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Review

IL-6 Trans-Signaling and the Soluble IL-6 Receptor in Acute Myocardial Infarction: From Inflammation to Remodeling

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Abstract

Acute myocardial infarction (AMI) is characterized by a rapid and coordinated inflammatory response that influences myocardial injury, repair, and long-term ventricular remodeling. Among inflammatory mediators, interleukin-6 (IL-6) has emerged as an important cytokine linking endogenous immune activation to systemic and local cardiovascular effects. In addition to classical IL-6 signaling through membrane-bound IL-6 receptors, soluble IL-6 receptor (sIL-6R)-mediated trans-signaling expands IL-6 responsiveness to cells lacking membrane-bound IL-6R expression, including endothelial cells, fibroblasts, and cardiomyocytes. Increasing evidence suggests that this pathway may contribute to vascular inflammation, leukocyte recruitment, microvascular dysfunction, and fibrotic remodeling, although direct evidence for sIL-6R-dependent trans-signaling in AMI remains limited and is often inferred from the broader IL-6 axis. In this narrative review, we summarize the molecular biology of IL-6 trans-signaling, examine the regulation and temporal dynamics of sIL-6R during acute myocardial injury, and discuss its potential role in plaque destabilization, infarct expansion, microvascular obstruction, and post-infarction remodeling. We further review the emerging evidence supporting the IL-6/sIL-6R axis as a biomarker framework and therapeutic target, while highlighting the interpretive limitations of circulating sIL-6R levels and the current lack of direct clinical evidence for selective trans-signaling inhibition in AMI. Finally, we outline key knowledge gaps and future directions for precision anti-inflammatory strategies in acute coronary syndromes.

Keywords: myocardial infarction; interleukin-6; receptors, interleukin-6; inflammation; ventricular remodeling; biomarkers

1. Introduction

Acute myocardial infarction (AMI) is increasingly recognized not only as an ischemic event caused by sudden coronary occlusion, but also as a highly dynamic inflammatory syndrome in which immune activation critically influences myocardial injury, repair, and long-term ventricular remodeling [1]. Following plaque rupture or erosion and subsequent coronary thrombosis, the ischemic myocardium rapidly releases ischemia-associated molecular signals that activate resident and circulating immune cells, endothelial cells, platelets, and fibroblasts [2]. This inflammatory response is essential for clearance of necrotic tissue and initiation of healing [3]. However, when excessive, prolonged, or dysregulated, it contributes to infarct expansion, microvascular dysfunction, extracellular matrix disorganization, adverse left ventricular remodeling, and progression to heart failure [4].

Among the cytokines involved in this process, interleukin-6 (IL-6) has emerged as an important mediator linking local tissue injury to systemic inflammatory activation [5]. IL-6 is rapidly induced in response to ischemic necrosis and reperfusion injury and exerts pleiotropic effects on vascular, immune, and stromal cells [6]. In the setting of acute coronary syndromes (ACS), IL-6 has been associated with plaque vulnerability, endothelial activation, leukocyte recruitment, prothrombotic signaling, and myocardial fibrosis, supporting its role as more than a passive biomarker of inflammation [7,8]. Importantly, the biological effects of IL-6 depend on its signaling mode (Fig. 1). Classical signaling is restricted to cells expressing membrane-bound IL-6 receptor (IL-6R), whereas trans-signaling occurs when IL-6 binds soluble IL-6R and activates glycoprotein 130 (gp130)-expressing cells that lack membrane IL-6R [9,10]. Trans-signaling is widely considered a more pro-inflammatory mode of IL-6 signaling in cardiovascular disease, but this distinction is not absolute and remains context-, cell type-, and time-dependent [11].

These considerations are particularly relevant in AMI, where the balance between necessary inflammation and excessive immune activation is a major determinant of outcome. The specific focus of this review is the soluble IL-6 receptor (sIL-6R)/soluble gp130 (sgp130)/trans-signaling axis in AMI, with emphasis on where direct evidence exists, where conclusions are inferred from broader IL-6 path-

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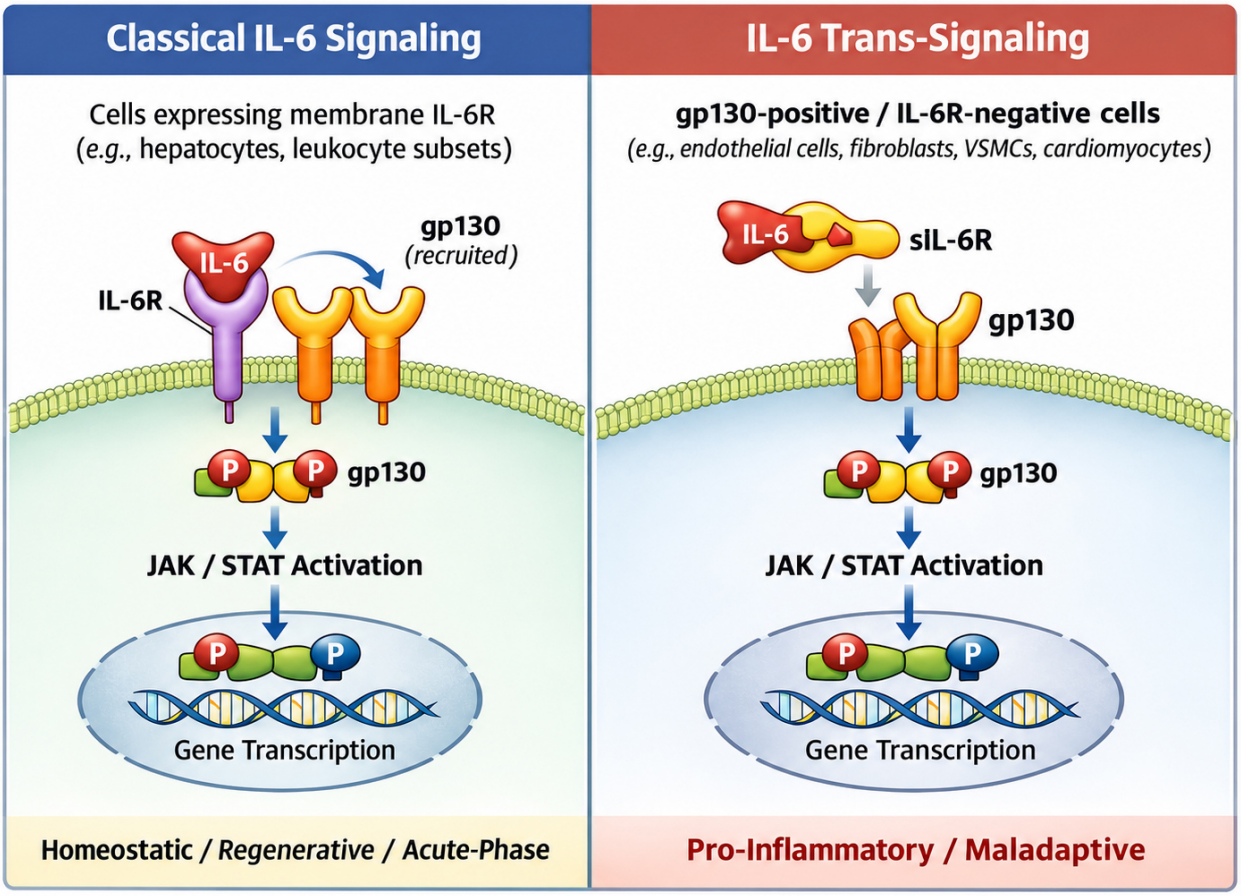


