

The *Yin-Yang* of osteopontin in nervous system diseases: damage versus repair

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Abstract

Osteopontin is a broadly expressed pleiotropic protein, and is attracting increased attention because of its role in the pathophysiology of several inflammatory, degenerative, autoimmune, and oncologic diseases. In fact, in the last decade, several studies have shown that osteopontin contributes to tissue damage not only by recruiting harmful inflammatory cells to the site of lesion, but also increasing their survival. The detrimental role of osteopontin has been indeed well documented in the context of different neurological conditions (i.e., multiple sclerosis, Parkinson's, and Alzheimer's diseases). Intriguingly, recent findings show that osteopontin is involved not only in promoting tissue damage (the *Yin*), but also in repair/regenerative mechanisms (the *Yang*), mostly triggered by the inflammatory response. These two apparently discordant roles are partly related to the presence of different functional domains in the osteopontin molecule, which are exposed after thrombin or metalloproteases cleavages. Such functional domains may in turn activate intracellular signaling pathways and mediate cell-cell and cell-matrix interactions. This review describes the current knowledge on the *Yin* and *Yang* features of osteopontin in nervous system diseases. Understanding the mechanisms behind the *Yin/Yang* would be relevant to develop highly specific tools targeting this multifunctional protein.

Key Words: Alzheimer's disease; cytokine; immunity; microglia; multiple sclerosis; neuroinflammation; neuroprotection; neurotoxicity; Parkinson's disease; Spp1; stroke

Introduction

Osteopontin (OPN) is a multifunctional molecule acting as both immobilized extracellular matrix protein and secreted free cytokine in body fluids (Rittling et al., 2015). OPN is expressed in several tissues and cell types (Braith et al., 2010), and its relevance in central nervous system (CNS) function and disease is corroborated by its widespread expression. In fact, OPN is present in virtually all types of neurons, glial (Jakovac et al., 2017), and immune cells that can either be resident or migrating into the CNS after crossing the blood-brain barrier and communicate with the CNS using molecular signaling cues (Rittling et al., 2015).

Understanding how OPN is processed and interacts with its natural ligands is of paramount importance for elucidating the complex role that this protein plays in nervous system disease.

OPN interacts with multiple integrins through its Arg–Gly–Asp (RGD) domain. In detail, $\alpha 9\beta 1$, $\alpha 4\beta 1$, and $\alpha 4\beta 7$ integrins bind to a cryptic SVVYGLR sequence, which is exposed upon thrombin cleavage occurring at the Arg168-Ser169 site near to the RGD motif (Ito et al., 2009). The thrombin

cleavage generates two OPN fragments: N-(OPN-N) and C-terminal (OPN-C): the latter binds to CD44, which is the other important receptor for OPN, in an RGD-independent manner. OPN-N promotes interleukin (IL)-17 secretion by T cells and favours migration by binding to $\alpha 9\beta 1$ and $\alpha 4\beta 1$ integrins, while OPN-C inhibits IL-10 secretion and favors cell-cell adhesion by interacting with CD44. Nonetheless, both fragments induce interferon- γ secretion by T cells and inhibit lymphocyte death (Boggio et al., 2016).

The binding of OPN to its cell surface receptors induces cellular signaling pathways, which regulate different functions, including cytokine secretion, apoptosis, cellular differentiation, adhesion and migration (Clemente et al., 2016). For example, OPN-mediated activation of the PI3K and P42/44 MAPK pathways exerts neuroprotective function in stroke (Meller et al., 2005), whereas involvement of ERK and JNK pathways promotes the expression of proinflammatory cytokines (e.g., IL-1 β , IL-17) leading to detrimental neuroinflammation (Wang et al., 2019).

Furthermore, OPN is target of the 20S proteasome, which cleaves full OPN and OPN-C generating peptides with strong

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chemotactic activity (Dianzani et al., 2017). Proteasome plays a crucial role in both neurodegenerative and autoimmune diseases (Bellavista et al., 2014) and a computational model describing the dynamic relationship between circulating OPN and proteasome was recently described (Dianzani et al., 2019).

OPN can also be processed by metalloproteinases (MMPs), such as MMP3 and MMP7 generating an OPN-N fragment containing the RGD sequence and a truncated motif (SVVYGLR) recognized by both $\alpha 4\beta 1$ and $\alpha 9\beta 1$ in the OPN-N generated by thrombin: *in vitro* these fragments enhance cell migration and OPN-N induces IL-17 secretion (Boggio et al., 2016). On the other hand, OPN cleavage by MMP12 results into fragments which are less pro-inflammatory compared to OPN full length molecule (Goncalves DaSilva et al., 2010).

Regenerative properties of OPN include plastic effects on mesenchymal and neural stem cells (Lee et al., 2018). Binding of OPN to CD44 induces migration of mesenchymal stem cells toward wounds, thus priming a repair process (Wang et al., 2017). In the CNS, several studies showed a neuroprotective and repair-promoting effect for OPN, in various diseases, including cerebrovascular disease (CVD) (Meller et al., 2005).

Most importantly, OPN interacts with microglial cells, showing synergistic functions with both the detrimental (M1) and the protective (M2) phenotypes of microglia (Rabenstein et al., 2016).

Finally, OPN is also expressed as intracellular protein (iOPN). OPN and iOPN share the same mRNA, but iOPN is generated from an alternative transcription starting site located after the signal peptide, which causes the cytosolic localization of iOPN. iOPN is involved in intracellular signaling pathways and binds different molecules such as some pattern-recognition receptors, the MYD88 (myeloid differentiation primary response gene 88) adapter, and the p85 α subunit of PI3K (Cantor et al., 2009; Leavenworth et al., 2015). iOPN might be involved in cell "proliferation" in the CNS: it is expressed in the brain cortex and upregulated in the right cortex during ischemia reperfusion.

All together, these findings strongly suggest that OPN plays both detrimental and protective roles in CNS, which depend upon either conformational changes in the OPN molecule or activation of specific signalling pathways.

This review focuses on dissecting the multiple roles of OPN in nervous system diseases, based on its two apparently discordant functions: tissue damage and repair.

