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REVIEW

Oncostatin M and Cardiovascular Diseases: A Narrative Review

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ABSTRACT

Cytokines like oncostatin M (OSM) influence inflammation and immune responses. Interleukin-6 is produced by immune, endothelial, and cardiac cells. OSM plays a role in cardiovascular diseases (CVDs), demonstrating cardioprotective effects by promoting cardiac cell survival and angiogenesis. It may also reduce vascular inflammation and help prevent atherosclerosis, a major risk factor for CVD. However, under certain conditions, OSM contributes to inflammation and tissue damage. It induces inflammatory cytokines, promotes vascular smooth muscle cell migration, and destabilizes atherosclerotic plaques, thereby increasing the likelihood of myocardial infarction or stroke. Elevated OSM levels are linked to worse outcomes in patients with heart failure and pulmonary arterial hypertension. The role of OSM in CVD is complex and context-dependent. Further research is needed to clarify its mechanisms and therapeutic potential. Since CVDs result from a combination of genetic, environmental, and behavioral factors rather than a single cytokine, diagnostic and treatment approaches should adopt a comprehensive clinical perspective.

Keywords: Cardiovascular diseases, interleukin-6, oncostatin M, inflammation, atherosclerosis, heart failure, pulmonary arterial hypertension

INTRODUCTION

Oncostatin M (OSM) is a cytokine involved in inflammation and immune responses. As a member of the interleukin-6 (IL-6) family, it is produced by immune, endothelial, and cardiac cells. OSM is linked to cardiovascular disease (CVD), a group of disorders affecting the heart and blood vessels. Its role in CVD is complex, displaying both protective and harmful effects.[1-5]

OSM activates the IL-6 signaling pathway, which regulates immune responses and tissue homeostasis. Under certain physiological conditions, OSM may be beneficial by reducing pro-inflammatory cytokines and increasing anti-inflammatory mediators, potentially helping to prevent atherosclerosis. It also supports vascular repair by stimulating endothelial cell proliferation and angiogenesis. However, in pathological conditions, OSM can exacerbate inflammation, fibrosis, and tissue damage. In myocardial infarction (MI) and heart failure (HF), OSM accelerates disease progression by enhancing immune cell activation and altering the extracellular matrix. Due to its dual effects, the impact of OSM on CVD depends on several factors, including the duration and severity of inflammation, coexisting health conditions, and the cellular environment.[6]

A temporary increase in OSM levels following injury may support recovery. However, prolonged overexpression of OSM can lead to sustained inflammation and fibrosis, contributing to worse CVD outcomes. Understanding these mechanisms is crucial for assessing OSM as a potential therapeutic target.[7] This paper aims to provide a comprehensive analysis of both the protective and harmful effects of OSM in CVD, filling the gap left by previous reviews and highlighting its therapeutic potential.

Mechanisms of Oncostatin M's Biphasic Effects

OSM exerts both beneficial and adverse effects through different mechanisms, depending on the context.

Beneficial effects: OSM supports tissue repair and regeneration by promoting endothelial cell proliferation, angiogenesis, and cardiomyocyte survival. It can also regulate immune cell activity, reducing excessive inflammation by lowering pro-inflammatory cytokine levels. Furthermore, OSM plays a role in extracellular matrix remodeling, aiding tissue recovery after injury.

Adverse effects: In pathological conditions, prolonged OSM signaling can drive chronic inflammation, fibrosis, and oxidative stress. It activates immune cells, increasing cytokine production and contributing to tissue damage. In HF and MI, persistent OSM expression leads to maladaptive remodeling, impairing cardiac function. Notably, its involvement in vascular smooth muscle cell migration and extracellular matrix degradation can accelerate the progression and destabilization of atherosclerotic plaques. Understanding the balance between these effects is crucial in

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evaluating whether targeting OSM would be beneficial or detrimental in different types of CVD.[8]

Molecular Mechanisms of Oncostatin M

OSM exerts its effects by interacting with specific signaling pathways and transcription factors. A significant portion of its signaling occurs through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, particularly via STAT3. STAT3 activation influences gene expression related to inflammation, cell survival, and tissue remodeling. While transient activation supports tissue repair, prolonged STAT3 signaling can lead to chronic inflammation and fibrosis. Additionally, OSM activates the mitogen-activated protein kinase and phosphoinositide 3-kinase (PI3K/AKT) pathways, which regulate cellular proliferation, survival, and angiogenesis, contributing to vascular repair.[9]

