Ageing Research Reviews 50 (2019) 43–57

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Effect of soluble cleavage products of important receptors/ligands on efferocytosis: Their role in inflammatory, autoimmune and cardiovascular disease

Amir Tajbakhsh[a], Seyed Mohammad Gheibi Hayat[b], Alexandra E. Butler[c], Amirhossein Sahebkar[d,e,f,*]

[a] Department of Modern Sciences and Technologies, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Department of Genetics, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[c] Diabetes Research Center, Qatar Biomedical Research Institute, Doha, Qatar
[d] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[e] Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[f] School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

Keywords:
Ectodomain cleavage
Shedding

ABSTRACT

Efferocytosis, the clearance of apoptotic cells (ACs), is a physiologic, multifaceted and dynamic process and a fundamental mechanism for the preservation of tissue homeostasis by avoiding unwanted inflammation and autoimmune responses through special phagocytic receptors. Defective efferocytosis is associated with several

Abbreviations: ABCA7, ATP-binding cassette transporter A7; ACs, apoptotic cells; ADAM, A disintegrin and metalloproteinase; ALL, acute lymphoblastic leukemia; AMI, acute myocardial infarction; ApoE, apolipoprotein E; APP, acute phase protein; C1q, complement 1q; Ca^{2+}, Calcium; Calr, calreticulin; CD, cluster differentiation; CD14, cluster of differentiation 14; CD200R, CD200 receptor; CD32b, inhibitory FcγRIIb; CD47, cluster differentiation 47; Cdkn2b, cyclin dependent kinase inhibitor 2B; CDKN2B, cyclin-dependent kinase inhibitor 2B; CLL, chronic lymphocytic leukemia; CRP, C-reactive protein; CTLA-4, cytotoxic T lymphocyte–associated antigen 4; CVD, cardiovascular disease; DAMPs, damage-associated molecular patterns; DAS/DAS28, Disease Activity Score; DCs, dendritic cells; DPC 333, ((2R)-2-((3R)-3-amino-3-2-oxopyrrolidinyl)-N-hydroxy-4- ethylpentanamide)); ECs, endothelial cells; eNOS, endothelial nitric oxide; ERK5, extracellular signal regulated kinase 5; esRAGE, endogenous secretory RAGE; FcγR/CD32b, Fc-Gamma Receptor; FcγR, Fc receptor; FL-RAGE, full length RAGE; G2A, G-protein–coupled receptor; Gas6, growth arrest-specific gene 6 product; GPI, glycosyl phosphotidyl inositol; GWASs, genome-wide association studies; HDL, high-density lipoproteins; HETEs, hydroxyeicosatetraenoic acids; HMGB1, high mobility group box-1 protein; HODEs, hydroxy octadecadienoic acids; HUVECs, human umbilical vein endothelial cells; ICH, intracerebral hemorrhage; IFN-γ, interferon gamma; IgGR, the IgG receptors; IRF5, interferon regulatory factor 5; IRF8, interferon regulatory factor 8; ITIM, immunoreceptor tyrosine-based inhibitory motif; LDL, low density lipoprotein; LFA-1, lymphocyte function-associated antigen 1; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; LPC, lysophosphotidylcholine; LPS, lipopolysaccharide; LRP, LDL receptor–related protein; ECs, endothelial cells; LRP1, low-density lipoprotein receptor (LDLR)-related protein 1; LysoPC, lysophosphatidylcholines; MAC, membrane attack complex; MAPK, mitogen activated kinase-like protein; mCD36, membrane CD36; M-CSF, macrophage colony-stimulating factor; MerTK, mer tyrosine kinase; MFG-E8, milk fat globule-EGF factor 8; MI, myocardial infarction; miRs, microRNAs; m-LOX-1, cell membrane; MMPs, matrix metalloproteinases; mPD-L1, membrane PD-L1; NCs, necrotic cells; NFκB, nuclear factor kappa-light-chain-enhancer of Activated B cells; Ox-LDL, oxidation of LDL; PAI-1, plasminogen activator inhibitor–1; PARP, poly(ADP-ribose) polymerase; PD-1, programmed death-1; PECAM-1/CD31, platelet–endothelial cell adhesion molecule-1; PFC, per-fluorocarbon emulsions; PI3K, phosphoinositide 3-kinase; PIP3, phosphatidylinositol triphosphate; PKC, Protein Kinase C; PLC, Phospholipase C; PPAR-δ/γ, peroxisome proliferator-activated receptor*delta/gamma*; Pros1, protein S; PRRs, pattern-recognition receptors; Ps, phosphatidylserine; PTB, phosphotyrosine-binding; PTX3, pentraxin 3; RA, rheumatoid arthritis; RAGE, receptor for advanced glycation endproducts; RANK, receptor activator of nuclear factor; RasGAP, activator protein of Ras-GTPase; ROS, reactive oxygen species; sCD163, soluble CD163; sCD200, soluble form of CD200; sCD200Fc, soluble CD200Fc; sCD36, soluble CD36; sCD47, soluble CD47; sCDllb/CD18, soluble CDllb/CD18; sFcγR/sCD32b, soluble forms of Fcγ receptors; SHIP, Src homology 2-containing inositol phosphatase; SHP, Src homology 2-containing tyrosine phosphatase; SIRP-α, signal regulatory protein alpha; Sirt1, sirtuin1; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index score; sLOX-1, soluble form; sLRP, soluble form of LRP; SM201, anti-FcγRIIB mAb; sMer, soluble form of MerTK; SOCS1, suppressor of cytokine 1; sPECAM-1, soluble PECAM-1; sRAGE, soluble Receptor for advanced glycation endproducts; SR-B1, scavenger receptor class B1; SSc, systemic sclerosis; STAT-1, signal transducer and activator of transcription 1; sTim, soluble Tim-3; suPAR/(CD87), soluble urokinase plasminogen activator receptor; TACE, tumor necrosis factor-alpha-converting enzyme; TCR, T cell receptor; TG2, transglutaminase 2; Tim, T-cell immunoglobulin- and mucin-domain-containing molecule; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TIMP-3, tissue inhibitors of metalloproteinases; TLR, toll-like receptor; TLR3, toll-like receptor 3; TLR9, toll-like receptor 9; TLT2, TREM-like protein 2; TNF-RI, TNF receptor I; TNF-α, tumor necrosis factor-α; TRAF6, tumor necrosis factor receptor-associated factor 6; TRPC3, transient receptor potential canonical 3; TSP-1, thrombospondin-1; UCP2, uncoupling protein 2; UPA, urokinase plasminogen activator; Vit-K, vitamin K; VSMCs, vascular smooth muscle cells

* Corresponding author at: Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad 9177948564, Iran.
E-mail address: sahebkara@mums.ac.ir (A. Sahebkar).

https://doi.org/10.1016/j.arr.2019.01.007
Received 26 October 2018; Received in revised form 4 January 2019; Accepted 8 January 2019
Available online 09 January 2019

Target therapy
Atherosclerosis
Metalloproteinase
Pharmacological effects

disease states, including cardiovascular disease and impaired immune surveillance, as occurs in cancer and autoimmune disease. A major cause of defective efferocytosis is non-functionality of surface receptors on either the phagocytic cells or the ACs, such as TAM family tyrosine kinase, which turns to a soluble form by cleavage/shedding or alternative splicing. Recently, soluble forms have featured prominently as potential biomarkers, indicative of prognosis and enabling targeted therapy using several commonly employed drugs and inhibitors, such as bleomycin, dexamethasone, statins and some matrix metalloproteinase inhibitors such as TAPI-1 and BB3103. Importantly, to design drug carriers with enhanced circulatory durability, the adaptation of soluble forms of physiological receptors/ligands has been purported. Research has shown that soluble forms are more effective than antibody forms in enabling targeted treatment of certain conditions, such as autoimmune diseases. In this review, we sought to summarize the current knowledge of these soluble products, how they are generated, their interactions, roles, and their potential use as biomarkers in prognosis and treatment related to inflammatory, cardiovascular, and autoimmune diseases.

1. Introduction

A growing body of literature has investigated clearance mechanisms of dying cells (apoptosis/necrotic bodies) in relation to critical disease, aiming to elucidate how body systems maintain homeostasis. Whilst immediate removal of dying cells with generation of healthy replacement cells is ideal, sometimes this process goes awry and either directly results in disease or indirectly contributes to disease initiation. In this regard, apoptotic cell (AC) phagocytosis by both professional and non-professional phagocytes, also known as efferocytosis, is central to maintaining tissue homeostasis, immunological tolerance, and regulating immune responses. Effective efferocytosis inhibits generation of necrotic cells (NCs) and thus maintains self-tolerance (Tajbakhsh et al., 2018). The immune response is a critical step in efferocytosis and plays an important role in regulation of effective efferocytosis.

Based on research by Aggarwal et al., efferocytosis is regulated through pro-inflammatory and anti-inflammatory mediators (Aggarwal and Natarajan, 1996; Michlewska et al., 2009). Efferocytosis is a remarkably adept mechanism, maintaining immune tolerance whilst permitting anti-bacterial immune responses (Hoffmann et al., 2001; van den Eijnde et al., 1998). Efferocytosis is a multifaceted and dynamic process coordinated *via* the interaction of several surface molecules, chemotactic molecules, adaptor microRNAs (miRs) and opsonin molecules, each of which serves a vital role (Ocaña-Guzman et al., 2018; Tajbakhsh et al., 2018) (Table 1). The factors involved in efferocytosis are either attached to the cell surface or present as soluble molecules in the microenvironment of the phagocytic cells. In this respect, epithelial and mucosal barriers, immune cells, pattern-recognition receptors (PRRs), soluble products, opsonins and cytokines are vital components of the innate defense system (Duffield, 2003). Additionally, the differentiation between ACs and live cells is determined by phagocytic receptors through recognition of “Don't Eat- or Eat-Me” signals on the cell surface (Abdolmaleki et al., 2018; Gheibi Hayat et al., 2018; Tajbakhsh et al., 2018). Viable cells present the native “Don’t Eat-Me” signals, such as cluster differentiation (CD) 31, CD46, CD47, plasminogen activator inhibitor–1 (PAI-1) and C1q (Abou-Raya and Abou-Raya, 2006; Litvack and Palaniyar, 2010; Ocaña-Guzman et al., 2018), on their surface. By contrast, ACs are no longer able to avoid complement uptake by macrophages and undergo removal through phagocytosis (Hakulinen et al., 2004). In addition, during the apoptotic process, cell surface blebs are produced comprised of intracellular components, some of which act as a “Find-Me” signal and alarm to phagocytic cells; lysophosphatidylcholines (LysoPC) and nucleotides (*e.g.* naked DNA)) are examples. These blebs are released, their signaling initiating rapid and effective cell clearance (Abou-Raya and Abou-Raya, 2006; Litvack and Palaniyar, 2010).

In some instances, the receptors and their ligands on phagocytic cells and ACs are intact, but efferocytosis is defective. This is because soluble products are also involved in efferocytosis; these come from phagocytosis receptors and involve shedding of ligand/receptor, resulting either in defective efferocytosis or, conversely, more efficient efferocytosis (Driscoll et al., 2013; Enocsson et al., 2015; Gandhi et al., 2014). Generally, soluble receptors may be generated *via* 2 different mechanisms: proteolytic cleavage of the full-length membrane-bound receptor or alternative splicing, one example being soluble receptor for advanced glycation end products (sRAGE) which can be generated by both pathways (Murase et al., 2000). Immune response regulation is one of the most important steps in efferocytosis and phagocytic cells play an essential role in stimulation of either pro-inflammatory or anti-inflammatory responses (Duffield, 2003; Rosenblum et al., 2015). Soluble factors/products regulate both the inflammatory and anti-inflammatory responses of phagocytic cells, as has been reported in several disease states, such as chronic inflammation, autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), atherosclerosis and cancer (Abou-Raya and Abou-Raya, 2006; Nativel et al., 2013; Tajbakhsh et al., 2018). Autoimmune disease

Table 1
The main molecules and pathways involved in efferocytosis in inflammation and atherosclerosis.

Steps		Molecules
Find Me signal		ApoE4, Fas ligand (CD95 L), Fractalkine (CX3CL1), G2A, Lyso PC, LPC.
Catch	Eat-Me signal	C1q, MFG-E8, TG2, Calr, LRP1, MerTK, Protein S, PTX3, SR-B1, Stabilin-2, Tim-1/Tim-4, TSP-1.
	Don’t Eat-Me signal	CD47, CD31, PAI-1, CD46, TIM-3, CD200, CD32b, PD-1 (CD-279).
Engulfing, process & anti-inflammatory		TLT2, ABCA7, Cathepsin G, CDKN2B, ERK5, IRF8, p21Cip1 (CDKN1A), p38, p38 MAPK activity, PPAR-γ, PPAR-δ/γ, Sirt1, TLR3, TLR9, TRAF6, TRPC3, UCP2, IRF5.

Abbreviations in order of appearance: ApoE: Apolipoprotein E; G2A: G-protein–coupled receptor; LysoPC, Lysophosphatidylcholine; HMGB1: High mobility group box-1 protein; C1q: Complement 1q; MFG-E8: Milk fat globule-EGF factor 8; LPC: Lysophosphotidylcholine; TG2: Transglutaminase 2; LRP1: Low-density lipoprotein receptor (LDLR)-related protein 1; Calr: Calreticulin; MerTK: Mer tyrosine kinase; PTX3: Pentraxin 3; SR-B1: Scavenger receptor class B1; Tim: T-cell immunoglobulin- and mucin-domain-containing molecule; TSP-1:Thrombospondin-1; CD47: Cluster differentiation 47; PAI-1: Plasminogen activator inhibitor-1; TLT2: TREM-like protein 2; ABCA7: ATP-binding cassette transporter A7; MAPK: mitogen activated kinase-like protein; CDKN2B: Cyclin-dependent kinase inhibitor 2B; ERK5: Extracellular signal regulated kinase 5; IRF8: Interferon regulatory factor 8; PPAR-δ/γ: Peroxisome proliferator-activated receptor delta/gamma; Sirt1: Sirtuin1; TLR3: Toll-like receptor 3; TLR9: Toll-like receptor 9; TRAF6: Tumor necrosis factor receptor-associated factor 6; TRPC3: Transient receptor potential canonical 3; UCP2: Uncoupling protein 2; IRF5: Interferon regulatory factor 5; TIM-3: T-cell immunoglobulin and mucin-domain containing-3: CD32b: Inhibitory FcγRIIb.

results from an imbalance between effectors and controlling mechanisms (Navegantes et al., 2017) and, therefore, it is critical to maintain immune cell tolerance. Atherosclerosis is associated with inflammation and the immune system plays a role in atherosclerotic plaque initiation/progression in the intima (Tajbakhsh et al., 2018); whilst numerous studies have shown the importance of receptors and ligands in the development of atherosclerosis, few have studied the importance of soluble compounds/products and shedding of targets related to efferocytosis. Hence, a greater understanding of the relationship between soluble products and their inhibitory/enhancing effects on the phagocytosis of ACs is crucial to allow for the design of appropriate treatment strategies (Litvack and Palaniyar, 2010). With this in mind, here we summarize the current state of knowledge regarding soluble products of receptor/ligand cleavage in inflammatory, autoimmune, and atherosclerotic disease.

1.1. Molecules and pathways involved in efferocytosis in atherosclerosis

Atherosclerosis is an inflammatory disease, and various factors and cells which are involved in inflammation might be implicated in the atherosclerotic plaque formation (Serhan et al., 2007). In addition, the development of atherosclerotic lesions is known to occur at vessel sites exposed to rapid changes in flow and this leads to disturbed blood flow (Chatzizisis et al., 2007). In this case, endothelial cells and related molecules, such as platelet endothelial cell adhesion molecule (PECAM-1/CD31), have a vital role in sensing shear stress. The dysfunction of this sensing by endothelial cells is involved in the pathogenesis of atherosclerosis (Chatzizisis et al., 2007; Stevens et al., 2008).

Furthermore, macrophage apoptosis is complex and is involved in the atherosclerotic process (Tabas, 2005). In this regard, apoptosis and clearance of ACs, efferocytosis, causes resolution of inflammation (Serhan et al., 2007). Effective phagocytosis by macrophages and efferocytosis appears to relieve atherosclerosis to some extent in the early phase of the atherosclerotic lesions (Tabas, 2005). Efferocytosis inhibits formation of plaque vulnerability, and secondary necrotic cores, as well as acute luminal thrombosis (Ravichandran and Lorenz, 2007; Virmani et al., 2002).

However, the increase in apoptotic macrophages or foam cell formation leads to defective efferocytosis that stimulates inflammatory responses and also secondary necrosis of the ACs *via* the release of inflammatory regulators in advanced lesions (Tabas, 2005). This process occurs together with enhancement of the atheromatous plaques, leading to an increase of NCs and subsequent plaque rupture (Tabas and Bornfeldt, 2016). Both genetic and experimental studies have demonstrated that defective efferocytosis is caused through dysregulation of receptors/ligands on the macrophages/ACs in atherogenesis (Kojima et al., 2017). Defective efferocytosis in advanced atheroma is a primary cause of necrotic core formation and thus leads to further friable plaque formation, an important aspect in atherosclerosis (Tabas, 2010). The major molecules and pathways involved in efferocytosis in inflammation and atherosclerosis are indicated in Table 1.

