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# The role of phosphatidylserine recognition receptors in multiple biological functions

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## Abstract

Apoptotic cells are rapidly engulfed and degraded by phagocytes through efferocytosis. Efferocytosis is a highly regulated process. It is triggered upon the activation of caspase-dependent apoptosis, which in turn promotes the expression of “eat me” signals on the surface of dying cells and the release of soluble “find me” signals for the recruitment of phagocytes. To date, many “eat me” signals have been recognized, including phosphatidylserine (PS), intercellular adhesion molecule-3, carbohydrates (e.g., amino sugars, mannose) and calreticulin. Among them, PS is the most studied one. PS recognition receptors are different functionally active receptors expressed by phagocytes. Various PS recognition receptors with different structure, cell type expression, and ability to bind to PS have been recognized. Although PS recognition receptors do not fall into a single classification or family of proteins due to their structural differences, they all share the common ability to activate downstream signaling pathways leading to the production of anti-inflammatory mediators. In this review, available evidence regarding molecular mechanisms underlying PS recognition receptor-regulated clearance of apoptotic cells is discussed. In addition, some efferocytosis-independent biological functions of PS recognition receptors are reviewed.

**Keywords:** Apoptosis, Efferocytosis, Macrophage, Phosphatidylserine, Phosphatidylethanolamine, Receptor

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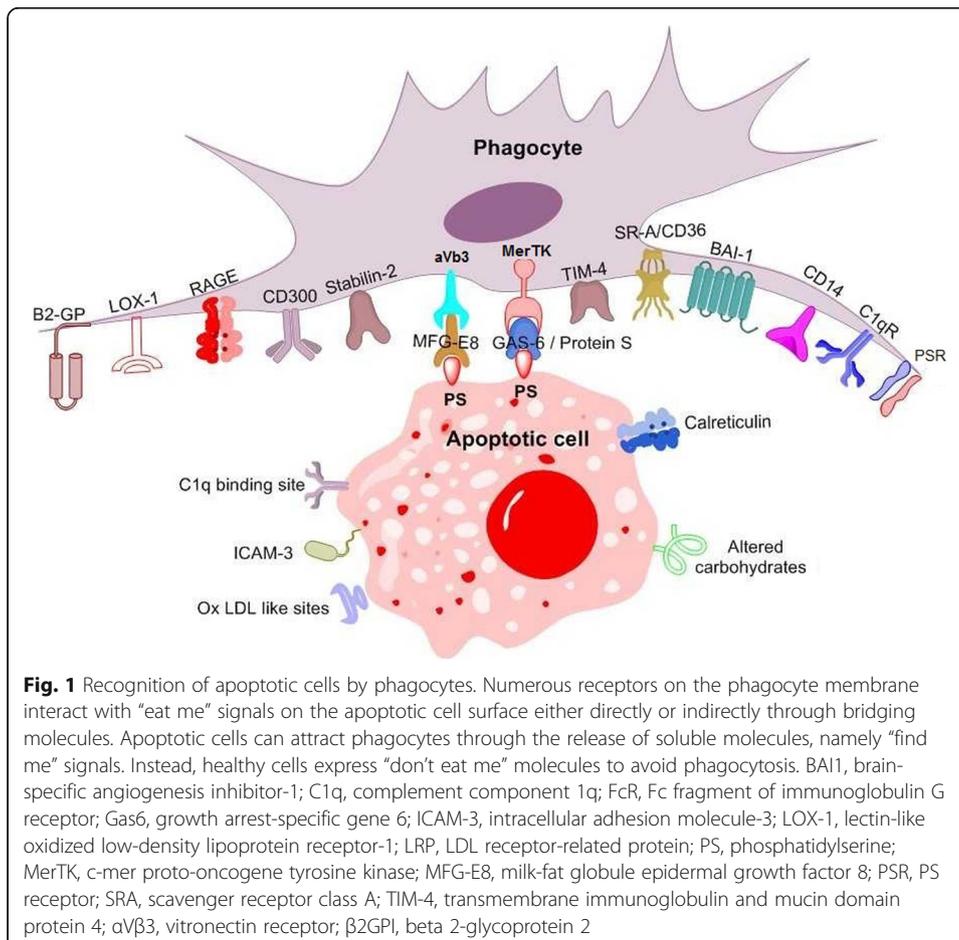
## Introduction

