Osteopontin: another piece in the systemic lupus erythematosus immunopathology puzzle

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ABSTRACT

Osteopontin (OPN) is a phosphoglycoprotein involved in bone remodelling, wound healing, cell adhesion, tissue remodelling, and immune response that is distributed widely in normal adult tissues. OPN biological activity is regulated by thrombin and matrix metalloproteinases (MMPs) cleavage, where the full-length (OPN-FL) protein and the cleaved OPN-N are associated with autoimmune diseases such as systemic lupus erythematosus (SLE). OPN overexpression has been associated with a predisposition to SLE and bad prognosis since OPN could mediate a sustained polyclonal B cell activation that besides to intracellular OPN (iOPN) form, promote the T follicular helper (T_{FH}) cells and enhance anti-nuclear antibody production. Currently, the role of OPN in lupus nephritis (LN) has been reported and extensively studied; however, no data are available about the potential mechanism of OPN in neuropsychiatric SLE (NPSLE). In this review, we highlighted the contribution of OPN and iOPN in LN and NPSLE immunopathology.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by systemic and local inflammation in multiple organs related to immune dysregulation by autoreactive T and B cells response, autoantibody production, immune complex deposition and, impaired clearance of apoptotic bodies (1). In SLE, imbalance of T-helper (T_H) cell cytokines production such as interferon-alpha (IFN-α) and the expression of IFN-inducible genes have been associated with the immunopathogenesis, determining as a "type I IFN signature" autoimmune disease (2, 3). The aetiology of SLE remains unclear and despite advances in SLE care, our knowledge of potential non-invasive markers or predictors of irreversible injury is still limited (4). Osteopontin (OPN) is a phosphorylated glycoprotein involved in bone homeostasis, wound healing, cell adhesion, angiogenesis, immune response, and tissue remodelling that have been implicated in the pathogenesis of SLE (4, 5). This protein is also known as secreted phosphoprotein 1 (SPP 1), bone sialoprotein 1 (BSP-1 or BNSP), 2ar, uropontin, *Rickettsia* resistance (Ric), and early T-lymphocyte activation-1 (Eta-1) (6). OPN is bound tightly to hydroxyapatite and has been found in osteoclasts indicating its role in anchoring the osteoblast to the bone surface (7). OPN is widely distributed in normal adult human tissues, being abundantly expressed by osteoclast and osteoblast in bone matrix and present in kidneys, epithelial cells of the gastrointestinal tract, gall bladder, pancreas, urinary and reproductive tracts, lungs, breast, salivary glands, sweat glands, inner ear, brain, decidua, placenta, arteries, human blood and body fluids such as urine and milk. Besides, OPN may also be produced by innate and adaptative immune cells and fibroblasts (8). Although OPN is involved in distinct physiological processes, also are associated with multiple pathologies including autoimmunity (9), chronic inflammation (6), muscle inflammation (10), kidney and bone diseases (11), cancer progression, metastasis and, poor prognosis factor (12) and it is considered a predictor marker of the cerebrovascular disease (13).