Fig. 1. Classical IL-6 signaling versus IL-6 trans-signaling. This schematic compares the two principal modes of IL-6 signaling. In classical signaling (left), IL-6 binds first to the membrane-bound IL-6 receptor (IL-6R) on IL-6R–expressing cells, and the resulting complex then recruits gp130, leading to gp130 dimerization and downstream JAK/STAT activation. Because membrane IL-6R expression is restricted, classical signaling occurs only in selected cell types, including hepatocytes and subsets of immune cells, and is often associated with homeostatic, regenerative, and acute-phase responses, although its effects remain context-dependent. In trans-signaling (right), IL-6 first binds to soluble IL-6 receptor (sIL-6R), and the IL-6/sIL-6R complex subsequently activates membrane-bound gp130 on cells that do not express membrane IL-6R. As gp130 is widely expressed, trans-signaling expands IL-6 responsiveness to a broader range of cardiovascular cells, including endothelial cells, fibroblasts, vascular smooth muscle cells, and cardiomyocytes, and has often been associated with pro-inflammatory and maladaptive responses, although its biological consequences remain context-, cell type-, and time-dependent. gp130, glycoprotein 130; VSMCs, vascular smooth muscle cells; JAK, Janus kinase; sIL-6R, soluble interleukin-6 receptor; STAT, signal transducer and activator of transcription. This figure was generated using ChatGPT (OpenAI, San Francisco, CA, USA) and subsequently reviewed by the authors for scientific accuracy.

way activity, and how this distinction affects biomarker interpretation and therapeutic translation [12]. This article is presented as a narrative review. Relevant literature was identified through PubMed/MEDLINE and Scopus searches up to March 2026 using combinations of the terms “interleukin-6”, “IL-6”, “soluble interleukin-6 receptor”, “sIL-6R”, “gp130”, “trans-signaling”, “myocardial infarction”, “acute coronary syndrome”, “ventricular remodeling”, “tocilizumab”, and “olamkicept”, supplemented by manual screening of reference lists. Priority was given to mechanistic studies, translational reports, AMI-specific clinical studies, and landmark intervention studies relevant to interpretation of the IL-6 pathway.

2. Biology of IL-6 Signaling Pathways

2.1 Classical IL-6 Signaling (Membrane-Bound IL-6R)

In the classical signaling pathway, IL-6 mediates its biological actions by binding to the IL-6R, an approximately 80 kDa type I transmembrane protein [13,14]. However, IL-6R alone cannot initiate signal transduction and requires association with the signal-transducing transmembrane protein gp130 [15]. Formation of the IL-6/IL-6R complex induces gp130 homodimerization, which subsequently activates intracellular signaling cascades [16]. While gp130 is widely expressed across many cell types, membrane-bound IL-6R is expressed only on selected cells,

including hepatocytes and certain immune cells such as monocytes, macrophages, dendritic cells, B cells and T cells [16,17,18]. Consequently, cells lacking membrane IL-6R cannot respond to IL-6 through the classical signaling pathway.

2.2 IL-6 Trans-Signaling via Soluble IL-6 Receptor

This limitation is overcome by the presence of a soluble IL-6 receptor (sIL-6R). The soluble receptor is generated either through proteolytic cleavage of the membrane-bound IL-6R or through alternative mRNA splicing [19]. When IL-6 binds to sIL-6R, an IL-6/sIL-6R complex is formed in the extracellular space. This complex can subsequently interact with gp130 on the surface of cells that do not express membrane-bound IL-6R, thereby initiating intracellular signaling [10]. This mechanism, known as IL-6 trans-signaling, expands the spectrum of IL-6-responsive cells beyond those expressing membrane-bound IL-6R [20,21]. Binding of this complex induces gp130 dimerization and activates downstream signaling pathways [16]. Importantly, IL-6 trans-signaling is strongly associated with pro-inflammatory responses in many experimental settings, although its biological effects remain context-dependent [11]. This pathway is particularly relevant in cell types such as endothelial cells, vascular smooth muscle cells, and fibroblasts, which typically express gp130 but lack membrane-bound IL-6R [10].

2.3 Role of gp130 and Downstream JAK/STAT Activation

Following formation of the IL-6/IL-6R receptor complex, intracellular signaling is initiated through the signal-transducing protein gp130. The IL-6/IL-6R complex binds to two gp130 molecules, resulting in gp130 dimerization and formation of a functional receptor complex that activates intracellular Janus kinases (JAKs), leading to phosphorylation of signal transducer and activator of transcription (STAT) factors, particularly STAT3 [15]. The intracellular domain of gp130 is constitutively associated with members of the JAK family, including JAK1, JAK2, and tyrosine kinase 2 (TYK2) [22]. Upon IL-6 binding and gp130 dimerization, these associated JAKs become activated through trans-autophosphorylation [20]. Activated JAKs then phosphorylate specific tyrosine residues on the cytoplasmic tail of gp130, thereby creating binding sites for downstream signaling molecules, including STATs [20]. STAT proteins, particularly STAT3, are subsequently phosphorylated, dimerize, and translocate to the nucleus where they regulate the transcription of genes involved in apoptosis, differentiation, immune cell activation, survival, and proliferation [22,23,24]. Although IL-6 and sIL-6R individually have no affinity for gp130, their complex binds gp130 with high affinity, thereby initiating the IL-6 signaling cascade [25].

