Biomedicine & Pharmacotherapy 140 (2021) 111776

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Review

The complex roles of efferocytosis in cancer development, metastasis, and treatment

Amir Tajbakhsh [a], Seyed Mohammad Gheibi hayat [b], Ahmad Movahedpour [c], Amir Savardashtaki [a,c,*], Reid Loveless [d], George E. Barreto [e,f], Yong Teng [d,g,h], Amirhossein Sahebkar [i,j,k,**]

[a] Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[b] Department of Medical Biotechnology, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[c] Department of Medical Biotechnology, School of Advanced Medical Sciences and Technologies Shiraz University of Medical Sciences, Shiraz, Iran
[d] Department of Oral Biology and Diagnostic Sciences, Dental College of Georgia, Augusta University, Augusta, GA 30912, USA
[e] Department of Biological Sciences, University of Limerick, Limerick, Ireland
[f] Health Research Institute, University of Limerick, Limerick, Ireland
[g] Georgia Cancer Center, Department of Biochemistry and Molecular Biology, Medical College of Georgia, Augusta University, Augusta, GA 30912, USA
[h] Department of Medical Laboratory, Imaging and Radiologic Sciences, College of Allied Health, Augusta University, Augusta, GA 30912, USA
[i] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[j] Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[k] School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

Keywords:
Efferocytosis
Cancer
Macrophages
Apoptosis
Immune cells
Treatment

ABSTRACT

When tumor cells are killed by targeted therapy, radiotherapy, or chemotherapy, they trigger their primary tumor by releasing pro-inflammatory cytokines. Microenvironmental interactions can also promote tumor heterogeneity and development. In this line, several immune cells within the tumor microenvironment, including macrophages, dendritic cells, regulatory T-cells, and $CD8^+$ and $CD4^+$ T cells, are involved in the clearance of apoptotic tumor cells through a process called efferocytosis. Although the efficiency of apoptotic tumor cell efferocytosis is positive under physiological conditions, there are controversies regarding its usefulness in treatment-induced apoptotic tumor cells (ATCs). Efferocytosis can show the limitation of cytotoxic treatments, such as chemotherapy and radiotherapy. Since cytotoxic treatments lead to extensive cell mortality, efferocytosis, and macrophage polarization toward an M2 phenotype, the immune response may get involved in tumor recurrence and metastasis. Tumor cells can use the anti-inflammatory effect of apoptotic tumor cell efferocytosis to induce an immunosuppressive condition that is tumor-tolerant. Since M2 polarization and efferocytosis are tumor-promoting processes, the receptors on macrophages act as potential targets for cancer therapy. Moreover, researchers have shown that efferocytosis-related molecules/pathways are potential targets for cancer therapy. These include phosphatidylserine and calreticulin, Tyro3, Axl, and Mer tyrosine kinase (MerTK), receptors of tyrosine kinase, indoleamine-2,3-dioxygenase 1, annexin V, CD47, TGF-β, IL-10, and macrophage phenotype switch are combined with conventional therapy, which can be more effective in cancer treatment. Thus, we set out to investigate the advantages and disadvantages of efferocytosis in treatment-induced apoptotic tumor cells.

1. Introduction

Efferocytosis, the clearance of apoptotic cells (ACs) without inflammatory responses, is involved in several pathways that regulate molecules critical to the resolution of inflammation [1–3]. Defective efferocytosis may result in several diseases, such as autoimmune

* Correspondence to: Department of Medical Biotechnology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz 71362 81407, Iran.
** Correspondence to: Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, P.O. Box: 91779-48564, Mashhad, Iran.
E-mail addresses: dashtaki@sums.ac.ir (A. Savardashtaki), sahebkara@mums.ac.ir (A. Sahebkar).

https://doi.org/10.1016/j.biopha.2021.111776
Received 28 March 2021; Received in revised form 22 May 2021; Accepted 24 May 2021
Available online 29 May 2021

disorders and cancers [2,4–7]. While cancer treatment modalities focus on killing cancer cells to prevent tumor development, inducing apoptotic tumor cells (ATCs) can act as a double-edged sword and, in fact, promote tumor development [8,9]. Tumor development is regulated by the crosstalk between tumor cells and other cell types within the microenvironment of a tumor, which contains proliferating cancer cells, tumor stroma, blood vessels, inflammatory cells, and several related tissue-type cells. Although signaling is bidirectional, the tumor microenvironment (TME) is created and regulated by tumor cells which tailor the molecular and cellular events within it to their own needs. And while numerous immune effector cells recruitment to the tumor site to perform their anti-tumor activities, these abilities are diminished in response to cancer-derived signals. In this line, immune effector cells in the microenvironment, such as macrophages, dendritic cells (DCs), regulatory T cells, and $CD8^+$ and $CD4^+$ T cells, are not only impaired in their anti-tumor activities but are co-opted to facilitate tumor development [10,11]. Previous studies report that losing cells in malignant disease is a critical component of tumor dynamics. Moreover, apoptosis is a routine process in high-grade malignancies, where high apoptosis indicators are associated with poor prognosis [12]. Alongside high apoptosis rates, tumors also have increased cell growth rates, a process that is frequently neglected but is critical in the tumor dynamics [13]. It should be noted that higher levels of ACs might be associated with weak prognosis by causatively getting involved in tumor growth [14–16]. In aggressive tumors, the frequency of ACs is usually low, but the rate of cell loss is high, indicating that AC clearance is rapid [17]. In other tumors, including specific categories of non-Hodgkin's lymphoma (NHL), however, increased numbers of ACs can be detected and are mostly connected to infiltrating tumor-associated macrophages (TAMs) [18]. Hence, it is suggested that apoptosis leads to oncogenesis *via* several pathways. These paths include: recruiting and appropriately activating TAMs to aid tumor development and progression, direct and indirect trophic effects leading to net rises in the number of tumor cells, and anti-inflammatory, as well as tolerogenic features, which inhibit anti--tumor immune responses [18].

In previous studies, it was shown that efferocytosis might be involved in all these paths or at least in one of them [19–27]. Thus, we set out to investigate the advantages and disadvantages of treatment-induced ATCs.