1.2. The relationship of molecules/pathways and solubilization related to efferocytosis

Numerous studies have revealed a number of membrane-anchored proteins that act as receptors or ligands and are released from the cell surface *via* cleavage by enzymes. The release of membrane proteins by cleavage has been purported to modify various cellular processes and is involved in a variety of disease pathologies (De Freitas et al., 2012; Driscoll et al., 2013; Friggeri et al., 2011; Gomez et al., 2012; Miller et al., 2010; Soto Pantoja et al., 2013; Vaisar et al., 2009). Recently, renewed interest in this process has stemmed from the fact that efferocytosis is regulated *via* certain receptors and is important in resolution of inflammation. When soluble levels of certain AC receptors are elevated, dysfunctional clearance of ACs results (Boersma et al., 2005; Driscoll et al., 2013; Hsu et al., 2003; Kenis et al., 2006; Sather et al., 2007). In addition, proteolytic cleavage is a mechanism by which soluble AC receptors can be released in chronic inflammation (Driscoll et al., 2013). Soluble receptors include the extracellular portions of receptors bound to membrane (Fig. 1) and can be produced from immunoglobulins, adhesion molecule receptors, and even tyrosine kinase

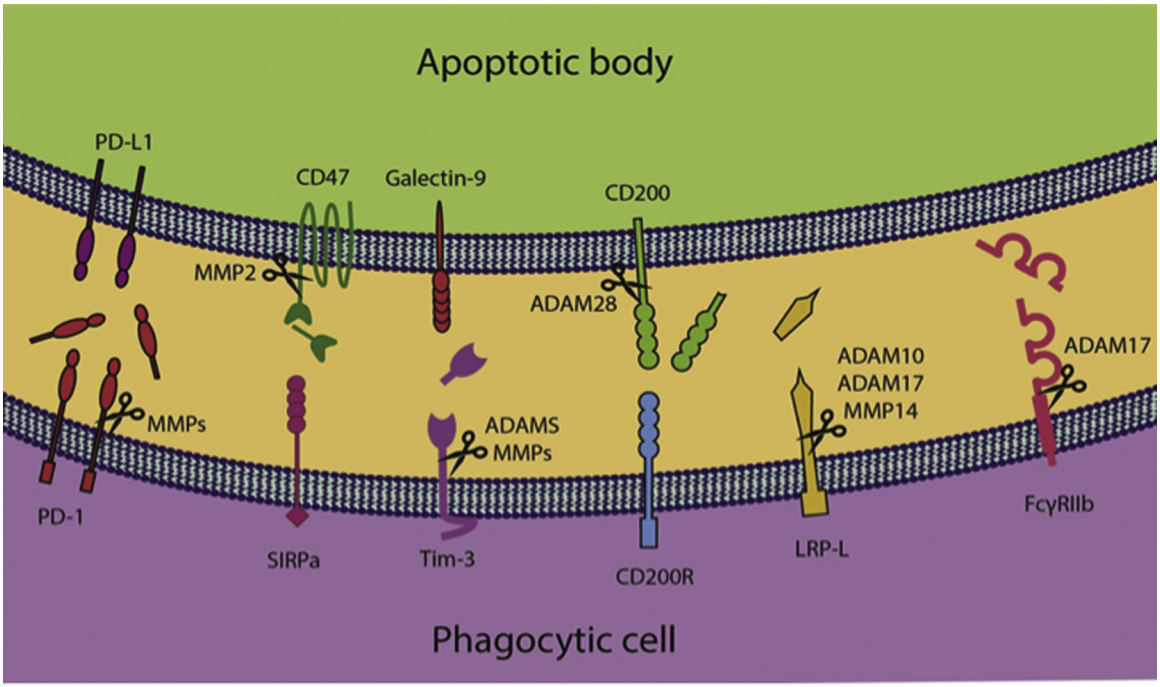

Fig. 1. Schematic presentations of the soluble products of ligands on the apoptotic cells and their receptors may relate to "Don't-Eat-Me" signal in the efferocytosis. Cleavage of ligands on the apoptotic body, which act as "Don't-Eat-Me" such as CD47, CD200 and PD-L1 may lead to increase of efferocytosis.
PD-1: Programmed death-1; **SIRPα:** Signal regulatory protein alpha; **Tim-3:** T-cell immunoglobulin and mucin-domain containing-3; **LRP-1:** LDL receptor–related protein; **FcRIIb(CD32b)**: Fc-Gamma Receptor.

receptors (Heaney and Golde, 1998). Hence, soluble receptors have been suggested as a source of accessible and non-invasive biomarkers (Tien et al., 2017). Furthermore, it is known that efferocytosis and anti-inflammatory consequences are limited *via* proteolytic cleavage of AC receptors from the macrophage surface (Driscoll et al., 2013). Receptors related to efferocytotic cleavage may result in reduction of efferocytosis (Table 2). Thus, dysfunction of these enzymes or dysfunction of their regulators may result in defective efferocytosis *via* increase of soluble receptors/ligands.

1.3. Inflammation resolution mediated by efferocytosis

Resolution of inflammation, as part of the host response, is a co-ordinated and active process mediated through biosynthesis of active mediators and which leads to the restoration of tissue homeostasis (1, 2). Defective resolution can result in chronic inflammation, additional tissue damage, and dysregulation of tissue homeostasis. Moreover, defective resolution has been implicated in several diseases, including atherosclerosis and the progression of autoimmunity (Nathan and Ding, 2010; Serhan et al., 2007). Undoubtedly, defective efferocytosis is an important hallmark of inappropriate inflammation resolution (Tabas, 2017). Efferocytosis contributes to resolution of inflammation through several important steps, including recognizing and engulfing ACs, which prevents AC distribution and accumulation of the M1 phenotype together with secretion of inflammatory agents and also by release of anti-inflammatory cytokines, such as IL-10, and TGF-β, which they release after effective clearance of ACs *via* efferocytosis (Tabas, 2017; Tajbakhsh et al., 2018). IL-10 and TGF-β have been implicated in NFκB suppression, and lead to inhibition of inflammation and restoration of tissue homeostasis (Cui et al., 2007; Fadok et al., 1992). IL-10 demonstrated anti-atherogenic effects through decreasing the infiltration of monocytes to the atherosclerotic plaque (Caligluri et al., 2003; Liu et al., 2006).

1.4. Efferocytosis regulation through ectodomain shedding by certain enzymes

Metalloproteases mediate cellular responses to stress by interacting with proteins at the cell surface. These enzymes regulate several processes such as ectodomain shedding, extracellular matrix binding, and proliferation (Fischer et al., 2004; Singh et al., 2009). Ectodomain shedding is an essential mechanism for membrane-anchored molecule proteolytic cleavage at the cell surface which results in the release of a soluble molecule into the microenvironment (Arribas and Borroto, 2002). Ectodomain shedding has a critical role in the modulation of immune responses through modulating the release of chemokines, cytokines, receptors of cytokines, and numerous membrane-anchored immuno-regulatory molecules (Chalaris et al., 2010; Garton et al., 2006). The metalloproteases are the main cleavage enzymes in cells, and play a central role in ectodomain shedding (Moss and Lambert, 2002). Tumor necrosis factor-alpha-converting enzyme (TACE/ADAM17) is one of the most well-known of the ADAM family members. TACE inhibitors prevent the release of the soluble form of tumor necrosis factor-α (TNF-α) (Moss and Lambert, 2002). ADAM17 sheds its substrates at a membrane-proximal site (Caescu et al., 2009); it cleaves numerous proteins at the cell surface that are involved in inflammation (Garton et al., 2006; Murphy et al., 2008). Deletion of ADAM17 increases macrophage mediated efferocytosis *in vivo*, leading to an augmented anti-inflammatory response (Driscoll et al., 2013). This shedding can prevent receptor function in macrophage-mediated AC engulfment (Sather et al., 2007). The soluble cleavage products may function as sequester ligands and decoy receptors (Sather et al., 2007). Shed receptors may act to regulate the biological activity of these ligands *via* acting as agonists or antagonists (Daub et al., 2010; Ho et al., 2015; Peschon et al., 1998).

1.5. CD47 as a "Don't Eat-Me" signal in efferocytosis

In contrast to "Eat-Me" signals exposed on ACs, live cells expose "Don't Eat-Me" or "Not Ready to Eat" signals to prevent efferocytosis, which suppresses or controls the immune system (Fig. 1). In this respect, surface expression of some receptors, such as CD47 and CD31, inhibits activated phagocytes from attempting to engulf live cells (Gardai et al., 2006; Grimsley and Ravichandran, 2003). Live cells seems to have the ability to internalize CD47 on the cell surface; tumor cells also express CD47 on their surface to prevent efferocytosis by phagocytic cells (Nilsson and Oldenborg, 2009). Soluble CD47 (sCD47), produced through proteolytic cleavage *via* MMP-2, has been target for therapy in recent years (Hsu et al., 2003; Miller et al., 2010; Soto Pantoja et al., 2013).

1.6. Efferocytosis regulation through Calr/LRP1

LDL receptor-related protein 1 (LRP1) is a vital intermediary for efferocytosis, as necessary ligands for stimulation of engulfment receptors on phagocytic cells. LRP1 ligands have a key role in the inhibition of atherosclerosis in efferocytosis (Boucher et al., 2003; Lillis et al., 2008). LRP1 loss leads to inflammation of the vasculature, defects in efferocytosis, increased necrotic core size, and extension of the atherosclerotic lesion. Remarkably, loss of these receptors in both professional efferocytes, such as macrophages and dendritic cells (DCs), or in non-professional phagocytes, such as vascular smooth muscle cells (VSMCs), is sufficient to increase the speed of development of atherogenesis (Tajbakhsh et al., 2018). Apolipoprotein E (ApoE), as a LRP1 ligand, inhibits microglia activation *via* a mechanism involving LRP1 (Pocivavsek et al., 2009). *LRP1* gene loss results in worsening of experimental autoimmune encephalomyelitis in microglia *in vivo* (Chuang et al., 2016). LRP1 is cleaved and shed from cell surfaces through ADAM10, MMP-14, and ADAM17 and a soluble form of LRP (sLRP) is produced (Gorovoy et al., 2010; Pocivavsek et al., 2009; Yamamoto et al., 2017) (Fig. 1). The sLRP1 concentration is raised in the plasma of humans with RA and systemic lupus erythematosis (SLE), and in mice treated with lipopolysaccharide (LPS) (30). LRP1 stimulates inflammatory mediator expression *via* macrophages (30). Moreover, sLRP1 can bind active proteins, such as thrombospondin type 1 motif, member 5 (ADAMTS-5), MMP-13, and tissue inhibitors of

Table 2
The main enzymes that are related to the shedding of receptors/ligands, which are involved in efferocytosis.

Molecules/regents	Products
ADAM10, ADAM9, ADAM17, & Furin (11, 32, 39, 40)	sMer, sAXL,
ADAM17 (41)	sCD36
ADAM10 (42)	sRAGE
ADAM10, ADAM17, & MMP-14 (43)	sLRP
MMP-2 (30, 31)	sCD47
MMP-3, MMP-8, MMP-9, & ADAM-10 (44)	sCD46
Calpain (45)	sPECAM-1
ADAM10, ADAM17 (32)	Integrin beta 2
MMPs, elastase, plasmin, cathepsin G & Phospholipases (12)	suPAR
TACE, & ADAM17 (13)	sKIM-1
MMP-9 &MMP-12(46)	sCD14
ADAM17 (47)	sFcγRIIIb
TACE, &ADAM17 (48)	sTNF-RI
ADAM10, &ADAM17 (49)	sTLR2
ADAM10, & ADAM17 (50)	sCD163
MMP2 (51)	sCD40
TACE, & ADAM17 (52, 53)	sLOX-1
ADAM28 (54)	sCD200
MMPs (55, 56)	sCD93

ADAM: Metalloproteinase family; **UPA**: Urokinase plasminogen activator; **MMPs**: Matrix metalloproteinases; **TNF-α**: Tumor necrosis factor α; **TACE**: TNF-α converting enzyme; **RAGE**: Receptor for advanced glycation endproducts; **LRP**: LDL receptor–related protein; **MQs**: Macrophages; **ECs:** Endothelial cells.

metalloproteinases (TIMP)-3, thereby inhibiting endocytosis (a form of active transport, which moves particles, such as parts of cells, large molecules, or whole cells, into a cell such as a phagocytic cell) (Scilabra et al., 2013; Yamamoto et al., 2017). LRP1 on the surface of phagocytic cells is activated by calreticulin (Calr), on the surface of ACs which, in turn, prompts the engulfment process (Boucher et al., 2003; Gold et al., 2010; Lillis et al., 2008; Reddy et al., 2002). Moreover, the loss of the cyclin dependent kinase inhibitor 2B (*Cdkn2b)* gene of *9p21* locus results in a reduction in *Calr* expression in atherosclerosis, causing resistance of phagocytic cells to efferocytosis (Kojima et al., 2014; Nanda et al., 2016; Tajbakhsh et al., 2016). Genome-wide association studies (GWASs) have discovered that the Calr ″Eat-Me″ ligand is decreased in patients with cardiovascular disease (CAD) (Kojima et al., 2014, 2017).

1.7. Efferocytosis regulation through platelet–endothelial cell adhesion molecule-1 (PECAM-1)/CD31

Previous studies have suggested that PECAM-1 (CD31) has a critical role in early and late stages of atherosclerotic plaque expansion in $ApoE^{-/-}$ mice (Caligiuri et al., 2005). PECAM-1/CD31 is expressed on endothelial cells (ECs), circulating leucocytes, and platelets and is integral to cell extravasation from the vascular space through the endothelium. PECAM-1 plays a vital role in leukocyte trans-endothelial migration. Blocking EC functional PECAM-1 using anti-PECAM antibody or soluble recombinant PECAM effectively inhibits trans-endothelial migration of leukocytes into atherosclerotic plaques (Muller et al., 1993). PECAM-1 up-regulation due to high shear stress could lead to advanced atherosclerosis, as increased leukocyte influx into the lesion will cause aggregation of circulating platelets (Litwin et al., 1997). Raised levels of the soluble PECAM-1 (sPECAM-1) have been noted in a number of different diseases, such as ischemic stroke (IS), atherosclerotic disease, multiple sclerosis (MS) and acute myocardial infarction (AMI) (Blann and McCollum, 1994; Losy et al., 1999; Serebruany et al., 1999; Zaremba and Losy, 2002). Wei et al. showed an association between PECAM-1/CD31 gene variations and sPECAM-1 levels in patients with IS (Wei et al., 2009). Naganuma et al. proposed that calpain, an intracellular calcium (Ca^{2+})-activated cysteine protease, is activated by high shear stress at the intracellular domain, resulting in shedding/cleavage of PECAM-1 (Naganuma et al., 2004). Losy et al. reported that sPECAM-1 is increased in sera of MS patients with active, gadolinium-enhancing lesions; sPECAM-1 has been suggested to play a role in the immune-modulatory mechanisms that prevent the migration of leukocytes in MS (Losy et al., 1999). Serebruany et al. reported that enhanced plasma sPECAM-1 may function as a biomarker for detection of patients with AMI (Serebruany et al., 1999).

1.8. Efferocytosis regulation through CD46

CD46 is a type 1 glycoprotein, a cofactor which acts to protect autologous cells from complement-mediated damage (Liszewski et al., 2000). CD46 cross-linking leads to a reduction of IL-12 secretion on the cell surface of monocytes (Karp et al., 1996). Several studies have shown that CD46 can regulate production of IL-2 and IL-10 and also immune responses *via* effects on $CD8^+$ (cytotoxic) T cells and proliferation of $CD4^+$ T cells (Elward et al., 2005; Marie et al., 2002). Elward et al. have shown that CD46 has a major role in innate immune recognition of ACs and NCs as a “Don’t Eat-Me” signal (Elward et al., 2005). During AC formation, CD46 translocates into the membrane from membrane stores and cytoplasmic/nuclear compartments. CD46 reduction leads to enhanced C3b deposition on the surface of ACs that attracts macrophages (Elward et al., 2005) (Fig. 2). CD46 cleavage *via* metalloproteinase is repressed by TAPI-1 and BB3103, two MMPs/TACE inhibitors often used experimentally (Hakulinen et al., 2004). Soluble CD46 (sCD46) cleavage from NCs form micro-particles of ACs that are enriched for CD46 (Elward et al., 2005). NC supernatants were extremely sCD46-enriched. NCs lack CD46 signal without involving the cleavage of poly(ADP-ribose) polymerase (PARP) and caspase 3. In contrast to what was previously thought, robust PARP and caspase 3 signals accompanied the lack of CD46 in the cytoplasmic or membrane and nuclear fractions in the ACs models (Elward et al., 2005). Cells induced to apoptosis quickly lost CD46 both *in vitro* and *in vivo* (Elward et al., 2005). An association has been shown between a reduction of CD46 and caspase 3 expression *in vitro* and the membrane attack complex (MAC), which was identified on NCs possibly as a consequence of CD46 cleaving into sCD46 (Elward et al., 2005). The MAC pores cause ion flux and influence several critical signaling pathways, with a number of downstream events. Much of the activity stimulated by MAC pore is highly pro-inflammatory (Morgan, 2016). The activation of complement and C1q binding and C3b is regularly accompanied *via* protein activation of the terminal complement complex and accumulation of the MAC, which in turn may result in cell lysis (Muller-Eberhard, 1986).