2.4 Biological Distinction Between Protective and Maladaptive Signaling

IL-6 exerts a wide range of biological effects, which can be either protective or detrimental depending on the signaling pathway involved. The two principal modes of IL-6 signaling (classical and trans-signaling) mediate overlapping but often distinct physiological and pathological responses. Classical IL-6 signaling is generally associated with regenerative, homeostatic, and anti-inflammatory functions of the cytokine [26]. It also plays a key role in the hepatic acute-phase response, an essential component of innate immunity [26,27]. In macrophages, classical IL-6 signaling can also promote differentiation toward the anti-inflammatory M2 phenotype, thereby contributing to the resolution of inflammation [22]. In addition, IL-6 is involved in liver regeneration, highlighting its role in tissue repair following injury [28].

The protective nature of classical IL-6 signaling is partly explained by the restricted expression of the membrane-bound IL-6 receptor to specific cell types, which allows the response to remain locally regulated. Under normal conditions, IL-6 is produced in relatively small amounts and primarily acts locally through paracrine signaling on nearby cells that express the membrane-bound IL-6R. In the circulation, IL-6 activity is further controlled by a natural regulatory system consisting of sIL-6R and gp130-related buffering mechanisms, thereby limiting excessive activation of IL-6 signaling pathways and maintaining immune homeostasis [24,29].

In contrast, growing evidence indicates that many, though not all, of the pro-inflammatory effects of IL-6 are mediated predominantly through trans-signaling rather than classical signaling [10,24]. Under pathological conditions, persistent activation of this pathway can shift IL-6 from a regulator of immune homeostasis to a mediator of chronic inflammation and tissue injury [24]. Sustained activation of IL-6 signaling, particularly through trans-signaling, promotes transcription of pro-inflammatory genes, immune dysregulation, and fibrotic remodeling [22].

In the cardiovascular system, this distinction is informative but should not be interpreted as absolute. IL-6 signaling through STAT3 in cardiac tissue may support cardiomyocyte survival during acute myocardial injury [30], whereas persistent or excessive pathway activation may contribute to pathological hypertrophy, fibrosis, and impaired contractile function [31]. In AMI, circulating IL-6 levels rise rapidly in response to ischemic injury and correlate with the magnitude of myocardial damage and the intensity of the inflammatory response [32]. Although this transient response may contribute to tissue repair, sustained activation of the IL-6 axis after infarction may promote adverse ventricular remodeling and contribute to progression toward ischemic heart failure [33].

3. Regulation and Sources of Soluble IL-6 Receptor

The sIL-6R is produced through two principal mechanisms [34]. First, proteolytic shedding of the membrane-bound IL-6R occurs at the cell surface, where metalloproteases such as ADAM10 and ADAM17 cleave the receptor and release its extracellular domain into the circulation. Second, alternative mRNA splicing produces an IL-6R transcript lacking the transmembrane domain, resulting in the secretion of a soluble receptor isoform. Together, these mechanisms regulate the availability of sIL-6R and thereby modulate the extent of IL-6 trans-signaling [35].

In the case of the IL-6R, this cleavage is mediated by metalloproteases of the ADAM family [24], particularly ADAM10 and ADAM17, resulting in the generation of sIL-6R [36,37]. Under conditions such as inflammation, cellular stress, hypoxia, or activation of protein kinase C (PKC), this shedding process is enhanced, leading to increased extracellular levels of sIL-6R [38]. The released sIL-6R can bind IL-6 and enable trans-signaling in cells that lack membrane-bound IL-6R. Concurrently, proteolytic shedding reduces the amount of membrane-bound IL-6R on the cell surface, thereby limiting classical IL-6 signaling [38,39]. Experimental work further indicates that the membrane-proximal stalk region of IL-6R is critical both for efficient receptor shedding and for preservation of classical IL-6 signaling, underscoring the close structural relationship between these two processes [40].

Besides proteolytic shedding, the sIL-6R can also arise from alternative splicing of IL-6R mRNA. In this mechanism, IL-6R pre-mRNA is spliced to exclude the transmembrane domain, producing a truncated receptor that is secreted as sIL-6R [35,36]. This soluble receptor retains its ability to bind IL-6 and can subsequently participate in IL-6 trans-signaling [41].

Following coronary occlusion, cardiac cells release IL-6, which contributes to the inflammatory response that develops after AMI [15]. Multiple cell types can produce IL-6 in this setting, including endothelial cells, vascular smooth muscle cells, cardiomyocytes, fibroblasts, resident macrophages, and infiltrating leukocytes [15]. During ischemia, several local inflammatory signals, including adenosine- and IL-1-related pathways, further amplify IL-6 production within the infarcted myocardium [15]. Cardiac fibroblasts, which normally maintain extracellular matrix integrity and regulate scar formation after injury, become strongly activated following ischemic damage and acquire a pro-inflammatory phenotype. Emerging evidence indicates that cardiac fibroblasts represent a major source of IL-6 in the infarcted myocardium, in addition to infiltrating immune cells, highlighting their central role in shaping post-infarction inflammation and ventricular remodeling [42].

Temporal Kinetics of sIL-6R in Acute Myocardial Injury

IL-6 rises rapidly after AMI as part of the early inflammatory response and may exert short-lived adaptive effects in the injured myocardium, including activation of survival signaling pathways [43]. However, circulating sIL-6R concentration alone should not be equated with trans-signaling intensity, which depends on the integrated balance among IL-6, sIL-6R, sgp130, membrane gp130 expression, and the relative formation of active binary versus inactive ternary complexes. The temporal behavior of sIL-6R differs from that of IL-6 and requires cautious interpretation. While IL-6 concentrations typically rise rapidly after ST-elevation myocardial infarction (STEMI) and gradually decline during recovery, sIL-6R levels tend to remain relatively stable or decrease during the early phase of injury [32]. This difference likely reflects distinct regulatory mechanisms, as IL-6 is actively produced by injured myocardium and inflammatory cells, while increased IL-6 activity may lead to consumption of circulating sIL-6R through formation of IL-6/sIL-6R complexes, contributing to reduced or stable receptor levels [39].