Osteopontin gene and protein structure

The OPN encoding gene *SPP1* (secreted phosphoprotein 1) is a member

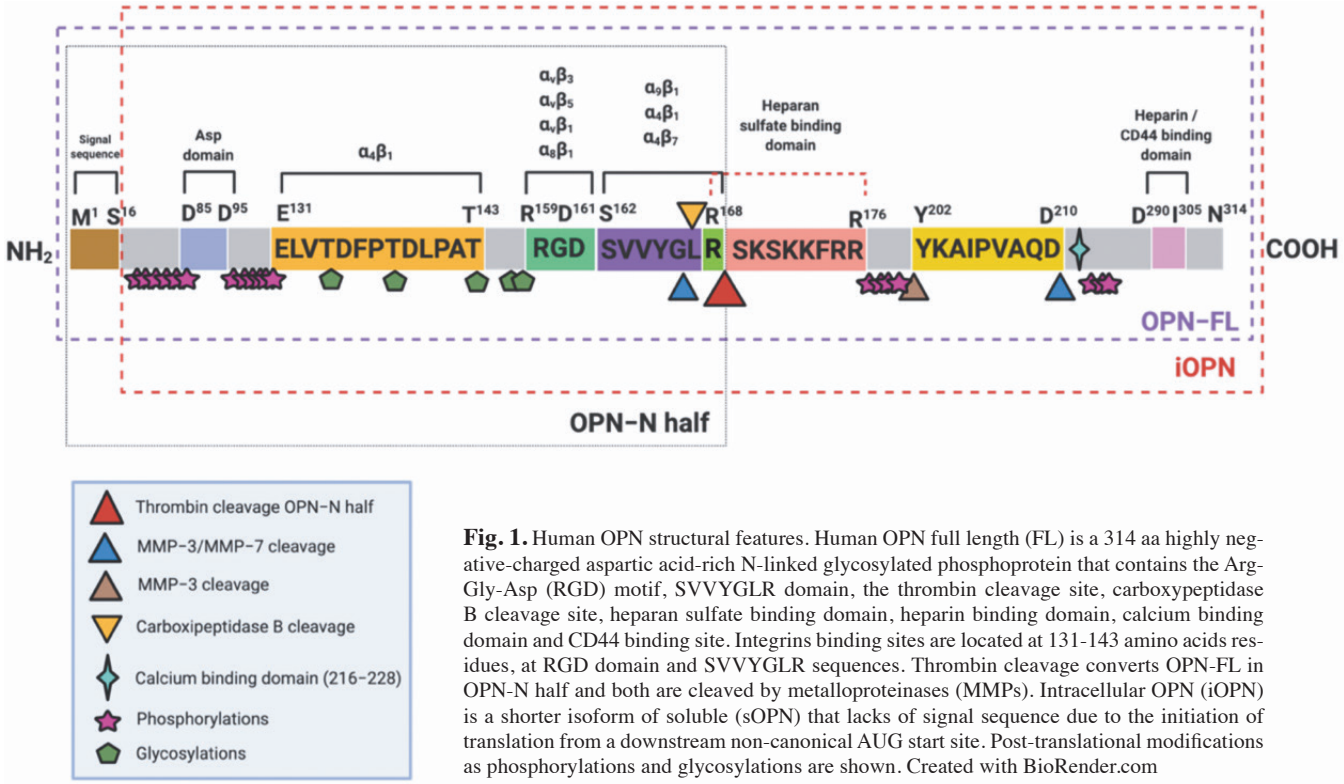

Fig. 1. Human OPN structural features. Human OPN full length (FL) is a 314 aa highly negative-charged aspartic acid-rich N-linked glycosylated phosphoprotein that contains the Arg-Gly-Asp (RGD) motif, SVVYGLR domain, the thrombin cleavage site, carboxypeptidase B cleavage site, heparan sulfate binding domain, heparin binding domain, calcium binding domain and CD44 binding site. Integrins binding sites are located at 131-143 amino acids residues, at RGD domain and SVVYGLR sequences. Thrombin cleavage converts OPN-FL in OPN-N half and both are cleaved by metalloproteinases (MMPs). Intracellular OPN (iOPN) is a shorter isoform of soluble (sOPN) that lacks of signal sequence due to the initiation of translation from a downstream non-canonical AUG start site. Post-translational modifications as phosphorylations and glycosylations are shown. Created with BioRender.com

of the SIBLING (Small Binding Ligand N-linked Glycoprotein) family of proteins. *SPP1* mapped on human chromosome 4q21-q25, spans approximately 11 kb, and consists of seven exons and six introns. The start codon is identified in exon 2 and the stop codon in exon 7. Nine hundred forty-two bases constitute the *SSP1* open reading frame (ORF); the 5' untranslated (5'-UTR) region includes exon 1 and the 3' UTR consists of 415 bases and comprises the last part of exon 7, including three polyadenylation signals (AATAA) (14). *SPP1* gives three different messenger RNA (mRNA) transcripts due to spliced isoforms: OPN-a, b and, c. OPN-a contains the coding information from all exons (314 aa, NCBI Accession NP_001035147.1), OPN-b lacks exon 5 that contains a cluster of phosphorylated Ser/Thr residues (aa 59-72 are missing from the sequence remaining 300 aa, NCBI Accession NP_000573.1) and OPN-c lacks exon 4 (aa 31-57 are missing from the sequence remaining 287 aa, NCBI Accession NP_001035149.1) unable to form polymeric complexes (15).

Human OPN is a highly negative-charged aspartic acid-rich N-linked glycosylated phosphoprotein of 314 aa with a predicted molecular weight that ranges from 41 to 75 kDa (16). OPN post-translational modification includes phosphorylation on Ser and Thr residues, O-linked glycosylation, sialylation, and Tyr sulfation (17). Proteolytic modifications in OPN by thrombin and matrix metalloproteinases (MMP)s cleavage sites reveal "cryptic" binding sites for integrins that regulate receptor recognition, adhesion and, migration (18). OPN-full length (FL) contains at least three functional cellular binding domains responsible for cell adhesion, spreading, and migration functions (18). One binding domain is the highly conserved Arg-Gly-Asp (RGD) motif located at ^{158}GRGDS^{162} residues that bind RGD-recognising integrins $\alpha_v\beta_3$, $\alpha_v\beta_1$, $\alpha_v\beta_5$, $\alpha_8\beta_1$, and confers cell properties such as adhesion, spreading, haptotaxis, cellular signalling and, endothelial regeneration (18) (Fig. 1).

The thrombin cleavage site is close to the RGD domain site (Arg^{168}-Ser^{169}) and converts the OPN-FL in OPN-R (also known as OPN-N) exposing an integrin-binding site and releasing a chemotactic C-terminal fragment (18, 19). An additional binding domain is identified at the Ser-Val-Val-Tyr-Glut-Leu-Arg (^{162}SVVYGLR^{168}) site that interacts with $\alpha_9\beta_1$ (20), $\alpha_4\beta_1$(21), and $\alpha_4\beta_7$ (22) expressed by neutrophils and lymphocytes (18). OPN biological activity also can be modulated by cleavage mediated by several MMPs including MMP1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, and MMP-25 (17, 23, 24). Besides, OPN is also the target of thrombin-activatable carboxypeptidase B (CBP), which removes the C-terminal Arg^{168} from OPN-R and converts it into OPN-Leu (OPN-L) inactivating the binding site for integrin $\alpha_9\beta_1$ (18, 19). OPN binds to multiple integrins that recognise the RGD-binding sequence, CD44, and also with extracellular matrix proteins such as fibronectin and collagen (25).

