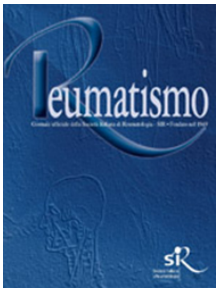

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The role of leukemia inhibitory factor in autoimmune disorders: insights into recovery and treatment

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Summary

Objective. Leukemia inhibitory factor (LIF) is a multifunctional cytokine involved in numerous physiological processes, including inflammation and immune response regulation. Recent studies have highlighted its potential role in the pathogenesis and treatment of autoimmune diseases such as rheumatoid arthritis (RA) and multiple sclerosis (MS). This review aims to investigate the role of LIF in various autoimmune disorders and its impact on the recovery and treatment of these diseases.

Methods. A comprehensive literature search was conducted using Google Scholar, PubMed, and Scopus databases. Relevant studies published up to December 2023 were identified using keywords such as "leukemia inhibitory factor", "autoimmune diseases", "rheumatoid arthritis" and "multiple sclerosis".

Results. The literature indicates that LIF has a dual role in autoimmune diseases. In RA, LIF plays an important role in the progression of joint damage by increasing the inflammatory response. In MS, LIF has been shown to promote remyelination and neuroprotection, suggesting its potential as a therapeutic agent. However, the precise mechanisms by which LIF modulates immune responses in these conditions remain incompletely understood.

Conclusions. LIF represents a promising target for treating autoimmune diseases, particularly RA and MS. Further research is required to elucidate its mechanisms of action and develop targeted therapies that can control its beneficial effects while minimizing potential adverse outcomes.

Introduction

One copy of the gene on chromosome 11 in mice and chromosome 22 in humans encodes the leukemia inhibitory factor (LIF) gene (1, 2). LIF, a versatile cytokine belonging to the interleukin (IL)-6 superfamily, exhibits multifunctional properties. Alongside LIF, this superfamily encompasses other members such as IL-6, IL-27, cardiotrophin-like cytokine, cardiotrophin-1, ciliary neurotrophic factor (CNTF), oncostatin M (OSM), and IL-11 (3-6). This cytokine binds to gp130, a receptor shared by other cytokines in the same family, as well as LIF receptor (LIFR) β (or gp190), which is unique to LIF (7-9). The binding of LIF to these receptors activates Janus kinase (JAK)1-associated signal transduction cascades, leading to the activation of the PI3K/AKT, MAPK, and JAK/STAT3 signaling pathways (10). LIF also regulates other signaling pathways, including YAP, Wnt/β-catenin, integrin, Toll/NF-κB, Notch, estrogen receptor, PTEN, VEGF/HIF1α, mTOR, IGF1, TGFβ, FGF, and ephrin pathways (6, 11, 12). Initially, LIF was recognized as a key element that triggers the final maturation of murine M1 myeloid leukemia cells while inhibiting their proliferation. Interestingly, LIF has also been acknowledged as the factor that inhibits the differentiation process, thereby preserving the pluripotency of mouse embryonic stem cells (6). Apart from its function in controlling the development and proliferation of myeloid leukemia cells and pluripotent stem cells, LIF is involved in various physiological and pathological processes, including metabolism, immune response, infection, inflammation, maternal reproduction, neurogenesis, neural regeneration and tissue/organ development (6, 10, 13). LIF is expressed in several cancers, including breast cancer, where its expression increases as the tumor progresses (14, 15). High levels of LIF expression in breast cancer tissues have been found to be associated with poor relapse-free survival, indicating that it could be a poor prognostic marker (16, 17). Similarly, LIF overexpression in osteosarcomas is associated with decreased survival, larger tumor size, and advanced stage (18). This occurs in multiple cancer types, such as chordomas (19), oral squamous cell carcinoma (20), nasopharyngeal carcinoma (21), pancreatic adenocarcinoma (22) , and cervical cancer (23).

