transcription factor. Immunity 27: 281-295, 2007.
4. Sallusto F, Lenig D, Forster R, Lipp M and Lanzavecchia A: Two subsets of memory T lymphocytes with distinct homing potentials and effector functions. Nature 401: 708-712, 1999.
5. Jameson SC and Masopust D: Understanding subset diversity in T cell memory. Immunity 48: 214-226, 2018.
6. Curtsinger JM, Schmidt CS, Mondino A, Lins DC, Kedl RM, Jenkins MK and Mescher MF: Inflammatory cytokines provide a third signal for activation of naive CD4+ and CD8+ T cells. J Immunol 162: 3256-3262, 1999.
7. Kaech SM and Cui W: Transcriptional control of effector and memory CD8+ T cell differentiation. Nat Rev Immunol 12: 749-761, 2012.
8. Huber M, Heink S, Grothe H, Guralnik A, Reinhard K, Elflein K, Hunig T, Mittrucker HW, Brustle A, Kamradt T and Lohoff M: A Th17-like developmental process leads to CD8(+) Tc17 cells with reduced cytotoxic activity. Eur J Immunol 39: 1716-1725, 2009.
9. Glenn JD, Smith MD, Calabresi PA and Whartenby KA: Mesenchymal stem cells differentially modulate effector CD8+ T cell subsets and exacerbate experimental autoimmune encephalomyelitis. Stem Cells 32: 2744-2755, 2014.
10. Huber M and Lohoff M: Change of paradigm: CD8+ T cells as important helper for CD4+ T cells during asthma and autoimmune encephalomyelitis. Allergo J Int 24: 8-15, 2015.
11. Griffith BD and Frankel TL: The aryl hydrocarbon receptor: Impact on the tumor immune microenvironment and modulation as a potential therapy. Cancers (Basel) 16: 472, 2024.
12. Niederkorn JY: Emerging concepts in CD8(+) T regulatory cells. Curr Opin Immunol 20: 327-331, 2008.
13. Dai Z, Zhang S, Xie Q, Wu S, Su J, Li S, Xu Y and Li XC: Natural CD8+CD122+ T cells are more potent in suppression of allograft rejection than CD4+CD25+ regulatory T cells. Am J Transplant 14: 39-48, 2014.
14. Schwartz RH: T cell anergy. Annu Rev Immunol 21: 305-334, 2003.
15. Wherry EJ and Kurachi M: Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol 15: 486-499, 2015.
16. Schietinger A and Greenberg PD: Tolerance and exhaustion: Defining mechanisms of T cell dysfunction. Trends Immunol 35: 51-60, 2014.
17. Utzschneider DT, Charmoy M, Chennupati V, Pousse L, Ferreira DP, Calderon-Copete S, Danilo M, Alfei F, Hofmann M, Wieland D, *et al*: T cell factor 1-expressing memory-like CD8(+) T cells sustain the immune response to chronic viral infections. Immunity 45: 415-427, 2016.
18. Beltra JC, Manne S, Abdel-Hakeem MS, Kurachi M, Giles JR, Chen Z, Casella V, Ngiow SF, Khan O, Huang YJ, *et al*: Developmental relationships of four exhausted CD8(+) T cell subsets reveals underlying transcriptional and epigenetic landscape control mechanisms. Immunity 52: 825-841.e8, 2020.
19. Masopust D, Awasthi A, Bosselut R, Brooks DG, Buggert M, Chamoto K, Cui W, Dong C, Farber DL, Gebhardt T, *et al*: Guidelines for T cell nomenclature. Nat Rev Immunol 26: 298-313, 2026.
20. Rausch L and Kallies A: Molecular mechanisms governing CD8 T cell differentiation and checkpoint inhibitor response in cancer. Annu Rev Immunol 43: 515-543, 2025.
21. Sterner RC and Sterner RM: CAR-T cell therapy: Current limitations and potential strategies. Blood Cancer J 11: 69, 2021.
22. Labanieh L, Majzner RG and Mackall CL: Programming CAR-T cells to kill cancer. Nat Biomed Eng 2: 377-391, 2018.
23. Schett G and June CH: CAR T cells in autoimmune disease: On the road to remission. Immunity 57: 2705-2709, 2024.

24. Mackensen A, Muller F, Mougiakakos D, Boltz S, Wilhelm A, Aigner M, Volkl S, Simon D, Kleyer A, Munoz L, *et al*: Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. Nat Med 28: 2124-2132, 2022.
25. Ahmad Z, Kahloan W and Rosen ED: Transcriptional control of metabolism by interferon regulatory factors. Nat Rev Endocrinol 20: 573-587, 2024.
26. Wang L, Zhu Y, Zhang N, Xian Y, Tang Y, Ye J, Reza F, He G, Wen X and Jiang X: The multiple roles of interferon regulatory factor family in health and disease. Signal Transduct Target Ther 9: 282, 2024.
27. Fujii Y, Shimizu T, Kusumoto M, Kyogoku Y, Taniguchi T and Hakoshima T: Crystal structure of an IRF-DNA complex reveals novel DNA recognition and cooperative binding to a tandem repeat of core sequences. EMBO J 8: 5028-5041, 1999.
28. Qin BY, Liu C, Lam SS, Srinath H, Delston R, Correia JJ, Derynck R and Lin K: Crystal structure of IRF-3 reveals mechanism of autoinhibition and virus-induced phosphoactivation. Nat Struct Biol 10: 913-921, 2003.