Osteopontin Exerts a Detrimental Role in Nervous System Diseases: the Yin

The first evidence of the OPN detrimental role in inflammatory CNS diseases was provided by Chabas et al. (2001). In this work, authors showed that OPN was the most abundant transcript present in both multiple sclerosis (MS) lesions and spinal cords of rats with experimental autoimmune encephalomyelitis (EAE), the animal model of MS. Moreover, OPN knock out (KO) mice displayed milder course of EAE and had remission. A subsequent study confirmed these findings by showing that administration of full length OPN resulted in exacerbation of EAE, but the OPN portion involved in progression of the disease remained unknown (Hur et al., 2007). In a more recent work, we demonstrated that OPN-C, generated upon thrombin cleavage, was the main driver of EAE (Boggio et al., 2016). Thrombin cleavage unmasks two binding sites for $\alpha 4\beta 1$ integrin, promoting diapedesis of T cells

in the CNS (Hur et al., 2007). In line, blockade of $\alpha 4\beta 1$ integrin inhibited relapses in MS patients.

OPN interacts with several integrins, including $\alpha \nu$ ($\beta 1$, $\beta 3$, or $\beta 5$) and ($\alpha 4$, $\alpha 5$, $\alpha 8$, or $\alpha 9$) $\beta 1$ integrins, and induces integrin-mediated signaling into the cell. In particular, the $\alpha 4\beta 1$ -OPN interaction blocks nuclear translocation of transcription factor forkhead box O3A (FOXO3A), inhibits transcription of pro-apoptotic genes, and upregulates expression of anti-apoptotic genes and T-helper (Th) 1- and Th17-type cytokines (Steinman et al., 1997). These direct OPN effects are specifically mediated by thrombin cleavage since administration of a thrombin inhibitor or mutated form of OPN lacking the thrombin cleavage site (Boggio et al., 2016) decreased EAE severity and inhibited expression of Th1 and Th17 cytokines (Boggio et al., 2016). Such results suggest that OPN may be a potential target of MS therapy.

In addition to its abundant presence in MS lesions, high levels of circulating OPN have been detected in several body fluids [i.e. cerebrospinal fluid (CSF), serum or plasma] of MS patients, suggesting that this protein may be exploited as biomarker to monitor disease activity and progression (Chiocchetti et al., 2005; Comi et al., 2012; Ferret-sena et al., 2016; Agah et al., 2018). Stratification of MS patients showed that OPN levels were increased especially in those with active disease (Szalardy et al., 2013). In addition, at MS diagnosis, high serum levels of OPN directly correlated with increased relapse rate during a ten-year-follow up (Clemente et al., 2017), while CSF levels of OPN increased during relapses (Borsen et al., 2011).

In EAE, increased release of circulating OPN is followed by anti-OPN autoantibodies (autoAb) production, which may favor disease remission (Steinman et al., 2003; Cappellano et al., 2012). Previous work from our group showed that both active and passive vaccination against OPN reduced T-cell secretion of IL-12 and interferon- γ and decreased EAE severity (Boggio et al., 2016; Clemente et al., 2017). Accordingly, we also found high levels of anti-OPN autoAbs in relapsing remitting MS patients, especially in the remission phase (Clemente et al., 2017).

OPN expression is also modulated by treatments. In both EAE and MS, administration of interferon- β ameliorated the disease course, reduced OPN serum level, and affected T cell migration *in vitro* (Chen et al., 2011). In EAE, Glatiramer acetate decreased expression of OPN in dendritic cells and chemokines in the brain (Begum-Haque et al., 2013). In addition, MS patients treated with Glatiramer acetate displayed decreased OPN serum levels (Kivisäkk et al., 2014). Consistently, Natalizumab, which is a highly effective MS therapy, was also able to markedly decrease OPN plasma levels in relapsing remitting patients (Iaffaldano et al., 2014).

Circulating OPN levels are higher in subjects at optic neuritis presentation compared to controls (Lochner et al., 2017), but they do not appear to predict either conversion toward clinically defined MS or long-term disability (Modvig et al., 2015). In analogy to MS, neuromyelitis optica patients display higher OPN plasma levels than healthy controls, particularly during relapses and if presenting greater disability. Interestingly, in neuromyelitis optica patients, the CSF OPN seems to interact with $\alpha \nu \beta 3$ integrin promoting macrophage chemotaxis by activation of phosphoinositide 3-kinase and the MEK1/2 signaling pathways (Kariya et al., 2015).

OPN was also investigated as a marker of inflammation in neuromuscular autoimmune disorders. Increase of circulating OPN was detected also in patients with Guillain-Barré

syndrome (Han et al., 2014). Once again, protein levels were higher in the acute *versus* recovery phase of the disease and correlated with disability scores (Han et al., 2014). Similar findings were obtained in myasthenia gravis (MG), where both in the human disease and the experimental rat model, OPN levels are increased (Xie et al., 2017; Zhao et al., 2020). Interestingly, data on the rat model show that OPN promotes disease progression by increasing Th1 and inhibiting regulatory T (Treg) cell responses (Zhao et al., 2020).

A detrimental role of OPN has also been suggested in neurodegenerative diseases, including Parkinson's disease (PD), Lewy body disease, and Alzheimer's disease (AD), possibly in relation to the triggering of a self-damaging inflammatory activity (Cappellano et al., 2013; Kustrimovic et al., 2018).

Increased OPN serum and CSF levels were detected in PD patients compared to healthy controls (Maetzler et al., 2007); and OPN serum levels directly correlated with dementia, while CSF levels with a severe motor phenotype (Maetzler et al., 2007). Similar findings were reported in Lewy body disease where serum and CSF levels of OPN are increased in patients compared to healthy controls. In addition, administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a toxic substance used to mimic PD in murine models, showed that OPN-KO mice display decreased vulnerability to damage induced by MPTP compared to wild type mice, in terms of both neuronal cell and tyrosine hydroxylase-positive fiber loss, and decreased activation of microglial cells (Maetzler et al., 2007).

High expression of OPN was firstly detected in hippocampal neurons from autopsy brains of AD patients, and a correlative mouse model (Rentsendorj et al., 2018). Notably, OPN was abundantly expressed in neurons surrounding amyloid plaques (Rentsendorj et al., 2018). AD patients displayed higher OPN CSF levels compared to controls, particularly in the early disease phases, when mini-mental state examination scores were still within normal values (Comi et al., 2010). For such reason, OPN has been investigated as biomarker to monitor conversion of mild cognitive impairment to AD, and Sun et al. (2013) detected higher OPN CSF levels in mild cognitive impairment subjects who converted to AD than in those without clinical conversion. Of note, while the CSF findings were concordant among studies, significantly increased OPN levels were detected in the serum of AD patients only in one study (Sun et al., 2013).

