Trends in Immunology

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Review

Reframing IL-27: a central regulator of CD8$^+$ T cell immunity

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Interleukin-27 (IL-27), a member of the IL-12 cytokine family, was long viewed primarily as a regulator of CD4$^+$ T cell immunity. Subsequent studies revealed that IL-27 also directly modulates CD8$^+$ T cells, displaying both stimulatory and inhibitory potential. Recent work extends this earlier literature, showing that IL-27 in infection and cancer can promote effector differentiation, sustain survival, and reverse dysfunction, often without the systemic toxicity associated with related cytokines. This review outlines the molecular features, signaling mechanisms, and cellular sources of IL-27, integrating emerging evidence from viral, tumor, and autoimmune settings. We propose that IL-27 operates not as an inherently pro- or anti-inflammatory cytokine but as a context-dependent tuner of CD8$^+$ T cell cytotoxic immunity, offering new opportunities for therapeutic exploitation.

IL-27: 20 years after

IL-27 was first described in the early 2000s as a cytokine that shapes CD4$^+$ T cell responses [1,2]. Early studies highlighted its ability to promote type 1 T helper cell (Th1) differentiation, limit Th17 expansion, and induce IL-10 production [2]. These findings initially defined IL-27 as a context-dependent cytokine capable of both activating and limiting immune responses. Consequently, the field centered on its regulatory activity within the CD4$^+$ T cell compartment, where its primary immunological role was thought to reside [3].

Over time, accumulating evidence has shown that IL-27 also acts directly on CD8$^+$ T cells, again underscoring its dual capacity to either promote or restrain their activity [3,4]. In viral infections, cancer, autoimmunity, and vaccination, IL-27 can enhance cytotoxic differentiation, support survival, sustain memory formation, and alleviate functional exhaustion [3,4]. However, in similar settings IL-27 can also limit T cell responses or be dispensable, as mice lacking the IL-27 receptor often display exacerbated inflammation in response to diverse challenges [3,4]. These findings reveal that IL-27 exerts both stimulatory and regulatory influences *in vivo*, depending on the context, timing, and disease setting.

This evolving view reflects a broader paradigm in cytokine biology: molecules such as IL-27 should not be defined as inherently pro- or anti-inflammatory but instead as context-dependent modulators that fine-tune immune responses. IL-27 is therefore not only a regulator of upstream helper circuits but also a direct instructor of CD8$^+$ T cell fate, being capable of adjusting cytotoxic immunity in a tissue- and signal-specific manner. The advent of single-cell technologies and mechanistic *in vivo* studies has now made it possible to revisit the role of IL-27 with a more integrated, systems-level perspective.

In this review we synthesize recent advances that helped in delineating the impact of IL-27 on CD8$^+$ T cells and relate them to earlier discoveries that laid the foundation for this field. By

Highlights

IL-27, long studied for its effects on CD4$^+$ T cells, is now recognized as a direct instructor of CD8$^+$ T cell fate in infection, cancer, and autoimmunity.

IL-27 signaling in CD8$^+$ T cells can both enhance cytotoxicity, proliferation, and recovery from exhaustion or dysfunction, while also restraining effector functions, in a context-dependent manner.

IL-27 fosters transcriptional rewiring of CD8$^+$ T cells and reinforces functionality and responsiveness to checkpoint blockade.

IL-27 treatment differs from related cytokines such as IL-12 and IL-2 by sustaining effector programs while minimizing bystander effects and systemic toxicity.

Targeted strategies, including recombinant cytokine delivery, oncolytic viruses, engineered T cells, and mRNA-based platforms, highlight IL-27 as a promising component of next-generation immunotherapies.

Significance

This review frames IL-27 as a central instructor of CD8$^+$ T cell immunity, moving beyond its traditional association with CD4$^+$ T cell regulation. By integrating earlier literature with recent mechanistic insights from infection, cancer and autoimmunity, we highlight IL-27 as a unique cytokine that can tune CD8$^+$ T functions in a context-dependent manner. Understanding the contextual logic of IL-27 signaling not only clarifies its dual roles across tissues but also positions it as a promising target for next-generation immunotherapies.

integrating both early and recent insights, we provide a unified view of the role of IL-27 in infection, cancer, and autoimmunity, and highlight its emerging potential as a therapeutic modulator of CD8$^+$ T cell immunity.

IL-27 structure and signaling

IL-27, a member of the **IL-12 cytokine family** (see Glossary), is a heterodimer composed of the subunits p28 and EBI3 (Figure 1). The p28 subunit is structurally related to IL-6, whereas EBI3 resembles the soluble receptor gp130. Although p28 can be secreted independently, it is inactive and may act as a decoy in some settings, whereas EBI3 can pair with p35 to form IL-35, which underscores the specificity of the IL-27 heterodimer [3,5].

