RESEARCH PAPER

EFFEROCYTOSIS: A DUAL ROLE IN IMMUNE TOLERANCE AND AUTOIMMUNE DISEASE DEVELOPMENT

Anastasia Vladimirovna Poznyak 1*, Gulalek Amanmyradovna Babaeva 2, Vasily Petrovich Karagodin 2, Ulyana Vyacheslavovna 4
Rozhkova 1, Stanislav Anatolievich Antonov 2, Aleksandra Sergeevna Utkina 3, Alexander Nikolaevich Orekhov 1 5
1Institute for Atherosclerosis Research, Osennyaya Moscow, Russia 7
2 Institute of General Pathology and Pathophysiology, 8, Baltiiskaya Street, 125315 Moscow, Russia 8
3 Department of Commodity Expertise and Customs Business, Plekhanov Russian University of Economics, 36, Stremyanny Lane, 115054 Mos- 9
cow, Russia
***Correspondence**: tehhy_85@mail.ru (AVP), alexandernikolaevichorekhov@gmail.com (ANO).
Author Contributions: Writing—original draft preparation, A.V.P.; writing—review and editing, N.A.M., U.V.R., S.A.A.,
A.S.U., A.N.O. All authors have read and agreed to the published version of the manuscript.
Funding: This research was funded by Russian Science Foundation, grant number 25-75-10012
Conflicts of Interest: The authors declare no conflict of interest.
Ethics Approval: Not applicable.
Consent to Participate: Not applicable.
Consent to Publish: Not applicable.
Data Availability Statement: Not applicable.

Abstract
Efferocytosis, the process of clearing apoptotic cells by specialized phagocytes, is essential for maintaining tissue homeostasis and preventing inflammation. This review explores the intricate mechanisms of efferocytosis, detailing the sequential stages defined by unique signals: “find-me,” “eat-me,” and the subsequent engulfment and digestion of dying cells. Specialized phagocytes, primarily macrophages and dendritic cells, utilize an array of receptors to interact with apoptotic cells, initiating intracellular signaling cascades that promote their clearance. Dysregulation of efferocytosis can result in deleterious outcomes, contributing to the pathogenesis of various autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD). In these conditions, the impaired recognition and clearance of apoptotic cells lead to chronic inflammation, secondary necrosis, and the release of autoantigens, which trigger autoimmune responses. This review highlights the biochemical underpinnings of efferocytosis and its significant role in immune regulation, emphasizing its potential as a therapeutic target for enhancing the resolution of inflammation in autoimmune diseases. Understanding the bidirectional relationship between efferocytosis and autoimmune pathology may provide novel insights into effective interventions for these conditions.

How to cite this article: Anastasia Vladimirovna Poznyak 1* Gulalek Amanmyradovna Babaeva 2 Vasily Petrovich Karagodin 2 Ulyana Vyacheslavovna 4. EFFEROCYTOSIS: A DUAL ROLE IN IMMUNE TOLERANCE AND AUTOIMMUNE DISEASE DEVELOPMENT. Int J Drug Deliv Technol. 2026;16(87s):634-657. DOI: 10.25258/ijddt.16.87s.64.

Introduction

The term "efferocytosis" (Greek "effere", to take a corpse to the grave, to bury) refers to a cellular process that involves the removal of apoptotic cells (ACs) by efferocytes. This process is incredibly important for the constant renewal of the body's cellular composition and the maintenance of organ function. Efferocytosis can be divided into several stages characterized by their own cellular biological markers, including "find me," "eat me," and "engulf and digest," unique receptors and ligands can be categorized based on the stage of the process in which they are involved [1].

Normally, efferocytosis is carried out by specialized phagocyte cells (more specifically, macrophages and dendritic cells [DCs]). On the other hand, non-specialized phagocytes (epithelial cells and fibroblasts) may also be involved. Rapid removal of ACs prevents secondary necrosis, while phagocytes that have captured ACs undergo further reprogramming, which accelerates resolution of inflammation and promotes tissue repair [2,3]. Dysregulation or dysfunction of efferocytosis leads to secondary necrosis of accumulated ACs and corresponding release of inflammatory mediators, as timely cell renewal and elimination of dying tissues do not occur. In addition, undegraded ACs release autoantigens, which can stimulate the production of autoantibodies [4,5]. As a consequence, impaired clearance of ACs is mostly associated with various autoimmune diseases, including systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and rheumatoid arthritis (RA) [6,7].

Mechanism of Efferocytosis

Efferocytosis is a crucial biological process where apoptotic cells are recognized, engulfed, and digested by phagocytes. This process maintains tissue homeostasis and prevents inflammation and autoimmune responses. The biochemical mechanisms underlying efferocytosis involve a complex interplay of signals and receptors [8-11]. The process of efferocytosis is briefly summarized in Figure 1.

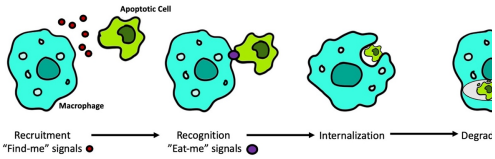


Figure 1. Key stages of efferocytosis. The process can be divided into 4 stages: 1) recruitment, which is based on the distant interaction of "find-me" signals secreted by apoptotic cell and the receptors on macrophage (or other phagocyte); 2) recognition, which is mediated by "eat-me" signals expressed on the surface of apoptotic cell; 3) internalization; 4) degradation of apoptotic cell within the phagocyte.

Phagocytes, such as macrophages, have receptors that recognize these "eat-me" signals. Among these receptors, the TAM (Tyro3, Axl, and MerTK) family of receptor tyrosine kinases plays a significant role. These receptors bind to PS indirectly through bridging molecules like Gas6 and Protein S [12,13]. Binding of these ligands to phosphatidylserine (PS) and the TAM receptors activates the receptors' tyrosine kinase activity, initiating a cascade of intracellular signaling pathways. Upon activation, the TAM receptors phosphorylate various adaptor proteins and activate downstream signaling pathways, including the PI3K/AKT pathway, which promotes actin cytoskeleton rearrangement necessary for the engulfment process [14,15]. Additionally, the Rac1 GTPase is activated, which further drives cytoskeletal changes, allowing the phagocyte to extend its membrane around the apoptotic cell, ultimately forming a phagosome [16,17].

Within the phagosome, the engulfed apoptotic cell is transported to lysosomes where it is degraded by lysosomal enzymes. The degradation products are then recycled or expelled by the phagocyte [18,19].

Concurrently, efferocytosis triggers anti-inflammatory signals. For instance, the binding of apoptotic cells to phagocyte receptors leads to the production of anti-inflammatory cytokines like transforming growth factor beta (TGF-β) and interleukin 10 (IL-10), while suppressing the production of pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β) [20,21]. This shift towards an anti-inflammatory profile helps prevent an immune response against the self-antigens of the apoptotic cells, contributing to immune tolerance and resolution of inflammation. Moreover, efferocytosis is tightly regulated by a balance of "find-me" and "don't-eat-me" signals. Apoptotic cells release soluble factors such as lysophosphatidylcholine (LPC) and fractalkine that act as "find-me" signals to attract phagocytes to the site of cell death [22,23]. Conversely, viable cells express "don't-eat-me" signals, such as CD47, which interact with signal regulatory protein alpha (SIRPα) on phagocytes to inhibit efferocytosis. Dysregulation of efferocytosis can lead to various pathological conditions. Impaired efferocytosis results in the accumulation of apoptotic cells, leading to secondary necrosis and the release of intracellular contents that can trigger inflammation and autoimmunity. Conversely, excessive efferocytosis, particularly in the context of cancer, can allow tumor cells to evade immune surveillance [24,25].

Table 1. Efferocytosis Signals and Their Roles

Signal Type	Examples	Role in Efferocytosis
Find-Me Signals	ATP, UTP, LPC, Fractalkine, S1P	Attract phagocytes to apoptotic cells
Eat-Me Signals	Phosphatidylserine (PS), Calreticulin, oxLDL	Facilitate phagocyte recognition and engulfment
Don't-Eat Signals	CD47	Inhibit phagocytosis of viable cells

"Find-Me" Signals

These signals released by apoptotic cells to attract phagocytes, facilitating the clearance of these dying cells before they undergo secondary necrosis and potentially trigger inflammation, ensure that apoptotic cells are swiftly and efficiently recognized and engulfed by phagocytes, thus maintaining tissue homeostasis and preventing inflammatory responses [26,27]. Key "find-me" signals include nucleotides like ATP and uridine-5′-triphosphate (UTP), lysophosphatidylcholine (LPC), fractalkine, and sphingosine-1-phosphate (S1P), each engaging specific receptors and pathways to guide phagocytes to the site of cell death. Nucleotides such as ATP and UTP are released through pannexin 1 channels, which are activated early in apoptosis [28]. These extracellular nucleotides bind to purinergic receptors on the surface of phagocytes, specifically P2Y2 receptors. The binding of ATP and UTP to P2Y2 receptors triggers a signaling cascade involving intracellular calcium influx and activation of downstream pathways such as the PI3K/AKT pathway, which ultimately enhances the motility of phagocytes towards the apoptotic cells [29-31].

LPC is another vital "find-me" signal. During apoptosis, LPC is generated by the enzymatic action of phospholipase A2 (PLA2) on membrane phospholipids [32]. LPC then binds to the G-protein coupled receptor G2A on phagocytes. This interaction activates signaling pathways that promote chemotaxis, guiding the phagocytes to the source of the LPC gradient, which is the dying cell [33,34]. Fractalkine, also known as CX3CL1, is a chemokine released in a soluble form by apoptotic cells through the action of metalloproteases. It binds to its receptor, CX3CR1, on phagocytes. This binding activates intracellular signaling cascades, including those mediated by the

PI3K/AKT and mitogen-activated protein kinase (MAPK) pathways, enhancing the migratory response of phagocytes towards the apoptotic cells [35,36].

Sphingosine-1-phosphate (S1P) is a lipid mediator released by apoptotic cells and binds to S1P receptors on phagocytes. The S1P receptor family, particularly S1P1, plays a role in regulating the migration of phagocytes towards the apoptotic cells. Upon binding S1P, these receptors activate various intracellular signaling pathways, such as the PI3K/AKT and MAPK pathways, which facilitate the directed movement of phagocytes [37-40]. These "find-me" signals create chemotactic gradients in the extracellular environment, allowing phagocytes to sense and move towards higher concentrations of these signals, leading them to the apoptotic cells. The precise and timely release of "find-me" signals is crucial for the efficient recognition and clearance of apoptotic cells, preventing the release of potentially pro-inflammatory intracellular contents and ensuring the resolution of inflammation [41,42].

In addition to their direct chemotactic effects, these "find-me" signals can also modulate the behavior of phagocytes, enhancing their readiness to engulf apoptotic cells upon arrival. For instance, the engagement of P2Y2 receptors by ATP/UTP not only directs migration but also primes the phagocytes for subsequent "eat-me" signal recognition and engulfment processes [43]. Similarly, fractalkine-CX3CR1 interaction not only attracts phagocytes but also influences their adhesion and activation states, preparing them for efficient efferocytosis. The integration of signals from ATP, UTP, LPC, fractalkine, and S1P ensures a coordinated response that enables phagocytes to locate, recognize, and engulf apoptotic cells effectively [44-46].

“Eat-Me” Signals

"Eat-me" signals in efferocytosis are another type of markers displayed on the surface of apoptotic cells that facilitate their recognition and engulfment by phagocytes. The primary "eat-me" signal is PS, a phospholipid normally located on the inner leaflet of the plasma membrane [47-49]. During apoptosis, scramblase enzymes are activated, and flippases are inhibited, causing PS to translocate to the outer leaflet of the membrane. This externalization of PS is a crucial signal for phagocytes to identify and bind apoptotic cells [50,51].

Phagocytes possess various receptors and bridging molecules that recognize PS. Direct receptors include TIM-4 and Stabilin-2, which bind to PS on the apoptotic cell surface. Bridging molecules such as annexin V, Gas6, and Protein S bind PS and subsequently interact with phagocyte receptors like the TAM family [52,53]. These interactions are pivotal in initiating the engulfment process. For instance, when Gas6 or Protein S binds to PS, they bridge the apoptotic cell to the MerTK receptor on the phagocyte, activating its tyrosine kinase activity. This activation triggers a signaling cascade involving phosphorylation of intracellular adaptor proteins and downstream effectors like PI3K and AKT, leading to cytoskeletal rearrangement necessary for phagocytosis [54-56].

Beyond PS, other "eat-me" signals include altered membrane glycosylation patterns, such as the exposure of calreticulin, a chaperone protein that translocates to the cell surface during apoptosis. Calreticulin is recognized by the low-density lipoprotein (LDL) receptor-related protein (LRP) on phagocytes. This interaction facilitates the binding and engulfment of the apoptotic cell [57-59].

Another important "eat-me" signal is the exposure of oxidized low-density lipoproteins (oxLDL) on the apoptotic cell surface. Scavenger receptors on phagocytes, such as CD36 and SR-A, recognize these oxidized lipids [60,61]. The binding of oxLDL to these receptors also promotes phagocytosis through signaling pathways that involve the rearrangement of the actin cytoskeleton [62,63].

In addition to these signals, complement proteins like C1q bind to apoptotic cells and interact with receptors such as CR3 and CR4 on phagocytes, further aiding in their clearance. The interaction of C1q with these receptors activates signaling pathways that enhance the phagocytic process, including the activation of the Rho family of GTPases, which regulate cytoskeletal dynamics [64-66].

The recognition and binding of "eat-me" signals by phagocytes initiate the engulfment of apoptotic cells into phagosomes, which subsequently fuse with lysosomes. The lysosomal enzymes then degrade the apoptotic cells, recycling their components for reuse by the phagocyte [67,68]. This process is tightly regulated to prevent an inflammatory response, as the clearance of apoptotic cells typically triggers the release of anti-inflammatory cytokines like TGF-β and IL-10, while suppressing pro-inflammatory signals [69-71].

Furthermore, apoptotic cells often downregulate or lose "don't-eat-me" signals such as CD47, which interacts with signal regulatory protein alpha (SIRPα) on phagocytes to inhibit phagocytosis. The absence of CD47 on apoptotic cells ensures that the "eat-me" signals are not counteracted, allowing efficient clearance [72-74].

Phagocytosis of Cellular Corpse

Upon binding the apoptotic cell, phagocytes extend their membrane around the target, a process facilitated by the activation of small GTPases like Rac1 and Cdc42, which drive actin polymerization and membrane protrusion [75-78]. The apoptotic cell is then internalized into a membrane-bound phagosome [79-87]. This phagosome subsequently fuses with lysosomes, forming a phagolysosome where lysosomal enzymes degrade the apoptotic cell components. These enzymes include proteases, nucleases, and lipases, which break down proteins, nucleic acids, and lipids, respectively. The degradation products are either recycled for use by the phagocyte or expelled [88,89].

The phagocytosis of apoptotic cells is accompanied by the release of anti-inflammatory cytokines such as TGF-β and IL-10, which help maintain tissue homeostasis and prevent an inflammatory response. This anti-inflammatory signaling is crucial for immune tolerance and the resolution of inflammation.

Conversely, the process suppresses the production of pro-inflammatory cytokines like TNF-α and IL-1β, ensuring that the clearance of apoptotic cells does not trigger an immune reaction [90,91]. Phagocytes are also influenced by "don't-eat-me" signals, such as CD47 on viable cells, which interacts with SIRPα on phagocytes to inhibit phagocytosis. During apoptosis, the downregulation or loss of CD47 ensures that "eat-me" signals predominate, allowing the efficient clearance of dying cells [92,93].