29. Xiao J, Li W, Zheng X, Qi L, Wang H, Zhang C, Wan X, Zheng Y, Zhong R, Zhou X, *et al*: Targeting 7-Dehydrocholesterol reductase integrates cholesterol metabolism and IRF3 activation to eliminate infection. Immunity 58: 1614, 2025.
30. Qin Z, Fang X, Sun W, Ma Z, Dai T, Wang S, Zong Z, Huang H, Ru H, Lu H, *et al*: Author correction: Deactylation by SIRT1 enables liquid-liquid phase separation of IRF3/IRF7 in innate antiviral immunity. Nat Immunol 27: 1528, 2026.
31. Gothe F, Stremenova Spegarova J, Hatton CF, Griffin H, Sargent T, Cowley SA, James W, Roppelt A, Shcherbina A, Hauck F, *et al*: Aberrant inflammatory responses to type I interferon in STAT2 or IRF9 deficiency. J Allergy Clin Immunol 150: 955-964.e16, 2022.
32. Honda K and Taniguchi T: IRFs: Master regulators of signalling by Toll-like receptors and cytosolic pattern-recognition receptors. Nat Rev Immunol 6: 644-658, 2006.
33. Man K, Gabriel SS, Liao Y, Gloury R, Preston S, Henstridge DC, Pellegrini M, Zehn D, Berberich-Siebelt F, Febbraio MA, *et al*: Transcription factor IRF4 promotes CD8+ T cell exhaustion and limits the development of Memory-like T cells during chronic infection. Immunity 47: 1129-1141.e5, 2017.
34. Miyagawa F, Zhang H, Terunuma A, Ozato K, Tagaya Y and Katz SI: Interferon regulatory factor 8 integrates T-cell receptor and cytokine-signaling pathways and drives effector differentiation of CD8 T cells. Proc Natl Acad Sci USA 109: 12123-12128, 2012.
35. Wang F, Sun F, Luo J, Yue T, Chen L, Zhou H, Zhang J, Yang C, Luo X, Zhou Q, *et al*: Loss of ubiquitin-conjugating enzyme E2 (Ubc9) in macrophages exacerbates multiple low-dose streptozotocin-induced diabetes by attenuating M2 macrophage polarization. Cell Death Dis 10: 892, 2019.
36. Zang N, Gan J, Chen Y, Huang Z, Xie C, Dang J, Huang C, Yang L, Chen X, Rong G, *et al*: TOPK suppresses the CD8+ T cell antitumor immunity via modulation of IRF5 expression. Cancer Commun (Lond) 46: 0021, 2026.
37. Kondo S, Schutte BC, Richardson RJ, Bjork BC, Knight AS, Watanabe Y, Howard E, de Lima RL, Daack-Hirsch S, Sander A, *et al*: Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes. Nat Genet 32: 285-289, 2002.
38. Zucchero TM, Cooper ME, Maher BS, Daack-Hirsch S, Nepomuceno B, Ribeiro L, Caprau D, Christensen K, Suzuki Y, Machida J, *et al*: Interferon regulatory factor 6 (IRF6) gene variants and the risk of isolated cleft lip or palate. N Engl J Med 351: 769-780, 2004.
39. Consortium IRFI, Fornes O, Jia A, Kuehn HS, Min Q, Pannicke U, Schleussner N, Thouenon R, Yu Z, de Los Angele s Astbury M, *et al*: A multimorphic mutation in IRF4 causes human autosomal dominant combined immunodeficiency. Sci Immunol 8: eade7953, 2023.
40. Wang G, Feng X and Ding J: Molecular basis for the functional roles of the multimorphic T95R mutation of IRF4 causing human autosomal dominant combined immunodeficiency. Structure 31: 1441-1451.e3, 2023.
41. Lança T, Ungerbäck J, Da Silva C, Joeris T, Ahmadi F, Vandamme J, Svensson-Frej M, Mowat AM, Kotarsky K, Sigvardsson M, *et al*: IRF8 deficiency induces the transcriptional, functional, and epigenetic reprogramming of cDC1 into the cDC2 lineage. Immunity 55: 1431-1447.e11, 2022.
42. Fabié A, Mai LT, Dagenais-Lussier X, Hammami A, van Grevenynghe J and Stäger S: IRF-5 promotes cell death in CD4 T cells during chronic infection. Cell Rep 24: 1163-1175, 2018.
43. Grajales-Reyes GE, Iwata A, Albring J, Wu X, Tussiwand R, Kc W, Kretzer NM, Briseño CG, Durai V, Bagadia P, *et al*: Batf3 maintains autoactivation of Irf8 for commitment of a CD8α(+) conventional DC clonogenic progenitor. Nat Immunol 16: 708-717, 2015.
44. Matsuyama T, Kimura T, Kitagawa M, Pfeffer K, Kawakami T, Watanabe N, Kundig TM, Amakawa R, Kishihara K, Wakeham A, *et al*: Targeted disruption of IRF-1 or IRF-2 results in abnormal type I IFN gene induction and aberrant lymphocyte development. Cell 75: 83-97, 1993.
45. Harada H, Fujita T, Miyamoto M, Kimura Y, Maruyama M, Furia A, Miyata T and Taniguchi T: Structurally similar but functionally distinct factors, IRF-1 and IRF-2, bind to the same regulatory elements of IFN and IFN-inducible genes. Cell 58: 729-739, 1989.