2. Efferocytosis: molecules and pathways

Efferocytosis quickly clears ACs through phagocytic cells and, therefore, typically acts to silence immune responses and promote

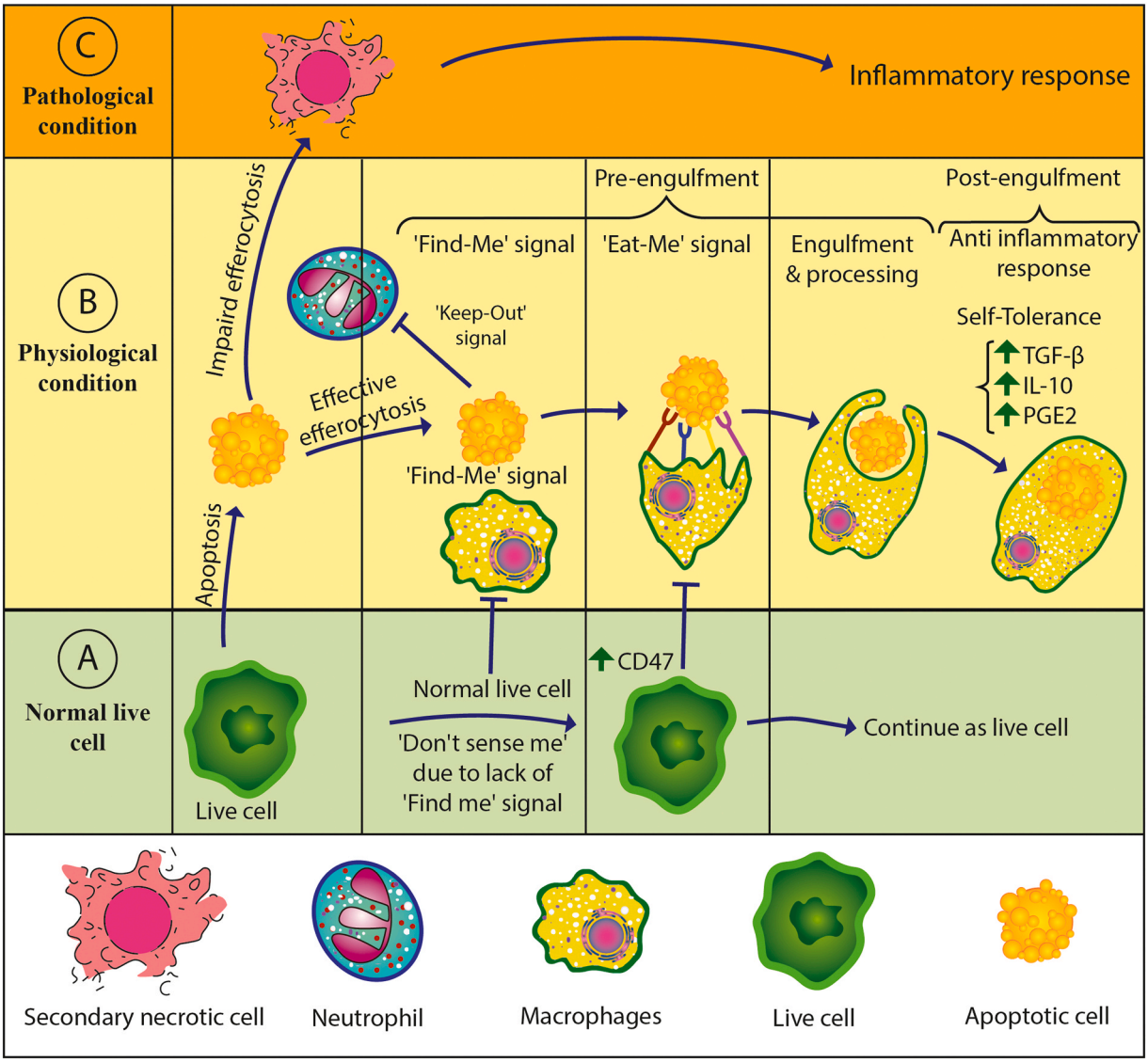

Fig. 1. The steps of efferocytosis steps in physiological and pathological conditions.

homeostasis [1,2,4,28,29]. This process, however, is complex and involves many factors/ pathways [2], though can be broadly separated into 5 main steps: 1) detection through "Find-Me"/"Keep-Out" signals (sensing and migration toward the ACs), 2) recognition through "Eat--Me"/"Don't-Eat-Me" signals (binding to the ACs), 3) engulfment, 4) processing (digestion of the ACs and debris), and 5) anti-inflammatory and self-tolerance responses [2,30,31] (Fig. 1). Firstly, ACs release "Find-Me" signals that trigger phagocyte cell migration towards them; these signals consist of the nucleotides UTP and ATP, the chemokine fractalkine (CX3CL1), and lipids sphingosine-1-phosphate (S1P) and lysophosphatidylcholine (LPC). After the "Find-Me" signal has been received, phagocytes can identify ACs by "Eat-Me" signal ligands, such as phosphatidylserine (PtdSer), that are found on ACs [2]. Following identification, phagocytic cells, particularly macrophages, then initiate the engulfment and processing of the ACs, which is critical to controlling anti-inflammatory responses [2]. In contrast to the "Eat-Me" signal, overexpressing "Don't-Find-Me" signals, such as CD31 and CD47, on live cells was shown to result in the inhibition of phagocytosis [32,33]. Unsurprisingly, tumor cells were also been found to overexpress CD47, serving to inhibit cancer-killing immune cells and prevent tumor cell recognition [34,35]. Nevertheless, there remains inadequate information on the interactions between ATCs and macrophages, as well as on how these interactions affect the remaining viable tumor cell population and their metastatic progression. Taken together, efferocytosis has gained the attention of many researchers because it can alter the immune response and lead to the immunosuppression of anti-tumor defenses, such as by generating anti-inflammatory mediators (*e.g.*, transforming growth factor-beta (TGF-β), prostaglandin E_2 (PGE2), and interleukin-10 (IL-10)) and inhibiting pro-inflammatory cytokines (*e.g.*, tumor necrosis factor (TNF)) [19,36].