1.9. Efferocytosis regulation through soluble CD200

The CD200 receptor (CD200R) is an anti-inflammatory glycoprotein expressed on the surface of myeloid cells, mainly in the M2a phenotypical profile of macrophages, as an anti-inflammatory response protein (Wright et al., 2000). CD200 suppresses macrophage-mediated phagocytosis *in vitro* (Ocaña-Guzman et al., 2018). Interestingly, interaction of CD200R and its ligand, CD200, prevents macrophage activation and enhances phagocytosis (Ocaña-Guzman et al., 2018). Thus, on balance,

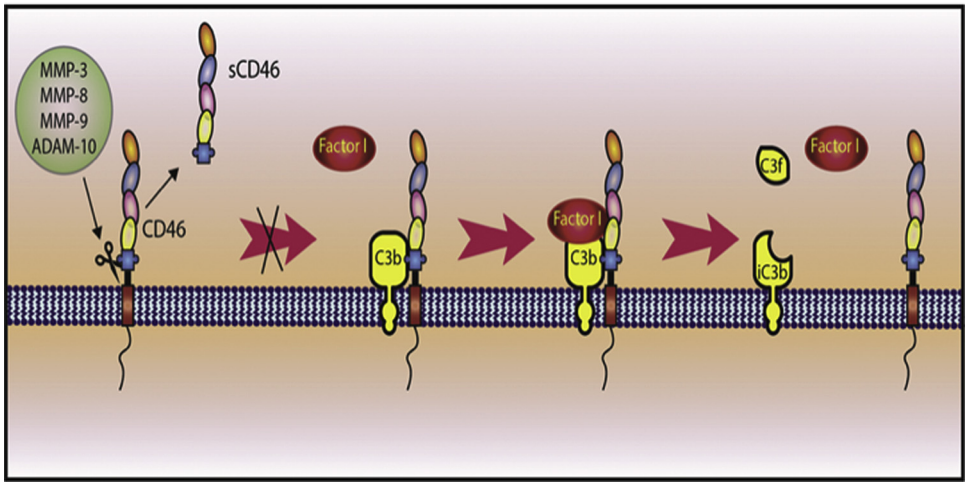

Fig. 2. The role of CD46 and sCD46 in efferocytosis. During AC formation, CD46 has been shown translocating into the membrane from membrane stores and cytoplasmic/nuclear compartments. CD46, a cofactor protein, binds to C3b and C4b to promote their cleavage mediated by factor I and leads to a “Don’t-Eat-Me” signal following an increase of iC3b (Liszewski et al., 2000). In contrast, CD46 reduction by cleavage by matrix metalloproteinases (MMP-8, MMP-9) and Disintegrin and metalloproteinases (ADAM-10), lead to enhanced C3b deposition on the surface of ACs that attracts MACROPHAGEs (Elward et al., 2005). **MMPs:** Matrix metalloproteinases; **ADAMs:** Disintegrin and metalloproteinases.

inhibition of macrophage activation can modulate immune disease but can promote tumor growth. The CD200R interaction with CD200 (as a ligand) in macrophages prompts phosphorylation of tyrosine residues present in the intracellular portion of CD200R, a family of non-receptor tyrosine kinases. The phosphorylation of residues of CD200R causes the adaptor protein Dok2 to bind to the phosphorylated tyrosine (PTB) which, in turn, initiates an inhibitory signaling cascade (Mihrshahi et al., 2009). When Dok2 is bound to the intracellular portion of CD200R, other proteins, like the activator protein of Ras-GTPase (RasGAP), may become involved (Mihrshahi et al., 2009). Prior research has suggested that recruitment of RasGAP is critical for preventing the signaling pathways of Ras-ERK and PI3K in human macrophages (Mihrshahi et al., 2009). Ras-ERK and PI3K pathways are vital for proliferation, cell growth, differentiation, and metabolism *via* activation of other transcription factors such as signal transducer and activator of transcription 1 (STAT-1). Moreover, STAT-1 is involved in macrophage activation *via* interferon gamma (IFN-γ) (Josephs and Sarker, 2015).

Twito et al. showed that CD200 cleavage by ADAM28 on B cells produces a soluble form of CD200 (sCD200) in serum (Twito et al., 2013) (Fig. 1). Expression of ADAM28 mRNA is associated with plasma sCD200 levels in chronic lymphocytic leukemia (CLL). siRNA for ADAM28 reduced sCD200 release from $CD200^+$ cells that were already transfected with ADAM28 gene into $CD200^+$ cells, thus having increased sCD200 release (Twito et al., 2013). Wong et al. proposed sCD200 as a non-invasive prognostic marker and therapeutic target for CLL (Wong et al., 2012).

Of interest are the differences between sCD200 and sCD200R1. sCD200 rescued macrophage fusion to form osteoclasts and macrophage activation downstream of receptor activator of nuclear factor (RANK), a member of the tumor necrosis factor receptor superfamily; by contrast, sCD200R1 prevented this process (Gorczynski, 2012). Furthermore, sCD200 acts through T_{reg} activation. T_{reg} activation led to T-cell inhibition *via* T_{reg} cell surface cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and ligands of programmed death-1 (PD-1) (PD-L1/2). The interface between sCD200, tumor CD200, and T_{reg} CD200R leads to T_{reg} activation and T-cell inhibition (Ring et al., 2017).

Li et al. demonstrated that CD200 was increased in early apoptotic cells when compared to live cells in SLE patients. Moreover, they suggested that expression and function of CD200 and CD200R1 are abnormal in SLE (Li et al., 2012). The interaction of CD200R1 *via* CD200 was found to require signaling through stimulating docking protein 2 phosphorylation or the adaptor protein DOK2 (p56doc-2). Soluble CD200Fc (sCD200Fc) may stimulate CD200/CD200R1 signaling *via* an effect on phosphorylation of DOK2 in $CD4^+$ T cells. It is known that CD200Fc prompts DOK2 phosphorylation in $CD4^+$ T cells. Thus, sCD200Fc *via* CD200R is an agonist of the CD200/CD200R1 signaling pathway, while the anti-CD200R1 antibody is an antagonist and has the potential to block the interaction between receptor and its ligand (Li et al., 2012).

1.10. The interaction of efferocytosis molecules and PD1-PDL-1

PD-L1, an immune checkpoint molecule, is expressed on macrophages, dendritic cells (DCs), T and B cells (Freeman et al., 2000). PD-L1 causes an inhibitory signal, which leads to the induction and maintenance of peripheral tolerance. PD-L1 is involved in the selection of T cells (positive and negative) in thymus (Keir et al., 2006). The expression of PD-L1 is promoted by MerTK as an immune checkpoint ligand to antagonize $CD8^+$ T cells on the tumor cells (Nguyen et al., 2014). In this way, tumour cells may use MerTK-driven efferocytosis for cancer progression (Nguyen et al., 2014). Moreover, PS by regulation of TAM receptors leads to PD-L1 expression on cancer cells, which may result in tumor immune progression and chemoresistance (Kasikara et al., 2017). PD-L1 has soluble forms and sPD-L1 levels are elevated when MMPs cleave the extracellular fraction of membrane PD-L1 (mPD-L1) (Chen et al., 2011) (Fig. 1). Consequently, the production of sPD-L1 is repressed *via* MMP inhibitors (Chen et al., 2011; Dai et al., 2014). Remarkably, sPD-1 and sPD-Ll have been shown to have opposite regulatory effects (Li et al., 2016). sPD-1 displays both functional agonism and antagonism. sPD-1 as an antagonist blocks and prevents the downstream immune regulatory effects of membrane bound PD-1on T cell activation. sPD-1 as an agonist shows immune regulation *via* limiting T cell receptor (TCR) prompted events (Kuipers et al., 2006; Song et al., 2011). In contrast, sPD-L1 binds to the PD-1 receptor on the T cell that then releases an inhibitory signal, thereby preventing activation and proliferation of T cells (Li et al., 2016).

Furthermore, Hassan et al. suggested that sPD-1 may have a role in the pathogenesis of RA since RA patients have raised levels of sPD-1, which are associated with Disease Activity Score (DAS/DAS28), and could therefore be a useful marker reflecting RA disease activity (Hassan et al., 2015).

1.11. Efferocytosis regulation through TIM

T-cell immunoglobulin- and mucin-domain-containing molecule (TIM)-3, as a negative regulator of T cell-mediated immune response, contributes to the phagocytosis of ACs through phosphatidylserine (Ps) and subsequently has a function in efferocytosis. (Kobayashi et al., 2007; Nakayama et al., 2009). Receptors, such as members of the TIM family, are utilized by phagocytic cells to internalize the AC detritus. In this respect, TIM-1 and 4 have been identified as bonding to PS (as an important “Eat-Me” signal in the efferocytosis) (Kobayashi et al., 2007) and TIM-3 may also bond to phospholipids such as PS (Nakayama et al., 2009). Tim-3 has potential to exert an effect on efferocytosis through regulation of macrophages and T cells, as blocking Tim-3 signaling by injection of soluble Tim-3 (*s*Tim) significantly increased CD36 expression in peritoneal macrophages and reduced inflammation in the liver. Tim-3 signaling may prevent macrophage activity and phagocytosis *in vivo* (Wang et al., 2017). A study by Geng et al. concluded that Tim-3 has a critical role in Th1-mediated auto- and alloimmune responses. This early evidence suggested that sTim-3 has a inhibitory effect on T cell-mediated immune response (Geng et al., 2006).

1.12. Efferocytosis regulation through TAM family (e.g., sMrt, sAXL)

The TAM family includes TYRO3, AXL, and MerTK receptor tyrosine kinases, which have complex and diverse roles in cell biology. The best known ligands for TAMs are the vitamin K (Vit-K) modified γ-carboxylated proteins, growth arrest-specific gene 6 product (Gas6) and protein S (Pros1), which are important ligands in efferocytosis (Anderson et al., 2003; Mark et al., 1996). AXL/MertK promote efferocytosis and trigger anti-inflammatory responses in macrophages through prevention of Toll-like receptor (TLR) signaling and enhancement of suppressor of cytokine 1 (SOCS1) and SOCS3 expression. SOCS proteins are intracellular, and inhibit cytokine signaling in various cell types (Rothlin et al., 2007; Zagorska et al., 2014). MerTK and AXL function are essential to immune homeostasis and accelerate immunoregulatory functions in atherosclerosis, Parkinson’s disease, intracerebral hemorrhage (ICH) and inflammatory and autoimmune diseases such as systemic lupus erythematosis (SLE) and MS (Chang et al., 2018; Nguyen et al., 2014; Recarte-Pelz et al., 2013). In addition, MerTK regulates pyrenocyte engulfment *via* central macrophages in erythroblastic islands and stimulates acute lymphoblastic leukemia (ALL) survival in the central nervous system (Krause et al., 2015; Toda et al., 2014). MerTK is expressed *via* macrophages and thus stimulates clearance of ACs and prevents the inflammatory response (Choi et al., 2013). The expression of MerTK is heterogenous among macrophage subsets, being frequently limited to anti-inflammatory “M2c” cells, differentiated through macrophage colony-stimulating factor (M-CSF) or glucocorticoids (Ambarus et al., 2012). Moreover, there is a soluble form of MerTK (sMer) in serum. The extracellular domain shedding of

MerTK receptor *via* macrophages acts as a decoy, resulting in atherosclerosis and phagocytosis (Law et al., 2015). Shedding of MerTK and AXL *via* ADAM9, ADAM10, ADAM17, and Furin (leads to increased mature ADAM10) contributes to soluble receptor forms (Chang et al., 2018; Suresh Babu et al., 2016; Weinger et al., 2009) (Fig. 3). MerTK and AXL may be cleaved from the cell membrane, reducing accessibility of cell surface receptors for initiation under inflammatory conditions (Caescu et al., 2009). The MerTK is cleaved *via* ADAM17, resulting in production of sMer (Thorp et al., 2011b). SMer and sAXL can be identified in the blood and tissue and sMer interferes with the binding of MerTK to ProS and GAS6. Disorders of AXL/MerTK ligand binding or deficiency of AXL/MerTK prevents AC efferocytosis and increases inflammatory cytokine production (Seitz et al., 2007). The sMer presents the inactive protein and prevents macrophage AC efferocytosis in mice (Sather et al., 2007). Cleavage of the MerTK receptor is facilitated *via* ADAM17 protein *via* a pathway requiring reactive oxygen species (ROS), p38 mitogen activated protein kinase (MAPK), and protein Kinase C (PKC), *in vivo* (Thorp et al., 2011a).

Conditions that result in an increase of ADAMs in cells leads to an increase of sMer. SMer is increased in response to high glucose treatment in macrophages, and it is associated with the increased expression of ADAM9 in human diabetic failing heart tissues (Suresh Babu et al., 2016). Additionally, several compounds resulting from the oxidation of hydroxy octadecadienoic acids (HODEs)) and polyunsaturated fatty acids (hydroxyeicosatetraenoic acids (HETEs) and are contained in the necrotic core of carotid plaques stimulate ADAM17 and may result in shedding of the MerTK extracellular domain and a rise to sMer in human carotid plaques (Schrijvers et al., 2007; Tabas, 2005). Defective efferocytosis causes development of the necrotic core, one factor contributing to plaque rapture and acute luminal thrombosis (Garbin et al., 2013).

MicroRNAs (miRs) modulate biological processes in disorders such as atherosclerosis, inflammation and wound healing. Mir-126 has a wide range of targets including cytokines and transmembrane proteins (Suresh Babu et al., 2016). Babu et al. reported that diabetes contributes to a reduction in miR-126 expression which, in turn, leads to ADAM9 up-regulation (Suresh Babu et al., 2016). Over-expression of ADAM9 results in formation of inactive sMer by proteolytic cleavage of MerTK (Suresh Babu et al., 2016).

1.13. Efferocytosis regulation through sTNF-RI

TNF-α and its receptors (TNF receptor I (TNF-RI) and TNF-RII) are present in soluble form, generated by extracellular domain cleavage of membrane integrated receptors (Galvani et al., 2000). Recent reports have suggested that more extensive damage to surrounding tissues, necrosis and an increase in chronic inflammation could be due to increased production of TNF-α at sites of inflammation which, in turn, result in repression of efferocytosis by neutrophils. Dexamethasone mimics the function of the anti-inflammatory cytokine IL-10 by preventing the generation of TNF-α in monocyte-derived macrophages (Michlewska et al., 2009). Furthermore, dexamethasone augments phagocytosis in monocyte-derived macrophages exposed to TNF-α. LPS and TNF-α prevent efferocytosis of neutrophils *via* monocyte-derived macrophages. The soluble form of TNF-RI (sTNF-RI) allows effective efferocytosis by binding extracellular TNF-α and thereby reducing its biological activity (Michlewska et al., 2009).

In addition, TNF-α is cleaved through TACE into a soluble cytokine. The active TNF-α release is decreased in ADAM17-deficient mice (Mohan et al., 2002). MMP1 and MMP-9 also are able to cleave pro-TNF (Mohan et al., 2002) (Fig. 4E). sTNF-RI is a chimeric protein containing a fragment crystallizable (Fc) region of human IgG1 (homodimer form) and has been shown to be a more potent inhibitor of TNF-α than the monomeric soluble form (Aggarwal and Natarajan, 1996). Galvani et al. suggested that sTNF-RI has potential as a prognostic factor in cancers such as melanoma (Galvani et al., 2000). Additionally, Michlewska et al. found that sTNF-RI reduced LPS prevention of phagocytosis (Michlewska et al., 2009).

1.14. Efferocytosis regulation through CD163$^+$

Macrophage activation leads to various phenotypes based upon different stimuli. Macrophages can be activated toward an M2 phenotype by IL-4, IL-10, and IL-13 (Higashi-Kuwata et al., 2009). M2 macrophages are associated with important cellular processes, including efferocytosis, neovascularization and wound healing (Mosser and Edwards, 2008; Zhong et al., 2018). Enhanced efferocytotic capability has been shown for M2 phenotypes, which can release anti-inflammatory cytokines, including TGF-β, as well as IL-10 (Huynh et al., 2002; Zhong et al., 2018).

