Research status and future perspectives of IL-27 in the treatment of stroke (Review)

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Abstract. Stroke is a life-threatening cerebrovascular disorder categorized into two major subtypes: Ischemic and hemorrhagic. Characterized by high morbidity and mortality rates, its clinical management remains challenging due to limited therapeutic options. Interleukin (IL)-27, a pleiotropic cytokine with demonstrated neuroprotective potential, has emerged as a promising candidate for stroke intervention. IL-27 exerts immunomodulatory effects within the central nervous system, including suppression of proinflammatory T-cell proliferation and induction of regulatory T-cell differentiation. These mechanisms collectively attenuate neuroinflammation, mitigate neuronal apoptosis and prevent neurodegenerative processes. The efficacy of IL-27 in reducing cerebral damage in both ischemic and hemorrhagic stroke models has been validated, although clinical translation remains to be achieved. The present review summarizes: i) The epidemiology of stroke; ii) the immunoregulatory functions of IL-27 and its neuroprotective mechanisms across stroke subtypes; iii) innovative brain-targeted delivery approaches; iv) IL-27 clinical applicability with supporting evidence; and v) possible risks and solutions in clinical applications. By collating the current knowledge, the present study provides a translational framework for advancing IL-27-based therapies in stroke management.

Contents

1. Introduction

Stroke represents a critical neurological emergency characterized by sudden cessation of brain perfusion, leading to rapid-onset neuronal degeneration (1,2). Clinically, it manifests in two distinct forms: Ischemic stroke (cerebral infarction due to thrombotic or embolic vessel obstruction) and hemorrhagic stroke (parenchymal or subarachnoid bleeding from cerebrovascular rupture). Established risk factors include hypertension, smoking, advanced age, diabetes, obesity, dyslipidemia, atrial fibrillation and genetic predisposition (3). As a major global public health burden, stroke affects ~15 million individuals annually (4). It ranks as the second leading cause of mortality worldwide, responsible for 11.8% of total mortalities (5-8). Stroke is also a major cause of long-term disabilities, including paralysis, speech difficulties and memory loss (9,10). While stroke is more common in men, women are more likely

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to succumb to it (11). Additionally, the risk factors for stroke may vary depending on ethnicity, with African-Americans and Hispanic-Americans having a greater incidence of stroke than White-Americans (5). Currently, stroke prevention and treatment options are limited, and there is an ongoing search for more effective drugs.

Interleukin (IL)-27, a member of the IL-12 cytokine family (12), is a pleiotropic immunomodulator that has demonstrated context-dependent dual functionality, exhibiting both pro-inflammatory and anti-inflammatory properties (13). Emerging evidence has revealed its neuroprotective potential in neurological disorders, including multiple sclerosis and Alzheimer's disease models, where IL-27 attenuates neuroinflammation and ameliorates neuronal injury (14,15). Notably, preclinical studies on both ischemic and hemorrhagic stroke have consistently highlighted IL-27's critical involvement in neuroimmune regulation and cerebroprotection (16,17). Supporting these observations, Martha *et al* (18) proposed IL-27 as a potential biomarker for predicting post-stroke infarct volume and cerebral edema formation in patients with acute ischemic stroke. Collectively, these findings position IL-27 as a key regulator in maintaining central nervous system (CNS) immune homeostasis, with dual capabilities in neurodegeneration prevention and neural tissue repair.

Despite the demonstrated therapeutic potential of IL-27 in stroke treatment, substantial challenges remain for translating these findings into clinical practice. Research in this field must address two fundamental questions: i) How to ensure consistent therapeutic effects and ii) how to identify optimal delivery approaches. The present review i) summarizes the current knowledge on stroke-related inflammatory pathways; ii) introduces IL-27's immunoregulatory functions; and iii) summarizes recent progress in IL-27-related stroke research. Furthermore, the promising application of engineered exosomes as delivery systems for IL-27 is explored, and both the obstacles and future perspectives for developing IL-27 into an effective stroke therapy are discussed.

2. Stroke and inflammation

Ischemic and hemorrhagic stroke. Ischemic and hemorrhagic stroke are the two primary types of stroke, each with distinct pathogenesis and clinical presentations (Fig. 1). From a pathophysiological perspective, ischemic stroke occurs when cerebral blood flow is compromised due to arterial occlusion or stenosis, resulting in cerebral ischemia (10). By contrast, hemorrhagic stroke develops from cerebrovascular rupture that causes intracranial bleeding (1). These stroke subtypes also exhibit distinct temporal progression patterns: Ischemic stroke typically manifests with progressive symptom onset, while hemorrhagic stroke presents abruptly. Neuroimaging serves as the diagnostic cornerstone for differentiating between these two cerebrovascular events. Ischemic stroke typically involves areas of cerebral infarction, indicating the presence of tissue damage due to inadequate blood flow. By contrast, patients with hemorrhagic stroke exhibit cerebral hemorrhage or hematoma, highlighting the presence of bleeding within the brain. Complications also vary between the two types of stroke. Hemorrhagic stroke can give rise to complications such as increased intracranial pressure, cerebral edema and rebleeding. These complications are relatively rare in patients with ischemic stroke (19,20).