IL-27 signals through a receptor composed of IL-27 receptor α (IL-27RA, also known as WSX-1 or TCCR) and gp130, the latter being shared with IL-6 and IL-11 receptors [2,5]. Upon cytokine binding, IL-27R recruits gp130 and activates the associated Janus kinases 1 and 2 (JAK1 and JAK2), as well as tyrosine kinase 2 (TYK2), which phosphorylate cytoplasmic motifs that serve as docking sites for **signal transducer and activator of transcription (STAT)** proteins [2] (Figure 1). In most immune cells, IL-27 primarily activates STAT1 and STAT3, and the balance between the two pathways is shaped by cell identity and context. STAT1 drives T-bet and IFN-γ production, whereas STAT3 promotes survival and IL-10 expression [6,7] (Figure 1). In some settings, IL-27 also engages STAT5, phosphoinositide 3-kinase (PI3K)–protein kinase B (PKB or AKT), and mitogen-activated protein kinase (MAPK) pathways [7,8], although these are less well characterized in CD8$^+$ T cells.

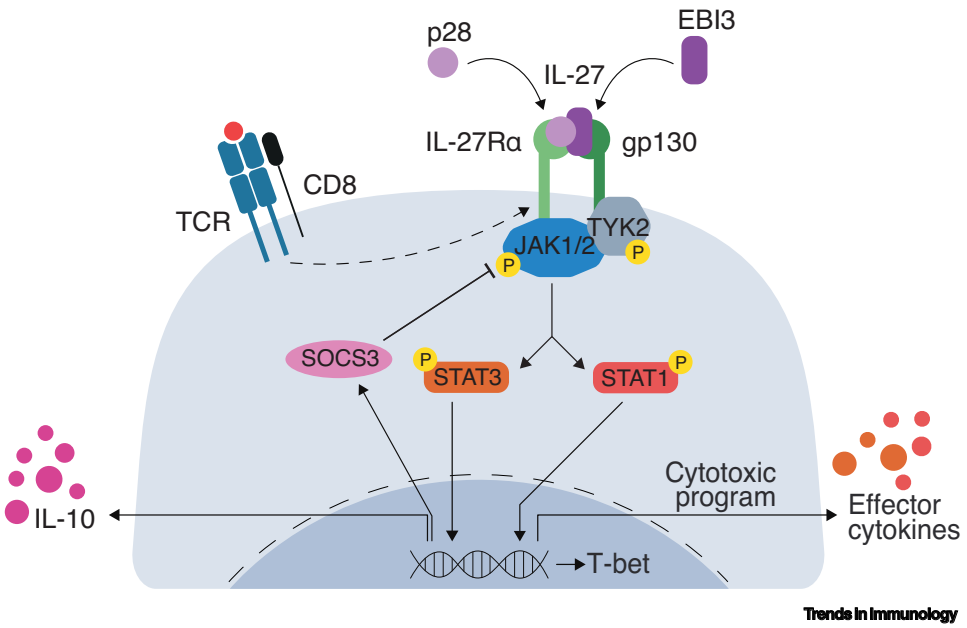

Figure 1. IL-27 signaling pathway in CD8$^+$ T cells. IL-27 is a heterodimer composed of the p28 and EBI3 subunits that signals through a receptor complex formed by IL-27RA and gp130. Engagement of IL-27 activates the Janus kinases 1 and 2 (JAK1/JAK2), and tyrosine kinase 2 (TYK2), leading to phosphorylation of signal transducer and activator of transcription factors 1 and 3 (STAT1 and STAT3). These transcription factors translocate to the nucleus and regulate key programs in CD8$^+$ T cells, including induction of T-bet, production of effector cytokines, and acquisition of a cytotoxic phenotype. STAT3 activation also drives suppressor of cytokine signaling 3 (SOCS3) and IL-10 expression, which contribute to negative feedback and regulatory outputs, highlighting the dual nature of IL-27 in balancing effector and regulatory functions. Abbreviations: P, phosphorylation; TCR, T cell receptor.

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IL-27Rα expression is inducible and is upregulated by T cell receptor (TCR) stimulation, interferons (IFNs), and inflammatory cytokines [3]. This regulation makes IL-27 responsiveness temporally gated and dependent on local immune activation. Receptor signaling also induces suppressor of cytokine signaling (SOCS) proteins, particularly SOCS3, which provide negative feedback to restrain prolonged signaling [9] (Figure 1). Beyond classical membrane-bound signaling, IL-27 may also act through soluble receptor components, a mechanism described for related cytokines but still under investigation for IL-27 [10]. Altogether, IL-27 is structurally conserved but functionally versatile, and is capable of integrating environmental cues to shape immune responses across contexts. Although most of its biology was initially defined in $CD4^+$ T cells and myeloid populations, recent evidence has clarified a direct, context-specific role in $CD8^+$ T cell programming – the focus of the following sections.

IL-27 cellular sources and regulation

The functional impact of IL-27 on T cells depends not only on receptor expression and downstream signaling but also on the local availability and cellular source of the cytokine. IL-27 is primarily produced by antigen-presenting cells (APCs), including dendritic cells (DCs), macrophages, and B cells [3,11]. Among these, **classical dendritic cells (cDCs)**, monocytes, and tissue-resident macrophages represent the most consistent and well-characterized sources [3]. cDC1s in particular dominate IL-27 production in both infection and tumor models, especially under type I IFN and Toll-like receptor (TLR) stimulation [12,13]. Insights into IL-27 production have been greatly advanced by the development of IL-27 reporter mice, such as IL-27p28–GFP knock-in models, which enable direct visualization of cytokine-producing cells *in vivo* [14]. These studies revealed that IL-27 expression is highly dynamic and confined to specific antigen-presenting cell subsets that integrate environmental cues, including type I IFNs and pattern-recognition receptor signals.