Clinical studies further support dynamic regulation of the IL-6 signaling system after AMI. In patients with STEMI undergoing primary percutaneous coronary intervention, circulating IL-6 levels increased markedly within the first 24 hours and subsequently declined below baseline by two weeks. In contrast, sIL-6R and soluble gp130 (sgp130) levels remained relatively stable at 24 hours, increased significantly by two weeks, and subsequently stabilized [32]. Another study demonstrated a biphasic decline in circulating sIL-6R levels after AMI, with decreases observed approximately 12 hours and again around three days after the event, likely reflecting early receptor consumption during the acute inflammatory response. sIL-6R levels gradually recovered during the later phase of infarct healing, suggesting dynamic regulation of IL-6 signaling during post-infarction remodeling [44]. Taken together, the coordinated changes in IL-6, sIL-6R, and gp130 after AMI suggest dynamic regulation of the trans-signaling axis during the transition from acute injury to infarct healing.

4. IL-6 Trans-Signaling in Acute Myocardial Infarction

4.1 Pre-AMI Plaque Inflammation and Destabilization

IL-6 trans-signaling is increasingly recognized as a potentially important contributor to the pathophysiology of AMI, linking vascular inflammation, immune activation, and thrombosis [45]. Through formation of the IL-6/sIL-6R complex and subsequent gp130 activation, trans-signaling may promote plaque inflammation and destabilization by enhancing inflammatory cell activation, matrix degradation, fibrous cap thinning, and necrotic core expansion, thereby favoring coronary thrombosis [46,47]. Locally elevated levels of IL-6 and IL-6 receptor components have been associated with plaque inflammation and

high-risk features, although much of this evidence reflects the broader IL-6 axis rather than direct demonstration of sIL-6R-dependent trans-signaling in culprit lesions [15]. Beyond vascular inflammation, the broader IL-6 pathway may also contribute to a prothrombotic environment by enhancing hepatic synthesis of acute-phase proteins and altering fibrinolytic balance, including increased fibrinogen and plasminogen activator inhibitor-1 (PAI-1), thereby providing an additional mechanistic link between inflammation and coronary thrombosis [15].

4.2 Acute Ischemia-Reperfusion Injury and Leukocyte Recruitment

Within the ischemic myocardium, IL-6 pathway activation amplifies chemokine production and leukocyte recruitment, thereby promoting oxidative injury and infarct expansion [48,49]. Experimental and observational data suggest that this inflammatory amplification may involve IL-6R-related signaling, but in most AMI studies the specific contribution of sIL-6R-mediated trans-signaling is inferred rather than measured directly. Thus, this phase is best interpreted as one in which the broader IL-6 pathway is clearly relevant, whereas direct evidence for trans-signaling remains limited.

4.3 Microvascular Obstruction and Endothelial Dysfunction

At the endothelial level, IL-6 trans-signaling is biologically plausible because endothelial cells respond to the IL-6/sIL-6R complex through gp130. This pathway may upregulate adhesion molecule expression, increase vascular permeability, and impair vasodilatory function, thereby promoting endothelial activation and microvascular dysfunction [50]. Clinically, elevated IL-6 levels have been associated with impaired myocardial perfusion and microvascular obstruction during STEMI [51], although these studies do not distinguish between classical signaling and trans-signaling and therefore should be interpreted as indirect support for involvement of the broader IL-6 axis [52].

In addition to its close relationship with the IL-1β–C-reactive protein (CRP) axis, IL-6 also interacts with tumor necrosis factor-α (TNF-α) within the vascular inflammatory environment. Experimental data suggest that combined IL-6 and TNF-α signaling amplifies endothelial oxidative stress, impairs nitric oxide bioavailability, and enhances adhesion molecule expression, thereby aggravating endothelial dysfunction and microvascular injury. This crosstalk may be particularly relevant in AMI, where cytokine-driven endothelial activation contributes to impaired tissue perfusion despite successful epicardial reperfusion [53]. Collectively, these data support a plausible role for IL-6 trans-signaling in linking coronary instability, acute ischemic injury, and microvascular dysfunction; however, much of the currently available AMI evidence reflects the broader IL-6 pathway rather than direct readouts of sIL-6R-dependent trans-signaling.

5. Role in Post-Infarction Remodeling

Beyond its role in plaque destabilization and acute injury, the IL-6 pathway also influences myocardial repair and post-infarction remodeling [54]. IL-6 expression rises rapidly in infarcted myocardium and remains elevated during the early inflammatory and reparative phases, while its biological impact likely depends on the balance between classical signaling and sIL-6R-mediated trans-signaling [30]. Experimental and clinical evidence links increased IL-6 pathway activity with impaired contractility, larger injury burden, and adverse ventricular remodeling [55,56]. However, the available literature is not entirely uniform, suggesting that the effects of IL-6 may depend on timing, model system, and the relative contribution of protective versus maladaptive signaling.

Cardiac fibroblasts represent another important target of IL-6 trans-signaling after myocardial injury, because they express gp130 but often rely on sIL-6R to respond fully to IL-6. Activation of STAT3 in these cells promotes fibroblast activation, proliferation, and differentiation into myofibroblasts. These activated cells increase extracellular matrix synthesis, particularly collagen deposition, thereby contributing to scar formation and structural remodeling [57]. Experimental models further suggest crosstalk between IL-6 signaling and profibrotic pathways such as the TGF-β/SMAD cascade, which may amplify extracellular matrix deposition and myocardial fibrosis [58]. Persistent activation of these pathways following myocardial infarction has been linked to exaggerated fibrotic responses and adverse structural remodeling [59].

5.1 Inflammatory-to-Reparative Transition

Effective infarct healing requires a tightly regulated transition from early inflammation to reparative scar formation, characterized by resolution of inflammation and formation of a stable fibrotic scar [60]. Dysregulated cytokine signaling, including sustained activation of the IL-6 axis, may disrupt this transition by prolonging inflammatory cell recruitment and altering fibroblast behavior within the injured myocardium [61]. Within this framework, persistent IL-6 trans-signaling may prolong inflammatory activation and shift myocardial healing toward maladaptive remodeling, although direct AMI-specific evidence remains limited and much of this interpretation is derived from broader pathway biology [62].