There are several commonalities between ischemic stroke and hemorrhagic stroke (21). First, both types of stroke present with similar symptoms, such as the sudden onset of a headache, impaired consciousness, limb paralysis and speech impairment. These symptoms serve as key indicators of neurological deficits. Second, both stroke types share several strategies for prevention and treatment. In the acute phase, anticoagulation therapy is often employed to prevent further clot formation or bleeding. Additionally, controlling blood pressure and blood glucose levels is crucial for managing the aftermath of both types of stroke. Rehabilitation, including physical and speech therapy, is also a common approach to aid in the recovery of motor skills and language abilities. These shared pathophysiological features underscore the necessity for an integrated, multidisciplinary strategy encompassing prevention, acute intervention and long-term rehabilitation in managing both ischemic and hemorrhagic stroke (19,20).

Commonalities and differences in inflammation among patients with stroke. Both types of stroke trigger an inflammatory response as part of the body's natural defense mechanism. When a stroke occurs, the body responds by sending immune cells to the damaged area to clear out the damaged tissue and begin the healing process (22-24). Inflammation is a natural response to this injury, but it can cause further damage to brain tissue through the release of harmful chemicals and enzymes. These pathophysiological processes may elevate thrombotic risk and induce vasoconstriction, thereby compromising cerebral perfusion. Furthermore, inflammatory cascades promote fibrotic scar formation (25), which impedes post-stroke neuroplasticity and functional recovery. While inflammation modulation constitutes a critical therapeutic target in stroke management, the inflammatory profiles exhibit both shared and distinct characteristics between ischemic and hemorrhagic stroke subtypes.

Both stroke subtypes share a common inflammatory cascade characterized by early activation of resident immune cells (microglia and astrocytes), which secrete proinflammatory mediators, including cytokines and chemokines (26). These signaling molecules recruit circulating leukocytes to the injury site, notably neutrophils, monocytes and various T cell subsets (27). Neutrophils exacerbate tissue damage through the release of reactive oxygen species and proteolytic enzymes (28). Monocytes subsequently differentiate into macrophage populations with distinct functional phenotypes (29).

The inflammatory responses in different stroke subtypes diverge in their primary origins. In ischemic stroke, inflammation predominantly stems from the ischemic core, where hypoperfusion-induced tissue necrosis releases damage-associated molecular patterns that activate the innate immune system (30). By contrast, in hemorrhagic stroke, blood in the brain parenchyma acts as an irritant and directly triggers inflammation (23). Second, the duration of inflammation is not the same. In ischemic stroke, the inflammatory response occurs in two phases: An acute phase, which starts immediately after the onset of ischemia, and a delayed or secondary phase, which occurs hours to days later. In hemorrhagic stroke,

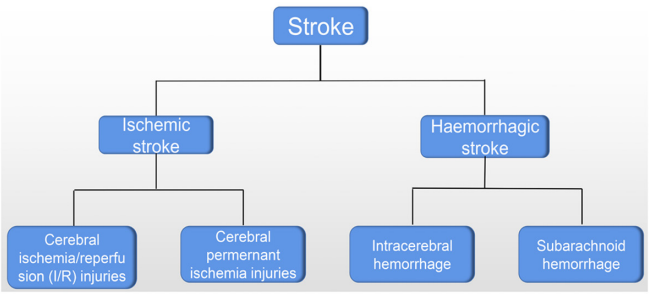

Figure 1. Stroke classification delineates distinct categories. Ischemic stroke refers to a localized, irreversible lesion stemming from compromised cerebral blood perfusion, leading to subsequent ischemic hypoxia necrosis. By contrast, hemorrhagic strokes arise from the rupture and hemorrhaging of cerebral blood vessels within the brain, with cerebral hemorrhage and subarachnoid hemorrhage constituting specific subtypes within the hemorrhagic stroke spectrum.

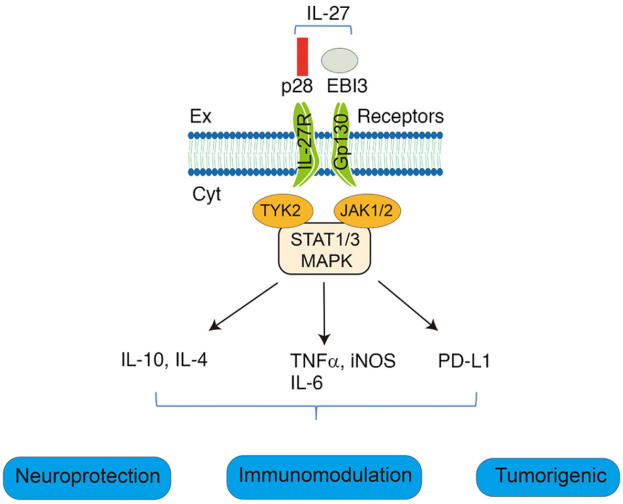

Figure 2. IL-27 and its receptors. The cytokine IL-27 is a heterodimeric protein that includes an α subunit (P28) and a β subunit (EBI3). The receptors of this cytokine are composed of two subunits (IL-27R and gp130) and are primarily heterodimers. Binding of IL-27 to its receptor leads to activation of the JAK/STAT and/or MAPK pathways, induction of anti-inflammatory proteins, reduction of proinflammatory proteins, and promotion of oncogenic proteins. Ex, extracellular space; Cyt, cytosol; IL, interleukin; gp, glycoprotein; iNOS, inducible nitrogen oxide synthase.

the inflammatory response is more acute and immediate, as bleeding into the brain tissue rapidly triggers the release of inflammatory molecules. Third, inflammatory cells have different activation patterns. Ischemic stroke is characterized by infiltrating immune cells, such as neutrophils and monocytes, into ischemic brain tissue (24). Hemorrhagic stroke elicits a distinct inflammatory response characterized by substantial erythrocyte extravasation and hemoglobin release. These blood components drive neuroinflammation through two primary mechanisms: Iron-mediated oxidative stress and direct activation of resident and infiltrating immune cells (31).