2.1. The role of efferocytosis in cancer

Several efferocytosis-related molecules are associated with cancer progression, such as CD47, Axl, MerTK, MFG-E8, PtdSer, Gas6, IL-10, and TGF-β [20–27], and strongly influence the activity of immune cells in the TME [37]. According to previous studies, chemotherapy and irradiation stimulate a cytokine storm in the tumor stroma, causing the release of tumor-promoting cytokines like IL-6 and TNF-α, as well as the activation of macrophages to generate pro-inflammatory mediators through ATCs [38–41]. While debris from dead and dying tumor cells can cause anti-tumor immunity [42], it can also condition the microenvironment to promote tumor expansion [43–45]. It should be mentioned that the immunosuppressive activity of cytokines during efferocytosis can further trigger the release of additional cytokines, stimulating the TME, augmenting cancer metastasis, and increasing anti-tumor immunity evasion [46]. In this regard, it is evident that cell death is a common event in solid tumors during their expansion, which can continue even in the face of cytotoxic therapy. Clearance of dead or dying cells in the TME by efferocytosis, therefore, is an immunosuppressive phenomenon [43]. In particular, the immunosuppressive phenotype generated by efferocytosis in tumors is achieved *via* a harmonized series of signaling episodes, such as from several compartments of the tumor milieu [43,47]. The phagocytic engulfment of ACs modulates cytokines, influences the degree of immune inhibition, and ensures inflammation is not prompted and tissues are not damaged [48–50]. Moreover, efferocytosis promotes a tolerogenic microenvironment by affecting the phenotype of antigen-presenting macrophages and DCs, leading to reduced antigen cross-presentation to T cells, reduced T cell clonal expansion, and decreased expansion of antigen-dependent anti-tumor immunity [31,37].

It has been shown that cytokines are related to wound healing and immune inhibition. In this respect, efferocytosis can prompt the release of wound healing and immunosuppressive cytokines, including IL-4, IL-10, IL-13, and TGF-β, but it suppresses IL-12 and interferon (IFN)-γ as pro-inflammatory cytokines [51,52].

Although imperfect clearance of ACs can encourage disease states, unimpaired efferocytosis may nevertheless lead to an increase in cancer incidence. Indeed, researches have shown that efferocytosis can contribute to the expansion of a more malignant TME and to tumor development [53,54]. Cytokines related to wound healing and immune inhibition can trigger the TME and permit resistance to anti-tumor immunity. Overexpressing multiple ligands and receptors has also been revealed to contribute to efferocytosis and tumorigenesis [52,54,55]. In particular, studies have shown that the Axl, Tyro-3, and MerTK receptors act as bridging factors between ACs and phagocytic cells through binding ligands like protein S and PtdSer growth arrest-specific gene 6 (Gas6) which are associated with different cancer types [52,56]. Activating Axl *via* phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and mitogen-actuated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) signaling pathways can aid the rapid growth and survival of tumor cells [52,55]. In fact, activating and/or overexpressing MerTK can boost oncogenic signaling pathways, such as the Janus kinase/ signal transducers and activators of transcription (JAK/STAT), Src/FAK, MAPK/ErK, and PI3K/Akt, leading to tumor cell survival, rapid growth, and metastasis [52,53]. MerTK expression by macrophages in the microenvironment may also support immune suppression and tumor metastasis [52,57].

2.2. Efferocytosis regulation by tumor-associated macrophages

TAMs are a common type of cell in the TME and represent a promising target for cancer therapeutics given their role in promoting cancer development [58,59]. The activation of macrophages can simultaneously influence the killing of tumor cells and the development and expansion of the tumor. Specifically, TAMs maintain their pro-tumor status through their anti-inflammatory, immunosuppressive, pro-angiogenic, trophic, and pro-metastatic functions [60,61].

Notably, the polarization of TAMs towards M2 macrophage actuation states plays an important role in development, tissue homeostasis, and wound alleviation. M2 type macrophages can inhibit inflammatory responses and enhance angiogenesis and tissue remodeling [62]. The activation mode of M2 is contrasted by classical or M1 actuation states which are cytocidal and tumoricidal. The factors produced by ACs, specifically the "Find-Me" signal S1P and the cytokine TGF-β, stimulate macrophage survival and polarize macrophages towards an anti-inflammatory and pro-tumor activation M2 type [63,64]. Chen et al. indicated that the tumor-recruited M2 phenotype promotes breast and gastric cancer metastasis *via* M2 macrophage-secreted chitinase-3-like protein 1 (CHI3L1) protein *in-vivo* [11]. Interestingly, the common pro-tumor properties of TAMs are also maintained by phagocytes actuated by interaction with ACs. Here, in phagocytes, ACs drive tolerogenic and anti-inflammatory immune responses with which they interact. Moreover, ACs may also promote growth factor generation and pro-angiogenic responses. It should be noted that constitutive apoptosis in tumor-cell sub-populations further serves a critical pro-tumor function by recruiting and activating TAMs, which go on to mediate matrix remodeling and increase metastasis. Of note, micro-vesicles exposing PtdSer generated *via* tumor cells have been reported to enhance metastatic activities *in-vivo* [65]. Moreover, pro-tumor stromal cell populations, such as myeloid suppressor cells, fibroblasts, and tumor-associated 'N2' neutrophils, as well as neighboring tumor cells, may be provided with pro-tumor signals by interacting with ATCs or their respective products [13,66].

2.3. The impact of efferocytosis on tumor radiotherapy outcomes

In general, the key objective of radiotherapy is to kill tumor cells and decrease tumor size. While the direct impact that cytotoxic treatment has on tumor cells is one determinant of radiotherapy success, patient treatment outcomes are also dependent on the subsequent inherent and adaptive immune responses that can select for tumor cells resistant to

local irradiation. Of course, another critical factor is the clearance of dead or dying tumor cells *via* phagocytic cells of the inherent immune system. Mature DCs and macrophages that engulf, process, and present antigens of ATCs to adaptive immune cells are capable of stimulating, skewing, or suppressing adaptive immune responses [67,68].