46. Sato M, Suemori H, Hata N, Asagiri M, Ogasawara K, Nakao K, Nakaya T, Katsuki M, Noguchi S, Tanaka N, *et al*: Distinct and essential roles of transcription factors IRF-3 and IRF-7 in response to viruses for IFN-alpha/beta gene induction. Immunity 13: 539-548, 2000.
47. Honda K, Yanai H, Negishi H, Asagiri M, Sato M, Mizutani T, Shimada N, Ohba Y, Takaoka A, Yoshida N and Taniguchi T: IRF-7 is the master regulator of type-I interferon-dependent immune responses. Nature 434: 772-777, 2005.
48. Tamura T, Tailor P, Yamaoka K, Kong HJ, Tsujimura H, O'Shea JJ, Singh H and Ozato K: IFN regulatory factor-4 and -8 govern dendritic cell subset development and their functional diversity. J Immunol 174: 2573-2581, 2005.
49. Suzuki S, Honma K, Matsuyama T, Suzuki K, Toriyama K, Akitoyo I, Yamamoto K, Suematsu T, Nakamura M, Yui K and Kumatori A: Critical roles of interferon regulatory factor 4 in CD11bhighCD8alpha-dendritic cell development. Proc Natl Acad Sci USA 101: 8981-8986, 2004.
50. Ainsua-Enrich E, Hatipoglu I, Kadel S, Turner S, Paul J, Singh S, Bagavant H and Kovats S: IRF4-dependent dendritic cells regulate CD8+ T-cell differentiation and memory responses in influenza infection. Mucosal Immunol 12: 1025-1037, 2019.
51. Chesler DA and Reiss CS: The role of IFN-gamma in immune responses to viral infections of the central nervous system. Cytokine Growth Factor Rev 13: 441-454, 2002.
52. Ganea D and Delgado M: Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) as modulators of both innate and adaptive immunity. Crit Rev Oral Biol Med 13: 229-237, 2002.
53. Yoo JK, Kim TS, Hufford MM and Braciale TJ: Viral infection of the lung: Host response and sequelae. J Allergy Clin Immunol 132: 1263-1277, 2013.
54. Penninger JM, Sirard C, Mittrücker HW, Chidgey A, Kozieradzki I, Nghiem M, Hakem A, Kimura T, Timms E, Boyd R, *et al*: The interferon regulatory transcription factor IRF-1 controls positive and negative selection of CD8+ thymocytes. Immunity 7: 243-254, 1997.
55. Ohteki T, Ho S, Suzuki H, Mak TW and Ohashi PS: Role for IL-15/IL-15 receptor beta-chain in natural killer 1.1+ T cell receptor-alpha beta+ cell development. J Immunol 159: 5931-5935, 1997.
56. Ma A, Koka R and Burkett P: Diverse functions of IL-2, IL-15, and IL-7 in lymphoid homeostasis. Annu Rev Immunol 24: 657-679, 2006.
57. Ohteki T, Maki C and Koyasu S: Overexpression of Bcl-2 differentially restores development of thymus-derived CD4-8+ T cells and intestinal intraepithelial T cells in IFN-regulatory factor-1-deficient mice. J Immunol 166: 6509-6513, 2001.
58. White LC, Wright KL, Felix NJ, Ruffner H, Reis LF, Pine R and Ting JP: Regulation of LMP2 and TAP1 genes by IRF-1 explains the paucity of CD8+ T cells in IRF-1-/-mice. Immunity 5: 365-376, 1996.
59. Huang Z, Zak J, Pratumchai I, Shaabani N, Vartabedian VF, Nguyen N, Wu T, Xiao C and Teijaro JR: IL-27 promotes the expansion of self-renewing CD8+ T cells in persistent viral infection. J Exp Med 216: 1791-1808, 2019.
60. Gun SY, Claser C, Teo TH, Howland SW, Poh CM, Chye RRY, Ng LFP and Renia L: Interferon regulatory factor 1 is essential for pathogenic CD8+ T cell migration and retention in the brain during experimental cerebral malaria. Cell Microbiol 20: e12819, 2018.
61. Yokota S, Yoshida O, Dou L, Spadaro AV, Isse K, Ross MA, Stolz DB, Kimura S, Du Q, Demetris AJ, *et al*: IRF-1 promotes liver transplant ischemia/reperfusion injury via hepatocyte IL-15/IL-15Ralpha production. J Immunol 194: 6045-6056, 2015.

62. Xu X, Zhang HG, Liu ZY, Wu Q, Yang PA, Sun SH, Chen J, Hsu HC and Mountz JD: Defective clearance of adenovirus in IRF-1 mice associated with defects in NK and T cells but not macrophages. Scand J Immunol 60: 89-99, 2004.
63. Brien JD, Daffis S, Lazear HM, Cho H, Suthar MS, Gale M Jr and Diamond MS: Interferon regulatory factor-1 (IRF-1) shapes both innate and CD8(+) T cell immune responses against West Nile virus infection. PLoS Pathog 7: e1002230, 2011.
64. Savitz J, McKinney BA, Meier TB, Zheng H, Ford BN, Yolken RH, Teague TK and Cole SW: Nuclear factor kappa-B cell (NF-κB), interferon regulatory Factor, and glucocorticoid receptor pathway activation in major depressive Disorder: The role of cytomegalovirus infection. Brain Behav Immun 123: 1052-1060, 2025.
65. Lukhele S, Rabbo DA, Guo M, Shen J, Elsaesser HJ, Quevedo R, Carew M, Gadalla R, Snell LM, Mahesh L, *et al*: The transcription factor IRF2 drives interferon-mediated CD8+ T cell exhaustion to restrict anti-tumor immunity. Immunity 55: 2369-2385.e10, 2022.