Macrophage polarization. Macrophages play a pivotal role in orchestrating inflammatory responses (32), with their functional polarization between classically activated (M1) and alternatively activated (M2) phenotypes being crucial for immune homeostasis (33,34). M1 macrophages, characterized by their proinflammatory properties, mediate inflammatory initiation and perpetuation through the secretion of cytokines, including TNF-α, IL-1β and IL-6. These cells perform essential immunological functions such as microbial phagocytosis, pathogen elimination and cellular debris clearance. Current therapeutic strategies for stroke emphasize modulating excessive M1-mediated neuroinflammation to prevent secondary neurological damage, reflecting the established clinical consensus.

M2 macrophages represent an alternatively activated phenotype that mediates tissue regeneration and inflammatory resolution. These immunoregulatory cells secrete anti-inflammatory cytokines, including IL-10 and TGF-β, while promoting key reparative processes such as extracellular matrix remodeling, neovascularization and efferocytosis. Their polarization is primarily driven by IL-4 and IL-13 secreted from T helper (Th)2 lymphocytes, eosinophils and basophils (35). Emerging evidence has demonstrated that M2 polarization significantly attenuates cerebral infarct volume and enhances neurological recovery in stroke models (36). Therapeutic induction of M2 phenotype can be accomplished through multiple strategies, including pharmacological interventions (statins and minocycline) or adoptive transfer of M2-polarized macrophages (37-41). Given their neuroprotective and reparative properties, targeted modulation of macrophage polarization toward the M2 phenotype offers considerable therapeutic potential for stroke treatment.

The aforementioned description illustrates the characterization of inflammation in both types of stroke. Although inflammation in the acute phase causes cellular damage, it is also crucial for cellular debris removal. Modulating the duration of the M1 and M2 phases is crucial to prevent prolonged damage and to promote nerve repair and regeneration.

3. IL-27 and inflammation

IL-27 and its receptor. IL-27 is a heterodimeric cytokine composed of p28 and EBI3 subunits that belongs to the IL-6/IL-12 superfamily (42). This immunoregulatory cytokine serves as a crucial modulator of both the adaptive and innate immune responses. Produced primarily by activated antigen-presenting cells, particularly macrophages and dendritic cells, IL-27 exerts pleiotropic effects on multiple lymphocyte populations, including natural killer (NK), B and T cells (43,44).

The IL-27 receptor is a heterodimeric complex composed of two distinct subunits: Glycoprotein 130 (gp130) and IL-27 receptor α (IL-27Rα) (45-47). IL-27Rα serves as the ligand-specific binding component, while gp130 functions as a shared signal-transducing subunit utilized by multiple cytokines (46). The IL-27Rα subunit demonstrates high-affinity binding to IL-27, initiating downstream signaling upon ligand engagement. Following IL-27 binding, IL-27Rα recruits gp130 to form a functional receptor complex. This activated receptor triggers multiple intracellular signaling cascades, most notably the PI3K-AKT, MAPK and JAK-STAT pathways, ultimately regulating diverse biological processes, including immune responses and inflammatory reactions (48-50) (Fig. 2).

IL-27 and immunomodulation. IL-27 has context-dependent immunomodulatory properties, exhibiting both pro-inflammatory and anti-inflammatory effects based on the specific immune microenvironment (51,52). The present study focused particularly on IL-27's regulatory effects on macrophage polarization. *In vitro* analyses have demonstrated that IL-27 treatment upregulates M1 macrophage markers, including nitric oxide synthase 2 and IFN-γ (53). Notably, in a murine inflammatory bowel disease model, while colonic epithelial cells and intact crypts showed no response to IL-27, tissue-resident macrophages displayed significant reactivity (53). Mechanistic studies have revealed that IL-27 enhances macrophage antiviral activity via phosphorylated STAT1 activation (54,55). In a separate acute lung injury-sepsis model, adipose-derived mesenchymal stem cell (ADMSC) exosomes attenuated inflammation and its sequelae, an effect that was paradoxically reversed by recombinant IL-27 administration (56). Further *in vitro* experiments showed that ADMSC-derived exosomes suppressed LPS-induced IL-27 secretion from macrophages (56,57). Notably, a comparative cellular study revealed species-specific responses: IL-27 exerted minimal effects on murine macrophages but significantly modulated human macrophages through STAT1/TLR pathway activation, resulting in decreased IL-10 production and pro-inflammatory activation. This response was rapidly terminated by LPS via p38-mediated inhibition of IL-27 signaling (57).

Beyond its role in promoting M1 polarization, IL-27 is capable of downregulating characteristic M2 markers (IL-10 and arginase-1) while inhibiting the secretion of anti-inflammatory cytokines (IL-13 and IL-4) (57-60). However, these observations primarily stem from single-factor experimental systems. In physiological contexts, macrophage polarization is dynamically regulated through complex interactions among multiple mediators. A previous study by Rückerl *et al* (61) revealed that IL-4, IL-10 and IL-27 collectively orchestrated macrophage activation via sequential upregulation of WSX-1 and IL-4Rα receptors on alternatively activated macrophages.