Efferocytosis is the clearance of apoptotic cells by either professional phagocytes, including macrophages and dendritic cells (DCs), or non-professional phagocytes, that is neighboring tissue cells (e.g., endothelial cells, epithelial cells, fibroblasts) acquiring a phagocyte-like phenotype [1–3]. At the earliest steps of cell death, soluble “find-me” signals attract phagocytes towards dying cells [4–7]. Subsequently, the exposure of phosphatidylserine (PS) on the apoptotic cell surface has a crucial role in facilitating specific recognition of dying cells by phagocytes [8] and triggering phagocytic cup formation [9]. PS, a negatively charged phospholipid normally confined to the inner



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plasma membrane leaflet by flippases, is externalized on the apoptotic cell surface by scramblases [6, 10–12]. Several molecules, including secreted soluble proteins [e.g., growth arrest-specific gene 6 (Gas6), protein S (ProS), and milk-fat globule epidermal growth factor 8 (MFG-E8)] and type I membrane proteins expressed on the phagocyte surface (e.g., CD300) may recognize PS. Ligation between PS on the apoptotic cell surface and PS recognition receptors is essential for phagocyte cup formation and engulfment [13]. In fact, the inhibition of either PS or PS recognition receptors has been reported to be sufficient to block apoptotic cell removal by phagocytes [14, 15]. Noteworthy, other molecules apart from PS have been recognized as “eat me” signals on the apoptotic cell surface [e.g., intercellular adhesion molecule-3 (ICAM-3), carbohydrates, and calreticulin] [16–20] (Fig. 1). However, whether their ligation with specific phagocyte receptors may further augment engulfment remains to be clarified [21]. In addition, a phospholipid other than PS [i.e., phosphatidylethanolamine (PE)] is asymmetrically expressed on the surface of apoptotic cells. However, its specific role in apoptosis has not been fully clarified. In this review, we will discuss the role of PS recognition receptors in efferocytosis. In addition, some efferocytosis-independent biological functions of PS recognition receptors will be reviewed.



### Exposure of PS: apoptotic and non-apoptotic role

Generally, exposure of PS on the membrane of apoptotic cells leads to cell removal by phagocytes through efferocytosis. In physiological conditions, as efferocytosis occurs efficiently and swiftly, it is hard to find free apoptotic corpses throughout body tissues, even when large numbers of cells undergo apoptosis. Such effective clearance of cells that are no longer desired or are functionally abnormal is crucial for the maintenance of tissue homeostasis and for the prevention of various diseases including cancer [22, 23], degenerative diseases of the central nervous system, atherosclerosis and autoimmune diseases [24–28]. Therefore, efferocytosis mediators may represent potential therapeutic targets for either the prevention or the treatment of these pathological conditions [29–31].

However, the binding between PS and the PS recognition receptor has a regulatory role also in different efferocytosis-independent biological processes [e.g., platelet activation [32], osteoblast-mediated mineralization [33], cell fusion [34], viral infections [35]]. Reportedly, PS exposure has a crucial role in axonal fusion, that is, the process in which a regrowing axon reconnects with its detached segment, leading to the structural and functional restoration of the injured neuron [36]. PS externalization, by facilitating cell-cell contact between myoblasts, seems to play a regulatory role in the early phases of myotube formation, that is, the fusion of an individual myoblast into multinucleated cells differentiating into myocytes [34]. PS is externalized by trophoblasts and mediates intertrophoblastic fusion during placental development [37]. Non-apoptotic macrophages are known to externalize PS and recognition of PS-expressing macrophages by CD36 triggers macrophage fusion, thereby mediating the formation of multinucleated giant cells [38, 39].