Some studies have been revealed an isotype of OPN that is not secreted and is retained in cells. Intracellular OPN (iOPN) was discovered in 1998 in an OPN knockout (KO) experiment by two different groups of researchers led by Denhardt (26) and Hogan (27). Afterward, Zohar and colleagues detected iOPN in calvarial rat cells (28) and Junaid *et al*. demonstrated the presence

of iOPN in human cells by confocal microscopy (29, 30). iOPN is a shorter isoform of soluble (sOPN) that lacks signal sequence due to the initiation of translation from a downstream non-canonical AUG start site (16). iOPN was found at perimembranous regions of cells and distributed in the cytoplasm (30), constituting an integral component of a CD44-ezrin/radixin/moesin attachment complex on the plasma membrane inner surface modulating cytoskeletal-related functions including cell motility, cell fusion, and survival (31).

OPN regulation of immune response

OPN is expressed in macrophages, dendritic cells (DC), plasmacytoid DC (pDC), natural killer (NK) cells and, eosinophils with pro and anti-inflammatory properties. In macrophages, OPN is induced by several inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin (IL) 1-β, interferon-gamma (IFN-γ) and, IL-6 (32, 33) and regulates the macrophage accumulation at sites of injury promoting T_{H1} cell-mediated immunity (34). In DC, OPN induces maturation through interaction with CD44 and α_v integrin and increasing the expression of costimulatory CD80/86 and MHC class II molecules (16, 35). In T cells, OPN was known as Eta-1 (early T lymphocyte activation gene 1) due to its role in the induction of cell-mediated immune responses through T cells regulation and its high expression in activated T cells while it was not expressed in naïve T-cells (23). Shinohara and colleagues demonstrate that T-bet (a T-box transcription factor) controls *SSP1* expression in T cells and promotes $CD4^+$ T helper (T_{H1}) cell lineage (36). OPN plays a pivotal role in developing, migration and, activation of NK cells (16, 37) and it has been demonstrated that OPN is expressed by functional human eosinophils acting as a chemoattractant for these cells *in vitro*, exerting a functional relevance in allergic airway inflammation (38).

Regarding iOPN, Shen *et al*. showed that $CD4^+$ T_H responses are iOPN dependent during differentiation for both follicular T cell (T_{FH}) and follicular regulatory (T_{FR}) cells. Such effect is related to T-cell COStimulator (ICOS) on T_{FH} and T_{FR} cells promoting the translocation of iOPN, allowing T_{FH}/T_{FR} initial commitment by acting as a scaffold to stabilise the binding between B cell lymphoma 6 protein (Bcl6), the Nucleosome Remodelling and Deacetylase (NuRD) complex and protection of the Bcl6/iOPN complex from proteasomal degradation (39). In summary, OPN can be found in a secreted (sOPN) and intracellular (iOPN) form, where sOPN is ubiquitously expressed exerting pleiotropic effects in proliferation, apoptosis, bone formation and, angiogenesis, whereas iOPN biological function is related to the regulation of cytoskeletal rearrangement and signal transduction pathways (30).

OPN implication in chronic inflammatory diseases

OPN is found overexpressed in chronic inflammatory diseases such as Crohn's disease (40), several types of cancer (41-43), autoimmune diseases (17), obesity (6) and, atherosclerosis (24) among others. OPN act as the pro-inflammatory molecule that recruits and modulates the function of macrophages and T cells in addition to enhancing T_{H1} cytokine expression (44). Some studies suggested that OPN may be considered a biomarker of chronic inflammatory diseases. In this regard, Genre and colleagues demonstrated that sOPN and angioipoietin-2 correlate with atherosclerosis in non-diabetic patients with ankylosing spondylitis (AS) (45) and Maniatis *et al*. observed that sOPN and osteoprotegerin are associated with coronary artery disease (CAD) (46).

OPN role in SLE immunopathology

Elevated sOPN levels were detected before and during relapses of several autoimmune diseases such as SLE, multiple sclerosis (MS), rheumatoid arthritis (RA), and AS (47), including their relevant experimental models (48). It has been documented that the detrimental activity of sOPN in autoimmune diseases is related to its ability to promote the secretion of IL-17 and IFN-γ in T cells and IL-6 in monocytes, in promoting lymphocyte adhesion and migration, inhibiting activation-induced cell death that is involved in the switching off the immune response and supporting T_{FH} differentiation (17). Some studies revealed that in SLE patients and autoimmune-prone lupus mice, OPN-FL and OPN-N correlate with autoimmune activity (49). In SLE patients, OPN enhances T_{H1} mediated inflammatory process by activating NK, T cells, macrophage migration, and producing proinflammatory cytokines such as IL-1 and TNF-α (2). In pediatric SLE patients, OPN can be used as a marker of poor outcomes during a 12-month follow-up, having the potential to predict increased cumulative disease activity and risk of organ damage (4). Alternatively, Wirestam and colleagues noted that sOPN correlates with disease activity in recent-onset SLE and with antiphospholipid syndrome, which could reflect global organ damage (3). Thus, OPN likely plays an important role in SLE pathogenesis.