Secretion of bioactive IL-27 requires the coexpression and proper folding of both p28 and EBI3 within the same APC, with p28 generally acting as the limiting subunit (Figure 2). p28 is

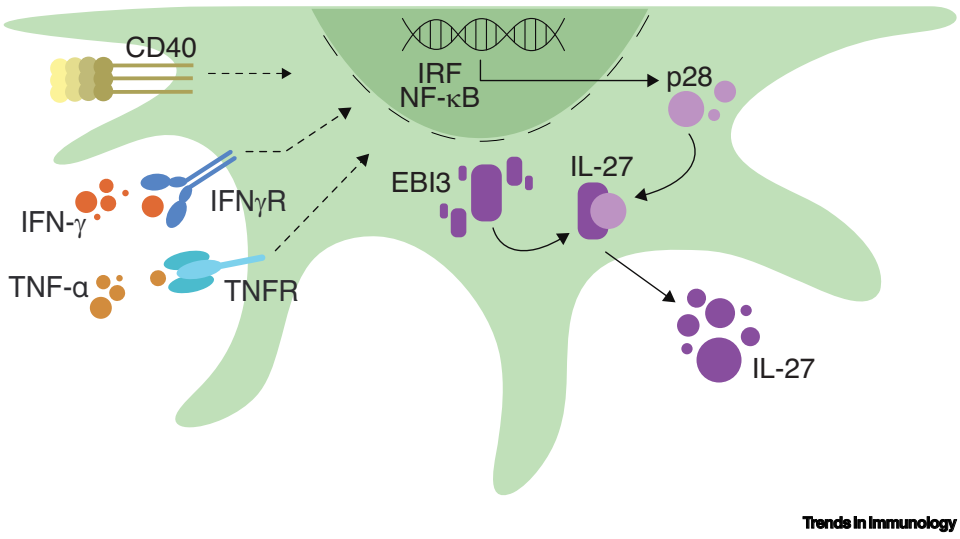

Figure 2. Regulation of IL-27 production by antigen-presenting cells (APCs). IL-27 is a heterodimer of the subunits p28 and EBI3 whose expression is induced in antigen-presenting cells (APCs) by signals downstream of CD40, IFNγR, and TNFR. Engagement of these receptors activates transcription factors such as interferon regulatory factors (IRFs) and NF-κB which drive *IL27* gene expression. Secretion of IL-27 requires coexpression and proper folding of both p28 and EBI3 within the same APC, and p28 generally acts as the limiting subunit. Abbreviations: IFN-γ, interferon γ; IFNγR, IFN-γ receptor; NF-κB: nuclear factor κ light-chain enhancer of activated B cells; TNF-α: tumor necrosis factor α; TNFR, TNF receptor.

Glossary

Adeno-associated virus (AAV): a small, non-pathogenic parvovirus that is widely used as a gene therapy vector because it can efficiently deliver genetic material to diverse tissues with low immunogenicity and long-term expression.

Classical dendritic cells (cDCs): professional antigen-presenting cells (APCs) that are specialized in capturing, processing, and presenting antigens to T cells. Subsets (cDC1 and cDC2) differentially prime $CD8^+$ and $CD4^+$ T cell responses.

Cytotoxic T lymphocytes (CTLs): $CD8^+$ T cells that are specialized in recognizing and killing infected or malignant cells through perforin and granzyme release and cytokine production, and play a central role in antiviral and antitumor immunity.

Ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1/CD39): an ectoenzyme expressed on subsets of T cells that hydrolyzes extracellular ATP to AMP and serves as a marker of both chronic activation/exhaustion and tissue-resident or tumor-reactive CTLs.

IL-12 cytokine family: a group of heterodimeric cytokines that pair in different combinations, this family includes IL-12, IL-23, IL-27, and IL-35.

Kupffer cells (KCs): specialized resident liver macrophages that sense and clear antigens from the blood and shape local immune responses through antigen presentation and cytokine release.

Lipid nanoparticles (LNPs): synthetic, nanoscale vesicles composed of ionizable lipids, cholesterol, phospholipids, and polyethylene glycol (PEG)-conjugated lipids that self-assemble to encapsulate and deliver nucleic acids.

Signal transducers and activators of transcription (STATs): a family of cytoplasmic transcription factors that mediate cellular responses to cytokines and growth factors through tyrosine phosphorylation-mediated activation.

Stem cell antigen 1 (SCA-1): a surface glycoprotein of the Ly6 family that is used as a marker of stem and progenitor cells in mice and is also upregulated on activated $CD8^+$ T cells as a sign of effector differentiation.

transcriptionally induced by interferon regulatory factor (IRF) and NF-κB family members downstream of inflammatory cues such as IFN-γ, TNF family members, CD40, poly(I:C), and bacterial products [15–19] (Figure 2). By contrast, EBI3 is more broadly and often constitutively expressed, which enables rapid heterodimer formation once p28 becomes available [20]. In tumors, IL-27 expression has been observed in DCs and tumor-associated macrophages [21,22].