Digestion and Immune Response

After apoptotic cells are recognized and engulfed by phagocytes, they are internalized into membrane-bound vesicles called phagosomes. These phagosomes then fuse with lysosomes to form phagolysosomes, where the engulfed cellular corpses are digested. Lysosomes contain a variety of hydrolytic enzymes, including proteases, nucleases, lipases, and glycosidases, which break down proteins, nucleic acids, lipids, and carbohydrates, respectively [94,95]. The acidic environment of the phagolysosome, maintained by proton pumps, optimizes the activity of these enzymes, ensuring the complete degradation of the apoptotic cell components. The resulting macromolecule fragments are then transported out of the phagolysosome and can be recycled by the phagocyte for biosynthetic processes or expelled as waste [96,97].

This digestive process is tightly regulated to prevent the release of potentially pro-inflammatory cellular contents. The efficient clearance and degradation of apoptotic cells prevent secondary necrosis, which would otherwise release intracellular components like DNA, RNA, and proteins into the extracellular space, potentially triggering an inflammatory response [98-100]. In addition to the physical containment and degradation of apoptotic cells, efferocytosis modulates the immune response through biochemical signaling that promotes an anti-inflammatory environment. Upon engulfment of apoptotic cells, phagocytes produce and release anti-inflammatory cytokines such as TGF-β and IL-10 [101-103]. TGF-β is a multifunctional cytokine that plays a crucial role in immunoregulation by inhibiting the activation and proliferation of immune cells, promoting the differentiation of regulatory T cells, and inducing the production of extracellular matrix components that contribute to tissue repair. IL-10 is another potent anti-inflammatory cytokine that suppresses the production of pro-inflammatory cytokines like TNF-α, IL-1β, and interleukin-6 (IL-6) by inhibiting the activation of NF-κB, a key transcription factor in the inflammatory response [104-106].

Additionally, efferocytosis influences the metabolic and functional state of phagocytes, enhancing their ability to resolve inflammation and promote tissue repair. For instance, the interaction of apoptotic cells with receptors on phagocytes, such as the TAM family receptors, initiates signaling pathways that not only facilitate the engulfment process but also modulate gene expression to favor an anti-inflammatory phenotype [107,108]. This includes the upregulation of genes involved in tissue repair, resolution of inflammation, and production of anti-inflammatory mediators. The PS exposure on apoptotic cells is crucial for these processes, as it is recognized by receptors and bridging molecules like Gas6 and Protein S, which activate MerTK signaling. The activation of MerTK leads to downstream signaling through pathways such as PI3K/AKT and MAPK, which contribute to the anti-inflammatory and tissue repair functions of phagocytes [109-111].

Furthermore, efferocytosis can induce a metabolic switch in phagocytes from glycolysis to oxidative phosphorylation, enhancing their ability to produce ATP efficiently and support the energy-intensive process of engulfing and digesting apoptotic cells. This metabolic reprogramming is also linked to the production of anti-inflammatory cytokines and the suppression of inflammatory responses [112].

Defective apoptotic-cell clearance in autoimmune disease

Impaired efferocytosis, also called defective apoptotic-cell clearance, is closely linked to the development and progression of autoimmune diseases due to the accumulation of apoptotic cells and the subsequent release of intracellular contents that trigger inflammatory and autoimmune responses [1,2]. Biochemically, this defective clearance can arise from several factors, including abnormalities in the expression or function of receptors and bridging molecules on phagocytes, deficiencies in signaling pathways, and the presence of autoantibodies that interfere with the recognition and engulfment of apoptotic cells. Bellow we will consider efferocytosis associated with several common autoimmune diseases.

Table 2. Causes of defective efferocytosis.

Cause	Description	Impact on Efferocytosis	Associated Conditions	References
Receptor/Bridging Molecule Abnormalities	Impairments in TIM-4, Stabilin-2, TAM receptors (Tyro3, Axl, MerTK) and bridging	Impairs binding and internalization of apoptotic cells	Autoimmune diseases like SLE	[113-116]

Cause	Description	Impact on Efferocytosis	Associated Conditions	References
	molecules (Gas6, Protein S)			
Complement Protein Deficiency	Deficiency in complement proteins like C1q that facilitates opsonization	Leads to defective clearance of apoptotic cells	Systemic lupus erythematosus (SLE)	[117, 118]
Intracellular Signaling Deficiencies	Impairments in signaling pathways (e.g., PI3K/AKT, Rho GTPases) crucial for phagocyte function	Disrupts cytoskeletal rearrangement necessary for engulfment	Various autoimmune diseases	[119, 120]
Autoantibodies	Presence of autoantibodies that interfere with recognition and clearance of apoptotic cells	Interferes with recognition, leading to accumulation and inflammation	Autoimmune diseases characterized by ANAs and anti-dsDNA	[121, 122]
Chronic Inflammation	Elevated pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6)	Alters the expression and function of phagocyte receptors and signaling	Autoimmune diseases, exacerbating tissue damage	[126, 127]
Genetic Factors	Polymorphisms in genes encoding efferocytosis proteins (e.g., C1q, MerTK)	Increases risk of defective clearance of apoptotic cells	Increased risk of autoimmune conditions	[128, 129]
Environmental Factors	Infections or drugs that trigger apoptosis and overwhelm phagocyte clearance capacity	Overwhelms phagocytes, increasing apoptotic cell accumulation	Potentially contributes to various autoimmune diseases	[130, 131]

Associations between efferocytosis and autoimmune diseases

Table 3. Implications of Impaired Efferocytosis in Autoimmune Diseases

Disease	Mechanism of Impairment	Consequences
Rheumatoid Arthritis (RA)	Inflammatory cytokines downregulate MerTK	Accumulation of apoptotic cells, chronic inflammation
Systemic Lupus Erythematosus (SLE)	Genetic deficiencies in complement proteins	Persistent apoptotic cells, autoantibody formation
Inflammatory Bowel Disease (IBD)	Genetic mutations impaired phagocytosis	Secondary necrosis, release of DAMPs promoting inflammation
Sjögren's Syndrome (SS)	Elevated pro-inflammatory cytokines	Chronic inflammation, autoantibody production
Type 1 Diabetes (T1D)	Cytokines alter phagocyte function	Accumulation of apoptotic β-cells, autoimmune response

Rheumatoid arthritis

In rheumatoid arthritis (RA), efferocytosis is impaired, contributing to chronic inflammation and autoimmunity. RA is an autoimmune disease characterized by chronic inflammation of the joints, leading to tissue damage and joint deformities. Biochemically, it involves the production of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), which form immune complexes that contribute to inflammation [132,133]. Inflammatory cytokines like TNF-α, IL-1β, and IL-6 play central roles in the pathogenesis of RA, promoting synovial inflammation and joint destruction. Synovial fibroblasts in RA exhibit an aggressive phenotype, secreting matrix metalloproteinases (MMPs) that degrade cartilage and bone. Defective efferocytosis in RA leads to the accumulation of apoptotic cells, which release intracellular contents and perpetuate inflammation [134-136]. The biochemical mechanisms underlying efferocytosis, as discussed above, involve a series of well-coordinated steps, starting with the exposure of "eat-me" signals on apoptotic cells, such as PS. In healthy individuals, PS is translocated to the outer leaflet of the plasma membrane during apoptosis due to the action of scramblase enzymes and inhibition of flippases. Phagocytes, such as macrophages, express receptors that recognize these signals, including TIM-4, Stabilin-2, and TAM family receptors (Tyro3, Axl, MerTK), which often interact with bridging molecules like Gas6 and Protein S. These interactions facilitate the binding and internalization of apoptotic cells [137-139].

In RA, several factors disrupt this process. Firstly, the inflammatory environment in RA joints, characterized by elevated levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, can inhibit the expression and function of efferocytosis receptors on phagocytes [140-142]. For instance, TNF-α has been shown to downregulate MerTK expression, impairing the phagocytic capacity of macrophages. Additionally, the oxidative stress present in RA joints can modify PS and other "eat-me" signals, making them less recognizable to phagocytes [143].

Another crucial aspect is the role of synovial fibroblasts, which in RA, transform into an aggressive phenotype, secreting matrix metalloproteinases (MMPs) and other degradative enzymes that can damage surrounding tissues and extracellular matrix components. These fibroblasts can produce factors that interfere with efferocytosis [144,145]. For example, they may release soluble CD95 (sCD95), which can bind to and neutralize CD95L, a ligand involved in the apoptosis of activated immune cells, thereby preventing the clearance of apoptotic cells. Moreover, autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs), prevalent in RA patients, can form immune complexes with their target antigens [146,147]. These immune complexes can opsonize apoptotic cells, altering their recognition by phagocytes and further impairing efferocytosis. The presence of these immune complexes can also activate complement pathways, leading to an inflammatory response that exacerbates the disease process [148].

Thus, impaired efferocytosis in RA leads to the accumulation of apoptotic cells in the synovial tissue, which can undergo secondary necrosis, releasing intracellular contents that act as damage-associated molecular patterns (DAMPs). These DAMPs, including high-mobility group box 1 (HMGB1) and DNA, can activate pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) on synovial macrophages and dendritic cells, perpetuating the inflammatory response [149-151]. The continued release of pro-inflammatory cytokines and chemokines attracts more immune cells to the synovium, creating a chronic inflammatory environment that contributes to joint destruction and the progression of RA [152-153].

In RA, there is also a defect in the production of anti-inflammatory mediators that typically follow

efferocytosis. Normally, the engulfment of apoptotic cells prompts phagocytes to release anti-inflammatory cytokines such as TGF-β and IL-10. These cytokines play crucial roles in resolving inflammation and promoting tissue repair [154]. However, in the inflamed RA synovium, the production of these cytokines is often insufficient, failing to counterbalance the pro-inflammatory signals. Furthermore, genetic factors can predispose individuals to impaired efferocytosis in RA. Polymorphisms in genes encoding for efferocytosis receptors or signaling molecules involved in apoptotic cell clearance can affect the efficiency of this process. Environmental factors, such as smoking, can also exacerbate these genetic predispositions by inducing oxidative stress and promoting the production of citrullinated proteins, which are targets for ACPAs [155,156].

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multifaceted autoimmune disease characterized by the production of autoantibodies against nuclear antigens, leading to widespread inflammation and tissue damage [157]. Biochemically, SLE involves a complex interplay of genetic, environmental, and hormonal factors that contribute to immune dysregulation. One of the hallmarks of SLE is the presence of anti-nuclear antibodies (ANAs), including anti-double-stranded DNA (anti-dsDNA) and anti-Smith (Sm) antibodies [158,159]. These autoantibodies form immune complexes with their respective antigens, which can deposit in tissues such as the kidneys, skin, and joints, triggering an inflammatory response through the activation of the complement system. The complement activation leads to the generation of C3a and C5a, potent chemoattractants that recruit inflammatory cells to the sites of immune complex deposition, further exacerbating tissue damage [160,161].

Genetically, polymorphisms in genes encoding for components of the immune system, such as those involved in the clearance of apoptotic cells and the regulation of immune tolerance, predispose individuals to SLE. For instance, deficiencies in early complement components like C1q, C2, and C4 are strongly associated with SLE, highlighting the importance of the complement system in apoptotic cell clearance and immune complex handling. The failure to efficiently clear apoptotic cells results in the persistence of cellular debris, which provides a source of autoantigens that can stimulate the production of autoantibodies [162,163].

In addition to genetic factors, environmental triggers such as ultraviolet (UV) radiation, infections, and certain medications can induce or exacerbate SLE by promoting apoptosis and enhancing the exposure of nuclear antigens. UV radiation, for example, can cause keratinocyte apoptosis, leading to the release of nuclear material and the formation of skin lesions typical of lupus [164-166].

The role of T cells and B cells in the pathogenesis of SLE is critical. Abnormal T cell function, including the altered expression of co-stimulatory molecules and cytokines, contributes to the activation and survival of autoreactive B cells [167,168]. These B cells produce autoantibodies, and their differentiation into plasma cells is driven by cytokines such as IL-6 and BAFF (B-cell activating factor), which are often elevated in SLE patients. Additionally, regulatory T cells (Tregs), which normally function to suppress autoimmune responses, are often dysfunctional or reduced in number in SLE, further contributing to the loss of immune tolerance [169,170].

Interferon-alpha (IFN-α) plays a significant role in SLE pathogenesis, often referred to as the "interferon signature." Elevated levels of IFN-α are observed in SLE patients, and this cytokine promotes the activation and differentiation of plasmacytoid dendritic cells (pDCs), leading to the enhanced production of autoantibodies and the perpetuation of the autoimmune response [171-173]. The source of IFN-α is typically the result of TLR (Toll-like receptor) activation by nucleic acid-containing immune complexes, which are internalized by pDCs and other immune cells [174,175].

The chronic inflammation in SLE leads to widespread tissue damage, particularly in the kidneys, where immune complex deposition in the glomeruli causes lupus nephritis, a major cause of morbidity and mortality in SLE patients [176,177]. The inflammatory milieu in SLE is characterized by elevated levels of pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, and IFN-γ, which contribute to the recruitment and activation of immune cells, perpetuating the cycle of inflammation and tissue damage [178,179].

Hormonal factors also play a role in SLE, as evidenced by the higher prevalence of the disease in women, particularly during reproductive years. Estrogens can modulate immune responses, enhancing the survival and activation of autoreactive B cells and promoting the production of autoantibodies [180,181].

In SLE, efferocytosis is notably defective, contributing to the persistence of apoptotic cells and the subsequent release of intracellular contents that drive inflammation and autoantibody production. The mechanisms underlying efferocytosis involve a series of finely tuned biochemical events [182,183]. Apoptotic cells expose "eat-me" signals, such as PS, on their outer membrane, which are recognized by receptors on phagocytes like macrophages and dendritic cells. In SLE, this recognition is impaired due to several factors [184,185]. Firstly, there are genetic deficiencies in components of the complement system, such as C1q, C2, and C4, which play a crucial

role in opsonizing apoptotic cells and facilitating their clearance. C1q binds to apoptotic cells and interacts with receptors on phagocytes, promoting their uptake. Deficiencies in these components reduce the efficiency of efferocytosis, allowing apoptotic cells to accumulate [186-189].

Moreover, SLE is characterized by the presence of autoantibodies against nuclear antigens, which can form immune complexes with exposed nuclear material from apoptotic cells. These immune complexes can interfere with the recognition and engulfment of apoptotic cells by phagocytes. Additionally, the immune complexes can activate the complement system, leading to inflammation and tissue damage [190,191]. The defective clearance of apoptotic cells results in secondary necrosis, where cell membranes rupture, releasing intracellular contents such as nucleic acids and proteins into the extracellular space. These materials act as damage-associated molecular patterns (DAMPs) that are recognized by pattern recognition receptors (PRRs) on immune cells, including Toll-like receptors (TLRs). Activation of TLRs, particularly TLR7 and TLR9, by nucleic acids leads to the production of type I interferons (IFNs), especially IFN-α, which is a key cytokine in the pathogenesis of SLE [192,193].

IFN-α promotes the maturation and activation of plasmacytoid dendritic cells (pDCs), further enhancing the production of autoantibodies and perpetuating the autoimmune response. The chronic exposure to self-antigens also drives the activation of autoreactive B and T cells, leading to sustained autoantibody production and inflammation [194,195]. Another significant factor contributing to defective efferocytosis in SLE is the pro-inflammatory environment. Elevated levels of cytokines such as TNF-α, IL-6, and interferon-gamma (IFN-γ) are common in SLE patients. These cytokines can alter the function of phagocytes, reducing their ability to recognize and engulf apoptotic cells. For example, TNF-α can downregulate the expression of receptors involved in efferocytosis, such as MerTK, on macrophages [196-198].