Concerning OPN contribution to lupus immunopathology in murine models of lupus, there have been observed that in MRL/1 mice, sOPN was upregulated in T cells which caused chronic and sustained polyclonal B cell activation at the onset and in the course of the autoimmune pathology (50). In OPN expressing transgenic mice, the titres of IgM anti-double-stranded (anti-dsDNA) and single-stranded DNA (anti-ssDNA) were elevated, suggesting that OPN is essential in the propagation/differentiation of B cells and autoantibodies production (51). On the other hand, in lupus-prone female BWF1 (f-BWF1) mice, sOPN was secreted by follicular $CD153^+$ senescence-associated T cells in spontaneous germinal centers (GC) inhibiting apoptotic cell engulfment and leading to pathogenic antinuclear antibody production that could increase autoimmunity risk related to age (52).

About the role of iOPN in SLE pathology, it has been observed that this intracellular form support T_{FH} and T_{FR}-cell differentiation and survival of B cells through the p85a-iOPN axis mediated by (ICOS)-Bcl6 pathway; this mechanism could explain the effect of OPN on B-cell-associated diseases since the increased expression of iOPN would

enhance T_{FH}-cell numbers increasing B-cell differentiation and antibody production (53).

Genetic and environmental factors could trigger immunological abnormalities and predispose to the development of autoimmunity. OPN expression is influenced by *SSP1* single nucleotide polymorphisms (SNP) and the human *SPP1* gene contains 310 variations (42). OPN involvement in SLE pathogenesis was described in some reports where *SPP1* SNPs are associated with susceptibility and sOPN overexpression (Table I) (54-64).

To date, no Genome-Wide Association Study (GWAS) identified any *SPP1* polymorphism associated with autoimmune diseases; however, when GWAS has been enriched and complemented by genome-wide expression profiling, the genome-wide differential analysis identified inflammatory pathways associated with SLE when OPN is included (17).

The immunopathology implications of sOPN and iOPN in SLE suggest that these molecules could be the subject of further analysis to determine a biomarker of specific organ damage, such as kidneys and central nervous system (CNS), among others. In this review, we focus on the evidence in both humans and murine models of lupus regarding the contribution of sOPN and iOPN in autoimmune disturbances in lupus nephritis (LN) and neuropsychiatric SLE (NPSLE).

OPN in lupus nephritis

The LN is the most common cause of morbidity and mortality among SLE patients (65, 66). In LN, neutrophils contribute to the pathogenesis through the formation of neutrophil extracellular traps (NETs) originated by neutrophil death that release neutrophil antibacterial and immunostimulatory proteins as well as histones and chromatin fibrils. NETs are considered a normal host defense cell death (called NETosis), also are a source of nuclear antigens that in LN-SLE contributing antigen-specific autoantibody production (65).

In normal kidney tissue, OPN was initially identified in the distal tubular epithelium as stone matrix involved in urinary stone formation and detected later expressed in ascending limbs of the loop of Henle (67), in the proximal tubular epithelium (68), in collecting duct epithelium and in urine (67) modulating angiotensin II-induced inflammation, oxidative stress, and fibrosis (69). Nevertheless, the OPN up-regulation of mRNA and protein levels was associated with glomerular fibrosis and with macrophage accumulation, proteinuria and, low creatinine clearance (68-71). Thus, macrophage and haematopoietic cells including neutrophils (72) express OPN and could be essential contributors to LN pathogenesis.

In 1998, Wuthrich and colleagues observed in MRL-Fas^{lpr} (lymphoproliferation strain) mice with LN, a prominent expression of OPN in proximal tubules that correlates with diffuse macrophage infiltration in kidneys (71). Further, Miyazaki *et al*. demonstrate in functional analysis of the MRL/Mp-Fas$^{lpr/lpr}$ strain developing LN, that *Spp1* (mouse *Opn* gene) allele associate with the induction of immunoglobulin (Ig) G and cytokines such as TNF-α, IL-1β, and IFN-γ in macrophages and splenocytes, suggesting that *Spp1* polymorphic variants entail functional differences in antibody production and LN development (73). On the other hand, Triantafyllopoulou and colleagues showed in the LN mouse model induced by polycytidylic acid, proliferative nephritis mediated by infiltrating macrophages that express higher mRNA *OPN* levels, that could be associated with glomerular crescent formation, fibrosis and, glomerular sclerosis (74).

Studies in SLE patients refer to OPN as a crucial molecule related to LN immunopathology. Wong and colleagues evidenced an association of OPN with LN in SLE patients, where high OPN concentrations correlated positively with SLE Disease Activity Index (SLEDAI), sitting OPN as an important cytokine for renal derangement mediated for T_{H1} response (2). Spinelli *et al*. observed significantly higher OPN levels in urine and serum of SLE patients with active LN regardless of the phase of renal activity and noted a direct correlation between low complement levels and sOPN serum concentration in patients with LN (75). Recently, Kitagori and colleagues detected high urine sOPN-N levels in LN patients, where LN patients with overt proteinuria had higher sOPN-N concentrations (76). Indeed, they also found a correlation between urine sOPN-N and urine thrombin activity in LN (77). On the other hand, Quaglia and colleagues demonstrated that the renin-angiotensin system antagonists can decrease sOPN levels in SLE patients with LN (78), and Brunner *et al*. founded that sOPN in combination with adiponectin predict chronic LN damage (79).