Beyond myeloid populations, several non-canonical sources of IL-27 have emerged. B cells can provide indispensable IL-27 during persistent lymphocytic choriomeningitis virus (LCMV) infection [23], and B-1a cells in the central nervous system can secrete IL-27 to limit Th17 responses and suppress neuroinflammation in models of experimental autoimmune encephalomyelitis [24]. Regulatory T cells (Tregs) in the gut have also been shown to produce IL-27 which contributes to local control of Th17-driven inflammation [25]. In some settings, stromal or epithelial cells express IL-27 subunits, although the extent of secretion and its functional relevance remain uncertain [11]. Altogether, all these findings highlight that IL-27 production is spatially and temporally restricted, shaped by tissue-specific cues and inflammatory mediators.

IL-27 tuning of CD8$^+$ T cell responses

Earlier studies showed that IL-27 could influence CD8$^+$ T cells, but mechanistic insights were limited [4,26]. In recent years, however, multiple reports have added insights into IL-27 shaping of CD8$^+$ T cell fate and function across infection, cancer, and autoimmunity (Table 1, Key Table). In the following sections we synthesize these findings according to their disease settings and highlight advances compared to the previous literature.

Infection

Chronic viral infections drive CD8$^+$ T cells into dysfunction or exhaustion, which represent a major barrier to effective immunity and immunotherapy [27,28]. Earlier work revealed that the effects of IL-27 on CD8$^+$ T cells can be a double-edged sword. A substantial body of studies demonstrated that IL-27 enhances antiviral CD8$^+$ T cell activity, and its signaling is required for the production of effector cytokines such as IFN-γ in multiple infection models [29–31]. Conversely, other reports described IL-27 as being inhibitory or dispensable, showing that it can restrain cytotoxic T cell expansion or memory formation, as observed in *Listeria monocytogenes*, murine cytomegalovirus (MCMV), and other infection contexts [32–36]. Together, these findings pointed to a context-dependent role for IL-27 in which its impact varies according to pathogen type, tissue environment, and phase of infection.

In recent years the activating function of IL-27 in antiviral CD8$^+$ T cell responses has become particularly evident. In humans, its essential role was revealed by individuals carrying biallelic *IL27RA* mutations who developed life-threatening Epstein–Barr virus (EBV) infections [37]. EBV typically establishes lifelong latency in B cells and is controlled by a robust CD8$^+$ T cell response [38]. In IL27RA-deficient individuals, CD8$^+$ T cells fail to activate STAT1 and STAT3 in response to IL-27, show impaired granzyme B and IFN-γ production, and upregulate exhaustion markers including LAG3 and 2B4/CD244. Mechanistically, EBV-infected B cells themselves produce IL-27 which acts as a costimulatory signal during naive CD8$^+$ T cell priming. These effects were most evident under low TCR stimulation a condition that mimics early infection when antigen availability is limited. Thus, IL-27 amplifies primary cytotoxic responses in humans and bridges priming, effector differentiation, and memory formation.

A particularly illustrative example of the role of IL-27 in rescuing antiviral CD8$^+$ T cell responses comes from chronic hepatitis B virus (HBV) infection [39]. HBV is a hepatotropic virus that often establishes lifelong persistence, largely because HBV-specific CD8$^+$ T cells, that although

Key table

Table 1. Summary of recent findings on IL-27-driven direct programming of CD8$^+$ T cells across contexts compared to control conditions[a]

General context	Disease context	Study model	IL-27 source	CD8$^+$ T cell outcome	Refs
Infection	Epstein–Barr virus infection (EBV)	**Human**	B cells	↑ CTL program (IFN-γ, GRZM-B) ↑ STAT1, STAT3 signaling ↓ Exhaustion markers (LAG3, 2B4)	Martin *et al.* [37]
	Hepatitis B virus infection (HBV)	**Mouse** (HBV replication-competent transgenic mouse model) **Human** (CHB – chronic HBV)	Liver-resident macrophages (Kupffer cells)	↑ CTL program (IFN-γ, GRZM-B, LAMP1) ↑ Activation markers (SCA-1, CD39, KLRG1, ICOS, CD44) ↑ Proliferation ↓ Exhaustion markers (TIM3, 2B4, TIGIT)	Venzin *et al.* [39]
	Human immunodeficiency virus (HIV)	**Human**	NA	↑ CTL program (IFN-γ) ↑ STAT1, T-bet signaling	Cheng *et al.* [46]
Tumors	Solid tumor	**Mouse** (MC38 colon cancer, B16-F10 melanoma, E0771 mammary tumor) **Human** (mUC –metastatic urothelial bladder carcinoma; mNSCLC – metastatic non-small cell lung carcinoma)	Tumor-associated macrophages (TAMs), DCs	↑ CTL program (IFN-γ, GRZM-B) ↑ STAT1, IRF1/8 signaling ↓ Exhaustion markers (TOX) ↑ Activation markers (SCA-1, Ly6C, PD-L1)	Bréart *et al.* [21]
	Solid tumor	**Mouse** (B16 melanoma)	DCs	↑ CTL program (IFN-γ)	Chudnovskiy *et al.* [12]
	Hematologic cancer	**Mouse** (*Eμ–TCL1* leukemic mouse model) **Human** (CLL)	NA	↑ CTL program (IFN-γ) ↑ Proliferation ↑ Activation markers (CD44) ↓ Exhaustion markers (TIGIT)	Pagano *et al.* [58]
	Solid tumor	**Mouse** (Neuro-2a neuroblastoma)	NA	↑ CTL program (GRZM-B, perforin) ↑ STAT1, STAT3 signaling ↑ Trafficking (CXCR3)	Gerhardt *et al.* [59]
	Solid tumor	**Mouse** (B16 melanoma, LLC Lewis lung carcinoma)	NA	↑ Effector program	LaFleur *et al.* [56]
Autoimmunity	Diabetes/Sjögren's disease	**Mouse** (non-obese diabetic/severe combined immunodeficiency, NOD-SCID)	NA	↑ Effector program (IFN-γ, T-bet) ↑ Activation markers (CD39, CD73)	Debreceni *et al.* [64]
	Multiple sclerosis	**Human**	NA	↑ STAT3 signaling ↑ Activation markers (CD95, ICAM-1, PD-L1)	Clénet *et al.* [65]