Additionally, oxidative stress, which is elevated in SLE, can modify apoptotic cells and their "eat-me" signals, making them less recognizable to phagocytes. The oxidative modifications can also affect the receptors and bridging molecules necessary for efficient efferocytosis. Furthermore, genetic factors such as polymorphisms in genes encoding for receptors and signaling molecules involved in efferocytosis can predispose individuals to impaired clearance of apoptotic cells. For instance, polymorphisms in the MerTK gene have been associated with reduced phagocytic function in SLE patients [199,200].

Hormonal factors, particularly estrogen, can influence efferocytosis. Estrogens have been shown to affect the function of immune cells, and their high levels during reproductive years could contribute to the higher prevalence of SLE in women. Estrogens can enhance the survival of autoreactive B cells and promote the production of autoantibodies, further contributing to the defective clearance of apoptotic cells [201,202]. In summary, defective efferocytosis in SLE is a result of a complex interplay of genetic, environmental, hormonal, and immune factors. The inability to efficiently clear apoptotic cells leads to the accumulation of cellular debris, the formation of immune complexes, chronic activation of the immune system, and sustained production of pro-inflammatory cytokines. These events perpetuate the cycle of inflammation and autoimmunity that characterizes SLE, highlighting the importance of efferocytosis in maintaining immune tolerance and preventing autoimmune diseases [203,204].

Inflammatory bowel disease

In IBD, efferocytosis is often impaired, contributing to the persistence of apoptotic cells and the release of pro-inflammatory mediators that exacerbate intestinal inflammation. The mechanisms of efferocytosis involve several key biochemical steps. Apoptotic cells display "eat-me" signals on their surface, which are recognized by phagocytic receptors on macrophages and dendritic cells. In IBD, various factors disrupt this process, leading to defective clearance of apoptotic cells [205,206]. Genetic predispositions, such as polymorphisms in genes related to autophagy and phagocytosis, can impair the efficiency of efferocytosis. For example, mutations in the ATG16L1 gene, which is crucial for autophagy and effective bacterial handling, have been associated with Crohn's disease and can affect the ability of macrophages to clear apoptotic cells and bacteria [207-209].

The inflammatory environment characteristic of IBD further impairs efferocytosis. Elevated levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and interleukin-6 (IL-6) can alter the function of phagocytes, reducing their capacity to engulf and digest apoptotic cells. TNF-α, in particular, can downregulate the expression of MerTK and other receptors involved in efferocytosis on macrophages, directly impairing their phagocytic function [210,211]. Additionally, oxidative stress, which is elevated in the inflamed intestinal mucosa of IBD patients, can modify PS and other "eat-me" signals on apoptotic cells, making them less recognizable to phagocytes. Oxidative stress can also damage phagocytes and affect the receptors and signaling pathways necessary for efficient efferocytosis [212,213].

Moreover, the gut microbiota, which is dysregulated in IBD, plays a significant role in modulating efferocytosis. Certain microbial metabolites, such as short-chain fatty acids (SCFAs), can enhance the efferocytic capacity of macrophages. However,

dysbiosis in IBD leads to a decrease in beneficial microbial metabolites and an increase in pathogenic bacteria that can further disrupt efferocytosis [214-216]. Defective efferocytosis in IBD leads to the accumulation of apoptotic cells, which undergo secondary necrosis and release intracellular contents, including damage-associated molecular patterns (DAMPs) like high-mobility group box 1 (HMGB1) and extracellular DNA. These DAMPs can activate pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) on immune cells, triggering the production of pro-inflammatory cytokines and perpetuating the inflammatory response [217,218].

Furthermore, the chronic inflammation in IBD creates a feedback loop where continuous recruitment and activation of immune cells, including neutrophils and macrophages, occur. These cells, in turn, produce more cytokines and reactive oxygen species (ROS), which further impair efferocytosis and promote tissue damage. Regulatory mechanisms that normally resolve inflammation and promote tissue repair are also disrupted in IBD [219,220]. For instance, the production of anti-inflammatory cytokines such as IL-10 and TGF-β, which are typically induced following efferocytosis, is often insufficient or ineffective in IBD. IL-10 and TGF-β play crucial roles in suppressing pro-inflammatory cytokine production and promoting regulatory T cell (Treg) function, but their impaired production or signaling in IBD contributes to the persistence of inflammation [221,222].

The impaired clearance of apoptotic cells and the resultant chronic inflammation in IBD not only cause tissue damage but also contribute to the disruption of the epithelial barrier. This barrier dysfunction allows for the translocation of luminal bacteria and antigens into the lamina propria, further activating the immune system and perpetuating the inflammatory cycle [223,224]. In summary, efferocytosis is a critical process for maintaining intestinal homeostasis, and its impairment in IBD is driven by a complex interplay of genetic, environmental, microbial, and immune factors. Defective efferocytosis leads to the accumulation of apoptotic cells, secondary necrosis, and the release of pro-inflammatory DAMPs, which perpetuate chronic inflammation and tissue damage. Understanding these mechanisms highlights the importance of targeting efferocytosis and its regulatory pathways as potential therapeutic strategies for IBD [224,225].

Sjögren's syndrome

In Sjögren's syndrome (SS), an autoimmune disease primarily affecting exocrine glands such as the salivary and lacrimal glands, efferocytosis is impaired, contributing to the chronic inflammation and tissue damage characteristic of the disease. Genetic predispositions play a significant role, as polymorphisms in genes related to immune regulation and apoptotic cell clearance are associated with the disease [226,227]. For instance, polymorphisms in the gene encoding for MerTK, a receptor crucial for the efficient clearance of apoptotic cells, can impair efferocytosis. This genetic susceptibility is compounded by environmental factors such as viral infections, which can induce apoptosis and overload the phagocytic capacity of immune cells. The chronic inflammatory environment in SS further impairs efferocytosis. Elevated levels of pro-inflammatory cytokines, such as TNF-α, IFN-γ, and IL-1β, are characteristic of SS and can alter the function of phagocytes [228-230]. TNF-α, for instance, can downregulate the expression of MerTK and other receptors involved in efferocytosis on macrophages, directly impairing their ability to clear apoptotic cells. Additionally, IFN-γ can activate macrophages in a way that promotes inflammation rather than resolution, further contributing to tissue damage [231,232].

Oxidative stress, which is elevated in SS, can modify PS and other "eat-me" signals on apoptotic cells, making them less recognizable to phagocytes. Oxidative stress can also damage phagocytes and affect the receptors and signaling pathways necessary for efficient efferocytosis. The impaired clearance of apoptotic cells in SS leads to their accumulation and secondary necrosis, releasing intracellular contents, including DAMPs such as high-mobility group box 1 (HMGB1) and extracellular DNA [233]. These DAMPs can activate pattern recognition receptors (PRRs) like TLRs and NOD-like receptors (NLRs) on immune cells, triggering the production of pro-inflammatory cytokines and perpetuating the inflammatory response [234].

Furthermore, the chronic inflammation in SS creates a feedback loop where continuous recruitment and activation of immune cells, including T and B lymphocytes, occur. These cells, in turn, produce more cytokines and autoantibodies, which further impair efferocytosis and promote tissue damage. Regulatory mechanisms that normally resolve inflammation and promote tissue repair are also disrupted in SS [235]. For example, the production of anti-inflammatory cytokines such as IL-10 and TGF-β, which are typically induced following efferocytosis, is often insufficient or ineffective in SS. IL-10 and TGF-β play crucial roles in suppressing pro-inflammatory cytokine production and promoting regulatory T cell (Treg) function, but their impaired production or signaling in SS contributes to the persistence of inflammation [236,237].

The impaired clearance of apoptotic cells and the resultant chronic inflammation in SS not only cause tissue damage but also lead to the formation of ectopic germinal centers within the salivary and lacrimal glands. These structures resemble lymphoid tissues and are sites where autoreactive B cells can be

activated and differentiate into plasma cells, producing autoantibodies such as anti-Ro/SSA and anti-La/SSB [238,239]. These autoantibodies form immune complexes with their target antigens, further contributing to tissue inflammation and damage. In summary, efferocytosis is a critical process for maintaining tissue homeostasis, and its impairment in Sjögren's syndrome is driven by a complex interplay of genetic, environmental, and immune factors. Defective efferocytosis leads to the accumulation of apoptotic cells, secondary necrosis, and the release of pro-inflammatory DAMPs, which perpetuate chronic inflammation and tissue damage. Understanding these mechanisms highlights the importance of targeting efferocytosis and its regulatory pathways as potential therapeutic strategies for Sjögren's syndrome [240,241].

Type 1 diabetes

The inflammatory environment characteristic of T1D often impairs efferocytosis. Elevated levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 are found in the pancreatic islets of T1D patients. These cytokines can alter the function of phagocytes, reducing their capacity to recognize and engulf apoptotic cells [242,243]. For example, TNF-α can downregulate the expression of MerTK and other receptors involved in efferocytosis on macrophages and dendritic cells, directly impairing their phagocytic function. Additionally, the presence of inflammatory cytokines can lead to the production of reactive oxygen species (ROS) and other mediators that damage both apoptotic cells and phagocytes, further disrupting the efferocytosis process [243].

The impaired clearance of apoptotic cells in T1D leads to their accumulation and secondary necrosis. This process releases intracellular contents, including damage-associated molecular patterns (DAMPs) such as high-mobility group box 1 (HMGB1) and extracellular DNA, which can act as potent pro-inflammatory signals [244,245]. These DAMPs activate pattern recognition receptors (PRRs) on immune cells, including TLRs and NOD-like receptors (NLRs), triggering an inflammatory cascade that exacerbates the autoimmune response. In T1D, the release of β-cell antigens from necrotic cells can further stimulate autoreactive T cells, perpetuating the destruction of insulin-producing β-cells in the pancreas [246,247].

In addition to genetic and inflammatory factors, hormonal influences can impact efferocytosis in T1D. For instance, insulin and other metabolic hormones can affect the function of immune cells and phagocytes. Dysregulation of these hormones in T1D may contribute to impaired efferocytosis and the development of autoimmunity. Moreover, the autoimmune destruction of pancreatic β-cells in T1D is associated with the infiltration of immune cells into the pancreatic islets, forming inflammatory infiltrates known as insulitis. This ongoing inflammation creates a hostile microenvironment that further impairs the ability of phagocytes to clear apoptotic cells and resolve inflammation effectively [248,249].

Systemic and multiple sclerosis

Both systemic and multiple sclerosis are impaired with changes in efferocytosis. In systemic sclerosis, genetic and environmental factors disrupt efferocytosis. For example, mutations in the genes encoding for components of the complement system, crucial for opsonizing and clearing apoptotic cells, can impair the efficiency of efferocytosis [250,251]. Complement components like C1q, C3, and C4 mark apoptotic cells for removal, and deficiencies in these components can lead to the accumulation of apoptotic cells and the development of autoimmunity. In SSc, the chronic inflammatory environment, characterized by elevated levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, alters the function of phagocytes, reducing their capacity to recognize and engulf apoptotic cells [252,253]. TNF-α, for example, can downregulate the expression of MerTK and other receptors involved in efferocytosis on macrophages and dendritic cells, directly impairing their phagocytic function. Additionally, oxidative stress, which is elevated in SSc, can modify PS and other "eat-me" signals on apoptotic cells, making them less recognizable to phagocytes and further disrupting the efferocytosis process [254].

In multiple sclerosis, efferocytosis is similarly impaired due to genetic, environmental, and immunological factors. MS is characterized by the autoimmune destruction of myelin, the protective sheath around nerve fibers in the central nervous system (CNS). The failure to efficiently clear apoptotic cells, including myelin debris, leads to chronic inflammation and further immune activation [255,256]. Genetic factors such as polymorphisms in the HLA-DRB1 gene, which is associated with an increased risk of MS, also play a role in impairing efferocytosis. In MS, the inflammatory milieu, with elevated levels of cytokines like IFN-γ, IL-17, and TNF-α, impairs the function of phagocytes. IFN-γ, for instance, can activate macrophages in a way that promotes inflammation rather than resolution, exacerbating tissue damage. Moreover, the presence of autoantibodies against myelin and other CNS components can form immune complexes with exposed antigens from apoptotic cells, interfering with their recognition and clearance [257,258].

The impaired clearance of apoptotic cells in both SSc and MS leads to their accumulation and secondary necrosis, releasing intracellular contents, including DAMPs such as HMGB1 and extracellular DNA. These DAMPs activate pattern recognition receptors (PRRs) on immune cells, including TLRs and NOD-like receptors (NLRs), triggering an inflammatory cascade that perpetuates the

autoimmune response [259,260]. The chronic exposure to self-antigens in SSc and MS drives the activation of autoreactive T and B cells, leading to sustained autoantibody production and inflammation. Regulatory mechanisms that normally resolve inflammation and promote tissue repair are also disrupted in SSc and MS. For example, the production of anti-inflammatory cytokines such as IL-10 and TGF-β, typically induced following efferocytosis, is often insufficient or ineffective in these diseases. IL-10 and TGF-β play crucial roles in suppressing pro-inflammatory cytokine production and promoting regulatory T cell (Treg) function, but their impaired production or signaling contributes to the persistence of inflammation [261,262].

Conclusion

In summary, efferocytosis is a critical biological process that plays a vital role in maintaining cellular homeostasis and preventing inflammatory responses. The intricate mechanisms underlying this process involve a series of well-orchestrated signaling pathways that enable phagocytes to recognize, engulf, and degrade apoptotic cells efficiently. When functioning properly, efferocytosis promotes immune tolerance and tissue repair. However, dysregulation of this essential process has profound implications for various autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease. The impaired clearance of apoptotic cells leads to their accumulation, triggering chronic inflammation and the release of pro-inflammatory mediators. This creates a vicious cycle that exacerbates tissue damage and perpetuates autoimmune responses.

Current research endeavors are focused on elucidating the molecular pathways involved in efferocytosis, as a deeper understanding of these mechanisms may facilitate the development of targeted therapies aimed at enhancing apoptotic cell clearance. Future studies should explore the interplay between the gut microbiome and efferocytosis, as this research could uncover novel strategies for improving immune regulation and potentially mitigating autoimmune conditions. Additionally, the prospect of personalized medicine—tailoring therapeutic interventions based on individual genetic and environmental factors—highlights the importance of advancing our knowledge in this area.

Ultimately, harnessing the power of efferocytosis may pave the way for novel therapeutic strategies that not only address the underlying mechanisms of autoimmune diseases but also promote optimal immune health. By integrating insights from efferocytosis research into clinical practice, we can strive to improve patient outcomes and enhance overall well-being in individuals affected by these chronic conditions.

Author Contributions: Writing—original draft preparation, A.V.P.; writing—review and editing, V.N.S., T.V.K., T.I.K., I.A.S., D.F.B., A.N.O, A.V.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Russian Science Foundation, grant number 24-15-00123

Conflicts of Interest: The authors declare no conflict of interest.

Ethics Approval: Not applicable.
Consent to Participate: Not applicable.
Consent to Publish: Not applicable.
Data Availability Statement: Not applicable.