Independent studies using proteomic approaches on CSF samples confirmed the sensitivity of OPN as AD marker, but they also highlighted its poor specificity since increases can be associated to most neurodegenerative diseases, a feature that poses important limitations to its use in a diagnostic setting.

CSF OPN levels were significantly increased also in frontotemporal dementia, since Mattson et al. found a direct correlation between levels of neurofilaments and OPN in the CSF of a small group of patients not stratified by genetic background (Mattsson et al., 2008). Then, a recent work showed that patients carrying the C9ORF72 expansion display higher levels than those carrying progranulin mutation (Heywood et al., 2018).

Similar findings were obtained in amyotrophic lateral sclerosis (ALS) in two independent studies displaying increased OPN levels in CSF of ALS patients compared to controls (Varghese et al., 2013). A significant increase of OPN expression in microglia of ALS, both in the human disease and animal

models, was detected in cases compared to controls (Silva et al., 2015). Notably, ablation of the OPN gene in SOD1G93A mice, an ALS model, causes delayed disease onset, followed by acceleration of progression, with a negligible impact on survival (Morisaki et al., 2016). Such findings collectively indicate that, in ALS, OPN may alternatively communicate with detrimental (M1) or protective microglia (M2), with a variable balance in the different disease stages and a net effect that cannot be accounted yet (Mousavi et al., 2020).

OPN has been studied as a determinant of CVD: its capacity to promote atherosclerosis may be exerted by inducing chemotaxis of endothelial cells via $\alpha\beta3$ integrin and activating inflammation in the vessel wall (Icer and Gezmen-Karadag 2018). Furthermore, comparison of subjects with and without atherosclerosis showed that plasma levels of trombin-cleaved OPN-N were increased in subjects with carotid atherosclerosis, especially in those presenting a symptomatic carotid stenosis (Kurata et al., 2012). Finally, plasma levels of OPN-N may serve as a marker of atherothrombosis since they are significantly increased in patients with acute atherothrombotic stroke compared to those without (Ozaki et al., 2017).

Osteopontin Exerts a Protective Role in Nervous System Diseases: the *Yang*

Several studies have demonstrated that OPN may also deliver pro-survival or anti-apoptotic signals to cells.

One important mechanism behind tissue protection and regeneration involves the upregulation of αV integrins. Experimental evidence from *in vivo* models of demyelination/remyelination showed that: i) OPN is upregulated in both demyelination and remyelination; ii) macrophages express higher OPN mRNA after damage; iii) interaction of OPN with αV integrins modulates the properties of oligodendrocyte precursors (Selvaraju et al., 2004). In animal models of PD, OPN expression, accompanied by upregulation of integrin receptor subunits, was detected in substantia nigra neurons following toxic lesions. Under *in vivo* and *in vitro* experimental conditions, findings indicate that: i) lipopolysaccharide administration to rats causes increase of integrin and CD44 expression, which are both receptors for OPN (Ailane et al., 2013); ii) pre-treatment with OPN protects mesencephalic cultures from damage induced by MPTP administration, through a decrease of activated M1 microglia (Broom et al., 2015).

The cleavage of OPN mediated by MMP may also be involved in protective mechanisms, since it can generate either a less inflammatory form of the protein or even peptides with anti-inflammatory properties (Goncalves DaSilva et al., 2010). Specifically, MMP-9 has been implicated in generating functional fragments that are more neuroprotective compared to the full length OPN.

In AD, evidence showed that OPN is involved in the clearance of amyloid plaques, a process which is essentially carried out by M2 microglia thanks to the contribution of synergistic signalling pathways (Sainaghi et al., 2017; Tondo et al., 2019). Moreover, in a double transgenic mouse model of AD, silencing of the OPN mRNA resulted in a functional impairment of microglia-mediated clearance of amyloid plaques (Rentsendorj et al., 2018).

Strong evidence also supports a protective/repair function of OPN in CVD. It has been proposed that OPN, with respect to CVD, may fit within the Goldilocks paradigm (who challenges the question "what is the right amount?") where an acute

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increase of OPN is protective, by attenuating the vascular calcification and promoting postischemic neovascularization. On the contrary, a chronic increase in OPN is clinically associated with an increased risk for a major adverse CVD event. Moreover, due to the existence of three OPN isoforms, further studies are needed to investigate which isoforms play a role in CVD progression (Lok and Lyle, 2019).

Several studies showed that OPN is involved in healing processes, scarring response, tissue remodeling after hypoxic injuries, and in promoting migration and differentiation of mesenchymal and neural stem cells after cellular damage (Icer et al., 2018).

In the CNS, ischemia-injured endothelium, glia and neurons activate an inflammatory response through release of cytokines/chemokines, and recruitment of resident glia and peripheral immune cells which, in turn, promote tissue regeneration (Ladwig et al., 2017). In rats, OPN is upregulated in the subacute stages of cerebral ischemia, particularly in macrophages and microglia in infarct/perinfarct regions. Findings suggest that OPN can polarize microglia towards an M2 phenotype and reduce lipopolysaccharide-stimulated M1 microglia (Rabenstein et al., 2016). In an animal model, intracerebroventricular OPN injection increased M2 glial cells in the infarct core/perinfarct zone and, in ipsilateral thalamus, reduced the accumulation of M1 activated microglia and increased stem cell proliferation (Ladwig et al., 2017, 2018). Modulating microglial polarization may thus be a promising target to attenuate secondary cell damage after cerebral ischemia (Orihuela et al., 2016). In the immature brain damaged by hypoxic-ischemic injury, intracerebroventricular injection of OPN decreased infarct volume and improved neurological outcomes. OPN-induced neuroprotection was associated with inhibition of caspase-3 cleavage and cell apoptosis, which was blocked by an integrin antagonist (Chen et al., 2011). iOPN can be also substrate of caspase-8, acting on a cleavage site located near the RGD domain of OPN and generating OPN fragments bearing the RGD domain capable to deliver survival/proliferative signals to cancer cells (Leung et al., 2016) and, possibly, neuroprotective effects.