Autoimmune diseases are due to an imbalance in the levels of proinflammatory and anti-inflammatory cytokines, resulting from the disruption of immunologic tolerance towards autoreactive immune cells (24). In the adaptive immune system, LIF plays a crucial role in promoting self-tolerance and regulating the activity of Treg cells by opposing IL-6. IL-6-mediated inflammation, including immunity driven by T helper 17 (TH17) cells, is strongly associated with autoimmune diseases when inappropriately activated. The LIF/IL-6 axis plays a key role in regulating the balance between inflammation and tissue repair in autoimmune diseases, such as multiple sclerosis (MS). IL-6 is mainly associated with inflammatory responses and the promotion of inflammation, while LIF is associated with the induction of immune tolerance (tolerogenicity) and regeneration of neural tissues. In this axis, LIF is capable of modulating IL-6 and prevent the destructive effects of inflammation caused by IL-6, thereby improving the condition of MS patients (25, 26). The objective of this review is to examine the involvement of LIF in various autoimmune disorders and its effect on the recovery and treatment of these diseases.

The role of leukemia inhibitory factor in rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that impacts the musculoskeletal system through progressive inflammation of the synovial joints. This disease can cause significant tissue damage in various organs, including the heart, blood vessels, lungs, kidneys, eyes, and skin, in addition to joints (27). Although it does not pose an immediate danger of death, this condition has a substantial influence on the everyday lives of the subjects. In conjunction with unappealing symptoms, it can lead to a shortened life expectancy, numerous long-term comorbidities, and destruction of joints (28).

Proinflammatory cytokines such as IL-6, interferon (IFN)-γ, IL-1β, and tumor necrosis factor (TNF)-α are elevated in the synovial fluid and synovial tissue of RA patients (29, 30). Elevated concentrations of

these cytokines result in the expansion of synovial tissue, which ultimately contributes to bone degradation in the nearby region and deterioration of the articular cartilage (31, 32).
In a study by Enomoto *et al.*, the levels of LIF in the synovial tissues of RA patients were investigated. The study demonstrated that the levels of LIF in synovial fluid were positively associated with IL-8, IL-6, and IL-1β. These cytokines were mainly produced by chondrocytes, endothelial cells, synovial fibroblasts, and monocyte macrophages, which also produced LIF. LIF was synthesized within the joints, and the level of LIF present in synovial fluids exhibited a notable correlation with both the peripheral leukocyte count and the concentration of C-reactive protein (CRP). The findings indicate that the presence of LIF plays a significant role in the progression of joint damage in individuals with RA by enhancing the inflammatory response (Figure 1) (33).
Chung *et al.* demonstrated that RA patients show significantly increased levels of IL-6, IL-11, and LIF in their serum when compared to healthy individuals. Additionally, patients with high disease activity experienced a significant decline in serum concentrations of IL-6 family cytokines after treatment with disease-modifying anti-rheumatic drugs. In this study, IL-11 and IL-6 levels decreased after treatment, but LIF levels did not. This result highlights the unique characteristics of LIF among IL-6 family cytokines and requires further investigation with a larger number of cases (34).
In the study of Okamoto *et al*., which investigated the synovial expression and serum levels of four cytokines from the IL-6 family, including IL-6, IL-11, LIF, and OSM in patients with RA, IL-6, LIF, and OSM were significantly increased at the site of disease activity in RA patients and only IL-6 correlated with the serum CRP level (35). In another study by Waring *et al*., it was found that RA patients who had high synovial fluid LIF levels had significantly higher serum and synovial fluid white blood cell counts (36).
In the study conducted by Nguyen *et al*., which was performed on synovial fibroblasts in the active and chronic stage of RA, a significant decrease in IL-6 production was observed when LIFR was blocked using siRNA or monoclonal antibody. Silencing LIFR or STAT4 also resulted in reduced IL-6 upon stimulation by various inflammatory factors, including TNF, IL-1β, and Toll-like receptor signaling, in addition to IL-17. In this study, it was determined that the autocrine circuit of LIF, LIFR, and STAT4 plays a vital role in the production of IL-6 and a set of other inflammatory mediators. These mediators are responsible for the recruitment and activation of leukocytes and other tissue cells (37). In general, fibroblasts play a crucial role in maintaining inflammation, and the effect of LIF in the production of inflammatory mediators by fibroblasts is of great importance in autoimmune diseases such as RA.