5.2 Scar Formation and Late Adverse Remodeling

Clinically, elevated circulating IL-6 levels during and after AMI have been associated with larger infarct size, reduced myocardial salvage, and a greater likelihood of adverse left ventricular remodeling. Persistent IL-6-associated inflammation and fibrosis may promote progressive ventricular dilatation, impaired systolic function, and ultimately the development of heart failure [63]. Additional clinical studies have linked higher IL-6 concentra-

tions after AMI with heart failure, reduced left ventricular ejection fraction, and increased cardiovascular or all-cause mortality, further supporting the relevance of the broader IL-6 pathway to post-infarction remodeling and prognosis [64,65]. Taken together, these findings support the relevance of the IL-6 pathway, and possibly trans-signaling, in adverse post-infarction remodeling and later heart failure.

Broader anti-inflammatory trial data provide indirect context for this pathway but should not be interpreted as direct evidence in AMI. In the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), inhibition of IL-1β reduced downstream IL-6/CRP signaling and cardiovascular events in stable post-myocardial infarction patients [66], whereas in Cardiovascular Inflammation Reduction Trial (CIRT) low-dose methotrexate failed to reduce IL-1β, IL-6, or CRP and did not improve outcomes [67]. These trials support the relevance of the IL-1β–IL-6–CRP inflammatory axis in residual inflammatory risk, but they were not conducted in the acute phase of myocardial infarction and do not establish a specific role for sIL-6R-dependent trans-signaling during AMI.

6. Biomarker and Prognostic Role of the IL-6/sIL-6R Axis in AMI

6.1 The Soluble IL-6 Receptor as a Biomarker in AMI

Traditional inflammatory markers such as CRP are well-established predictors of outcome after STEMI, but their clinical utility is limited by their downstream nature, which provides only indirect insight into the mechanisms driving post-infarction inflammation [68]. In contrast, sIL-6R may serve as a potential biomarker reflecting aspects of IL-6 pathway regulation, although circulating concentrations do not directly measure trans-signaling activity [17,65]. By enabling formation of the IL-6/sIL-6R complex, it expands IL-6 responsiveness to gp130-expressing cells and provides a biologically plausible link between inflammatory signaling and adverse cardiovascular effects after AMI (Table 1).

6.2 Association With Infarct Size and Microvascular Obstruction

The relationship between the IL-6 axis and myocardial injury appears to depend on both the timing of assessment and the specific component measured. During the acute phase of STEMI, circulating IL-6 levels rise rapidly and have been associated with infarct size and the severity of microvascular obstruction (MVO) [69]. Often referred to as the no-reflow phenomenon, MVO reflects persistent microvascular dysfunction despite successful epicardial reperfusion and is a major determinant of adverse remodeling and increased mortality [70]. Cardiac magnetic resonance studies have shown that higher early IL-6 concentrations are associated with larger MVO burden and reduced myocardial salvage [69].

By contrast, sIL-6R often demonstrates a flatter temporal profile during the first days after infarction, suggesting that it may reflect a different dimension of IL-6 pathway biology [17]. In this context, the sIL-6R/IL-6 ratio may provide complementary information. A reduced ratio early after STEMI may indicate relative excess of unbuffered IL-6 activity and a shift toward enhanced trans-signaling, a pattern that has been associated with larger infarct size and impaired cardiac function during follow-up. Thus, while IL-6 may better reflect acute inflammatory injury, sIL-6R and related ratios may offer additional insight into pathway balance and subsequent remodeling risk.

6.3 Comparison With IL-6, CRP and NT-proBNP

Compared with conventional biomarkers such as CRP and NT-proBNP, the IL-6 axis may provide more direct information about inflammatory pathway activation [71]. IL-6 acts upstream of the hepatic acute-phase response and may therefore capture early monocytic and endothelial activation before downstream markers such as CRP begin to rise [72]. In the FROG-ICU study of critically ill patients, IL-6 was a stronger predictor of 90-day mortality than CRP [73]. Similarly, in stable coronary artery disease, IL-6 has shown independent associations with major adverse events and cardiovascular mortality even after adjustment for CRP and troponin levels [74]. Within this framework, sIL-6R may provide complementary rather than competing information, potentially reflecting a more sustained inflammatory vulnerability than standard markers capture [65]. However, whether IL-6-axis biomarkers provide incremental prognostic value beyond troponin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), CRP, infarct size by cardiac magnetic resonance, and conventional clinical risk scores remains uncertain.

6.4 Kinetic Profile and Prognostic Stratification

The temporal behavior of IL-6 pathway components after myocardial infarction supports the concept of a dynamic transition from acute inflammation to later structural remodeling. IL-6 typically peaks within the first 24 hours after reperfusion and then declines rapidly, consistent with its role in the immediate inflammatory response. In contrast, sIL-6R and sgp130 tend to remain relatively stable early after infarction and may increase later, persisting for weeks or even months after percutaneous coronary intervention (PCI) [32,75]. This delayed pattern raises the possibility that the trans-signaling axis remains relevant beyond the initial necrotic phase and may contribute to subsequent ventricular remodeling, although these biomarker patterns are not equivalent to direct measurement of trans-signaling intensity.

In patients with STEMI, elevated sIL-6R levels measured during the acute phase have been independently associated with long-term adverse cardiovascular events and mortality, whereas sgp130 showed no significant associa-

Table 1. Biomarker interpretation of the IL-6/sIL-6R/sgp130 axis in acute myocardial infarction: biological relevance, limitations, and clinical potential.

Biomarker	What it reflects biologically	Potential clinical relevance in AMI	Main interpretive limitation	Provides information relevant to trans-signaling?
IL-6	Upstream inflammatory cytokine; acute-phase driver	Associated with infarct size, microvascular obstruction, and early outcomes	Does not distinguish classical from trans-signaling; highly time-dependent	Yes, indirect
sIL-6R	Soluble receptor enabling IL-6 responses in gp130-expressing cells	May reflect pathway balance and remodeling risk	Circulating level alone does not equal trans-signaling activity	Yes, indirect
sgp130	Endogenous inhibitor/buffer of IL-6 trans-signaling	May improve interpretation when combined with IL-6 and sIL-6R	Limited AMI-specific data; not informative alone	Yes, indirect
sIL-6R/IL-6 ratio	Surrogate of ligand–receptor balance	May help identify relative excess of IL-6 activity	Indirect, non-standardized, and timing-sensitive	Yes, surrogate
B/T ratio	Derived surrogate indicator of the balance between active IL-6/sIL-6R binary complexes and sgp130-neutralized ternary complexes	May better approximate trans-signaling balance and inflammatory risk	Investigational; limited clinical validation in AMI	Yes, derived surrogate
CRP/hs-CRP	Downstream acute-phase reactant	Established inflammatory prognostic marker after AMI	Reflects broader inflammation, not specific IL-6 trans-signaling	No, nonspecific
NT-proBNP	Marker of hemodynamic stress and ventricular dysfunction	Useful comparator for heart failure risk and prognosis	Not specific to inflammatory signaling	No

