Neural repair function of osteopontin in stroke and stroke-related diseases (Review)

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Abstract. Stroke, including hemorrhagic stroke and ischemic stroke, is a common disease of the central nervous system. It is characterized by a high mortality and disability rate and is closely associated with atherosclerosis, hypertension hyperglycemia, atrial fibrillation and unhealthy living habits. The continuous development of surgery and medications has decreased the mortality rate of patients with stroke and has greatly improved the disease prognosis. At present, the direction of clinical treatment and research has gradually shifted to the repair of nerve function after stroke. Osteopontin (OPN) is a widely distributed extracellular matrix protein. Due to its structural characteristics, OPN can be cut and modified into terminal fragments with different functions, which play different roles in various pathophysiological processes, such as formation of tumors, inflammation and autoimmune diseases. It has also become a potential diagnostic and therapeutic marker. In order to comprehensively analyze the specific role of OPN in nerve repair and its relationship with stroke and stroke-related diseases, the following key words were used: 'Osteopontin, stroke, atherosis, neuroplasticity, neural repair'. PubMed, Web of Science and Cochrane articles related to OPN were searched and summarized. The present review describes the OPN structure, isoforms, functions and its neural repair mechanism, and its association with the occurrence and development of stroke and related diseases was explored.

Contents

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1. Introduction

Acute brain injury, which includes ischemic stroke, hemorrhagic stroke, subarachnoid hemorrhage and traumatic brain injury, is one of the leading causes of mortality and disability (1,2). These acute brain injuries pose a heavy socio-economic burden. The continuous development of surgery and medications has decreased the mortality rate of patients with stroke and has greatly improved the disease prognosis (3). At present, the direction of clinical treatment and research has gradually shifted to the repair of nerve function following stroke (4-6). Notably, acute neurological diseases share numerous common pathophysiological processes, which include cellular apoptosis, neuroinflammation and blood-brain barrier (BBB) disruption, and they are closely associated with atherosclerosis, hypertension, hyperglycemia, atrial fibrillation and unhealthy living habits (7).

Osteopontin (OPN) is a widely distributed extracellular matrix (ECM) protein (8). Due to its structural characteristics, OPN can be cut and modified into terminal fragments with different functions, which play different roles in various pathophysiological processes, such as tumor formation, inflammation and autoimmune diseases (9). It has also become a potential diagnostic and therapeutic marker (10,11).

In the present review article, the basic structure of OPN was explained in detail and the description of its different functions through different segments was discussed. The neural repair mechanism of OPN was also elucidated with regard to the three following aspects: i) Induction of synaptic reconnection and enhancement of neuroplasticity by OPN, ii) induction of microglia migration and iii) differentiation and improvement of vascular remodeling. In addition, its association with the occurrence and development of stroke and related diseases was explored. Finally, the possible role of OPN in the treatment of central nervous system (CNS) diseases was explored, to provide further research directions for clinical treatment.

2. Biological properties of OPN

OPN was discovered in the 1980s and it was initially identified in osteoblasts; it is a negatively charged phosphorylated

glycoprotein present in the ECM, which was named for its ability to mediate the connection of tissue cells to the bone matrix and its involvement in bone matrix mineralization (12) and reabsorption. It is widely distributed in the human body (13) and its expression is activated under the action of hypoxia, hyperglycemia and a variety of cytokines, such as TNF-α, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), TGF-β and vascular endothelial growth factor (VEGF). In addition, OPN can be secreted by different types of cells, including macrophages, T lymphocytes, smooth muscle cells, endothelial cells, cardiomyocytes and fibroblasts (14), and subsequently participates in various pathophysiological processes, such as tumor infiltration and transformation, cell proliferation and migration, as well as immune response and injury (15,16).

