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*Correspondence: sicheng@ncrcnd.org.cn

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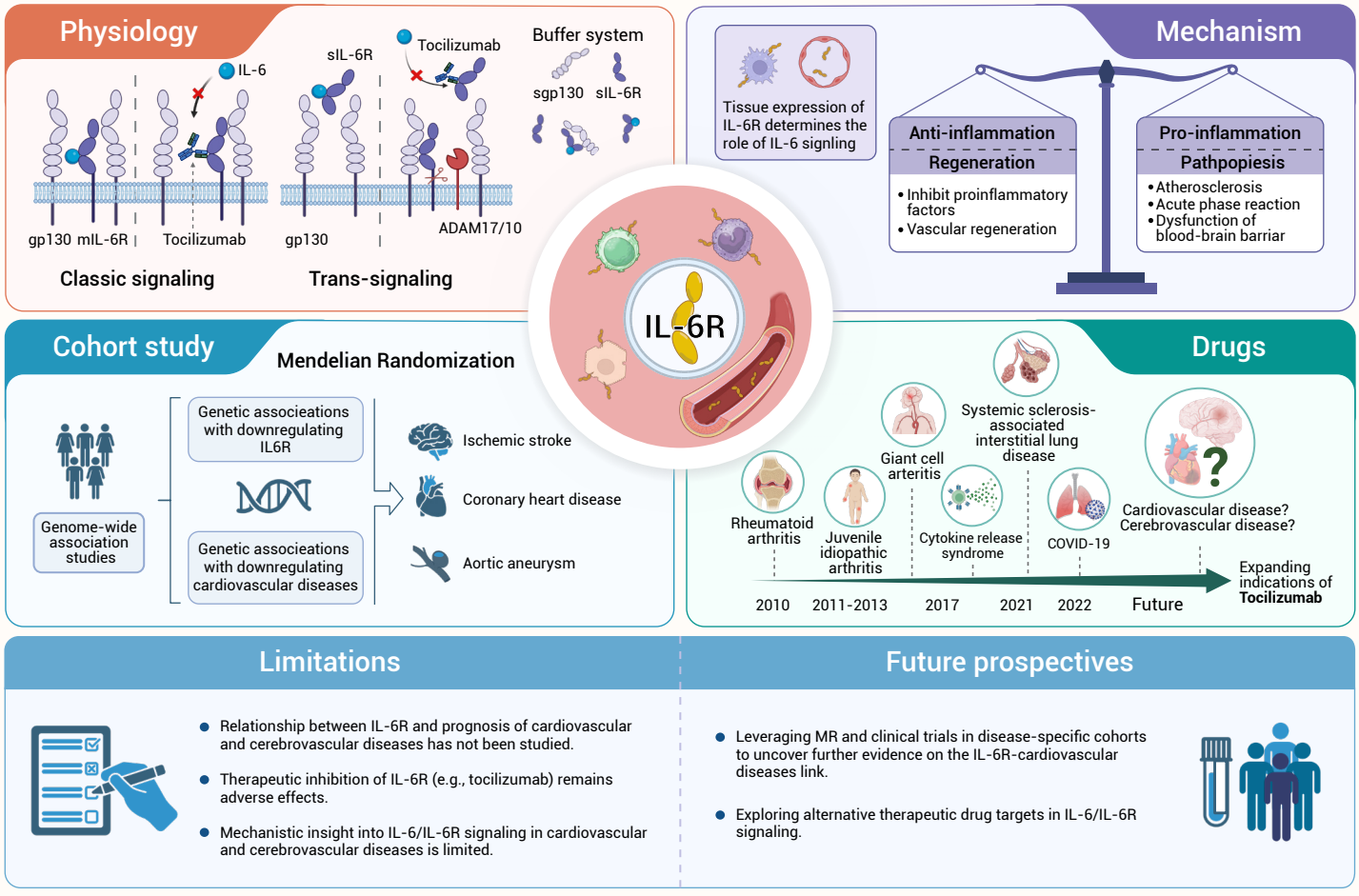
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Interleukin-6 receptor (IL-6R) plays a pivotal role in pathogenesis of cardiovascular and cerebrovascular diseases.
- IL-6R is associated with cardiovascular and cerebrovascular diseases in cohort studies.
- IL-6R will be a promising drug target in cardiovascular and cerebrovascular diseases.

REVIEW Basic Medicine

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The role of interleukin-6 receptor in cardiovascular and cerebrovascular diseases

Junkai Zou,[1,2,4] Zhanyu Wang,[2,4] Minghui Jiang,[1] Yuan Yang,[3] Rong Liu,[1,2] Jianping Wu,[2] Hao Li,[1,2] Yongjun Wang,[1,2] and Si Cheng[1,2,*]

[1]Center of excellence for Omics Research (CORe), China National Clinical Research Center for Neurological Diseases and Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China

[2]Beijing Key Laboratory of Drug and Device Research and Development for Cerebrovascular Disease, Beijing 100070, China

[3]Clinical Pharmacy Center, The First Affiliated Hospital of Kunming Medical University, Kunming 650032, China

[4]These authors contributed equally

*Correspondence: sicheng@ncrcnd.org.cn

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Interleukin-6 receptor (IL-6R) plays a pivotal role in Interleukin-6 (IL-6) signaling, which is an important pathogenic mechanism of cardiovascular and cerebrovascular diseases. IL-6R exists as membrane-bound and soluble forms and signals through classic, trans-, and cluster signaling that converge on JAK–STAT3, MAPK/ERK and PI3K–Akt pathways, while the IL-6 buffer system modulates signal intensity. Experimental studies show that IL-6 signaling drives acute-phase responses, dyslipidemia, endothelial activation, leukocyte recruitment, blood–brain barrier disruption, angiogenesis, and vascular remodeling. IL-6R is an important therapeutic target in inflammation, as evidenced by the approval of monoclonal antibodies like tocilizumab, sarilumab, and satralizumab. In addition, other emerging IL-6R-directed biologics and trans-signaling-selective approaches show promising anti-inflammatory activity in immune-mediated diseases. Mendelian randomization (MR) analyses using IL-6R variants as instruments indicate that partial lifelong downregulation of IL-6 signaling causally reduces the risk of coronary heart disease, ischemic stroke, abdominal aortic aneurysm, and other vascular phenotypes. Early clinical trials suggest tocilizumab has acceptable cardiovascular safety and improvements in acute inflammatory response, myocardial injury, and salvage. We propose that IL-6R might be a promising biomarker and therapeutic target for cardiovascular prevention and treatment. This review will summarize the role of IL-6R in cardiovascular and cerebrovascular diseases with reference to historical literature and discuss its potential clinical applications. Future studies should build large scale specific disease cohorts and further explore novel interventions targeting IL-6R signaling to advance the implementation of anti-inflammatory therapeutic strategies in this field.

INTRODUCTION

The cDNA of IL-6 (previously called BSF-2/IFNβ2) was first cloned in 1986,[1] and subsequently, the same team cloned the cDNA of IL-6R from human NK-like cell line in 1988.[2] IL-6R exists in two forms: membrane-bound IL-6R (mIL-6R) and soluble IL-6R (sIL-6R). These two receptor forms allow IL-6 to signal either in a membrane-restricted fashion or in a more systemic manner. IL-6 binding to mIL-6R induces "classic signaling", whereas its binding to sIL-6R induces "trans-signaling".[3] Given that IL-6 is a pleiotropic cytokine, the coexistence of mIL-6R and sIL-6R, together with the comparatively restricted expression pattern of mIL-6R, helps to explain how IL-6 can exert distinct context-dependent effects.[4,5] Therefore, IL-6R can be described as a key hub for IL-6 to exert multiple functions, highlighting it as an attractive therapeutic target to modulate IL-6 driven inflammation. Based on these mechanistic insights, three monoclonal antibodies targeting the IL-6R—tocilizumab, sarilumab, and satralizumab—have been launched. They inhibit both mIL-6R and sIL-6R and have demonstrated significant efficacy in treating immune diseases. Because of significant role of inflammation in the pathogenesis of cardiovascular and cerebrovascular diseases, the IL-6/IL-6R signaling has attracted growing interest beyond classical immune-mediated disorders.[6] In recent years, accumulating Mendelian randomization evidence have linked IL-6R to cardiovascular and cerebrovascular diseases, providing broad prospects for expanding the indications of IL-6R blocking drugs. In this review, we focus on IL-6R in cardiovascular and cerebrovascular diseases. However, current research remains limitations including the unelucidated relationship between IL-6R and cardiovascular disease prognosis, the persistent side effects of IL-6R inhibition (e.g., tocilizumab), and the incomplete mechanistic understanding of IL-6/IL-6R signaling in cardiovascular pathophysiology. We first summarize the physiological and pathological roles of IL-6R and its signaling pathways in the cardiovascular and cerebrovascular system, and then review cohort studies of IL-6R, and finally discuss IL-6R targeted therapies and their potential clinical applications.