An indirect neuroprotective effect of OPN may be ascribed to the decrease of inducible nitric oxide synthesis. Accordingly, in models of experimental brain ischemia, OPN-KO mice display a widespread neurodegeneration that is absent in wild type animals and can be limited by blockade of inducible nitric oxide synthase (Ladwig et al., 2018).

Furthermore, OPN promotes repair by attracting neuroblasts from the subventricular zone to the injured region (Yan et al., 2009). Rogall et al. (2018) confirmed that, in mice, OPN enhanced neuroblast migration after ischemia, expanded neuroblast population, and recruited progenitors from the contralateral hemisphere.

Finally, recent work explored the proangiogenic potential of a 20-amino-acid OPN peptide (OPNpt20) in a rat focal cerebral ischemia model. Findings showed that RGD and serine-leucine-alanine-tyrosine motifs of OPNpt20 induced endothelial cell proliferation, migration, and tube formation. The RGD motif interacted with endogenous $\alpha v \beta 3$ -integrin stimulating angiogenesis (Lee et al., 2018).

Evidence of a protective role of OPN was obtained also in hemorrhagic stroke models. In a subarachnoid hemorrhage animal model, an indirect protective effect of OPN was mediated by downregulation of iNOS expression via

inhibition of STAT phosphorylation, suppression of MMP-9 activation, and activation of MAP kinases with a protection against blood-brain barrier disruption (Suzuki et al., 2010). The administration of recombinant OPN (intranasally and intracerebroventricularly) in experimental subarachnoid hemorrhage was able to restore smooth muscle cell integrity, thus acting on a mechanism involved in the pathophysiology of early brain injury after hemorrhage (Wu et al., 2016). In an intracerebral hemorrhage model, OPN administration reduced brain edema and improved clinical outcome (Gong et al., 2018). Such protective effects were ascribed to two possibly synergistic mechanisms: i) inhibition of JAK2/STAT1 pathway triggered by integrin- $\beta 1$ signalling, with a potent anti-inflammatory effect (Gong et al., 2018), and ii) activation of the PI3K/Akt/GSK-3 β signaling pathway exerting an anti-apoptotic effect (Zang et al., 2018).

A regenerative effect of OPN was also evaluated at the level of the spinal cord and peripheral nerves. In a rodent model of spinal cord injury, Anderson et al. (2018) were able to stimulate the regrowth of propriospinal axons into a full spinal segment beyond lesion centers, thus forming terminal-like contacts, and conveying a significant return of electrophysiological conduction capacity across lesions. OPN was used to reactivate intrinsic propriospinal neuronal growth capacity using adeno-associated viral vectors to deliver either PTEN knockdown, or to express OPN, IGF1 and ciliary neurotrophic factor. To increase axon growth-supportive substrates and chemoattract axons, they delivered fibroblast and epidermal growth factors, and glial-derived growth factor (Anderson et al., 2018).

At peripheral level, the role of OPN was investigated in relation to Schwann cells, which are known to secrete several soluble factors involved in motor axons regeneration. Experiments showed that OPN mRNA expression was increased in Schwann cells of sciatic nerves both after nerve injury and in experimental autoimmune neuritis (Ahn et al., 2004). In this scenario, OPN does not seem to be necessary to induce sensory axonal regeneration but rather motor axonal regeneration. Sciatic nerve transection induced upregulation of OPN and expression returned to baseline levels following regeneration. Moreover, old OPN-KO mice had significantly fewer regenerating axons, reduced re-innervation of neuromuscular junctions, and significant impairment in functional motor recovery compared with equal in age wild type mice, but this effect was not confirmed in young mice. More recently, evidence on a protective effect of circulating OPN in breast cancer patients with taxane-induced polyneuropathy was provided (Pizzamiglio et al., 2020).

Conclusions

In this review, we tried to shed light into a complex scenario where OPN takes part in two apparently antithetical functions, i.e., nervous tissue damage and repair: The *Yin* and the *Yang* (Figure 1).

These heterogenous and even opposite effects may have several explanations: (i) the wide expression of OPN in different cell types; (ii) its interaction with and recruitment of different immune and glial cell; (iii) the formation of fragments/peptides with different functional capacities; and finally (iv) the presence of several functional sites interacting with distinct receptors which can activate multiple intracellular signaling pathways and mediate cell-cell and cell-matrix interactions by shaping the immune responses (Prete et al., 2019) (Figure 1B).

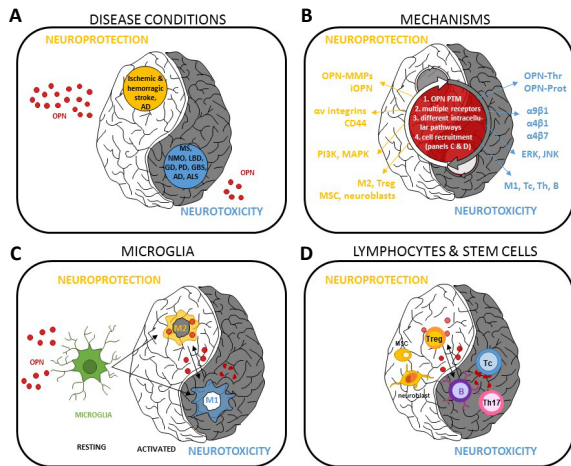


Figure 1 | The Yin and the Yang of OPN activity in the brain.

(A) Disease conditions in which detrimental versus protective OPN activities have been documented. (B) The Yin and Yang effect of OPN may be the consequence of (1) its PTM including proteases cleavage (thrombin, proteasome and MMPs) with the formation of fragments/peptides with different functional capacities, as well as differential transcription site; (2) the presence of several functional sites interacting with distinct receptors (CD44 and integrin) which (3) can activate multiple intracellular signalling pathways (PI3K, MAPK, ERK, and JNK). Collectively this leads to the (4) recruitment and differentiation of cells with neuroprotective or neurotoxic activity (see panels C and D). (C) Microglia consists of resident macrophage-like immune cells in the central nervous system and plays a vital role in both physiological and pathological conditions. Under physiological conditions, most microglia remains in a resting state; on the contrary under pathologic conditions (such as trauma, ischemia, and infections), microglia is activated. Based on the OPN stimuli of microglia, OPN can shape either proinflammatory M1 or anti-inflammatory M2 phenotypes promoting detrimental or protective functions. (D) OPN participates in recruiting and activating stem cells, including MSC and neuronal stem cells, as well as both effector and regulatory T cells. AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; ERK: extracellular signal-regulated kinase; GBS: Guillain-Barré syndrome; GD: Gaucher's disease; JNK: c-Jun N-terminal kinase; LBD: Lewy body dementia; MAPK: mitogen-activated protein kinase; MMPs: metalloproteinases; MS: multiple sclerosis; MSCs: mesenchymal stem cells; NMO: neuromyelitis optica; OPN: osteopontin; PD: Parkinson's disease; PI3K: phosphoinositide 3-kinase; PTM: post-translational modifications; Treg: regulatory T cells.