[a]Arrows indicate increased (↑) or decreased (↓) expression/production. Earlier studies and a more comprehensive list of references can be found in the main text.

numerically present, become dysfunctional and progressively lose cytotoxicity and cytokine production [40,41]. Recent work has identified a liver-centric help circuit in which antigen-experienced CD4$^+$ T cells reprogram **Kupffer cells (KCs)** through CD40–CD40L interactions [39]. Licensed KCs then secrete IL-27, which acts directly on HBV-specific CD8$^+$ T cells to reinstate effector differentiation, proliferation, and cytokine production [39]. IL-27 proved to be indispensable in this process: its blockade abrogated CD8$^+$ T cell rescue, and exogenous recombinant IL-27 was sufficient to restore cytotoxicity and intrahepatic viral control without detectable systemic toxicity [39]. IL-27-driven rescue was characterized by recovery of granzyme B

and IFN-γ, enhanced proliferation, and upregulation of surface markers such as **ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1/CD39)** and **stem cell antigen 1 (SCA-1)** [39]. Notably, SCA-1 expression had been previously associated with IL-27 signaling in cytotoxic and memory precursor-like effector CD8$^+$ T cells [42,43]. Importantly, the relevance of this pathway extends to humans: *ex vivo* stimulation of T cells from chronically infected patients showed that IL-27 selectively enhances HBV-specific CD8$^+$ T cell IFN-γ production [39]. Together, these findings establish IL-27 as an indispensable cytokine produced by licensed KCs that directly converts dysfunctional, hepatocyte-primed, CD8$^+$ T cells into functional effectors that can control viral replication [39]. Beyond redefining the liver as an autonomous site of immune instruction, this work positions IL-27 as the crucial mediator of intrahepatic T cell cooperation and a tractable therapeutic target [39]. The ability of IL-27 to restore cytotoxicity in patient-derived HBV-specific CD8$^+$ T cells underscores its translational potential placing it at the center of future strategies aimed at reversing T cell dysfunction to achieve functional cure [39].

Other chronic infections show similar patterns. In hepatitis C virus (HCV) infection, IL-27 transcripts were significantly reduced in blood from patients compared to healthy controls, suggesting that impaired availability may contribute to defective cytotoxic responses [44]. A recent study in HIV-infected individuals has further demonstrated the capacity of IL-27 to restore cytotoxic function in exhausted CD8$^+$ T cells. HIV infection is characterized by persistent immune activation, and virus-specific CD8$^+$ T cells exhibit an exhausted phenotype that limits their ability to eliminate infected cells [45]. In this work, the global transcriptomic changes induced in CD8$^+$ T cells treated with IL-27 *ex vivo* were analyzed, and IL-27 treatment was shown to improve the phenotype and function of HIV-specific CD8$^+$ T cells as well as enhancing their IFN-γ production [46]. At the transcriptional level, IL-27 stimulation triggered the expression of genes associated with IFN/STAT1 signaling pathway activation and antiviral responses [46]. Mechanistically, these effects were found to depend on STAT1 and T-bet signaling, which underscores the transcriptional integration of IL-27 cues in supporting CD8$^+$ T cell effector programs [46].

Together, these recent studies establish IL-27 as a context-dependent amplifier of antiviral CD8$^+$ T cell function. Its unifying role is to sustain cytotoxicity and survival under conditions of chronic antigen exposure or suboptimal costimulation – precisely the settings where T cells are most vulnerable. This functional logic has drawn increasing attention to IL-27 in cancer immunology where CD8$^+$ T cells face comparable barriers.

Tumors

In the tumor microenvironment, CD8$^+$ T cells are exposed to chronic antigen, suppressive signals, and metabolic constraints that blunt cytotoxicity and promote exhaustion [28,47,48]. These conditions mirror chronic viral infection, suggesting that cytokines capable of rescuing antiviral CD8$^+$ T cells may hold similar promise in cancer. Early studies hinted at the antitumor potential of IL-27 through its ability to promote IFN-γ production [49–53]. However, in parallel with its activating effects, IL-27 has also been shown to induce inhibitory receptor programs and dampen cytotoxic activity in some contexts which underscores its dual regulatory nature [54].