MOLECULAR STRUCTURE, TISSUE EXPRESSION AND PHYSIOLOGICAL FUNCTIONS OF IL-6R

Molecular structure

The cDNA of IL-6R encodes a protein of 468 amino acids, which is organized into four main parts: a signal peptide, an extracellular region, a transmembrane domain, and a cytoplasmic domain.[1] The extracellular region contains three domains (D1, D2, D3) and a flexible stalk region.[7] Among them D1 is an Ig-like domain, while D2 and D3 constitute the cytokine-binding domains of IL-6R. IL-6 binds to the outer elbow region formed at the junction between D2 and D3, which is characterized by four loops from D2 [S106–N110 (L1), K133–P138 (L2), A160–F168 (L3), Q190–G193 (L4)] and three loops from D3 [S227–R233 (L5), M250–H256 (L6), Q276–Q281 (L7)]. These loops create a long, narrow potential binding groove that is stabilized by the rigid D2–D3 framework of the cytokine-binding domains. IL-6 interacts with residues located in several of these loops.[8,9] The Ig-like D1 domain is not required for ligand binding or the initiation of signaling, it has been implicated in regulating receptor internalization and maintaining protein stability.[10] The mature 80-kDa mIL-6R is a glycosylated form of the predicted 50-kDa precursor. Compared with mIL-6R, sIL-6R has a molecular mass that is 25–30 kDa smaller.[11,12] This size difference reflects the absence of the transmembrane and cytoplasmic domain in sIL-6R, which is produced through the generation processes such as proteolytic cleavage and alternative splicing.

Tissue expression

As a type I transmembrane protein, the expression profile of mIL-6R exhibits marked tissue specificity. Early studies demonstrated that human hepatocytes endogenously express mIL-6R, and that its mRNA levels can be further upregulated upon stimulation with IL-6 or IL-1, indicating that hepatocytes are important target cells for IL-6 classic signaling.[13,14] mIL-6R also can be detected on monocytes and monocyte-derived macrophages and both $CD4^+$ and $CD8^+$ T cells.[15,16] In contrast, resting B cells do not express mIL-6R on their surface, whereas stimulation with Pokeweed Mitogen (PWM) induces mIL-6R expression in the IgD^- large B cell and small B cell populations, while IgD^+ small B cells remain mIL-6R negative.[16] Skeletal muscle fibers also express mIL-6R, and its expression is modulated by exercise and pathological conditions.[17] Whether vascular endothelial cells express mIL-6R remains a matter of debate. Early studies have suggested that most endothelial cells lack mIL-6R on their surface and express only gp130.[18] However, more recent studies have successively reported that brain microvascular endothelial cells (BMVECs), human umbilical vein endothelial cells (HUVECs), retinal endothelial cells and human microvascular endothelial cells (HMEC-1) do express mIL-6R and are capable of mediating classic IL-6 signaling.[19-21] In response to the activation of IL-6, mIL-6R expression increase in HUVECs and HMEC-1,

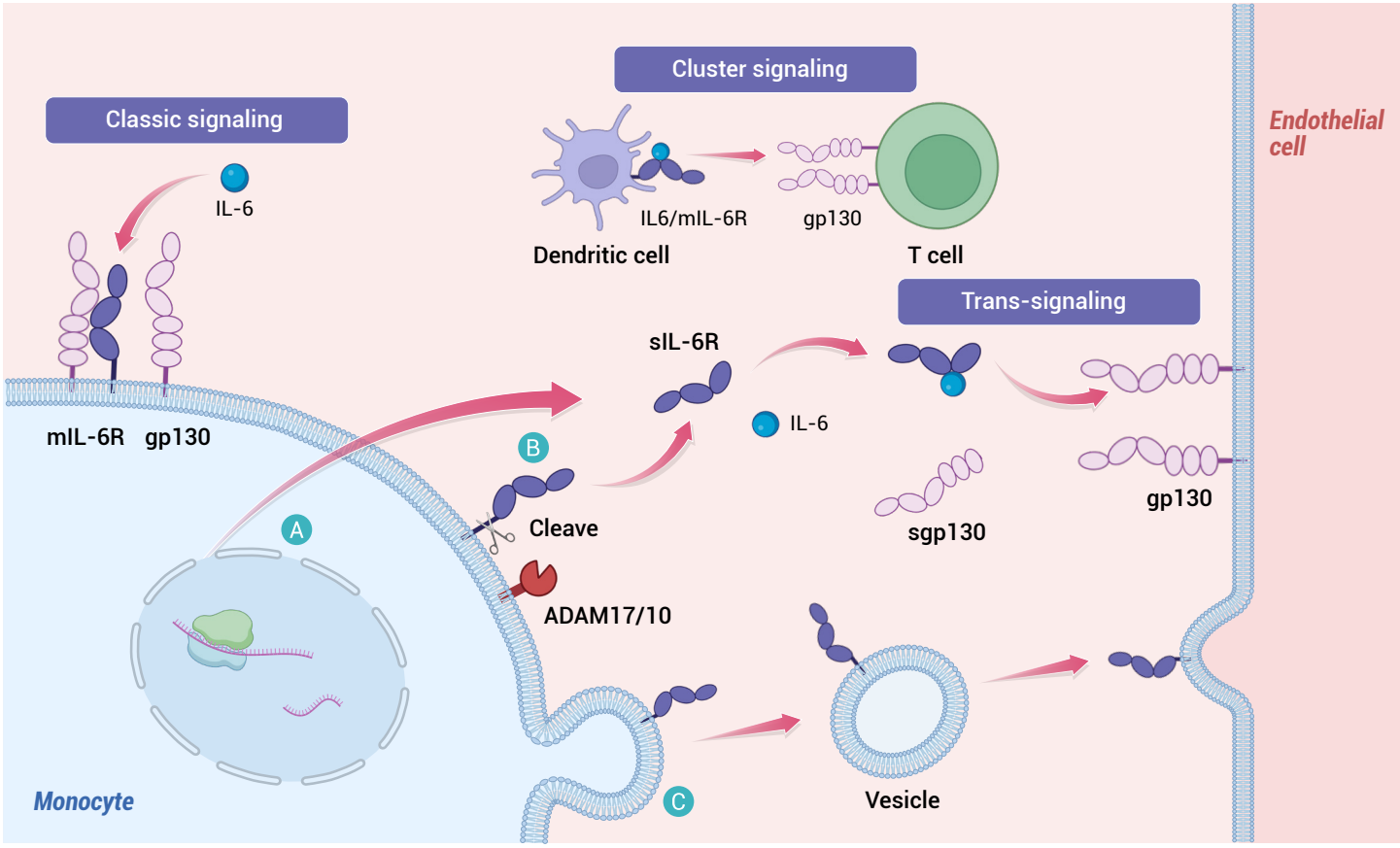

Figure 1. The three signaling modes of IL-6 and the three production mechanisms of sIL-6R. Classic signaling: IL-6 binds to membrane-bound IL-6R and induces the classical pathway. **Trans-signaling**: IL-6 binds to soluble IL-6R, which then binds to gp130 and induces the trans-signaling pathway. **Cluster signaling**: A cell presents IL-6/mIL-6R complexes to gp130-expressing cells and induces cluster signaling (A) Alternative splicing of IL-6R mRNA produces a transcript that encodes a soluble IL-6R, which is translated and directly released into the extracellular space. (B) Proteolytic cleavage of mIL-6R from the cell membrane, predominantly mediated by ADAM17/10, which shed mIL-6R by cleaving it at a membrane stalk region. (C) sIL-6R can be released on extracellular vesicles. Extracellular vesicles have the capacity to fuse with other cells and thereby transfer their IL-6R to cells lacking mIL-6R on their cell surface.

supporting sustained IL-6 signaling.

sIL-6R exists in biological fluids. Under non-pathological conditions, the baseline levels of sIL-6R in adult male are 76.6 ± 19.3 ng/ml in serum, 3.7 ± 1.3 ng/ml in urine, 1.6 ± 0.4 ng/ml in cerebrospinal fluid and 11.6 ± 3.3 ng/ml in synovial fluid respectively.[22,23] There are three main mechanisms for the production of sIL-6R. First, proteolytic cleavage of mIL-6R from the cell membrane, predominantly mediated by the A disintegrin and metalloproteinase 17 and 10 (ADAM17 and ADAM10), which shed mIL-6R by cleaving it at a membrane stalk region.[24,25] Second, alternative splicing of IL-6R mRNA produces a transcript that encodes a soluble IL-6R, which is translated and directly released into the extracellular space.[26-28] This mechanism has been described in humans but not in mice.[29] Third, sIL-6R can be released on extracellular vesicles. Unlike the sIL-6R produced by the above two mechanisms, which lack transmembrane and cytoplasmic domains, cells release extracellular vesicles into their surroundings that contain full-length receptors themselves . Extracellular vesicles have the capacity to fuse with other cells and thereby transfer their IL-6R to cells lacking mIL-6R on their cell surface.[29,30] (Figure 1)