2.3.1. Regulating the immune response to radiotherapy- and chemotherapy-induced apoptotic tumor cells

Conventional cancer therapies heavily rely on radiotherapy and chemotherapy. These modalities attempt to directly eliminate tumor cells, but, as mentioned previously, their rate of success can depend on inherent and adaptive anti-tumor immune responses [69,70]. During these therapies, DCs require signaling by toll-like receptor (TLR)-4 and the respective adaptor myeloid differentiation primary response 88 (MyD88) for effective processing and cross-presentation of the antigen from ATCs. Apetoh et al. indicated that TLR4 loss-of-function allele relapses more rapidly following radiotherapy or chemotherapy in patients with breast cancer. Here, it was shown that TLR-4 and high-mobility group box 1 (HMGB1) play an important role in initiating immune responses against radiotherapy- and chemotherapy-produced dying tumor cells, likely modulating the capability of DCs to process and present the tumor-related antigens *in-vivo* [69,71].

2.3.2. Stimulating or inhibiting the effect of debris on tumor growth

It was shown that treatment-generated tumor cell debris (TCDs) can stimulate tumor growth and possibly affect cancer treatments [72–74]. Additional studies have similarly reported that therapy-produced debris can trigger tumor development by stimulating pro-inflammatory and pro-tumorigenic cytokines *in-vitro* and *in-situ* grafted tumor models [75,76]. In effect, debris-stimulated tumor growth might be a pivotal factor to consider in the context of cancer treatments, like chemotherapy, targeted therapy, and radiation, as even in the absence of genetically resistant mutants, tumor cells will frequently escape cytotoxic treatment and exhibit more resilient phenotypes [77]. Even though tumor size is reduced during therapy, the continual generation of AC debris preserves tumor growth by promoting the release of tumor-enhancing cytokines by macrophages. On the other hand, however, defective efferocytosis and the resulting aggregation of ACs in tissues may trigger an inflammatory response [78] that acts in an adjuvant manner, where immunogenic tumor cell death occurs secondary to the administration of chemotherapeutic agents, uptake of cell debris by DCs, presentation of antigens, and activation of adaptive immunity [79,80]. Nonetheless, TCDs generated *via* radiation, the Herpes simplex virus thymidine kinase/ganciclovir system, photodynamic treatment, or radio-frequency ablation might suppress tumor growth with the aid of induced anti-tumor immunity [42,81–86]. On the other hand, quick tumor development has an invariable correlation with ATCs mortality due to the formation of undesirable conditions, including hypoxia and AC debris accumulation [14,15,87,88]. Hence, both natural and therapy-induced ACTs can lead to tumor progression [89].

Furthermore, there exists to some degree a conundrum in the use of cytotoxic therapy for non-progressive cancers, where therapy-induced debris might accidentally trigger the proliferation of small or dormant tumors [90–92]. In particular, the PtdSer "Eat-Me" has an important role in the debris stimulation of tumors, and when it is neutralized on ACs with annexin V (Anx5), which binds PtdSer with high affinity, or anti-PtdSer antibodies, such as Bavituximab, the therapeutic activity of chemotherapy is restored in debris-triggered breast and non-small-cell lung cancers [93–95]. Anx5 was shown to enhance the immunogenicity of tumor cells and decrease tumor development by inhibiting the immunosuppressive effects of PtdSer [23,96–98]. In the TME, these materials promote anti-tumor immunity by stimulating M1 phenotype polarization, reducing M2-like TAMs, promoting DCs maturation and antigen presentation, and increasing the presence of $CD8^+$ cytotoxic T cells [95,99–101].

2.3.3. Efferocytosis regulation by calreticulin in the tumor microenvironment

Calreticulin, an endoplasmic reticulum chaperone protein, is suggested to have a role in immunomodulation by glycoprotein assembly and secretion and Ca^{2+} sequestration [102–104]. An "Eat-Me" signal resulting from calreticulin's translocation to the cell membrane enhances the efferocytosis of ACs and clearance of tumor cells [105,106]. Furthermore, calreticulin affects the activation of phagocytes and the production of cytokines [107]. The knockdown of its *CALR* gene is also associated with the inhibition of cell migration and proliferation *in-vitro* and *in-vivo* [108]. Through TLRs and Bruton's tyrosine kinase (Btk), it is indicated that calreticulin can act as a targeted cancer therapy for phagocytosis, given that Btk regulates the exposure of calreticulin on the cell surface through TLRs [109]. Feng et al. have accordingly suggested that cancer therapy can be significantly enhanced by combining CD47 blockade with TLR/Btk activation [109]. In line with this, other experiments have indicated that delivering multiple immunoadjuvants together (*e.g.*, TLR-7 agonists and anti-CD47 antibodies) leads to a greater immune response [110]. Furthermore, CD47 functionalization has been shown to improve the ability of drug-delivery nanoparticles to evade macrophages [111].

2.3.4. Efferocytosis regulation by macrophage metabolism mediated by CD47

CD47 is a "Don't-Eat-Me" signal that is overexpressed by many cancers [27]. CD47 on live cells blocks the phagocytic function of macrophages by binding to the signal regulatory protein α (SIRPα)-receptor present on the cell surface of phagocytes [34]. It has been shown that efferocytosis is regulated by CD47-mediated macrophage metabolism and that stimulation with a CpG oligodeoxynucleotide, TLR-9 agonist induces changes in the central carbon metabolism of macrophages, enabling anti-tumor activity, such as engulfment of $CD47^+$ cancer cells [24]. It is indicated that TLR9 expressed by cancer cells is important for tumor development by activating polymorphonuclear-myeloid-derived suppressor cells (MDSCs), which enhance the immunosuppression of T cells by signal transducer and activator of transcription (STAT3) in prostate cancer [112]. TLR9 exhibits immunosuppressive effects by stimulating and recruiting regulatory T cells (T_{regs}) and MDSCs proliferation in the TME of pancreatic carcinoma [113]. However, CpG activation prompts a metabolic condition, requiring the oxidation of fatty acid and the shunting of tricarboxylic acid cycle intermediates for lipid biosynthesis [24]. Changes in lipid metabolism might alter the properties of the plasma membrane in macrophages that promote efferocytosis [114]. It was found that the enhancement of membrane fluidity triggered *via* CpG, which depends on acetyl-CoA shunting for *de novo* lipogenesis. In line with this, membrane fluidity regulates phagocytic synapses with CD47-SIRPα signaling as well as receptor clustering [115,116].

