Elevation of Serum Oncostatin M Level in Acute Ischaemic Stroke: A Review

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Stroke, a neurovascular disorder, is one of the main causes of mortality and disability worldwide. There are several mechanisms of stroke, with inflammatory response being a key factor, with previous studies have concluding the involvement of oncostatin M (OSM) in inflammatory response. This review aims to analyze current knowledge to explain the elevation of serum OSM expression in acute ischaemic stroke (AIS). Information was gathered from the PubMed database on landmark studies on the relevance of serum OSM in AIS, and it was concluded that hypoxia and stagnant blood flow, which are involved in the typical pathophysiology of AIS, induced an inflammatory signalling pathway. OSM, a member of cytokine interleukin-6, participates in inflammatory responses in a dual manner: pro-inflammatory and anti-inflammatory. We concluded the elevation of serum OSM level in patients with AIS was due to an inflammatory response triggered by AIS. Cardioembolic stroke, a subtype of AIS, triggered a higher inflammatory substrate response in the circulatory system, explaining why serum OSM elevation is significant compared to other subtypes of acute ischaemic stroke.

Introduction

The term 'stroke' is used to describe an adverse clinical state involving interference of blood circulation to the brain due to obstruction or rupture of blood vessels.[1] Stroke was previously categorized into a cardiovascular disorder until the release of the International Classification of Disease 11 (ICF-11) in 2018, when stroke was recognized as a neurological disorder.[2] For the past decade, it has been ranked the second most common cause of death, and a major cause of disability worldwide.[3] Between the two subtypes of stroke, haemorrhagic and ischaemic, ischaemic stroke is the more common subtype, accounting for up to 87% of stroke cases in the United States.[4] The prevalence of stroke is also affected by demographics, being more prevalent in developing countries.[3] In 2017, it was recorded that stroke and ischaemic heart disease was the leading cause of mortality and disability nationally in China.[5] Acute ischaemic stroke (AIS) is a type of stroke that progresses rapidly over a short period of time. In addition to symptomatic treatment and secondary prevention, the management of AIS is focused on reperfusion through intravenous thrombolysis and endovascular thrombectomy; both of which aim to reduce disability, but are highly dependent on time.[6] It is important that the thrombi derived from patients with AIS are highly heterogeneous, as this affects the choice of available treatment options and recovery prognosis. Thrombi with a higher composition of red blood cells (RBCs) tend to have a good prognosis, whereas thrombi with a higher fibrin composition have a tendency to be stiff, making it harder to treat and therefore leading to a poorer prognosis.[7]

Several methods have been established to classify the characteristics of stroke. The most widely used classification system is the Trial of Org 10 172 for Acute Stroke Treatment (TOAST), introduced in 1993.[8] With the advancement of research and technologies, several classification systems have been assembled based on different approaches, such as the Causative Classification System (CCS) and Chinese Ischemic Stroke Subclassification (CISS).[9] Amongst other classification methods not mentioned here, atherosclerosis and cardioembolic (CE) subtypes were mentioned in the above examples. Although the occurrence of the CE subtype is less than the AS subtype (accounting for about 25% of AIS cases on average), it is often more severe and more prone to early and late recurrences.[10]

Recent studies relating to inflammation and cancer inhibition have brought oncostatin M (OSM), a group of glycoproteins (gp), to researchers attention. OSM is a member of the interleukin 6 (IL-6) cytokine sharing a signalling pathway with gp130.[10] The mechanism of engagement is through a second receptor, either through type 1 (Leukemia Inhibitory Factor Receptor α [LIFRα]) or type 2 (OSM receptor β chain [OSMRβ]), before engaging with gp130 and OSMR.[11,12] A study reported that OSM had a neuroprotective function related to ischaemic-reperfusion brain injury, which leads to a potential therapeutic effect.[12] This review aims to explore the current understanding behind the elevation of serum OSM in patients with AIS.

Methods

We searched the National Center for Biotechnology Information (NCBI) PubMed database for studies that link OSM and AIS. We explored the pathophysiology of AIS, the mechanism of action of OSM to find the cause of serum OSM elevation in AIS and the distinguished traits of the CE subtype that are associated with significant elevation of serum OSM level. An advanced search using MeSH terms was implemented using the search strategy ("acute ischemic stroke" OR "stroke" OR "AIS"), "neuroinflammation," and ("oncostatin M" OR "OSM"). A search filter was set for all types of articles in English with free full text. Studies that contained the information above were selected for both animal tests and human trials. We focused on the objectives of the studies, the test subjects and the findings. Results from the selected studies were analyzed and presented in this review article.