Physiological functions of IL-6R

Under physiological conditions, the role of IL-6R is mainly to mediate immune functions through classical signaling.[31] In adaptive immunity, the canonical lineage effects are on $CD4^+$ T cells: IL-6 signaling induces $BCL6^+$ Tfh cells (early via STAT1 plus STAT3, and later by cell-intrinsic IL-6 signals that sustain Tfh responses) and, with TGF-β, diverts naive CD4 cells from $Foxp3^+$ Treg toward Th17 through gp130–STAT3.[32] Th17 cells physiologically protect barrier sites against extracellular bacteria and fungi by inducing neutrophil-recruiting and epithelial antimicrobial programs.[33] Activated B cells differentiate toward the plasmablast/plasma cell lineage upon IL-6 binding to surface mIL-6R.[1] In physiological humoral immune responses, IL-6R signaling enhances antibody production by supporting activated B-cell differentiation in concert with T-cell help, CD40 engagement, and IL-21, rather than acting as a sufficient autonomous driver of plasma-cell formation.[34] Beyond leukocytes, hepatocyte mIL-6R/gp130 supports liver protection and regeneration after injury or partial hepatectomy.[14] In skeletal muscle, local IL-6 signaling drives satellite-cell proliferation, cyclin D1 induction, and myonuclear accretion during loading or damage; human exercise-biopsy studies show satellite-cell pSTAT3 with IL-6R/gp130 induction.[35] Human metabolic studies show IL-6 increases skeletal-muscle glucose handling and exercise-related lipolysis.[36] In hematopoiesis, trans-signaling confers responsiveness of largely IL-6R-negative human $CD34^+$ progenitors, synergizes with thrombopoietin and IL-3, and increases megakaryopoiesis through gp130.[37] Human biallelic *IL-6R* deficiency causes recurrent bacterial skin and respiratory infections with strikingly blunted inflammatory responses and near-absent CRP induction despite high circulating IL-6, establishing a nonredundant role for IL-6R in the acute-phase response and antibacterial host defense.[38] Given the important physiological functions of IL-6R, therapeutic strategies targeting IL-6R should aim for rebalancing of the physiological network rather than a substantial or complete inhibition of IL-6R.

SIGNALINGS AND DOWNSTREAM PATHWAYS OF IL-6R

Extracellularly, IL-6 transmits signals through three modes: Classic signaling, Trans-signaling, and Cluster signaling.[39] In the classic signaling, IL-6 binds to the D2 and D3 domains of mIL-6R and recruits membrane-bound gp130, whereas in the trans-signaling pathway IL-6 forms a dimeric complex with sIL-6R to activate membrane-associated gp130.[40] Two IL-6/IL-6R/gp130 units assemble into a 2:2:2 hexameric complex, and signal transduction is initiated through gp130-mediated activation of intracellular path-

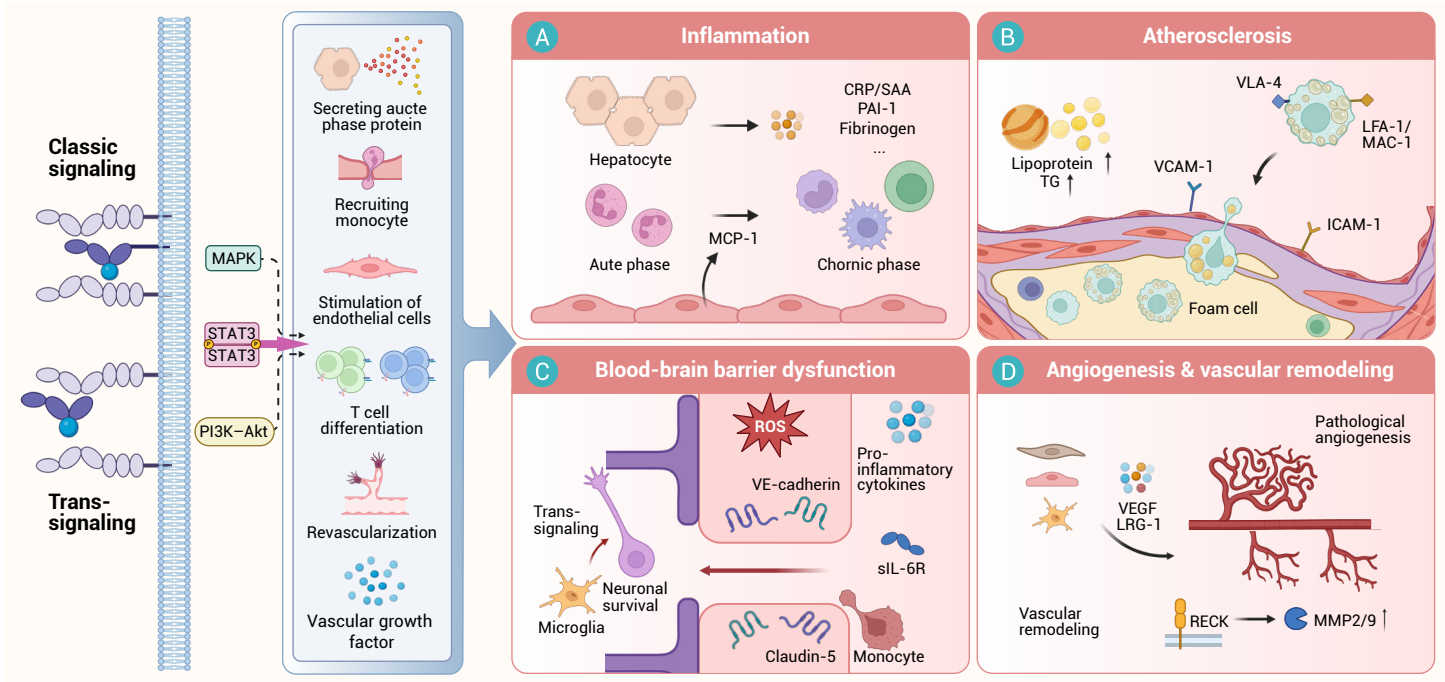

Figure 2. IL-6R mediated pathological mechanisms in cardiovascular and cerebrovascular disease Both classic and trans-signaling via IL-6/IL-6R activate the JAK–STAT3, MAPK and PI3K–Akt pathways. These downstream pathways regulate multiple biological processes, including acute-phase protein production, monocyte recruitment, endothelial cell activation, T-cell differentiation, angiogenesis, and vascular growth factor production, ultimately contributing to the following pathological changes: (A) IL-6/IL-6R signaling activates hepatocytes, leading to robust production of acute-phase proteins, including CRP, SAA, PAI-1, and fibrinogen. Activated endothelial cells secrete MCP-1, which recruits monocytes/macrophages and initiates chronic inflammation. (B) IL-6/IL-6R signaling upregulates the expression of VCAM-1 and ICAM-1 on endothelial cells, as well as their cognate ligands VLA-4 and LFA-1/MAC-1 on macrophages. These changes potentiate adhesion and chemotaxis, facilitating the migration of foam cells into the intima and thereby promoting the formation of atherosclerotic plaques. In addition, IL-6/IL-6R signaling increases very low-density lipoprotein (VLDL) and triglyceride (TG) levels. (C) IL-6/IL-6R signaling downregulates the expression of claudin-5 and VE-cadherin. Together with other pro-inflammatory mediators, this disrupts the integrity of the blood-brain barrier (BBB). The compromised BBB then allows monocytes and neutrophils to infiltrate the brain parenchyma, thereby amplifying neuroinflammatory injury. sIL-6R that crosses the BBB may also mediate, microglia-dependent pro-survival effects on newborn neurons via trans-signaling. (D) IL-6/IL-6R signaling orchestrates angiogenesis by promoting the release of factors such as VEGF and LRG1, which facilitate vascular regeneration, while downregulating remodeling-associated factors such as RECK, thereby modulating both physiological and pathological angiogenic processes.

ways.[41] Classic signaling exerts anti-inflammatory and tissue-protective effects. Because the expression profile of mIL-6R is relatively restricted, classic signaling is confined to specific cell types, thereby avoiding indiscriminate stimulation of broadly distributed cells and providing an inherent level of spatial control. In parallel, classic signaling induces the release of anti-inflammatory mediators such as IL-1 receptor antagonist, IL-10, and cortisol, and promotes expression of the negative feedback regulator suppressor of cytokine signaling 3(SOCS3), thus enabling self-limitation of the response.[42,43] By contrast, trans-signaling is predominantly pro-inflammatory and pathogenic. Given that gp130 is expressed on virtually all cell types, IL-6 through its binding with sIL-6R, can activate cells that do not express mIL-6R, resulting in a more widespread inflammatory response. In cluster signaling, a cell presents IL-6/mIL-6R complexes to gp130-expressing cells. For example, IL-6 bound to IL-6R on dendritic cells can be presented to cognate T cells, where it induces gp130 homodimerization and activation; this mode of signaling is critical for the generation of pathogenic Th17 cells.[44] (Figure 1)