Notably, IL-27 exhibits distinct immunomodulatory properties in inflammatory microenvironments following tissue injury. In a murine peritonitis model, IL-27 administration significantly reduced peritoneal fluid concentrations of the chemokines MCP-1/CCL2, KC/CXCL1 and MIP-1α/CCL3, while simultaneously inhibiting neutrophil mobilization from bone marrow, ultimately attenuating innate immune-mediated inflammation (62). In a previous study on a combined alcohol-burn injury model, gut-specific IL-27 downregulation could be therapeutically reversed, with exogenous IL-27 promoting intestinal epithelial proliferation, suppressing proinflammatory cytokines and enhancing IL-10 production, thus collectively restoring intestinal barrier homeostasis (63). Further mechanistic insights emerged from a rat spondyloarthritis study, where recombinant IL-27 ameliorated disease progression by selectively inhibiting IL-17/TNF-producing $CD4^+$ T cells (64). This finding was corroborated by cellular coculture experiments showing IL-27's dual capacity to suppress Th17 responses (reducing IL-17 production) while promoting regulatory responses (enhancing IL-10 secretion) in conventional dendritic cell-$CD4^+$ T cell interactions. These collective findings highlight the therapeutic potential of IL-27 as a multifunctional immunomodulator capable of resolving inflammation across diverse pathological contexts.

IL-27 generally exhibits pleiotropic effects on T cell subsets, promoting $CD8^+$ T and Th1 cell activation, while facilitating the differentiation of type 1 regulatory and follicular helper T cells. Conversely, it suppresses the functional responses of regulatory T (Treg), Th17, Th9 and Th2 cell populations (44,65-70). However, existing literature presents some contradictory findings regarding these immunomodulatory effects (71-73). The precise mechanisms underlying IL-27-mediated T cell regulation in post-stroke conditions remain to be fully elucidated, as T cell differentiation dynamics are influenced by microenvironmental cues. This knowledge gap highlights the need for further mechanistic investigations to elucidate the context-dependent actions of IL-27 in stroke pathophysiology.

IL-27 and stroke. Post-stroke neuroinflammatory responses trigger significant upregulation of IL-27 expression in the brain parenchyma, as demonstrated in multiple experimental stroke models (74-76). Clinical evidence further supports the diagnostic potential of IL-27, with serum IL-27α levels showing promise as a predictive biomarker for ischemic stroke occurrence (77). Notably, in patients undergoing emergency endovascular treatment for large vessel occlusion, circulating IL-27 levels were found to correlate with both infarct volume and development of post-ischemic cerebral edema (18). These findings collectively suggest that IL-27 may serve as both a pathophysiological mediator and clinically relevant biomarker in cerebrovascular events.

While existing studies have established that brain injury induces IL-27 upregulation, conclusive evidence for its neuroprotective effects remained elusive until recent preclinical investigations. Emerging data from animal models strongly support IL-27's therapeutic potential in stroke management. In cerebral ischemia-reperfusion models, IL-27 administration demonstrated neuroprotection by activating the gp130/STAT3 signaling pathway to attenuate neuronal apoptosis (16) and modulating cytokine balance through downregulation of proinflammatory mediators (TNF-α, IL-1β and MCP-1), while upregulating anti-inflammatory factors (IL-10 and TGF-β). Notably, in rodent models of hemorrhagic stroke, elevated IL-27 levels were observed in both CNS and peripheral circulation following brain injury (17). Mechanistic studies revealed that IL-27 exerted its beneficial effects through regulating bone marrow neutrophil maturation, suppressing the production of proinflammatory and cytotoxic substances, and promoting the expression of iron-chelating molecules critical for hematoma resolution (17). These multifaceted actions collectively contribute to reduced cerebral edema, enhanced hematoma clearance and improved neurological outcomes (16,17).

Beyond its implications in stroke, emerging evidence underscores IL-27's neuroprotective and regenerative capacities across various neurological disorders. In multiple sclerosis, IL-27 exhibits dual anti-inflammatory and immunomodulatory effects by suppressing Th17 cell differentiation while promoting Treg cell development, positioning it as both a neuroprotective agent and therapeutic candidate (78,79). Conversely, reduced IL-27 levels in patients with Parkinson's

disease are associated with neuroinflammation and cognitive decline, although its precise pathogenic role requires further investigation (80). Experimental studies on autoimmune encephalomyelitis have revealed that intrathecal delivery of IL-27-expressing lentiviral vectors attenuates neuroinflammation through two distinct mechanisms: i) Suppressing GM-CSF production in $CD4^+$ T cells; and ii) upregulating PD-L1 expression in both CNS-resident and infiltrating myeloid cells (81,82). Retinal degeneration models have further demonstrated IL-27's protective effects, showing increased arginase-1^+ neuroprotective microglia in the photoreceptor layer alongside elevated IL-27 levels, which collectively enhance photoreceptor survival (83). Additional findings have indicated that IL-27 reduces photoreceptor apoptosis while decreasing retinal concentrations of proinflammatory mediators (IL-12, IL-18 and CCL22) (84). Furthermore, vascular regeneration plays a crucial role in poststroke recovery. Notably, IL-27 promotes the endothelial differentiation of cardiac stem cells (85), suggesting potential angiogenic properties. However, direct evidence for IL-27-mediated cerebrovascular regeneration post-stroke remains to be established. Collectively, these studies highlight IL-27's multifaceted role in stroke pathophysiology, encompassing immunomodulation, neuroprotection and tissue repair. Future research should focus on elucidating the molecular mechanisms underlying these diverse functions of IL-27 in order to fully exploit its therapeutic potential in stroke management.