More recent work has however positioned IL-27 as a central regulator of tumor-specific CD8$^+$ T cell responses, with strong evidence demonstrating its ability to drive cytotoxic differentiation, support survival, and potentiate immunotherapy. Pivotal studies demonstrated that IL-27 signaling is essential for CD8$^+$ T cell function within tumors [21]. Transcriptomic analyses of human and mouse tumor datasets have linked **cytotoxic T lymphocyte (CTL)** signatures to IL-27 expression, and functional studies showed that IL-27RA-deficient CD8$^+$ T cells fail to accumulate, exert cytotoxicity, or respond to checkpoint blockade [21]. In this model, IL-27 was produced by

intratumoral DCs and macrophages, and acted directly on $CD8^+$ T cells to sustain effector gene expression, limit exhaustion, and enforce tumor control [21]. Therapeutic IL-27 receptor agonism, either through plasmid delivery or recombinant protein, expanded tumor-specific $CD8^+$ T cells, upregulated granzyme B, PD-1, CD39, and SCA-1, and improved tumor clearance [21]. Strikingly, IL-27 synergized with PD-L1 blockade even in tumors that are typically resistant to immunotherapy, such as mammary carcinoma and melanoma, without overt toxicity [21]. Epigenetic profiling further revealed that IL-27 programs a distinct cytotoxic state through STAT1/3 and IRF1 activation, enhancing metabolic fitness and proliferation while avoiding terminal exhaustion [21].

These findings were extended by studies identifying IL-27 as a key effector cytokine produced by DCs that sustain tumor-specific T cell responses [12]. Using proximity-dependent labeling [55] and single-cell analysis, the authors showed that the DC subset responsible for presenting tumor antigens in both draining lymph nodes and tumor sites was also a dominant IL-27 source [12]. DC-specific deletion of *Il27* impaired tumor control and reduced $CD8^+$ T cell IFN-γ production, which underscores DC-derived IL-27 as a non-redundant link between innate sensing, antigen presentation, and cytotoxic T cell activation [12].

An additional layer of complexity has recently been uncovered through large-scale CRISPR screens in $CD8^+$ T cells [56]. These studies identified the E3 ubiquitin ligase STUB1 and its partner CHIC2 as negative regulators that limit T cell responsiveness to cytokines in the tumor microenvironment. Loss of this pathway increased IL-27Rα expression, enhanced responsiveness to IL-27, and improved tumor control, demonstrating that $CD8^+$ T cell sensitivity to IL-27 is actively constrained and can be therapeutically modulated [56].

The role of IL-27 also extends to hematologic malignancies such as chronic lymphocytic leukemia (CLL), where $CD8^+$ T cells often display an exhausted phenotype [57]. In mouse models and patient samples, IL-27 deficiency exacerbated disease, whereas supplementation restored $CD8^+$ T cell activation, proliferation, and cytotoxicity [58]. *In vitro*, IL-27 enhanced the ability of both murine and human $CD8^+$ T cells to kill autologous leukemic cells, which highlights its therapeutic potential in this setting [58].

These findings raise the question of how IL-27 compares to related cytokines such as IL-12. Both cytokines can induce CD39 on $CD8^+$ T cells, but the resulting phenotypes are distinct. IL-12-driven $CD39^+$ T cells coexpress high levels of PD-1, TIM-3, and LAG-3, and show reduced cytotoxicity, consistent with a more exhausted profile [59]. By contrast, IL-27-induced $CD39^+$ T cells express PD-1 but lack the triple-positive exhausted signature, retain degranulation capacity, and produce IL-2, suggesting preservation of effector potential and memory precursor traits [59]. Notably, IL-27 can even attenuate IL-12-mediated upregulation of inhibitory receptors, which points to a protective effect against terminal exhaustion [59]. Together, these findings reveal that IL-27 and IL-12 drive overlapping but distinct effector programs, highlighting the need to define the unique molecular and functional signature of IL-27-driven cytotoxicity in the tumor microenvironment [59]. Altogether, these recent studies establish IL-27 as a cell-intrinsic driver of tumor-specific $CD8^+$ T cell responses which bridges innate and adaptive immunity and offers a promising lever for cancer immunotherapy.

Autoimmunity

The role of IL-27 in autoimmunity further illustrates its ambivalent nature. In several autoimmune settings, loss of IL-27 signaling exacerbates proinflammatory T cell responses, indicating that IL-27 can exert protective, immunoregulatory effects in these contexts [60,61]. However, in other models, IL-27 appears to be dispensable or has a limited influence on specific $CD8^+$ T

cell subsets, which highlights that its impact on autoimmunity is highly context-dependent [62]. Although fewer in number, recent reports have also examined its impact on $CD8^+$ T cells in this context. In particular, work in a murine model of type 1 diabetes provided a clearer definition of IL-27 signaling by showing that genetic ablation of *Il27* or its receptor *IL27ra* completely prevented disease onset, including associated Sjögren-like manifestations [63]. Mechanistically, IL-27 was required to drive the differentiation and accumulation of T-bet$^+$, IFN-γ-producing $CD8^+$ T cells within pancreatic islets, thereby mediating β-cell destruction [63]. Along the same line, follow-up work from the same group demonstrated in murine models of Sjögren's syndrome that IL-27 is crucial for the differentiation of pathogenic $CD8^+$ T cells infiltrating the lacrimal glands and thereby exacerbates local tissue damage [64]. In this setting, the PD-1$^+$$CD8^+$ T cell subset emerged as the main population shaped by IL-27 signaling, characterized by the expression of CD39 and CD73 [64].