Intracellularly, three major pathways are engaged: the JAK–STAT3 pathway, the ERK/MAPK pathway, and the PI3K–Akt pathway.[45–47] Recent experimentally based computational models indicate that classic and trans-signaling have comparable intrinsic potency in activating these downstream pathways, without major qualitative differences. The more prominent downstream activation often observed with trans-signaling is primarily attributable to the limited availability of mIL-6R in classic signaling relative to the abundant and sustained supply of sIL-6R in trans-signaling.[48,49]

THE BUFFER SYSTEM IN THE BLOOD

In the circulation, a naturally occurring soluble gp130 (sgp130) is present, which the neutralizes IL-6/sIL-6R dimeric complex by binding to it and forming an inactive trimeric complex, thereby preventing excessive activation of IL-6–driven inflammatory pathways, functioning as a buffer system.[50] In the serum of healthy individuals, IL-6 concentrations range from 1–5 pg/mL, sIL-6R from 20–80 ng/mL, and sgp130 from 250–400 ng/mL, with the overall buffering capacity primarily determined by the level of sIL-6R.[51,52] During inflammation, IL-6 levels can increase up to 1,000-fold, whereas sIL-6R and sgp130 typically rise only two- to five-fold.[3] One study showed that in severe COVID-19 this buffer system is driven to its limits, characterized by a relative insufficiency of sgp130 and altered proportions of dimeric and trimeric complexes, leaving substantial residual pro-inflammatory IL-6 activity.[53] Notably, even in individuals with mild disease who have clinically recovered, sIL-6R levels can remain elevated over the long term, suggesting persistent remodeling of the IL-6 signaling buffer system.[54]

PATHOLOGICAL MECHANISMS MEDIATED BY IL-6/IL-6R SIGNALING

Inflammation

Inflammation plays a crucial role in the development and progression of cardiovascular and cerebrovascular diseases. As the specific binding receptor for IL-6, IL-6R is a key molecule in activating inflammatory pathways. Through classical signaling transduction, IL-6R initiates acute inflammatory responses, laying the foundation for subsequent pathological damage. In hepatocytes, IL-6R induces ERK/MAPK and JAK-STAT3 downstream pathways and drive the synthesis of a broad array of acute-phase proteins, including C-reactive protein (CRP), serum amyloid A (SAA), complement C3, fibrinogen, hepcidin, haptoglobin, thrombopoietin, and α1-antichymotrypsin, while simultaneously suppressing the expression of albumin and cytochrome P450.[14,55,56] Among these acute-phase proteins, increased production of fibrinogen altogether with plasminogen activator inhibitor-1 (PAI-1) enhance coagulation and inhibit endogenous fibrinolysis, promoting arterial thrombosis. Activation of JAK–STAT3, NF-κB, and MAPK downstream pathways of IL-6/IL-6R signaling (including classic and trans-signaling) further prompts vascular endothelial cells and macrophages to secrete substantial amounts of pro-inflammatory cytokines such as IL-6, tumor necrosis factor α (TNF-α), and IL-1β within hours. This forms an acute inflammatory positive feedback

loop wherein IL-6/IL-6R signaling induces pro-inflammatory cytokine secretion, which in turn promotes enhanced IL-6 production and activates trans-signaling to rapidly amplify local inflammatory responses.[57] As acute inflammation persists, sIL-6R promotes chronicity of inflammation through trans-signaling, driving pathological changes throughout the course of cardiovascular and cerebrovascular disease. Trans-signaling via activation of JAK/STAT3 and PI3K/AKT pathways induces the expression and release of monocyte chemoattractant protein-1 (MCP-1) in vascular endothelial cells.[21] MCP-1 plays a pivotal role in chronic inflammation by recruiting monocytes and guiding them across the endothelium into the subendothelial space, where they transform into foam cells, giving rise to fatty streaks that ultimately evolve into atherosclerotic plaques.[58] (Figure 2A)

Atherosclerosis

Atherosclerosis is the common pathological substrate of coronary heart disease and large artery atherosclerosis ischemic stroke, and it is fundamentally a chronic inflammatory disease of the vessel wall.[6] Given its central role and complexity, this mechanism warrants separate consideration in the subsequent section. Downstream IL-6/IL-6R signaling promotes endothelial activation; activated endothelial cells upregulate the leukocyte adhesion molecules VCAM-1 and ICAM-1, while monocytes/macrophages express very late antigen-4 (VLA-4) and lymphocyte function-associated antigen-1/macrophage-1 antigen (LFA-1/MAC-1), which bind to VCAM-1 and ICAM-1, respectively.[59-61] This facilitates firm adhesion to the endothelium and transmigration into the intima, exacerbating chronic vascular wall inflammation and ultimately contributing to plaque formation, destabilization, and vascular events.[62,63] These infiltrating cells secrete significant quantities of matrix metalloproteinases (MMP-1, MMP-9, MMP-12), which catalyze the degradation of interstitial collagen and elastin in the fibrous cap, leading to cap thinning, diminished tensile strength, and ultimately heightened plaque instability.[64-67] IL-6/IL-6R signaling promotes cardiovascular risk by regulating plasma lipoproteins: it favors secretion of apolipoprotein B (apoB)-containing lipoproteins by increasing availability of apoB through changes in *apob* gene transcription and therefore increases very low-density lipoprotein (vLDL) and triglyceride (TG) levels.[68] IL-6/IL-6R signaling also increases levels of lipoprotein(a) [Lp(a)], a causal risk factor for atherosclerotic cardiovascular disease.[69] Lp(a) comprises apo(a) as a structural subunit, upregulates β2 integrin MAC-1 and enhances monocyte endothelial adhesion.[70] Furthermore, elevated CRP and SAA induce complement activation and remodeling of high-density lipoprotein (HDL), impairing its capacity for reverse cholesterol transport and thereby accelerating atherosclerosis progression.[71] (Figure 2B)

Blood-brain barrier dysfunction

In the central nervous system, IL-6R exerts context-dependent effects, with blood-brain barrier (BBB) endothelial cells serving as a major cellular target in its pro-inflammatory and BBB-disrupting actions, while activated microglia can also support neuronal survival and promote vascular repair in specific injury contexts. Under physiological conditions, BBB endothelial cells express mIL-6R, an expression that is further upregulated by IL-6 stimulation. Upon activation, IL-6 signaling downregulates the transcription of tight junction protein claudin-5 and adherens junction protein VE-cadherin, thereby disrupting BBB integrity.[72,73] MAPK/ERK and JAK/STAT3 pathways lead to the secretion of chemokines such as C-X-C motif chemokine ligands (CXCL1, CXCL5, CXCL6, and CXCL8), while activation of astrocytes and microglia via the NF-κB pathway promotes the release of pro-inflammatory cytokines and the generation of large amounts of reactive oxygen species (ROS), further damaging neurons and the BBB.[74] Once the BBB is compromised, circulating monocytes and neutrophils infiltrate the brain parenchyma through the injured vessel wall. In contrast to its pro-inflammatory effects during BBB injury, IL-6R may also exert context-dependent reparative functions after brain injury. Animal study suggests exogenous sIL-6R may access to the brain parenchyma even when the BBB remains intact, implying that sIL6R can enter the brain parenchyma from the circulation and mediate trans-signaling.[75] In experimental brain injury, repopulating microglia promote hippocampal neurogenesis and neuroprotection by inducing an IL-6 trans-signaling that enhances newborn neuron survival and improves cognitive recovery.[76] Additionally, data from mice with cerebrovascular injury indicate that a subset of microglia, namely repair-associated microglia (RAMs), promote vascular repair and neural tissue recovery by expressing vascular endothelial growth factor A (VEGFA) upon activation of IL-6 signaling (both classical and trans-signaling may be involved).[77] (Figure 2C)

Angiogenesis and vascular remodeling

Vascular regeneration and remodeling are major determinants of clinical outcomes in cardiovascular and cerebrovascular diseases.[78] After ischemic stroke, the IL-6R signaling can activate JAK/STAT3 pathway in endothelial cells to support reparative angiogenesis. In a mouse MCAO model, endothelial cell–specific STAT3 deletion did not alter infarct size at day 2 but markedly reduced vascular density and endothelial proliferation at day 28, leading to worse long-term functional recovery.[79,80] Across inflammatory and injury-repair models, IL-6/IL-6R singling activates JAK/STAT3 through trans-signaling to enhance stromal cell secreting vascular endothelial growth factor (VEGF), and therefore mediating angiogenesis by establishing a critical stromal/immune-to-endothelial paracrine axis. In vitro and in vivo evidence consistently shows that IL-6/sIL-6R preferentially induces VEGF production in stromal or myeloid cells rather than directly in endothelial cells, and the resulting VEGF-rich microenvironment promotes endothelial migration, sprouting, and tube formation;[81-85] this program can be reinforced by transcriptional regulators such as Specificity Protein 4 Sp4.[86,87] The IL-6R also participates in the regulation of vascular remodeling. One mechanism involves suppression of the membrane protein reversion-inducing cysteine-rich protein with kazal motifs (RECK) through competitive interaction and downregulation at the genetic level, thereby unleashing the activity of multiple proteases. RECK is an endogenous inhibitor of ADAM10/17 and MMP-2/7, and maintaining or enhancing RECK expression can constrain adverse cardiac and vascular remodeling.[88,89] Studies have shown that RECK physically interacts with IL-6R and gp130 and inhibits IL-6–induced migration and proliferation of vascular smooth muscle cells (VSMCs), suggesting that RECK acts as a negative regulator of IL-6R–related vascular inflammation and structural remodeling with potential protective effects.[90] Another mechanism involves IL-6R-mediated regulation of the angiogenic factor leucine-rich alpha-2-glycoprotein 1 (LRG1). Blockade of IL-6R with tocilizumab downregulates LRG1 expression, whereas local upregulation of LRG1 promotes neovascularization but is frequently accompanied by abnormal vascular structure and function.[91,92] Mechanistically, LRG1 alters the balance of transforming growth factor-β (TGF-β) signaling in endothelial cells, shifting it toward the ALK1–SMAD1/5/8 pro-angiogenic pathway and thereby driving pathological angiogenesis and vascular dysfunction.[93] (Figure 2D)