Based on the cited evidence, sOPN and sOPN-N could be employed as useful urine biomarkers of chronic kidney damage in SLE (79, 80).

OPN in neuropsychiatric lupus

The SLE immunopathogenesis causes neuropsychiatric symptoms even in the absence of apparent CNS inflammation, which could be driven by the innate immune system independent of adaptive immunity (81). The NPSLE is classified as a focal and diffuse disease, where diffuse disease includes depression, anxiety, memory impairment, and general cognitive decline (82, 83). The American College of Rheumatology (ACR) established a standard nomenclature with case definitions for 19 neuropsychiatric conditions in SLE patients, of which 12 are related to CNS manifestations (81). The neuropsychiatric conditions are present in around 15 to 85% of SLE patients (84, 85), where some NPSLE patients present uncommon manifestations such as acute confusion, psychosis and, myelopathy in <5%, and around <1% present aseptic meningitis, movement disorders and, lupus demyelination (86). CNS symptoms of SLE have been recorded in extensive multi-center studies and have evidenced that the most common manifestations are cognitive impairment, mood disturbance and, headache (87). To date, the mechanisms that underlying NPSLE are largely unexplained, especially those involving cells of the innate and adaptive immune system and their products, such as sOPN and iOPN. Nonetheless, the available evidence in non-autoimmune neurodegenerative

Table I. *SPP1* SNP association studies with SLE.

Author/ year	Population	Subjects	*SPP1 SNP*	sOPN levels	Main findings	Ref
Forton *et al*., 2002	AC	81 SLE 79 C	707C/T (rs1126616)	–	CT and TT are associated with opportunistic infections (p=0.0598) and renal insufficiency (p=0.0431).	(54)
D´Alfonso *et al*., 2005	Italian	394 SLE 479 C	-1748A/G (rs2728127), -1282A/G, -616G/T (rs2853744), -443T/C, -156G/GG (rs7687316), -66T/G (rs2853744), IV3-42A/C, +282T/C ($Asp^{80}Asp$, rs4754), +351T/C ($Thr^{103}Thr$), +750C/T ($Ala^{236}Ala$, rs11226616), +1083A/G (rs1126772), +1158A/G, +1239A/C (rs9138)	SLE=5.32±0.55 ng/mL C=4.94±0.55 ng/mL	156G and +1239C were significantly -increased in SLE patients (p=0.006 and (p=0.00094, respectively) compared with C genotype. Significant association was seen between lymphadenopathy and -156G (p=0.0011). Increased OPN serum level in C carrying +1239C (p=0.002).	(55)
Xu *et al*., 2007	Han Chinese	18 M-SLE 140 W-SLE 180 C	9250C/T	–	TT genotype frequency was significantly lower in SLE than C (p<0.05), while TC genotype frequency was significantly higher in SLE than C (p<0.05). TT genotype frequency was lower in LN (p<0.05).	(56)
Han *et al*., 2008	USA	701 EA-SLE 434 AA-SLE 1309 EA-C 700 AA-C	-1748A/G (rs2728127), -616G/T (rs2853744), rs11730582, rs2853749, rs11728697, rs6840362, rs6811536, rs10516799, rs1126616, +1083A/G (rs1126772), +1239A/C (rs9138)	–	rs1126616T and rs9138C significantly associated with higher SLE risk in males (p=0.0005, OR=1.73, 95% CI=1.28–2.33). Significant gen-gender interactions in rs1126772 and rs9138 (p=0.001 and p=0.0006, respectively). rs1126616T-rs1126772A-rs9138C haplotype analysis demonstrated significant association with SLE in general (p=0.02, OR=1.30, 95% CI=1.08–1.57), especially in males (p=0.0003, OR=2.42, 95% CI=1.51–3.89).	(57)
Kim *et al*., 2009	Korean	39 SLE 104 C	9250C/T	SLE=49.13±26.71 ng/mL C=28.49±18.39 ng/mL	9250T genotype was frequent in SLE. sOPN in 39 SLE patients were significantly higher than in 20 C (p<0.05). Increased sOPN was associated with SLEDAI (r=0.337, p<0.05).	(58)
Kariuki *et al*., 2009	AA, EA, H	323 SLE 40 M-SLE 283 W-SLE (146 AA, 108 EA, 69 H) 141 C	rs10516800, rs11730582, rs28357094, rs2853749, rs11728697, rs6532040, +1083A/G (rs1126772), +1239A/C (rs9138), rs7655182	M-SLE=8.00±3.50 ng/mL, W-SLE=7.00±3.00 ng/mL C=3.00±1.50 ng/mL	rs9138C was associated with higher sOPN and IFN-α in men (p=0.001 and p=0.0006, respectively) and in women showed age-related genetic effect on both sOPN and IFN-α (p=0.0001). rs11730582 and rs28357094 were associated with anti-RNP antibodies (p=0.038, OR=2.9 and p=0.021, OR=3.9 respectively) in AA.	(59)
Trivedi *et al*., 2011	AA, EA, HA, ASA	252 SLE (145 AA, 67 EA, 23 HA, 11 ASA)	rs11730582, rs28357094, rs6532040, +1239A/C (rs9138)	–	rs9138C was associated with photosensitivity in SLE (p=1x10^{-3}, OR=3.2, 95% CI=1.6–6.5). rs11730582C was associated with thrombocytopenia (p=0.023, OR=2.1) and hemolytic anemia (p=0.036, OR=2.6)	(60)
Salimi *et al*., 2016	Iranian	163 SLE 180 C	707C/T (rs1126616)	SLE=50.6±22 ng/mL C=35.6±15.8 ng/mL	rs1126616 C/T was not associated with SLE susceptibility. TT genotype frequency was higher in LN. sOPN were significantly higher in SLE than C (p≤0.001).	(61)
Lee *et al*., 2016	Meta-analysis	1938 SLE 3037 C	707T/C (rs1126616), +1083G/A (rs1126772), +1239C/A (rs9138), 9250C/T	–	In this meta-analysis, no association was found between SLE and 707T/C and 1083G/A while a significant association was identified between 1239C in SLE (p=0.040, OR=1.192, 95% CI=1.008–1.410) and between 9250C and Asian SLE (p=2.5 x 10^{-7}, OR=2.070, 95% CI=1.570–2.73).	(62)
Pasha *et al*., 2019	Egyptian	80 SLE 80 C	707C/T (rs1126616)	SLE=38.97±5.2 ng/mL C=11.2±3.4 ng/mL	rs1126616 TT genotype and T allele were significantly in SLE than C (p=0.003 and p≤0.001, respectively). sOPN was significantly elevated in SLE with LN (p≤0.001), arthritis (p≤0.001), mucocutaneous (p=0.02) and haematological manifestations (p≤0.001).	(63)
Kaleta *et. al*., 2020	Polish	83 SLE 100 C	707 C/T (rs1126616)	–	rs1126616 CT and TT were frequent in SLE than C genotype (p=0.037).	(64)