The role of leukemia inhibitory factor in multiple sclerosis

MS is a persistent inflammatory and demyelinating condition of the central nervous system (CNS) that commonly impacts individuals aged 20 to 40 years, showing a higher prevalence among women compared to men (38, 39). The location of CNS lesions determines the clinical manifestations of MS and can include visual and sensory disturbances, cognitive deficits, pain, fatigue, spasticity, coordination impairment, and motor dysfunction (40). The disease is complex, with several genes and environmental factors, such as vitamin D, smoking, obesity, Epstein-Barr virus infection, and ultraviolet B-light exposure, contributing to disease susceptibility (41, 42). MS is considered a two-stage disease, with early inflammation causing relapsing-remitting disease and delayed neurodegeneration causing non-relapsing progression, such as secondary and primary progressive MS (41, 43, 44).
Enhancing evidence demonstrates that T helper cells, particularly IL-17 producing Th17 cells and IFN-ɣ producing T helper 1 (Th1) cells, play a critical role in MS pathogenesis, while regulatory T cells function to suppress the autoimmune response (45). Since LIF stimulates neurite outgrowth and promotes the survival of oligodendrocytes and neurons (46-48), it has been proposed as a potential candidate for the treatment of MS (1, 49-50). The effect of LIF in MS are summarized in Table 2.

Neural progenitor cells (NPCs) have been extensively studied as a potential therapeutic approach for MS, as they can repair damaged myelin tissue and differentiate into oligodendrocytes (51). NPCs produce various neurotrophins and cytokines, including LIF, BMP4, brain-derived neurotrophic factor, and TNF-α, some of which possess immunoregulatory activity by inhibiting inflammatory responses (52, 53). NPC-secreted factors can also block pathogenic Th17 cell differentiation. The research conducted by Wei Cao *et al.* on the key factor(s) that play a significant role in the immunoregulatory properties of NPCs in vitro and in vivo, showed LIF as the pivotal element directly responsible for the efficacy of NPC treatment in experimental autoimmune encephalomyelitis (EAE) through its ability to inhibit the differentiation of Th17 cells (45).

The expression of LIF remains undetectable in the healthy CNS. However, it exhibits an increase in response to different types of neuronal distress, such as injury, spinal cord ischemia, nerve injury, and MS lesions. T cells and macrophages secrete LIF in MS lesions (46). Studies conducted on mice that lack LIF, CNTF, or their shared receptor subunit gp130 have demonstrated the essential role of LIFR signaling in facilitating axon growth and providing neuroprotection in response to conditioning lesions. LIF directly stimulates neurite outgrowth, which is critical for axonal regeneration in neurons (48). In MS, progressive demyelination and the ongoing immune response compromise axonal integrity and conductance, leading to increased disability in patients (49). Two independent studies revealed that the introduction of LIF can impede demyelination and halt the demise of oligodendrocytes in a murine model of spinal cord injury (54, 55). While Azari *et al.* ascribe this protective impact to direct survival signaling in oligodendrocytes (34), Kerr and Patterson did not detect the presence of the LIFR in these cells (33). Instead, the latter proposed that protection is achieved *via* the indirect impact of LIF on a supporting cell type, which subsequently triggers upregulation of insulin-like growth factor 1, a key factor essential for the sustenance of oligodendrocytes (54). Numerous *in vitro* experiments have demonstrated the direct impact of LIF on the myelinating cells within the CNS. LIF treatment protects cultured oligodendrocytes against IFN-ɣ mediated cell death and TNF-α; these inflammatory cytokines are increased in MS (47, 56). Astrocytes promote myelin formation in mixed cultures through the secretion of LIF in reaction to adenosine triphosphate released by axons following an action potential (57). The induction of an anti-apoptotic reaction in oligodendrocytes by LIF is achieved through the upregulation of 14-3-3 proteins and the activation of Akt (47).

Therapeutic CNS-targeted treatment with LIF has been shown to improve symptoms and increase the number of Treg cells in the CNS of EAE mice. LIF treatment also expands Treg cell numbers in memory CD4+ T cell cultures from healthy controls and MS patients with low serum levels of IL-6 (58). LIF has emerged as a remarkably encouraging treatment option for individuals diagnosed with MS. LIF therapy could increase the generation of Treg cells, allowing for CNS repair and limiting inflammatory tissue injury. Additionally, LIF can induce axonal remyelination and regeneration and directly promote the survival of oligodendrocytes and neurons. It upregulates 14-3-3 proteins and activates Akt, inducing an anti-apoptotic response in oligodendrocytes (Figure 2).