66. Ren G, Cui K, Zhang Z and Zhao K: Division of labor between IRF1 and IRF2 in regulating different stages of transcriptional activation in cellular antiviral activities. Cell Biosci 5: 17, 2015.
67. Wang Y, Liu DP, Chen PP, Koeffler HP, Tong XJ and Xie D: Involvement of IFN regulatory factor (IRF)-1 and IRF-2 in the formation and progression of human esophageal cancers. Cancer Res 67: 2535-2543, 2007.
68. Simon AK, Desrois M and Schmitt-Verhulst AM: Interferon-regulatory factors during development of CD4 and CD8 thymocytes. Immunology 91: 340-345, 1997.
69. Arakura F, Hida S, Ichikawa E, Yajima C, Nakajima S, Saida T and Taki S: Genetic control directed toward spontaneous IFN-alpha/IFN-beta responses and downstream IFN-gamma expression influences the pathogenesis of a murine psoriasis-like skin disease. J Immunol 179: 3249-3257, 2007.
70. Hida S, Ogasawara K, Sato K, Abe M, Takayanagi H, Yokochi T, Sato T, Hirose S, Shirai T, Taki S and Taniguchi T: CD8(+) T cell-mediated skin disease in mice lacking IRF-2, the transcriptional attenuator of interferon-alpha/beta signaling. Immunity 13: 643-655, 2000.
71. Taki S: Type I interferons and autoimmunity: Lessons from the clinic and from IRF-2-deficient mice. Cytokine Growth Factor Rev 13: 379-391, 2002.
72. Tokumaru S, Yamamoto Y, Yoshizawa K, Soejima Y, Sanjo H and Taki S: Interferon regulatory factor-2 is required for the establishment of the gut intraepithelial T-cell compartment. Int Immunol 35: 231-241, 2023.
73. Sheikh AA and Utzschneider DT: IRF2 integrates inflammatory signals to balance T cell exhaustion. Immunity 55: 2225-2227, 2022.
74. Shao L, Srivastava R, Delgoffe GM, Thorne SH and Sarkar SN: An IRF2-Expressing oncolytic virus changes the susceptibility of tumor cells to antitumor T cells and promotes tumor clearance. Cancer Immunol Res 12: 779-790, 2024.
75. Yan Y, Zheng L, Du Q, Yazdani H, Dong K, Guo Y and Geller DA: Interferon regulatory factor 1(IRF-1) activates anti-tumor immunity via CXCL10/CXCR3 axis in hepatocellular carcinoma (HCC). Cancer Lett 506: 95-106, 2021.
76. Zhou S, Lu C, Liu G, Hu Q and Yang J: IRF1 expression might be a biomarker of CD8+ T cell infiltration in cutaneous melanoma. Expert Rev Clin Immunol 18: 1319-1327, 2022.
77. Huang Z, Zhao C, Qing F and Zheng L: The role of IRF-1 in mediating T-cell immune imbalance in systemic lupus erythematosus and the construction of a diagnostic model. Autoimmunity 58: 2581723, 2025.
78. Kasuga Y, Zhu B, Jang KJ and Yoo JS: Innate immune sensing of coronavirus and viral evasion strategies. Exp Mol Med 53: 723-736, 2021.
79. McLane LM, Abdel-Hakeem MS and Wherry EJ: CD8 T cell exhaustion during chronic viral infection and cancer. Annu Rev Immunol 37: 457-495, 2019.
80. Simons KH, de Vries MR, de Jong RCM, Peters HAB, Jukema JW and Quax PHA: IRF3 and IRF7 mediate neovascularization via inflammatory cytokines. J Cell Mol Med 23: 3888-3896, 2019.
81. IRF3 and IRF7 require SIRT1 for liquid-liquid phase separation and transactivation of IFN-1. Nat Immunol 23: 1144-1145, 2022.
82. Tucker MH, Yu W, Menden H, Xia S, Schreck CF, Gibson M, Louiselle D, Pastinen T, Raje N and Sampath V: IRF7 and UNC93B1 variants in an infant with recurrent herpes simplex virus infection. J Clin Invest 133: e154016, 2023.
83. Zemke NR and Berk AJ: The adenovirus E1A C terminus suppresses a delayed antiviral response and modulates RAS signaling. Cell Host Microbe 22: 789-800.e5, 2017.
84. Ng D, Maitre B, Cummings D, Lin A, Ward LA, Rahbar R, Mossman KL, Ohashi PS and Gommerman JL: A Lymphotoxin/Type I IFN axis programs CD8+ T cells to infiltrate a Self-Tissue and propagate immunopathology. J Immunol 195: 4650-4659, 2015.
85. Stockenhuber K, Hegazy AN, West NR, Ilott NE, Stockenhuber A, Bullers SJ, Thornton EE, Arnold IC, Tucci A, Waldmann H, *et al*: Foxp3+ T reg cells control psoriasiform inflammation by restraining an IFN-I-driven CD8+ T cell response. J Exp Med 215: 1987-1998, 2018.
86. Xu HC, Grusdat M, Pandyra AA, Polz R, Huang J, Sharma P, Deenen R, Kohrer K, Rahbar R, Diefenbach A, *et al*: Type I interferon protects antiviral CD8+ T cells from NK cell cytotoxicity. Immunity 40: 949-960, 2014.