Moreover, PS exposure has a crucial role in different infections. The presence of PS on the surface of some enveloped and non-enveloped viruses (i.e., apoptotic mimicry) has been reported to promote viral infectivity by facilitating viral entry in host cells expressing PS recognition receptors and enhancing immune escape by infected cells [40–42]. In addition, during infections by different pathogens [e.g., human immunodeficiency virus (HIV), hepatitis C virus (HCV), *Plasmodium*, *Leishmania* or *Mycobacterium leprae*], anti-phospholipid antibodies, including anti-PS, are detectable in the serum of a high percentage of patients [43, 44]. In the case of *Plasmodium* infection, the binding between anti-PS antibodies and infected PS-exposing erythrocytes has been suggested to have a crucial role in the removal of intracellular pathogens. Indeed, although infected PS-exposing erythrocytes express high levels of CD47, a “do-not-eat-me” signal [45], their interaction with anti-PS antibodies mediates their phagocytosis and exerts a protective effect against *Plasmodium* [44]. Furthermore, the binding of soluble PS released by tumor cells to the PS receptor (PSR) has been shown to result in the production of anti-inflammatory mediators that block antitumor immune responses [e.g., tumor growth factor (TGF)- $\beta$ , interleukin (IL)-10 and prostaglandin E2 (PGE2)] [46].

Several members of the galectin family induce the exposure of PS on the surface of inflammatory cells. However, Gal-1- and Gal-3-induced externalization of PS promote differential responses in T cells and neutrophils. Gal-3, but not Gal-1, induces both PS exposure and apoptosis in primary activated human T cells, whereas both Gal-1 and Gal-3 induce PS exposure but not cell death in neutrophils. Noteworthy, although in some conditions galectin-induced PS exposure does not occur in cells undergoing apoptosis, it can induce cell paraparesis, that is, sensitization to phagocytic clearance

[47]. Indeed, in some circumstances galectin-induced PS exposure is independent of evident alterations in mitochondrial potential, caspase activation, membrane morphology or cell death typically seen in apoptotic cells [47]. Also, it may be fully reverted after galectin removal without determining any subsequent alteration in cell viability [47]. Such phagocytic removal of living cells promoted by Gal-1 and Gal-3-induced PS externalization represents a peculiar model of cellular turnover and regulation of various cellular processes, including cellular trafficking and immunological synapse formation [48, 49].

### **PS recognition receptors**

#### ***Biological functions of PS recognition by TAM family members/ProS/Gas6***

Axl (also known as UFO), Tyro3 and Mer are members of a subfamily of receptor tyrosine kinases (RTKs) named TAM (from the first letters of Tyro3, Axl, and Mer) [50]. They were identified as PS recognition receptors by using anti-PS antibodies to screen the human cDNA expression library from B lymphoblastoid lgT11 [51], and by polymerase chain reaction (PCR) amplification using degenerate oligonucleotides [52]. Axl, Tyro3 and Mer bind to the carboxy terminal domains of their ligands (i.e., ProS and Gas6) [53], which in turn bind to PS through their amino terminal domains [54–56], thereby acting as ‘bridges’ between PS on apoptotic cells and TAM receptors on phagocytes [57]. Noteworthy, ProS has no affinity for Axl [58], while Gas6 binding to Axl occurs with a higher affinity as compared to Gas binding to Mer and Tyro3 [59]. Upon ligation with either ProS or Gas6, the dimerization of TAM receptors occurs, leading to the phosphorylation of tyrosine residues in their cytoplasmic region [60] and to the activation of different downstream signaling pathways.

TAM receptors may be variably expressed in different tissues and cell types. Tyro3 is expressed in prostate, cerebral cortex and olfactory bulb. Axl is expressed in lipopolysaccharide-treated macrophages, osteoblasts, uterus and ovary. Mer is expressed in resident peritoneal macrophages, lung, small intestine and retinal pigment epithelial cells [13].

Under physiological conditions, TAM receptors are involved in either efferocytosis-dependent or efferocytosis-independent biological processes, including the regulation of inflammatory cytokine release, cell proliferation/survival, cell adhesion and migration, platelet activation and thrombus formation [61, 62].

Several studies have recognized the oncogenic role of the abnormal expression of TAM receptors in a wide variety of tumors [63, 64]. On the one hand, excessive TAM receptor activation may promote tumor immune escape through the induction of an immunosuppressive response in the tumor microenvironment [65–67]. On the other hand, TAM receptor activation may stimulate tumor cell proliferation and survival by increasing the production and release of TGF- $\beta$  [68]. Therefore, therapeutic inhibition of TAM receptors may represent a potential strategy to inhibit tumor progression [69, 70].

Moreover, TAM receptors have been reported to have a crucial role in the regulation of immune response in different pathological conditions. Accordingly, the inhibition of TAM receptor-activated intracellular signaling pathways has been suggested to have a therapeutic role in the treatment of sepsis and post-transplantation organ rejection [71]. By contrast, sustained TAM receptor inhibition has been associated with the

pathogenesis of various autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis [66, 72–74].