2.3.5. Apoptosis and efferocytosis regulation by phosphatidylserine and calreticulin in the tumor microenvironment

The constitutive apoptosis of tumor-cell populations offers an immunosuppressive, nonphlogistic environment that can protect malignant tissue from potent anti-tumor immune mechanisms. Hence, it was concluded that the targeting of molecules exposed on or produced by ACs, such as PtdSer, can increase tumor regression by activating the host anti-tumor immune response. The blockade of PtdSer triggers an adaptive immune response against ACs, causing autoantibody generation and anti-tumor immunity [23,117,118]. Nevertheless, the cellular environment of the exposed PtdSer might be necessary, since the exogenous labeling of tumor cells with PtdSer liposomes might lead to the engulfment of cells by DCs, eliciting an anti-tumor immune response and preventing tumor progression [119].

Hypoxia is a critical factor in cancer progression and is linked to chemotherapy and radiotherapy resistance in solid tumors [120–122]. Hypoxic stress results in PtdSer exposure, however, this is not a

guarantee that apoptosis will occur. Hypoxia is also involved in cancer cells immune, triggering an immunosuppressive TME through transcriptional and translational regulation [123,124]. Under hypoxic stress, the TME also releases molecules that induce the differentiation of TAMs into M2 type or recruit suppressor cells derived from myeloid lineage [125]. However, hypoxia can also increase the immunogenicity of tumor cells [126]. In this case, immunogenic tumor cell death is prompted by increasing exposure of calreticulin on the cell surface following endoplasmic reticulum stress [126]. Moreover, it has been indicated that hypoxia-induced increase in calreticulin, although not CD47, enhances anticancer immunity *in-vivo* [126].

A few studies showed that PtdSer is exposed to the luminal surface of tumor vasculature, even when apoptosis is not evident [127,128]. The PtdSer-exposure can be enhanced *via* radiotherapy and chemotherapy, which might have treatment advantages *in-vivo* [100,129]. PtdSer can mediate the homeostatic interaction with ACs and their environment. Furthermore, PtdSer-containing liposomes can prevent anti-tumor cytotoxicity *via* macrophages [19,130]. It is, therefore, suggested that targeting ACs or PtdSer can provide a strong approach to unleash the anti-tumor potency in TAMs, for instance, with classical (M1) stimuli. In fact, signaling pathways that are independent of PtdSer can be actuated in response to ACs [13]. In this line, targeting PtdSer (*e.g.*, BPRDP056) demonstrates efficacy in pre-clinical breast, pancreatic, lung, and brain tumor models [95,99,100,118,131].

2.3.6. Efferocytosis regulation by the TAM receptors Tyro3, Axl, and MerTK in the tumor microenvironment

The TAM receptor tyrosine kinases Tyro3, Axl, and MerTK are expressed in both healthy and diseased tissues and activated by the binding of the bridging ligand Protein S or GAS6 with apoptotic PtdSer [132]. Notably, these receptors are overexpressed in cancer as oncogenes and can be found throughout the TME, aiding in the survival of tumor cells, such as through anticancer therapy resistance [132,133]. Taken alongside their pro-oncogenic and immune-inhibiting features, these pathways have subsequently emerged as important avenues for potential cancer therapy using small molecule inhibitors [134]. These TAM receptors were identified as co-stimulatory molecules on human T cells [132]. MerTK, for example, can modulate T cell memory response and appears to be a late co-stimulatory molecule on T cells [135]. In this regard, these TAM receptors are promising therapeutic targets on TAMs. The TAM receptors enhance efferocytosis by macrophages, binding to the "Eat-Me" signal PtdSer on AC membranes *via* Protein S and Gas6. Following, macrophages are polarized towards the M2 phenotype and increase their secretion of immunosuppressive cytokines [58].

The M2 phenotype has been revealed to progress prostate cancer bone metastasis [136]. Administration of the chemotherapy medication trabectedin, however, reduced the M2 phenotype *in-vivo*, as well as bone tumor growth after PC-3 prostate cancer cell intracardiac inoculation [136]. Similar results were also seen from the pretreatment of PC-3 cells with trabectedin prior to their injection [136]. Furthermore, Crittenden et al. showed that MerTK is significantly upregulated by TAMs after radiation-induced tumor cell death. Thus, reduced MerTK, or the prevention of TGF-β by SM16, an orally active TGF-beta type I receptor inhibitor, combined with radiation mediates post-radiation tumor development to a better extent than radiation alone [137]. Moreover, Stanford et al. indicated that MerTk and TGF-β blockade decreased postpartum tumor metastasis of breast cancers *in-vivo* [21].

It is also indicated that monoclonal antibodies, including GMAB1, a high-affinity anti-3'-isoLM1/3',6'-isoLD1 IgG, and GMAB2, bind neutralized Gas6 ligand to the Axl receptor and inhibit apoptosis and cancer progression in pancreatic ductal adenocarcinoma [138,139]. Utilizing warfarin, however, to regulate the Gas6-mediated activation of Axl might block pancreatic ductal adenocarcinoma metastasis [140]. Using the small molecule inhibitors RU-301 and RU- 302 to bind to Axl and Gas6 may also prove to be useful [141].

Lastly, overexpression of Tyro3 can stimulate tumor cell proliferation, cancer invasion, metastasis, as well as chemotherapy resistance that is associated with reduced overall survival in colorectal, hepatocellular, and breast cancer patients [142].