SPP1: sialoprotein 1; SNP: single nucleotide polymorphism; sOPN: soluble osteopontin; SLE: systemic lupus erythematosus patients; C: controls; OPN: osteopontin; USA: United States of America; M-SLE: men with systemic lupus erythematosus; W-SLE: women with systemic lupus erythematosus; AC: American Caucasian; EA: European American; EA-SLE: European American with systemic lupus erythematosus; EA-C: European American Control; AA African American; AA-SLE: African American with Systemic Lupus Erythematosus; AA-C: African American Control; H: Hispanic; HA: Hispanic American; ASA: Asian American; LN: lupus nephritis; OR: odds ratio; CI: confidence interval; SLEDAI: SLE Disease Activity Index; IFN-α: interferon alpha; RNP: ribonucleoprotein.

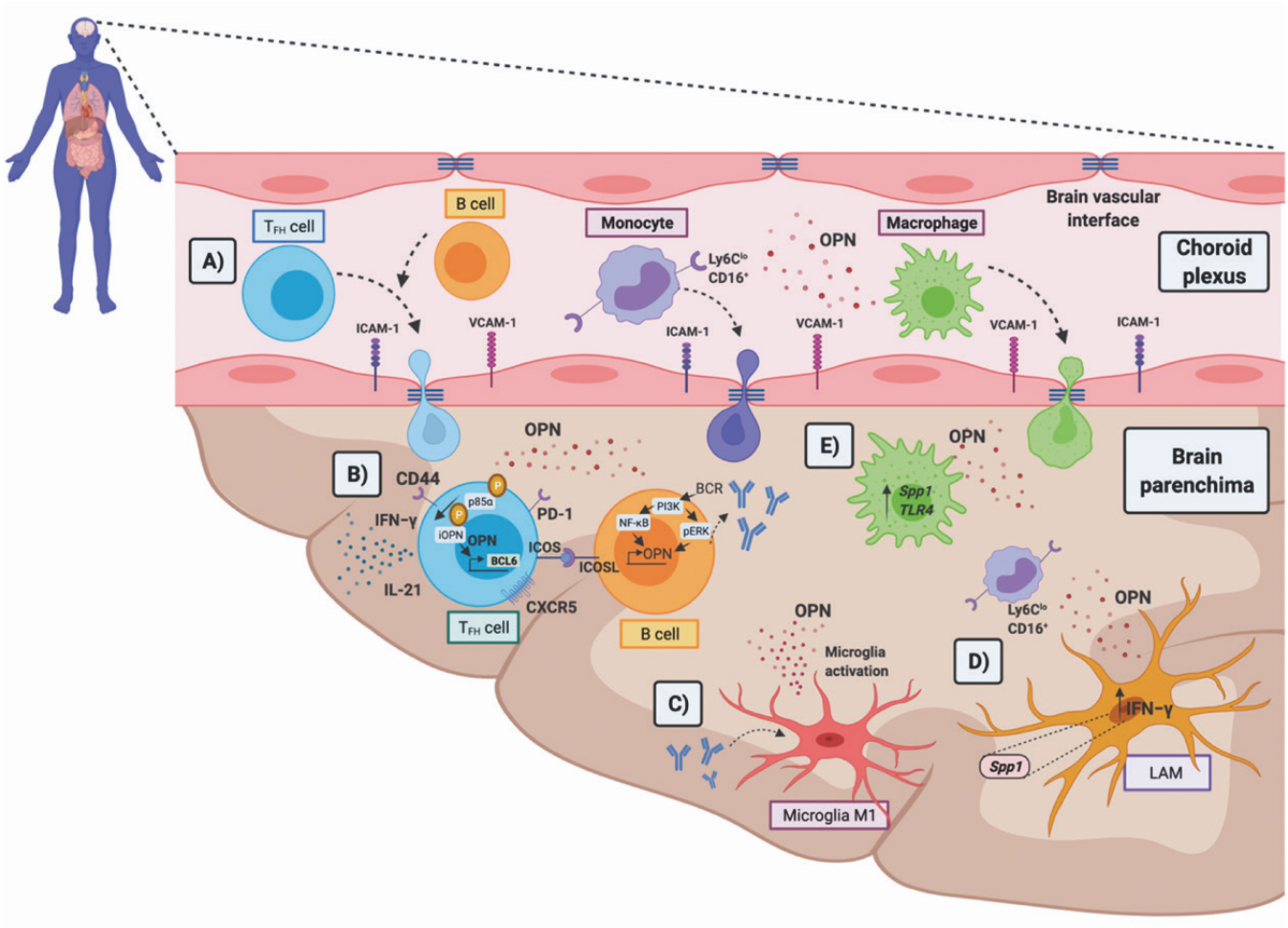

Fig. 2. Hypothesis on the contribution of OPN in NPSLE suggested by experimental findings.
A: Cellular infiltration into the central nervous system (CNS) is produced by the expression of adhesion molecules ICAM-1, VCAM-1 and OPN in both choroid plexus (CP) and periventricular endothelium and allow the pass of immune cells.
B: $CD4^+$ T cells activated as T_{FH} like phenotype infiltrates through the CP and express surface markers as ICOS, PD-1, CXCR5, Bcl-6, IL-21 and CD44 and interact with B cells to produce autoantibodies and IFN-γ. sOPN expressed by T_{FH} and B cells could modify the brain microenvironment activating microglia.
C: Autoantibodies production can induce M1 activation of brain microglia and induce sOPN secretion.
D: "Lupus-associated microglia" (LAM) are upregulated of IFN-γ responsive genes expression, where *Spp1* (mouse *OPN* gene) are differentially expressed in presence of $Ly6C^{lo}$ monocytes. E) In "NP-SLE" signature microglia *Spp1* and *Tlr4* are upregulated in macrophages. Created with BioRender.com.

diseases and murine models of brain disease suggests that OPN could participate in the neurodegenerative disturbances process.

OPN and iOPN have been associated with neuroinflammation and cognitive impairment in chronic viral infections. In this regard, it has been found that OPN is elevated within the brain in several neurogenerative disorders, including Human Immunodeficiency Virus (HIV)-associated cognitive disorder, where sOPN would aid macrophage survival. its brain accumulation and activate microglia (88, 89). Additionally, sOPN concentrations were found elevated in CNS after ischaemic and traumatic brain injuries, indicating that sOPN may contribute to neurodegenerative diseases (90, 91). To address the suggested role of OPN in NPSLE pathophysiology, we expose the main experimental findings in murine models of lupus-related to cognitive disturbances.