Finally, a variable association has been described between TAM receptor activation and atherosclerosis progression. Accordingly, defective Mer function has been reported to induce the accumulation of apoptotic foam cells and the formation of necrotic cores within atherosclerotic plaques [75–77], whereas Gas6 binding to TAM receptors has been shown to promote atherogenesis by increasing endothelial activation, monocyte chemotaxis and vascular smooth muscle cell (VSMC) differentiation into foam cells [78, 79].

### ***Biological functions of PS recognition by TIM family members***

Members of the transmembrane immunoglobulin and mucin domain (TIM) family are a group of proteins (i.e., TIM-1, TIM-2, TIM-3, TIM-4) which are variably expressed on the inflammatory cell surface and have a crucial role in the regulation of immune responses. The TIM family consists of three members in humans and four members in mice [80]. Among them, TIM-1 and TIM-4 act as PS recognition receptors, whereas TIM-2 and TIM-3 do not have noticeable PS-binding activity [81].

TIM-1, also known as kidney injury molecule-1 (KIM-1), is a type 1 membrane receptor [82]. It is a proximal tubular cell (PTC) surface protein which is expressed in a wide range of kidney diseases. Upon PS recognition [83] it mediates the conversion of tubular epithelial cells into non-professional phagocytes [84], thereby promoting efferocytosis of apoptotic cells and exerting a protective effect against acute kidney injury [85–90]. However, KIM-1 binding to PS exerts nephroprotective action also through efferocytosis-independent mechanisms, that is, the limitation of renal epithelial cell damage through the inhibition of  $G\alpha_{12}$  [91] or the promotion of tubular epithelium repair through activation of the extracellular signal-regulated kinase (ERK)/mitogen-activated protein (MAP) kinase (MAPK) signaling pathway [92].

Moreover, KIM-1 also plays an immunoregulatory role by controlling Th2, Th1, and Th17 cell differentiation [93] and the activation of B cells, DCs, and natural killer (NK) cells [94]. Specifically, KIM-1-mediated efferocytosis induces a pro-tolerogenic immune response, leading to the inhibition of CD4 T-cell proliferation and to the activation of regulatory T cells [95].

TIM-4 is expressed in a variety of resident macrophages, including peritoneal macrophages, hepatic Kupffer cells, skin CD169+ macrophages [59, 96] and CD4+ tangible body macrophages at Peyer patches of the small intestine [97]. It binds to PS via the IgG domain. TIM-4 itself is not able to mediate efferocytosis [98] and requires TAM receptors [59]. Accordingly, macrophages expressing both TIM-4 and TAM receptors (e.g., skin macrophages, resident peritoneal macrophages and Kupffer cells) [59] engulf apoptotic cells in two steps, that is, tethering and tickling [99]. In the tethering step, TIM-4 firmly binds to PS and recruits apoptotic cells to the macrophage surface. In the tickling step, soluble “bridge” proteins (e.g., ProS, Gas6 and MFG-E8) bind to PS on the apoptotic cell surface and to PS recognition receptors on phagocytes, thereby promoting phagocytic cup formation and engulfment. In different tumors TIM-4 has been described as an oncogenic driver which promotes tumor cell proliferation and facilitates immune escape by tumor cells through the induction of an immunosuppressive response in the tumor microenvironment [100–102].

### ***Biological functions of other PS recognition receptors***

Many other cell surface molecules have been shown to recognize PS, including brain-specific angiogenesis inhibitor 1 (BAI1), lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), stabilin-1 and stabilin-2, CD300a, CD300b, CD300f, receptor for advanced glycosylation end products (RAGE), complement component 1q (C1q),  $\beta$ 2-glycoprotein I ( $\beta$ 2GPI), annexins, integrins  $\alpha$ V $\beta$ 3/ $\beta$ 5, and PSR [103]. Some of these PS recognition receptors have signaling ability, while others mainly act as tethering and adhesion molecules. Their role in multiple biological functions will be discussed in the following section.

### ***Biological functions of PS recognition by annexins, $\beta$ 2GPI and C1q***

All annexin family molecules, except for one, act as bridging molecules between PS on the apoptotic cell surface and PS recognition receptors on the phagocyte surface [104].