Disruptions in signaling regulation can contribute to abnormal vascular remodeling and atherosclerosis. The methylation of NF-κB activates key transcription factors such as nuclear factor-kappa B (NF-κB) and hypoxia-inducible factor-1 alpha, leading to increased production of pro-inflammatory cytokines and exacerbating inflammation in CVD. While NF-κB promotes blood vessel growth in low-oxygen conditions, prolonged activation under chronic stress can result in detrimental vascular responses.[10]

Coronary Artery Disease

OSM contributes to atherosclerosis by affecting vascular smooth muscle cells. It interacts with the Yes-associated protein (YAP), linking endplate osteosclerosis to macrophage activity. Patients with CAD who have multiple severe blockages show increased OSM levels, which are associated with coronary artery calcium scores. Additionally, conditions such as obesity and diabetes mellitus (DM) influence OSM production, potentially promoting the formation of calcified plaques.[5-8,10-12]

Shear stress may drive atherosclerotic plaque formation through the YAP-OSM pathway, which could play a role in diabetes-related CVDs. Further research is needed to confirm the clinical significance of YAP in CVD.[13-19]

Myocardial Infarction

OSM levels increase after MI, suggesting a role in post-MI inflammation. It activates immune cells and amplifies inflammation, potentially exacerbating cardiac tissue damage. However, some studies indicate that OSM also supports tissue repair and regeneration. OSM levels peak five days after MI before gradually declining. It may reduce inflammatory monocytes while promoting the presence of resident macrophages that aid in healing. Further research using tissue-specific OSM gene deletion models is needed to confirm these findings.[20-24]

Heart Failure

OSM levels are elevated in HF patients and interact with parathyroid hormone and vitamin D. OSM has both harmful and beneficial effects on the heart. It contributes to inflammation, fibrosis, oxidative stress, and cell apoptosis, all of which worsen HF. However, it also promotes angiogenesis, which may aid in tissue regeneration. Further research is necessary to clarify OSM's role in HF and its potential as a therapeutic target.[25]

Ischemic Stroke

OSM's role in stroke is complex. It can trigger inflammation, leading to increased brain damage, but it may also have neuroprotective effects. OSM supports factors that enhance neuronal survival and promote tissue repair. Its impact likely depends on OSM levels, timing, and biochemical interactions in the brain.

Atrial Fibrillation

OSM may play a role in atrial fibrillation (AF) by influencing inflammation and fibrosis. Chronic inflammation disrupts normal electrical signaling in the heart, increasing the risk of AF. Additionally, OSM promotes fibrosis, which stiffens cardiac tissue and further impairs electrical conduction. However, the exact mechanisms remain unclear and require further investigation.[26]

Pulmonary Arterial Hypertension

OSM may contribute to pulmonary arterial hypertension (PAH) by driving inflammation, fibrosis, and vascular remodeling. It promotes the release of inflammatory mediators and activates immune cells, leading to pulmonary vessel constriction and increased pressure. Fibrosis worsens these effects by making blood vessels more rigid. Further studies are needed to clarify OSM's role in the development and progression of PAH.

Recent Studies

Elevated OSM receptor levels in patients with multiple sclerosis suggest increased OSM signaling.[27] Research on atherosclerosis treatment with OSM should also consider its effects on tissue remodeling, angiogenesis, bleeding, anemia, and NMDA- and glutamate-induced neurotoxicity. Patients with comorbid conditions may require careful monitoring or exclusion to ensure optimal therapy.[28] OSM is implicated in muscular atrophy, bone resorption, fibrosis, and cardiac dysfunction in cancer cachexia.[29] Preoperative plasma OSM levels may help identify infection risks in patients with left ventricular assist devices.[30] Additionally, the dual-sensitive hydrogel approach proposed by Jiang et al.[31] could influence tissue engineering for MI repair and drug delivery.

OSM may influence tissue engineering strategies for MI repair. The OSM receptor gene variant rs1316887 is linked to plaque vulnerability but does not contribute to overall CVD risk.[32] Gajawada et al.[33] found that granuloma formation results from chemoattraction rather than macrophage proliferation. Drug screening targeting the oncostatin/Reg3 axis may have implications for HF.