87. Ghazarian M, Revelo XS, Nohr MK, Luck H, Zeng K, Lei H, Tsai S, Schroer SA, Park YJ, Chng MHY, *et al*: Type I interferon responses drive intrahepatic T cells to promote metabolic syndrome. Sci Immunol 2: eaai7616, 2017.
88. Gracias DT, Stelekati E, Hope JL, Boesteanu AC, Doering TA, Norton J, Mueller YM, Fraietta JA, Wherry EJ, Turner M, *et al*: The microRNA miR-155 controls CD8(+) T cell responses by regulating interferon signaling. Nat Immunol 14: 593-602, 2013.
89. Perez RK, Gordon MG, Subramaniam M, Kim MC, Hartoularos GC, Targ S, Sun Y, Ogorodnikov A, Bueno R, Lu A, *et al*: Single-cell RNA-seq reveals cell type-specific molecular and genetic associations to lupus. Science 376: eabf1970, 2022.
90. Kruse B, Buzzai AC, Shridhar N, Braun AD, Gellert S, Knauth K, Pozniak J, Peters J, Dittmann P, Mengoni M, *et al*: CD4+ T cell-induced inflammatory cell death controls immune-evasive tumours. Nature 618: 1033-1040, 2023.
91. Duong E, Fessenden TB, Lutz E, Dinter T, Yim L, Blatt S, Bhutkar A, Wittrup KD and Spranger S: Type I interferon activates MHC class I-dressed CD11b+ conventional dendritic cells to promote protective anti-tumor CD8+ T cell immunity. Immunity 55: 308-323.e9, 2022.
92. Ghosh R, Joshi G, Shrimali NM, Bhardwaj K, Chorol T, Thinlas T, Koul PA, Prchal JT and Guchhait P: Tibetan PHD2D4E;C127S variant protects from viral diseases in hypoxia, but predispose to infections in normoxia via HIFα:IFN axis. PLoS Pathog 21: e1013296, 2025.
93. Liu SS, Bai TT, Que TL, Luo A, Liang YX, Song YX, Liu TY, Chen JW, Li J, Li N, *et al*: PI3K/AKT mediated de novo fatty acid synthesis regulates RIG-1/MDA-5-dependent type I IFN responses in BVDV-infected CD8+T cells. Vet Microbiol 291: 110034, 2024.
94. Ysebrant de Lendonck L, Tonon S, Nguyen M, Vandevenne P, Welsby I, Martinet V, Molle C, Charbonnier LM, Leo O and Goriely S: Interferon regulatory factor 3 controls interleukin-17 expression in CD8 T lymphocytes. Proc Natl Acad Sci USA 110: E3189-E3197, 2013.
95. Huber M, Suprunenko T, Ashhurst T, Marbach F, Raifer H, Wolff S, Strecker T, Viengkhou B, Jung SR, Obermann HL, *et al*: IRF9 prevents CD8+ T cell exhaustion in an extrinsic manner during acute lymphocytic choriomeningitis virus infection. J Virol 91: e01219-17, 2017.
96. Zimmermannova O, Ferreira AG, Ascic E, Velasco Santiago M, Kurochkin I, Hansen M, Met O, Caiado I, Shapiro IE, Michaux J, *et al*: Restoring tumor immunogenicity with dendritic cell reprogramming. Sci Immunol 8: eadd4817, 2023.
97. Bosteels C, Neyt K, Vanheerswynghels M, van Helden MJ, Sichien D, Debeuf N, De Prijck S, Bosteels V, Vandamme N, Martens L, *et al*: Inflammatory Type 2 cDCs acquire features of cDC1s and macrophages to orchestrate immunity to respiratory virus infection. Immunity 52: 1039-1056.e9, 2020.
98. Gatti G, Betts C, Rocha D, Nicola M, Grupe V, Ditada C, Nunez NG, Roselli E, Araya P, Dutto J, *et al*: Correction to: High IRF8 expression correlates with CD8 T cell infiltration and is a predictive biomarker of therapy response in ER-negative breast cancer. Breast Cancer Res 23: 48, 2021.
99. Poschel DB, Kehinde-Ige M, Klement JD, Yang D, Merting AD, Savage NM, Shi H and Liu K: IRF8 regulates intrinsic ferroptosis through repressing p53 expression to maintain tumor cell sensitivity to cytotoxic T lymphocytes. Cells 12: 310, 2023.
100. McDaniel MM, Kottyan LC, Singh H and Pasare C: Suppression of inflammasome activation by IRF8 and IRF4 in cDCs is critical for T cell priming. Cell Rep 31: 107604, 2020.

101. Nixon BG, Kuo F, Ji L, Liu M, Capistrano K, Do M, Franklin RA, Wu X, Kansler ER, Srivastava RM, *et al*: Tumor-associated macrophages expressing the transcription factor IRF8 promote T cell exhaustion in cancer. Immunity 55: 2044-2058.e5, 2022.
102. Sun L, St Leger AJ, Yu CR, He C, Mahdi RM, Chan CC, Wang H, Morse HC III and Egwuagu CE: Interferon regulator Factor 8 (IRF8) Limits ocular pathology during HSV-1 infection by restraining the activation and expansion of CD8+ T cells. PLoS One 11: e0155420, 2016.
103. Intlekofer AM, Takemoto N, Wherry EJ, Longworth SA, Northrup JT, Palanivel VR, Mullen AC, Gasink CR, Kaech SM, Miller JD, *et al*: Effector and memory CD8+ T cell fate coupled by T-bet and eomesodermin. Nat Immunol 6: 1236-1244, 2005.