$\beta$ 2GPI, a well-known phospholipid-binding molecule [105, 106], is expressed by hepatocytes, endothelial cells and placental villous tissues [107]. It can bind to PS-exposing targets and help their interaction with macrophages through the generation of a specific bridging moiety [108].

C1q is the first component of the complement cascade pathway, which is part of the innate immune system. Unlike most complement proteins, which are produced by hepatocytes, C1q is mainly produced by macrophages [109]. C1q binding to PS mediates opsonization and phagocytosis of apoptotic cell debris and other PS-exposing targets, playing a crucial role in regulation of the immune response [110–114]. In addition, C1q has been shown to slow atherosclerosis progression by promoting macrophage survival and foam cell efferocytotic capacity in the early phases of atherosclerosis [115, 116].

### ***Biological functions of PS recognition by receptors of CD300 family***

Receptors of the CD300 family are type I transmembrane proteins that contain a single IgV-like extracellular domain with two disulfide bonds and intracellular immunoreceptor tyrosine-based inhibition motifs (ITIMs) [117]. Among the seven members of this family, only three CD300 molecules (i.e., CD300a, CD300b, and CD300f) have the ability to recognize PS exposed on the outer leaflet of activated cell membranes [118–120].

CD300a is expressed by myeloid cells [121], lymphoid cells, monocytes, macrophages, mast cells, granulocytes, DCs, NK cells and subsets of B and T cells [121]. Importantly, CD300a does not seem to be involved in efferocytosis. Its main function is the transduction of an inhibitory signal in mast cells leading to the reduced production of pro-inflammatory mediators [121].

CD300f is commonly expressed by myeloid cell lineages and increases myeloid cell efferocytotic ability [122]. In addition, it exerts an immunoregulatory function by inhibiting DC-mediated antigen-specific T-cell responses [123].

Both CD300a and CD300c may promote viral infections either by facilitating the binding between PS-containing viral particles and host cells or by easing viral escape mechanisms [124]. Noteworthy, these receptors have demonstrated great potential as therapeutic targets in the treatment of different diseases, including cancer, infectious diseases, allergies and other pathological conditions [118].

***Biological functions of PS recognition by BAI1, LOX-1 and stabilin1/2***

BAI1 is a transmembrane protein and a member of the adhesion-type G-protein-coupled receptor family with the ability of binding to PS via thrombospondin type 1 repeats. BAI1 is expressed in macrophages, myoblasts, glial and neuronal cells. It promotes the engulfment of apoptotic cells by forming a complex with engulfment and cell motility (ELMO)/dedicator of cytokinesis 1 (Dock180)/Rac and participating in the uptake process via actin cytoskeleton remodeling [125, 126]. In addition, under physiological conditions BAI1 promotes mammalian myogenesis by facilitating the myoblast fusion process [127].

LOX-1 is a type II membrane protein with a C-type lectin-like domain. It shows the ability to bind to various ligands, including modified lipoproteins [e.g., oxidized low-density lipoproteins (oxLDLs), acetylated low-density lipoproteins (acLDLs)], negatively charged phospholipids [e.g., PS and phosphatidylinositol (PI)] [128] and other ligands expressed by apoptotic cells, activated platelets and bacteria [129]. LOX-1 promotes efferocytosis by mediating the recognition of PS-containing apoptotic bodies [11, 130]. Importantly, LOX-1 also acts as a scavenger receptor mediating the uptake of oxLDLs by macrophages in atherosclerotic plaques [131, 132]. Accordingly, soluble LOX-1 (sLOX-1) has been suggested as a biomarker of cardiovascular risk and LOX-1 receptor blockade has been proposed as a potential therapeutic target for reduction of cardiovascular damage in systemic lupus erythematosus [132].