OPN essential motifs and its physiological functions. The OPN gene is located on chromosome 4 (4q13) of the human genome and on mouse chromosome 5 in the small integrin-binding ligand N-linked glycoprotein cluster. It consists of 314 amino acids and contains an arginine-glycine-aspartate (RGD) recognition sequence, a SVVYGLR sequence (SLAYGLR sequence in mice), a thrombin cleavage site (RSK), a calcium-binding site and two heparin-binding sites (17). One of the thrombin cleavage sites is located near one of the two heparin-binding structural domains. When thrombin cleaves the Arg168-Ser169 site near the RGD sequence, the hidden SVVYGLR sequence is exposed, producing two fragments, the N-terminal fragment (trOPN-N) and the C-terminal fragment (trOPN-C) (18); trOPN-N consists of mainly negatively charged acidic amino acids, whereas all positively charged heparin-binding domains are located in the trOPN-C (19). OPN functions as a cell signaling molecule by the following two mechanisms: The first involves the N-terminal using the intramolecular RGD sequence to bind to integrin family molecules, such as αvβ1, αvβ3, αvβ5, α8β1 and α5β1, whereas the SVVYGLR domain can also bind to integrins α9β1, α4β1 and α4β7 following exposure, promoting the secretion of IFN-γ in T cells and cell migration by binding to α9β1 and α4β1 (20,21). The second involves the C-terminus binding to the cluster of differentiation (CD) 44 variant of the cell surface adhesion glycoprotein in a non-RGD-dependent manner to inhibit IL-7 secretion and promote intercellular adhesion. Therefore, different terminal fragments may have different functions (22). For example, in T cells, trOPN-N promotes IL-17 secretion, whereas trOPN-C inhibits IL-10 secretion (23). In monocytes, IL-6 secretion is mainly induced by trOPN-N. Clemente *et al* (24) demonstrated that the inhibitory effect of trOPN-C on cell adhesion was dependent on its phosphorylation.

OPN can also exert its biological activity following cleavage by metalloproteinases (MMPs). OPN contains three cleavage sites for MMPs, located in the following amino acid regions: Gly166-Leu167, Ala201-Tyr202 and Asp210-Leu211. Cleavage by MMP-3 and MMP-7 similarly produces trOPN-N fragments containing both the RGD sequence and the SVVYGLR motifs, whereas cleavage by MMP-12 can produce an OPN fragment with anti-inflammatory activity (25).

Functional diversity of OPN. The functional diversity of OPN is mainly attributed to the following two points: Firstly, there are three known splice variants of the OPN isoforms, namely OPN-a (full-length OPN), OPN-b (exon 5 deletion) and OPN-c (exon 4 deletion); all three belong to the highly conserved structural domains, yet they have different functions. Among them, OPN-b and OPN-c are associated with cancer progression and poor prognosis (26). Secondly, selective splicing and post-translational modifications, such as phosphorylation, glycosylation, sulphation, enzymatic cleavage and protein cross-linking, generate different biologically active forms of OPN, the roles of which may be determined by cell type, cell origin and the cellular microenvironment. Furthermore, it is widely accepted that splicing primarily occurs in tumor cells. Cleavage in these cells initiates pro-tumorigenic activity, promoting tumor growth and metastasis (27). Subsequent studies have also demonstrated that splicing variants of OPN contribute to vascular calcification (28-30).

3. Neural repair mechanism of OPN

In the CNS, OPN is a multifunctional and inducible ECM glycoprotein, which plays an important role in Alzheimer's disease, Parkinson's disease, multiple sclerosis and other neurodegenerative pathologies (31-33). It is both a component of the ECM of normal CNS tissues and a key factor in tissue repair and ECM remodeling following CNS injury. It exerts neuroprotective, immunomodulatory and antiapoptotic effects in the acute phase following brain injury. Previous studies have revealed that intranasal administration or intracerebroventricular injection of exogenous OPN has neuroprotective effects and improves the neurological outcome following stroke (34-36). Its neurorestorative mechanisms have been mainly identified in the following areas: Neural plasticity, microglia and vascular remodeling.