Recent preclinical studies have established the therapeutic potential of IL-27 in stroke management. Luo *et al* (16) demonstrated that intraperitoneal administration of recombinant mouse IL-27 (10 μg/kg/day), initiated within 30 min post-middle cerebral artery occlusion (MCAO) and continued daily for 7 days, significantly attenuated ischemia-reperfusion injury. Similarly, Zhao *et al* (17) reported that intravenous IL-27 treatment (50 ng/kg) initiated 30 min after intracerebral hemorrhage (ICH), followed by subcutaneous administration for 6 consecutive days, improved functional outcomes in ICH models. Emerging evidence has suggested that IL-27 exhibits synergistic effects when combined with other therapeutic modalities. Particularly promising are combination therapies with immune checkpoint inhibitors (anti-PD-1/PD-L1), vaccine-based approaches and vitamin D supplementation (86-88). These findings suggest that combinatorial treatment strategies incorporating IL-27 may represent a novel therapeutic paradigm for stroke. Future clinical translation should focus on optimizing these combination protocols to maximize neuroprotection while minimizing potential side effects.

IL-27 and PANoptosis. PANoptosis is a newly identified mode of programmed cell death that activates a series of cellular death processes, such as pyroptosis, apoptosis and necroptosis, initiating potent inflammatory responses after ischemic stroke (89,90). Prior studies demonstrated that activating the TLR4/NF-κB signaling pathway induces multiple pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 (91,92). These pro-inflammatory cytokines trigger cell death by binding to their respective receptors and activating downstream signal transduction (93). Caspase-8 is a PANoptosome component scaffold that regulates the three cell death pathways (pyroptosis, apoptosis and necroptosis) (94). Earlier reports have indicated that the binding of TNF-α to TNFR1 activates caspase-8 and triggers cell death (95). As aforementioned, IL-27 can attenuate inflammation after stroke. Thus, based on the TLR4/NF-κB/TNF-α pathway, future studies focused on inflammation-PANoptosis are needed to investigate how IL-27 improves post-stroke.

IL-27 and mitophagy. Ischemic stroke is usually accompanied by neuroinflammation, which is related to unsuitable activation of Nod-like receptor protein 3 (NLRP3) (96). Research has demonstrated that reactive oxygen species (ROS) play a key role in exacerbating the expression of NLRP3 inflammasome, which triggers an inflammatory response that can promote neuronal damage post-stroke. Mitochondrial autophagy, termed mitophagy, involves removing disrupted mitochondria and maintaining cellular homeostasis (97). Upon ischemic injury, mitochondria dysfunction leads to the production of plenty amounts of ROS and reduced clearance. As several studies have reported, obstruction of the mitophagy process results in the insufficient degrading of damaged mitochondria and facilitates the onset of neuroinflammation (98-101). Recent studies found that PTEN-induced kinase 1 and Parkin regulate mitophagy, which is important in attenuating inflammation by cleaning damaged mitochondria (98,99). Sufficient mitophagy will decrease the amounts of pro-inflammatory cytokines, which are the crucial mediators of neuroinflammation after cerebral ischemia (100,101). The previous findings indicated that IL-27 effectively inhibits the inflammatory response by modulating the ROS/NF-κB/NLRP3 axis in lung carcinogenesis (102). However, IL-27 mediates mitophagy and inhibits inflammation following cerebral ischemia remains uncovered.

4. Blood-brain barrier (BBB) and engineered exosome delivery strategies

The therapeutic application of IL-27 faces marked limitations due to the BBB, a highly selective vascular interface that protects the CNS. This specialized structure, composed of endothelial tight junctions, astrocytic end-feet and pericytes, forms a formidable neurovascular unit that actively excludes neurotoxic compounds and pathogens, regulates nutrient and metabolite transport, and restricts the penetration of ~98% of small-molecule drugs (103). While essential for CNS homeostasis, the BBB's restrictive properties substantially impair drug delivery to brain parenchyma, particularly for protein-based therapeutics such as IL-27, ultimately compromising their potential clinical efficacy in neurological disorders. Various approaches have been proposed to overcome the challenge of BBB penetration for protein drugs, including brain-targeted delivery systems, transporter inhibitors, brain penetration enhancement technologies and gene therapy (104,105). However, these solutions have their own limitations and associated risks. Consequently, further research and exploration are warranted to address the issue of BBB penetration by IL-27.

Exosomes, which are nanoscale extracellular vesicles (measuring 30-150 nm) actively secreted by cells, serve as pivotal mediators of intercellular communication and participate in diverse pathophysiological processes (33). In stroke

therapeutics, exosome-based drug delivery has emerged as a particularly promising strategy, demonstrating substantial translational potential in preclinical studies (106-108). Notably, stem cell-derived exosomes have shown remarkable therapeutic efficacy across multiple stroke subtypes through several synergistic mechanisms, including immunomodulation of both innate and adaptive immune responses, reduction of neuroinflammation and oxidative stress, inhibition of apoptotic pathways, secretion of neurotrophic factors, and promotion of angiogenesis and neurogenesis (109-112). These multifaceted actions collectively contribute to neural repair and functional recovery following cerebrovascular injury.

Beyond their inherent therapeutic properties, exosomes have garnered notable attention as natural nanoscale drug delivery vehicles. Engineered exosomes are particularly promising for CNS-targeted therapy due to their following properties: i) Overcoming the BBB through receptor-mediated transcytosis; ii) enhancing drug accumulation at lesion sites via active targeting; and iii) reducing off-target effects through their biocompatible nature. This targeted delivery approach markedly improves the therapeutic index by maximizing local drug concentrations while minimizing systemic exposure and associated toxicity. Notably, immune cell-derived exosomes (particularly those from macrophages, neutrophils and NK cells) exhibit ideal characteristics for brain-targeted delivery, since their membrane proteins retain native chemotactic properties that facilitate precise homing to inflammatory lesions, efficient BBB penetration and selective cellular uptake. These intrinsic targeting capabilities make immune cell exosomes superior candidates for neurological applications compared to synthetic delivery systems (113-116).