The role of leukemia inhibitory factor in psoriasis

Psoriasis is a chronic autoimmune skin disease with inflammatory features that result from genetic and environmental factors. It is a significant public health concern, with a considerable impact on patient quality of life (59, 60). The etiology of psoriasis is not fully understood, but risk factors associated with its exacerbation or triggering include smoking, alcohol consumption, high body mass index, medications, stress, physical trauma, infectious agents, and genetic predisposition (61, 62). Disturbances in cytokine biology, including overexpression of LIF, IFN-γ, TNF-α, granulocyte-macrophage colony-stimulating factor, GROα, IL-8, IL-2, IL-6, IL-β, and IL-1α, have been observed in psoriasis (63, 64).

LIF has been demonstrated to play a role in skin inflammation in both humans and mice. Human keratinocytes (KCs) in culture have been found to consistently produce both LIFR and LIF (1, 51).

Stimulation of KC with LIF has been shown to trigger the secretion of IL-8 and IL-1 proteins (Figure 3) (51). Elevated levels of LIF mRNA have been observed in the affected skin of individuals with psoriasis, a finding that correlates with markedly increased levels of IL-8 mRNA (63).
In a 1997 study, Bonifati *et al.* investigated the production of LIF and OSM in psoriasis by analyzing the supernatants of short-term organ cultures of non-lesional and lesional skin of patients with active plaque-type psoriasis and of normal skin of healthy volunteers. The study demonstrated a direct association between the amounts of IL-8 and LIF in the supernatants of lesional skin, suggesting that IL-8 and LIF could be functionally related in psoriasis. The study offered novel insights into the presence of alternative regulators in the inflammatory processes associated with psoriasis (64).

The role of leukemia inhibitory factor in inflammatory bowel disease
Inflammatory bowel disease (IBD) comprises a collection of chronic inflammatory conditions affecting the gastrointestinal tract, such as ulcerative colitis (UC) and Crohn's disease (CD), predominantly impacting individuals between the ages of 20 and 40 years (65). There has been a recent rise in the worldwide prevalence of IBD (66, 67). CD can affect any part of the digestive tract, while UC is limited to the colon. Both diseases can cause severe complications and have a significant impact on patient quality of life (68).
During gut inflammation, the microbiota experiences stress that leads to the secretion of cytokines from host cells. One of these cytokines, LIF, is upregulated in mice with DSS-induced colitis and is also elevated in patients with UC (69). The pathogenesis of various autoimmune diseases is significantly influenced by the presence of Th17 cells (45). Th17 cells also have crucial roles in driving intestinal inflammation in IBD. The study carried out by Zhang *et al*. revealed that the activation of STAT4 through LIF had a diminishing effect on the proportion of Th17 cells in the lamina propria of a mouse colitis model. Importantly, this reduction was related to the presence of STAT4 (Figure 4) (70). Activation of STAT4 through the IL-12 signaling pathway facilitates the transformation of naive CD4+ T cells into Th1 cells, whereas activation of STAT3 *via* the IL-6 signaling pathway drives the differentiation of naive CD4+ T cells into Th17 cells (71, 72). The findings demonstrated that both activated STAT4 and STAT3 have the capability to attach to identical DNA sequences, such as the recently identified AGG elements located on the IL17A/F promoters, as well as the traditional cis-inducible elements. However, the competition between STAT4 and STAT3 was encouraged by LIF, resulting in increased occupancy of these elements by STAT4 and decreased expression of the *IL17A/F* genes. Consequently, STAT4 displays reduced efficiency as a transcription factor when exposed to LIF in Th17 cells. The study results demonstrated that the suppressive impact of LIF on Th17 cells was dependent on STAT3 and STAT4. As a result, it was concluded that the absence of STAT3 during ILC3-cell development prevented LIF from influencing *IL17* gene expression. This clarifies the minimal effect of LIF on the accumulation of ILC3s in wild-type or Stat4_/_ colitis mice. Therefore, LIF plays a central role in promoting intestinal epithelial cells (IECs) proliferation by activating STAT3 and in restricting Th17-cell differentiation by activating STAT4. The STAT activation pattern of LIF varied in IECs and lamina propria leukocytes (LPLs). In IECs, LIF primarily triggers the activation of STAT3 to counteract the actions of STAT4 and stimulate the expression of YAP, ultimately facilitating the proliferation of epithelial cells. In LPLs, the activation of STAT4 by LIF was found to result in the suppression of STAT3 activity during the regulation of IL17 promoter (Table 1) (70).
LIF plays a defensive role in experimental colitis by enhancing the regeneration of epithelial cells and inhibiting the differentiation of Th17 cells. Considering the upstream miRNA of LIF and the effects of the miRNA/LIF axis *in vivo* and *in vitro*, the upstream miRNA of human LIF, miR-29c-3p, was successfully identified by researchers through the analysis of five bioinformatics software tools. Moreover, the presence of a conserved binding site in the 3′-UTR of human LIF was confirmed through luciferase reporter assay. IECs play a crucial role in both physically blocking invasive foreign pathogens