Neural plasticity. Following induction of a stroke, the neuronal synapses surrounding the damaged brain tissue may experience structural and functional damage; however, there is still a partial plasticity (37), the process of which involves axon sprouting, synapse formation and synaptic remodeling (38); this suggests that neuroplasticity is the basis of neural repair following brain injury (39). Cortical connectivity is primarily facilitated through excitatory synapses on dendritic spines. Synaptophysin is a crucial factor in assessing neuroplasticity (40). This is due to the role of the ECM protein family in the regulation of synaptic controllability (41). It was speculated that OPNs could perform the same function following induction of a stroke and this hypothesis was experimentally confirmed (42,43). OPN can induce synaptic reconnection and regenerate damaged axons in the presence of insulin-like growth factor (IGF)1 or brain-derived nerve growth factor. During the subacute phase of stroke, increased turnover of dendritic spines provides an optimal time window for neuroplasticity to occur. Experimental evidence has revealed that during the subacute phase of stroke, which is administered on day 7, synapse-associated proteins in the peri-infarct zone can be activated, neuroplasticity can be regulated and synaptic reconnection can be induced, thereby aiding in nerve repair (44).

Microglia. Microglia are the earliest cells to respond to CNS injury. They are usually in a resting state and are activated under the action of various pathological factors.

The functions of activated microglia include proliferation, migration and the release of inflammatory factors (45). Following activation, microglia differentiate into two distinct phenotypes: Pro-inflammatory (M1) and anti-inflammatory (M2) (46). The M1 phenotype releases destructive mediators, such as TNF-α, inducible nitric oxide synthase (iNOS) and IL-1β, while the M2 phenotype primarily produces beneficial mediators that have anti-inflammatory and neuroprotective functions (47).

As an inflammatory chemokine, OPN can play the following roles: i) Induction of microglia migration towards the lesion site, ii) regulation of the function of microglia and induction of the differentiation of microglia into the M2 phenotype, and iii) induction of the separation of microglia with the M2 phenotype from the overlapping region. In addition, it may increase the survival of microglia under stress and inhibit the generation of superoxide by microglia, or even scavenge oxygen free radicals directly. All the aforementioned effects are beneficial to the short-term and long-term prognosis following stroke (48).

Vascular remodeling. Vascular remodeling refers to various morphological and structural changes of vascular cells following injury. Its cytological basis is the migration and proliferation of mesial vascular smooth muscle cells (VSMC) to the subintima, resulting in tube wall thickening and increased vascular resistance and reactivity. When the blood vessel suffers from mechanical injury, such as increased pressure or volume load, VSMC changes from a highly differentiated contractile phenotype to an undifferentiated synthetic phenotype, which proliferates, migrates and secretes a large amount of ECM to the subintima. OPN is one of the ECM proteins that is more closely related to migration and adhesion (49) and is closely related to the proliferation of VSMCs (50). The N-terminal fragment of OPN cleaved by thrombin binds to the integrins avβ1, avβ3 and avβ5, which play an adhesive role between cells and between cells and matrix. Therefore, following binding of OPN to integrin avβ3, the adhesion plaque is formed, which in turn activates the expression of focal adhesion kinase (FAK). FAK activates PI3K via binding to phosphorylated adhesion spot kinase antibody (Tyr397), which promotes cell adhesion, migration and proliferation. Moreover, OPN induces VSMC proliferation by activating MMPs and downregulating actin and calmodulin via regulation of extracellular signaling pathways. Therefore, it has been revealed that the expression of OPN in VSMCs following vascular injury is significantly increased (51,52).

By contrast, VEGF is a dimeric polypeptide expressed by neurons, astrocytes and endothelial cells in the CNS and OPN can upregulate the expression of VEGF in the peri-infarct region for the purpose of vascular remodeling, thereby restoring neurological function (53).

4. Role of OPN in stroke and stroke-related diseases

The functional diversity of OPN in stroke diseases is closely related to its neural repair mechanism and some of the mechanisms overlap with each other. In this section, the specific roles played by OPN in these diseases are summarized.

OPN and atherosclerotic plaques. Atherosclerosis is an inflammatory disease and inflammatory processes occur throughout all stages of the development of atherogenesis. The inflammatory response that occurs within the carotid atherosclerotic plaque can increase the vulnerability of the plaque by inducing neointimal formation and intraplaque hemorrhage; therefore, the number of macrophages within the plaque is an important determinant of plaque stability (54), namely, an increase in the number of macrophages decreases the stability of the plaque. Vascular calcification is a pathological manifestation of atherosclerosis in which senescent VSMCs are converted to osteoblasts, which promote calcification of the inner wall of the blood vessel, similar to bone formation, to increase the stability of plaques, prevent them from rupturing and dislodging, and therefore reducing the likelihood of cardiovascular and cerebrovascular events.