Recent advances in exosome engineering have focused on precision targeting through surface protein modification to enhance therapeutic delivery. In a murine model of ischemic stroke, cyclo(RGDyK) peptide-functionalized exosomes derived from bone marrow mesenchymal stem cells significantly improved the targeted delivery of curcumin to ischemic regions, thus potentiating its anti-inflammatory and anti-apoptotic effects (117). Similarly, AS1411 aptamer-conjugated macrophage-derived exosomes have demonstrated enhanced BBB penetration capability, markedly improving the precision and efficacy of sonodynamic therapy in glioblastoma treatment (118). Emerging targeting strategies have further expanded the repertoire of exosome-based CNS delivery systems, including neuropilin-1-targeted peptides for vascular targeting, Angiopep-2 peptides for low-density lipoprotein receptor-related protein-1-mediated transport, T7 peptide-modified chimeric antigen receptors for selective neuronal uptake, transferrin receptor-targeting approaches for receptor-mediated transcytosis and ANG-TRP-PK1 peptide sequences for enhanced parenchymal penetration. These engineering approaches collectively represent remarkable progress in overcoming the BBB limitation for neurological therapeutics (115,119-122).

As IL-27 is a protein, it can also be transported to the site of injury via engineered exosomes (123). This approach allows synergistic harnessing of the therapeutic potential of both exosomes and IL-27. Although exosome delivery holds great promise in the realm of stroke treatment, its practical application remains primarily confined to laboratory investigations and clinical trials. Further research endeavors are imperative to ascertain the safety, efficacy and optimal methodologies for its implementation.

Exosomes, nanoparticles and cells: Pros and cons in delivery. Exosomes, nanoparticles and engineered cells stand out as the main approaches for targeted brain delivery, each with strengths and weaknesses (124). Nanoparticles excel with their potential for large-scale manufacturing and customizable surface modifications, enabling the fine-tuning of size and shape to enhance drug delivery efficacy. They also offer precise control over the release kinetics of medications, accommodating a broad spectrum of drugs, from hydrophilic to lipophilic. However, nanoparticle-based therapies face several limitations, including rapid clearance by the immune system, potential immunogenicity and toxicity, and difficulties in achieving tissue- or cell-specific targeting (125). Consequently, regulatory oversight for nanomedicine is stringent, underscoring the need for meticulous safety and efficacy assessments.

Engineered cells represent a highly promising drug delivery platform, particularly induced pluripotent stem cells and other stem cell types such as totipotent stem cells, unipotent stem cells (126). These modified cells function as sophisticated therapeutic systems, capable of serving as 'living drug factories' that provide sustained therapeutic molecule production while responding to specific microenvironmental cues for controlled drug release. However, this approach has its challenges. The intricacies of cellular manipulation and genetic engineering can be daunting and engender ethical considerations. The host's physiological environment may compromise the cells' survival, proliferation and efficacy post-implantation, and there is the ever-present risk of triggering immune reactions or being eliminated by the immune system (127). Thus, despite their vast potential, the path to clinical realization for engineered cells is fraught with considerable complexity.

Beyond the aforementioned methods, exosomes stand out as a potent candidate for drug delivery. These engineered cellular systems exhibit several therapeutic advantages, including precise tissue targeting capability, low systemic toxicity profiles, diminished immunogenic potential and the capacity to overcome critical biological barriers such as the BBB (128). Additionally, they can transport various bioactive molecules, including proteins, lipids, RNA and DNA. The innate targeting abilities of exosomes, particularly those originating from specific cells, can be significantly amplified through surface modifications, employing techniques of genetic engineering or chemical approaches. However, this delivery method has its challenges. The intricate process of exosome isolation and purification demands considerable resources and sophistication, and their capacity to carry drugs is modest compared with that of other delivery systems (129). Additionally, the state of the donor cells can influence the biogenesis and secretion of exosomes. These complexities highlight the challenges that must be addressed to fully realize the clinical potential of exosomes.

From a translational perspective, while nanoparticle and cellular therapies have reached relative maturity, exosomes exhibit superior safety profiles and targeting precision. Consequently, exosomes may be considered as the optimal delivery vehicle for IL-27. The following section will focus

on the strategic implementation of exosome-based delivery systems.

5. Challenges and limitations of using IL-27 as a drug

Cost. Despite the numerous benefits of IL-27 as a protein-based therapeutic agent, it is crucial to acknowledge its associated limitations. Foremost among these is the substantial cost associated with protein-based medications, including production, transportation and preservation expenses.

Safety concerns and toxicities. IL-27 is considered to be a cytokine, and, in previous research, it did not cause significant toxicity or tissue damage (130). The therapeutic potential of IL-27 is further supported by its demonstrated low toxicity in animal models, which may be attributed to its limited induction of IFN *in vivo* (131). While IL-27 itself exhibits excellent tolerability with minimal toxicity, recombinant protein formulations may potentially trigger immune responses, leading to allergic reactions and impaired immune tolerance. Recent studies have explored adeno-associated virus (AAV) vectors for IL-27 delivery, demonstrating several advantages (86,132). First, AAV-IL-27 effectively suppresses tumor cell proliferation while maintaining low toxicity. Second, this approach significantly reduces Tregs without inducing autoimmunity. Third, AAV-IL-27 can be administered either locally or systemically while retaining its biological activity (86,87). These findings suggest that optimizing AAV vector delivery systems and incorporating chemical modifications to reduce immunogenicity may enhance both safety and efficacy, thereby expanding therapeutic applications.