Another key point is the role of the soluble form of OPN as a biomarker, which may be measured in several biological fluids to monitor and prognose several diseases. However, detection of high concentrations of OPN in different yet related diseases represents an important limitation to its use as a specific marker. There is a critical unmet need for translational and clinical investigations to verify the performance of OPN as injury or repair biomarker candidate in the clinical setting. We speculate that the role of OPN in CNS diseases may follow the Goldilocks principle; on one hand too little OPN might impede both the tissue injury and wound healing responses; on the other hand, too much OPN might lead to excessive tissue injury.

Most evidence supports OPN as a "Yin" damage biomarker since serum OPN levels are increased in several immune-related systemic disorders (rheumatoid arthritis, lupus, Sjögren's disease, colitis, liver diseases) (Rittling et al., 2015) and inflammatory diseases of the nervous system, mainly reported in MS (Agah et al., 2018), but also in neuromyelitis optica (Kariya et al., 2015) and Guillain-Barré syndrome (Han et al., 2014). Most prognostic evidence was obtained in MS. Otherwise, CSF OPN levels were associated with poor outcome in central nervous system lymphoma (Strehlow et al., 2016) and neurodegenerative disorders. Consistently, increased levels of CSF OPN have been found in mild cognitive impairment converting to AD (Carecchio and Comi, 2011).

In conclusion, currently available literature indicates that OPN may serve as a biomarker to monitor and predict the course of immune mediated diseases of the nervous system, including neurodegenerative diseases in which a relevant role for immune mediated mechanisms has been documented (Cappellano et al., 2013; Comi and Tondo, 2017). Regarding the possibility that OPN may also serve as a therapeutic target in such diseases, further knowledge is needed, since enhancing or decreasing of OPN activity may have distinct effects in different diseases or even different stages in the same disease.

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References

- Agah E, Zardoui A, Saghadzadeh A, Ahmadi M, Tafakhori A, Rezaei N (2018) Osteopontin (OPN) as a CSF and blood biomarker for multiple sclerosis: a systematic review and meta-analysis. *PLoS One* 13:e0190252.
- Ahn M, Lee Y, Moon C, Jin JK, Matsumoto Y, Koh CS, Kim HM, Shin T (2004) Upregulation of osteopontin in Schwann cells of the sciatic nerves of Lewis rats with experimental autoimmune neuritis. *Neurosci Lett* 372:137-141.
- Ailane S, Long P, Jenner P, Rose S (2013) Expression of integrin and CD44 receptors recognising osteopontin in the normal and LPS-lesioned rat substantia nigra. *Eur J Neurosci* 38:2468-2476.
- Anderson MA, O'Shea TM, Burda JE, Ao Y, Barlately SL, Bernstein AM, Kim JH, James ND, Rogers A, Kato B, Wollenberg AL, Kawaguchi R, Coppola G, Wang C, Deming TJ, He Z, Courtine G, Sofroniew MV (2018) Required growth facilitators propel axon regeneration across complete spinal cord injury. *Nature* 561:396-400.
- Begum-Haque S, Christy M, Wang Y, Kasper E, Ochoa-Reparaz J, Smith JY, Haque A, Kasper LH (2013) Glatiramer acetate biases dendritic cells towards an anti-inflammatory phenotype by modulating OPN, IL-17, and RORyt responses and by increasing IL-10 production in experimental allergic encephalomyelitis. *J Neuroimmunol* 254:117-124.
- Bellavista E, Santoro A, Galimberti D, Comi C, Luciani F, Mishto M (2014) Current understanding on the role of standard and immunoproteasomes in inflammatory/immunological pathways of multiple sclerosis. *Autoimmune Dis* 2014:739705.
- Boggio E, Dianzani C, Gigliotti CL, Soluri MF, Clemente N, Cappellano G, Toth E, Raineri D, Ferrara B, Comi C, Dianzani U, Chiochetti A (2016) Thrombin cleavage of osteopontin modulates its activities in human cells in vitro and mouse experimental autoimmune encephalomyelitis in vivo. *J Immunol Res* 2016:9345495.