Findings

Neuroinflammatory in acute ischaemic stroke

The term 'neuroinflammation' has been widely used to refer to inflammatory responses found in neural cells following injuries, including stroke. Multiple processes have been proposed to explain the brain injury caused by ischaemia, including excitotoxicity, oxidative stress and inflammation.[13] Although the manifestation of post-ischaemic inflammation can occur days or weeks after the event, the inflammatory cascade is initiated as immediately after the occurrence of vessel occlusion.[14] In a study published by Anrather and Iadecola in 2016, the authors described the pathway from a hypoxic state to an inflammatory response in the stroke area in the brain.[15] To begin with, a stagnant blood flow triggers stress on the vascular endothelium and platelets. This signals an adhesion molecule P-selectin to accumulate on the surface of cells within minutes after activation. Selectins are important in controlling the circulation of leukocytes.[16] Inflammation cascades continue to occur in several areas, including the brain parenchyma. One of the earliest events is the release of danger-/damage-associated molecular patterns (DAMP) from injured and dying neurons, which together with other components finally activates the pattern recognition receptor on microglia, brain resident immune cells and astrocytes.[17–20] Microglia are activated in the brain due to the rise of extracellular ATP from depolarization of neurons.[21] These DAMPs and other cytokines can penetrate the blood—brain barrier (BBB) and enter the circulation, which then triggers a systemic inflammatory response. This systemic inflammatory response is characterized by the increase of serum several cytokine expressions including IL-6, which is why IL-6 is found to be elevated in patients with AIS.[22,23] Neuroinflammation may increase potential additional harm, resulting in cell death, but at the same time, it has a helpful effect in promoting healing. This neuroinflammatory response is recorded to be present in all subtypes of stroke, but is deemed amplified in the CE subtype.[24]

Cardioembolic subtype

While stroke has been recategorized as a neurological disorder, it is still a common practice to observe cardiac injury following cerebrovascular disease.[25] The second leading cause of mortality following ischaemic stroke has been reported to be cardiovascular complications. It has also been reported that the risk of cardiac complications in proportional to the severity of ischaemia.[26] A study by Maida et al. focused on neuroinflammatory mechanisms in CE ischaemic stroke. The authors reported an accumulation of evidence demonstrating that ischaemic stroke initiates a complex process involving genetic, molecular and cellular changes. Phlogosis plays a critical part in this mechanism, both in the central and peripheral nervous systems.[22] Another study recorded that systemic inflammation participated in the pathological process that led to cardioembolism, suggesting that a higher inflammatory substrate could be found in CE stroke compared to the other subtypes.[27] With growing evidence indicating neuroinflammation preceeding AIS leads to an increase of cytokines and chemokines that stimulate infiltration of leukocytes into the cerebral parenchyma. If an extensive area of cerebral tissue is affected it could induce a higher neuroinflammatory response.[22]

Oncostatin M

There have been studies into OSM since 1986 when it was first identified in the conditioned media of phorbol 12-myristate 13-acetate (PMA)-treated U937 monocytic cells.[28] OSM belongs to the IL-6 family of cytokines which contribute to communication and signalling pathways. Several studies have recorded the involvement of OSM in physiological and pathophysiological activities, including haematopoiesis, mesenchymal stem cell differentiation, fibrosis, nociception, inflammation, metabolism and cancer.[29–33] The biological activities of OSM vary in different species, according to the concentration of ligands and specific cell types.[29,34] In animal models, mouse OSM (mOSM) only binds to OSMRβ/gp130 in mice, whereas human OSM (hOSM) signals both LIFRβ and OSMRβ, specifically called type I receptor complex (LIFRβ/gp130) or type II receptor complex (OSMRβ/gp130).[35,36] Hermanns et al. reported that OSM possessed the broadest signalling profile, which comprised Janus kinase (JAK)/signal transducer and activator of transcription (STAT), mitogen-activated protein kinases (MAPK) – including extracellular signal-regulated kinase (ERK), p38 and Jun NH_2-terminal kinase (JNK) – the phosphatidylinositol-3-kinase (PI3K)/Akt and the protein kinase C delta (PKCδ) pathways.[29] This broad signalling profile was due to OSM comprising BC loops, a unique helical loop on OSM between its B and C helices that is not found on other IL-6 family cytokines, that act as a steric barrier for OSMRβ and LIFRβ. As a result, OSM initially binds with gp130 before signalling OSMRβ or LIFRβ.[37]