AMI, acute myocardial infarction; B/T ratio, binary-to-ternary complex ratio; CRP, C-reactive protein; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sIL-6R, soluble interleukin-6 receptor; sgp130, soluble glycoprotein 130.

tion after multivariable adjustment [65]. However, the absence of serial biomarker measurements limits conclusions regarding their temporal dynamics and potential involvement in post-infarction remodeling. Accordingly, serial assessment of IL-6 axis components, rather than isolated single time-point measurements [76], may offer a more informative strategy for identifying patients at risk for adverse left ventricular remodeling. This concept is consistent with findings from other inflammatory pathways, in which soluble mediators such as soluble IL-1 receptor 2 have also been associated with left ventricular remodeling after STEMI, supporting the broader value of inflammation-based risk stratification in post-infarction recovery [77].

6.5 Potential Role in Personalized Risk Assessment

Beyond individual biomarker levels, the balance among IL-6, sIL-6R, and sgp130 may provide a more refined estimate of inflammatory risk. Under physiological conditions, sgp130 acts as a natural inhibitor of trans-signaling by binding IL-6/sIL-6R complexes and preventing their interaction with membrane gp130. In ACS, this regulatory balance may be disturbed, favoring a shift toward enhanced pro-inflammatory signaling [17]. On this basis, the binary-to-ternary complex ratio (B/T ratio) has been proposed as a surrogate indicator of trans-signaling balance, reflecting the relative proportion of active IL-6/sIL-6R binary complexes compared with inactive ternary complexes containing sgp130 [17,78].

A higher B/T ratio has been associated with an increased risk of future cardiovascular events in men without established cardiovascular disease, whereas this association was not statistically significant in women [78]. Furthermore, higher B/T ratios have been reported in postmenopausal women with coronary artery disease compared with controls, although the association was not independently significant after multivariable adjustment [75]. Among patients with STEMI, higher sIL-6R concentrations have also been associated with increased risk of adverse clinical outcomes, including all-cause mortality [65]. Taken together, these findings support the potential prognostic relevance of the IL-6/sIL-6R/sgp130 axis, while also underscoring that direct trans-signaling activity is better captured by integrated pathway measures than by sIL-6R concentration alone.

Table 2. Key studies on the IL-6/sIL-6R/sgp130 axis in acute myocardial infarction: evidence type and relevance to trans-signaling.

Study	Study type/ population	Main variable	Main finding	Evidence type	Relevance to trans-signaling
Ueda et al. [44]	Observational/AMI	sIL-6R	sIL-6R decreased after AMI	Observational clinical	Indirect
Groot et al. [48]	Observational/ STEMI + PCI	sIL-6R	Higher sIL-6R associated with reduced reperfusion	Observational clinical	Indirect
Groot et al. [32]	Observational/ STEMI	IL-6	Higher IL-6 associated with impaired cardiac function	Observational clinical	Indirect (broader IL-6 axis)
Tøllefsen et al. [69]	Observational/ STEMI	IL-6	Higher IL-6 associated with larger infarct size and adverse events	Observational clinical	Indirect (broader IL-6 axis)
Ritschel et al. [65]	Observational/ STEMI	sIL-6R, sgp130	Higher sIL-6R independently associated with long-term events and mortality; sgp130 was not significant after adjustment	Observational clinical	Indirect (circulating biomarkers)
Baran et al. [17]	Experimental/ mechanistic	IL-6, sIL-6R, sgp130 complexes	Defined balance between classical and trans-signaling complexes	Experimental/ mechanistic	Direct mechanistic support
Miri et al. [78]	Observational/ cardiovascular population	B/T ratio	Higher B/T ratio associated with future cardiovascular events in men; association less consistent and not clearly significant in women.	Observational clinical	More direct, but not AMI-specific
George et al. [81]	Experimental/ reperfused MI model	sgp130Fc	Selective blockade reduced inflammation, infarct size, and LV dysfunction	Experimental/ preclinical	Direct
Broch et al. [79] (ASSAIL-MI)	Randomized/ STEMI	Tocilizumab	IL-6R blockade improved myocardial salvage	Randomized clinical trial	Indirect for trans-signaling
Huse et al. [80]	Randomized substudy/STEMI	Tocilizumab, immune profile	IL-6 inhibition attenuated innate inflammatory response	Randomized clinical substudy	Indirect for trans-signaling

AMI, acute myocardial infarction; ASSAIL-MI, ASSessing the Effect of Anti-IL-6 Treatment in Myocardial Infarction; B/T ratio, binary-to-ternary complex ratio; CV, cardiovascular; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention; sIL-6R, soluble interleukin-6 receptor; sgp130, soluble glycoprotein 130; STEMI, ST-elevation myocardial infarction.

However, current evidence remains limited by relatively small study populations, heterogeneous sampling time points, and incomplete distinction between circulating biomarker levels and direct trans-signaling activity. Additional challenges include assay standardization, biological variability, renal function, age, systemic inflammatory burden, and comorbidities that may influence circulating concentrations. Representative clinical and mechanistic studies supporting these observations are summarized in Table 2 (Ref. [17,32,44,48,65,69,78,79,80,81]). Further prospective studies are needed to determine whether integrated biomarker approaches improve risk stratification and guide personalized anti-inflammatory strategies in AMI.

7. Therapeutic Targeting of IL-6 Trans-Signaling

The recognition of IL-6 as an important mediator of atherosclerotic inflammation and myocardial injury has prompted growing interest in targeted therapeutic intervention (Table 3). However, the pleiotropic nature of IL-6 creates a major pharmacologic challenge. While excessive IL-6 activity may contribute to maladaptive inflammation and tissue damage, the cytokine also participates in physiological processes such as host defense, acute-phase signaling, tissue repair, and regeneration. For this reason, indiscriminate inhibition of the entire IL-6 pathway may not be biologically optimal in the setting of AMI [82].