OPN is a potent inhibitor of mineral formation in VSMCs. As a potent inhibitor of soft tissue mineralization, OPN inhibits ectopic calcification in the cardiovascular system by inhibiting the growth of apatite crystals, which directly reduces the calcification process. By causing mineral dissolution at the site of calcified material, which promotes reabsorption of the calcified material (55), the level of OPN expression is independently associated with carotid plaque stability. Concomitantly, as a chemokine for macrophages and T cells, OPN is also involved in the development of atherosclerosis (56). OPN induces oxidative stress, accelerates atherosclerosis formation and stimulates the release of vascular endothelial and smooth muscle cells under the action of angiotensin; this leads to elevated expression levels of OPN, which mediate inflammatory responses. Subsequently, this results in thinning of the fibrous cap of the plaque and enlargement of the lipid core; the plaque becomes more vulnerable and it is more likely to cause stroke events. Notably, according to Wolak *et al* (57), full-length OPN and trOPN-C were expressed at similar levels in both highly inflamed and low-inflamed plaques, whereas the expression of trOPN-N was significantly increased in highly inflamed plaques, suggesting that in carotid artery specimens, the severity of inflammation is associated only with the expression of trOPN-N and is independent of the expression level of full-length OPN or trOPN-C.

In addition, a plasma trOPN-N level >5.47 pmol/l is an independent predictor of atherosclerotic plaque formation, even within 3 h following stroke onset, and therefore it possesses early diagnostic value (58). An additional study indicated that patients with elevated plasma OPN were more likely to develop carotid artery stenosis; they also exhibited higher mean carotid intima-media thickness than the normal group, suggesting that OPN may be a predictor of atherosclerosis (59).

OPN and hypertension. Hypertension is a disease characterized by elevated arterial blood pressure in the systemic circulation caused by a combination of risk factors and is an independent risk factor for stroke. In various animal models of hypertension, serum OPN levels increase with elevated blood pressure (60,61). It has been confirmed that the association between OPN and hypertension is mainly due to the following mechanisms of action: i) Angiotensin (Ang) II: Ang II is a peptide, which is converted by Ang I under the action of Ang-converting enzyme and its main function is to constrict

blood vessels, leading to an increase in blood pressure and an increase in the excitability of the sympathetic nervous system, which in turn results in an accelerated heart rate, enhanced cardiac contractility and increased cardiac ejection. Ang II upregulates OPN expression, induces the proliferation and migration of VSMCs and leads to the increase in blood pressure. Moreover, Ang II induces the expression of OPN in the arterial wall as one of the factors contributing to atherosclerosis (62,63). ii) Vascular mechanical strain: The PIK3/AKT signaling pathway is involved in a variety of cellular processes. In VSMCs, OPN activates the PIK3/AKT signaling pathway by inducing FAK phosphorylation, causing vascular mechanical strain and sequentially stimulating the expression of OPN. iii) Vascular remodeling: The blood vessels of patients with long-term hypertension will have a certain degree of vascular remodeling, which is a self-protection mechanism of the human body and the pathological basis for the occurrence of hypertension. As mentioned in the previous section, OPN participates in vascular remodeling by means of VSMC migration, which causes an increase in blood pressure via vascular remodeling and inflammatory cell recruitment.