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- Börnsen L, Khademi M, Olsson T, Sørensen PS, Sellebjerg F (2011) Osteopontin concentrations are increased in cerebrospinal fluid during attacks of multiple sclerosis. *Mult Scler* 17:32-42.
- Braitch M, Constantinescu C (2010) The Role of Osteopontin in Experimental Autoimmune Encephalomyelitis (EAE) and Multiple Sclerosis (MS). *Inflamm Allergy Drug Targets* 9:249-256.
- Broom L, Jenner P, Rose S (2015) Increased neurotrophic factor levels in ventral mesencephalic cultures do not explain the protective effect of osteopontin and the synthetic 15-mer RGD domain against MPP+ toxicity. *Exp Neurol* 263:1-7.
- Cantor H, Shinohara ML (2009) Regulation of T-helper-cell lineage development by osteopontin: the inside story. *Nat Rev Immunol* 9:137-141.
- Cappellano G, Orilieri E, Woldetsadik AD, Boggio E, Soluri MF, Comi C, Sblattero D, Chiochetti A, Dianzani U (2012) Anti-cytokine autoantibodies in autoimmune diseases. *Am J Clin Exp Immunol* 1:136-146.
- Cappellano G, Carecchio M, Fleetwood T, Magistrelli L, Cantello R, Dianzani U, Comi C (2013) Immunity and inflammation in neurodegenerative diseases. *Am J Neurodegener Dis* 2:89-107.
- Carecchio M, Comi C (2011) The role of osteopontin in neurodegenerative diseases. *J Alzheimer Dis* 25:179-185.
- Chabas D, Baranzini SE, Mitchell D, Bernard CC, Rittling SR, Denhardt DT, Sobel RA, Lock C, Karpuj M, Pedotti R, Heller R, Oksenberg JR, Steinman L (2001) The influence of the proinflammatory cytokine, osteopontin, on autoimmune demyelinating disease. *Science* 294:1731-1735.
- Chen W, Ma Q, Suzuki H, Hartman R, Tang J, Zhang JH (2011) Osteopontin reduced hypoxia-ischemia neonatal brain injury by suppression of apoptosis in a rat pup model. *Stroke* 42:764-769.
- Chiochetti A, Comi C, Indelicato M, Castelli L, Mesturini R, Bensi T, Mazarino MC, Giordano M, D'Alfonso S, Richiardi-Momigliano P, Liguori M, Zorzon M, Amoroso A, Trojano M, Monaco F, Leone M, Magnani C, Dianzani U (2005) Osteopontin gene haplotypes correlate with multiple sclerosis development and progression. *J Neuroimmunol* 163:172-178.
- Clemente N, Comi C, Raineri D, Cappellano G, Vecchio D, Orilieri E, Gigliotti CL, Boggio E, Dianzani C, Sorosina M, Martinelli-Boneschi F, Caldano M, Bertolotto A, Ambrogio L, Sblattero D, Cena T, Leone M, Dianzani U, Chiochetti (2017) A role of anti-osteopontin antibodies in multiple sclerosis and experimental autoimmune encephalomyelitis. *Front Immunol* 8:321.
- Clemente N, Raineri D, Cappellano G, Boggio E, Favero F, Soluri MF, Dianzani C, Comi C, Dianzani U, Chiochetti A (2016) Osteopontin bridging innate and adaptive immunity in autoimmune disease. *J Immunol Res* 2016:7675437.
- Comi C, Cappellano G, Chiochetti A, Orilieri E, Buttini S, Ghezzi L, Galimberti D, Guerini F, Barizzone N, Perla F, Leone M, D'Alfonso S, Caputo D, Scarpini E, Cantello R, Dianzani U (2012) The impact of osteopontin gene variations on multiple sclerosis development and progression. *Clin Dev Immunol* 2012:212893.
- Comi C, Carecchio M, Chiochetti A, Nicola S, Galimberti D, Fenoglio C, Cappellano G, Monaco F, Scarpini E, Dianzani U (2010) Osteopontin is increased in the cerebrospinal fluid of patients with Alzheimer's disease and its levels correlate with cognitive decline. *J Alzheimers Dis* 19:1143-1148.
- Comi C, Tondo G (2017) Insights into the protective role of immunity in neurodegenerative disease. *Neural Regen Res* 12:64-65.
- Dianzani C, Bellavista E, Liepe J, Verderio C, Martucci M, Santoro A, Chiochetti A, Gigliotti CL, Boggio E, Ferrara B, Riganti L, Keller C, Janek K, Niewianda A, Fenoglio C, Sorosina M, Cantello R, Kloetzel PM, Stumpf MP, Paul F, et al. (2017) Extracellular proteasome-osteopontin circuit regulates cell migration with implications in multiple sclerosis. *Sci Rep* 7:43718.
- Dianzani C, Vecchio D, Clemente N, Chiochetti A, Martinelli Boneschi F, Galimberti D, Dianzani U, Comi C, Mishto M, Liepe J (2019) Untangling extracellular proteasome-osteopontin circuit dynamics in multiple sclerosis. *Cells* 8:262.
- Ferret-Sena V, Maia ESA, Sena A (2016) Natalizumab treatment modulates peroxisome proliferator-activated receptors expression in women with multiple sclerosis. *PPAR Res* 2016:5716415.