7.1 Evidence From Clinical Trials

Initial clinical evidence supporting therapeutic inhibition of the IL-6 pathway in AMI came from studies using tocilizumab, a humanized monoclonal antibody that blocks both membrane-bound and soluble IL-6 receptors. In patients with non-ST-elevation myocardial infarction (NSTEMI), a single dose of tocilizumab significantly reduced systemic inflammatory activity and attenuated tro-

Table 3. Therapeutic strategies related to the IL-6 pathway in acute myocardial infarction: target, signaling specificity, and current level of evidence.

Strategy/agent	Main target	Effect on classical signaling	Effect on trans-signaling	AMI-specific evidence	Main limitation
Tocilizumab	Membrane-bound and soluble IL-6 receptor	Blocked	Blocked	Clinical data in NSTEMI and STEMI, including ASSAIL-MI	Does not isolate selective trans-signaling inhibition
sgp130Fc (olamkicept)	IL-6/sIL-6R complex	Preserved	Selectively blocked	Preclinical MI models only	No direct AMI clinical trial evidence
Canakinumab	IL-1β upstream of IL-6	Indirectly reduced	Indirectly reduced	No acute AMI trial evidence; contextual CV data only	Does not specifically test IL-6 trans-signaling
Methotrexate (low dose)	Broad inflammatory pathways	No consistent effect	No consistent effect	No supportive AMI evidence; negative contextual data	Not specific for IL-6 biology
Ziltivekimab	IL-6 ligand	Reduced	Reduced	No direct AMI evidence	Not selective for trans-signaling

AMI, acute myocardial infarction; ASSAIL-MI, ASSessing the Effect of Anti-IL-6 Treatment in Myocardial Infarction; CV, cardiovascular; IL-1β, interleukin-1 beta; IL-6, interleukin-6; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; sIL-6R, soluble interleukin-6 receptor; sgp130Fc, soluble glycoprotein 130 Fc fusion protein; STEMI, ST-elevation myocardial infarction.

ponin T release, suggesting a possible reduction in myocardial injury [83].

These observations were extended in the ASSessing the Effect of Anti-IL-6 Treatment in Myocardial Infarction (ASSAIL-MI) trial, a randomized, double-blind, placebo-controlled study that randomized 199 patients with STEMI undergoing primary percutaneous coronary intervention. Participants received either a single infusion of tocilizumab or placebo before PCI. The primary endpoint, myocardial salvage index assessed by cardiac magnetic resonance imaging 3 to 7 days after PCI, was significantly improved in the tocilizumab group [79]. Subanalyses further suggested that this effect was associated with attenuation of the innate inflammatory response, including a faster decline in circulating neutrophils and a lower neutrophil-to-lymphocyte ratio, both of which correlated with lower peak troponin levels and greater myocardial salvage [80].

Importantly, however, the currently available clinical evidence in AMI relates to broad IL-6 receptor blockade rather than selective inhibition of trans-signaling [84]. Tocilizumab therefore cannot establish the specific therapeutic value of sIL-6R-dependent trans-signaling inhibition. Although these studies support the therapeutic relevance of the broader IL-6 pathway, they do not isolate the specific contribution of trans-signaling. In addition, the ASSAIL-MI trial was not powered to detect differences in long-term clinical outcomes such as major adverse cardiovascular events, and the optimal timing, duration, and safety profile of IL-6 pathway inhibition in AMI remain to be fully established [79,85].

7.2 Concept of Selective Trans-Signaling Blockade

To address the limitations of global IL-6 inhibition, selective strategies targeting trans-signaling have been developed. The best-characterized of these is soluble glycoprotein 130 fragment crystallizable (sgp130Fc), commercially known as olamkicept, a recombinant fusion protein composed of the extracellular portion of gp130 linked to the Fc fragment of human IgG1 (Fig. 2). Unlike tocilizumab, sgp130Fc does not bind free IL-6 or membrane-bound IL-6R. Instead, it selectively binds the IL-6/sIL-6R complex and thereby blocks trans-signaling while preserving classical signaling [11]. By selectively inhibiting trans-signaling while preserving classical signaling, sgp130Fc offers a more refined approach than pan-IL-6 blockade.

Experimental evidence supports this concept. In a rat model of reperfused myocardial infarction, selective inhibition of trans-signaling with sgp130Fc reduced neutrophil and macrophage infiltration, decreased infarct size, and preserved left ventricular function at 28 days [81]. By contrast, broad IL-6 inhibition did not produce comparable benefit. These findings suggest that selective trans-signaling blockade may attenuate maladaptive inflammation without interfering to the same extent with reparative processes such as wound healing and scar formation, which may depend in part on intact classical signaling.

Although these data provide strong mechanistic support for selective trans-signaling inhibition, direct clinical evidence for sgp130-based strategies in AMI is not yet available. At present, the therapeutic promise of this approach in myocardial infarction remains preclinical.