M2 macrophages (CD163$^+$) have many receptors, including CD163, the hemoglobin scavenger receptor (Mosser and Edwards, 2008). Prior

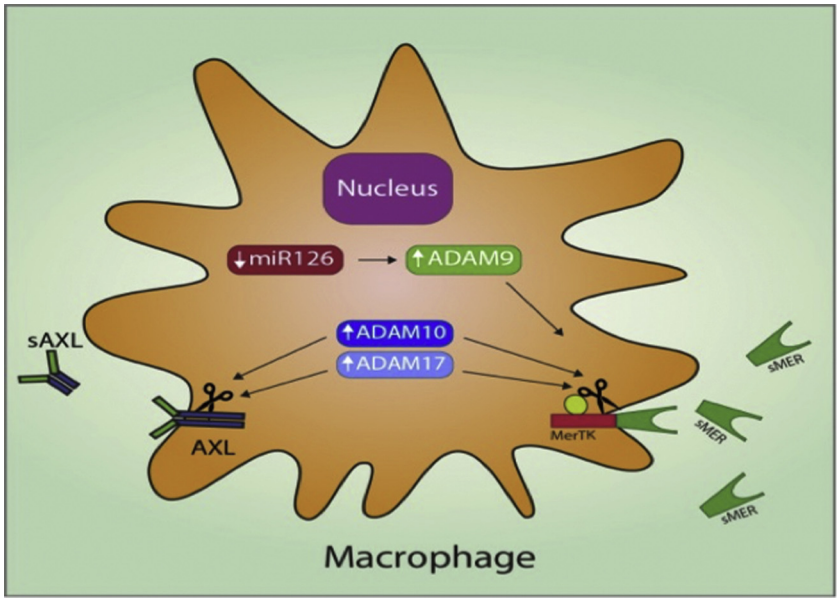

Fig. 3. Shedding of MertK and AXL, as a TAM family, *via* the ADAM9, ADAM10, and ADAM17, contribute to receptor soluble forms (Chang et al., 2018; Suresh Babu et al., 2016; Weinger et al., 2009). MertK and AXL may be cleaved from the cell membrane, reducing accessibility of the cell surface receptors for initiation under inflammatory conditions (Caescu et al., 2009). MerTK is shown to be cleaved *via* ADAM17 resulting in production of sMer (Thorp et al., 2011b). SMer could complicate the binding of MerTK with ProS and GAS6 (Seitz et al., 2007). Moreover, reduction in miR-126 expression, which in turn leads to ADAM9 up-regulation (Suresh Babu et al., 2016). Given that, over-expression of ADAM9 results in formation of inactive sMer by proteolytic cleavage of MerTK (Suresh Babu et al., 2016).
MMPs: Matrix metalloproteinases; **ADAMs:** Disintegrin and metalloproteinases; **miR**: MicroRNA; **MerTK:** Mer tyrosine kinase;

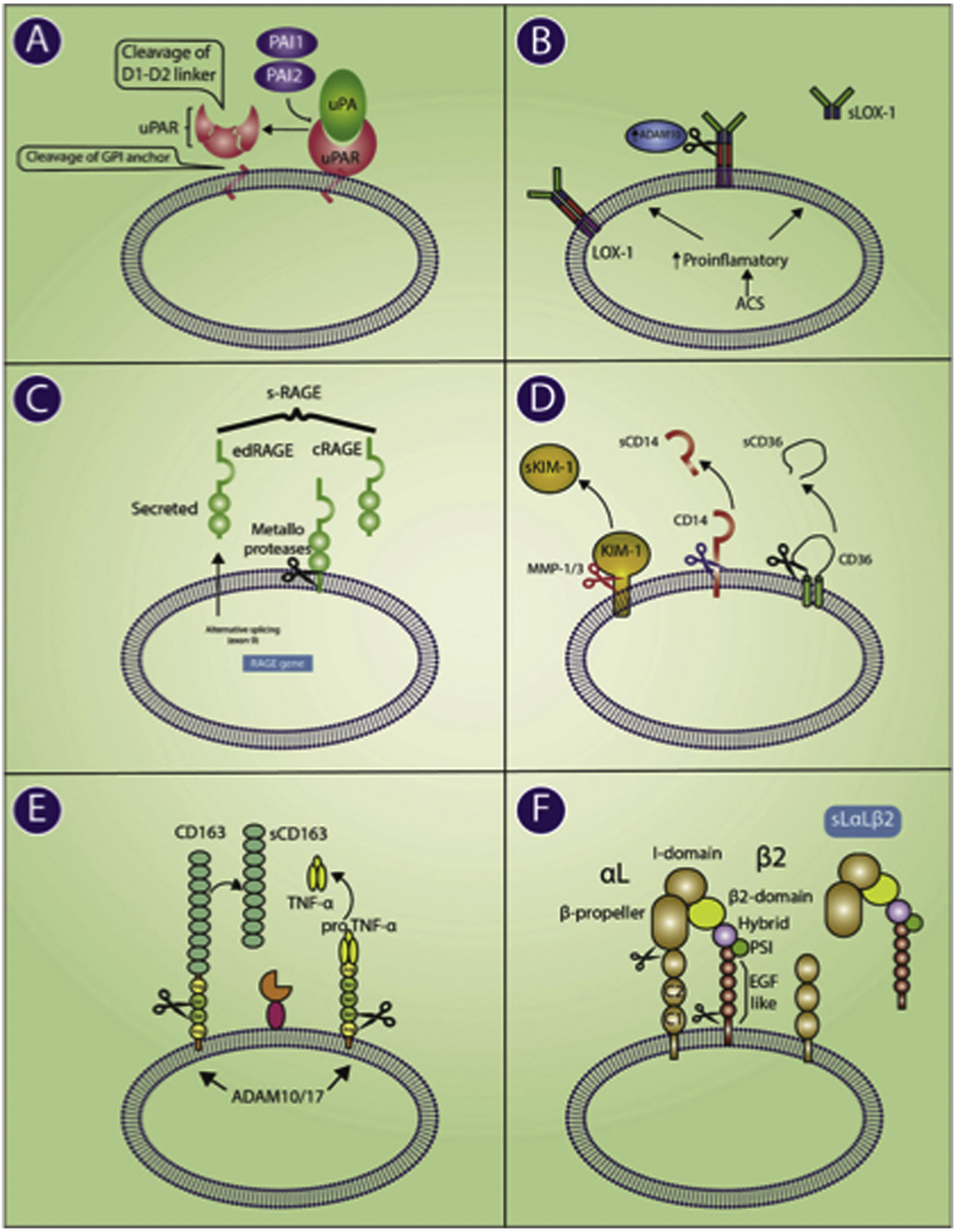

Fig. 4. Schematic showing the soluble products relating to the major receptors of efferocytosis. Cleavage of these receptors may lead to reduction of efferocytosis. **A:** suPAR is produced by MMPs, elastase, plasmin, cathepsin G & Phospholipases (Enocsson et al., 2015). **B:** sLOX-1 is produced by TACE & ADAM17 (Dreymueller et al., 2012; Zhao et al., 2011). **C:** sRAGE is produced by ADAM10 (Herold et al., 2007). **D:** sKIM-1 is produced by TACE, & ADAM17 (Gandhi et al., 2014), sCD14 is produced by MMP-9 and MMP-12 (Senft et al., 2005), sCD36 is produced by ADAM17 (Novak and Thorp, 2013). **E:** sCD163 is cleaved by ADAM10, & ADAM17 (Zhi et al., 2017) sTNF-RI is produced by TACE, &ADAM17 (Ichimura et al., 1998). **F:** αLβ2 integrin is produced by ADAM10, ADAM17 (Gomez et al., 2012).
MMPs: Matrix metalloproteinases; **ADAMs:** Disintegrin and metalloproteinases; **ADAM**: Metalloproteinase family; **UPA**: Urokinase plasminogen activator; **MMPs**: Matrix metalloproteinases; **TNF-α**: Tumor necrosis factor α; **TACE**: TNF-α converting enzyme; **RAGE**: Receptor for advanced glycation end products; **LRP**: LDL receptor–related protein; **MQs**: Macrophages; **ECs:** Endothelial cells.

research suggests that CD163 can be shed from monocytes and macrophages to induce soluble CD163 (sCD163) in response to pathological inflammatory conditions (ZHOU et al., 2016). SCD163 shedding is effected by proteolytic enzymes (Hintz et al., 2002). CD163 cleavage is effected by MMPs activated by oxidative stress, and an inflammatory stimulus results in release of sCD163 (Shimizu et al., 2012). LPS can enhance the levels of sCD163 mediated by ADAM17 (Periyalil et al., 2015) (Fig. 4E). After shedding into the circulation, sCD163 is stable and detectable in serum. Oxidative stress (*e.g.* diabetes mellitus), inflammatory stimuli (*e.g.* hemorrhagic fever with renal syndrome), and

wound healing (*e.g.* fibrotic diseases and the remodeling of connective tissues) can result in release of sCD163 from the cell surface through proteolytic cleavage (Frings et al., 2002; Levy et al., 2007; Wang et al., 2014). The significant negative association demonstrated between membrane CD163 expression and sCD163 levels suggests that plasma sCD163 may arise from circulating monocytes (Davis and Zarev, 2005). Furthermore, sCD163 actively prevents lymphocyte proliferation and T-lymphocyte activation (Timmermann et al., 2004). Greisen et al. reported that sCD163, a specific M2 macrophage activation marker, correlates with disease activity markers before treatment in early RA (Greisen et al., 2015). Levels of sMer, which are associated with sCD163 levels, correlate with SLE Disease Activity Index (SLEDAI) score (Zizzo et al., 2013a). MerTK and CD163 are both able to stimulate release of IL-10 from M2c phenotypes, as well as protecting macrophages against oxidative stress and consequent apoptosis (Anwar et al., 2009; Nielsen et al., 2010; Zizzo et al., 2012). Increased release of sMer and sCD163 may result in defective functioning of M2c macrophages, which could then lead to defective efferocytosis, chronic inflammation, and autoimmunity (Zizzo et al., 2013b). Hassan et al. reported raised serum sCD163 serum levels in patients with systemic sclerosis (SSc), a chronic autoimmune disorder, suggesting that macrophages are involved in the pathogenesis of systemic sclerosis (Hassan et al., 2016).

1.15. Efferocytosis regulation through Cluster of differentiation 14 (CD14)

Monocyte surface molecule CD14 is a central element in the immune response. CD14 is a glycosyl phosphotidyl inositol-(GPI)-anchored membrane glycoprotein expressed on macrophages/ monocytes, and neutrophils (Haziot et al., 1988). Cell surface CD14 binds to LPS and non-microbial ligands in the presence of LPS binding protein, contributing to activation of TLRs and downstream pro-inflammatory pathway signaling (Tobias and Ulevitch, 1993; Wright et al., 1990). Recent research suggests that CD14 is involved in inflammation and apoptosis (Männel and Echtenacher, 2000). CD14 also presents as a soluble form (sCD14) (Bazil et al., 1989) (Fig. 4D). Surface expression of CD14 is reduced after cell activation in monocytes and sCD14 is released (Bufler et al., 1995). Two sources are responsible for generation of sCD14, secretion from liver and through enzymatic cleavage of GPI-anchored cell membrane-bound CD14 (Bazil et al., 1989; Durieux et al., 1994; Pan et al., 2000). sCD14 may result in activation by LPS of cells with mCD14 which includes ECs and SMCs (Juan et al., 1995; Pugin et al., 1993). LPS is an activator of monocytes and prompts production of sCD14. Various TLR ligands can cause CD14 down-regulation on monocytes (Shive et al., 2015). The sCD14 dimer could be influenced by AC clearance and involved in efferocytosis (Litvack and Palaniyar, 2010). Defective AC clearance occurred in $CD14^{-/-}$ mice. The phosphatidylglycerol present on the dying cells, as a ligand, is recognized by CD14. (Kuronuma et al., 2009; Litvack and Palaniyar, 2010; Numata et al., 2010). Previous studies have shown that sCD14 levels enhance inflammatory diseases and atherosclerosis (Juan et al., 1995; Pugin et al., 1993; Reiner et al., 2013). A study by Reiner et al. demonstrated that sCD14 predicts incipient cardiovascular disease (CVD), especially in older age people (Reiner et al., 2013). IL-6 prompts hepatic expression of sCD14 in response to inflammation (Bas et al., 2004). Circulating sCD14 is regarded as an acute phase protein (APP), one of many proteins stimulated in the early response to inflammation (Bas et al., 2004).

1.16. Efferocytosis regulation through endogenous secretory RAGE (esRAGE) as a soluble form

The receptor for advanced glycation end products (RAGE) is a multiligand signal transduction receptor, and regulates responses to cell danger, damage, and stress (Ma et al., 2012). RAGE is expressed at low levels in adult cells such as macrophages (Demling et al., 2006). RAGE is now known to act as a PS receptor on alveolar macrophages, which leads to recognition and AC clearance (Friggeri et al., 2011; He et al., 2011). RAGE mediates responses to both forms of inflammation, including acute and chronic, and is complicated in several disease such as diabetes, atherosclerosis, cancer development and Alzheimer's disease (Hudson et al., 2008; Ma et al., 2012; Yan et al., 2009). RAGE also exists as a soluble (sRAGE) and is formed *via* both proteolytic cleavage of full length (fl)-RAGE and alternative mRNA splicing, a soluble form called endogenous secretory (esRAGE) (Kalea et al., 2009; Zhang et al., 2008) (Fig. 4C). SRAGE is formed *via* proteolytic cleavage of the mRAGE through ADAM10 (Kalea et al., 2009; Zhang et al., 2008). SRAGE has two functions, including: decoy receptor and pro-inflammatory. SRAGE can act as an extracellular decoy receptor, antagonizing fl-RAGE and other receptors through binding damage-associated molecular patterns (DAMPs), and preventing leukocyte recruitment in chronic and acute inflammatory response (Herold et al., 2007). However, sRAGE demonstrates pro-inflammatory properties *via* interface with Mac-1, as a pro-inflammatory phenotype (Liliensiek et al., 2004; Pullerits et al., 2006). SRAGE repressed inflammation in $IL\text{-}10^{-/-}$ mice, reduced activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), and decreased expression of inflammatory cytokines such as Il-12 (Chavakis et al., 2004; Hofmann et al., 1999). The reduced ability to engulf apoptotic neutrophils and thymocytes was demonstrated in the macrophages from transgenic $RAGE^{-/-}$ mice. RAGE can increase efferocytosis by binding to PS on pretreated $RAGE^{+/+}$ macrophages. RAGE overexpression leads to an enhanced ability to engulf ACs in human embryonic kidney 293 cells. Additionally, treatment with sRAGE increases phagocytosis of ACs *via* macrophages in both $RAGE^{+/+}$ and $RAGE^{-/-}$ animals (Friggeri et al., 2011).

1.17. Efferocytosis regulation through soluble integrin beta 2 (β2) (CD11b)

The integrin family of transmembrane receptors is involved in the interactions between cells and their environment which, in turn, regulate several functions integral to cellular physiology, including cell proliferation, differentiation, and migration (Winograd-Katz et al., 2014). In this respect, the main members of the integrin family, which regulate leukocyte-endothelial interactions, are the β2 integrins lymphocyte function-associated antigen 1 (LFA-1) (αlβ2; CD11a/CD18), the β1 integrin VLA-4 (α4β1; CD49d/CD29), and Mac-1 (αMβ2; CD11b/CD18) (Ley et al., 2007). A large number of these adhesion proteins are cleaved and shed *via* ADAM10 and ADAM17 (Garton et al., 2006; Gjelstrup et al., 2010). Gomez et al. demonstrated shedding mediated by the metalloproteinase integrin β2 leads to stimulation of macrophage efflux from inflammatory zones, and the release of heterodimers of soluble integrin. These events may limit local inflammation (Gomez et al., 2012). Previous research showed proteolytic cleavage of integrin β2 (soluble integrin β2) increases the resolution of inflammation by macrophages *via* active MMP-9 *in vitro* and *in vivo* (Vaisar et al., 2009) (Fig. 4F). Antagonism of phagocyte interactions with iC3b and inflamed endothelium can be achieved with human soluble CDllb/CD18 (sCDllb/CD18) and its functional form. Expression of a recombinant sCDllb/CD18 seems to preserve functional integrity. SCDllb/CD18 binds to iC3b *in vitro* (Dana et al., 1993). Previous research indicates that opsonization *via* iC3b results in a rise in AC engulfment by the CD18/CD11b and CD18/CD11c expressed on macrophages (Mevorach et al., 1998). CD11b is vital for the engulfment of iC3b-opsonized ACs by macrophages (Mevorach et al., 1998). A study by Schif-Zuck et al. found that macrophages convert from the $CD11b^{high}$ to the $CD11b^{low}$ phenotype after interaction with ACs *ex vivo*. Subsequently, macrophages with $CD11b^{low}$ engulfed apoptotic PMN more than macrophages with $CD11b^{high}$; effective efferocytosis produces $CD11b^{low}$ macrophages, which are vital for resolving acute inflammation (Schif-Zuck et al., 2011).