Stabilin-1 and stabilin-2 are multifunctional receptors, which share structural similarities but have significant functional differences. Structurally, stabilin-1 is a type-1 transmembrane receptor with a short cytoplasmic tail [133] and a scarce ligand repertoire. It is expressed in macrophages and in non-continuous sinusoidal endothelial cells of liver [134], spleen, lymph nodes and adrenal cortex [135–137]. The involvement of stabilin-1 in direct cell-cell communications appears to be crucial for cell migration [133], tissue homeostasis [138], and tumor development [139]. Stabilin-1-expressing macrophages have a pivotal role in maintaining tissue homeostasis and protecting against organ fibrosis in chronic liver injury [140]. In addition, stabilin-1 expression on macrophages contributes to the induction of an immunosuppressive profile in normal pregnancy of humans and to the maintenance of vascular integrity through the clearance of infected apoptotic endothelial cells in sepsis [141–143]. Finally, a stabilin-1-mediated pro-atherogenic effect has been suggested, as stabilin-1-expressing circulating monocytes of patients with familial hypercholesterolemia (FH) have shown increased CD36-mediated uptake of oxLDL [133]. Stabilin-2 is highly expressed in non-continuous sinusoidal endothelium of spleen, liver [134], lymph nodes and bone marrow [144] but shows restricted expression on a few macrophages including alveolar macrophages [138], and human monocyte-derived macrophages (HMDMs) [145]. Unlike stabilin-1, stabilin-2 seems to be a proper clearance receptor for hyaluronic acid (HA) on sinusoidal endothelial cells in the liver and a scavenger receptor for modified unwanted-self products [133, 135, 146]. Given the inhibitory action of HA in tumor cell metastasis, stabilin-2 inhibition, leading to elevated circulating HA levels, has been suggested as a potential antitumor strategy [147].

### ***Biological functions of PS recognition by MFG-E8***

MFG-E8 is a secreted glycoprotein which shows structural similarity to the coagulation factors V and VIII. Its second EGF-like domain consists of an RGD motif with the ability to bind to integrin  $\alpha V\beta 3/5$  in phagocytes [148]. MFG-E8 is broadly expressed in different organs and tissues (e.g., spleen, liver, lungs, kidneys, intestine, and mammary glands) by macrophages, DCs, fibroblasts, epithelial cells and osteoclasts [149, 150]. Integrin-binding activity is essential for a wide variety of MFG-E8-mediated efferocytosis-dependent/independent biological functions [151]. MFG-E8 inhibits neutrophil migration through  $\alpha V\beta 3$ -integrin-mediated MAP kinase activation [152]. MFG-E8 also promotes macrophage M2 polarization in the tumor microenvironment, thereby promoting local immune suppression and facilitating tumor progression and metastasis [153, 154]. Consistent with MFG-E8-mediated anti-inflammatory activity, reduced MFG-E8 levels have been associated with an increased incidence of microvascular complications in patients with type 2 diabetes [155]. A variable association between MFG-E8 expression levels and autoimmune diseases has been described [156]. Accordingly, MFG-E8 is considered as a protective factor in the pathogenesis of rheumatoid arthritis [157], while high serum MFG-E8 levels or abnormally highly glycosylated serum MFG-E8 levels have been reported in some systemic lupus erythematosus patients [156, 158]. Septic shock is promoted by reduced serum levels of MFG-E8, resulting in defective efferocytosis [159]. Further, MFG-E8 deficiency in macrophages has been associated with reduced phagocytic clearance of apoptotic cells within atherosclerotic plaques, promoting atherosclerosis progression [160]. Accordingly, a genome-wide association meta-analysis showed that *MFG-E8* as a contributory gene of coronary artery disease [161]. Finally, the ability of some enveloped viruses to infect integrin- and TAM receptor-presenting cells has been reported to be facilitated through the surface expression of MFG-E8 and Gas6 [162].

### ***Biological functions of PS recognition by PSR***

Using an established monoclonal antibody (i.e., mAb 217) binding both human and mouse macrophages and inhibiting the engulfment of apoptotic cells, the identification of a PS-binding membrane protein, that is, PSR, was prompted [163]. PSR, also named Jumonji domain-containing protein 6 (JMJD6), is a type II membrane protein expressed on macrophages, epithelial cells and fibroblasts [163]. Unlike other PS recognition receptors, PSR shows a low phospholipid-binding affinity and specificity for PS [164]. PSR-mediated phagocytosis has a crucial role in the maintenance of tissue homeostasis [165] and in regulation of the immune response [166]. PSR regulates the recognition and internalization of apoptotic photoreceptors and the conservation of retinal tissue architecture after retinal detachment [167]. Moreover, in central retinal vein occlusion (CRVO) red blood cell adhesion is facilitated by the interaction between PS RBC and endothelial PS receptor [168]. The clearance of PS-exposing particles present in the vascular wall, which is mediated by PSR, is important for the prevention of inflammation associated with necrosis, calcification and also elimination of thrombogenic factors. However, some studies revealed that PSR is also crucial for tissue remodeling and differentiation of various organs during embryogenesis through efferocytosis-independent molecular pathways

[169–171]. In fact, homomultimers of PSR may function as scaffolding nuclear proteins with histone arginine demethylase activity regulating gene expression [172–178]. The upregulation of PSR has been described as an oncogenic driver in some tumor types [175, 176, 179, 180].