OPN and ischemic stroke. The main injury mechanism of ischemic stroke is a series of cascading reactions such as neuronal apoptosis, oxidative stress, inflammation and BBB disruption on the basis of acute ischemia and hypoxia in neural tissues, which continuously aggravates the brain injury and ultimately leads to permanent local necrosis of neural tissues and neurological deficits. Current clinical therapeutic strategies to protect the brain following ischemic stroke mainly aim at protecting the BBB, promoting glial cell proliferation, pro-angiogenesis and anti-inflammation. It is important to note that promoting the restoration of blood flow to the infarcted area following ischemic stroke is crucial for restoring blood and oxygen supply to the infarcted area and reducing neuronal apoptosis. However, attenuating the systemic inflammatory response and inhibiting the neuronal pathways that trigger the inflammatory response are also potential therapeutic targets for patients with stroke (64). In the middle cerebral artery occlusion animal model, OPN mRNA and protein levels were increased 12 h following occlusion. OPN mRNA was mainly noted in the peri-infarct area within 48 h and peaked at 5 days, showing a 49.5-fold increase compared with the control group. The expression of the mRNA was noted in large quantities in the core area of the infarct and disappeared in the peri-infarct area. The main source of OPN was activated microglia and macrophages in the infarct center and peri-infarct area. The mechanism is considered to be attributed to OPN promoting repair by activating migration of neural stem cells from the subventricular region to the injured region following the onset of ischemic stroke (65,66). Rogall *et al* (67) demonstrated that OPN enhanced post-ischemic neural stem cell migration, expanded the neural stem cell population and recruited progenitor cells from the contralateral hemisphere in mice. Neural stem cells migrate towards the infarct core and differentiate into damaged neuronal cells, such as neurons and astrocytes (68).

Firstly, the expression and interaction of OPN with its receptor integrin αvβ3 promotes the activation of glial cells, migration and the formation of a glial scar following localized cerebral infarction. It also plays a role in wound healing following focal stroke (69). Secondly, the binding of the RGD and SLAY motif of OPN with integrin αvβ3 also plays a crucial part in promoting cerebrovascular formation following ischemic stroke (70). Experimental confirmation has demonstrated that rats with ischemic stroke treated with OPN peptides containing both RGD and SLAY motifs exhibit a significant increase in the length of blood vessels in the cerebral infarct foci and cause a significant reduction in the infarct volume (71). Thirdly, OPN containing the RGD sequence can also exert anti-inflammatory effects via integrin αvβ3 (72). Following ischemia, the inflammatory response in the brain tissue lasts for 8-24 weeks, followed by a second inflammatory burst at weeks 4-8. During this period, elevated levels of OPN and MMPs can be noted, which drive liquefactive necrosis of the brain tissue following stroke (73). As aforementioned in *Vascular remodeling*, OPN exhibits chemotactic and adhesive effects, which can promote the migration of inflammatory cells to the injured site. Neural stem cells (NSCs) treated with OPN exhibited a significant increase in migratory distance and expansion, particularly between the 7th and 28th day (74). However, further research is required to determine the duration of the anti-inflammatory effects of OPN.

OPN and hemorrhagic stroke. The pathological study of patients with cerebral hemorrhage reveals that during intracerebral hemorrhage, the hematoma compresses surrounding brain tissues, causing primary damage. In addition, microglia increase and secrete inflammatory factors and the inflammatory response leads to secondary brain injury. Under the stimulation of inflammatory factors and the stress response, secondary brain ischemia occurs and ultimately leads to the death of brain cells in patients. As cerebral hemorrhage progresses, the response of the body to stress is amplified, leading to changes in the internal environment and the hypothalamic function. This reduces catechol synthesis and can cause neurological hypoplasia. Inflammatory factors are known to play a significant role in this process. The reduction of the inflammatory response is widely recognized as an effective way to decrease the mortality of patients with cerebral hemorrhage.

In neuroinflammation, OPN exhibits a dual role as a cytokine, with both pro-inflammatory and anti-inflammatory effects. This is due to the presence of different functional domains that are exposed following cleavage of the OPN molecule by thrombin or MMPs (75). These domains can activate intracellular signaling pathways, such as the PI3K and p42/44 MAPK pathways and the ERK and JNK pathways, and mediate interactions between cells and the ECM. Numerous studies have confirmed that OPN has a pro-inflammatory role in certain autoimmune diseases (76,77). Its pro-inflammatory activity is more pronounced following thrombin cleavage, while trOPN-C exerts an anti-inflammatory effect. In cases of acute brain injury, OPN can exacerbate neuroinflammation, leading to increased brain injury. However, its negative feedback mechanism aids the maintenance of inflammation homeostasis and promotes the remission of brain injury by coordinating the inflammatory cascade response, including both pro-inflammatory and anti-inflammatory factors in the acute phase (78).

iNOS-derived nitric oxide activates MMP-9, which is involved in neuroinflammation, cell death and BBB disruption (79). OPN is involved in inducing the iNOS pathway and in suppressing iNOS expression following acute brain injury by inhibiting the Janus kinase (JAK)/STAT1 pathway, which is closely related to iNOS (80). In addition to the JAK/STAT1 pathway, OPN also downregulates iNOS by promoting microglia differentiation towards the M2 phenotype and reducing M1 phenotype expression of iNOS.