1.18. Efferocytosis regulation through soluble urokinase plasminogen activator receptor suPAR/ (CD87)

uPAR is a multi-ligand receptor expressed on several cell types, such as macrophages and neutrophils. uPAR and its receptor are involved in a range of processes, such as inflammation, proteolysis, cell migration, and angiogenesis (Thuno et al., 2009). uPAR is a GPI-anchored protein (Yang et al., 2010). In addition to the receptor form of uPAR, there is a soluble form of this receptor (suPAR) (Fig. 4A). SuPAR has been suggested as an inflammation biomarker, and is involved in tissue in several diseases including cardiovascular disease (CVD), SLE, rheumatic diseases, hepatitis, renal disorders, and carcinoma (Berres et al., 2012; D'mello et al., 2009; Sehestedt et al., 2011; Sjöwall et al., 2015; Thuno et al., 2009; Wei et al., 2011). Park et al. revealed enhanced macrophage efferocytosis of apoptotic neutrophils when uPAR was knocked-out in either neutrophils or macrophages. Interestingly, when both macrophages and neutrophils were knocked-out, efferocytosis did not increase (Park et al., 2009). Efferocytosis improved when exogenous suPAR was added to cell lines or *in vivo* (Park et al., 2009). Yang *et al.* verified that uPAR recognizes and internalizes ACs *in vivo* and *in vitro*. AC engulfing activity was reduced by macrophages in $uPAR^{-/-}$ mice. SuPAR and polyclonal anti-uPAR antibodies repressed the internalization of ACs *via* macrophages which, in turn, reduce efferocytosis. Based on a study by Yang et al., there was no defect in $uPAR^{-/-}$ macrophage uptake of live cells, but there was a defect for ACs. Phagocytosis mediated by uPAR of ACs was blocked *via* annexin V in the presence of Ca^{2+} in a HEK 293 cell line expressing human full-length uPAR (293-uPAR). Lack of kininogen, a uPAR-binding protein, in serum decreased the engulfment of ACs *in vitro* (Yang et al., 2010). Hodges et al. suggested that suPAR is a prognostic marker of atherosclerosis in CVD (Hodges et al., 2015).

1.19. Efferocytosis regulation through sCD36

The CD36 receptor plays a major role in the uptake of modified LDL, leading to lipid loading in macrophages (Kunjathoor et al., 2002). CD36 proteolysis, mediated by ADAM17, is a critical post-translational mechanism for the regulatory phagocytosis of ACs, in inflammation and inflammatory resolution (Driscoll et al., 2013). Macrophage CD36 surface levels are higher when ADAM17 is lacking, which results in a reduction in soluble CD36 (sCD36) levels (Driscoll et al., 2013) (Fig. 4D). ADAM17 cleaves membrane CD36 (mCD36) on macrophages which results in shedding of sCD36. Blocking of CD36 eliminates efferocytosis *via* Adam17-null macrophages, a process that also leads to more rapid resolution of inflammation *in vivo*. Loss of CD36 results in decreased efferocytosis which delays inflammation resolution. Expression of CD36 stimulates efferocytosis and an anti-inflammatory response in macrophages, increasing inflammation resolution in $ADAM17^{-/-}$ macrophages (Novak and Thorp, 2013). Chmielewski et al. indicated that sCD36 levels were associated with diabetes mellitus, type 2 diabetes risk and chronic kidney disease (Chmielewski et al., 2010; Handberg et al., 2010). The levels of sCD36 have been suggested to predict cardiovascular mortality in patients (Chmielewski et al., 2010).

2. Benefits of soluble products in efferocytosis as targets

2.1. Soluble receptors as therapy

Soluble receptors have been suggested as a novel form of therapy in clinical medicine. Soluble receptors are attractive as anti-cytokine mediators. They have some advantages over anti-cytokine antibodies, including high specificity, high affinity binding, and ability to stimulate the immune response. Moreover, the soluble receptors are easily distributed within a fluid compartment offering an added advantage to their function in human disease. Soluble receptors could be engineered to improve or change their biological activity. Beside being targeted therapies, they can also act as disease markers, allowing a simple blood draw to offer information concerning diagnosis, prognosis and about effective clearance of intravenously controlled colloidal drug carriers. Furthermore, soluble receptors may act like hormones. Below, we outline some advantages of soluble receptors.

2.2. Therapeutic inhibition of soluble TNF promotes remyelination by increasing myelin phagocytosis by microglia

Karamita et al. showed that sTNF production stimulates the pro-inflammatory function of microglia in demyelination in the brain. Moreover, sTNF prevents the effective function of phagocytic CNS macrophages in clearing debris of myelin and permitting remyelination in a mouse model of demyelination and remyelination. Thus, selective inhibition of sTNF through CNS-penetrating molecules, XPro1595 and TNF-signaling inhibitor for example, offers a potential therapy for stimulating remyelination and neuroprotection in diseases such as multiple sclerosis (MS) (Karamita et al., 2017).

2.3. Using sCD47 as an inhibitor of the uptake of perfluorocarbon emulsions (PFC) by macrophages

Rapid clearance of colloidal drug carriers such as liposomes, polyplexes, and emulsions *via* the mononuclear phagocyte system is a major problem for drug delivery (Moghimi et al., 2001). There have been numerous studies to investigate the ability of the circulatory durability of colloidal drug carriers as therapeutic materials. In this respect, PEGylation seems to be a popular approach for regulating particulate surfaces to prolong circulatory lifetimes (Collard et al., 2000). Designing compatible colloidal carriers or other carriers with enhanced circulatory durability have a similar physiologic basis to soluble form of receptors/ligands (Moghimi et al., 2001). A study by Hsu et al. investigated the potential of sCD47 to prevent uptake of per-fluorocarbon emulsions (PFC) *via* macrophages (Hsu et al., 2003). They showed that it is possible to use sCD47 protein to antagonize phagocytosis of colloidal drug carriers by macrophages (Hsu et al., 2003).

2.4. "Velcro" engineering of high affinity CD47 ectodomain as signal regulatory protein α (SIRPA) antagonists that enhance antibody-dependent cellular phagocytosis

Velcro engineering is a potent tool to improve protein-protein interactions. Velcro-CD47 may be used as an adjuvant for immunotherapy for cancer *in vitro*. Signal regulatory protein alpha (SIRPα) is blocked by soluble high affinity CD47 (shaCD47). CD47, as a marker of self on cancer cells, activates SIRPα on macrophages, recruiting Src homology region 2 domain-containing phosphatase-1 (SHP-1) and -2 tyrosine phosphatases and inhibiting phagocytosis of cancer cells by macrophages. ShaCD47, as a competitive antagonist, inhibits the CD47 on the surface of cancer cells from engaging SIRPα on macrophages (Ho et al., 2015).

2.5. Recombinant soluble CD93 proteins with EGF-like domains (rCD93D123, with domains 1, 2, and 3; and rCD93D23, with domains 2 and 3)

Work on rCD93D23 has shown that it is more potent than rCD93D123 in promoting the proliferation and migration of human umbilical vein endothelial cells (HUVECs). MMP-2 generation was enhanced after the HUVECs were treated with rCD93D23. Additionally, rCD93D23 stimulated differentiation of HUVECs *via* phosphoinositide 3-kinase (PI3K)/Akt/endothelial nitric oxide (eNOS) synthase and extracellular signal-regulated kinases-1/2 signaling. Studies show that the soluble EGF-like domain comprising CD93 protein is a angiogenic factor acting on the endothelium (Kao et al., 2012).

2.6. Inhibition of foam cell formation using a soluble CD68-Fc fusion protein

Lipid-rich atheromatous plaque weakening *via* dependent degradation by MMP leads to an increased incidence of acute coronary events. Hence, prevention of MMP activity is of great importance in reduction of unstable angina and myocardial infarction (MI) (Rouis, 2005). CD68 belongs to class D of the scavenger receptors and is a member of the lysosomal-associated membrane protein family. CD68 is found in several cell types, including macrophages, Langerhans cells and dendritic cells (DCs), and it binds and internalizes modified lipoproteins (Ramprasad et al., 1996). Daub et al. provided evidence that CD68-Fc decreased macrophage foam cell formation *in vitro*. This was caused both by interference of CD68-Fc with OxLDL uptake into macrophages and platelets and by preventing phagocytosis of platelet/OxLDL. MMP expression in macrophages was repressed by CD68-Fc treatment. Furthermore, CD68-Fc decreased MMP-9 activity, a critically important protease in foam cell production, atheroprogression, and plaque rupture (Daub et al., 2010). Therefore, CD68-Fc appears to be a new tool for inhibition of macrophage foam cell formation (Daub et al., 2010).

3. Conclusion

With regard to efferocytosis, recent work has highlighted alternative ways that ACs can be recognized. Efferocytosis is closely linked to the immune system and is involved in many aspects of macrophage-mediated clearance such as modulation of MMPs and production of soluble receptors. The immune system can use a varied range of opsonins and receptors to sense the existence of late ACs/NCs, a process which could lead to the recruitment of additional phagocytes to sites of inflammation and modulate the appropriate immune response. Specific decrease or blocking of inflammatory regulators or direct administration or stimulation of the mediators in anti/soluble forms that increase the suppressive action of macrophages may have therapeutic potential. Additionally, monitoring soluble receptor levels may provide additional information about human diseases, serving as biomarkers or prognostic markers. Special soluble receptors such as CD47 could serve as enhancers of drug half-life in the circulation. Greater understanding of efferocytosis and the role of soluble products should prompt further research to more fully delineate this pathway and, ultimately, to design more effective treatments. Thus, efferocytosis is an important topic, and warrants additional research.

Conflict of interest

There is no conflict of interest to declare.

References

Abdolmaleki, F., Farahani, N., Gheibi Hayat, S.M., Pirro, M., Bianconi, V., Barreto, G.E., Sahebkar, A., 2018. The role of efferocytosis in autoimmune diseases. Front. Immunol. 9, 1645.

Abou-Raya, A., Abou-Raya, S., 2006. Inflammation: a pivotal link between autoimmune diseases and atherosclerosis. Autoimmun. Rev. 5, 331–337.

Aggarwal, B.B., Natarajan, K., 1996. Tumor necrosis factors: developments during the last decade. Eur. Cytokine Netw. 7, 93–124.

Ambarus, C.A., Krausz, S., van Eijk, M., Hamann, J., Radstake, T.R., Reedquist, K.A., Tak, P.P., Baeten, D.L., 2012. Systematic validation of specific phenotypic markers for in vitro polarized human macrophages. J. Immunol. Methods 375, 196–206.

Anderson, H.A., Maylock, C.A., Williams, J.A., Paweletz, C.P., Shu, H., Shacter, E., 2003. Serum-derived protein S binds to phosphatidylserine and stimulates the phagocytosis of apoptotic cells. Nat. Immunol. 4, 87–91.

Anwar, A., Keating, A.K., Joung, D., Sather, S., Kim, G.K., Sawczyn, K.K., Brandao, L., Henson, P.M., Graham, D.K., 2009. Mer tyrosine kinase (MerTK) promotes macrophage survival following exposure to oxidative stress. J. Leukoc. Biol. 86, 73–79.

Arribas, J., Borroto, A., 2002. Protein ectodomain shedding. Chem. Rev. 102, 4627–4638.

Bas, S., Gauthier, B.R., Spenato, U., Stingelin, S., Gabay, C., 2004. CD14 is an acute-phase protein. J. Immunol. 172, 4470–4479.

Bazil, V., Baudys, M., Hilgert, I., Stefanova, I., Low, M.G., Zbrozek, J., Horejsi, V., 1989. Structural relationship between the soluble and membrane-bound forms of human monocyte surface glycoprotein CD14. Mol. Immunol. 26, 657–662.

Berres, M.L., Schlosser, B., Berg, T., Trautwein, C., Wasmuth, H.E., 2012. Soluble urokinase plasminogen activator receptor is associated with progressive liver fibrosis in hepatitis C infection. J. Clin. Gastroenterol. 46, 334–338.

Blann, A.D., McCollum, C.N., 1994. Circulating endothelial cell/leukocyte adhesion molecules in atherosclerosis. Thromb. Haemost. 72, 151–154.

Boersma, H.H., Kietselaer, B.L., Stolk, L.M., Bennaghmouch, A., Hofstra, L., Narula, J., Heidendal, G.A., Reutelingsperger, C.P., 2005. Past, present, and future of annexin A5: from protein discovery to clinical applications. J. Nucl. Med. 46, 2035–2050.

Boucher, P., Gotthardt, M., Li, W.P., Anderson, R.G., Herz, J., 2003. LRP: role in vascular wall integrity and protection from atherosclerosis. Science (New York, N.Y.) 300, 329–332.

Bufler, P., Stiegler, G., Schuchmann, M., Hess, S., Kruger, C., Stelter, F., Eckerskorn, C., Schutt, C., Engelmann, H., 1995. Soluble lipopolysaccharide receptor (CD14) is released via two different mechanisms from human monocytes and CD14 transfectants. Eur. J. Immunol. 25, 604–610.

Caescu, C.I., Jeschke, G.R., Turk, B.E., 2009. Active-site determinants of substrate recognition by the metalloproteinases TACE and ADAM10. Biochem. J. 424, 79–88.

Caligiuri, G., Groyer, E., Khallou-Laschet, J., Zen, A.A.H., Sainz, J., Urbain, D., Gaston, A.-T., Lemitre, M., Nicoletti, A., Lafont, A., 2005. Reduced immunoregulatory $CD31^+$ T cells in the blood of atherosclerotic mice with plaque thrombosis. Arterioscler. Thromb. Vasc. Biol. 25, 1659–1664.

Caligluri, G., Rudling, M., Ollivier, V., Jacob, M.-P., Michel, J.-B., Hansson, G.K., Nicoletti, A., 2003. Interleukin-10 deficiency increases atherosclerosis, thrombosis, and low-density lipoproteins in apolipoprotein E knockout mice. Mol. Med. 9, 10–17.

Chalaris, A., Adam, N., Sina, C., Rosenstiel, P., Lehmann-Koch, J., Schirmacher, P., Hartmann, D., Cichy, J., Gavrilova, O., Schreiber, S., Jostock, T., Matthews, V., Hasler, R., Becker, C., Neurath, M.F., Reiss, K., Saftig, P., Scheller, J., Rose-John, S., 2010. Critical role of the disintegrin metalloprotease ADAM17 for intestinal inflammation and regeneration in mice. J. Exp. Med. 207, 1617–1624.

Chang, C.-F., Goods, B.A., Askenase, M.H., Hammond, M.D., Renfroe, S.C., Steinschneider, A.F., Landreneau, M.J., Ai, Y., Beatty, H.E., da Costa, L.H.A., Mack, M., Sheth, K.N., Greer, D.M., Huttner, A., Coman, D., Hyder, F., Ghosh, S., Rothlin, C.V., Love, J.C., Sansing, L.H., 2018. Erythrocyte efferocytosis modulates macrophages towards recovery after intracerebral hemorrhage. J. Clin. Invest. 128, 607–624.

Chatzizisis, Y.S., Coskun, A.U., Jonas, M., Edelman, E.R., Feldman, C.L., Stone, P.H., 2007. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. J. Am. Coll. Cardiol. 49, 2379–2393.

Chavakis, T., Bierhaus, A., Nawroth, P.P., 2004. RAGE (receptor for advanced glycation end products): a central player in the inflammatory response. Microbes Infect. 6, 1219–1225.

Chen, Y., Wang, Q., Shi, B., Xu, P., Hu, Z., Bai, L., Zhang, X., 2011. Development of a sandwich ELISA for evaluating soluble PD-L1 (CD274) in human sera of different ages as well as supernatants of PD-L1 + cell lines. Cytokine 56, 231–238.

Chmielewski, M., Bragfors-Helin, A.-C., Stenvinkel, P., Lindholm, B., Anderstam, B., 2010. Serum soluble CD36, assessed by a novel monoclonal antibody-based sandwich ELISA, predicts cardiovascular mortality in dialysis patients. Clin. Chim. Acta 411, 2079–2082.

Choi, J.Y., Park, H.J., Lee, Y.J., Byun, J., Youn, Y.S., Choi, J.H., Woo, S.Y., Kang, J.L., 2013. Upregulation of Mer receptor tyrosine kinase signaling attenuated lipopolysaccharide-induced lung inflammation. J. Pharmacol. Exp. Ther. 344, 447–458.

Chuang, T.Y., Guo, Y., Seki, S.M., Rosen, A.M., Johanson, D.M., Mandell, J.W., Lucchinetti, C.F., Gaultier, A., 2016. LRP1 expression in microglia is protective during CNS autoimmunity. Acta Neuropathol. Commun. 4, 68.

Collard, W.T., Yang, Y., Kwok, K.Y., Park, Y., Rice, K.G., 2000. Biodistribution, metabolism, and in vivo gene expression of low molecular weight glycopeptide polyethylene glycol peptide DNA co-condensates. J. Pharm. Sci. 89, 499–512.

Cui, D., Thorp, E., Li, Y., Wang, N., Yvan-Charvet, L., Tall, A.R., Tabas, I., 2007. Pivotal advance: macrophages become resistant to cholesterol-induced death after phagocytosis of apoptotic cells. J. Leukoc. Biol. 82, 1040–1050.