References

1. Mertens, C., Marques, O., Horvat, N. K., Simonetti, M., Muckenthaler, M. U., & Jung, M. (2021). The Macrophage Iron Signature in Health and Disease. *International journal of molecular sciences*, *22*(16), 8457. https://doi.org/10.3390/ijms22168457
2. Ge, Y., Huang, M., & Yao, Y. M. (2022). Efferocytosis and Its Role in Inflammatory Disorders. *Frontiers in cell and developmental biology*, *10*, 839248. https://doi.org/10.3389/fcell.2022.839248
3. Li, Q., Liu, H., Yin, G., & Xie, Q. (2024). Efferocytosis: Current status and future prospects in the treatment of autoimmune diseases. *Heliyon*, *10*(7), e28399. https://doi.org/10.1016/j.heliyon.2024.e28399
4. Tajbakhsh A, Rezaee M, Barreto GE, Moallem SA, Henney NC, Sahebkar A. The role of nuclear factors as "Find-Me"/alarmin signals and immunostimulation in defective efferocytosis and related disorders. Int Immunopharmacol. 2020 Mar;80:106134. doi: 10.1016/j.intimp.2019.106134. Epub 2020 Jan 10. PMID: 31931365.
5. Ma, Y., Kemp, S. S., Yang, X., Wu, M. H., & Yuan, S. Y. (2023). Cellular mechanisms underlying the impairment of macrophage efferocytosis. *Immunology letters*, *254*, 41–53. https://doi.org/10.1016/j.imlet.2023.02.001
6. Pabón-Porras, M. A., Molina-Ríos, S., Flórez-Suárez, J. B., Coral-Alvarado, P. X., Méndez-Patarroyo, P., & Quintana-López, G. (2019). Rheumatoid arthritis and systemic lupus erythematosus: Pathophysiological mechanisms related to innate immune system. *SAGE open medicine*, *7*, 2050312119876146. https://doi.org/10.1177/2050312119876146
7. Richter, P., Macovei, L. A., Mihai, I. R., Cardoneanu, A., Burlui, M. A., & Rezus, E. (2023). Cytokines in Systemic Lupus Erythematosus-Focus on TNF-α and IL-17. *International journal of molecular sciences*, *24*(19), 14413. https://doi.org/10.3390/ijms241914413
8. Doran, A. C., Yurdagul, A., Jr, & Tabas, I. (2020). Efferocytosis in health and disease. *Nature reviews. Immunology*, *20*(4), 254–267. https://doi.org/10.1038/s41577-019-0240-6

9. Moon, B., Yang, S., Moon, H., Lee, J., & Park, D. (2023). After cell death: the molecular machinery of efferocytosis. *Experimental & molecular medicine*, *55*(8), 1644–1651. https://doi.org/10.1038/s12276-023-01070-5
10. Glassman, F. Y., Dingman, R., Yau, H. C., & Balu-Iyer, S. V. (2020). Biological Function and Immunotherapy Utilizing Phosphatidylserine-based Nanoparticles. *Immunological investigations*, *49*(7), 858–874. https://doi.org/10.1080/08820139.2020.1738456
11. Shlomovitz, I., Speir, M., & Gerlic, M. (2019). Flipping the dogma - phosphatidylserine in non-apoptotic cell death. *Cell communication and signaling : CCS*, *17*(1), 139. https://doi.org/10.1186/s12964-019-0437-0
12. Myers, K. V., Amend, S. R., & Pienta, K. J. (2019). Targeting Tyro3, Axl and MerTK (TAM receptors): implications for macrophages in the tumor microenvironment. *Molecular cancer*, *18*(1), 94. https://doi.org/10.1186/s12943-019-1022-2
13. Han, M., Ryu, G., Shin, S. A., An, J., Kim, H., Park, D., Lee, D. H., & Lee, C. S. (2021). Physiological Roles of Apoptotic Cell Clearance: Beyond Immune Functions. *Life (Basel, Switzerland)*, *11*(11), 1141. https://doi.org/10.3390/life11111141
14. Linger, R. M., Keating, A. K., Earp, H. S., & Graham, D. K. (2008). TAM receptor tyrosine kinases: biologic functions, signaling, and potential therapeutic targeting in human cancer. *Advances in cancer research*, *100*, 35–83. https://doi.org/10.1016/S0065-230X(08)00002-X
15. Mikolajczyk, A., Mitula, F., Popiel, D., Kaminska, B., Wieczorek, M., & Pieczykolan, J. (2022). Two-Front War on Cancer-Targeting TAM Receptors in Solid Tumour Therapy. *Cancers*, *14*(10), 2488. https://doi.org/10.3390/cancers14102488
16. Mao, Y., & Finnemann, S. C. (2015). Regulation of phagocytosis by Rho GTPases. *Small GTPases*, *6*(2), 89–99. https://doi.org/10.4161/21541248.2014.989785
17. Rosales, C., & Uribe-Querol, E. (2017). Phagocytosis: A Fundamental Process in Immunity. *BioMed research international*, *2017*, 9042851. https://doi.org/10.1155/2017/9042851
18. Lancaster, C. E., Fountain, A., Dayam, R. M., Somerville, E., Sheth, J., Jacobelli, V., Somerville, A., Terebiznik, M. R., & Botelho, R. J. (2021). Phagosome resolution regenerates lysosomes and maintains the degradative capacity in phagocytes. *The Journal of cell biology*, *220*(9), e202005072. https://doi.org/10.1083/jcb.202005072
19. Lu, N., & Zhou, Z. (2012). Membrane trafficking and phagosome maturation during the clearance of apoptotic cells. *International review of cell and molecular biology*, *293*, 269–309. https://doi.org/10.1016/B978-0-12-394304-0.00013-0
20. Qiu H, Shao Z, Wen X, Liu Z, Chen Z, Qu D, Ding X, Zhang L. Efferocytosis: An accomplice of cancer immune escape. Biomed Pharmacother. 2023 Nov;167:115540. doi: 10.1016/j.biopha.2023.115540. Epub 2023 Sep 21. PMID: 37741255.
21. Wang, L., Li, H., Tang, Y., & Yao, P. (2021). Potential Mechanisms and Effects of Efferocytosis in Atherosclerosis. *Frontiers in endocrinology*, *11*, 585285. https://doi.org/10.3389/fendo.2020.585285
22. Kumar, S., Calianese, D., & Birge, R. B. (2017). Efferocytosis of dying cells differentially modulate immunological outcomes in tumor microenvironment. *Immunological reviews*, *280*(1), 149–164. https://doi.org/10.1111/imr.12587
23. Tajbakhsh, A., Kovanen, P. T., Rezaee, M., Banach, M., Moallem, S. A., & Sahebkar, A. (2020). Regulation of efferocytosis by caspase-dependent apoptotic cell death in atherosclerosis. *The international journal of biochemistry & cell biology*, *120*, 105684. https://doi.org/10.1016/j.biocel.2020.105684
24. Kelley, S. M., & Ravichandran, K. S. (2021). Putting the brakes on phagocytosis: "don't-eat-me" signaling in physiology and disease. *EMBO reports*, *22*(6), e52564. https://doi.org/10.15252/embr.202152564
25. Werfel, T. A., & Cook, R. S. (2018). Efferocytosis in the tumor microenvironment. *Seminars in immunopathology*, *40*(6), 545–554. https://doi.org/10.1007/s00281-018-0698-5
26. Ravichandran K. S. (2010). Find-me and eat-me signals in apoptotic cell clearance: progress and conundrums. *The Journal of experimental medicine*, *207*(9), 1807–1817. https://doi.org/10.1084/jem.20101157
27. Arandjelovic, S., & Ravichandran, K. S. (2015). Phagocytosis of apoptotic cells in homeostasis. *Nature immunology*, *16*(9), 907–917. https://doi.org/10.1038/ni.3253
28. Xiao, L., Zhang, L., Guo, C., Xin, Q., Gu, X., Jiang, C., & Wu, J. (2024). "Find Me" and "Eat Me" signals: tools to drive phagocytic processes for modulating antitumor immunity. *Cancer communications (London, England)*, *44*(7), 791–832. https://doi.org/10.1002/cac2.12579
29. Woods, L. T., Forti, K. M., Shanbhag, V. C., Camden, J. M., & Weisman, G. A. (2021). P2Y receptors for extracellular nucleotides:

Contributions to cancer progression and therapeutic implications. *Biochemical pharmacology*, *187*, 114406. https://doi.org/10.1016/j.bcp.2021.114406

30. Shihan, M., Novoyatleva, T., Lehmeyer, T., Sydykov, A., & Schermuly, R. T. (2021). Role of the Purinergic P2Y2 Receptor in Pulmonary Hypertension. *International journal of environmental research and public health*, *18*(21), 11009. https://doi.org/10.3390/ijerph182111009
31. Arnaud-Sampaio, V. F., Rabelo, I. L. A., Bento, C. A., Glaser, T., Bezerra, J., Coutinho-Silva, R., Ulrich, H., & Lameu, C. (2020). Using Cytometry for Investigation of Purinergic Signaling in Tumor-Associated Macrophages. *Cytometry. Part A : the journal of the International Society for Analytical Cytology*, *97*(11), 1109–1126. https://doi.org/10.1002/cyto.a.24035
32. Yang, W. J., Cao, R. C., Xiao, W., Zhang, X. L., Xu, H., Wang, M., Zhou, Z. T., Chen, H. J., Xu, J., Chen, X. M., Zeng, J. L., Li, S. J., Luo, M., Han, Y. J., Yang, X. B., Feng, G. D., Lu, Y. H., Ni, Y. Y., Wu, C. G., Bai, J. J., … Zhang, G. W. (2022). Acinar ATP8b1/LPC pathway promotes macrophage efferocytosis and clearance of inflammation during chronic pancreatitis development. *Cell death & disease*, *13*(10), 893. https://doi.org/10.1038/s41419-022-05322-6
33. Hochreiter-Hufford, A., & Ravichandran, K. S. (2013). Clearing the dead: apoptotic cell sensing, recognition, engulfment, and digestion. *Cold Spring Harbor perspectives in biology*, *5*(1), a008748. https://doi.org/10.1101/cshperspect.a008748
34. Lauber K, Bohn E, Kröber SM, Xiao YJ, Blumenthal SG, Lindemann RK, Marini P, Wiedig C, Zobywalski A, Baksh S, Xu Y, Autenrieth IB, Schulze-Osthoff K, Belka C, Stuhler G, Wesselborg S. Apoptotic cells induce migration of phagocytes via caspase-3-mediated release of a lipid attraction signal. Cell. 2003 Jun 13;113(6):717-30. doi: 10.1016/s0092-8674(03)00422-7. PMID: 12809603.
35. Rivas-Fuentes, S., Salgado-Aguayo, A., Arratia-Quijada, J., & Gorocica-Rosete, P. (2021). Regulation and biological functions of the CX3CL1-CX3CR1 axis and its relevance in solid cancer: A mini-review. *Journal of Cancer*, *12*(2), 571–583. https://doi.org/10.7150/jca.47022
36. Szukiewicz D. (2024). CX3CL1 (Fractalkine)-CX3CR1 Axis in Inflammation-Induced Angiogenesis and Tumorigenesis. *International journal of molecular sciences*, *25*(9), 4679. https://doi.org/10.3390/ijms25094679
37. Xiao, S., Peng, K., Li, C. *et al.* The role of sphingosine-1-phosphate in autophagy and related disorders. *Cell Death Discov.* **9**, 380 (2023). https://doi.org/10.1038/s41420-023-01681-x
38. Blaho, V. A., & Hla, T. (2014). An update on the biology of sphingosine 1-phosphate receptors. *Journal of lipid research*, *55*(8), 1596–1608. https://doi.org/10.1194/jlr.R046300
39. Bryan, A. M., & Del Poeta, M. (2018). Sphingosine-1-phosphate receptors and innate immunity. *Cellular microbiology*, *20*(5), e12836. https://doi.org/10.1111/cmi.12836
40. Weigert, A., Olesch, C., & Brüne, B. (2019). Sphingosine-1-Phosphate and Macrophage Biology-How the Sphinx Tames the Big Eater. *Frontiers in immunology*, *10*, 1706. https://doi.org/10.3389/fimmu.2019.01706
41. Elliott, M. R., & Ravichandran, K. S. (2016). The Dynamics of Apoptotic Cell Clearance. *Developmental cell*, *38*(2), 147–160. https://doi.org/10.1016/j.devcel.2016.06.029
42. Rochette, L., Dogon, G., Rigal, E., Zeller, M., Cottin, Y., & Vergely, C. (2023). Interplay between efferocytosis and atherosclerosis. *Archives of cardiovascular diseases*, *116*(10), 474–484. https://doi.org/10.1016/j.acvd.2023.07.007
43. Westman, J., Grinstein, S., & Marques, P. E. (2020). Phagocytosis of Necrotic Debris at Sites of Injury and Inflammation. *Frontiers in immunology*, *10*, 3030. https://doi.org/10.3389/fimmu.2019.03030
44. Elliott, M. R., Koster, K. M., & Murphy, P. S. (2017). Efferocytosis Signaling in the Regulation of Macrophage Inflammatory Responses. *Journal of immunology (Baltimore, Md. : 1950)*, *198*(4), 1387–1394. https://doi.org/10.4049/jimmunol.1601520
45. Pratima B, Nalini N. Efferocytosis: An Interface between Apoptosis and Pathophysiology. IntechOpen; 2021 Nov 15. doi: 10.5772/intechopen.97819
46. Mike JK, Ferriero DM. Efferocytosis Mediated Modulation of Injury after Neonatal Brain Hypoxia-Ischemia. Cells. 2021 Apr 27;10(5):1025. doi: 10.3390/cells10051025. PMID: 33925299; PMCID: PMC8146813.
47. Karaji N, Sattentau QJ. Efferocytosis of Pathogen-Infected Cells. Front Immunol. 2017 Dec 22;8:1863. doi: 10.3389/fimmu.2017.01863. PMID: 29312342; PMCID: PMC5743670.
48. Martinez J. (2017). Prix Fixe: Efferocytosis as a Four-Course Meal. *Current topics in microbiology and immunology*, *403*, 1–36. https://doi.org/10.1007/82_2015_467
49. Khalaji, A., Yancheshmeh, F. B., Farham, F., Khorram, A., Sheshbolouki, S., Zokaei, M., Vatankhah, F., & Soleymani-Goloujeh, M. (2023). Don't eat me/eat me signals as a novel strategy in cancer

immunotherapy. *Heliyon*, *9*(10), e20507. https://doi.org/10.1016/j.heliyon.2023.e20507