Additionally, IL-6R promotes Th17 and Tfh differentiation and suppresses Treg generation via STAT3, breaking immune tolerance and augmenting autoantibody responses.[94] In large-vessel vasculitis, the myocardium and vascular wall are chronically exposed to a Th17/Tfh-driven inflammatory milieu, fostering granulomatous vascular inflammation and intimal proliferative remodeling.[95]

Animal studies have shown that blockade of sIL-6R–mediated trans-signaling markedly attenuates angiotensin II (AngII)–induced blood pressure elevation, indicating that the IL-6/sIL-6R pathway mediates the pressor effects of AngII.[96] Mechanistically, IL-6/sIL-6R upregulates type 1 AngII receptor (AT_1R) expression in the vascular wall and kidney, rendering blood vessels and glomeruli more sensitive to AngII and thereby enhancing renin–angiotensin–aldosterone system (RAAS)–mediated vasoconstriction and sodium and water retention.[97] These changes ultimately lead to elevated blood pressure and, by promoting arteriolosclerosis, endothelial dysfunction, and reduced vascular compliance, drive the development of cerebral small vessel disease and lacunar infarction.

COHORT STUDY ON THE ASSOCIATION BETWEEN IL-6R AND RISK OF CARDIOVASCULAR AND CEREBROVASCULAR DISEASES

Association studies

In primary prevention cohorts, the relative levels of sIL-6R and sgp130 are more informative for cardiovascular risk prediction than their absolute concentrations. A pooled analysis in the general population found that sIL-6R neither independently predicted cardiovascular events nor reflected the severity of atherosclerosis.[98] In contrast, another study reported that expo-

sure to elevated serum sIL-6R levels was associated with an increased risk of myocardial infarction, while sgp130 may modulate this association. In a Swedish cohort of 60-year-olds, the ratio of IL-6:sIL-6R dimers to IL-6:sIL-6R:sgp130 trimers—calculated from serum concentrations of IL-6, sIL-6R, and sgp130—revealed that a higher dimer/trimer ratio, reflecting stronger IL-6 trans-signaling activity, independently predicted an elevated risk of future cardiovascular events, suggesting that this ratio may serve as a novel biomarker of IL-6–related cardiovascular risk.[99]

Beyond primary prevention, sIL-6R levels have also demonstrated prognostic value in secondary prevention settings. In a cohort of ST-segment elevation myocardial infarction (STEMI) patients undergoing emergency percutaneous coronary intervention (PCI), only those with baseline sIL-6R levels in the highest quartile showed a significantly increased risk of subsequent composite cardiovascular events and all-cause mortality, whereas IL-6 and sgp130 had no independent prognostic value. This underscores the importance of IL-6 receptor–mediated signaling in long-term outcomes following acute myocardial infarction.[100] Although circulating sIL-6R has been investigated as a potential biomarker in coronary artery disease, its interpretation requires caution. Similar to other soluble receptors, such as ST2 (sIL-33R), which has independent prognostic value in patients with chronic heart failure,[101,102] sIL-6R may partly reflect disease risk and prognosis in coronary artery disease. However, circulating sIL-6R levels are also substantially influenced by systemic inflammation and genetic background.[103,104] Therefore, sIL-6R should not be regarded as a stand-alone disease-specific biomarker, but rather as a context-dependent indicator that needs to be interpreted together with other inflammatory and cardiovascular markers.

Mendelian randomization studies

Beyond prospective epidemiological studies demonstrating the correlationship between IL-6R and risk of cardiovascular events, Mendelian randomization studies can reveal the causal relationship between exposure and outcomes.[105] Mendelian randomization is an analytic framework in which randomly allocated germline genetic variants are used as proxies for perturbations of disease risk factors or drug targets.[106]

In MR studies of IL-6R and cardiovascular diseases, investigators have sought genetically model a state of lifetime inhibition of IL-6 signaling. To achieve this, the *IL-6R* functional missense single nucleotide polymorphism (SNP), rs2228145 (Asp358Ala), has commonly been used as the core instrumental variable. This variant alters the cleavage of IL-6R by ADAM17/10, rendering mIL-6R more susceptible to shedding into sIL-6R and therefore downregulate the IL-6 signaling. This effect is corroborated by tocilizumab, a monoclonal antibody that blocks both mIL-6R and sIL-6R.[107] Additional instruments can be selected from variants located within a cis region around *IL-6R* that are associated with circulating CRP levels. As a downstream biomarker of IL-6 signal transduction, CRP is frequently used to quantify the extent of IL-6 signaling downregulation.[108] Besides, with the advancement of proteome detection technology, variants affecting circulation level of sIL-6R can also be selected to capture the putative protective effect of the buffer system. Buffer system selectively inhibits trans-signaling and prevents excessive activation of inflammatory signaling. Because allocation of these variants in the population approximates randomization in a clinical trial, the resulting comparisons are intrinsically less affected by confounding from environmental and behavioral factors, as well as by reverse causation.[109] By examining the association between genetic proxies for reduced IL-6 signaling and cardiovascular outcomes, one can infer the causal effect of IL-6 signaling on cardiovascular disease risk.

Genetically proxied downregulation of IL-6R-mediated IL-6 signaling exhibits a causal protective association with multiple cardiovascular and cerebrovascular diseases (Table 1). For coronary heart disease (CHD), a meta-analysis of 34 studies (25,458 cases/100,740 controls) reveals that the minor allele of rs7529229 (in strong linkage disequilibrium with rs2228145) reduces the risk of fatal and nonfatal CHD events (OR = 0.95, $P = 1.53 \times 10^{-5}$), validating IL-6R as a potential therapeutic target.[110] This finding is consistent with the protective effect observed in a study using 44 CRP-associated SNPs to instrument the inhibition of the IL-6 signaling.[111] Extending to other cardiovascular conditions, MR studies have further confirmed that inhibition of the IL-6 pathway confers protective effects against coronary artery disease (CAD), myocardial infarction (MI), atrial fibrillation (AF), and aortic stenosis, as well as a combined protective effect against composite cardiovascular diseases.[112,113] Additionally, genetically proxied downregulation of IL-6R-mediated IL-6 signaling exhibits a causal protective association with cerebrovascular and other vascular diseases: in ischemic stroke, MR analyses using CRP-associated SNPs (including rs2228145) demonstrate that attenuated IL-6 signaling lowers overall ischemic stroke risk (OR = 0.89, $P = 3.3 \times 10^{-3}$), with pronounced effects on large-artery atherosclerotic and small-vessel stroke (though discrepant results emerge in GIGASTROKE datasets, and no significant association is observed with arteriolosclerotic cerebral small vessel disease).[114-116] Regarding peripheral artery disease (PAD), genetically predicted elevated plasma sIL-6R levels correlate with reduced PAD risk (OR = 0.97, $P = 2.0 \times 10^{-6}$), suggesting sIL-6R-mediated attenuation of IL-6 classic signaling exerts protective effects.[117] For aortic aneurysm (AA), genetically proxied IL-6 signaling downregulation confers protection against abdominal AA, but shows no significant weaker effects on thoracic aortic or intracranial AA, indicating vascular bed-specific impacts of IL-6 signaling.[118,119] Additionally, MR studies highlight that higher circulating sIL-6R levels consistently reduce the risk of multiple vascular diseases—including AF, CAD, PAD, and AAA, proposing that pharmacologically augmenting the IL-6/sIL-6R/ sgp130 buffer system may represent a novel strategy for cardiovascular disease prevention.[119]