D'mello, V., Singh, S., Wu, Y., Birge, R.B., 2009. The urokinase plasminogen activator receptor promotes efferocytosis of apoptotic cells. J. Biol. Chem. 284, 17030–17038.

Dai, S., Jia, R., Zhang, X., Fang, Q., Huang, L., 2014. The PD-1/PD-Ls pathway and autoimmune diseases. Cell. Immunol. 290, 72–79.

Dana, N., Fathallah, D.M., Arnaout, M.A., 1993. Function of a Soluble Human β2 Integrin CD11b/CD18, Structure, Function, and Regulation of Molecules Involved in Leukocyte Adhesion. Springer, pp. 34–44.

Daub, K., Siegel-Axel, D., Schönberger, T., Leder, C., Seizer, P., Müller, K., Schaller, M., Penz, S., Menzel, D., Büchele, B., Bültmann, A., Münch, G., Lindemann, S., Simmet, T., Gawaz, M., 2010. Inhibition of foam cell formation using a soluble CD68-Fc fusion protein. J. Mol. Med. 88, 909–920.

Davis, B.H., Zarev, P.V., 2005. Human monocyte CD163 expression inversely correlates with soluble CD163 plasma levels. Cytometry B Clin. Cytom. 63, 16–22.

De Freitas, A., Banerjee, S., Xie, N., Cui, H., Davis, K.I., Friggeri, A., Fu, M., Abraham, E., Liu, G., 2012. Identification of TLT2 as an engulfment receptor for apoptotic cells. J. Immunol. 188, 6381–6388.

Demling, N., Ehrhardt, C., Kasper, M., Laue, M., Knels, L., Rieber, E.P., 2006. Promotion of cell adherence and spreading: a novel function of RAGE, the highly selective differentiation marker of human alveolar epithelial type I cells. Cell Tissue Res. 323, 475–488.

Dreymueller, D., Pruessmeyer, J., Groth, E., Ludwig, A., 2012. The role of ADAM-mediated shedding in vascular biology. Eur. J. Cell Biol. 91, 472–485.

Driscoll, W.S., Vaisar, T., Tang, J., Wilson, C.L., Raines, E.W., 2013. Macrophage ADAM17 deficiency augments CD36-dependent apoptotic cell uptake and the linked anti-inflammatory phenotype. Circ. Res. 113, 52–61.

Duffield, J.S., 2003. The inflammatory macrophage: a story of Jekyll and Hyde. Clin. Sci. (Lond., Engl.: 1979) 104, 27–38.
Durieux, J.J., Vita, N., Popescu, O., Guette, F., Calzada-Wack, J., Munker, R., Schmidt, R.E., Lupker, J., Ferrara, P., Ziegler-Heitbrock, H.W., et al., 1994. The two soluble forms of the lipopolysaccharide receptor, CD14: characterization and release by normal human monocytes. Eur. J. Immunol. 24, 2006–2012.
Elward, K., Griffiths, M., Mizuno, M., Harris, C.L., Neal, J.W., Morgan, B.P., Gasque, P., 2005. CD46 plays a key role in tailoring innate immune recognition of apoptotic and necrotic cells. J. Biol. Chem. 280, 36342–36354.
Enocsson, H., Sjowall, C., Wettero, J., 2015. Soluble urokinase plasminogen activator receptor–a valuable biomarker in systemic lupus erythematosus? Clin. Chim. Acta 444, 234–241.
Fadok, V.A., Voelker, D.R., Campbell, P.A., Cohen, J.J., Bratton, D.L., Henson, P.M., 1992. Exposure of phosphatidylserine on the surface of apoptotic lymphocytes triggers specific recognition and removal by macrophages. J. Immunol. (Baltimore, Md.: 1950) 148, 2207–2216.
Fischer, O.M., Hart, S., Gschwind, A., Prenzel, N., Ullrich, A., 2004. Oxidative and osmotic stress signaling in tumor cells is mediated by ADAM proteases and heparin-binding epidermal growth factor. Mol. Cell. Biol. 24, 5172–5183.
Freeman, G.J., Long, A.J., Iwai, Y., Bourque, K., Chernova, T., Nishimura, H., Fitz, L.J., Malenkovich, N., Okazaki, T., Byrne, M.C., Horton, H.F., Fouser, L., Carter, L., Ling, V., Bowman, M.R., Carreno, B.M., Collins, M., Wood, C.R., Honjo, T., 2000. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J. Exp. Med. 192, 1027–1034.
Friggeri, A., Banerjee, S., Biswas, S., De Freitas, A., Liu, G., Bierhaus, A., Abraham, E., 2011. Participation of the receptor for advanced glycation end products in efferocytosis. J. Immunol. 186, 6191–6198.
Frings, W., Dreier, J., Sorg, C., 2002. Only the soluble form of the scavenger receptor CD163 acts inhibitory on phorbol ester-activated T-lymphocytes, whereas membrane-bound protein has no effect. FEBS Lett. 526, 93–96.
Galvani, V., Pretnar Hartman, K., Rupreht, R.R., Novakovic, S., Stabuc, B., Ocvirk, J., Menart, V., Gaberc Porekar, V., Stalc, A., Rozman, P., Curin Serbec, V., 2000. Soluble tumor necrosis factor receptor I (sTNFRI) as a prognostic factor in melanoma patients in Slovene population. Pflugers Archiv: Eur. J. Physiol. 440, R61–63.
Gandhi, R., Yi, J., Ha, J., Shi, H., Ismail, O., Nathoo, S., Bonventre, J.V., Zhang, X.Z., Gunaratnam, L., 2014. Accelerated receptor shedding inhibits kidney injury molecule-1 (KIM-1)-mediated efferocytosis. Am. J. Physiol.-Renal Physiol. 307, F205–F221.
Garbin, U., Baggio, E., Stranieri, C., Pasini, A., Manfro, S., Mozzini, C., Vallerio, P., Lipari, G., Merigo, F., Guidi, G., Cominacini, L., Fratta Pasini, A., 2013. Expansion of necrotic core and shedding of Mertk receptor in human carotid plaques: a role for oxidized polyunsaturated fatty acids? Cardiovasc. Res. 97, 125–133.
Gardai, S.J., Bratton, D.L., Ogden, C.A., Henson, P.M., 2006. Recognition ligands on apoptotic cells: a perspective. J. Leukoc. Biol. 79, 896–903.
Garton, K.J., Gough, P.J., Raines, E.W., 2006. Emerging roles for ectodomain shedding in the regulation of inflammatory responses. J. Leukoc. Biol. 79, 1105–1116.
Geng, H., Zhang, G.-M., Li, D., Zhang, H., Yuan, Y., Zhu, H.-G., Xiao, H., Han, L.-F., Feng, Z.-H., 2006. Soluble form of T cell Ig mucin 3 is an inhibitory molecule in T cell-mediated immune response. J. Immunol. 176, 1411–1420.
Gheibi Hayat, S.M., Bianconi, V., Pirro, M., Sahebkar, A., 2018. Efferocytosis: molecular mechanisms and pathophysiological perspectives. Immunol. Cell Biol. https://doi.org/10.1111/imcb.12206. [Epub ahead of print].
Gjelstrup, L.C., Boesen, T., Kragstrup, T.W., Jorgensen, A., Klein, N.J., Thiel, S., Deleuran, B.W., Vorup-Jensen, T., 2010. Shedding of large functionally active CD11/CD18 Integrin complexes from leukocyte membranes during synovial inflammation distinguishes three types of arthritis through differential epitope exposure. J. Immunol. (Baltimore, Md.: 1950) 185, 4154–4168.
Gold, L.I., Eggleton, P., Sweetwyne, M.T., Van Duyn, L.B., Greives, M.R., Naylor, S.M., Michalak, M., Murphy-Ullrich, J.E., 2010. Calreticulin: non-endoplasmic reticulum functions in physiology and disease. FASEB J. 24, 665–683.
Gomez, I.G., Tang, J., Wilson, C.L., Yan, W., Heinecke, J.W., Harlan, J.M., Raines, E.W., 2012. Metalloproteinase-mediated shedding of integrin β2 promotes macrophage efflux from inflammatory sites. J. Biol. Chem. 287, 4581–4589.
Gorczynski, R.M., 2012. CD200:CD200R-mediated regulation of immunity. ISRN Immunol. 2012, 18.
Gorovoy, M., Gaultier, A., Campana, W.M., Firestein, G.S., Gonias, S.L., 2010. Inflammatory mediators promote production of shed LRP1/CD91, which regulates cell signaling and cytokine expression by macrophages. J. Leukoc. Biol. 88, 769–778.
Greisen, S.R., Moller, H.J., Stengaard-Pedersen, K., Hetland, M.L., Horslev-Petersen, K., Junker, P., Ostergaard, M., Hvid, M., Deleuran, B., 2015. Macrophage activity assessed by soluble CD163 in early rheumatoid arthritis: association with disease activity but different response patterns to synthetic and biologic DMARDs. Clin. Exp. Rheumatol. 33, 498–502.
Grimsley, C., Ravichandran, K.S., 2003. Cues for apoptotic cell engulfment: eat-me, don't eat-me and come-get-me signals. Trends Cell Biol. 13, 648–656.
Hakulinen, J., Junnikkala, S., Sorsa, T., Meri, S., 2004. Complement inhibitor membrane cofactor protein (MCP; CD46) is constitutively shed from cancer cell membranes in vesicles and converted by a metalloproteinase to a functionally active soluble form. Eur. J. Immunol. 34, 2620–2629.
Handberg, A., Norberg, M., Stenlund, H., Hallmans, G., Attermann, J., Eriksson, J.W., 2010. Soluble CD36 (sCD36) clusters with markers of insulin resistance, and high sCD36 is associated with increased type 2 diabetes risk. J. Clin. Endocrinol. Metab. 95, 1939–1946.
Hassan, W.A., Baraka, E.A., Fouad, N.A., 2015. Clinical significance of soluble programmed death-1(sPD-1) in rheumatoid arthritis patients: relation to disease activity and functional status. Egypt. Rheumatol. 37, 165–169.
Hassan, W.A.S.E., Baraka, E.A.E., Elnady, B.M., Gouda, T.M., Fouad, N., 2016. Serum Soluble CD163 and its association with various disease parameters in patients with systemic sclerosis. Eur. J. Rheumatol. 3, 95–100.
Haziot, A., Chen, S., Ferrero, E., Low, M., Silber, R., Goyert, S., 1988. The monocyte differentiation antigen, CD14, is anchored to the cell membrane by a phosphatidylinositol linkage. J. Immunol. 141, 547–552.
He, M., Kubo, H., Morimoto, K., Fujino, N., Suzuki, T., Takahasi, T., Yamada, M., Yamaya, M., Maekawa, T., Yamamoto, Y., Yamamoto, H., 2011. Receptor for advanced glycation end products binds to phosphatidylserine and assists in the clearance of apoptotic cells. EMBO Rep. 12, 358–364.
Heaney, M.L., Golde, D.W., 1998. Soluble receptors in human disease. J. Leukoc. Biol. 64, 135–146.
Herold, K., Moser, B., Chen, Y., Zeng, S., Yan, S.F., Ramasamy, R., Emond, J., Clynes, R., Schmidt, A.M., 2007. Receptor for advanced glycation end products (RAGE) in a dash to the rescue: inflammatory signals gone awry in the primal response to stress. J. Leukoc. Biol. 82, 204–212.
Higashi-Kuwata, N., Makino, T., Inoue, Y., Takeya, M., Ihn, H., 2009. Alternatively activated macrophages (M2 macrophages) in the skin of patient with localized scleroderma. Exp. Dermatol. 18, 727–729.
Hintz, K.A., Rassias, A.J., Wardwell, K., Moss, M.L., Morganelli, P.M., Pioli, P.A., Givan, A.L., Wallace, P.K., Yeager, M.P., Guyre, P.M., 2002. Endotoxin induces rapid metalloproteinase-mediated shedding followed by up-regulation of the monocyte hemoglobin scavenger receptor CD163. J. Leukoc. Biol. 72, 711–717.
Ho, C.C.M., Guo, N., Sockolosky, J.T., Ring, A.M., Weiskopf, K., Özkan, E., Mori, Y., Weissman, I.L., Garcia, K.C., 2015. "Velcro" engineering of high affinity CD47 ectodomain as signal regulatory protein α (SIRPα) antagonists that enhance antibody-dependent cellular phagocytosis. J. Biol. Chem. 290, 12650–12663.
Hodges, G.W., Bang, C.N., Wachtell, K., Eugen-Olsen, J., Jeppesen, J.L., 2015. suPAR: a new biomarker for cardiovascular disease? Can. J. Cardiol. 31, 1293–1302.
Hoffmann, P.R., deCathelineau, A.M., Ogden, C.A., Leverrier, Y., Bratton, D.L., Daleke, D.L., Ridley, A.J., Fadok, V.A., Henson, P.M., 2001. Phosphatidylserine (PS) induces PS receptor-mediated macropinocytosis and promotes clearance of apoptotic cells. J. Cell Biol. 155, 649–659.
Hofmann, M.A., Drury, S., Fu, C., Qu, W., Taguchi, A., Lu, Y., Avila, C., Kambham, N., Bierhaus, A., Nawroth, P., Neurath, M.F., Slattery, T., Beach, D., McClary, J., Nagashima, M., Morser, J., Stern, D., Schmidt, A.M., 1999. RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. Cell 97, 889–901.
Hsu, Y.C., Acuna, M., Tahara, S.M., Peng, C.A., 2003. Reduced phagocytosis of colloidal carriers using soluble CD47. Pharm. Res. 20, 1539–1542.
Hudson, B.I., Carter, A.M., Harja, E., Kalea, A.Z., Arriero, M., Yang, H., Grant, P.J., Schmidt, A.M., 2008. Identification, classification, and expression of RAGE gene splice variants. FASEB J. 22, 1572–1580.
Huynh, M.L., Fadok, V.A., Henson, P.M., 2002. Phosphatidylserine-dependent ingestion of apoptotic cells promotes TGF-beta1 secretion and the resolution of inflammation. J. Clin. Invest. 109, 41–50.
Ichimura, T., Bonventre, J.V., Bailly, V., Wei, H., Hession, C.A., Cate, R.L., Sanicola, M., 1998. Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. J. Biol. Chem. 273, 4135–4142.
Josephs, D.H., Sarker, D., 2015. Pharmacodynamic biomarker development for PI3K pathway therapeutics. Transl. Oncogenomics 7, 33–49.
Juan, T.S.-C., Kelley, M.J., Johnson, D.A., Busse, L.A., Hailman, E., Wright, S.D., Lichenstein, H.S., 1995. Soluble CD14 truncated at amino acid 152 binds lipopolysaccharide (LPS) and enables cellular response to LPS. J. Biol. Chem. 270, 1382–1387.
Kalea, A.Z., Reiniger, N., Yang, H., Arriero, M., Schmidt, A.M., Hudson, B.I., 2009. Alternative splicing of the murine receptor for advanced glycation end-products (RAGE) gene. FASEB J. 23, 1766–1774.
Kao, Y.C., Jiang, S.J., Pan, W.A., Wang, K.C., Chen, P.K., Wei, H.J., Chen, W.S., Chang, B.I., Shi, G.Y., Wu, H.L., 2012. The epidermal growth factor-like domain of CD93 is a potent angiogenic factor. PLoS One 7.
Karamita, M., Barnum, C., Möbius, W., Tansey, M.G., Szymkowski, D.E., Lassmann, H., Probert, L., 2017. Therapeutic inhibition of soluble brain TNF promotes remyelination by increasing myelin phagocytosis by microglia. JCI Insight 2, e87455.
Karp, C.L., Wysocka, M., Wahl, L.M., Ahearn, J.M., Cuomo, P.J., Sherry, B., Trinchieri, G., Griffin, D.E., 1996. Mechanism of suppression of cell-mediated immunity by measles virus. Science (New York, N.Y.) 273, 228–231.
Kasikara, C., Kumar, S., Kimani, S., Tsou, W.I., Geng, K., Davra, V., Sriram, G., Devoe, C., Nguyen, K.Q.N., Antes, A., Krantz, A., Rymarczyk, G., Wilczynski, A., Empig, C., Freimark, B., Gray, M., Schlunegger, K., Hutchins, J., Kotenko, S.V., Birge, R.B., 2017. Phosphatidylserine sensing by TAM receptors regulates AKT-dependent chemoresistance and PD-L1 expression. Mol. Cancer Res. 15, 753–764.
Keir, M.E., Liang, S.C., Guleria, I., Latchman, Y.E., Qipo, A., Albacker, L.A., Koulmanda, M., Freeman, G.J., Sayegh, M.H., Sharpe, A.H., 2006. Tissue expression of PD-L1 mediates peripheral T cell tolerance. J. Exp. Med. 203, 883–895.
Kenis, H., van Genderen, H., Deckers, N.M., Lux, P.A., Hofstra, L., Narula, J., Reutelingsperger, C.P., 2006. Annexin A5 inhibits engulfment through internalization of PS-expressing cell membrane patches. Exp. Cell Res. 312, 719–726.
Kobayashi, N., Karisola, P., Peña-Cruz, V., Dorfman, D.M., Jinushi, M., Umetsu, S.E., Butte, M.J., Nagumo, H., Chernova, I., Zhu, B., Sharpe, A.H., Ito, S., Dranoff, G., Kaplan, G.G., Casasnovas, J.M., Umetsu, D.T., DeKruyff, R.H., Freeman, G.J., 2007. T cell Immunoglobulin Mucin Protein (TIM)-4 binds phosphatidylserine and mediates uptake of apoptotic cells. Immunity 27, 927–940.
Kojima, Y., Downing, K., Kundu, R., Miller, C., Dewey, F., Lancero, H., Raaz, U., Perisic, L., Hedin, U., Schadt, E., Maegdefessel, L., Quertermous, T., Leeper, N.J., 2014.