#### ***Biological functions of PS recognition by RAGE***

RAGE is a transmembrane receptor of the immunoglobulin superfamily which binds to advanced glycation end products (AGEs) [181, 182]. RAGE activation has a crucial role in the pathogenesis of diabetic vascular complications [183–185], diabetic dyslipidemia [186] and diabetic nephropathy [187, 188]. In fact, AGE/RAGE signaling stimulates the production of reactive oxygen species (ROS) and inflammatory markers [189, 190]. In addition, the ligation of RAGE is one of the major means by which AGEs may impair cholesterol efflux and reverse cholesterol transport (RCT). Accordingly, RAGE binding to AGEs has been shown to suppress ATP-binding cassette sub-family G member 1 (ABCG1) and ATP-binding cassette transporter A1 (ABCA1) expression by macrophages. Also, RAGE activation has been associated with reduced circulating HDL levels in diabetic mice [186]. Accordingly, the regulation of AGE/RAGE signaling by miRNAs has been investigated as a therapeutic strategy against diabetes complications [191].

However, as a multiligand receptor, RAGE can also bind to PS and exert, like other PS recognition receptors, both efferocytosis-dependent and efferocytosis-independent biological functions. Accordingly, RAGE has been reported to modulate alveolar macrophage phagocytosis [192] and its dysfunction has been implicated in the abnormal remodeling of alveolar epithelium occurring in the pathogenesis of lung fibrosis [193]. In addition, RAGE has been shown to affect the expression of cell cycle genes modulating the G1/S phase transition [194, 195] and to stimulate phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway activation [196], thereby playing a crucial role in the development and progression of a number of tumor types [197].

#### **Phosphatidylethanolamine: as functional as PS or not?**

Under certain conditions, including apoptosis, tumor-related angiogenesis, infections, and blood coagulation, loss of asymmetry of the plasma membrane of different cell types is observed, due to diminished activity of flippases and reduced transport of both PS and PE to the cytosolic face of the cell membrane [198].

Emoto and colleagues presented for the first time direct evidence that both PE and PS are externalized on the cell membrane surface during the early stages of apoptosis [199]. It is likely that PE exposure may promote apoptosis. Indeed, exogenous PE was reported to induce apoptosis in human hepatoma HepG2 cells through activation of the bcl-2/bax pathway [200]. In addition, Umeda and Emoto showed that the transbilayer PE redistribution in the plasma membrane was increased in apoptotic blebs, suggesting a role of PE in the reorganization of cytoskeletal structures during apoptosis [201]. However, the role of PE in efferocytosis is controversial and needs to be further explored. In this regard, a number of studies indicate that besides PS, PE can also act as a ligand for CD300a on the surface of phagocytes. However, the interaction between PE-exposing apoptotic cells and CD300a on phagocytes down-regulates the removal of apoptotic cells [120, 202]. In addition, another PS receptor involved in the regulation of

phagocyte-mediated removal of dying cells, that is, Gas6, does not show any ability to bind to PE, suggesting the hypothesis that PE, unlike PS, does not have a crucial role in efferocytosis [54].