and facilitating the communication between commensal microorganisms and immune cells, thus serving as a vital component of the body's defense mechanisms (73, 74). Previous reports indicated a decrease in miR-29c-3p expression in the HCT116 human colon cancer cell line, while there was a significant increase in LIF levels in the inflamed IECs of mice with colitis (70, 75). The latest findings from in vitro research indicate that miR-29c-3p plays a pro-inflammatory role in gut inflammation, whereas LIF functions as a protective factor. Consequently, the primary evidence highlights the indispensable function of the miR-29c-3p/LIF axis in controlling intestinal inflammation. The overexpression of miR-29c-3p fosters inflammation by repressing LIF expression, both in vivo and in vitro. The potential of utilizing the differential expression profile of LIF and miR-29c-3p in inflamed colon lesions as a biomarker for UC is noteworthy. This finding suggests that the miR-29c-3p/LIF pathway could be targeted for therapeutic interventions in the treatment of UC (76).

The role of leukemia inhibitory factor in other autoimmune disease

Immunoglobulin A nephropathy

Immunoglobulin A (IgA) nephropathy (IgAN) is a condition characterized by kidney damage resulting from the presence of immune deposits formed by circulating immune complexes. They are composed of autoantigen Gd-IgA1, which is targeted by Gd-IgA1-specific autoantibodies, leading to an autoimmune response within the kidneys. The expression of OSM and LIF in mucosal tissues, along with their immunoregulatory properties, has been linked to the development of IgAN (24, 25). At the initial stage of the disease, upper respiratory tract infections are commonly observed and are known to exacerbate the manifestations experienced by patients with IgAN. A previous study showed that IL-6 induces abnormal signaling in IgA1-producing cells from IgAN patients, leading to elevated production of Gd-IgA1. Abnormal LIF/STAT1 signaling offers an alternative route that may result in excessive production of Gd-IgA1 in IgAN. The phenotype correlated with the chromosome 22q12 GWAS locus could be elucidated by this explanation. Aberrant LIF/STAT1 signaling and the accompanying Src-family PTKs might be considered viable targets for diagnosis and treatment in IgAN (77).

Dermatomyositis

Dermatomyositis (DM) is an inflammatory disease of the muscles, skin, and joints. Recently, many myositis-specific autoantibodies were found in the patients' serum, which is related to the characteristics of the disease. *MDA5* antibody-positive DM is characterized as amyopathic DM with rapidly progressive interstitial lung disease (RP-ILD). Ichimura *et al*. studied the role of LIF in anti-MDA5 antibody-positive RP-ILD. The level of LIF in serum samples and healthy people was measured by the enzyme-linked immunoassay (ELISA) method. The results showed that the serum level of LIF was significantly increased in positive anti-MDA5 antibody patients and that LIF may be associated with the pathogenesis of anti-MDA5 antibody-positive ILD. This theory still needs more research (78).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a complex, multisystemic autoimmune disease characterized by the production of autoantibodies that lead to chronic inflammation and organ damage (79). Viallard *et al.* conducted a study on the level of LIF in the peripheral blood cells of SLE patients. They used the ELISA technique to measure cytokines in the supernatants of 48-hour cultures of whole blood cells from SLE patients and controls. The patients were divided into two groups according to disease activity: patients with high disease activity showed higher LIF concentrations. It seems that LIF can be a potential indicator of disease activity in SLE (80).

Conclusions

In general, LIF has different effects on various autoimmune diseases. As mentioned, it has a protective role in some autoimmune diseases such as MS and can be considered a therapeutic factor in its recovery process. LIF stimulates neurite outgrowth and prevents demyelination, arrests oligodendrocyte death, and induces an anti-apoptotic response in oligodendrocytes. However, LIF has destructive and inflammatory effects in other diseases. It contributes to joint destruction and has an inflammatory role in RA, as well as an inflammatory role in psoriasis. In the context of IBD, LIF has a protective function by promoting epithelium reconstruction and inhibiting Th17 cell differentiation. LIF plays a central role in promoting IEC proliferation by activating STAT3 and restricting Th17 cell differentiation by activating STAT4.