Blood-brain barrier permeabilisation

The CNS is considered an immune-privileged site regulated by the blood-brain barrier (BBB) that prevents the pass of immune cells and mediators from the circulation to the brain. Disruption of brain vascular integrity could increase the BBB permeability allowing the extravasation of immune cells and their products such as cytokines and autoantibodies (83, 92). It has been determined that the NPLSE disease requires several conditions such as the production of neurotoxic antibodies plus an insult to BBB integrity, mainly associated with infections (87). In NPLSE development, the cellular infiltration to the brain is through the choroid plexus (CP) and the periventricular endothelium by the expression of adhesion molecules ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) (92) and by OPN (expressed in the CP in EAE model and in the experimental vascular dementia related to BBB impairment) (91, 93) (Fig. 2A).

In the literature, only one study that analyses the possible involvement of

sOPN in NSPLE patients related to BBB impairment and was conducted by Kitagori and colleagues, where detected significantly higher sOPN-FL levels in the cerebrospinal fluid (CSF) of NPSLE patients in comparison to non-NPSLE patients. Furthermore, sOPN-FL concentrations in the CSF were correlated with IgG index and albumin quotient (method to evaluate the functional status of BBB and intrathecal IgG synthesis for the CNS), indicating that sOPN-FL could be employed as a potential marker for NPSLE (77). Nevertheless, there are many unknowns about the involvement of OPN in NPLSE that must be resolved with the support of experimental models of brain disease.

Innate and adaptive immune cells in the brain

The neuropsychiatric manifestations of NPSLE can be reproduced in experimental lupus models based on the fact that they exhibited behavioural changes such as depression-like behavior, anxiety-like behaviour, and cognitive dysfunction similar to NPLSE neuropathology (81, 94). In the MRL/MpJ-fas^{lpr} mice model, which exhibits a prominent neurobehavioral phenotype, it has been observed that the CD4$^+$ T cells activated as T_{FH} like phenotype, infiltrates through the CP to the brain under the transcriptional regulation of Bcl-6 and interact with B cells to produce autoantibodies and secrete significant levels of IFN-γ. These T_{FH} also express signature surface markers as ICOS, PD-1 (Programmed cell Death protein 1), C-X-C chemokine receptor type 5 (CXCR5), IL-21 and, CD44 and may produce large amounts of sOPN, hence it can be considered an important effector cells related to sOPN secretion in the brain (94, 95) (Fig 2B).