In addition to supporting causal inference, MR can also be used to analyze population subgroups, investigate drug combinations, and evaluate side effects.[111] A subgroup analysis explored associations with cardiovascular events stratifying by baseline high-sensitive CRP (hsCRP) levels and cardiovascular risk factors. hsCRP had a linear dose–response association with CVD risk that was broadly consistent across population subgroups, suggesting that IL-6 signaling inhibition benefit would likely scale with the absolute hsCRP reduction achieved. Notably, among individuals with low-density lipoprotein cholesterol (LDL-C) ≥160 mg/dL, the risk increase associated with higher IL-6 signaling was more pronounced. In addition, another 2×2 factorial MR analysis demonstrated that genetically reduced IL-6 signaling and genetically reduced LDL-C have additive effects in lowering the risk of cardiovascular diseases. This implies that priority candidates may be those with elevated baseline hsCRP, particularly when LDL-C is also high, therefore, future clinical trials could investigate combination strategies pairing IL-6 inhibition with LDL-C–lowering therapies (statins, proprotein convertase subtilisin/kexin type 9 inhibitors, ezetimibe) for cardiovascular prevention.[120,121] To assess side effects of IL-6 signaling inhibition, phenome-wide association study (PheWAS) in UK Biobank linked genetically reduced IL-6 signaling to increased risks of several infections and immune-related conditions but more favorable cardiometabolic profile.[122] Nevertheless, genetically higher sIL-6R levels were associated with longer parental lifespan, indicating that the overall effect of IL-6R blockade is likely beneficial.[112]

Despite many strengths, the use of MR to guide drugs development has important limitations. First, genetic downregulation of the IL-6 signaling represents lifelong modulation and may not fully mimic the effects of short- or medium-term pharmacologic treatment.[123] Second, most GWAS data are derived from European populations, limiting the generalizability of findings to other ancestries and environmental contexts.[124] Third, MR is inherently challenged by horizontal pleiotropy: cis protein quantitative trait loci (pQTLs) for IL-6R may also act as trans pQTLs for other proteins, potentially violating the exclusion restriction assumption. Given the pervasive pleiotropy in the human genome, even extensive sensitivity analyses cannot completely exclude such bias.[125]

DRUGS TARGETING IL-6R

Nowadays, three types of monoclonal antibodies that selectively inhibit the IL-6R have been approved for clinical use, and several drugs are being investigated (Table 2). Most of them are indicated for immune system diseases such as rheumatoid arthritis and juvenile idiopathic arthritis.

Approved drugs

Tocilizumab (Actemra) is the first-in-class humanized IgG1 monoclonal antibody that targets IL-6R. It binds specifically to both mIL-6R and sIL-6R, thereby simultaneously blocking both classic and trans-signaling pathways.

Table 1. MR research of IL-6R and cardio-cerebrovascular diseases.

Reference	Exposure: IV selection	Outcome	Effect
Daniel et al. The Lancet. 2012	**IL-6R blockade:** IL6R SNP rs7529229 (associated with IL6 in 16 studies, n=28,639)	CHD (25,458 cases/100,740 controls)	Decreased odds of CHD events
Seamus et al. European Heart Journal. 2013	**IL-6R-mediated downregulation of IL-6 signaling:** Asp358Ala (rs2228145)	AAA (4,524 cases/15,710 controls)	Lower risk of AAA
Ellie et al. Circulation: Genomic and Precision Medicine. 2019	**IL-6R-mediated downregulation of IL-6 signaling:** Asp358Ala (rs2228145)	AAA growth: 2863 AAA cases across 9 prospective cohorts	Protective against AAA growth, but not statistically significant
Mickael et al. npj Genomic Medicine. 2019	**sIL6R:** 34 IL6R cis variants linked to plasma sIL6R levels (n = 3301)	AF (case/control: 60,620/970,216), Any Stroke (40,585/406,111), CAD (122,733/424,528), AAA (821/352,557)	Lower risks of AF, stroke, CAD, and AAA
Marios et al. Circulation: Genomic and Precision Medicine. 2020	**IL-6R-mediated downregulation of IL-6 signaling:** 7 IL6R cis SNPs linked to lower CRP	IS (MEGASTROKE: 34,217 cases/404,630 controls), CAD (CARDIoGRAMplusC4D: 60,801 cases/123,504 controls)	Lower risks of stroke and CAD
Marios et al. Circulation. 2021	**IL-6R-mediated downregulation of IL-6 signaling:** 7 *IL6R* cis SNPs linked to lower CRP	1428 clinical outcomes in up to 339,256 White British individuals from the UKB	Lower risks of CAD and AAA
Michael et al. Circulation Research. 2021	**sIL6R:** 15 SNPs linked to plasma sIL6R (IMPROVE: n = 3394)	PAD (MVP: 35,042 cases/247,115 controls)	Lower risk of PAD
Marios et al. Journal of the American Heart Association. 2022	**IL-6 signaling inhibition:** genetic risk score (GRS) constructed from 26 IL6R cis variants linked to CRP (CHARGE and UKB)	CVD (UKB: 51,429 cases/356,796 controls)	Lower risk of CVD
Marios et al. BMC Medicine. 2022	**IL-6 signaling inhibition:** GRS constructed from 26 IL6R cis variants linked to CRP (CHARGE and UKB)	CVD across population subgroups (UKB: 397,060 White British individuals)	Linear dose–response with CVD risk (stratified by baseline hsCRP)
Jonathan et al. Scientific Reports. 2023	**IL-6R blockade (tocilizumab):** 18 *IL6R* SNPs linked to CRP (CHARGE and UKB)	Aortic stenosis (10 European cohorts: 13,765 cases/640,102 controls)	Reduced risk of aortic stenosis
Yanchen et al. International Immunopharmacology. 2024	**IL-6R blockade (tocilizumab):** 18 *IL6R* SNPs linked to CRP (CHARGE and UKB)	SVS (GIGASTROKE: 13,620 cases/1,227,999 controls)	Reduced risk of SVS
Guangyang et al. Scientific Reports. 2024	**IL-6R blockade:** 44 SNPs linked to CRP (UKB: 353,466 Europeans)	CHD (51,098 cases/402,635 controls), HF (33,250 cases/420,483 controls), HTN (137,312 cases/316,345 controls), MI (28,546 cases/378,019 controls), and AF (55,853 cases/231,952 controls)	Reduced risks of CHD and MI; no significant effect on HTN, HF and AF
Stephen et al. Arteriosclerosis, Thrombosis, and Vascular Biology. 2025	**IL-6 signaling inhibition:** 7 *IL6R* cis SNPs linked to lower CRP/Asp358Ala (rs2228145)	AAA (AAAgen consortium: 39,221 cases/1,086,107 controls, UKB (1963 cases/365,680 controls, and FinnGen: 3869 cases/381,977 controls)	Reduced risk of AAA
Zihao et al. International Journal of Biological Macromolecules. 2025	**sIL6R:** cis-pQTLs (deCODE: 35,559; UKB-PPP: 54,219)	AA (FinnGen: 8125 cases/381,977 controls)	Reduced risk of AA
Larissa et al. Journal of the American Heart Association. 2025	**IL-6 signaling inhibition:** 26 variants linked to lower CRP/Asp358Ala (rs2228145)	Arteriolosclerotic cerebral small vessel disease	No significant effect
Mengmeng et al. International Journal of Cardiology. 2025	**IL-6 signaling inhibition:** 6 SNPs linked to CRP (n = 204,402); sIL6R: 29 variants linked to plasma sIL6R levels (n = 3301)	AA (Europeans: 3230 cases/475,964 controls)	Reduced risk of AA

AA: aortic aneurysm; AAA: abdominal AA; AF: atrial fibrillation; CHD: coronary heart disease; CVD: cardiovascular disease; HF: heart failure; HTN: hypertension; IS: ischemic stroke; MI: myocardial infarction; PAD: peripheral artery disease; SVS: small-vessel stroke.

Tocilizumab was initially approved for rheumatoid arthritis (RA) in 2010.[126] Following its initial approval, its indications have been subsequently expanded to include giant cell arteritis (GCA), systemic sclerosis-associated interstitial lung disease (SSc-ILD), polyarticular juvenile idiopathic arthritis (PJIA), systemic juvenile idiopathic arthritis (SJIA), and cytokine release syndrome (CRS).[127-130] Based on clinical trial data showing that, tocilizumab improved survival and other clinical outcomes of hospitalized COVID-19 patients with hypoxemia and systemic inflammation, Actemra received

Table 2. Approved drugs targeting IL-6R.

No.	Generic Name	Principle of Action	Indication(s)	Dosage Form	Approved Time	Brand Name Developer(s)
1	Tocilizumab	Inhibiting IL-6 signaling through competitive binding mIL-6R and sIL-6R	RA, GCA, SSc-ILD, PJIA SJIA, CRS, COVID-19	IV/SC	2010	Actemra Chugai/Roche
2	Sarilumab		GCA, RA, PMR	SC	2017	Kevzara Regeneron/Sanofi
3	Satralizumab		AQP4 antibody positive NMOSD	SC	2020	Enspryng Chugai/Roche
4	Tocilizumab-bavi		RA, PJIA, SJIA	IV	2023	Tofidence Bio-Thera
5	Tocilizumab-aazg		RA, GCA, PJIA, SJIA	IV/SC	2024	Tyenne Fresenius
6	Tocilizumab-anoh		RA, GCA, PJIA, SJIA COVID-19	IV/SC	2025	Avtozma Celltrion

RA: Rheumatoid Arthritis; GCA: Giant Cell Arteritis; SSc-ILD: Systemic Sclerosis-associated Interstitial Lung Disease; PJIA: Polyarticular Juvenile Idiopathic Arthritis; SJIA: Systemic Juvenile Idiopathic Arthritis; CRS: Cytokine Release Syndrome; COVID-19: Coronavirus Disease 2019; PMR: Polymyalgia Rheumatica; AQP4: Aquaporin-4; NMOSD: Neuromyelitis Optica Spectrum Disorders; IV: Intravenous; SC: Subcutaneous.