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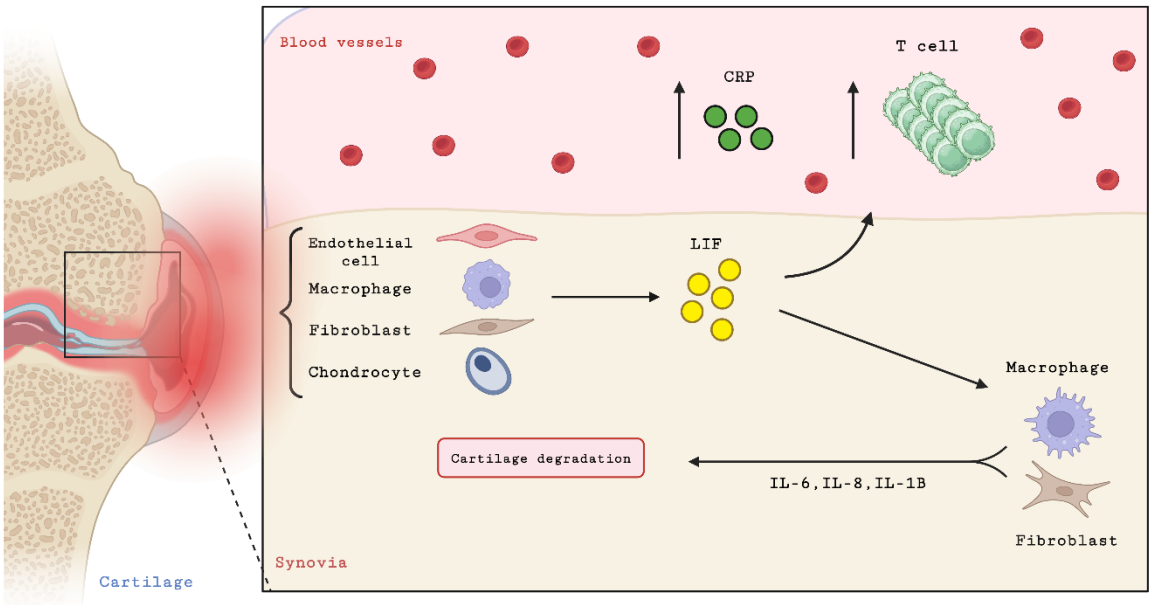

Figure 1. Leukemia inhibitory factor (LIF) is produced by endothelial cells, macrophages, fibroblasts, and chondrocytes within the joints and increases C-reactive protein (CRP) concentrations and the number of T cells in the blood. It also induces macrophages and fibroblasts in the synovial fluid to produce interleukin (IL)-6, IL-8, and IL-1B that promote cartilage degradation. Figure created using BioRender.