50. Hankins, H. M., Baldridge, R. D., Xu, P., & Graham, T. R. (2015). Role of flippases, scramblases and transfer proteins in phosphatidylserine subcellular distribution. *Traffic (Copenhagen, Denmark)*, *16*(1), 35–47. https://doi.org/10.1111/tra.12233
51. Nagata, S., Suzuki, J., Segawa, K., & Fujii, T. (2016). Exposure of phosphatidylserine on the cell surface. *Cell death and differentiation*, *23*(6), 952–961. https://doi.org/10.1038/cdd.2016.7
52. Mehrotra, P., & Ravichandran, K. S. (2022). Drugging the efferocytosis process: concepts and opportunities. *Nature reviews. Drug discovery*, *21*(8), 601–620. https://doi.org/10.1038/s41573-022-00470-y
53. Hawkins, L. A., & Devitt, A. (2013). Current understanding of the mechanisms for clearance of apoptotic cells-a fine balance. *Journal of cell death*, *6*, 57–68. https://doi.org/10.4137/JCD.S11037
54. Parinot, C., Chatagnon, J., Rieu, Q., Roux, S., Néel, D., Hamieh, F., & Nandrot, E. F. (2024). Gas6 and Protein S Ligands Cooperate to Regulate MerTK Rhythmic Activity Required for Circadian Retinal Phagocytosis. *International journal of molecular sciences*, *25*(12), 6630. https://doi.org/10.3390/ijms25126630
55. Park, S. Y., & Kim, I. S. (2017). Engulfment signals and the phagocytic machinery for apoptotic cell clearance. *Experimental & molecular medicine*, *49*(5), e331. https://doi.org/10.1038/emm.2017.52
56. Bao HR, Chen JL, Li F, Zeng XL, Liu XJ. Relationship between PI3K/mTOR/RhoA pathway-regulated cytoskeletal rearrangements and phagocytic capacity of macrophages. Braz J Med Biol Res. 2020 Jun 3;53(7):e9207. doi: 10.1590/1414-431X20209207. PMID: 32520207; PMCID: PMC7279697.
57. Boada-Romero, E., Martinez, J., Heckmann, B. L., & Green, D. R. (2020). The clearance of dead cells by efferocytosis. *Nature reviews. Molecular cell biology*, *21*(7), 398–414. https://doi.org/10.1038/s41580-020-0232-1
58. Fucikova, J., Kepp, O., Kasikova, L. *et al.* Detection of immunogenic cell death and its relevance for cancer therapy. *Cell Death Dis* **11**, 1013 (2020). https://doi.org/10.1038/s41419-020-03221-2
59. Sheng, Y. R., Hu, W. T., Chen, S., & Zhu, X. Y. (2024). Efferocytosis by macrophages in physiological and pathological conditions: regulatory pathways and molecular mechanisms. *Frontiers in immunology*, *15*, 1275203. https://doi.org/10.3389/fimmu.2024.1275203
60. Silverstein, R. L., & Febbraio, M. (2009). CD36, a scavenger receptor involved in immunity, metabolism, angiogenesis, and behavior. *Science signaling*, *2*(72), re3. https://doi.org/10.1126/scisignal.272re3
61. Park, Y. CD36, a scavenger receptor implicated in atherosclerosis. *Exp Mol Med* **46**, e99 (2014). https://doi.org/10.1038/emm.2014.38
62. Ganesan R, Henkels KM, Wrenshall LE, Kanaho Y, Di Paolo G, Frohman MA, Gomez-Cambronero J. Oxidized LDL phagocytosis during foam cell formation in atherosclerotic plaques relies on a PLD2-CD36 functional interdependence. J Leukoc Biol. 2018 May;103(5):867-883. doi: 10.1002/JLB.2A1017-407RR. Epub 2018 Apr 14. PMID: 29656494; PMCID: PMC5951301.
63. Rezende, L., Couto, N. F. D., Fernandes-Braga, W., Epshtein, Y., Alvarez-Leite, J. I., Levitan, I., & Andrade, L. O. (2022). OxLDL induces membrane structure rearrangement leading to biomechanics alteration and migration deficiency in macrophage. *Biochimica et biophysica acta. Biomembranes*, *1864*(9), 183951. https://doi.org/10.1016/j.bbamem.2022.183951
64. Noris, M., & Remuzzi, G. (2013). Overview of complement activation and regulation. *Seminars in nephrology*, *33*(6), 479–492. https://doi.org/10.1016/j.semnephrol.2013.08.001
65. Merle, N. S., Noe, R., Halbwachs-Mecarelli, L., Fremeaux-Bacchi, V., & Roumenina, L. T. (2015). Complement System Part II: Role in Immunity. *Frontiers in immunology*, *6*, 257. https://doi.org/10.3389/fimmu.2015.00257
66. Vandendriessche, S., Cambier, S., Proost, P., & Marques, P. E. (2021). Complement Receptors and Their Role in Leukocyte Recruitment and Phagocytosis. *Frontiers in cell and developmental biology*, *9*, 624025. https://doi.org/10.3389/fcell.2021.624025
67. Nössing, C., & Ryan, K. M. (2023). 50 years on and still very much alive: 'Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics'. *British journal of cancer*, *128*(3), 426–431. https://doi.org/10.1038/s41416-022-02020-0
68. Lee, H. J., Woo, Y., Hahn, T. W., Jung, Y. M., & Jung, Y. J. (2020). Formation and Maturation of the Phagosome: A Key Mechanism in Innate Immunity against Intracellular Bacterial Infection. *Microorganisms*, *8*(9), 1298.

https://doi.org/10.3390/microorganisms8091298

69. Szondy, Z., Sarang, Z., Kiss, B., Garabuczi, É., & Köröskényi, K. (2017). Anti-inflammatory Mechanisms Triggered by Apoptotic Cells during Their Clearance. *Frontiers in immunology*, *8*, 909. https://doi.org/10.3389/fimmu.2017.00909
70. Ramos, C., Oehler, R. Clearance of apoptotic cells by neutrophils in inflammation and cancer. *Cell Death Discov.* **10**, 26 (2024). https://doi.org/10.1038/s41420-024-01809-7
71. Sanjabi S, Zenewicz LA, Kamanaka M, Flavell RA. Anti-inflammatory and pro-inflammatory roles of TGF-beta, IL-10, and IL-22 in immunity and autoimmunity. Curr Opin Pharmacol. 2009 Aug;9(4):447-53. doi: 10.1016/j.coph.2009.04.008. Epub 2009 May 29. PMID: 19481975; PMCID: PMC2755239.
72. Maute, R., Xu, J., & Weissman, I. L. (2022). CD47-SIRPα-targeted therapeutics: status and prospects. *Immuno-oncology technology*, *13*, 100070. https://doi.org/10.1016/j.iotech.2022.100070
73. Logtenberg, M. E. W., Scheeren, F. A., & Schumacher, T. N. (2020). The CD47-SIRPα Immune Checkpoint. *Immunity*, *52*(5), 742–752. https://doi.org/10.1016/j.immuni.2020.04.011
74. Polara, R., Ganesan, R., Pitson, S.M. *et al.* Cell autonomous functions of CD47 in regulating cellular plasticity and metabolic plasticity. *Cell Death Differ* (2024). https://doi.org/10.1038/s41418-024-01347-w
75. 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. *Frontiers in immunology*, *9*, 1645. https://doi.org/10.3389/fimmu.2018.01645
76. Kinchen JM, Ravichandran KS. Phagosome maturation: going through the acid test. Nat Rev Mol Cell Biol. 2008 Oct;9(10):781-95. doi: 10.1038/nrm2515. PMID: 18813294; PMCID: PMC2908392.
77. Horst, A. K., Tiegs, G., & Diehl, L. (2019). Contribution of Macrophage Efferocytosis to Liver Homeostasis and Disease. *Frontiers in immunology*, *10*, 2670. https://doi.org/10.3389/fimmu.2019.02670
78. Vorselen D. (2022). Dynamics of phagocytosis mediated by phosphatidylserine. *Biochemical Society transactions*, *50*(5), 1281–1291. https://doi.org/10.1042/BST20211254
79. Bhattacharya, S., McElhanon, K. E., Gushchina, L. V., & Weisleder, N. (2016). Role of phosphatidylinositol-4,5-bisphosphate 3-kinase signaling in vesicular trafficking. *Life sciences*, *167*, 39–45. https://doi.org/10.1016/j.lfs.2016.10.018
80. Penberthy, K. K., & Ravichandran, K. S. (2016). Apoptotic cell recognition receptors and scavenger receptors. *Immunological reviews*, *269*(1), 44–59. https://doi.org/10.1111/imr.12376
81. Pisko J, Špirková A, Čikoš Š, Olexiková L, Kovaříková V, Šefčíková Z, Fabian D. Apoptotic cells in mouse blastocysts are eliminated by neighbouring blastomeres. Sci Rep. 2021 Apr 29;11(1):9228. doi: 10.1038/s41598-021-88752-0. PMID: 33927296; PMCID: PMC8085119.
82. Naeini, M.B., Bianconi, V., Pirro, M. *et al.* The role of phosphatidylserine recognition receptors in multiple biological functions. *Cell Mol Biol Lett* **25**, 23 (2020). https://doi.org/10.1186/s11658-020-00214-z
83. Cockram, T. O. J., Dundee, J. M., Popescu, A. S., & Brown, G. C. (2021). The Phagocytic Code Regulating Phagocytosis of Mammalian Cells. *Frontiers in immunology*, *12*, 629979. https://doi.org/10.3389/fimmu.2021.629979
84. Uribe-Querol E, Rosales C. Phagocytosis: Our Current Understanding of a Universal Biological Process. Front Immunol. 2020 Jun 2;11:1066. doi: 10.3389/fimmu.2020.01066. PMID: 32582172; PMCID: PMC7280488.
85. Torres-Gomez, A., Cabañas, C., & Lafuente, E. M. (2020). Phagocytic Integrins: Activation and Signaling. *Frontiers in immunology*, *11*, 738. https://doi.org/10.3389/fimmu.2020.00738
86. Jaumouillé, V., & Waterman, C. M. (2020). Physical Constraints and Forces Involved in Phagocytosis. *Frontiers in immunology*, *11*, 1097. https://doi.org/10.3389/fimmu.2020.01097
87. Mylvaganam, S., Freeman, S. A., & Grinstein, S. (2021). The cytoskeleton in phagocytosis and macropinocytosis. *Current biology : CB*, *31*(10), R619–R632. https://doi.org/10.1016/j.cub.2021.01.036
88. Bonam, S. R., Wang, F., & Muller, S. (2019). Lysosomes as a therapeutic target. *Nature reviews. Drug discovery*, *18*(12), 923–948. https://doi.org/10.1038/s41573-019-0036-1
89. Trybus W, Trybus E, Król T. Lysosomes as a Target of Anticancer Therapy. Int J Mol Sci. 2023 Jan 22;24(3):2176. doi: 10.3390/ijms24032176. PMID: 36768500; PMCID: PMC9916765.
90. Dutta S, Mukherjee A, Nongthomba U. Before the "cytokine storm": Boosting efferocytosis as an effective strategy against SARS-CoV-2 infection and associated complications. Cytokine Growth Factor Rev. 2022 Feb;63:108-118. doi: 10.1016/j.cytogfr.2022.01.002. Epub 2022 Jan 8. PMID: 35039221; PMCID: PMC8741331.

91. Kourtzelis, I., Hajishengallis, G., & Chavakis, T. (2020). Phagocytosis of Apoptotic Cells in Resolution of Inflammation. *Frontiers in immunology*, *11*, 553. https://doi.org/10.3389/fimmu.2020.00553
92. Zhao, H., Song, S., Ma, J., Yan, Z., Xie, H., Feng, Y., & Che, S. (2022). CD47 as a promising therapeutic target in oncology. *Frontiers in immunology*, *13*, 757480. https://doi.org/10.3389/fimmu.2022.757480
93. Feng, M., Jiang, W., Kim, B. Y. S., Zhang, C. C., Fu, Y. X., & Weissman, I. L. (2019). Phagocytosis checkpoints as new targets for cancer immunotherapy. *Nature reviews. Cancer*, *19*(10), 568–586. https://doi.org/10.1038/s41568-019-0183-z
94. Gray, M. A., Choy, C. H., Dayam, R. M., Ospina-Escobar, E., Somerville, A., Xiao, X., Ferguson, S. M., & Botelho, R. J. (2016). Phagocytosis Enhances Lysosomal and Bactericidal Properties by Activating the Transcription Factor TFEB. *Current biology : CB*, *26*(15), 1955–1964. https://doi.org/10.1016/j.cub.2016.05.070
95. Peña-Ramos, O., Chiao, L., Liu, X., Yu, X., Yao, T., He, H., & Zhou, Z. (2022). Autophagosomes fuse to phagosomes and facilitate the degradation of apoptotic cells in *Caenorhabditis elegans*. *eLife*, *11*, e72466. https://doi.org/10.7554/eLife.72466
96. Cossarizza, A., Chang, H. D., Radbruch, A., Akdis, M., Andrä, I., Annunziato, F., Bacher, P., Barnaba, V., Battistini, L., Bauer, W. M., Baumgart, S., Becher, B., Beisker, W., Berek, C., Blanco, A., Borsellino, G., Boulais, P. E., Brinkman, R. R., Büscher, M., Busch, D. H., … Zimmermann, J. (2017). Guidelines for the use of flow cytometry and cell sorting in immunological studies. *European journal of immunology*, *47*(10), 1584–1797. https://doi.org/10.1002/eji.201646632
97. Cossarizza, A., Chang, H. D., Radbruch, A., Acs, A., Adam, D., Adam-Klages, S., Agace, W. W., Aghaeepour, N., Akdis, M., Allez, M., Almeida, L. N., Alvisi, G., Anderson, G., Andrä, I., Annunziato, F., Anselmo, A., Bacher, P., Baldari, C. T., Bari, S., Barnaba, V., … Zychlinsky, A. (2019). Guidelines for the use of flow cytometry and cell sorting in immunological studies (second edition). *European journal of immunology*, *49*(10), 1457–1973. https://doi.org/10.1002/eji.201970107
98. Blander J. M. (2017). The many ways tissue phagocytes respond to dying cells. *Immunological reviews*, *277*(1), 158–173. https://doi.org/10.1111/imr.12537
99. Zhang, M., Lin, Y., Chen, R. *et al*. Ghost messages: cell death signals spread. *Cell Commun Signal* **21**, 6 (2023). https://doi.org/10.1186/s12964-022-01004-0
100. Purnama, C.A., Meiliana, A., Barliana, M.I. *et al.* Update of cellular responses to the efferocytosis of necroptosis and pyroptosis. *Cell Div* **18**, 5 (2023). https://doi.org/10.1186/s13008-023-00087-6
101. Kanuri, S. Repercussions of microglial efferocytosis on neurodegeneration in Alzheimer's Disease (AD): a double-edged sword and perplexing factor warranting scrutiny in AD research. *Egypt J Neurol Psychiatry Neurosurg* **60**, 81 (2024). https://doi.org/10.1186/s41983-024-00853-5
102. Ma, Y., Jiang, T., Zhu, X., Xu, Y., Wan, K., Zhang, T., & Xie, M. (2024). Efferocytosis in dendritic cells: an overlooked immunoregulatory process. *Frontiers in immunology*, *15*, 1415573. https://doi.org/10.3389/fimmu.2024.1415573
103. Mihaila, A. C., Ciortan, L., Tucureanu, M. M., Simionescu, M., & Butoi, E. (2024). Anti-Inflammatory Neutrophils Reprogram Macrophages toward a Pro-Healing Phenotype with Increased Efferocytosis Capacity. *Cells*, *13*(3), 208. https://doi.org/10.3390/cells13030208
104. Deng, Z., Fan, T., Xiao, C., Tian, H., Zheng, Y., Li, C., & He, J. (2024). TGF-β signaling in health, disease, and therapeutics. *Signal transduction and targeted therapy*, *9*(1), 61. https://doi.org/10.1038/s41392-024-01764-w
105. Li, Y., Fan, W., Link, F., Wang, S., & Dooley, S. (2021). Transforming growth factor β latency: A mechanism of cytokine storage and signalling regulation in liver homeostasis and disease. *JHEP reports : innovation in hepatology*, *4*(2), 100397. https://doi.org/10.1016/j.jhepr.2021.100397
106. Hatamzade Esfahani, N.; Day, A.S. The Role of TGF-β, Activin and Follistatin in Inflammatory Bowel Disease. *Gastrointest. Disord.* **2023**, *5*, 167-186. https://doi.org/10.3390/gidisord5020015
107. Yurdagul A., Jr (2021). Metabolic Consequences of Efferocytosis and its Impact on Atherosclerosis. *Immunometabolism*, *3*(2), e210017. https://doi.org/10.20900/immunometab20210017
108. Rothlin CV, Carrera-Silva EA, Bosurgi L, Ghosh S. TAM receptor signaling in immune homeostasis. Annu Rev Immunol. 2015;33:355-91. doi: 10.1146/annurev-immunol-032414-112103. Epub 2015 Jan 14. PMID: 25594431; PMCID: PMC4491918.
109. Greenlee-Wacker M. C. (2016). Clearance of apoptotic neutrophils and resolution of inflammation. *Immunological reviews*, *273*(1), 357–370. https://doi.org/10.1111/imr.12453