104. Pearce EL, Mullen AC, Martins GA, Krawczyk CM, Hutchins AS, Zediak VP, Banica M, DiCioccio CB, Gross DA, Mao CA, *et al*: Control of effector CD8+ T cell function by the transcription factor eomesodermin. Science 302: 1041-1043, 2003.
105. Yao S, Buzo BF, Pham D, Jiang L, Taparowsky EJ, Kaplan MH and Sun J: Interferon regulatory factor 4 sustains CD8(+) T cell expansion and effector differentiation. Immunity 39: 833-845, 2013.
106. Man K, Miasari M, Shi W, Xin A, Henstridge DC, Preston S, Pellegrini M, Belz GT, Smyth GK, Febbraio MA, *et al*: The transcription factor IRF4 is essential for TCR affinity-mediated metabolic programming and clonal expansion of T cells. Nat Immunol 14: 1155-1165, 2013.
107. Chapman NM, Zeng H, Nguyen TM, Wang Y, Vogel P, Dhungana Y, Liu X, Neale G, Locasale JW and Chi H: mTOR coordinates transcriptional programs and mitochondrial metabolism of activated Treg subsets to protect tissue homeostasis. Nat Commun 9: 2095, 2018.
108. Nayar R, Schutten E, Bautista B, Daniels K, Prince AL, Enos M, Brehm MA, Swain SL, Welsh RM and Berg LJ: Graded levels of IRF4 regulate CD8+ T cell differentiation and expansion, but not attrition, in response to acute virus infection. J Immunol 192: 5881-5893, 2014.
109. Conley JM, Gallagher MP, Rao A and Berg LJ: Activation of the tec kinase ITK controls graded IRF4 expression in response to variations in TCR signal strength. J Immunol 205: 335-345, 2020.
110. Cho HS, Ha S, Shin HM, Reboldi A, Hall JA, Huh JR, Usherwood EJ and Berg LJ: CD8+ T cells require ITK-mediated TCR signaling for migration to the intestine. Immunohorizons 4: 57-71, 2020.
111. Cao Y, Li H, Sun Y, Chen X, Liu H, Gao X and Liu X. Interferon regulatory factor 4 regulates thymocyte differentiation by repressing Runx3 expression. Eur J Immunol 40: 3198-3209, 2010.
112. Zou D, Fu J, Guo Z and Chen W: Interferon regulatory factor 4 deficiency in CD8+ T cells abrogates terminal effector differentiation and promotes transplant acceptance. Immunology 161: 364-379, 2020.
113. Raczkowski F, Ritter J, Heesch K, Schumacher V, Guralnik A, Hocker L, Raifer H, Klein M, Bopp T, Harb H, *et al*: The transcription factor Interferon Regulatory Factor 4 is required for the generation of protective effector CD8+ T cells. Proc Natl Acad Sci USA 110: 15019-15024, 2013.
114. Nowyhed HN, Huynh TR, Thomas GD, Blatchley A and Hedrick CC: Cutting Edge: The orphan nuclear receptor Nr4a1 regulates CD8+ T cell expansion and effector function through direct repression of Irf4. J Immunol 195: 3515-3519, 2015.
115. Li Q, Yan Y, Liu J, Huang X, Zhang X, Kirschning C, Xu HC, Lang PA, Dittmer U, Zhang E, *et al*: Toll-Like receptor 7 activation enhances CD8+ T cell effector functions by promoting cellular glycolysis. Front Immunol 10: 2191, 2019.
116. Huber M and Lohoff M: IRF4 provides rations for cytotoxic CD8(+) T cell soldiers. Immunity 39: 797-799, 2013.
117. Li X, Zhai S, Zhang J, Zhang D, Wang S, Wang L and Yu J: Interferon regulatory Factor 4 correlated with immune cells infiltration could predict prognosis for patients with lung adenocarcinoma. Front Oncol 11: 698465, 2021.
118. Baharom F, Ramirez-Valdez RA, Tobin KKS, Yamane H, Dutertre CA, Khalilnezhad A, Reynoso GV, Coble VL, Lynn GM, Mule MP, *et al*: Intravenous nanoparticle vaccination generates stem-like TCF1+ neoantigen-specific CD8+ T cells. Nat Immunol 22: 41-52, 2021.
119. Kwon H, Schafer JM, Song NJ, Kaneko S, Li A, Xiao T, Ma A, Allen C, Das K, Zhou L, *et al*: Androgen conspires with the CD8+ T cell exhaustion program and contributes to sex bias in cancer. Sci Immunol 7: eabq2630, 2022.
120. Pais Ferreira D, Silva JG, Wyss T, Fuertes Marraco SA, Scarpellino L, Charmoy M, Maas R, Siddiqui I, Tang L, Joyce JA, *et al*: Central memory CD8+ T cells derive from stem-like Tcf7hi effector cells in the absence of cytotoxic differentiation. Immunity 53: 985-1000.e11, 2020.
121. Pick J, Arra A, Lingel H, Hegel JK, Huber M, Nishanth G, Jorch G, Fischer KD, Schluter D, Tedford K, *et al*: CTLA-4 (CD152) enhances the Tc17 differentiation program. Eur J Immunol 44: 2139-2152, 2014.
122. Huber M, Heink S, Pagenstecher A, Reinhard K, Ritter J, Visekruna A, Guralnik A, Bollig N, Jeltsch K, Heinemann C, *et al*: IL-17A secretion by CD8+ T cells supports Th17-mediated autoimmune encephalomyelitis. J Clin Invest 123: 247-260, 2013.