OPN also plays a role in reducing cerebral edema. The development of cerebral edema is time-dependent, peaking between 24 to 72 h following hemorrhage. At this time, the expression level of OPN also reaches its peak. Pretreatment with recombinant OPN via lateral ventricle injection prior to induction of intracerebral hemorrhage was revealed to slow down the development of cerebral edema and improve the neurological function of mice (81). Therefore, it can be expected to be used as a therapeutic agent for acute brain injury.

5. Outlook on the clinical application of OPN

Due to the increasing awareness of stroke disease in recent years, as well as the continuous development of various treatment methods, such as minimally invasive and interventional, the survival rate of patients with stroke has been significantly improved. However, neurological impairment caused by stroke remains a major issue to be solved. Therefore, the identification of more effective nerve repair measures to promote nerve repair following stroke is imperative in order to improve the rehabilitation level and quality of life of patients with stroke.

Based on the aforementioned summary of findings, it can be deduced that with regard to ischemic stroke, OPN plays a neuroprotective role by promoting the migration of neural stem cells, as well as angiogenesis and anti-inflammatory functions. In intracerebral hemorrhage diseases, OPN also has a dual synergistic anti-inflammatory and pro-inflammatory role. In a rat model of subarachnoid hemorrhage, intranasal administration of rOPN improved neurological dysfunction, reduced neutrophil infiltration and the expression levels of pro-inflammatory microglia markers to reduce inflammation following subarachnoid hemorrhage (82). iNOS can be downregulated by OPN via the JAK/STAT1 pathway and by promoting microglia differentiation into the M2 phenotype, so as to reduce cell death and protect the BBB. In addition, OPN also reduces the development of cerebral edema. However, it is important to note that due to the different subtypes and different terminal fragments of OPN, as well as the role of its post-translational modification, it may exhibit structural and functional differences in different tissues and diseases. Therefore, treatment with exogenous OPN may produce conflicting results. However, it can still be surmised that OPN is expected to become a new therapeutic direction for nerve repair following stroke. Moreover, a previous study has demonstrated that early-stage IGF1/OPN treatment is a promising therapeutic strategy (83).

In addition to its neural repair function, the predictive value of OPN as a biomarker is an important aspect that requires investigation. OPN is involved in the sole pathophysiological process of stroke; the level of plasma OPN can aid in the prognosis of stroke (84-87). Moreover, OPN can also be used as a biomarker for chronic diseases, such as hypertension. Certain studies have revealed that OPN levels in patients with chronic kidney disease, hypertension and diabetes are higher than those noted in normal subjects (88-91). As aforementioned, in carotid plaque specimens, the severity of inflammation is associated with the expression of trOPN-N, and a plasma trOPN-N level >5.47 pmol/l is an independent predictor of atherosclerotic plaque formation. However, additional research is required to confirm these data. It is well-known that for patients diagnosed with carotid atherosclerosis, aggressive lipid-lowering treatment with statins can inhibit carotid plaque vulnerability; moreover, clinical studies have reported that statin therapy can promote the decrease of serum OPN levels (92,93).

It has been experimentally confirmed (94) that early induction of OPN expression following vascular transplantation can increase MMP activity and proliferation of VSMCs; therefore, it may be considered that OPN plays an important role in the process of neointimal hyperplasia following coronary artery bypass transplantation. It has also been revealed that OPN can be selectively expressed in the rat neointima following carotid balloon angioplasty (95). Considering the important role of OPN in vascular remodeling and its relationship with VSMC adhesion and migration, it can be hypothesized that treatment with an anti-OPN antibody prior to carotid endarterectomy can reduce the possibility of carotid intima hyperplasia. It can be expected that OPN plays an important role in the treatment of carotid artery restenosis following vascular reconstruction.

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CL contributed to the conception and design of the study. XS searched and sorted the literature, and wrote the manuscript. Data authentication is not applicable. Both authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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