- Goncalves DaSilva A, Liaw L, Yong VW (2010) Cleavage of osteopontin by matrix metalloproteinase-12 modulates experimental autoimmune encephalomyelitis disease in C57BL/6 mice. *Am J Pathol* 177:1448-1458.
- Gong L, Manaenko A, Fan R, Huang L, Enkhjargal B, McBride D, Ding Y, Tang J, Xiao X, Zhang JH (2018) Osteopontin attenuates inflammation via JAK2/STAT1 pathway in hyperglycemic rats after intracerebral hemorrhage. *Neuropharmacology* 138:160-169.
- Han RK, Cheng YF, Zhou SS, Guo H, He RD, Chi LJ, Zhang LM (2014) Increased circulating Th17 cell populations and elevated CSF osteopontin and IL-17 concentrations in patients with Guillain-Barré syndrome. *J Clin Immunol* 34:94-103.
- Heywood WE, Hallqvist J, Heslegrave AJ, Zetterberg H, Fenoglio C, Scarpini E, Rohrer JD, Galimberti D, Mills K (2018) CSF pro-orexin and amyloid-β38 expression in Alzheimer's disease and frontotemporal dementia. *Neurobiol Aging* 72:171-176.
- Hur EM, Youssef S, Haws ME, Zhang SY, Sobel RA, Steinman L (2007) Osteopontin induced relapse and progression of autoimmune brain disease through enhanced survival of activated T cells. *Nat Immunol* 8:74-83.
- Iaffaldano P, Ruggieri M, Viterbo RGE, Mastrapasqua M, Trojano M (2014) The improvement of cognitive functions is associated with a decrease of plasma Osteopontin levels in Natalizumab treated relapsing multiple sclerosis. *Brain Behav Immun* 35:176-181.
- Icer MA, Gezmen-Karadag M (2018) The multiple functions and mechanisms of osteopontin. *Clin Biochem* 59:17-24.
- Ito K, Kon S, Nakayama Y, Kurotaki D, Saito Y, Kanayama M, Kimura C, Diao H, Morimoto J, Matsui Y, Ueda T (2009) The differential amino acid requirement within osteopontin in alpha4 and alpha9 integrin-mediated cell binding and migration. *Matrix Biol* 28:11-19.
- Jakovac H, Grubic Kezele T, Šuurovic S, Mulac-Jerjevic B, Radošević-Stašić B (2017) Osteopontin-metallothionein I/II interactions in experimental autoimmune encephalomyelitis. *Neuroscience* 350:133-145.
- Kariya Y, Kariya Y, Saito T, Nishiyama S, Honda T, Tanaka K, Yoshida M, Fujihara K, Hashimoto Y (2015) Increased cerebrospinal fluid osteopontin levels and its involvement in macrophage infiltration in neuromyelitis optica. *BBA Clin* 3:126-134.
- Kivisäkk P, Healy BC, Francois K, Gandhi R, Gholipour T, Egorova S, Sevdalinova V, Quintana F, Chitnis T, Weiner HL, Khoury SJ (2014) Evaluation of circulating osteopontin levels in an unselected cohort of patients with multiple sclerosis: relevance for biomarker development. *Mult Scler* 20:438-444.
- Kurata M, Okura T, Kumon Y, Tagawa M, Watanabe H, Nakahara T, Tsuchihata M, Higaki J, Nose M (2012) Plasma thrombin-cleaved osteopontin elevation after carotid artery stenting in symptomatic ischemic stroke patients. *Hypertens Res* 35:207-212.
- Kustrimovic N, Comi C, Magistrelli L, Rasini E, Legnaro M, Bombelli R, Aleksic I, Blandini F, Minafra B, Riboldazzi G, Sturchio A, Mauri M, Bono G, Marino F, Cosentino M (2018) Parkinson's disease patients have a complex phenotypic and functional Th1 bias: cross-sectional studies of CD4+ Th1/Th2/T17 and Treg in drug-naïve and drug-treated patients. *J Neuroinflammation* 15:205.
- Ladwig A, Rogall R, Hucklenbroich J, Willuweit A, Schoeneck M, Langen KL, Fink GR, Rueger MA, Schroeter M (2018) Osteopontin attenuates secondary neurodegeneration in the thalamus after experimental stroke. *J Neuroimmune Pharmacol* 14:295-311.
- Ladwig A, Walter HL, Hucklenbroich J, Willuweit A, Langen KJ, Fink GR, Rueger MA, Schroeter M (2017) Osteopontin augments M2 microglia response and separates M1- and M2-polarized microglial activation in permanent focal cerebral ischemia. *Mediators Inflamm* 2017:7189421.
- Leavenworth JW, Verbinnen B, Yin J, Huang H, Cantor H (2015) A p85α-osteopontin axis couples the receptor ICOS to sustained Bcl-6 expression by follicular helper and regulatory T cells. *Nat Immunol* 16:96-106.
- Lee H, Jin YC, Kim SW, Kim ID, Lee HK, Lee JK (2018) Proangiogenic functions of an RGD-SLAY-containing osteopontin icosamer peptide in HUVECs and in the posts ischemic brain. *Exp Mol Med* 50:e430.