110. Birge, R., Boeltz, S., Kumar, S. *et al*. Phosphatidylserine is a global immunosuppressive signal in efferocytosis, infectious disease, and cancer. *Cell Death Differ* **23**, 962–978 (2016). https://doi.org/10.1038/cdd.2016.11
111. Yan D, Huelse JM, Kireev D, Tan Z, Chen L, Goyal S, Wang X, Frye SV, Behera M, Schneider F, Ramalingam SS, Owonikoko T, Earp HS, DeRyckere D, Graham DK. MERTK activation drives osimertinib resistance in EGFR-mutant non-small cell lung cancer. J Clin Invest. 2022 Aug 1;132(15):e150517. doi: 10.1172/JCI150517. PMID: 35708914; PMCID: PMC9337831.
112. Trzeciak, A., Wang, Y. T., & Perry, J. S. A. (2021). First we eat, then we do everything else: The dynamic metabolic regulation of efferocytosis. *Cell metabolism*, *33*(11), 2126–2141. https://doi.org/10.1016/j.cmet.2021.08.001
113. Atkin-Smith G. K. (2021). Phagocytic clearance of apoptotic, necrotic, necroptotic and pyroptotic cells. *Biochemical Society transactions*, *49*(2), 793–804. https://doi.org/10.1042/BST20200696
114. He Y, Sun MM, Zhang GG, Yang J, Chen KS, Xu WW, Li B. Targeting PI3K/Akt signal transduction for cancer therapy. Signal Transduct Target Ther. 2021 Dec 16;6(1):425. doi: 10.1038/s41392-021-00828-5. PMID: 34916492; PMCID: PMC8677728.
115. Lam, A. L., & Heit, B. (2021). Having an Old Friend for Dinner: The Interplay between Apoptotic Cells and Efferocytes. *Cells*, *10*(5), 1265. https://doi.org/10.3390/cells10051265
116. Yurdagul, A., Jr, Doran, A. C., Cai, B., Fredman, G., & Tabas, I. A. (2018). Mechanisms and Consequences of Defective Efferocytosis in Atherosclerosis. *Frontiers in cardiovascular medicine*, *4*, 86. https://doi.org/10.3389/fcvm.2017.00086
117. Bohlson, S. S., O'Conner, S. D., Hulsebus, H. J., Ho, M. M., & Fraser, D. A. (2014). Complement, c1q, and c1q-related molecules regulate macrophage polarization. *Frontiers in immunology*, *5*, 402. https://doi.org/10.3389/fimmu.2014.00402
118. Hulsebus, H. J., O'Conner, S. D., Smith, E. M., Jie, C., & Bohlson, S. S. (2016). Complement Component C1q Programs a Pro-Efferocytic Phenotype while Limiting TNFα Production in Primary Mouse and Human Macrophages. *Frontiers in immunology*, *7*, 230. https://doi.org/10.3389/fimmu.2016.00230
119. Zheng, W., Zhou, Z., Guo, X., Zuo, X., Zhang, J., An, Y., Zheng, H., Yue, Y., Wang, G., & Wang, F. (2023). Efferocytosis and Respiratory Disease. *International journal of molecular sciences*, *24*(19), 14871. https://doi.org/10.3390/ijms241914871
120. Sós, L., Garabuczi, É., Sághy, T., Mocsár, G., & Szondy, Z. (2022). Palmitate Inhibits Mouse Macrophage Efferocytosis by Activating an mTORC1-Regulated Rho Kinase 1 Pathway: Therapeutic Implications for the Treatment of Obesity. *Cells*, *11*(21), 3502. https://doi.org/10.3390/cells11213502
121. Elkon K. B. (2018). Review: Cell Death, Nucleic Acids, and Immunity: Inflammation Beyond the Grave. *Arthritis & rheumatology (Hoboken, N.J.)*, *70*(6), 805–816. https://doi.org/10.1002/art.40452
122. Singhal, A., & Kumar, S. (2022). Neutrophil and remnant clearance in immunity and inflammation. *Immunology*, *165*(1), 22–43. https://doi.org/10.1111/imm.13423
123. Thurman, J. M., & Yapa, R. (2019). Complement Therapeutics in Autoimmune Disease. *Frontiers in immunology*, *10*, 672. https://doi.org/10.3389/fimmu.2019.00672
124. Kouser L, Madhukaran SP, Shastri A, Saraon A, Ferluga J, Al-Mozaini M, Kishore U. Emerging and Novel Functions of Complement Protein C1q. Front Immunol. 2015 Jun 29;6:317. doi: 10.3389/fimmu.2015.00317. PMID: 26175731; PMCID: PMC4484229.
125. Marshall, J.S., Warrington, R., Watson, W. *et al.* An introduction to immunology and immunopathology. *Allergy Asthma Clin Immunol* **14** (Suppl 2), 49 (2018). https://doi.org/10.1186/s13223-018-0278-1
126. Zhao, H., Wu, L., Yan, G. *et al.* Inflammation and tumor progression: signaling pathways and targeted intervention. *Sig Transduct Target Ther* **6**, 263 (2021). https://doi.org/10.1038/s41392-021-00658-5
127. Turner, M. D., Nedjai, B., Hurst, T., & Pennington, D. J. (2014). Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. *Biochimica et biophysica acta*, *1843*(11), 2563–2582. https://doi.org/10.1016/j.bbamcr.2014.05.014
128. Tajbakhsh, A., Gheibi Hayat, S. M., Movahedpour, A., Savardashtaki, A., Loveless, R., Barreto, G. E., Teng, Y., & Sahebkar, A. (2021). The complex roles of efferocytosis in cancer development, metastasis, and treatment. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *140*, 111776. https://doi.org/10.1016/j.biopha.2021.111776
129. Zhang, Y., Wang, Y., Ding, J., & Liu, P. (2022). Efferocytosis in multisystem diseases (Review). *Molecular medicine reports*, *25*(1), 13. https://doi.org/10.3892/mmr.2021.12529

130. Qiu, C. C., Caricchio, R., & Gallucci, S. (2019). Triggers of Autoimmunity: The Role of Bacterial Infections in the Extracellular Exposure of Lupus Nuclear Autoantigens. *Frontiers in immunology*, *10*, 2608. https://doi.org/10.3389/fimmu.2019.02608
131. Majai, G., Kiss, E., Tarr, T., Zahuczky, G., Hartman, Z., Szegedi, G., & Fésüs, L. (2014). Decreased apopto-phagocytic gene expression in the macrophages of systemic lupus erythematosus patients. *Lupus*, *23*(2), 133–145. https://doi.org/10.1177/0961203313511557
132. Sircana, M. C., Erre, G. L., Castagna, F., & Manetti, R. (2024). Crosstalk between Inflammation and Atherosclerosis in Rheumatoid Arthritis and Systemic Lupus Erythematosus: Is There a Common Basis?. *Life (Basel, Switzerland)*, *14*(6), 716. https://doi.org/10.3390/life14060716
133. de Brito Rocha, S., Baldo, D.C. & Andrade, L.E.C. Clinical and pathophysiologic relevance of autoantibodies in rheumatoid arthritis. *Adv Rheumatol* **59**, 2 (2019). https://doi.org/10.1186/s42358-018-0042-8
134. Ji, M., Ryu, H. J., & Hong, J. H. (2021). Signalling and putative therapeutic molecules on the regulation of synoviocyte signalling in rheumatoid arthritis. *Bone & joint research*, *10*(4), 285–297. https://doi.org/10.1302/2046-3758.104.BJR-2020-0331.R1
135. Zheng, Y., Wei, K., Jiang, P., Zhao, J., Shan, Y., Shi, Y., Zhao, F., Chang, C., Li, Y., Zhou, M., Lv, X., Guo, S., & He, D. (2024). Macrophage polarization in rheumatoid arthritis: signaling pathways, metabolic reprogramming, and crosstalk with synovial fibroblasts. *Frontiers in immunology*, *15*, 1394108. https://doi.org/10.3389/fimmu.2024.1394108
136. Qian, H., Deng, C., Chen, S. *et al.* Targeting pathogenic fibroblast-like synoviocyte subsets in rheumatoid arthritis. *Arthritis Res Ther* **26**, 103 (2024). https://doi.org/10.1186/s13075-024-03343-4
137. Tajbakhsh, A., Kovanen, P. T., Rezaee, M., Banach, M., & Sahebkar, A. (2019). Ca^{2+} Flux: Searching for a Role in Efferocytosis of Apoptotic Cells in Atherosclerosis. *Journal of clinical medicine*, *8*(12), 2047. https://doi.org/10.3390/jcm8122047
138. Zheng, D. J., Abou Taka, M., & Heit, B. (2021). Role of Apoptotic Cell Clearance in Pneumonia and Inflammatory Lung Disease. *Pathogens (Basel, Switzerland)*, *10*(2), 134. https://doi.org/10.3390/pathogens10020134
139. Kim EH, Wong SW, Martinez J. Programmed Necrosis and Disease:We interrupt your regular programming to bring you necroinflammation. Cell Death Differ. 2019 Jan;26(1):25-40. doi: 10.1038/s41418-018-0179-3. Epub 2018 Oct 22. PMID: 30349078; PMCID: PMC6294794.
140. Pandolfi, F., Franza, L., Carusi, V., Altamura, S., Andriollo, G., & Nucera, E. (2020). Interleukin-6 in Rheumatoid Arthritis. *International journal of molecular sciences*, *21*(15), 5238. https://doi.org/10.3390/ijms21155238
141. Molnar, V., Matišić, V., Kodvanj, I., Bjelica, R., Jeleč, Ž., Hudetz, D., Rod, E., Čukelj, F., Vrdoljak, T., Vidović, D., Starešinić, M., Sabalić, S., Dobričić, B., Petrović, T., Antičević, D., Borić, I., Košir, R., Zmrzljak, U. P., & Primorac, D. (2021). Cytokines and Chemokines Involved in Osteoarthritis Pathogenesis. *International journal of molecular sciences*, *22*(17), 9208. https://doi.org/10.3390/ijms22179208
142. Docherty, S., Harley, R., McAuley, J.J. *et al.* The effect of exercise on cytokines: implications for musculoskeletal health: a narrative review. *BMC Sports Sci Med Rehabil***14**, 5 (2022). https://doi.org/10.1186/s13102-022-00397-2
143. Du, Q., Dickinson, A., Nakuleswaran, P., Maghami, S., Alagoda, S., Hook, A. L., & Ghaemmaghami, A. M. (2024). Targeting Macrophage Polarization for Reinstating Homeostasis following Tissue Damage. *International journal of molecular sciences*, *25*(13), 7278. https://doi.org/10.3390/ijms25137278
144. Matsuda, K., Shiba, N., & Hiraoka, K. (2023). New Insights into the Role of Synovial Fibroblasts Leading to Joint Destruction in Rheumatoid Arthritis. *International journal of molecular sciences*, *24*(6), 5173. https://doi.org/10.3390/ijms24065173
145. Kemble, S., & Croft, A. P. (2021). Critical Role of Synovial Tissue-Resident Macrophage and Fibroblast Subsets in the Persistence of Joint Inflammation. *Frontiers in immunology*, *12*, 715894. https://doi.org/10.3389/fimmu.2021.715894
146. Kurma, K., Boizard-Moracchini, A., Galli, G., Jean, M., Vacher, P., Blanco, P., & Legembre, P. (2021). Soluble CD95L in cancers and chronic inflammatory disorders, a new therapeutic target?. *Biochimica et biophysica acta. Reviews on cancer*, *1876*(2), 188596. https://doi.org/10.1016/j.bbcan.2021.188596
147. Le Gallo, M., Poissonnier, A., Blanco, P., & Legembre, P. (2017). CD95/Fas, Non-Apoptotic Signaling Pathways, and Kinases. *Frontiers in immunology*, *8*, 1216. https://doi.org/10.3389/fimmu.2017.01216
148. Markiewski MM, Lambris JD. The role of complement in inflammatory diseases from

behind the scenes into the spotlight. Am J Pathol. 2007 Sep;171(3):715-27. doi: 10.2353/ajpath.2007.070166. Epub 2007 Jul 19. PMID: 17640961; PMCID: PMC1959484.

149. Brahadeeswaran, S., & Tamizhselvi, R. (2024). Consequence of alcohol intoxication-mediated efferocytosis impairment. *Frontiers in immunology*, *15*, 1386658. https://doi.org/10.3389/fimmu.2024.1386658
150. Schuermans, S., Kestens, C. & Marques, P.E. Systemic mechanisms of necrotic cell debris clearance. *Cell Death Dis* **15**, 557 (2024). https://doi.org/10.1038/s41419-024-06947-5
151. Gorgulho, C. M., Romagnoli, G. G., Bharthi, R., & Lotze, M. T. (2019). Johnny on the Spot-Chronic Inflammation Is Driven by HMGB1. *Frontiers in immunology*, *10*, 1561. https://doi.org/10.3389/fimmu.2019.01561
152. Ding, Q., Hu, W., Wang, R., Yang, Q., Zhu, M., Li, M., Cai, J., Rose, P., Mao, J., & Zhu, Y. Z. (2023). Signaling pathways in rheumatoid arthritis: implications for targeted therapy. *Signal transduction and targeted therapy*, *8*(1), 68. https://doi.org/10.1038/s41392-023-01331-9
153. Fang, Q., Zhou, C., & Nandakumar, K. S. (2020). Molecular and Cellular Pathways Contributing to Joint Damage in Rheumatoid Arthritis. *Mediators of inflammation*, *2020*, 3830212. https://doi.org/10.1155/2020/3830212
154. Lin, D., Kang, X., Shen, L., Tu, S., Lenahan, C., Chen, Y., Wang, X., & Shao, A. (2020). Efferocytosis and Its Associated Cytokines: A Light on Non-tumor and Tumor Diseases?. *Molecular therapy oncolytics*, *17*, 394–407. https://doi.org/10.1016/j.omto.2020.04.010
155. Cuda, C. M., Pope, R. M., & Perlman, H. (2016). The inflammatory role of phagocyte apoptotic pathways in rheumatic diseases. *Nature reviews. Rheumatology*, *12*(9), 543–558. https://doi.org/10.1038/nrrheum.2016.132
156. Waterborg, C. E. J., Beermann, S., Broeren, M. G. A., Bennink, M. B., Koenders, M. I., van Lent, P. L. E. M., van den Berg, W. B., van der Kraan, P. M., & van de Loo, F. A. J. (2018). Protective Role of the MER Tyrosine Kinase *via* Efferocytosis in Rheumatoid Arthritis Models. *Frontiers in immunology*, *9*, 742. https://doi.org/10.3389/fimmu.2018.00742
157. Lou, H., Ling, G. S., & Cao, X. (2022). Autoantibodies in systemic lupus erythematosus: From immunopathology to therapeutic target. *Journal of autoimmunity*, *132*, 102861. https://doi.org/10.1016/j.jaut.2022.102861
158. Wu, H., Zhao, M., Tan, L., & Lu, Q. (2016). The key culprit in the pathogenesis of systemic lupus erythematosus: Aberrant DNA methylation. *Autoimmunity reviews*, *15*(7), 684–689. https://doi.org/10.1016/j.autrev.2016.03.002
159. Choi, M. Y., & Costenbader, K. H. (2022). Understanding the Concept of Pre-Clinical Autoimmunity: Prediction and Prevention of Systemic Lupus Erythematosus: Identifying Risk Factors and Developing Strategies Against Disease Development. *Frontiers in immunology*, *13*, 890522. https://doi.org/10.3389/fimmu.2022.890522
160. Wang, S. S. Y., Tang, H., Loe, M. W. C., Yeo, S. C., & Javaid, M. M. (2024). Complements and Their Role in Systemic Disorders. *Cureus*, *16*(1), e52991. https://doi.org/10.7759/cureus.52991
161. Banda NK, Hyatt S, Antonioli AH, White JT, Glogowska M, Takahashi K, Merkel TJ, Stahl GL, Mueller-Ortiz S, Wetsel R, Arend WP, Holers VM. Role of C3a receptors, C5a receptors, and complement protein C6 deficiency in collagen antibody-induced arthritis in mice. J Immunol. 2012 Feb 1;188(3):1469-78. doi: 10.4049/jimmunol.1102310. Epub 2011 Dec 28. PMID: 22205026; PMCID: PMC3262949.
162. Ghodke-Puranik, Y., & Niewold, T. B. (2015). Immunogenetics of systemic lupus erythematosus: A comprehensive review. *Journal of autoimmunity*, *64*, 125–136. https://doi.org/10.1016/j.jaut.2015.08.004
163. Cui, Y., Sheng, Y., & Zhang, X. (2013). Genetic susceptibility to SLE: recent progress from GWAS. *Journal of autoimmunity*, *41*, 25–33. https://doi.org/10.1016/j.jaut.2013.01.008
164. Pan, Q., Chen, J., Guo, L., Lu, X., Liao, S., Zhao, C., Wang, S., & Liu, H. (2019). Mechanistic insights into environmental and genetic risk factors for systemic lupus erythematosus. *American journal of translational research*, *11*(3), 1241–1254.
165. Wolf, S. J., Estadt, S. N., Gudjonsson, J. E., & Kahlenberg, J. M. (2018). Human and Murine Evidence for Mechanisms Driving Autoimmune Photosensitivity. *Frontiers in immunology*, *9*, 2430. https://doi.org/10.3389/fimmu.2018.02430
166. Eloranta, M. L., & Rönnblom, L. (2016). Cause and consequences of the activated type I interferon system in SLE. *Journal of molecular medicine (Berlin, Germany)*, *94*(10), 1103–1110. https://doi.org/10.1007/s00109-016-1421-4
167. Paredes, J. L., Fernandez-Ruiz, R., & Niewold, T. B. (2021). T Cells in Systemic Lupus Erythematosus. *Rheumatic diseases*