OSM plays a role in acute intestinal ischemia-reperfusion injury (AIIRI). While OSM receptor deficiency delays lung injury, it increases the risk of renal failure. More OSM receptor-deficient mice succumbed to AIIRI, suggesting that immunomodulation in AIIRI may elevate OSM levels.[34] Insulin resistance (IR) indices, such as QUICKI and HOMA, correlate with OSM and may serve as simpler alternatives to other IR markers.[35] In type 2 DM patients with acute coronary syndrome, measuring regenerating islet-derived protein 3-beta (Reg3β) and OSM levels alongside traditional cardiac markers may aid diagnosis.[36] Stawski and Trojanowska[37] reviewed OSM's role in fibrotic processes, including inflammation, vascular dysfunction, and fibroblast activation. In mice, cholesteryl ester transfer protein reduced atherosclerosis. Additionally,

higher serum OSM levels were associated with improved post-coronary heart disease survival, suggesting a potential cardiovascular benefit.[38]

Setiadi et al.[39] demonstrated that neutrophil-derived OSM directly affects endothelial cell function through paracrine signaling during both normal and pathological inflammation. Han et al.[40] found that in middle cerebral artery occlusion stroke rats, the brain produces OSM and upregulates SDF-1, enhancing the migration of bone marrow-derived mesenchymal stem cells (BMSC). OSM and BMSCs together improve BMSC graft efficacy and neurofunctional recovery. Table 1 summarizes the key findings from recent studies.

CONCLUSION

OSM regulates inflammation and immune responses, influencing cardiomyocyte viability, angiogenesis, and inflammation in CVD. While it may support cardiac tissue healing and reduce atherosclerosis, it can also intensify inflammation and tissue damage. Elevated OSM levels are linked to worse outcomes in HF and PAH. Its role in CVD is complex and depends on various factors. Further research is needed to clarify its mechanisms and therapeutic potential. Given that CVD results from multiple contributing factors, clinical evaluation and patient-centered care should be prioritized in its management.

Table 1. Key findings from recent studies

Authors/reference no.	Subjects	Main theme
Hermans et al.[27]	MS patients	OSM's role in MS pathology. MS patients exhibited increased OSM receptor expression in lymphocytes, suggesting enhanced OSM signaling. OSM production is elevated in MS brain lesions
Rankouhi et al.[28]	Review	The impact of OSM on tissue remodeling, angiogenesis, bleeding, anemia, and NMDA- and glutamate-induced neurotoxicity should be considered in atherosclerosis treatment. Comorbid patients may require careful monitoring or exclusion for optimal therapy
Jengelley et al.[29]	Patients	OSM contributes to local muscle atrophy, systemic bone loss, tissue fibrosis, and cardiac failure in the absence of IL-6, indicating a role in cancer cachexia
Setiadi et al.[30]	Patients with LVAD	Preoperative plasma OSM levels may help predict infection risk in LVAD patients
Jiang et al.[31]	MI patients	Dual-sensitive hydrogels offer a novel approach in tissue engineering for MI repair and drug delivery
van Keulen et al.[32]	Humans	The OSM receptor gene variant rs1316887 is linked to increased plaque vulnerability but does not contribute to coronary calcification or overall CVD risk. The influence of OSM signaling on plaque morphology occurs through unknown mechanisms. OSM-OSM receptor and leukemia inhibitory factor receptor do not appear to elevate CVD risk
Gajawada et al.[33]	Patients with cardiac sarcoidosis	Granuloma formation is driven by chemoattraction rather than macrophage proliferation. Screening drugs via the oncostatin/Reg3 axis may contribute to heart failure
Young et al.[34]	Mice	OSM plays a role in AIIRI. OSM receptor deficiency delays lung damage but leads to renal failure. AIIRI mortality is higher in OSM receptor-deficient mice, suggesting that AIIRI immunomodulation could enhance OSM activity
Akarsu et al.[35]	Patients with IR	IR indices (QUICKI and HOMA) are associated with OSM and could serve as alternative IR markers for simplicity
Midhuna et al.[36]	Patients with T2DM	Regenerating islet-derived protein 3-beta (Reg3β) and OSM levels, alongside cardiac markers, may aid in diagnosing ACS in T2DM patients
Stawski and Trojanowska[37]	Fibrotic diseases	OSM contributes to fibrotic processes, including inflammation, vascular dysfunction, and fibroblast activation. In mice, CETP was found to reduce atherosclerosis
Keulen et al.[38]	CETP mice and humans	Elevated serum OSM levels were linked to improved post-CHD survival, suggesting a potential cardiovascular benefit
Setiadi et al.[39]	Endothelial cells	Neutrophil-derived OSM directly affects endothelial cell function through paracrine signaling during both normal and pathological inflammation

LVAD: Left ventricular assist devices, T2DM: Type 2 diabetes mellitus, IR: Insulin resistance, CETP: Cholesteryl ester transfer protein, CHD: Coronary heart disease, MI: Myocardial infarction, OSM: Oncostatin M, MS: Multiple sclerosis, IL-6: Interleukin-6, ACS: Acute coronary syndrome

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