123. Laribi B, Sahraian MA, Shekarabi M, Emamnejad R, Marzban M, Sadaghiani S and Izad M: Characterization of CD4+ and CD8+ T cell subsets and interferon regulatory factor 4 (IRF4) in MS patients treated with fingolimod (FTY-720): A Follow-up study. Iran J Allergy Asthma Immunol 17: 346-360, 2018.
124. Miyakoda M, Honma K, Kimura D, Akbari M, Kimura K, Matsuyama T and Yui K: Differential requirements for IRF4 in the clonal expansion and homeostatic proliferation of naive and memory murine CD8(+) T cells. Eur J Immunol 48: 1319-1328, 2018.
125. Harberts A, Schmidt C, Schmid J, Reimers D, Koch-Nolte F, Mittrucker HW and Raczkowski F: Interferon regulatory factor 4 controls effector functions of CD8+ memory T cells. Proc Natl Acad Sci USA 118: e2014553118, 2021.
126. Solouki S, Huang W, Elmore J, Limper C, Huang F and August A: TCR signal strength and antigen affinity regulate CD8(+) memory T cells. J Immunol 205: 1217-1227, 2020.
127. Wu H, Witzl A and Ueno H: Assessment of TCR signal strength of antigen-specific memory CD8+ T cells in human blood. Blood Adv 3: 2153-2163, 2019.
128. Behr FM, Parga-Vidal L, Kragten NAM, van Dam TJP, Wesselink TH, Sheridan BS, Arens R, van Lier RAW, Stark R and van Gisbergen K: Tissue-resident memory CD8+ T cells shape local and systemic secondary T cell responses. Nat Immunol 21: 1070-1081, 2020.
129. Topham DJ and Reilly EC: Tissue-resident memory CD8+ T cells: From phenotype to function. Front Immunol 9: 515, 2018.
130. Lu L, Zhu F, Zhang M, Li Y, Drennan AC, Kimpara S, Rumball I, Selzer C, Cameron H, Kellicut A, *et al*: Gene regulation and suppression of type I interferon signaling by STAT3 in diffuse large B cell lymphoma. Proc Natl Acad Sci USA 115: E498-E505, 2018.
131. Icardi L, Lievens S, Mori R, Piessevaux J, De Cauwer L, De Bosscher K and Tavernier J: Opposed regulation of type I IFN-induced STAT3 and ISGF3 transcriptional activities by histone deacetylases (HDACS) 1 and 2. FASEB J 26: 240-249, 2012.
132. Icardi L, Mori R, Gesellchen V, Eyckerman S, De Cauwer L, Verhelst J, Vercauteren K, Saelens X, Meuleman P, Leroux-Roels G, *et al*: The Sin3a repressor complex is a master regulator of STAT transcriptional activity. Proc Natl Acad Sci USA 109: 12058-12063, 2012.
133. Jung IY, Narayan V, McDonald S, Rech AJ, Bartoszek R, Hong G, Davis MM, Xu J, Boesteanu AC, Barber-Rotenberg JS, *et al*: BLIMP1 and NR4A3 transcription factors reciprocally regulate antitumor CAR T cell stemness and exhaustion. Sci Transl Med 14: eabn7336, 2022.
134. Luo H and Tian M: Transcription factors PU.1 and IRF4 regulate activation induced cytidine deaminase in chicken B cells. Mol Immunol 47: 1383-1395, 2010.
135. Li P, Spolski R, Liao W, Wang L, Murphy TL, Murphy KM and Leonard WJ: BATF-JUN is critical for IRF4-mediated transcription in T cells. Nature 490: 543-546, 2012.
136. Tsao HW, Kaminski J, Kurachi M, Barnitz RA, DiIorio MA, LaFleur MW, Ise W, Kurosaki T, Wherry EJ, Haining WN and Yosef N: Batf-mediated epigenetic control of effector CD8+ T cell differentiation. Sci Immunol 7: eabi4919, 2022.
137. Vecellio M, Roberts AR, Cohen CJ, Cortes A, Knight JC, Bowness P and Wordsworth BP: The genetic association of RUNX3 with ankylosing spondylitis can be explained by allele-specific effects on IRF4 recruitment that alter gene expression. Ann Rheum Dis 75: 1534-1540, 2016.
138. Seo H, Gonzalez-Avalos E, Zhang W, Ramchandani P, Yang C, Lio CJ, Rao A and Hogan PG: BATF and IRF4 cooperate to counter exhaustion in tumor-infiltrating CAR T cells. Nat Immunol 22: 983-995, 2021.

139. Xin G, Schauder DM, Lainez B, Weinstein JS, Dai Z, Chen Y, Esplugues E, Wen R, Wang D, Parish IA, *et al*: A Critical role of IL-21-Induced BATF in sustaining CD8-T-Cell-mediated chronic viral control. Cell Rep 13: 1118-1124, 2015.
140. Grusdat M, McIlwain DR, Xu HC, Pozdeev VI, Knievel J, Crome SQ, Robert-Tissot C, Dress RJ, Pandyra AA, Speiser DE, *et al*: IRF4 and BATF are critical for CD8+ T-cell function following infection with LCMV. Cell Death Differ 21: 1050-1060, 2014.
141. Chang YK, Zuo Z and Stormo GD: Quantitative profiling of BATF family proteins/JUNB/IRF hetero-trimers using Spec-seq. BMC Mol Biol 19: 5, 2018.