clinics of North America, *47*(3), 379–393. https://doi.org/10.1016/j.rdc.2021.04.005

168. Karrar, S., & Cunninghame Graham, D. S. (2018). Abnormal B Cell Development in Systemic Lupus Erythematosus: What the Genetics Tell Us. *Arthritis & rheumatology (Hoboken, N.J.)*, *70*(4), 496–507. https://doi.org/10.1002/art.40396
169. Parodis, I., Long, X., Karlsson, M. C. I., & Huang, X. (2023). B Cell Tolerance and Targeted Therapies in SLE. *Journal of clinical medicine*, *12*(19), 6268. https://doi.org/10.3390/jcm12196268
170. Möckel, T., Basta, F., Weinmann-Menke, J., & Schwarting, A. (2021). B cell activating factor (BAFF): Structure, functions, autoimmunity and clinical implications in Systemic Lupus Erythematosus (SLE). *Autoimmunity reviews*, *20*(2), 102736. https://doi.org/10.1016/j.autrev.2020.102736
171. Postal, M., Vivaldo, J. F., Fernandez-Ruiz, R., Paredes, J. L., Appenzeller, S., & Niewold, T. B. (2020). Type I interferon in the pathogenesis of systemic lupus erythematosus. *Current opinion in immunology*, *67*, 87–94. https://doi.org/10.1016/j.coi.2020.10.014
172. Spinelli, F. R., Berti, R., Farina, G., Ceccarelli, F., Conti, F., & Crescioli, C. (2023). Exercise-induced modulation of Interferon-signature: a therapeutic route toward management of Systemic Lupus Erythematosus. *Autoimmunity reviews*, *22*(10), 103412. https://doi.org/10.1016/j.autrev.2023.103412
173. Bruera, S., Chavula, T., Madan, R., & Agarwal, S. K. (2023). Targeting type I interferons in systemic lupus erythematous. *Frontiers in pharmacology*, *13*, 1046687. https://doi.org/10.3389/fphar.2022.1046687
174. Lind, N.A., Rael, V.E., Pestal, K. *et al.* Regulation of the nucleic acid-sensing Toll-like receptors. *Nat Rev Immunol* **22**, 224–235 (2022). https://doi.org/10.1038/s41577-021-00577-0
175. Londe, A. C., Fernandez-Ruiz, R., Julio, P. R., Appenzeller, S., & Niewold, T. B. (2023). Type I Interferons in Autoimmunity: Implications in Clinical Phenotypes and Treatment Response. *The Journal of rheumatology*, *50*(9), 1103–1113. https://doi.org/10.3899/jrheum.2022-0827
176. Obrișcă, B., Sorohan, B., Tuță, L., & Ismail, G. (2021). Advances in Lupus Nephritis Pathogenesis: From Bench to Bedside. *International journal of molecular sciences*, *22*(7), 3766. https://doi.org/10.3390/ijms22073766
177. Musa R, Brent LH, Qurie A. Lupus Nephritis. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499817/
178. Umare, V., Pradhan, V., Nadkar, M., Rajadhyaksha, A., Patwardhan, M., Ghosh, K. K., & Nadkarni, A. H. (2014). Effect of proinflammatory cytokines (IL-6, TNF-α, and IL-1β) on clinical manifestations in Indian SLE patients. *Mediators of inflammation*, *2014*, 385297. https://doi.org/10.1155/2014/385297
179. Li, X., Li, C., Zhang, W. *et al.* Inflammation and aging: signaling pathways and intervention therapies. *Sig Transduct Target Ther* **8**, 239 (2023). https://doi.org/10.1038/s41392-023-01502-8
180. Kim, J. W., Kim, H. A., Suh, C. H., & Jung, J. Y. (2022). Sex hormones affect the pathogenesis and clinical characteristics of systemic lupus erythematosus. *Frontiers in medicine*, *9*, 906475. https://doi.org/10.3389/fmed.2022.906475
181. Pan, Q., Chen, X., Liao, S., Chen, X., Zhao, C., Xu, Y. Z., & Liu, H. F. (2019). Updated advances of linking psychosocial factors and sex hormones with systemic lupus erythematosus susceptibility and development. *PeerJ*, *7*, e7179. https://doi.org/10.7717/peerj.7179
182. Zhang M, Wei J, Sun Y, He C, Ma S, Pan X, Zhu X. The efferocytosis process in aging: Supporting evidence, mechanisms, and therapeutic prospects for age-related diseases. J Adv Res. 2024 Mar 17:S2090-1232(24)00109-7. doi: 10.1016/j.jare.2024.03.008. Epub ahead of print. PMID: 38499245.
183. Schilperoort, M., Ngai, D., Sukka, S. R., Avrampou, K., Shi, H., & Tabas, I. (2023). The role of efferocytosis-fueled macrophage metabolism in the resolution of inflammation. *Immunological reviews*, *319*(1), 65–80. https://doi.org/10.1111/imr.13214
184. Hou, G., Wang, X., Wang, A., Yuan, L., Zheng, Q., Xiao, H., & Wang, H. (2024). The role of secreted proteins in efferocytosis. *Frontiers in cell and developmental biology*, *11*, 1332482. https://doi.org/10.3389/fcell.2023.1332482
185. Trahtemberg, U., & Mevorach, D. (2017). Apoptotic Cells Induced Signaling for Immune Homeostasis in Macrophages and Dendritic Cells. *Frontiers in immunology*, *8*, 1356. https://doi.org/10.3389/fimmu.2017.01356
186. Colonna, L., Parry, G. C., Panicker, S., & Elkon, K. B. (2016). Uncoupling complement C1s activation from C1q binding in apoptotic cell phagocytosis and immunosuppressive capacity. *Clinical immunology (Orlando, Fla.)*, *163*, 84–90. https://doi.org/10.1016/j.clim.2015.12.017

187. Macedo, A. C., & Isaac, L. (2016). Systemic Lupus Erythematosus and Deficiencies of Early Components of the Complement Classical Pathway. *Frontiers in immunology*, *7*, 55. https://doi.org/10.3389/fimmu.2016.00055
188. Dunkelberger, J., Song, WC. Complement and its role in innate and adaptive immune responses. *Cell Res* **20**, 34–50 (2010). https://doi.org/10.1038/cr.2009.139
189. Dalakas, M.C., Alexopoulos, H. & Spaeth, P.J. Complement in neurological disorders and emerging complement-targeted therapeutics. *Nat Rev Neurol* **16**, 601–617 (2020). https://doi.org/10.1038/s41582-020-0400-0
190. Mistry, P., & Kaplan, M. J. (2017). Cell death in the pathogenesis of systemic lupus erythematosus and lupus nephritis. *Clinical immunology (Orlando, Fla.)*, *185*, 59–73. https://doi.org/10.1016/j.clim.2016.08.010
191. Yang, F., He, Y., Zhai, Z., & Sun, E. (2019). Programmed Cell Death Pathways in the Pathogenesis of Systemic Lupus Erythematosus. *Journal of immunology research*, *2019*, 3638562. https://doi.org/10.1155/2019/3638562
192. Murao, A., Aziz, M., Wang, H., Brenner, M., & Wang, P. (2021). Release mechanisms of major DAMPs. *Apoptosis : an international journal on programmed cell death*, *26*(3-4), 152–162. https://doi.org/10.1007/s10495-021-01663-3
193. Bertheloot, D., Latz, E. & Franklin, B.S. Necroptosis, pyroptosis and apoptosis: an intricate game of cell death. *Cell Mol Immunol* **18**, 1106–1121 (2021). https://doi.org/10.1038/s41423-020-00630-3
194. Cao W. (2014). Pivotal Functions of Plasmacytoid Dendritic Cells in Systemic Autoimmune Pathogenesis. *Journal of clinical & cellular immunology*, *5*(2), 212. https://doi.org/10.4172/2155-9899.1000212
195. Psarras, A., Alase, A., Antanaviciute, A. *et al.* Functionally impaired plasmacytoid dendritic cells and non-haematopoietic sources of type I interferon characterize human autoimmunity. *Nat Commun* **11**, 6149 (2020). https://doi.org/10.1038/s41467-020-19918-z
196. Mann, V., Sundaresan, A., & Shishodia, S. (2024). Overnutrition and Lipotoxicity: Impaired Efferocytosis and Chronic Inflammation as Precursors to Multifaceted Disease Pathogenesis. *Biology*, *13*(4), 241. https://doi.org/10.3390/biology13040241
197. Podolska, M. J., Biermann, M. H., Maueröder, C., Hahn, J., & Herrmann, M. (2015). Inflammatory etiopathogenesis of systemic lupus erythematosus: an update. *Journal of inflammation research*, *8*, 161–171. https://doi.org/10.2147/JIR.S70325
198. Tajbakhsh, A., Gheibi Hayat, S. M., Butler, A. E., & Sahebkar, A. (2019). Effect of soluble cleavage products of important receptors/ligands on efferocytosis: Their role in inflammatory, autoimmune and cardiovascular disease. *Ageing research reviews*, *50*, 43–57. https://doi.org/10.1016/j.arr.2019.01.007
199. McGaha, T. L., & Karlsson, M. C. (2016). Apoptotic cell responses in the splenic marginal zone: a paradigm for immunologic reactions to apoptotic antigens with implications for autoimmunity. *Immunological reviews*, *269*(1), 26–43. https://doi.org/10.1111/imr.12382
200. Lv, H., Hua, Q., Wang, Y., Gao, Z., Liu, P., Qin, D., & Xu, Y. (2023). Mapping the knowledge structure and emerging trends of efferocytosis research: a bibliometric analysis. *American journal of translational research*, *15*(2), 1386–1402.
201. Constantin, A. M., & Baicus, C. (2023). Estradiol in Systemic Lupus Erythematosus. *Acta endocrinologica (Bucharest, Romania : 2005)*, *19*(2), 274–276. https://doi.org/10.4183/aeb.2023.274
202. Yang, Q., Kennicott, K., Zhu, R., Kim, J., Wakefield, H., Studener, K., & Liang, Y. (2023). Sex hormone influence on female-biased autoimmune diseases hints at puberty as an important factor in pathogenesis. *Frontiers in pediatrics*, *11*, 1051624. https://doi.org/10.3389/fped.2023.1051624
203. Kimani, S. G., Geng, K., Kasikara, C., Kumar, S., Sriram, G., Wu, Y., & Birge, R. B. (2014). Contribution of Defective PS Recognition and Efferocytosis to Chronic Inflammation and Autoimmunity. *Frontiers in immunology*, *5*, 566. https://doi.org/10.3389/fimmu.2014.00566
204. Razi, S., Yaghmoorian Khojini, J., Kargarijam, F., Panahi, S., Tahershamsi, Z., Tajbakhsh, A., & Gheibihayat, S. M. (2023). Macrophage efferocytosis in health and disease. *Cell biochemistry and function*, *41*(2), 152–165. https://doi.org/10.1002/cbf.3780
205. Wang, E. J., Wu, M. Y., Ren, Z. Y., Zheng, Y., Ye, R. D., Tan, C. S. H., Wang, Y., & Lu, J. H. (2023). Targeting macrophage autophagy for inflammation resolution and tissue repair in inflammatory bowel disease. *Burns & trauma*, *11*, tkad004. https://doi.org/10.1093/burnst/tkad004
206. Zhang, J., Ding, W., Zhao, M., Liu, J., Xu, Y., Wan, J., & Wang, M. (2022). Mechanisms of efferocytosis in determining inflammation resolution: Therapeutic potential and the association with cardiovascular disease. *British journal of*