Cyclin-dependent kinase inhibitor 2B regulates efferocytosis and atherosclerosis. J. Clin. Invest. 124, 1083–1097.
Kojima, Y., Weissman, I.L., Leeper, N.J., 2017. The role of efferocytosis in atherosclerosis. Circulation 135, 476–489.
Krause, S., Pfeiffer, C., Strube, S., Alsadeq, A., Fedders, H., Vokuhl, C., Loges, S., Waizenegger, J., Ben-Batalla, I., Cario, G., Moricke, A., Stanulla, M., Schrappe, M., Schewe, D.M., 2015. Mer tyrosine kinase promotes the survival of t(1;19)-positive acute lymphoblastic leukemia (ALL) in the central nervous system (CNS). Blood 125, 820–830.
Kuipers, H., Muskens, F., Willart, M., Hijdra, D., van Assema, F.B., Coyle, A.J., Hoogsteden, H.C., Lambrecht, B.N., 2006. Contribution of the PD-1 ligands/PD-1 signaling pathway to dendritic cell-mediated CD4+ T cell activation. Eur. J. Immunol. 36, 2472–2482.
Kunjathoor, V.V., Febbraio, M., Podrez, E.A., Moore, K.J., Andersson, L., Koehn, S., Rhee, J.S., Silverstein, R., Hoff, H.F., Freeman, M.W., 2002. Scavenger receptors class A-I/II and CD36 are the principal receptors responsible for the uptake of modified low density lipoprotein leading to lipid loading in macrophages. J. Biol. Chem. 277, 49982–49988.
Kuronuma, K., Mitsuzawa, H., Takeda, K., Nishitani, C., Chan, E.D., Kuroki, Y., Nakamura, M., Voelker, D.R., 2009. Anionic pulmonary surfactant phospholipids inhibit inflammatory responses from alveolar macrophages and U937 cells by binding the lipopolysaccharide-interacting proteins CD14 and MD-2. J. Biol. Chem. 284, 25488–25500.
Law, A.L., Parinot, C., Chatagnon, J., Gravez, B., Sahel, J.A., Bhattacharya, S.S., Nandrot, E.F., 2015. Cleavage of Mer tyrosine kinase (MerTK) from the cell surface contributes to the regulation of retinal phagocytosis. J. Biol. Chem. 290, 4941–4952.
Levy, A.P., Purushothaman, K.R., Levy, N.S., Purushothaman, M., Strauss, M., Asleh, R., Marsh, S., Cohen, O., Moestrup, S.K., Moller, H.J., Zias, E.A., Benhayon, D., Fuster, V., Moreno, P.R., 2007. Downregulation of the hemoglobin scavenger receptor in individuals with diabetes and the Hp 2-2 genotype: implications for the response to intraplaque hemorrhage and plaque vulnerability. Circ. Res. 101, 106–110.
Ley, K., Laudanna, C., Cybulsky, M.I., Nourshargh, S., 2007. Getting to the site of inflammation: the leukocyte adhesion cascade updated. Nat. Rev. Immunol. 7, 678–689.
Li, Y., Zhao, L.-d., Tong, L.-s., Qian, S.-n., Ren, Y., Zhang, L., Ding, X., Chen, Y., Wang, Y.-x., Zhang, W., Zeng, X.-f., Zhang, F.-c., Tang, F.-l., Zhang, X., Ba, D.-n., He, W., Cao, X.-t., Lipsky, P.E., 2012. Aberrant CD200/CD200R1 expression and function in systemic lupus erythematosus contributes to abnormal T-cell responsiveness and dendritic cell activity. Arthritis Res. Ther. 14 R123-R123.
Li, Y., Xiao, Y., Su, M., Zhang, R., Ding, J., Hao, X., Ma, Y., 2016. Role of soluble programmed death-1 (sPD-1) and sPD-ligand 1 in patients with cystic echinococcosis. Exp. Ther. Med. 11, 251–256.
Liliensiek, B., Weigand, M.A., Bierhaus, A., Nicklas, W., Kasper, M., Hofer, S., Plachky, J., Grone, H.J., Kurschus, F.C., Schmidt, A.M., Yan, S.D., Martin, E., Schleicher, E., Stern, D.M., Hammerling, G.G., Nawroth, P.P., Arnold, B., 2004. Receptor for advanced glycation end products (RAGE) regulates sepsis but not the adaptive immune response. J. Clin. Invest. 113, 1641–1650.
Lillis, A.P., Van Duyn, L.B., Murphy-Ullrich, J.E., Strickland, D.K., 2008. The low density lipoprotein receptor-related protein 1: unique tissue-specific functions revealed by selective gene knockout studies. Physiol. Rev. 88, 887–918.
Liszewski, M.K., Leung, M., Cui, W., Subramanian, V.B., Parkinson, J., Barlow, P.N., Manchester, M., Atkinson, J.P., 2000. Dissecting sites important for complement regulatory activity in membrane cofactor protein (MCP; CD46). J. Biol. Chem. 275, 37692–37701.
Litvack, M.L., Palaniyar, N., 2010. Soluble innate immune pattern-recognition proteins for clearing dying cells and cellular components: implications on exacerbating or resolving inflammation. Innate Immun. 16, 191–200.
Litwin, M., Clark, K., Noack, L., Furze, J., Berndt, M., Albelda, S., Vadas, M., Gamble, J., 1997. Novel cytokine-independent induction of endothelial adhesion molecules regulated by platelet/endothelial cell adhesion molecule (CD31). J. Cell Biol. 139, 219–228.
Liu, Y., Li, D., Chen, J., Xie, J., Bandyopadhyay, S., Zhang, D., Nemarkommula, A.R., Liu, H., Mehta, J.L., Hermonat, P.L., 2006. Inhibition of atherogenesis in LDLR knockout mice by systemic delivery of adeno-associated virus type 2-hIL-10. Atherosclerosis 188, 19–27.
Losy, J., Niezgoda, A., Wender, M., 1999. Increased serum levels of soluble PECAM-1 in multiple sclerosis patients with brain gadolinium-enhancing lesions. J. Neuroimmunol. 99, 169–172.
Ma, W.C., Rai, V., Hudson, B.I., Song, F., Schmidt, A.M., Barile, G.R., 2012. RAGE binds C1q and enhances C1q-mediated phagocytosis. Cell. Immunol. 274, 72–82.
Männel, D.N., Echtenacher, B., 2000. TNF In the Inflammatory Response, Cd14 in the Inflammatory Response. Karger Publishers, pp. 141–161.
Marie, J.C., Astier, A.L., Rivailler, P., Rabourdin-Combe, C., Wild, T.F., Horvat, B., 2002. Linking innate and acquired immunity: divergent role of CD46 cytoplasmic domains in T cell induced inflammation. Nat. Immunol. 3, 659–666.
Mark, M.R., Chen, J., Hammonds, R.G., Sadick, M., Godowsk, P.J., 1996. Characterization of Gas6, a member of the superfamily of G domain-containing proteins, as a ligand for Rse and Axl. J. Biol. Chem. 271, 9785–9789.
Mevorach, D., Mascarenhas, J.O., Gershov, D., Elkon, K.B., 1998. Complement-dependent clearance of apoptotic cells by human macrophages. J. Exp. Med. 188, 2313–2320.
Michlewska, S., Dransfield, I., Megson, I.L., Rossi, A.G., 2009. Macrophage phagocytosis of apoptotic neutrophils is critically regulated by the opposing actions of pro-inflammatory and anti-inflammatory agents: key role for TNF-alpha. FASEB J. 23, 844–854.
Mihrshahi, R., Barclay, A.N., Brown, M.H., 2009. Essential roles for Dok2 and RasGAP in CD200 receptor-mediated regulation of human myeloid cells. J. Immunol. 183, 4879–4886.
Miller, T.W., Isenberg, J.S., Shih, H.B., Wang, Y., Roberts, D.D., 2010. Amyloid-beta inhibits No-cGMP signaling in a CD36- and CD47-dependent manner. PLoS One 5, e15686.
Moghimi, S.M., Hunter, A.C., Murray, J.C., 2001. Long-circulating and target-specific nanoparticles: theory to practice. Pharmacol. Rev. 53, 283–318.
Mohan, M.J., Seaton, T., Mitchell, J., Howe, A., Blackburn, K., Burkhart, W., Moyer, M., Patel, I., Waitt, G.M., Becherer, J.D., Moss, M.L., Milla, M.E., 2002. The tumor necrosis factor-alpha converting enzyme (TACE): a unique metalloproteinase with highly defined substrate selectivity. Biochemistry 41, 9462–9469.
Morgan, B.P., 2016. The membrane attack complex as an inflammatory trigger. Immunobiology 221, 747–751.
Moss, M.L., Lambert, M.H., 2002. Shedding of membrane proteins by ADAM family proteases. Essays Biochem. 38, 141–153.
Mosser, D.M., Edwards, J.P., 2008. Exploring the full spectrum of macrophage activation. Nat. Rev. Immunol. 8, 958–969.
Muller, W.A., Weigl, S.A., Deng, X., Phillips, D.M., 1993. PECAM-1 is required for transendothelial migration of leukocytes. J. Exp. Med. 178, 449–460.
Muller-Eberhard, H.J., 1986. The membrane attack complex of complement. Annu. Rev. Immunol. 4, 503–528.
Murase, T., Kume, N., Kataoka, H., Minami, M., Sawamura, T., Masaki, T., Kita, T., 2000. Identification of soluble forms of lectin-like oxidized LDL Receptor-1. Arterioscler. Thromb. Vasc. Biol. 20, 715–720.
Murphy, G., Murthy, A., Khokha, R., 2008. Clipping, shedding and RIPping keep immunity on cue. Trends Immunol. 29, 75–82.
Naganuma, Y., Satoh, K., Yi, Q., Asazuma, N., Yatomi, Y., Ozaki, Y., 2004. Cleavage of platelet endothelial cell adhesion molecule-1 (PECAM-1) in platelets exposed to high shear stress. J. Thromb. Haemost. 2, 1998–2008.
Nakayama, M., Akiba, H., Takeda, K., Kojima, Y., Hashiguchi, M., Azuma, M., Yagita, H., Okumura, K., 2009. Tim-3 mediates phagocytosis of apoptotic cells and cross-presentation. Blood 113, 3821–3830.
Nanda, V., Downing, K.P., Ye, J., Xiao, S., Kojima, Y., Spin, J.M., DiRenzo, D., Nead, K.T., Connolly, A.J., Dandona, S., Perisic, L., Hedin, U., Maegdefessel, L., Dalman, J., Guo, L., Zhao, X., Kolodgie, F.D., Virmani, R., Davis Jr., H.R., Leeper, N.J., 2016. CDKN2B regulates TGFbeta signaling and smooth muscle cell investment of hypoxic neovessels. Circ. Res. 118, 230–240.
Nathan, C., Ding, A., 2010. Nonresolving inflammation. Cell 140, 871–882.
Nativel, B., Marimoutou, M., Thon-Hon, V.G., Gunasekaran, M.K., Andries, J., Stanislas, G., Planesse, C., Da Silva, C.R., Cesari, M., Iwema, T., Gasque, P., Viranaicken, W., 2013. Soluble HMGB1 is a novel adipokine stimulating IL-6 secretion through RAGE receptor in SW872 preadipocyte cell line: contribution to chronic inflammation in fat tissue. PLoS One 8, e76039.
Navegantes, K.C., de Souza Gomes, R., Pereira, P.A.T., Czaikoski, P.G., Azevedo, C.H.M., Monteiro, M.C., 2017. Immune modulation of some autoimmune diseases: the critical role of macrophages and neutrophils in the innate and adaptive immunity. J. Transl. Med. 15, 36.
Nguyen, K.Q., Tsou, W.I., Calarese, D.A., Kimani, S.G., Singh, S., Hsieh, S., Liu, Y., Lu, B., Wu, Y., Garforth, S.J., Almo, S.C., Kotenko, S.V., Birge, R.B., 2014. Overexpression of MERTK receptor tyrosine kinase in epithelial cancer cells drives efferocytosis in a gain-of-function capacity. J. Biol. Chem. 289, 25737–25749.
Nielsen, M.J., Moller, H.J., Moestrup, S.K., 2010. Hemoglobin and heme scavenger receptors. Antioxid. Redox Signal. 12, 261–273.
Nilsson, A., Oldenborg, P.A., 2009. CD47 promotes both phosphatidylserine-independent and phosphatidylserine-dependent phagocytosis of apoptotic murine thymocytes by non-activated macrophages. Biochem. Biophys. Res. Commun. 387, 58–63.
Novak, M.L., Thorp, E.B., 2013. Shedding light on impaired efferocytosis and nonresolving inflammation. Circ. Res. 113, 9–12.
Numata, M., Chu, H.W., Dakhama, A., Voelker, D.R., 2010. Pulmonary surfactant phosphatidylglycerol inhibits respiratory syncytial virus–induced inflammation and infection. Proc. Natl. Acad. Sci. U. S. A. 107, 320–325.
Ocaña-Guzman, R., Vázquez-Bolaños, L., Sada-Ovalle, I., 2018. Receptors that inhibit macrophage activation: mechanisms and signals of regulation and tolerance. J. Immunol. Res. 2018, 14.
Pan, Z., Zhou, L., Hetherington, C.J., Zhang, D.-E., 2000. Hepatocytes contribute to soluble CD14 production, and CD14 expression is differentially regulated in hepatocytes and monocytes. J. Biol. Chem. 275, 36430–36435.
Park, Y.-J., Liu, G., Tsuruta, Y., Lorne, E., Abraham, E., 2009. Participation of the urokinase receptor in neutrophil efferocytosis. Blood 114, 860–870.
Periyalil, H.A., Wood, L.G., Scott, H.A., Jensen, M.E., Gibson, P.G., 2015. Macrophage activation, age and sex effects of immunometabolism in obese asthma. Eur. Respir. J. 45, 388–395.
Peschon, J.J., Slack, J.L., Reddy, P., Stocking, K.L., Sunnarborg, S.W., Lee, D.C., Russell, W.E., Castner, B.J., Johnson, R.S., Fitzner, J.N., Boyce, R.W., Nelson, N., Kozlosky, C.J., Wolfson, M.F., Rauch, C.T., Cerretti, D.P., Paxton, R.J., March, C.J., Black, R.A., 1998. An essential role for ectodomain shedding in mammalian development. Science (New York, N.Y.) 282, 1281–1284.
Pocivavsek, A., Mikhailenko, I., Strickland, D.K., Rebeck, G.W., 2009. Microglial low-density lipoprotein receptor-related protein 1 modulates C-Jun N-terminal kinase activation. J. Neuroimmunol. 214, 25–32.
Pugin, J.M., Schürer-Maly, C., Leturcq, D., Moriarty, A., Ulevitch, R.J., Tobias, P.S., 1993. Lipopolysaccharide activation of human endothelial and epithelial cells is mediated by lipopolysaccharide-binding protein and soluble CD14. Proc. Natl. Acad. Sci. 90, 2744–2748.
Pullerits, R., Brisslert, M., Jonsson, I.M., Tarkowski, A., 2006. Soluble receptor for advanced glycation end products triggers a proinflammatory cytokine cascade via beta2 integrin Mac-1. Arthritis Rheum. 54, 3898–3907.