- Leung DT, Lim PL, Cheung TH, Wong RRY, Yim SF, Ng MHL, Tam FCH, Chung TKH, Wong YF (2016) Osteopontin fragments with intact thrombin-sensitive site circulate in cervical cancer patients. *PLoS One* 11:e0160412.
- Lochner P, Cantello R, Fassbender K, Lesmeister M, Nardone R, Siniscalchi A, Clemente N, Naldi A, Coppo L, Brigo F, Comi C (2017) Longitudinal assessment of transorbital sonography, visual acuity, and biomarkers for inflammation and axonal injury in optic neuritis. *Dis Markers* 2017:5434310.
- Lok ZSY, Lyle AN (2019) Osteopontin in vascular disease. *Arterioscler Thromb Vasc Biol* 39:613-622.
- Maetzler W, Berg D, Schalamberidze N, Melms A, Schott K, Mueller JC, Liaw L, Gasser T, Nitsch C (2007) Osteopontin is elevated in Parkinson's disease and its absence leads to reduced neurodegeneration in the MPTP model. *Neurobiol Dis* 25:473-482.
- Maetzler W, Michelis J, Tomiuk J, Melms A, Becker C, Gasser T, Schulte C, Berg D (2009) A single-nucleotide polymorphism of the osteopontin gene may contribute to a susceptibility to Lewy body disease. *J Neural Transm* 116:599-605.
- Mattsson N, Rüttschi U, Pijnenburg YA, Blankenstein MA, Podust VN, Li S, Fagerberg I, Rosengren L, Blennow K, Zetterberg H (2008) Novel cerebrospinal fluid biomarkers of axonal degeneration in frontotemporal dementia. *Mol Med Rep* 1:757-776.
- Meller R, Stevens SL, Minami M, Cameron JA, King S, Rosenzweig H, Doyle K, Lessov NS, Simon RP, Stenzel-Poore MP (2005) Neuroprotection by osteopontin in stroke. *J Cereb Blood Flow Metab* 25:217-225.
- Modvig S, Degn M, Roed H, Sørensen TL, Larsson HB, Langkilde AR, Frederiksen JL, Sellebjerg F (2015) Cerebrospinal fluid levels of chitinase 3-like 1 and neurofilament light chain predict multiple sclerosis development and disability after optic neuritis. *Mult Scler* 21:1761-1770.
- Morisaki Y, Niikura M, Watanabe M, Onishi K, Tanabe S, Moriwaki Y, Okuda T, Ohara S, Murayama S, Takao M, Uchida S, Yamanaka K, Misawa H (2016) Selective expression of osteopontin in ALS-resistant motor neurons is a critical determinant of late phase neurodegeneration mediated by matrix metalloproteinase-9. *Sci Rep* 6:27354.
- Mousavi S V, Agah E, Tafakhori A (2020) The role of osteopontin in amyotrophic lateral sclerosis: a systematic review. *Arch Neurosci* 7:e94205.
- Orihuela R, McPherson CA, Harry GJ (2016) Microglial M1/M2 polarization and metabolic states. *Br J Pharmacol* 173:649-665.
- Ozaki S, Kurata M, Kumon Y, Matsumoto S, Tagawa M, Watanabe H, Ohue S, Higaki J and Ohnishi T (2017) Plasma thrombin-cleaved osteopontin as a potential biomarker of acute atherothrombotic ischemic stroke. *Hypertens Res* 40:61-66.
- Pizzamiglio C, Ripellino P, Prandi P, Clemente N, Saggia C, Rossi V, Strigaro G, Bonda PLF, Comi C, Cantello R (2020) Nerve conduction, circulating osteopontin and taxane-induced neuropathy in breast cancer patients. *Neurophysiol Clin* 50:47-54.
- Prete A, Scutera S, Sozzani S, Musso, T (2019) Role of osteopontin in dendritic cell shaping of immune responses. *Cytokine Growth Factor Rev* 50:19-28.
- Rabenstein M, Vay SU, Flitsch LJ, Fink GR, Schroeter M, Rueger MA (2016) Osteopontin directly modulates cytokine expression of primary microglia and increases their survival. *J Neuroimmunol* 299:130-138.
- Rentsendorj A, Sheyn J, Fuchs DT, Daley D, Salumbides BC, Schubloom HE, Hart NJ, Li S, Hayden EY, Teplow DB, Black KL, Koronyo Y, Koronyo-Hamaoui M (2018) A novel role for osteopontin in macrophage-mediated amyloid- β clearance in Alzheimer's models. *Brain Behav Immun* 67:163-180.
- Rittling SR, Singh R (2015) Osteopontin in immune-mediated diseases. *J Dent Res* 94:1638-1645.
- Rogal R, Rabenstein M, Vay S, Bach A, Pikhovych A, Baermann J, Hoehn M, Couillard-Despres S, Fink GR, Schroeter M, Rueger MA (2018) Bioluminescence imaging visualizes osteopontin-induced neurogenesis and neuroblast migration in the mouse brain after stroke. *Stem Cell Res Ther* 9:182.
- Sainaghi PP, Bellan M, Lombino F, Alciato F, Carecchio M, Galimberti D, Fenoglio C, Scarpini E, Cantello R, Pirisi M, Comi C (2017) Growth arrest specific 6 concentration is increased in the cerebrospinal fluid of patients with Alzheimer's disease. *J Alzheimers Dis* 55:59-65.
- Selvaraju R, Bernasconi L, Losberger C, Graber P, Kadi L, Avellana-Adalid V, Picard-Riera N, Baron Van Evercooren A, Cirillo R, Kosco-Vilbois M, Feger G, Papoian R, Boschert U (2004) Osteopontin is upregulated during in vivo demyelination and remyelination and enhances myelin formation in vitro. *Mol Cell Neurosci* 25:707-721.
- Silva K, Hope-Lucas C, White T, Hairston TK, Rameau T, Brown A (2015) Cortical neurons are a prominent source of the proinflammatory cytokine osteopontin in HIV-associated neurocognitive disorders. *J Neurovirol* 21:174-185.
- Steinman L (1997) Some misconceptions about understanding autoimmunity through experiments with knockouts. *J Exp Med* 185:2039-2041.
- Steinman L, Youssef S, Van Venrooij N, Chabas D, Baranzini SE, Rittling S, Denhardt D, Sobel RA, Lock C, Pedotti R, Oksenberg JR (2003) Response to comment on "the influence of the proinflammatory cytokine, osteopontin, on autoimmune demyelinating disease". *Science* 299:1845.
- Strehlow F, Bauer S, Martus P, Weller M, Roth P, Schlegel U, Seidel S, Scheibenbogen C, Korfel A, Kreher S (2016) Osteopontin in cerebrospinal fluid as diagnostic biomarker for central nervous system lymphoma. *J Neurooncol* 129:165-171.
- Sun Y, Yin XS, Guo H, Han RK, He RD, Chi LJ (2013) Elevated osteopontin levels in mild cognitive impairment and Alzheimer's disease. *Mediators Inflamm* 2013:615745.
- Suzuki H, Hasegawa Y, Kanamaru K, Zhang JH (2010) Mechanisms of osteopontin-induced stabilization of blood-brain barrier disruption after subarachnoid hemorrhage in rats. *Stroke* 41:1783-1790.
- Szalardy L, Zadori D, Simu M, Bencsik K, Vecsei L, Klivenyi P (2013) Evaluating biomarkers of neuronal degeneration and neuroinflammation in CSF of patients with multiple sclerosis-osteopontin as a potential marker of clinical severity. *J Neurol Sci* 331:38-42.
- Tondo G, Perani D, Comi C (2019) TAM receptor pathways at the crossroads of neuroinflammation and neurodegeneration. *Dis Markers* 2019:2387614.
- Varghese AM, Sharma A, Mishra P, Vijayalakshmi K, Harsha HC, Sathyaprabha TN, Bharath SM, Nalini A, Alladi PA, Raju TR (2013) Chitotriosidase - a putative biomarker for sporadic amyotrophic lateral sclerosis. *Clin Proteomics* 10:19.
- Wang J, Huang J, Zhu M, Chen S, Chen C, Miao C, He H, Song Y (2019) Osteopontin potentiates PM-induced IL-1 α and IL-1 β production via the ERK/JNK signaling pathway. *Ecotoxicol Environ Saf* 171:467-474.
- Wang W, Li P, Li W, Jiang J, Cui Y, Li S, Wang Z (2017) Osteopontin activates mesenchymal stem cells to repair skin wound. *PLoS One* 12:e0185346.
- Wu J, Zhang Y, Yang P, Enkhjargal B, Manaenko A, Tang J, Pearce WJ, Hartman R, Obenaus A, Chen G, Zhang JH (2016) Recombinant osteopontin stabilizes smooth muscle cell phenotype via integrin receptor/integrin-linked kinase/Rac-1 pathway after subarachnoid hemorrhage in rats. *Stroke* 47:1319-1327.
- Xie Y, Li H, Sun L, Kusner LL, Wang S, Meng Y, Zhang X, Hong Y, Gao X, Li Y, Kaminski HJ (2017) The role of osteopontin and its gene on glucocorticoid response in myasthenia gravis. *Front Neurol* 8:230.
- Yan YP, Lang BT, Vemuganti R, Dempsey RJ (2009) Osteopontin is a mediator of the lateral migration of neuroblasts from the subventricular zone after focal cerebral ischemia. *Neurochem Int* 55:826-832.
- Zang W, Cui Y, Gao J, Li R, Jiang X, Tian Y, Wang K, Cui J (2018) Recombinant osteopontin improves neurological functional recovery and protects against apoptosis via PI3K/Akt/GSK-3 β pathway following intracerebral hemorrhage. *Med Sci Monit* 24:1588-1596.
- Zhao J, Jing J, Zhao W, Li W, Hou L, Zheng C, Kong Q, Li W, Yao X, Chang L, Li H, Mu L, Wang G, Wang J (2020) Osteopontin exacerbates the progression of experimental autoimmune myasthenia gravis by affecting the differentiation of T cell subsets. *Int Immunopharmacol* 82:106335.

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