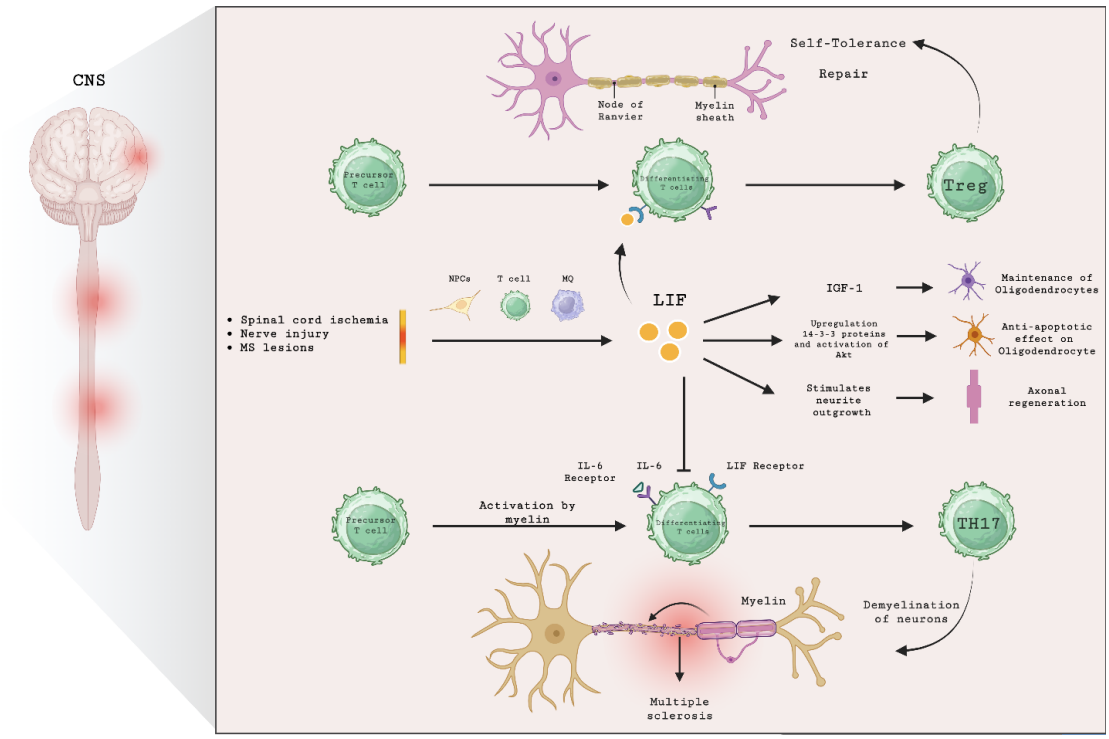

Figure 2. Spinal cord ischemia, nerve injury, and multiple sclerosis (MS) lesions induce leukemia inhibitory factor (LIF) production in NPCs, T cells, and macrophages. T cell progenitors differentiate into Treg cells and induce tolerance, thereby repairing damaged myelin. Figure created using BioRender.

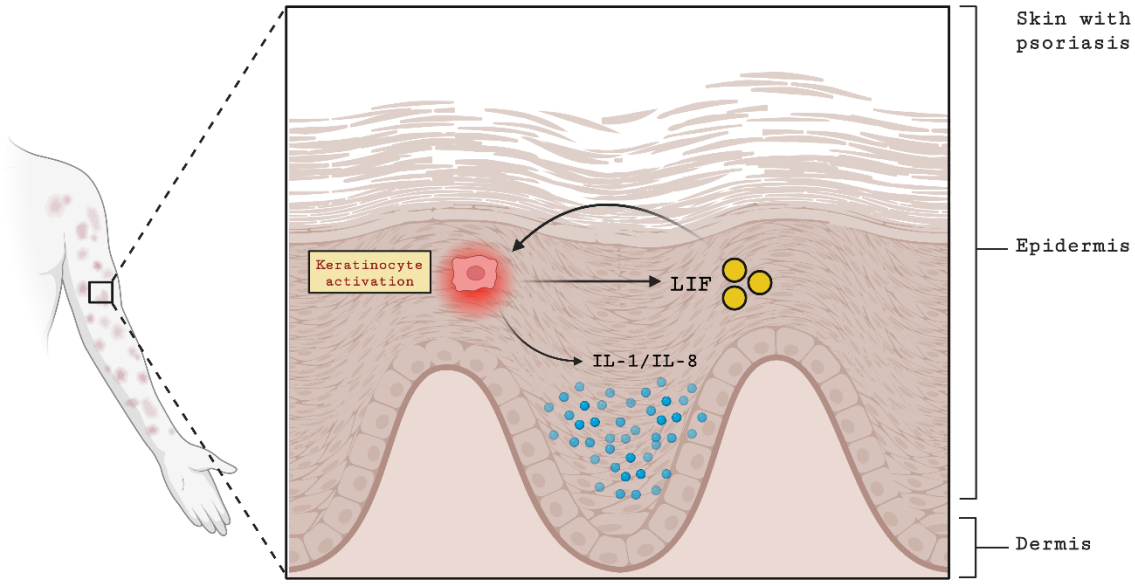

Figure 3. In psoriatic skin, leukemia inhibitory factor (LIF) is produced by active keratinocytes and stimulates the secretion of interleukin (IL)-8 and IL-1 cytokines with an autocrine effect on these cells. Figure created using BioRender.