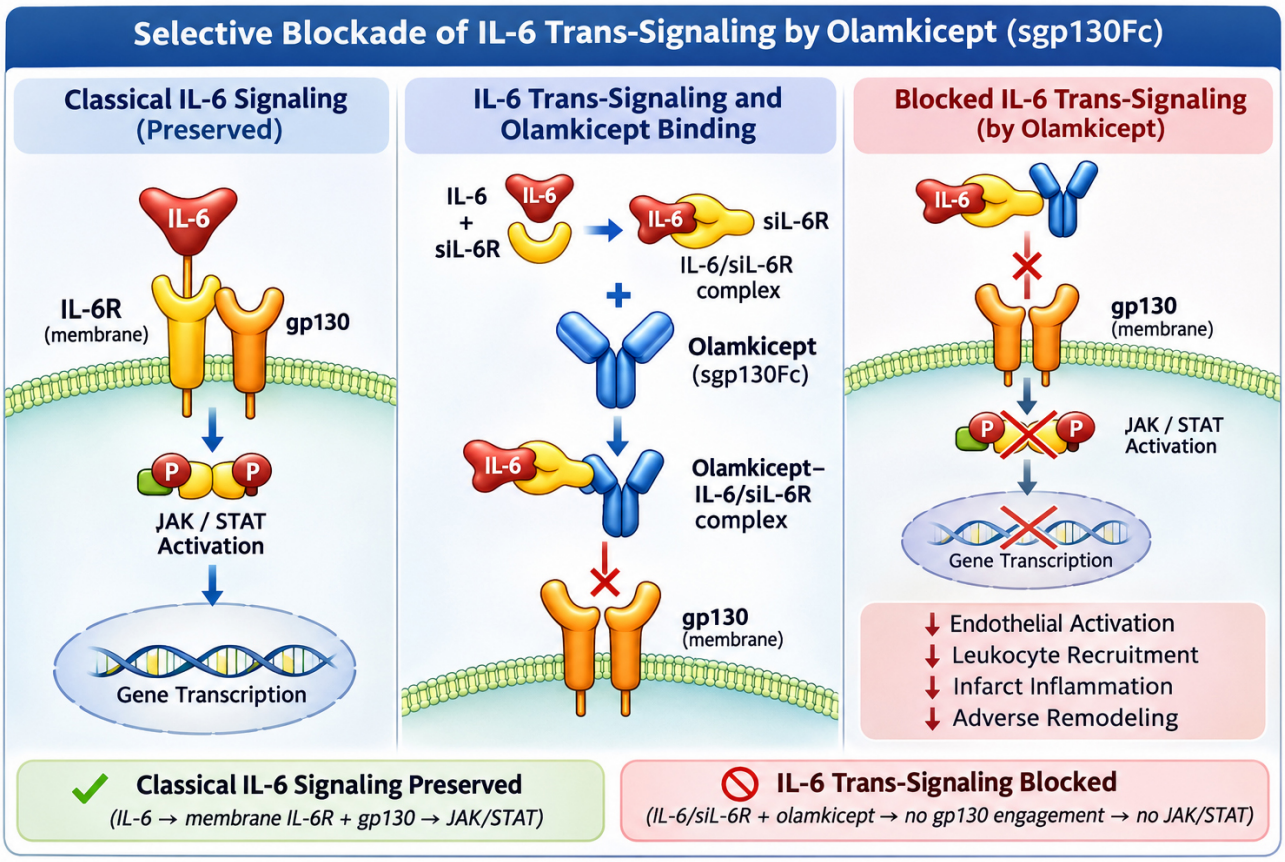


Fig. 2. Selective blockade of IL-6 trans-signaling by olamkicept (sgp130Fc). This schematic illustrates the proposed mechanism of selective IL-6 trans-signaling inhibition. Olamkicept, a soluble gp130Fc fusion protein, binds the extracellular IL-6/sIL-6R complex and prevents its interaction with membrane-bound gp130 on target cells, thereby inhibiting downstream JAK/STAT3 activation. The membrane-bound gp130 receptor and intracellular signaling components are depicted to illustrate the signaling events prevented by olamkicept, rather than signaling activated by the inhibitor. Classical IL-6 signaling through membrane-bound IL-6R is generally preserved. This selective approach is biologically attractive and supported by preclinical studies, whereas direct clinical evidence in AMI remains lacking. This figure was generated using ChatGPT (OpenAI, San Francisco, CA, USA) and subsequently reviewed by the authors for scientific accuracy.

7.3 Potential Advantages Over Global Cytokine Suppression

Selective trans-signaling blockade may offer therapeutic advantages over broader IL-6 inhibition, as suggested by preclinical evidence [81]. By preserving classical signaling, it may attenuate infarct-related inflammation and remodeling without fully suppressing protective immune and reparative responses. This theoretical advantage distinguishes it not only from broad IL-6 receptor antagonism, but also from more generalized cytokine inhibition strategies, in which reduced inflammatory events may be offset by infection-related safety concerns, as illustrated in CANTOS [86]. From a translational perspective, this selectivity is particularly relevant in AMI, where excessive inflammation and tissue repair occur simultaneously and where overt immunosuppression may be undesirable. However, any anti-cytokine strategy in AMI must also consider potential effects on host defense, wound healing, infarct repair, and infection risk, particularly if treatment is administered too early, too broadly, or for too long [87,88,89]. In this context, selective trans-signaling inhibition represents a promising precision-based anti-inflammatory strategy. Broader IL-6-directed approaches, including ligand-targeting strategies such as ziltivekimab, may further clarify the clinical value of IL-6 inhibition in cardiovascular disease, although AMI-specific data remain lacking [90].

8. Knowledge Gaps and Future Directions

Despite growing interest in IL-6 trans-signaling in AMI, several important knowledge gaps remain. First, the relative contribution of classical and trans-signaling during the different phases of AMI has not been fully clarified [91]. Second, available clinical studies are limited by modest sample sizes, heterogeneous sampling time points, and incomplete integration of IL-6, sIL-6R, and sgp130 measurements with imaging and outcome data, and a lack of direct

readouts of trans-signaling activity. Third, confounding by systemic inflammation, comorbidities, renal function, and uncertain patient selection further complicates clinical interpretation. Fourth, although selective trans-signaling inhibition is biologically attractive, direct clinical evidence in AMI is still lacking [92]. Future research should therefore focus on better phenotyping of the IL-6/sIL-6R/sgp130 axis, defining its temporal relationship with infarct healing and ventricular remodeling, and identifying the patients most likely to benefit from targeted anti-inflammatory intervention [93]. Such efforts may help establish trans-signaling not only as a mechanistic pathway, but also as a clinically actionable target in precision cardiovascular medicine [94].

9. Conclusion

IL-6 signaling plays an important role in the inflammatory response to AMI, and accumulating evidence suggests that sIL-6R-mediated trans-signaling may represent a relevant and potentially maladaptive component of this biology. By expanding IL-6 responsiveness to endothelial cells, fibroblasts, and other gp130-expressing cells, trans-signaling may contribute to plaque instability, microvascular dysfunction, infarct expansion, and adverse ventricular remodeling. However, direct AMI-specific evidence remains limited, and many current clinical inferences derive from the broader IL-6 pathway rather than from direct readouts of trans-signaling. Accordingly, the IL-6/sIL-6R/sgp130 axis should be viewed as a promising mechanistic and translational framework, but not yet as a sufficiently validated clinically actionable target in AMI.

Author Contributions

AM, ST, GKas and NPEK designed the manuscript structure and developed the overall concept. AM, MK, SS, and GKar performed the literature search. AM, MK, SS, GKar, ST, GKas, and NPEK drafted and revised the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT in order to check spelling, grammar and to generate figures. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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