Human data further support this duality: in multiple sclerosis patients, IL-27 and IL-27Rα levels are elevated in serum and cerebrospinal fluid, but $CD8^+$ T cells exhibit altered responsiveness accompanied by exaggerated STAT3 activation and induction of inhibitory pathways [65]. These findings suggest that IL-27 in autoimmune settings can act as a driver of chronic inflammation by sustaining or misguiding $CD8^+$ T cell effector programs. Taken together, these studies indicate that IL-27 can promote pathogenic $CD8^+$ T cell responses in autoimmune settings, although the available data remain limited compared to infection or cancer contexts. By contrast, the broader role of IL-27 in autoimmunity, particularly in $CD4^+$ T cells, has been explored in greater depth and has highlighted both pro- and anti-inflammatory functions; we direct readers to dedicated reviews for a more comprehensive discussion [3,11,20,66].

Therapeutic perspectives: IL-27 as a $CD8^+$ T cell immune modulator

The accumulating evidence that IL-27 directly promotes cytotoxic $CD8^+$ T cell responses has sparked interest in its therapeutic potential to enhance antiviral and antitumor immunity [67]. The most direct strategy has involved systemic administration of recombinant IL-27, which in preclinical models increases $CD8^+$ T cell cytotoxicity and improves control of viral burden or tumor growth [21,39]. These findings support the concept that IL-27 functions as a physiological costimulatory cytokine that can restore effective $CD8^+$ T cell responses when administered exogenously. A notable feature that distinguishes IL-27 from other family members such as IL-2 or IL-12 is its favorable safety profile: whereas these cytokines often trigger severe systemic toxicity [68], IL-27 shows robust immunostimulatory effects without comparable adverse events [21,39]. The basis for this low toxicity remains incompletely understood, but may reflect its strict dependency on concomitant TCR signaling, which limits off-target activation in the absence of antigen [39]. In addition, IL-27 can induce IL-10 expression even in $CD8^+$ T cells, which establishes a self-regulatory loop that tempers excessive inflammation while preserving cytotoxic function [42,69–72]. Such intrinsic regulatory mechanisms may also compensate for the loss of Tregs observed in some settings following IL-27 exposure [73]. Collectively, these features make IL-27 an appealing candidate where durable $CD8^+$ T cell activity is desired without provoking systemic immune pathology.

One promising avenue is its use as a vaccine adjuvant. Early studies demonstrated that IL-27 is required for the proper shaping of T cell responses following subunit immunization and identified IL-27 expression as a potential prognostic correlate for vaccine-induced immunity [32]. Other works have also highlighted its antiviral activity [74] and demonstrate that IL-27 is required for optimal vaccine-induced $CD8^+$ T cell expansion through metabolic rewiring [75]. To improve efficacy and restrict exposure, several targeted delivery approaches have been explored. Oncolytic viruses encoding IL-27 promote local cytokine production within tumors increasing $CD8^+$ T cell

infiltration and tumor control [76]. **Adeno-associated virus (AAV)** vectors that produce IL-27 similarly inhibit tumor growth, partly by remodeling myeloid niches that sustain T cell responses [77]. Another approach is molecular targeting: engineered IL-27 fusion proteins selectively accumulate in tumors and enhance local infiltration of cytotoxic T cells [78].

Cell-based delivery strategies have also been developed. OT-1 $CD8^+$ T cells transduced with IL-27 showed enhanced cytotoxicity, delayed tumor progression, and prolonged survival [79]. Chimeric antigen receptor (CAR)-natural killer (NK) cells engineered to secrete IL-27 exhibited superior proliferation and antitumor activity, suggesting similar potential for CAR-T applications [80]. **Lipid nanoparticles (LNPs)** harboring *IL27* mRNA have been tested as versatile delivery platforms. *IL27* mRNA-loaded LNPs promoted myeloid production of IL-27 and boosted $CD8^+$ proliferation and cytotoxicity in both vaccination and tumor models [81]. In the same study, administration of exogenous IL-27 rescued $CD8^+$ T cell activity in type I IFN-deficient hosts, indicating that many of the protective effects traditionally attributed to IFNs are, at least in part, mediated through IL-27 [81]. These findings align with earlier work showing that IL-27 is necessary to maintain $CD8^+$ T cell effector function under persistent IFN signaling [29]. Together, these studies reveal an obligate relationship between type I IFN and IL-27: IFNs induce IL-27 which in turn is necessary to sustain $CD8^+$ T cell functionality. This interplay appears to be not merely correlative but mechanistic, and positions IL-27 as a key mediator of IFN-driven T cell support and a promising therapeutic target to preserve cytotoxic immunity when type I IFN signaling is impaired or chronically stimulated. In some cases, however, it is worth mentioning that IL-27 therapeutic efficacy required combination with IL-12 [82], echoing earlier studies in which IL-27 synergized with IL-2 to induce regression of metastatic neuroblastoma [83].

These observations support a model in which IL-27 not only acts as a stand-alone modulator but also functions as a valuable partner in combination regimens. Its ability to restore effector function while avoiding the systemic toxicity of related cytokines makes IL-27 particularly attractive as an adjuvant for checkpoint blockade or other immunomodulators [21]. Although still early in development, these insights set the stage for rational integration of IL-27 into next-generation immunotherapies.