Ramprasad, M.P., Terpstra, V., Kondratenko, N., Quehenberger, O., Steinberg, D., 1996. Cell surface expression of mouse macrosialin and human CD68 and their role as macrophage receptors for oxidized low density lipoprotein. Proc. Natl. Acad. Sci. U. S. A. 93, 14833–14838.
Ravichandran, K.S., Lorenz, U., 2007. Engulfment of apoptotic cells: signals for a good meal. Nat. Rev. Immunol. 7, 964–974.
Recarte-Pelz, P., Tàssies, D., Espinosa, G., Hurtado, B., Sala, N., Cervera, R., Reverter, J.C., de Frutos, P.G., 2013. Vitamin K-dependent proteins GAS6 and Protein S and TAM receptors in patients of systemic lupus erythematosus: correlation with common genetic variants and disease activity. Arthritis Res. Ther. 15.
Reddy, S.M., Hsiao, K.H., Abernethy, V.E., Fan, H., Longacre, A., Lieberthal, W., Rauch, J., Koh, J.S., Levine, J.S., 2002. Phagocytosis of apoptotic cells by macrophages induces novel signaling events leading to cytokine-independent survival and inhibition of proliferation: activation of Akt and inhibition of extracellular signal-regulated kinases 1 and 2. J. Immunol. 169, 702–713.
Reiner, A.P., Lange, E.M., Jenny, N.S., Chaves, P.H.M., Ellis, J., Li, J., Walston, J., Lange, L.A., Cushman, M., Tracy, R.P., 2013. Soluble CD14. genomewide association analysis and relationship to cardiovascular risk and mortality in older adults. Arterioscler. Thromb. Vasc. Biol. 33, 158–164.
Ring, E.K., Markert, J.M., Gillespie, G.Y., Friedman, G.K., 2017. Checkpoint proteins in pediatric brain and extracranial solid tumors: opportunities for immunotherapy. Clin. Cancer Res. 23, 342–350.
Rosenblum, M.D., Remedios, K.A., Abbas, A.K., 2015. Mechanisms of human autoimmunity. J. Clin. Invest. 125, 2228–2233.
Rothlin, C.V., Ghosh, S., Zuniga, E.I., Oldstone, M.B., Lemke, G., 2007. TAM receptors are pleiotropic inhibitors of the innate immune response. Cell 131, 1124–1136.
Rouis, M., 2005. Matrix metalloproteinases: a potential therapeutic target in atherosclerosis. Curr. Drug Targets Cardiovasc. Haematol. Disord. 5, 541–548.
Sather, S., Kenyon, K.D., Lefkowitz, J.B., Liang, X., Varnum, B.C., Henson, P.M., Graham, D.K., 2007. A soluble form of the Mer receptor tyrosine kinase inhibits macrophage clearance of apoptotic cells and platelet aggregation. Blood 109, 1026–1033.
Schif-Zuck, S., Gross, N., Assi, S., Rostoker, R., Serhan, C.N., Ariel, A., 2011. Saturated-efferocytosis generates pro-resolving CD11b low macrophages: modulation by resolvins and glucocorticoids. Eur. J. Immunol. 41, 366–379.
Schrijvers, D.M., De Meyer, G.R., Herman, A.G., Martinet, W., 2007. Phagocytosis in atherosclerosis: molecular mechanisms and implications for plaque progression and stability. Cardiovasc. Res. 73, 470–480.
Scilabra, S.D., Troeberg, L., Yamamoto, K., Emonard, H., Thøgersen, I., Enghild, J.J., Strickland, D.K., Nagase, H., 2013. Differential regulation of extracellular tissue inhibitor of metalloproteinases-3 levels by cell membrane-bound and shed low density lipoprotein receptor-related protein 1. J. Biol. Chem. 288, 332–342.
Sehestedt, T., Lyngbæk, S., Eugen-Olsen, J., Jeppesen, J., Andersen, O., Hansen, T.W., Linneberg, A., Jørgensen, T., Haugaard, S.B., Olsen, M.H., 2011. Soluble urokinase plasminogen activator receptor is associated with subclinical organ damage and cardiovascular events. Atherosclerosis 216, 237–243.
Seitz, H.M., Camenisch, T.D., Lemke, G., Earp, H.S., Matsushima, G.K., 2007. Macrophages and dendritic cells use different Axl/Mertk/Tyro3 receptors in clearance of apoptotic cells. J. Immunol. (Baltimore, Md.: 1950) 178, 5635–5642.
Senft, A.P., Korfhagen, T.R., Whitsett, J.A., Shapiro, S.D., LeVine, A.M., 2005. Surfactant protein-D regulates soluble CD14 through matrix metalloproteinase-12. J. Immunol. (Baltimore, Md.: 1950) 174, 4953–4959.
Serebruany, V.L., Murugesan, S.R., Pothula, A., Semaan, H., Gurbel, P.A., 1999. Soluble PECAM-1, but not P-Selectin, nor osteonectin identify acute myocardial infarction in patients presenting with chest pain. Cardiology 91, 50–55.
Serhan, C.N., Brain, S.D., Buckley, C.D., Gilroy, D.W., Haslett, C., O'Neill, L.A., Perretti, M., Rossi, A.G., Wallace, J.L., 2007. Resolution of inflammation: state of the art, definitions and terms. FASEB J. 21, 325–332.
Shimizu, K., Ogawa, F., Yoshizaki, A., Akiyama, Y., Kuwatsuka, Y., Okazaki, S., Tomita, H., Takenaka, M., Sato, S., 2012. Increased serum levels of soluble CD163 in patients with scleroderma. Clin. Rheumatol. 31, 1059–1064.
Shive, C.L., Jiang, W., Anthony, D.D., Lederman, M.M., 2015. Soluble CD14 is a non-specific marker of monocyte activation. AIDS 29, 1263–1265.
Singh, B., Schneider, M., Knyazev, P., Ullrich, A., 2009. UV-induced EGFR signal transactivation is dependent on proligand shedding by activated metalloproteases in skin cancer cell lines. Int. J. Cancer 124, 531–539.
Sjöwall, C., Martinsson, K., Cardell, K., Ekstedt, M., Kechagias, S., 2015. Soluble urokinase plasminogen activator receptor levels are associated with severity of fibrosis in nonalcoholic fatty liver disease. Transl. Res. 165, 658–666.
Song, M.-Y., Park, S.-H., Nam, H.J., Choi, D.-H., Sung, Y.-C., 2011. Enhancement of vaccine-induced primary and memory CD8+ T-cell responses by soluble PD-1. J. Immunother. 34, 297–306.
Soto Pantoja, D.R., Kaur, S., Miller, T.W., Isenberg, J.S., Roberts, D.D., 2013. Leukocyte Surface Antigen CD47. UCSD Molecule Pages 2.
Stevens, H.Y., Melchior, B., Bell, K.S., Yun, S., Yeh, J.-C., Frangos, J.A., 2008. PECAM-1 is a critical mediator of atherosclerosis. Dis. Model. Mech. 1, 175–179.
Suresh Babu, S., Thandavarayan, R.A., Joladarashi, D., Jeyabal, P., Krishnamurthy, S., Bhimaraj, A., Youker, K.A., Krishnamurthy, P., 2016. MicroRNA-126 overexpression rescues diabetes-induced impairment in efferocytosis of apoptotic cardiomyocytes. Sci. Rep. 6, 36207.
Tabas, I., 2005. Consequences and therapeutic implications of macrophage apoptosis in atherosclerosis: the importance of lesion stage and phagocytic efficiency. Arterioscler. Thromb. Vasc. Biol. 25, 2255–2264.
Tabas, I., 2010. Macrophage death and defective inflammation resolution in atherosclerosis. Nat. Rev. Immunol. 10, 36–46.
Tabas, I., 2017. 2016 Russell Ross memorial lecture in vascular biology: molecular-cellular mechanisms in the progression of atherosclerosis. Arterioscler. Thromb. Vasc. Biol. 37, 183–189.
Tabas, I., Bornfeldt, K.E., 2016. Macrophage phenotype and function in different stages of atherosclerosis. Circ. Res. 118, 653–667.
Tajbakhsh, A., Khorrami, M.S., Hassanian, S.M., Aghasizade, M., Pasdar, A., Maftouh, M., Tabatabai, E., Parizadeh, S.M., Fazeli, M., Ferns, G.A., Ghayour-Mobarhan, M., Avan, A., 2016. The 9p21 locus and its potential role in atherosclerosis susceptibility; molecular mechanisms and clinical implications. Curr. Pharm. Des. 22, 5730–5737.
Tajbakhsh, A., Rezaee, M., Kovanen, P.T., Sahebkar, A., 2018. Efferocytosis in atherosclerotic lesions: malfunctioning regulatory pathways and control mechanisms. Pharmacol. Ther.
Thorp, E., Vaisar, T., Subramanian, M., Mautner, L., Blobel, C., Tabas, I., 2011a. Shedding of the mer tyrosine kinase receptor is mediated by ADAM17 protein through a pathway involving reactive oxygen species, protein kinase C delta, and p38 mitogen-activated protein kinase (MAPK). J. Biol. Chem. 286, 33335–33344.
Thorp, E., Vaisar, T., Subramanian, M., Mautner, L., Blobel, C., Tabas, I., 2011b. Shedding of the Mer tyrosine kinase receptor is mediated by ADAM17 protein through a pathway involving reactive oxygen species, protein kinase Cdelta, and p38 mitogen-activated protein kinase (MAPK). J. Biol. Chem. 286, 33335–33344.
Thuno, M., Macho, B., Eugen-Olsen, J., 2009. suPAR: the molecular crystal ball. Dis. Markers 27, 157–172.
Tien, W.-S., Chen, J.-H., Wu, K.-P., 2017. SheddomeDB: the ectodomain shedding database for membrane-bound shed markers. BMC Bioinformatics 18, 42.
Timmermann, M., Buck, F., Sorg, C., Högger, P., 2004. Interaction of soluble CD163 with activated T lymphocytes involves its association with non-muscle myosin heavy chain type A. Immunol. Cell Biol. 82, 479.
Tobias, P.S., Ulevitch, R.J., 1993. Lipopolysaccharide binding protein and CD14 in LPS dependent macrophage activation. Immunobiology 187, 227–232.
Toda, S., Segawa, K., Nagata, S., 2014. MerTK-mediated engulfment of pyrenocytes by central macrophages in erythroblastic islands. Blood 123, 3963–3971.
Twito, T., Chen, Z., Khatri, I., Wong, K., Spaner, D., Gorczynski, R., 2013. Ectodomain shedding of CD200 from the B-CLL cell surface is regulated by ADAM28 expression. Leuk. Res. 37, 816–821.
Vaisar, T., Kassim, S.Y., Gomez, I.G., Green, P.S., Hargarten, S., Gough, P.J., Parks, W.C., Wilson, C.L., Raines, E.W., Heinecke, J.W., 2009. MMP-9 Sheds the β2 Integrin Subunit (CD18) from Macrophages. Mol. Cell. Proteom. 8, 1044–1060.
van den Eijnde, S.M., Boshart, L., Baehrecke, E.H., De Zeeuw, C.I., Reutelingsperger, C.P., Vermeij-Keers, C., 1998. Cell surface exposure of phosphatidylserine during apoptosis is phylogenetically conserved. Apoptosis 3, 9–16.
Virmani, R., Burke, A.P., Kolodgie, F.D., Farb, A., 2002. Vulnerable plaque: the pathology of unstable coronary lesions. J. Interv. Cardiol. 15, 439–446.
Wang, J., Guo, W., Du, H., Yu, H., Jiang, W., Zhu, T., Bai, X., Wang, P., 2014. Elevated soluble CD163 plasma levels are associated with disease severity in patients with hemorrhagic fever with renal syndrome. PLoS One 9, e112127.
Wang, Z., Sun, D., Chen, G., Li, G., Dou, S., Wang, R., Xiao, H., Hou, C., Li, Y., Feng, J., Shen, B., Han, G., 2017. Tim-3 inhibits macrophage control of Listeria monocytogenes by inhibiting Nrf2. Sci. Rep. 7, 42095.
Wei, Y.S., Lan, Y., Liu, Y.G., Meng, L.Q., Xu, Q.Q., Xie, H.Y., 2009. Platelet-endothelial cell adhesion molecule-1 gene polymorphism and its soluble level are associated with ischemic stroke. DNA Cell Biol. 28, 151–158.
Wei, C., El Hindi, S., Li, J., Fornoni, A., Goes, N., Sageshima, J., Maiguel, D., Karumanchi, S.A., Yap, H.-K., Saleem, M., Zhang, Q., Nikolic, B., Chaudhuri, A., Daftarian, P., Salido, E., Torres, A., Salifu, M., Sarwal, M.M., Schaefer, F., Morath, C., Schwenger, V., Zeier, M., Gupta, V., Roth, D., Rastaldi, M.P., Burke, G., Ruiz, P., Reiser, J., 2011. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. Nat. Med. 17, 952.
Weinger, J.G., Omari, K.M., Marsden, K., Raine, C.S., Shafit-Zagardo, B., 2009. Up-regulation of soluble Axl and Mer receptor tyrosine kinases negatively correlates with Gas6 in established multiple sclerosis lesions. Am. J. Pathol. 175, 283–293.
Winograd-Katz, S.E., Fässler, R., Geiger, B., Legate, K.R., 2014. The integrin adhesome: from genes and proteins to human disease. Nat. Rev. Mol. Cell Biol. 15, 273.
Wong, K.K., Brenneman, F., Chesney, A., Spaner, D.E., Gorczynski, R.M., 2012. Soluble CD200 is critical to engraft chronic lymphocytic leukemia cells in immunocompromised mice. Cancer Res. 72, 4931–4943.
Wright, S.D., Ramos, R.A., Tobias, P.S., Ulevitch, R.J., Mathison, J.C., 1990. CD14, a receptor for complexes of lipopolysaccharide (LPS) and LPS binding protein. Science (New York, N.Y.) 249, 1431–1433.
Wright, G.J., Puklavec, M.J., Willis, A.C., Hoek, R.M., Sedgwick, J.D., Brown, M.H., Barclay, A.N., 2000. Lymphoid/Neuronal cell surface OX2 glycoprotein recognizes a novel receptor on macrophages implicated in the control of their function. Immunity 13, 233–242.
Yamamoto, K., Santamaria, S., Botkjaer, K.A., Dudhia, J., Troeberg, L., Itoh, Y., Murphy, G., Nagase, H., 2017. Inhibition of Shedding of Low-Density Lipoprotein Receptor–Related Protein 1 Reverses Cartilage Matrix Degradation in Osteoarthritis. Arthritis Rheumatol. 69, 1246–1256.
Yan, S.F., Ramasamy, R., Schmidt, A.M., 2009. Receptor for AGE (RAGE) and its ligands-cast into leading roles in diabetes and the inflammatory response. J. Mol. Med. 87, 235–247.
Yang, A.Z., Dai, J.H., Birge, R.B., Wu, Y., 2010. The role of urokinase receptor (uPAR) in efferocytosis: uPAR engulfs apoptotic cells via a phosphatidylserine pathway mediated by plasma high molecular weight kininogen. Blood 116 410-410.
Zagorska, A., Traves, P.G., Lew, E.D., Dransfield, I., Lemke, G., 2014. Diversification of TAM receptor tyrosine kinase function. Nat. Immunol. 15, 920–928.
Zaremba, J., Losy, J., 2002. sPECAM-1 in serum and CSF of acute ischaemic stroke patients. Acta Neurol. Scand. 106, 292–298.
Zhang, L., Bukulin, M., Kojro, E., Roth, A., Metz, V.V., Fahrenholz, F., Nawroth, P.P., Bierhaus, A., Postina, R., 2008. Receptor for advanced glycation end products is

subjected to protein ectodomain shedding by metalloproteinases. J. Biol. Chem. 283, 35507–35516.
Zhao, X.Q., Zhang, M.W., Wang, F., Zhao, Y.X., Li, J.J., Wang, X.P., Bu, P.L., Yang, J.M., Liu, X.L., Zhang, M.X., Gao, F., Zhang, C., Zhang, Y., 2011. CRP enhances soluble LOX-1 release from macrophages by activating TNF-alpha converting enzyme. J. Lipid Res. 52, 923–933.
Zhi, Y., Gao, P., Xin, X., Li, W., Ji, L., Zhang, L., Zhang, X., Zhang, J., 2017. Clinical significance of sCD163 and its possible role in asthma (Review). Mol. Med. Rep. 15, 2931–2939.
Zhong, X., Lee, H.N., Kim, S.H., Park, S.A., Kim, W., Cha, Y.N., Surh, Y.J., 2018. Myc-nick promotes efferocytosis through M2 macrophage polarization during resolution of inflammation. FASEB J. 32, 5312–5325.
Zhou, D., WANG, Y., CHEN, L., ZHANG, W., LUAN, J., 2016. Soluble CD163: a novel biomarker with diagnostic and therapeutic implications in autoimmune diseases. J. Rheumatol. 43, 830–831.
Zizzo, G., Hilliard, B.A., Monestier, M., Cohen, P.L., 2012. Efficient clearance of early apoptotic cells by human macrophages requires M2c polarization and MerTK induction. J. Immunol. (Baltimore, Md.: 1950) 189, 3508–3520.
Zizzo, G., Guerrieri, J., Dittman, L.M., Merrill, J.T., Cohen, P.L., 2013a. Circulating levels of soluble MER in lupus reflect M2c activation of monocytes/macrophages, autoantibody specificities and disease activity. Arthritis Res. Ther. 15, R212.
Zizzo, G., Guerrieri, J., Dittman, L.M., Merrill, J.T., Cohen, P.L., 2013b. Circulating levels of soluble MER in lupus reflect M2c activation of monocytes/macrophages, autoantibody specificities and disease activity. Arthritis Res. Ther. 15.