pharmacology, *179*(23), 5151–5171. https://doi.org/10.1111/bph.15939

207. Green, D., Oguin, T. & Martinez, J. The clearance of dying cells: table for two. *Cell Death Differ* **23**, 915–926 (2016). https://doi.org/10.1038/cdd.2015.172
208. Nuij, V. J. A. A., Peppelenbosch, M. P., van der Woude, C. J., & Fuhler, G. M. (2017). Genetic polymorphism in ATG16L1 gene is associated with adalimumab use in inflammatory bowel disease. *Journal of translational medicine*, *15*(1), 248. https://doi.org/10.1186/s12967-017-1355-9
209. Li, Y., & Law, H. K. W. (2022). Deciphering the role of autophagy in the immunopathogenesis of inflammatory bowel disease. *Frontiers in pharmacology*, *13*, 1070184. https://doi.org/10.3389/fphar.2022.1070184
210. Strober W, Fuss IJ. Proinflammatory cytokines in the pathogenesis of inflammatory bowel diseases. Gastroenterology. 2011 May;140(6):1756-1767. doi: 10.1053/j.gastro.2011.02.016. PMID: 21530742; PMCID: PMC3773507.
211. Rea, I. M., Gibson, D. S., McGilligan, V., McNerlan, S. E., Alexander, H. D., & Ross, O. A. (2018). Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. *Frontiers in immunology*, *9*, 586. https://doi.org/10.3389/fimmu.2018.00586
212. Boldyreva, L. V., Morozova, M. V., Saydakova, S. S., & Kozhevnikova, E. N. (2021). Fat of the Gut: Epithelial Phospholipids in Inflammatory Bowel Diseases. *International journal of molecular sciences*, *22*(21), 11682. https://doi.org/10.3390/ijms222111682
213. Bode, K., Hauri-Hohl, M., Jaquet, V., & Weyd, H. (2023). Unlocking the power of NOX2: A comprehensive review on its role in immune regulation. *Redox biology*, *64*, 102795. https://doi.org/10.1016/j.redox.2023.102795
214. Bernardi, F., D'Amico, F., Bencardino, S., Faggiani, I., Fanizza, J., Zilli, A., Parigi, T. L., Allocca, M., Danese, S., & Furfaro, F. (2024). Gut Microbiota Metabolites: Unveiling Their Role in Inflammatory Bowel Diseases and Fibrosis. *Pharmaceuticals (Basel, Switzerland)*, *17*(3), 347. https://doi.org/10.3390/ph17030347
215. Qiu, P., Ishimoto, T., Fu, L., Zhang, J., Zhang, Z., & Liu, Y. (2022). The Gut Microbiota in Inflammatory Bowel Disease. *Frontiers in cellular and infection microbiology*, *12*, 733992. https://doi.org/10.3389/fcimb.2022.733992
216. El-Sayed, A., Kapila, D., Taha, R. S. I., El-Sayed, S., Mahen, M. R. A., Taha, R., & Alrubaiy, L. (2024). The Role of the Gut Microbiome in Inflammatory Bowel Disease: The Middle East Perspective. *Journal of personalized medicine*, *14*(6), 652. https://doi.org/10.3390/jpm14060652
217. Chen, R., Kang, R. & Tang, D. The mechanism of HMGB1 secretion and release. *Exp Mol Med* **54**, 91–102 (2022). https://doi.org/10.1038/s12276-022-00736-w
218. Morioka, S., Maueröder, C., & Ravichandran, K. S. (2019). Living on the Edge: Efferocytosis at the Interface of Homeostasis and Pathology. *Immunity*, *50*(5), 1149–1162. https://doi.org/10.1016/j.immuni.2019.04.018
219. Schett, G., Neurath, M.F. Resolution of chronic inflammatory disease: universal and tissue-specific concepts. *Nat Commun* **9**, 3261 (2018). https://doi.org/10.1038/s41467-018-05800-6
220. Saez, A., Herrero-Fernandez, B., Gomez-Bris, R., Sánchez-Martinez, H., & Gonzalez-Granado, J. M. (2023). Pathophysiology of Inflammatory Bowel Disease: Innate Immune System. *International journal of molecular sciences*, *24*(2), 1526. https://doi.org/10.3390/ijms24021526
221. Komai, T., Inoue, M., Okamura, T., Morita, K., Iwasaki, Y., Sumitomo, S., Shoda, H., Yamamoto, K., & Fujio, K. (2018). Transforming Growth Factor-β and Interleukin-10 Synergistically Regulate Humoral Immunity *via* Modulating Metabolic Signals. *Frontiers in immunology*, *9*, 1364. https://doi.org/10.3389/fimmu.2018.01364
222. Steen, E. H., Wang, X., Balaji, S., Butte, M. J., Bollyky, P. L., & Keswani, S. G. (2020). The Role of the Anti-Inflammatory Cytokine Interleukin-10 in Tissue Fibrosis. *Advances in wound care*, *9*(4), 184–198. https://doi.org/10.1089/wound.2019.1032
223. Stolfi, C., Maresca, C., Monteleone, G., & Laudisi, F. (2022). Implication of Intestinal Barrier Dysfunction in Gut Dysbiosis and Diseases. *Biomedicines*, *10*(2), 289. https://doi.org/10.3390/biomedicines10020289
224. Thoo, L., Noti, M. & Krebs, P. Keep calm: the intestinal barrier at the interface of peace and war. *Cell Death Dis* **10**, 849 (2019). https://doi.org/10.1038/s41419-019-2086-z
225. Delfini, M., Stakenborg, N., Viola, M. F., & Boeckxstaens, G. (2022). Macrophages in the gut: Masters in multitasking. *Immunity*, *55*(9), 1530–1548. https://doi.org/10.1016/j.immuni.2022.08.005
226. de Paiva, C. S., & Pflugfelder, S. C. (2020). Mechanisms of Disease in Sjögren Syndrome-New Developments and Directions. *International journal of molecular sciences*, *21*(2), 650. https://doi.org/10.3390/ijms21020650

227. Sarmiento-Monroy JC, Mantilla RD, Rojas-Villarraga A, et al. Sjögren's syndrome. In: Anaya JM, Shoenfeld Y, Rojas-Villarraga A, et al., editors. Autoimmunity: From Bench to Bedside [Internet]. Bogota (Colombia): El Rosario University Press; 2013 Jul 18. Chapter 28. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459485/
228. Wanke, F., Gutbier, S., Rümmelin, A., Steinberg, M., Hughes, L. D., Koenen, M., Komuczki, J., Regan-Komito, D., Wagage, S., Hesselmann, J., Thoma, R., Brugger, D., Christopeit, T., Wang, H., Point, F., Hallet, R., Ghosh, S., Rothlin, C. V., Patsch, C., & Geering, B. (2021). Ligand-dependent kinase activity of MERTK drives efferocytosis in human iPSC-derived macrophages. *Cell death & disease*, *12*(6), 538. https://doi.org/10.1038/s41419-021-03770-0
229. Yin, C., & Heit, B. (2021). Cellular Responses to the Efferocytosis of Apoptotic Cells. *Frontiers in immunology*, *12*, 631714. https://doi.org/10.3389/fimmu.2021.631714
230. Gordon, S., & Plüddemann, A. (2018). Macrophage Clearance of Apoptotic Cells: A Critical Assessment. *Frontiers in immunology*, *9*, 127. https://doi.org/10.3389/fimmu.2018.00127
231. Chen, R., Zhang, H., Tang, B. *et al.* Macrophages in cardiovascular diseases: molecular mechanisms and therapeutic targets. *Sig Transduct Target Ther* **9**, 130 (2024). https://doi.org/10.1038/s41392-024-01840-1
232. Ross, E. A., Devitt, A., & Johnson, J. R. (2021). Macrophages: The Good, the Bad, and the Gluttony. *Frontiers in immunology*, *12*, 708186. https://doi.org/10.3389/fimmu.2021.708186
233. Cabrera, J. T. O., & Makino, A. (2022). Efferocytosis of vascular cells in cardiovascular disease. *Pharmacology & therapeutics*, *229*, 107919. https://doi.org/10.1016/j.pharmthera.2021.107919
234. Yu, L., Gao, F., Li, Y., Su, D., Han, L., Li, Y., Zhang, X., & Feng, Z. (2024). Role of pattern recognition receptors in the development of MASLD and potential therapeutic applications. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *175*, 116724. https://doi.org/10.1016/j.biopha.2024.116724
235. Sugimoto, M. A., Sousa, L. P., Pinho, V., Perretti, M., & Teixeira, M. M. (2016). Resolution of Inflammation: What Controls Its Onset?. *Frontiers in immunology*, *7*, 160. https://doi.org/10.3389/fimmu.2016.00160
236. Zhao, Y., Simon, M., Seluanov, A., & Gorbunova, V. (2023). DNA damage and repair in age-related inflammation. *Nature reviews. Immunology*, *23*(2), 75–89. https://doi.org/10.1038/s41577-022-00751-y
237. Hu, P., Wang, M., Gao, H., Zheng, A., Li, J., Mu, D., & Tong, J. (2021). The Role of Helper T Cells in Psoriasis. *Frontiers in immunology*, *12*, 788940. https://doi.org/10.3389/fimmu.2021.788940
238. Yura, Y., & Hamada, M. (2023). Outline of Salivary Gland Pathogenesis of Sjögren's Syndrome and Current Therapeutic Approaches. *International journal of molecular sciences*, *24*(13), 11179. https://doi.org/10.3390/ijms241311179
239. Qi, W., Tian, J., Wang, G., Yan, Y., Wang, T., Wei, Y., Wang, Z., Zhang, G., Zhang, Y., & Wang, J. (2024). Advances in cellular and molecular pathways of salivary gland damage in Sjögren's syndrome. *Frontiers in immunology*, *15*, 1405126. https://doi.org/10.3389/fimmu.2024.1405126
240. Brilland, B., Vinatier, E., Subra, J. F., Jeannin, P., Augusto, J. F., & Delneste, Y. (2021). Anti-Pentraxin Antibodies in Autoimmune Diseases: Bystanders or Pathophysiological Actors?. *Frontiers in immunology*, *11*, 626343. https://doi.org/10.3389/fimmu.2020.626343
241. Liu, J., Cao, X. RBP–RNA interactions in the control of autoimmunity and autoinflammation. *Cell Res* **33**, 97–115 (2023). https://doi.org/10.1038/s41422-022-00752-5
242. Dos Santos Haber, J. F., Barbalho, S. M., Sgarbi, J. A., de Argollo Haber, R. S., de Labio, R. W., Laurindo, L. F., Chagas, E. F. B., & Payão, S. L. M. (2023). The Relationship between Type 1 Diabetes Mellitus, TNF-α, and IL-10 Gene Expression. *Biomedicines*, *11*(4), 1120. https://doi.org/10.3390/biomedicines11041120
243. Cano-Cano, F., Gómez-Jaramillo, L., Ramos-García, P., Arroba, A. I., & Aguilar-Diosdado, M. (2022). IL-1β Implications in Type 1 Diabetes Mellitus Progression: Systematic Review and Meta-Analysis. *Journal of clinical medicine*, *11*(5), 1303. https://doi.org/10.3390/jcm11051303
244. Amarante-Mendes, G. P., Adjemian, S., Branco, L. M., Zanetti, L. C., Weinlich, R., & Bortoluci, K. R. (2018). Pattern Recognition Receptors and the Host Cell Death Molecular Machinery. *Frontiers in immunology*, *9*, 2379. https://doi.org/10.3389/fimmu.2018.02379
245. Zhang, S., Zhong, J., Yang, P., Gong, F., & Wang, C. Y. (2009). HMGB1, an innate alarmin, in the pathogenesis of type 1 diabetes. *International journal of clinical and experimental pathology*, *3*(1), 24–38.
246. Giambra, V., Pagliari, D., Rio, P., Totti, B., Di Nunzio, C., Bosi, A., Giaroni, C.,

Gasbarrini, A., Gambassi, G., & Cianci, R. (2023). Gut Microbiota, Inflammatory Bowel Disease, and Cancer: The Role of Guardians of Innate Immunity. *Cells*, *12*(22), 2654. https://doi.org/10.3390/cells12222654

247. Farrugia, M., & Baron, B. (2017). The Role of Toll-Like Receptors in Autoimmune Diseases through Failure of the Self-Recognition Mechanism. *International journal of inflammation*, *2017*, 8391230. https://doi.org/10.1155/2017/8391230
248. Girard, D., & Vandiedonck, C. (2022). How dysregulation of the immune system promotes diabetes mellitus and cardiovascular risk complications. *Frontiers in cardiovascular medicine*, *9*, 991716. https://doi.org/10.3389/fcvm.2022.991716
249. Christ, A., Lauterbach, M., & Latz, E. (2019). Western Diet and the Immune System: An Inflammatory Connection. *Immunity*, *51*(5), 794–811. https://doi.org/10.1016/j.immuni.2019.09.020
250. Kiss MG, Binder CJ. The multifaceted impact of complement on atherosclerosis. Atherosclerosis. 2022 Jun;351:29-40. doi: 10.1016/j.atherosclerosis.2022.03.014. Epub 2022 Mar 17. PMID: 35365353.
251. Zhao, J., Zhang, W., Wu, T., Wang, H., Mao, J., Liu, J., Zhou, Z., Lin, X., Yan, H., & Wang, Q. (2021). Efferocytosis in the Central Nervous System. *Frontiers in cell and developmental biology*, *9*, 773344. https://doi.org/10.3389/fcell.2021.773344
252. Coss, S. L., Zhou, D., Chua, G. T., Aziz, R. A., Hoffman, R. P., Wu, Y. L., Ardoin, S. P., Atkinson, J. P., & Yu, C. Y. (2023). The complement system and human autoimmune diseases. *Journal of autoimmunity*, *137*, 102979. https://doi.org/10.1016/j.jaut.2022.102979
253. Lintner, K. E., Wu, Y. L., Yang, Y., Spencer, C. H., Hauptmann, G., Hebert, L. A., Atkinson, J. P., & Yu, C. Y. (2016). Early Components of the Complement Classical Activation Pathway in Human Systemic Autoimmune Diseases. *Frontiers in immunology*, *7*, 36. https://doi.org/10.3389/fimmu.2016.00036
254. Deng, T., Xu, J., Wang, Q., Wang, X., Jiao, Y., Cao, X., Geng, Q., Zhang, M., Zhao, L., & Xiao, C. (2024). Immunomodulatory effects of curcumin on macrophage polarization in rheumatoid arthritis. *Frontiers in pharmacology*, *15*, 1369337. https://doi.org/10.3389/fphar.2024.1369337
255. Papiri, G., D'Andreamatteo, G., Cacchiò, G., Alia, S., Silvestrini, M., Paci, C., Luzzi, S., & Vignini, A. (2023). Multiple Sclerosis: Inflammatory and Neuroglial Aspects. *Current issues in molecular biology*, *45*(2), 1443–1470. https://doi.org/10.3390/cimb45020094
256. Lubetzki, C., & Stankoff, B. (2014). Demyelination in multiple sclerosis. *Handbook of clinical neurology*, *122*, 89–99. https://doi.org/10.1016/B978-0-444-52001-2.00004-2
257. Shahbazi, M., Abadi, J. S. A., Roshandel, D., Koochaki, M., Amiri, H., Kohansal, R., Baghbanian, S. M., & Zamani, M. (2017). Combination of interleukin-10 gene promoter polymorphisms with HLA-DRB1*15 allele is associated with multiple sclerosis. *The Indian journal of medical research*, *145*(6), 746–752. https://doi.org/10.4103/ijmr.IJMR_1225_15
258. Grajchen, E., Hendriks, J.J.A. & Bogie, J.F.J. The physiology of foamy phagocytes in multiple sclerosis. *acta neuropathol commun* **6**, 124 (2018). https://doi.org/10.1186/s40478-018-0628-8
259. Mahaling, B., Low, S. W. Y., Beck, M., Kumar, D., Ahmed, S., Connor, T. B., Ahmad, B., & Chaurasia, S. S. (2022). Damage-Associated Molecular Patterns (DAMPs) in Retinal Disorders. *International journal of molecular sciences*, *23*(5), 2591. https://doi.org/10.3390/ijms23052591
260. Zhang, Yy., Ning, Bt. Signaling pathways and intervention therapies in sepsis. *Sig Transduct Target Ther* **6**, 407 (2021). https://doi.org/10.1038/s41392-021-00816-9
261. van Langelaar, J., Rijvers, L., Smolders, J., & van Luijn, M. M. (2020). B and T Cells Driving Multiple Sclerosis: Identity, Mechanisms and Potential Triggers. *Frontiers in immunology*, *11*, 760. https://doi.org/10.3389/fimmu.2020.00760
262. Sun, L., Su, Y., Jiao, A. *et al.* T cells in health and disease. *Sig Transduct Target Ther* **8**, 235 (2023). https://doi.org/10.1038/s41392-023-01471-y