Table 3. IL-6R targeting drugs in clinical development.

No.	Drug Code	Principle of Action	Indication(s)	Highest Phase	NCT Number	Developer
1	BCD-089 Levilimab	Inhibiting IL-6 signaling through competitive binding mIL-6R and sIL-6R	RA	Phase 3	NCT04227366	Biocad
			COVID-19	Phase 3	NCT04397562	
2	VDJ001		RA	Phase 3	NCT06726096	VDJBio
			iMCD	Phase 2	NCT05345522	
3	HS628		RA	Phase 3	NCT06048224	Hisun
4	ALX-0061 Vobarilizumab		RA	Phase 2b	NCT02287922	Ablynx
			SLE	Phase 2	NCT02437890	
5	TJ301 IV Olamkicept	Binding IL-6/sIL-6R complex	UC	Phase 2	NCT03235752	I-Mab

RA: Rheumatoid Arthritis; COVID-19: Coronavirus Disease 2019; iMCD: Idiopathic Multicentric Castleman Disease; SLE: Systemic Lupus Erythematosus UC: Ulcerative Colitis.

formal approval in December 2022 for use in hospitalized adult patients with severe COVID-19.[131] Tocilizumab-bavi (Tofidence), tocilizumab-aazg (Tyenne), and tocilizumab-anoh (Avtozma) are biosimilar products to Actemra that were approved in 2023, 2024, and 2025, respectively. These agents are highly comparable to originator tocilizumab in structure and pharmacokinetic properties, and clinical studies have demonstrated no clinically meaningful differences in efficacy or safety.[132-134]

Similar to tocilizumab, sarilumab specifically targets IL-6R and was approved in 2017. Unlike tocilizumab, sarilumab is a fully human monoclonal antibody with lower immunogenicity, higher affinity (20-fold), and greater potency in blocking IL-6 signaling (4-fold).[135] It is currently indicated primarily for adult patients with RA who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs), for patients with polymyalgia rheumatica (PMR) with an unsatisfactory response or intolerance to glucocorticoid tapering, and for patients with pJIA.[136-138]

Satralizumab also targets IL-6R and was approved in 2020, mainly for the treatment of aquaporin-4 antibody (AQP4-IgG)–positive neuromyelitis optica spectrum disorder (NMOSD).[139,140] Satralizumab represents a second-generation IL-6R inhibitor derived from tocilizumab. It utilizes a novel, pH-dependent recycling antibody technology that extends its circulation time and exhibits approximately 4-fold higher affinity for the IL-6R than tocilizumab.[141]

Drugs in Clinical Development

VDJ001 is a novel recombinant humanized monoclonal antibody directed against the IL-6R. As an analogue of tocilizumab, it exhibits improved affinity and in vitro activity.[142] It has completed Phase 2 development in RA and progressed into Phase 3 trials; the efficacy and safety of this drug are currently being evaluated in patients with idiopathic multicentric Castleman disease (iMCD). HS628 is another tocilizumab biosimilar that demonstrated a high degree of similarity to tocilizumab in a phase I clinical study.[143] It is currently being evaluated in a Phase 3 trial in RA, comparing the efficacy and safety of HS628 versus tocilizumab, each administered in combination with methotrexate, in patients with active RA.[144] ALX-0061 (vobarilizumab) is a bispecific Nanobody with high affinity for IL-6R(200-fold than tocilizumab) and an extended half-life achieved by targeting human serum albumin. Multiple Phase 3 studies in RA and systemic lupus erythematosus (SLE) have demonstrated its ability to effectively suppress IL-6–mediated inflammatory responses.[145] Levilimab is a fully human monoclonal antibody that blocks both sIL-6R and mIL-6R. Phase 3 clinical trials have been completed in RA and COVID-19.[146,147] In 2020, the Russian Ministry of Health approved levilimab for the treatment of severe COVID-19, and it is currently marketed only in Russia.

In addition to these monoclonal antibodies, several antagonistic strategies targeting the IL-6 signaling through novel mechanisms are under development. One example is olamkicept, a fusion protein composed of the extracellular domain of gp130 linked to the Fc portion of IgG (Table 3).[148] sgp130Fc selectively binds IL-6/sIL-6R complexes and blocks their interaction with membrane-bound gp130, thereby specifically inhibiting IL-6 trans-signaling without interfering with IL-6 classic signaling via mIL-6R. This selective blockade strategy is expected to attenuate harmful systemic inflammation. A

Table 4. Clinical trials of targeting IL-6R in cardiovascular diseases.

	NCT01331837	NCT00535782	NCT01491074	NCT03004703	NCT06238024
Study Objective	To assess the risk of MACE in patients with RA treated with tocilizumab compared to those treated with etanercept	To investigate the effects of tocilizumab on lipids, arterial stiffness, and markers of atherogenic risk in patients with moderate to severe active RA	To validate that tocilizumab would attenuate inflammation, and secondarily reduce TnT release in NSTEMI	To evaluate the effect of tocilizumab on myocardial salvage in acute STEMI	To determine the safety and potential efficacy of tocilizumab in patients with acute ischaemic stroke undergoing EVT for large-vessel occlusion
Study design	Randomized, open-label, parallel-group	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Multicentre, randomised, double-blind, placebo-controlled
Study phase	Phase 4	Phase 3	Phase 2	Phase 2	Phase 2
Sample size	n = 3080	n=132	n=117	n=199	n=108
Population	Patients who had an inadequate response to conventional synthetic disease-modifying antirheumatic drugs and who had at least 1 cardiovascular risk factor	Patients with RA of >6 months duration and on methotrexate for at least 12 weeks before entering study, at a stable dose of 7.5-25 mg/week for the last 8 weeks	Patients with NSTEMI at a median of 2 days after symptom onset	Patients admitted with STEMI within 6h of symptom onset	Patients with acute ischaemic stroke undergoing EVT
Intervention	1:1 receive either open-label tocilizumab (IV at 8 mg/kg/month) or etanercept (IV at 50 mg/week) until they switched to another RA therapy or for up to 4.9 years	1:1 receive 8 mg/kg tocilizumab or placebo (IV every 4 weeks) plus MTX 7.5-25 mg (oral or parenteral) weekly for the first 24 weeks	1:1 receive a single dose of 280 mg tocilizumab (IV) or placebo, prior to coronary angiography	1:1 receive a single dose of 280 mg tocilizumab (IV) or placebo during PCI	1:1 receive a single dose of 240 mg tocilizumab (IV) or placebo within 24 h after stroke onset
Primary Outcome	Comparison of time to first occurrence of MACE	Change from baseline to week 12 in sLDL particle numbers and aortic PWM	Between-group difference in the AUC for hsCRP (days 1–3)	Myocardial salvage index after 3 to 7 days	The change in infarct volume from baseline to 72h
Result	MACE risk was similar between groups (HR 1.05, 95% CI 0.77–1.43)	sLDL: No significant difference (MD 0.0 mmol/L; 95% CI 115.0–115.0) PWV: Greater decrease with placebo (MD 0.79 m/s; 95% CI 0.22–1.35) TC, LDL-C, VLDL: Greater increase with tocilizumab vs. placebo	Tocilizumab markedly reduced hsCRP exposure and hsTnT release compared with placebo (2.1 times and 1.5 times)	Tocilizumab increased myocardial salvage index (5.6 percent more than versus placebo)	Tocilizumab decreased infarct volume median change in infarct volume: placebo 27.0 mL (range 7.6–62.4), tocilizumab 8.8 mL (IQR 3.4–20.6).
Researcher/Country	Thomas R Fleming USA	Naveed Sattar UK	Lars Gullestad Norway	Lars Gullestad Norway	Chuanjie Wu China

MACE: Major Adverse Cardiovascular Events; **RA**: Rheumatoid Arthritis; **IV**: Intravenous; **HR**: Hazard Ratio; **MTX**: Methotrexate **sLDL**: small Low-Density Lipoprotein; **PWM**: Pulse Wave Velocity; **MD**: Mean Difference; **TC**: Total Cholesterol; **LDL-C**: Low-Density Lipoprotein Cholesterol; **VLDL**: Very-Low-Density Lipoprotein; **STEMI**: ST-Elevation Myocardial Infarction; **NSTEMI**: Non-ST-Elevation Myocardial Infarction; **TnT**: Troponin T; **AUC**: Area Under the Curve; **PCI**: Percutaneous Coronary Intervention; **EVT**: Endovascular Treatment; **IQR**: Interquartile Range.

phase 2 clinical trial in ulcerative colitis has been completed and showed a greater likelihood of clinical response.[149] Notably, a case report described the attenuation of arterial wall inflammation in a patient with atherosclerotic cardiovascular disease treated with olamkicept, without perturbation of lipoprotein metabolism, suggesting that olamkicept may represent a promising therapeutic option for ASCVD.[150]

CLINICAL TRIALS

Mechanistic, observational, and Mendelian randomization studies have progressively clarified the role of the IL-6/IL-6R signaling in cardiovascular diseases. This raises the clinically important possibility that targeting this signaling may become a viable anti-inflammatory strategy for cardiovascular diseases. It also motivates interest in extending IL-6R inhibitors beyond immune-mediated indications. Accordingly, tocilizumab has been conducted for clinical trials to explore its potential in this field (Table 4).