Stability. Protein-based therapeutics are characterized by their relatively short plasma half-life and susceptibility to enzymatic degradation *in vivo*, often requiring repeated administration to maintain clinically effective concentrations. Therefore, it is imperative to explore methodologies that can prolong the half-life of protein drugs and attenuate their release rate. Presently, PEGylation stands out as the predominant technique by enhancing the stability of protein drugs and extending their circulation period via augmenting their additional volume (133). Another viable approach involves modifying the Fc region of protein drugs to extend their half-life within the body (134). Furthermore, refining the structure of protein drugs through alterations in their amino acid sequence or the incorporation of stabilizers can increase their stability. These strategies can be implemented individually or in conjunction, thereby enhancing therapeutic effectiveness and diminishing the need for frequent dosing.

Tumorigenic and antitumor properties. The multifaceted nature of IL-27 in immunomodulation has led to controversy over its tumor-suppressive and tumor-promoting activities (135). The majority of previous studies support that IL-27 exhibits antitumor effects by inducing tumor-specific Th1 and cytotoxic T lymphocyte responses, and directly impeding tumor cell proliferation, survival, invasion and angiogenesis (87,88). However, contradictory findings indicate that IL-27 upregulates the transcription factor nuclear factor IL-3 regulated, which synergizes with T-bet to enhance Tim-3 expression. Previous studies have demonstrated that IL-27 signaling is essential to generate Tim-3$^+$ exhausted T cells and to facilitate tumor progression. These observations suggest that IL-27-mediated induction of immune checkpoint molecules, including PD-L1 and Tim-3, may promote tumor immune evasion (136,137). Notably, the recent development of SRF388, an IL-27-targeting monoclonal antibody, represents a remarkable therapeutic advance. By blocking IL-27 receptor engagement, SRF388 enhances antitumor immunity within the tumor microenvironment (138). SRF388 has progressed to phase II clinical trials, indicating a promising avenue for therapeutic intervention. These advancements underscore the need of comprehensively assessing the application scenarios and contraindications of IL-27 before considering its utilization as a therapeutic agent for stroke treatment.

Pro-inflammatory and anti-inflammatory properties. IL-27 exhibits a dual role in immune regulation (139). Initially characterized as a pro-inflammatory cytokine (140,141), IL-27 exhibits canonical inflammatory features, including: i) Signal transduction primarily through the JAK/STAT and MAPK/ERK pathways (141,142); ii) production during effector immune responses (137,143); iii) structural similarity to other pro-inflammatory cytokines (IL-35, IL-23, IL-12 and IL-6) (144,145); and iv) capacity to promote T lymphocyte proliferation and activate NK cells (146). The pro-inflammatory mechanism involves sequential events. Binding to the WSX-1 receptor subunit induces rapid STAT3 phosphorylation within 30 min (144), subsequently driving the production of CXCL-10, which is a key mediator of monocyte-derived pro-inflammatory cytokine release (135,143). Conversely, IL-27 also possesses well-documented anti-inflammatory properties that are context-dependent, including the suppression of pro-inflammatory cytokines (TNF-α, IFN-γ, IL-17 and IL-21) and the concurrent upregulation of immunoregulatory IL-10 production (135,139). While current stroke research predominantly focuses on IL-27's anti-inflammatory effects, emerging evidence have revealed that neutrophils recruited during the pro-inflammatory phase may paradoxically contribute to neuroprotection and axonal regeneration (17,147). These findings highlight the need for further investigation into the complex, biphasic mechanisms of IL-27 in post-stroke recovery.

Limitations of animal models of ischemic stroke. Human stroke comprises ~85% ischemic and ~10% hemorrhagic cases (148). Current preclinical research utilizes several animal models to study ischemic stroke pathogenesis. Global ischemia models, typically induced by permanent vertebral artery ligation and/or transient bilateral common carotid artery occlusion, present several limitations, including technically challenging surgical procedures, frequent seizure induction and lower clinical relevance compared to that of focal ischemia models (149).

Focal ischemia models, particularly MCAO, are superior in replicating human stroke pathophysiology by showing a distinct ischemic penumbra analogous to human stroke, large reproducible infarct volumes and realistic ischemia-reperfusion injury dynamics. However, MCAO models exhibit notable differences from human stroke, including frequent hypothalamic damage (which is rare in humans), inability to simulate thrombolytic reperfusion hemodynamics and infarct

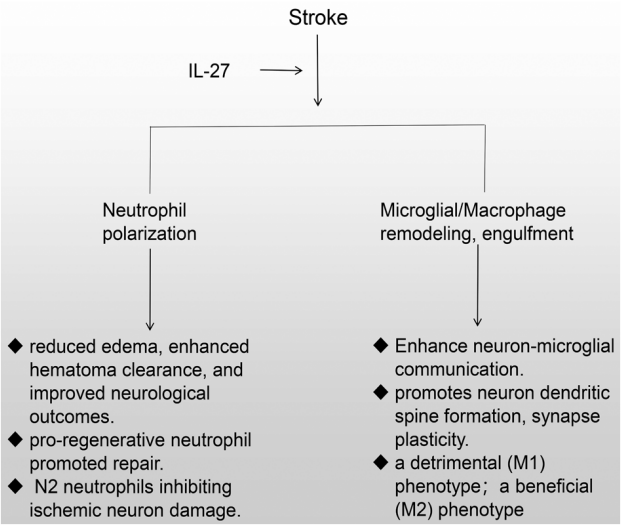

Figure 3. Pivotal role of IL-27 in modulating immune responses post-stroke. IL-27 is instrumental in mitigating edema, fostering pro-regenerative processes and preventing ischemic neuronal damage by stimulating neutrophil polarization subsequent to stroke. Furthermore. IL-27 can induce a microglial/macrophage-mediated immune reaction, enhancing neuron-microglial communication and supporting synaptic plasticity. IL, interleukin.

volumes (21-45% of ipsilateral hemisphere) that model malignant infarction (39% in humans) rather than typical stroke (4-14% hemisphere involvement) (149,150).