Concluding remarks

Over the past two decades IL-27 has evolved from a relatively unknown cytokine to a multifaceted regulator of T cell immunity [3,11,66]. Although early studies emphasized its effects on $CD4^+$ T cell function [84], recent work has uncovered a more complex and instructive role for IL-27 in shaping $CD8^+$ T cell responses. Across diverse disease settings, including viral infections [37,39,46], cancer [12,21,56,58,59], and autoimmunity [64,65], IL-27 has been established as a cytokine that can fine-tune $CD8^+$ T cell effector differentiation, expand protective immunity, restore function in exhausted cells, and, in a context-dependent manner, restrain cytotoxic activity to limit immunopathology.

Looking ahead, several challenges define the next phase of IL-27 research (see Outstanding questions). From a T cell biology perspective, we still lack a complete understanding of which $CD8^+$ T cell subsets are most responsive to IL-27 and at what stage of their development and differentiation they are receptive. Although IL-27 is thought to act most effectively in the presence of antigen recognition and on antigen-experienced cells, it remains unclear whether short-lived effectors, memory precursors, or tissue-resident populations are preferentially sustained. Current evidence suggests that memory $CD8^+$ T cells may be relatively insensitive to IL-27, but this requires systematic investigation [34]. Clarification of this hierarchy will shed light on how IL-27 balances cytotoxicity and longevity and thereby inform strategies to selectively enhance beneficial T cell programs. Temporal determinants of responsiveness will be equally important: the

Outstanding questions

Which $CD8^+$ T cell subsets are most responsive to IL-27, and does IL-27 differentially influence the development of short-lived effectors, memory precursors, or tissue-resident populations?

What are the temporal determinants of IL-27 responsiveness? Is there a critical window during priming or chronic stimulation when IL-27 is most effective or required?

What are the tissue-specific cues that regulate IL-27 production and bioavailability, and how do local microenvironments (such as tumor niches, mucosal sites, or barrier tissues) differentially shape its function?

Can IL-27 be harnessed therapeutically without triggering pathogenic outcomes, such as the promotion of regulatory or autoimmune-prone T cell programs?

How does IL-27 compare to or complement other immunostimulatory cytokines, particularly IL-12 and IL-2, in terms of epigenetic reprogramming, metabolic control, and exhaustion prevention?

Which delivery strategies offer the optimal balance of efficacy, safety, and tissue targeting for IL-27-based therapies?

How do genetic variants in *IL27* or *IL27RA* influence susceptibility to infections, cancer progression, or therapeutic response?

Finally, could IL-27 serve as a biomarker of therapeutic response or resistance to guide patient stratification in infection, cancer, and vaccination?

identification of critical windows during priming or chronic stimulation when IL-27 is most effective could refine both experimental and therapeutic approaches.

We also still lack a complete picture of how IL-27 signaling interfaces with other cytokine networks. It remains unclear how IL-27 synergizes with proinflammatory cues such as IL-2, IL-12, or IFNs, and how it is specifically connected to regulatory pathways such as IL-10. Along the same line, it will be important to determine how IL-27 behaves in combination with other immunotherapies, as it has interestingly shown promise when paired with PD-L1 blockade [21]. Understanding how these signals converge to shape $CD8^+$ T cell fate under chronic or tissue-specific stimulation will be crucial for predicting IL-27 context-dependent outcomes and for designing interventions that harness its stimulatory potential while limiting immunopathology.

Tissue context might further complicate IL-27 biology, as observed for other cytokines such as IL-2 [85]. The cellular source and bioavailability are likely key determinants of its activity, further shaped by stromal interactions, vascular access, hormonal signals, and the surrounding inflammatory milieu. Distinct environments, including tumor niches, mucosal sites, and barrier tissues, may differentially shape IL-27 production and function, and ultimately define whether it acts as a proinflammatory booster or a regulator that restrains immunopathology. Dissection of these microenvironmental influences, through spatial transcriptomics, organoid cocultures, or single-cell perturbation studies, will be crucial to decode its contextual logic.

What sets IL-27 apart from other $CD8^+$ T cell-stimulating cytokines is its remarkable context-sensitivity coupled to low systemic toxicity [21,39]. This feature has much relevance for the study of new avenues for therapeutic exploitation. The central challenge ahead is to harness the benefits of IL-27 without inadvertently promoting regulatory or autoimmune-prone programs. Comparative studies with IL-12, IL-2, and related cytokines may reveal complementary or synergistic effects on epigenetic remodeling, metabolic fitness, and exhaustion prevention guiding rational combination therapies. Optimized delivery strategies, including local, timed, or cell-targeted approaches, will likely be necessary to maximize efficacy while minimizing off-target effects.

Genetic variants in *IL27* or *IL27RA*, already linked to susceptibility to viral infections, may similarly influence responses in cancer and autoimmunity [37]. Such variants could also modulate therapeutic outcomes and thus offer an entry point for precision immunology. Moreover, IL-27 itself – instead of transcriptional signatures of IL-27-responsive T cell programs – could serve as biomarkers of therapeutic response or resistance, enabling patient stratification and adaptive intervention strategies.

In sum, the next phase of IL-27 research must integrate subset specificity, temporal responsiveness, tissue context, genetic determinants, and therapeutic design to fully exploit its immunoregulatory potential. Decoding these layers will not only deepen our understanding of T cell regulation but also lay the foundation for next-generation, tissue-targeted immunotherapies with durable and safe efficacy.

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