Several lines of evidence show that PE exposure on the cell surface is involved in a number of additional cell biological events apart from apoptosis and efferocytosis. Thus, for instance, PE expression on the outer face of the cell membrane is increased at the surface of the cleavage furrow which forms between two mitotic daughter cells and has a crucial role in the dynamics of contractile ring formation. PE redistribution from the inner to the outer leaflet of the membrane of endothelial cells is a feature of tumor vasculature in and around hypoxic areas, suggesting that PE could hold promise as a target for anti-tumor drugs and as a biomarker for tumor imaging [203]. There is evidence showing that PS exposure has a crucial role in certain infections. Indeed, recognition of PE-exposing viruses by two PS receptors (i.e., TIM-1 and TIM-4) has a pivotal role in the immune response against infections by numerous pathogenic viruses, including Ebola, West Nile and dengue viruses. Also, PE expression on the surface of intestinal epithelial cells may promote infection by enterohemorrhagic *Escherichia coli* (EHEC) [204]. Therefore, PE might be used as a broad-spectrum antimicrobial target [205, 206]. In addition, PE may enhance the cell membrane disruption by prefibrillar islet amyloid polypeptide protein (IAPP), an amyloidogenic protein. Indeed, although PE hampers the interaction of prefibrillar IAPP with cell membranes, it promotes IAPP-mediated cytotoxicity by favoring the growth of fibers on the membrane surface via a detergent-like mechanism [207]. Moreover, PE exposure by endothelial cells is involved in activation of the protein C anticoagulant pathway [208]. Finally, there are some studies reporting the ability of PE to interact with annexins within cell membranes, which may represent a unique model of regulation of different biological events [209].

### Concluding remarks

Apoptotic cell removal by phagocytes requires close collaboration between apoptotic cells and phagocytes. At the early stages of apoptosis, dying cells expose PS as an “eat me” signal. Subsequently, various receptors expressed by phagocytes, which can bind PS either directly or indirectly, promote apoptotic cell engulfment. Notably, accumulating evidence has elucidated the molecular mechanisms of PS externalization and the role of PS recognition receptors, their subunit structures, and their signaling pathways, including in efferocytosis-independent biological processes. Although extensive studies by several groups have greatly improved knowledge on multiple physiological functions of PS recognition receptors, some unanswered questions about the role of PS receptors in different pathological conditions need more investigations in order to fine-tune potential therapeutic strategies targeting these molecules.

Although PS has been widely studied, much less information is available about the function of PE exposure in apoptosis and efferocytosis, as well as other cellular processes. This might be partly due to the lack of particular detection systems with ability to discriminate between PE, PS or other phospholipids. However, the development of PE-specific probes allowing for the molecular imaging of cell death and other biological processes both in vitro and in vivo is expected to help unravel the specific role of PE exposure on the cell surface.

### Abbreviations

ABCA1: ATP-binding cassette transporter A1; ABCG1: ATP-binding cassette sub-family G member 1; acLDLs: acetylated low-density lipoprotein; AGEs: Advanced glycation end products; Akt: Protein kinase B; BAI1: Brain-specific angiogenesis inhibitor 1; C1q: Complement component 1q; CRVO: Central retinal vein occlusion; DCs: Dendritic cells; Dock180: Dedicator of cytokinesis 1; ELMO: Engulfment and cell motility; ERK: Extracellular signal-regulated kinase; FH: Familial hypercholesterolemia; Gas6: Growth arrest-specific gene 6; HA: Hyaluronic acid; HMDM: Human monocyte-derived macrophage; ICAM-3: Intercellular adhesion molecule-3; ITIMs: Immunoreceptor tyrosine-based inhibition motifs; JMJD6: Jumonji domain-containing protein 6; KIM-1: kidney injury molecule-1; LOX-1: Lectin-like oxidized low-density lipoprotein receptor-1; MAP: Mitogen-activated protein; MAPK: Mitogen-activated protein kinase; MFG-E8: Milk fat globule EGF factor 8; NK: Natural killer; oxLDL: oxidized low-density lipoprotein; PCR: Polymerase chain reaction; PE: Phosphatidylethanolamine; PI: Phosphatidylinositol; PI3K: Phosphoinositide 3-kinase; ProS: Protein S; PS: Phosphatidylserine; PSR: PS receptor; PTC: Proximal tubular cell; RAGE: Receptor for advanced glycosylation end products; RCT: Reverse cholesterol transport; ROS: Reactive oxygen species; RTKs: Receptor tyrosine kinases; sLOX-1: soluble LOX-1; TGF- $\beta$ : Tumor growth factor- $\beta$ ; TIM: Transmembrane immunoglobulin and mucin domain; VSMC: Vascular smooth muscle cell;  $\beta$ 2GPI:  $\beta$ 2-glycoprotein I

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### Authors' contributions

AS and MBN conceived the subject matter and designed the review. MBM wrote the original draft. AS, VB and MP critically revised the first draft. All authors approved the final version.

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