2.3.7. Efferocytosis regulation by MER Tyrosine Kinase (MerTK), and indoleamine-2,3-dioxygenase 1 (IDO1)

Efferocytosis inhibits ACs from undergoing necrosis and releasing their inflammatory contents after apoptosis [2,4,143]. Moreover, efferocytosis prevents tissue damage and maintains tissue homeostasis by promoting immunosuppressive cytokines increasing tolerance to ACs-derived antigens [2,31]. which partially tolerates cancer cells evading treatment-induced apoptosis with deleterious consequences after cytotoxic cancer treatment in the TME. It was shown that after $HER2^{+}$ mammary tumors were treated with the cancer therapeutic lapatinib, efferocytosis cleared ATCs in the TME and the levels of immunosuppressive cytokines, as well as MDSCs and T_{regs}, increased *in-vivo* [144]. On the contrary, defective efferocytosis induced secondary necrosis of ACs and failed to increase tumor immunosuppressive cytokines, MDSCs, and T_{regs}. It was further shown that efferocytosis triggers the expression of IFN-γ, stimulating indoleamine-2,3-dioxygenase (IDO) 1 expression, an immune regulator that contributes to antigen tolerance. Inhibiting efferocytosis together with IDO1 reduces AC- and NC-induced immunosuppressive phenotypes in tumor residual disease, blocks tumor metastasis, and causes tumor regression *in-vivo*. Thus, apoptotic and necrotic tumor cells modulate the TME through distinct ways including efferocytosis and IDO1. These distinct pathways by inducing immune-suppressing leukocytes and cytokines can enhance tumor 'homeostasis' and development [144]. Furthermore, it is reported that genetic ablation of IDO T_{regs} leads to a defect in the tolerance to antigens associated with ATCs in mice [145].

2.3.8. Tumor therapy by targeting of Mer Proto-Oncogene, Tyrosine Kinase (MerTK)

It is essential to consider the risks of blocking efferocytosis, which is a potential tumor treatment approach, and necrotic cell (NCs) lysis of dying cells, tissue injury, inflammation, and autoimmunity [21,146]. Another study showed that the inability of postpartum efferocytosis in the mammary gland can cause inflammation and scarring and interfere with lactation [146]. The blockage of MerTK, however, might lower the expression levels of wound healing cytokines, producing a condition in which tumor cells have a lower probability of escaping immune targeting and metastasizing. Moreover, MerTK can promote the expression of programmed cell death ligand 1 (PD-L1), an immune checkpoint ligand expressed on tumor cells that antagonizes $CD8^{+}$ T-cells [53,147]. Blockage of MerTK, therefore, might directly contribute to the stimulation of anti-tumor immune invasion by reversing the immunosuppressive ability of the tumor cell. Together, researchers have proposed that multiple MerTK suppressors, such as UNC569, UNC2025, BMS-777607, AT9283, Neratinib/HKI-272, and UNC2881, show promise for treating cancer [148–152].

2.3.9. Efferocytosis regulation by complement component 1q (C1q) in the tumor microenvironment

C1q is involved in immune and non-immune cell activities, such as the clearance of ACs, placental expansion, and sensorial synaptic pruning. It has been reported that C1q can encourage tumor progression by facilitating adhesion, proliferation, migration, angiogenesis, and metastasis [153,154]. In fact, C1q is highly expressed in all malignant pleural mesothelioma (MPM) histotypes, a rare form of cancer commonly linked to the exposure of asbestos [155]. When C1q is bound to hyaluronic acid, it can facilitate the adhesion, as well as growth and proliferation of mesothelioma cells (MES) by increasing ERK1/2, stress-activated protein kinase/c-Jun NH(2)-terminal kinase (SAPK/JNK), and p38 phosphorylation, without activating the complement cascade [155]. C1q is also reported to be involved in tumor immune infiltration (*e.g.*, follicular helper T cells, memory B cells, and CD8

T cells) in osteosarcoma and may represent a useful prognostic factor for predicting the metastasis and prognosis of osteosarcoma patients [156].

2.3.10. Efferocytosis regulation by high-mobility group box 1 (HMGB1) in cancer therapy

Many proteins perform intracellular and extracellular duties that contribute to the recruitment of immune cells. During chronic damage and metabolic perturbation, such proteins can be critical to the complex pro-inflammatory episodes that lead to the repair of damaged tissues and restore organ dysfunction. It was shown that the pharmacological selection of the damage-associated molecular patterns (DAMPs), as called alarmins, can have some benefits. Nonetheless, alarmins provide local and systemic contributions that depend on respective post-translational alteration modes, differential receptor involvement, and other cellular influences [157,158]. HMGB1 can bind to TLRs and the receptor for advanced glycation end products (RAGE). Notably, the biological impacts of HMGB1 can depend on its level of expression and subcellular position. When a tumor is developing, HMGB1 has been described as both a pro-tumoral and anti-tumoral protein through its promotion or suppression of tumor growth, angiogenesis, and metastasis [159]. This is in line with other reports that HMGB1 possesses both oncogenic and tumor-inhibiting roles during the progression and treatment of tumors [160]. In addition, HMGB1-mediated immunogenic cell mortality might contribute to the immune-mediated elimination of tumors during radiotherapy or chemotherapy [69,161,162]. The release of dying tumor cells or exposure to DAMPs, such as ATP, heat shock proteins (HSP), and HMGB1, can lead to immunogenic cell death. These DAMPs benefit the maturation, antigen uptake, and antigen presentation of DCs and can be used as immunological adjuvants to active cytotoxic T lymphocyte responses [163].