The production of OSM in the human body is derived from multiple sources, mainly the cells of the immune system: dendritic cells, neutrophils, monocytes/macrophages and T cells.[38–40] Regardless of any existing inflammation, haematopoietic cells of the bone marrow also produce OSM, explaining why a low concentration of serum OSM can be found in a normal healthy body.[41] While previous studies focus on the role of OSM with regard to inflammation, cell proliferation and haematopoiesis, increasing evidence reported the involvement of OSM in the nervous system. In the central nervous system, OSM is mainly expressed by neurons, astrocytes and microglia.[42–44] OSM has been implicated in the homeostasis of neural progenitor cells (NPCs) in physiological settings, a pool of cells for the production of new neural cells located in the subventricular zone, hippocampus and olfactory bulb in the adult mammalian brain.[45–48] It has been reported that the number of OSMRβ-positive neurons in the site of injury was significantly decreased following a sciatic nerve axotomy.[49] OSM has been shown to decrease NMDA-induced neuronal death and inhibit excitotoxic injury *in vivo*.[50] OSM-based treatment also showed a reduction in lesion size after a spinal cord hemisection and improved functional recovery and neurite outgrowth in an animal model.[51] Although several studies reported neuroprotective properties of OSM, some studies also reported contradictory findings. A study reported OSM derived from mononuclear cells induced apoptosis in primary neurons.[52] Contradictory roles of OSM might be correlated with different experimental settings, cell types, stimuli and recruitment of receptors.[35]

In inflammatory conditions, OSM is significantly involved in both acute and chronic phases, leading to tissue fibrosis and cancer, and is also

expressed by immune cells after a variety of soluble mediators.[53] A double-side effect of OSM can act as an anti- or pro-inflammatory action. This is due to the ability of OSM to either directly recruit or activate innate immune cells, or indirectly regulate stromal cells located in the area of injury.[54,55] In pro-inflammatory activities, OSM has been recognized to induce target cells to release cytokines and chemokines, such as CXCL3, CCL2, CCL5, and CCL20,[56] which proceed with neutrophils and monocyte/macrophage recruitment, creating a positive amplification of OSM's effect. In chronic inflammatory conditions, an overexpression of OSM/OSMβR is often found, where OSM sustains inflammation and promotes fibrosis.[36] OSM concentration is relatively modest in a normal healthy condition and multiple studies have confirmed a significant increase in OSM from a few hours after the onset of stroke that can persist for up to 90 days following cerebral ischaemia.[29,57] Although previous studies identified OSMβ expression in several cell types in the brain (neurons and astrocytes, but not microglia), the OSMβ expression profile proceeding onset of stroke is still unclear.[58] OSMβ protects against ischaemic/reperfusion (I/R)-induced cerebral injury by activating the JAK2/STAT3 cascade, but it is not clear whether JAK2/STAT3 is necessary for OSMβ-mediated protection *in vivo*. Still, OSM is considered to be a promising therapeutic agent in rats and humans.[35]

Discussion

Everything related to AIS, from onset to treatment, is time critical. Understanding the mechanism of AIS helps to identify the pathophysiological nature of AIS, as well as appropriate responses in order to develop target-specific treatments. This review article reported the three major mechanisms of neurological damage following an infarct and stroke: loss of neurons, excessive production of reactive oxygen species and inflammation.[59–61] Among the three mechanisms, we focused on the inflammation response. In an ischaemic environment, glial cells such as astrocytes and microglia, together with endothelial cells and leukocytes, release various pro-inflammatory agents and initiate signalling cascades facilitated by chemokines, cytokines and other enzymes. During the review process, we specifically focused on OSM.

OSM stands out due to its wide range of cascading capabilities and its neuroprotective properties. In addition to that, hOSM is correlated with

both type 1 and type 2 signalling pathways, whereas mOSM is only associated with type 2 signalling pathways. This allows researchers to conclude a certain degree of representation between animal models and humans. It has been known that OSM exists in a normal, healthy human body and is significantly elevated in inflammatory conditions, including AIS. Unfortunately, the present understanding of the minimum threshold that causes OSM elevation is still unknown. Due to its nature, OSM can act as an anti- and pro-inflammatory agent, which causes a dilemma in finding the appropriate usage of OSM related to AIS. OSM can be measured through enzyme linked immunosorbent assay (ELISA), which is a strength for its practical accessibility.

We identified several limitations reported in past studies. It was reported that a close interaction between pro-inflammatory and anti-inflammatory molecules during the early stages of stroke was present, but the precise understanding in the process that modulates the interaction was still lacking. Studies about the correlation between OSM and its properties in the nervous system are still very limited. There is also a limitation of data availability on the neuroinflammation association with cardioembolism, meaning that future studies are needed to accurately determine the reasoning behind CE stroke.

Conclusion

This review was designed to assess current knowledge about the relationship between serum OSM and AIS. Hypoxia and stagnant blood flow trigger inflammatory responses from the tissue. Inflammatory responses following AIS can be found as early as a few hours after onset of AID and can last for days. This inflammatory response triggers the signalling pathway of OSM through the activation of cytokines. There are multiple producers of OSM in the body. OSM is known to have a dual effect: to induce inflammation and to respond to inflammation. Several studies have reported the elevation of OSM levels in AIS, notably in CE. The significant increase in the CE subtype is due to a higher concentration of inflammatory substrates in the circulation expressing the OSM. With a lack of published studies around OSM levels in humans, further research should be carried out to further investigate the findings reported in animal studies, as well as the association between neuroinflammation and cardioembolism. ❑

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