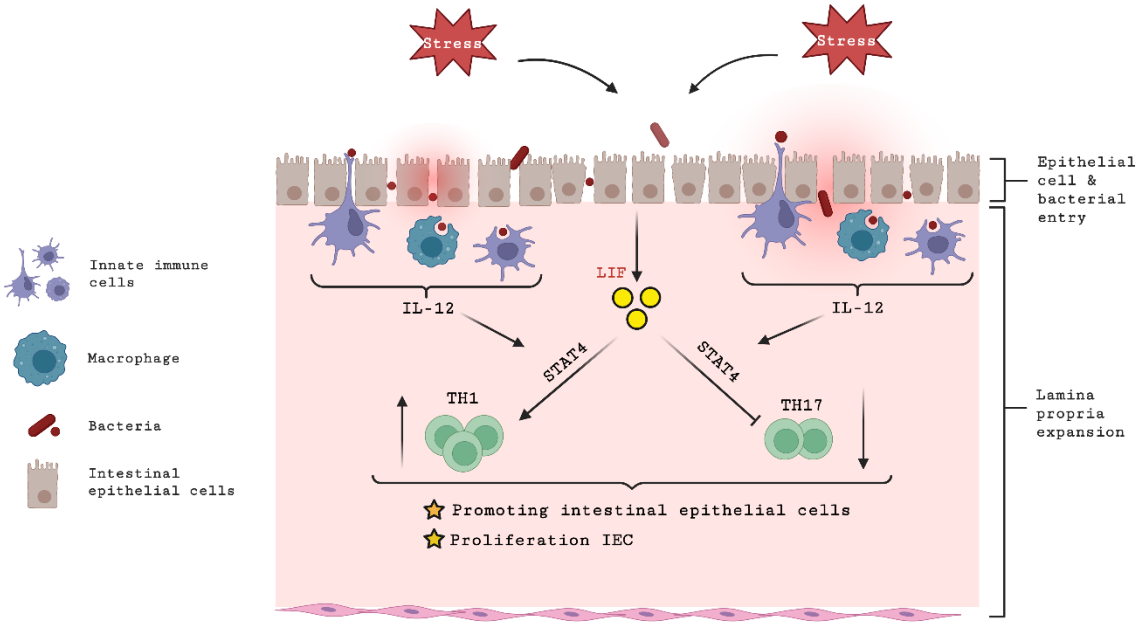

Figure 4. During intestinal inflammation, stressed epithelial cells secrete leukemia inhibitory factor (LIF). LIF inhibits the differentiation of TH17 cells through the activation of STAT4 and drives the differentiation towards TH1, causing the proliferation of intestinal epithelial cells. Figure created using BioRender.

Table 1. The effect of leukemia inhibitory factor on autoimmune disease.

Type of autoimmune disease	Type of study		Effect	Author	Ref
	In vivo	*In vitro*			
RA	✓		Inflammatory mediators that recruit or activate leukocytes	Nguyen *et al.*	(37)
RA	✓		Proinflammatory secretion profile	Enomoto *et al.*	(33)
RA	✓		Pathogenesis of RA	Chung *et al.*	(34)
IBD	✓	✓	Inhibits Th17 accumulation and promotes repair of damaged intestinal epithelium	Zhang *et al.*	(70)
IBD	✓	✓	MiR-29c-3p/LIF pathway serves as a potential therapeutic target	Guo *et al.*	(76)
Psoriasis	✓		Pathogenesis and maintenance of disease	Bonifati *et al.*	(64)
Psoriasis	✓		Inflammation	Szepietowski *et al.*	(63)

RA, rheumatoid arthritis; IBD, inflammatory bowel disease; Th17, T helper 17; LIF, leukemia inhibitory factor.

Table 2. The effect of leukemia inhibitory factor in multiple sclerosis.

Type of study		Effect	Author	Ref
In vivo	*In vitro*			
✓		Regulating Th17 cell differentiation	Nguyen *et al.*	(37)
✓	✓	Enhancing Treg numbers	Enomoto *et al.*	(33)
✓		Protect axons from acute inflammatory destruction	Chung *et al.*	(34)
✓		Important role in the process of remyelination	Szepietowski *et al.*	(63)
	✓	Identification of small and portable molecules producing LIF	Zhang *et al.*	(70)
✓	✓	Limits autoimmune-mediated demyelination	Guo *et al.*	(76)
✓	✓	Myelin repair	Bonifati *et al.*	(64)
✓	✓	Protect oligodendrocytes against TNF-a induced apoptosis.	Szepietowski *et al.*	(63)
✓		Arrests oligodendrocyte death and demyelination	Szepietowski *et al.*	(63)
	✓	Antiapoptotic response in oligodendrocytes	Szepietowski *et al.*	(63)