DAMPs polarize macrophages towards the M1 phenotype, which contributes to anti-tumor functions [37]. Moreover, obstructing the HMGB-TLR4 pathway prevents the immunogenic cell death-related anticancer immune response resulting from chemotherapy both *in-vitro* and *in-vivo* [69,164]. In addition, when HMGB1 is released from necrotic cancer cells under chemotherapy treatment, it can promote metastasis in the remaining cancer cells in a RAGE-dependent manner [165]. Therefore, blockage of HMGB1-RAGE signaling enhances chemotherapy efficacy [166]. TLR4 in DCs is crucial to HMGB1-mediated immunogenic cell death and tumor clearance, while RAGE in cancer cells is necessary for HMGB1-mediated survival following chemotherapy. Even though ACs and NCs are capable of releasing HMGB1, HMGB1 released from ACs differ in that they can tolerate immunity [167]. The rapid clearance of ACs by efferocytosis leads to the inhibition of HMGB1 release. Furthermore, HMGB1 bound to T cell immunoglobulin- and mucin domain (TIM)-3 in tumor-associated DCs (TADCs) can be essential for the immune evasion of tumor cells in response to chemotherapy and vaccines, suggesting that there exists a balanced system between TLR4 and TIM-3 in DCs [164,168]. During chemotherapy, the clearance of immunogenic cell death-mediated tumors depends on several factors, such as tumor type, which can act in a tumor cell transplant model or an immunogenic 3-methylcholanthrene-induced fibrosarcoma model but not a spontaneous mammary tumor models [169]. Additionally, TLR2 in TADCs might mediate the regression of T cell-dependent brain tumors in anti-brain cancer immunotherapy [170].

It is widely accepted that extracellular HMGB1 serves a pro-tumor function given its respective chemokines, cytokines, and growth activities. On the contrary, intracellular HMGB1 plays an anti-tumor role because of its ability to sustain autophagy activity and genome stability during tumor growth. Interestingly, extracellular HMGB1 leads to immunogenic cell death-related anti-tumor immunity in the initial phase of chemotherapy but can stimulate residual tumor survival in the later phases of chemotherapy. Additionally, suppressing the intracellular expression of HMGB1 might prevent autophagy and increase apoptosis by boosting the efficacy of the anticancer treatments [160,171].

2.3.11. Efferocytosis regulation by C-X-C Motif Chemokine Ligand 5 (CXCL5) in metastatic tumor growth

It is suggested that the expression of CXCL5, a pro-inflammatory cytokine, was induced through the efferocytosis of prostate tumor cells by macrophages *via* the stimulation of STAT3 and NF-κB(p65) signaling *in-vitro* [172]. Tumors triggered by apoptosis show higher expression of CXCL5, and CXCL5 deficiency reduces tumor development. It has been further indicated that peripheral blood monocytes are more efferocytotic in patients with prostate cancer who have bone metastasis *in-vivo*. Moreover, CXCL5 serum levels are higher in patients with metastatic prostate cancer. It, therefore, seems that the efferocytosis of ATCs by myeloid phagocytes prompts inflammation mediated by CXCL5 and tumor growth in the bone [172]. The CXCL5/ CXCL8 cluster might serve as a prognostic signal for hepatocellular carcinoma and a possible biomarker to direct the identification of hepatocellular carcinoma patients for immunotherapy using immune checkpoint inhibitors [173].

2.3.12. Efferocytosis regulation by the SIAH2-NRF1 axis in mitochondria

It is indicated that Siah E3 ubiquitin protein ligase 2-(SIAH2)- nuclear respiratory factor 1 (NRF1) axis remodels the TME by controlling several processes, such as tumor mitochondrial activity, the polarization of TAMs, and cell death [174,175]. These events can lead to tumor maintenance, as well as development. The expression of nuclear-encoded mitochondrial genes (NEMGs) and mitochondrial activity are decreased in hypoxic tumors [176]. In line with this, hypoxia-activated SIAH2 downregulates the expression of NEMGs, such as pyruvate dehydrogenase beta, by degrading NRF1, resulting in an enhanced pro-tumor immune response. Reducing NRF1 degradation by hypoxia prevents the polarization of TAMs. Moreover, NRF1 degradation stimulates tumor cells to become more responsive to apoptosis in a Fas-associated protein with a death domain (FADD)-dependent manner, leading to secondary necrosis due to the impairment of efferocytosis [174]. The accumulation of NRF1 increases FADD-dependent apoptosis and prevents efferocytosis *in-vivo* [174].

2.3.13. Efferocytosis regulation by reactive oxygen species (ROS)

JS-K is a nitric oxide donor, which blocks tumor cell proliferation and stimulates AC death *in-vivo*. In addition to inhibiting the proliferation of gastric cancer cells *in-vitro* and *in-vivo*, JS-K also stimulates mitochondrial apoptosis. In this line, JS-K might target the mitochondrial respiratory chain (MRC) complexes I and IV and antioxidant enzymes to exert reactive oxygen species (ROS)-dependent anti-tumor activity. JS-K triggers an accumulation of ROS, and ROS clearance *via* antioxidant reagents reverses JS-K-stimulated toxicity *in-vitro* and *ex-vivo*. It is indicated that ROS mediates the anti-tumor effects of JS-K in gastric cancer, in which JS-K down-regulates MRC complex I and IV proteins, leading to decreased MRC complex I and IV function and ROS generation. JS-K inhibits the expression of antioxidant enzymes such as copper-zinc-containing superoxide dismutase (Cu,Zn-SOD) and catalase, leading to the reduction of antioxidant enzyme activity and the suppression of ROS clearance [177]. Generating ROS *via* oxidative stress also results in the externalization of PtdSer on the cell surface [178,179].

Thus, the inhibition of extracellular ROS (*e.g.*, by nanoscavenger) is a promising strategy to improve cancer immunotherapy efficacy [180].

2.3.14. Efferocytosis regulation by epithelial-mesenchymal transition (EMT)

The epithelial-mesenchymal transition (EMT) as a biological process occurs under both physiological and pathological conditions. Under pathological conditions, like cancer, EMT is induced by different pathways. In this case, the mesenchymal properties of epithelial cells result in enhanced motility and metastasis [181–183]. Cytokines involved in anti-tumor immune inhibition within the TME are also known for their

respective contributions to the EMT of tumor cells [50]. TGF-β is the most important EMT inducer and acts by binding to receptor tyrosine kinases. The TGF-β pathway cooperates in regulating repressor genes with *Zeb1*, *Snail*, *Slug,* and *Twist* during EMT initiation. It is executed by repressing E-cadherin expression which actuates the cascade of this cellular phenomenon [184,185]. In particular, switching E-cadherin to N-cadherin leads to the alteration of vimentin and keratin cell surface proteins, causing the cell shape to change from epithelial to mesenchymal [186,187].