The photothrombotic stroke model offers distinct advantages for investigating cellular and molecular mechanisms of neurodegeneration, neuroprotection and neuroregeneration. However, this model presents several limitations when compared to human ischemic stroke pathology, including pronounced edema formation, minimal penumbral region and inability to replicate ischemia-reperfusion dynamics (149).

The thromboembolic model represents another approach to studying transient focal cerebral ischemia. This technique involves arterial occlusion through either exogenous thrombin administration or injection of macrospheres/microspheres into the internal carotid artery. While clinically relevant to human stroke mechanisms, this model suffers from poor reproducibility in terms of infarct location, size and ischemic duration (149).

Collectively, these experimental models contribute valuable insights into stroke pathophysiology. However, the translational gap remains notable, with numerous therapeutics demonstrating efficacy in animal models but failing to show comparable benefits in human clinical trials. This discrepancy likely derives from two key factors: i) Oversimplified pathophysiology of current animal models compared to the complexity of human stroke and ii) inadequate preclinical evaluation methods that poorly predict clinical outcomes. Addressing these limitations through improved model systems and more rigorous translational paradigms represents a critical need in stroke research.

6. Potential therapeutic mechanisms

The recently recognized heterodimeric member of the IL-6/IL-12 family of cytokines (151), IL-27, exhibits potent antitumor effects in multiple tumor models and independence from toxicity in preclinical trials (130). Emerging evidence suggests that IL-6 can stimulate neurogenesis and influence neural differentiation under stress conditions (152). Similarly, IL-27 may potentially play a similar role in post-stroke neurogenesis. Current research indicates that neuroinflammation and iron dyshomeostasis contribute to neuronal death in various CNS disorders (153). Due to its established anti-inflammatory properties, IL-27 may modulate the expression of key iron regulatory proteins (hepcidin, ferroportin-1 and divalent metal transporter 1), thereby reducing iron accumulation and preventing ferroptosis in neural cells. In the context of ischemic stroke pathogenesis, cerebrovascular occlusion or stenosis represents the primary pathological event. Notably, while IL-27 has been shown to promote tumor cell proliferation, survival and angiogenesis (51), these same properties could be therapeutically harnessed to enhance cerebral angiogenesis and improve perfusion in ischemic brain regions. This dual functionality positions IL-27 as a promising candidate for developing novel stroke treatment strategies targeting both neuroprotection and vascular repair.

The exact time window for using IL-27 as a therapeutic agent remains contradictory. A study indicated that IL-27 was injected within 30 min after the MCAO operation, resulting in IL-27 ameliorating the neurological function, reducing neuron death, upregulating anti-inflammatory factors and downregulating pro-inflammatory factors (16). Similarly, the IL-27 treatment was initiated 30 min after the hemorrhagic stroke, leading to improved neurological outcomes (17). Paradoxically, Furukawa *et al* (154) showed that mice lacking IL-27 showed reduced infarction area and suppressed inflammatory cytokines in the acute stage of intracerebral ischemia. Additionally, Li *et al* (155) reported recovery after stroke is associated with axonal sprouting in the cortex adjacent to the infarct. The gene expression level of IL-27 was upregulated in sprouting neurons from the peri-infarct cortex after 7 days of stroke (155). Li *et al* (155) also demonstrated that growth differentiation factor 10 (GDF10) was induced in sprouting neurons during the initiation phase of axonal sprouting, 7 days after stroke. Mice received a stroke in the forelimb motor cortex, followed 7 days later by administration of hydrogel of GDF10, which releases GDF10 over 2-3 weeks, stimulates axonal outgrowth, and improves functional recovery (156). Thus, IL-27 potentially enhances axonal sprouting and triggers neuronal growth programs at the subacute phase. In summary, future studies are needed to explore the accurate timing of IL-27 administration after stroke in depth.

7. Conclusions

In conclusion, IL-27 upregulation following stroke demonstrates neuroprotective potential through dual mechanisms of inflammation suppression (via M2 polarization) and enhanced tissue regeneration (Fig. 3). While engineered exosomes offer promising targeted delivery capabilities, clinical translation faces several challenges, as follows: i) Dosage precision is critical, as the neurogenic and proliferative effects of IL-27 may pose oncogenic risks; ii) temporal specificity is required, since acute-phase pro-inflammatory cytokine release (IL-6, IL-1β and TNF-α) exacerbates injury, whereas subacute/chronic phase M1-to-M2 transition promotes angiogenesis and

neuroprotection; and iii) mechanistic uncertainties persist regarding IL-27-mediated regulation of PANoptosis and mitophagy post-stroke. Future research should prioritize comprehensive safety profiling and development of clinically viable delivery systems to optimize therapeutic outcomes.

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Availability of data and materials

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Authors' contributions

WLiu, ZZo, ZZh and HY wrote the original draft, and reviewed and edited the manuscript. WLi, GY and JZ reviewed and edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors that they have no competing interests.

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