142. Kurachi M, Barnitz RA, Yosef N, Odorizzi PM, DiIorio MA, Lemieux ME, Yates K, Godec J, Klatt MG, Regev A, *et al*: The transcription factor BATF operates as an essential differentiation checkpoint in early effector CD8+ T cells. Nat Immunol 15: 373-383, 2014.
143. Murphy TL, Tussiwand R and Murphy KM: Specificity through cooperation: BATF-IRF interactions control immune-regulatory networks. Nat Rev Immunol 13: 499-509, 2013.
144. Harrer DC, Bezler V, Hartley J, Herr W and Abken H: IRF4 downregulation improves sensitivity and endurance of CAR T cell functional capacities. Front Immunol 14: 1185618, 2023.
145. Beguelin W, Teater M, Gearhart MD, Calvo Fernandez MT, Goldstein RL, Cardenas MG, Hatzi K, Rosen M, Shen H, Corcoran CM, *et al*: EZH2 and BCL6 cooperate to assemble CBX8-BCOR complex to repress bivalent promoters, mediate germinal center formation and lymphomagenesis. Cancer Cell 30: 197-213, 2016.
146. Gay-Mimbrera J, Lozano-Ojalvo D, Gómez-Arias PJ, Rivera-Ruiz I, Aguilar-Luque M, Mochón-Jiménez C, Andújar Pulido E, Pérez-Alegre M, Guttman-Yassky E and Ruano J: Comprehensive single-cell chromatin and transcriptomic profiling of peripheral immune cells in nonsegmental vitiligo. Br J Dermatol 193: 115-124, 2025.
147. Thompson CD, Matta B and Barnes BJ: Therapeutic targeting of IRFs: Pathway-dependence or Structure-Based? Front Immunol 9: 2622, 2018.
148. Geng F, Chen J, Song B, Tang Z, Li X, Zhang S, Yang T, Liu Y, Mo W, Zhang Y, *et al*: Chaperone- and PTM-mediated activation of IRF1 tames radiation-induced cell death and the inflammatory response. Cell Mol Immunol 21: 856-872, 2024.
149. Rios CI, DiCarlo AL and Marzella L: Cutaneous radiation injuries: Models, assessment and treatments. Radiat Res 194: 310-313, 2020.
150. Chu Y, Li R, Qian L, Liu F, Xu R, Meng F, Ke Y, Shao J, Yu L, Liu Q and Liu B: Tumor eradicated by combination of imiquimod and OX40 agonist for in situ vaccination. Cancer Sci 112: 4490-4500, 2021.
151. Adams S, Kozhaya L, Martiniuk F, Meng TC, Chiriboga L, Liebes L, Hochman T, Shuman N, Axelrod D, Speyer J, *et al*: Topical TLR7 agonist imiquimod can induce immune-mediated rejection of skin metastases in patients with breast cancer. Clin Cancer Res 18: 6748-6757, 2012.
152. Oya K, Nakamura Y, Zhenjie Z, Tanaka R, Okiyama N, Ichimura Y, Ishitsuka Y, Saito A, Kubota N, Watanabe R, *et al*: Combination treatment of topical imiquimod Plus Anti-PD-1 antibody exerts significantly potent antitumor effect. Cancers (Basel) 13: 3948, 2021.
153. Ishiguro K, Kitajima H, Niinuma T, Maruyama R, Nishiyama N, Ohtani H, Sudo G, Toyota M, Sasaki H, Yamamoto E, *et al*: Dual EZH2 and G9a inhibition suppresses multiple myeloma cell proliferation by regulating the interferon signal and IRF4-MYC axis. Cell Death Discov 7: 7, 2021.
154. Ma Y, Walsh MJ, Bernhardt K, Ashbaugh CW, Trudeau SJ, Ashbaugh IY, Jiang S, Jiang C, Zhao B, Root DE, *et al*: CRISPR/Cas9 screens reveal Epstein-barr Virus-transformed B cell host dependency factors. Cell Host Microbe 21: 580-591.e7, 2017.
155. Suleman M, Murshed A, Imran K, Khan A, Ali Z, Albekairi NA, Wei DQ, Yassine HM and Crovella S: Abrogation of ORF8-IRF3 binding interface with Carbon nanotube derivatives to rescue the host immune system against SARS-CoV-2 by using molecular screening and simulation approaches. BMC Chem 18: 99, 2024.
156. Agius MP, Song C, Liu Q, Iemura T, Hevenor L, Payne NC, Pistofidis RS, Pantano L, Zhao H, Seo HS, *et al*: Pharmacological targeting of IRF4 as a therapeutic strategy for multiple myeloma. Nat Chem Biol: May 28, 2026 (Epub ahead of print). doi: 10.1038/s41589-026-02228-8.
157. Zhang XJ, Jiang DS and Li H: The interferon regulatory factors as novel potential targets in the treatment of cardiovascular diseases. Br J Pharmacol 172: 5457-5476, 2015.
158. Alosaimi B, Awadalla M, Alturaiki W, Chen Z, Zhang Z, Zhu A, Rebh F, Alshukairi AN, Zhao J and Alkadi HS: A 10 year Long-Lived cellular and humoral MERS-CoV immunity Cross-recognizing the Wild-type and variants of SARS-CoV-2: A Potential One-way MERS-CoV Cross-protection toward a Pan-coronavirus vaccine. J Med Virol 97: e70071, 2025.

Copyright © 2026 Wang et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.