Microglial cells

sOPN is expressed by T_{FH} cells (96) and could be responsible for modifying the brain microenvironment through microglia stimuli. The microglia are resident macrophage-like immune cells in CNS which constitute 10-20% of glia cells that, under homeostatic conditions, perform continuous immune surveillance of the brain parenchyma and provide trophic support to the neurons (97, 98). In the presence of immune triggers, the microglia become activated and may change to the M1 pro-inflammatory or M2 anti-inflammatory phenotypes. (97, 99). If the microglia are activated to the M1 phenotype, produce pro-inflammatory cytokines and chemokines inside the brain parenchyma, becoming an essential interface mediating immune response in the neurodegeneration process (97, 100). An indication of the possible implication of the M1 microglia in NPLSE was observed by Yang *et al*., where demonstrate that the serum of SLE patients can modify the microglia phenotype to M1 in both *in vitro* and *in vivo* experiments, suggesting that IgG in lupus sera can induce M1 activation of brain microglia (97) (Fig 2C). Regarding OPN, it has been observed that is produced by microglia under stress conditions being an "oxidative stress-sensitive cytokine" that increases microglial survival, affects phagocytic activity and, modulates the neuron-inflammation (98). The possible involvement of OPN in the NPSLE pathogenesis can be studied in experimental lupus models where the participation of innate and adaptive immunity can be addressed together with the study of microglia and brain microenvironment.

In a study carried out by Nomura *et al*. in lupus-prone mice, the participation of CNS resident cells and cells of innate and adaptive immune was shown in the development of experimental neuropathology. An increased number of T cells and Ly6C^{lo} monocytes (mouse counterparts of human CD14$^+$ classical monocytes) were detected in the CNS tissue and exclusive primed status of microglia that exhibit a unique low-grade chronic inflammatory status termed "lupus-associated microglia" (LAM), characterised by the upregulation of neurodegeneration-related genes and IFN-responsive genes expression. *Spp1* as well *Ccl5* and *Cxcl10* were detected differentially expressed in LAM, which could show the participation of microglia in OPN expression (81) (Fig 2D).

Makinde and colleagues founded in SLE-prone mice CReCOM (Caspase-8 Removed CD11c-specific Overactive MyD88), a novel microglia-specific transcriptional "NPSLE signature" related to lipid metabolism, scavenger receptor activity and, downregulation of inflammatory and chemotaxis process. It is important to point out that these "NPSLE signature" microglia could be enriched with the gene profile expression of another subset of microglia termed disease-associated microglia (DAM) that, along with infiltrating macrophages, correlated with clinical severity of behavioral deficits in CReCOM SLE-prone mice. Through transcriptional profiles analysis, the "NPSLE" signature microglia showed genes related to positive regulation of macrophage activation, while immune effector process and response to IFN-γ including *Spp1* and *Tlr4* are upregulated in macrophages (101) (Fig 2E). Thus, sOPN and iOPN could modulate the microglia activity through interaction with infiltrating macrophages and allow T cell polarisation of incoming CNS-reactive T cell, promoting the survival of activated T cells that alter the expression of proapoptotic proteins (102), contributing to the pathogenesis of neurodegenerative autoimmune disorders (100, 103).

In summary, OPN is one key molecule involved in neuroinflammation that may reflect the ongoing inflammation process in CNS. Significantly elevated sOPN levels were detected in the plasma and CSF of neurodegenerative disorders and correlate with cognitive impairment (89, 104). For example, in Alzheimer's disease, in addition to high concentrations of OPN concentrations in CSF, an increased OPN expression in the pyramidal neurons of the CA1 region of the hippocampus was detected, which could exacerbate the abnormal immune response by enhancing the survival of activated T cells (105).

On the flip side, the detrimental role of OPN in the context of diverse neurological conditions such as NPSLE, could partly be related to the presence of different functional domains in OPN molecules (106). The cleavage of OPN by MMPs exposes the RGD/SVVYGLR sequences and generates an integrin-binding OPN fragment that could

stimulate the reactive microglia (107). Further studies are needed to elucidate the molecular mechanisms that underlie the microglial inflammatory responses related to sOPN, iOPN, and their excised forms in the context of neuropathological features of NPLSE.

Conclusions

OPN is a pleiotropic glycoprotein that plays an essential role in immune responses and inflammation. In this review, we highlighted the contribution of sOPN and iOPN in the context of organ-specific damage of SLE such as LN and NPLSE immunopathogenesis. Based on experimental findings and previously reported results, OPN may be proposed as a potential urine biomarker in SLE patients because it reflects chronic kidney damage. Regarding NPSLE, OPN can be involved in CNS detrimental effects by stimulating pro-inflammatory mediators, inhibiting the apoptosis of autoreactive immune cells and, modulating microglia reactivity during the neurodegenerative process. Nevertheless, further studies are needed to address a possible therapeutic approach that regulates the function of OPN in the neuropathogenesis of autoimmune diseases.

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