In earlier clinical trials, elevations in serum lipids (e.g., total cholesterol, LDL-C, triglycerides, VLDL) were observed in patients treated with tocilizumab compared to placebo.[151-153] To systematically assess cardiovascular safety, a Phase 4, open-label, randomized trial enrolled 3,080 patients who had RA with cardiovascular risk factors. It compared continued treatment with tocilizumab, 8 mg/kg intravenously monthly, against the tumor necrosis factor inhibitor (TNFi) etanercept, 50 mg intravenously weekly, until patients switched therapy or for up to 4.9 years, using the time to the first major adverse cardiovascular event (MACE) as the primary endpoint. Etanercept was selected as an active comparator given the generally favorable cardiovascular profile reported for TNFi therapy in prior cohorts.[154-156] During follow-up, MACE risk was similar between groups (HR 1.05, 95% CI 0.77–1.43).[157] Overall, despite lipid elevations, IL-6R blockade has at least not been linked to a meaningful increase in MACE risk. This is consistent with earlier retrospective evidence.[158,159]

More recent trials in patients with acute myocardial infarction suggest that, while maintaining cardiovascular safety, IL-6R blockade may also provide

prognostic benefit.[160] In a Phase 2, double-blind, placebo-controlled trial involving 117 patients with recent NSTEMI (median 2 days post-event), a single dose of 280 mg tocilizumab was injected before coronary angiography. Compared to placebo, tocilizumab significantly attenuated the acute inflammatory response and myocardial injury, reducing hsCRP and high-sensitivity troponin T levels by approximately 2.1-fold and 1.5-fold, respectively. These findings indicate that IL-6R blockade may mitigate inflammation and limit ischemia–reperfusion injury.[161]

In STEMI, an important determinant of prognosis is myocardial salvage, defined as the extent to which ischemic myocardium recovers after reperfusion. A multicenter, double-blind, Phase 2 trial evaluated the effect of IL-6R blockade on myocardial salvage in 195 STEMI patients treated with primary PCI. Patients were randomized to receive a single 280-mg intravenous dose of tocilizumab or placebo during the procedure. Tocilizumab treatment resulted in 5.6 percent greater myocardial salvage index compared to placebo, accompanied by reductions in microvascular obstruction and inflammatory burden. Thus, the inhibition of IL-6 signaling with tocilizumab promotes myocardial salvage following acute STEMI.[162]

In acute ischemic stroke, inhibition of IL-6 signaling with tocilizumab may attenuate infarct progression. A multicenter, double-blind, Phase 2 IRIS trial (NCT06238024) evaluated the effect of IL-6R blockade on infarct evolution in 108 patients with anterior-circulation large-vessel occlusion undergoing endovascular treatment. Patients were randomized to receive a single 240-mg intravenous dose of tocilizumab or placebo within 24 hours of stroke onset. Tocilizumab significantly attenuated the increase in infarct volume at 72 hours compared with placebo (placebo: median 27.0 mL [range 7.6–62.4]; tocilizumab: median 8.8 mL [IQR 3.4–20.6]; adjusted difference in cube root: −0.41 [95% CI −0.79 to −0.03], P = 0.04), along with reductions in systemic inflammatory markers and no increase in safety events. The team has registered a Phase 3 IRIS-2 trial (NCT07263776) with the primary outcome of 3-month mRS score, and patient recruitment is ongoing.[163]

In addition, evidence from upstream anti-inflammatory trials further supports the potential cardiovascular relevance of the IL-6 signaling. CANTOS provided definitive proof that targeting inflammation can reduce cardiovascular event risk. The trial enrolled 10,061 post-MI patients with hsCRP ≥2 mg/L and randomized them to multiple doses of canakinumab or placebo. At 48 months, cardiovascular event risk was reduced versus placebo (HR range 0.85–0.93 across doses) and CRP reductions are also substantial (approximately 26–41%), these effects were independent of changes in lipid levels.[164-166]

For IL-6, the same group conducted a Phase 2 trial (RESCUE) to evaluate the impact of the IL-6 monoclonal antibody ziltivekimab on multiple inflammatory and thrombotic biomarkers. Among 264 high-risk atherosclerotic patients with stage 3–5 chronic kidney disease (CKD) and hsCRP ≥2 mg/L, ziltivekimab produced large, dose-dependent hsCRP reductions at 12 weeks (approximately 77–92%), versus minimal change with placebo. Dose-dependent reductions were also observed in thrombotic biomarkers such as fibrinogen, serum amyloid A, and lipoprotein(a).[167,168] A Phase 3 outcomes trial of this antibody (ZEUS) is currently underway, using major adverse cardiovascular events (including myocardial infarction, stroke, and cardiovascular death) as the primary endpoint to directly determine whether IL-6 inhibition can reduce cardiovascular and cerebrovascular events.[169]

CONCLUSIONS AND FUTURE PROSPECTIVES

Since the discovery of IL-6R, its roles in inflammation and tumor biology have been extensively investigated, and IL-6R–targeting agents such as tocilizumab have been used to treat immune diseases. Since the milestone report in 2012 that genetically downregulated IL-6R confers protection against coronary heart disease, an increasing number of investigators have employed Mendelian randomization to examine the relationship between IL-6R and a spectrum of cardiovascular and cerebrovascular diseases. On this basis, whether therapeutic interventions targeting this signaling could represent an important future direction for anti-inflammatory treatment in cardiovascular and cerebrovascular medicine, and whether the indications of IL-6R inhibitors can be expanded from traditional immune-mediated diseases to cardiovascular and cerebrovascular diseases, has become a clinically relevant question.

There remain gaps in this field that deserve further investigation. First, current Mendelian randomization studies on IL-6R and cardiovascular and cerebrovascular disease have focused primarily on disease occurrence, the relationship between IL-6R and post-event prognosis has not yet been systematically investigated. Given that IL-6 levels may rise sharply after an acute cardiovascular or cerebrovascular event (by more than 1000-fold), large, dedicated disease-specific cohorts are needed to clarify whether IL-6R-targeted agents can be used for secondary prevention or prognostic intervention. Such studies should include collection of blood samples early after symptom onset and long-term follow-up to obtain detailed outcome data. Second, the mechanisms underlying the protective effects of IL-6 signaling downregulation on cardiovascular and cerebrovascular risk remain to be elucidated. Evidence suggests that IL-6R will be a promising drug target; however, the precise underlying mechanisms in cardiovascular and cerebrovascular diseases remain elusive, with a lack of animal and population-based studies. Although some investigators have used multi-omics approaches combined with Mendelian randomization to identify downstream candidates (such as CXCL10 and oncostatin M receptor, OSMR) as potential causal mediators, the precise biological mechanisms are still limited.[170,171] Notably, the mechanisms in cerebrovascular diseases may be even more intricate than those in cardiovascular diseases and may vary across different subtypes and stages. Elucidating the mechanistic relationship between IL-6R and cardiovascular and cerebrovascular diseases is meaningful for expanding the indications of the IL-6R inhibitors. Third, because IL-6/IL-6R signaling plays essential roles in physiological responses, current approaches involving systemic blockade of the IL-6R may still lead to adverse effects, such as severe systemic infections. In addition to directly inhibiting mIL-6R and sIL-6R, more selective therapeutic strategies merit exploration.[62,103] The recombinant sgp130 fusion protein olamkicept (sgp130Fc) has been developed to selectively inhibit IL-6 trans-signaling and has now entered clinical testing. Given its demonstrated cardiovascular benefits in animal studies and case reports, olamkicept represents a promising candidate for expanding into the cardiovascular therapeutic area.[150,172] Furthermore, the development of novel drugs targeting alternative nodes within the IL-6 signaling holds significant potential, offering a next-generation strategy for the treatment of cardiovascular and cerebrovascular diseases.

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AUTHOR CONTRIBUTIONS

S.C. supervised and revised the manuscript. Y.W., J.W. and H.L. supervised the manuscript. J.Z., Z.W and M.J. wrote and edited the manuscript. J.Z., Z.W., M.J. and Y.Y. contributed to figure and table preparation. R.L. participated in information searching and manuscript discussions. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created in this study.