Based on previous studies, conditioned medium extracted from macrophages subjected to ACs suppresses TGF-β1-induced EMT, such as by causing a loss of E-cadherin, synthesizing N-cadherin and α-smooth muscle actin, and stimulating EMT-actuating transcription agents, such as Zeb1/2, Snail1/2, and Twist1 in lung cancer cells *in-vitro* [188,189]. In fact, the activity of apoptotic cancer cell-induced peroxisome proliferator-activated receptor gamma (PPARγ) in macrophages, enhanced the phosphatase and tensin homolog (PTEN) contents secreted in exosomes, which was subsequently used by recipient lung cancer cells [189]. Besides, the injection of apoptotic 344SQ cells blocked lung metastasis by increasing PPARγ/PTEN signaling in tumor cells and TAMs *in-vivo*. GW9662, a PPARγ antagonist, leads to reduced PPARγ/PTEN signaling, a reduction in EMT-activating transcription factors, including Snai1 and Zeb1, and reversed the anti-metastatic effect of apoptotic 344SQ injection [189]. Yoon et al. suggested that instilling ACs can inhibit bleomycin-mediated EMT in primary mice alveolar type II epithelial cells *in-vivo* [188]. Thus, the anti-EMT programming of macrophages by ACs may supervise the gradual fibrotic reactions by generating potent paracrine EMT suppressors, such as curcumin [190].

2.3.15. Efferocytosis regulation by long-term exposure to inflammation in the tumor microenvironment

The differences between acute and chronic conditions of inflammation in the TME have been characterized [191–193]. It was observed that chronic inflammation was a key factor in the tumorigenesis of several solid tumors [194,195] and that long-term exposure to acute inflammatory mediators leads to chronic inflammation [192]. The activation of DCs has a profound effect on adaptive immunity, although might be differentially impacted based on the duration of activation, as prolonged activation might exhaust immune cells. Long-term activated DC1s by LPS and IFNγ initiate apoptosis with IL-10 induction based on efferocytosis and TYRO3, Axl, and MerTK receptors. IL-12p70 and IL-10 levels are positively associated with short-term activation and inversely associated with long-term activation. On the other hand, short-term stimulated $CD1a^{+}$ DCs exhibit an increase in IL-12p70 expression, while long-term stimulated $CD1a^{-}$ DCs undergo apoptosis and secrete IL-10. The IFN-γ response is regulated by IL-12p70, as a significant decrease in IFN-γ was detected following blockage with an IL-12p70 neutralizing antibody. Collectively, long-term activated DC1s change their profile toward tumor promotion and an anti-inflammatory phenotype [191].

Furthermore, micromolar concentrations of benzyl isothiocyanate-induced dying leukemic U937 cells liberate lower levels of IL-8 and monocyte chemoattractant protein-1, which might disrupt efferocytosis by macrophages *in-vivo* [196].

3. Conclusions and public health relevance

Apoptotic cell clearance leads to the release of growth agents and the signaling activity of molecules that contribute to the maintenance of tissue homeostasis. Thus, to prevent the permeation of intracellular contents leading to inflammation and tissue damage, ACs are cleared from tissues by phagocytes. Moreover, efferocytosis leads to the tolerance of self-antigen immunity and, when defective, consequently contributes to tissue damage and disease progression. One central feature of efferocytosis in wound healing is the production and release of cytokines through phagocytes that work to eliminate inflammation and promote tissue repair. Nevertheless, cytokines that contribute to immune inhibition are also known to contribute to the TME, promoting tumor cell death and increasing the evasion of anti-tumor immunity. Conversely, conventional cancer therapies can also be involved in tumor progression, where the tumor cell debris produced as a result of chemotherapy may promote tumorigenesis by releasing pro-inflammatory cytokines. In this case, efferocytosis has an important role in the establishment of the TME and the expansion and metastasis of tumors. Therefore, since immune mechanisms can lead to recurrence and metastasis of cancer, it is essential to use factors or pathways that increase efferocytosis but have minimal effect on anti-inflammatory cytokine expression. Understanding the complexity of ATC signaling across viable tumor cells and phagocytic cells in the tumor context may be a major milestone in the improvement of tumor therapeutic results, as well as the inhibition of metastasis through the selection of host and ATC interactions. In addition, the majority of anticancer treatments stimulate malignant cell apoptosis. Consequently, it is necessary to have sufficient knowledge of efferocytosis and immune responses to discover novel modalities that limit cancer development and relapse. Future studies are warranted to determine the circumstances under which anti-tumor immunity is suppressed or activated by therapy-generated cell debris. Collectively, it seems that the efferocytosis of ATCs can result in tumor development as well as metastasis by producing anti-inflammatory and, more importantly, tolerogenic cytokines in the TME. Therefore, it can be concluded that several ACs's elements, such as anti-inflammatory mediators, growth factors, and cytokines are capable of providing suitable targets for anti-cancer therapy.

Funding

This project has been conducted by a grant from cancer research center of cancer institute of Iran (Shams cancer charity, Grant No: 37312-202-01-97) and a Grant No. 960206 of the Biotechnology Development Council of the Islamic Republic of Iran.

Conflict of interest statement

The authors have declared no conflict of interest.

Acknowledgments

The authors wish to thank Mr. H. Argasi at the Research Consultation Center (RCC) of Shiraz University of Medical Sciences for his invaluable assistance in editing this manuscript.

References

[1] A. Tajbakhsh, V. Bianconi, M. Pirro, S.M. Gheibi Hayat, T.P. Johnston, A. Sahebkar, Efferocytosis and atherosclerosis: regulation of phagocyte function by MicroRNAs, Trends Endocrinol. Metab. 30 (9) (2019) 672–683.
[2] A. Tajbakhsh, M. Rezaee, P.T. Kovanen, A. Sahebkar, Efferocytosis in atherosclerotic lesions: malfunctioning regulatory pathways and control mechanisms, Pharmacol. Ther. 188 (2018) 12–25.
[3] M. Bäck, Jr Yurdagul A, I. Tabas, K. Öörni, P.T. Kovanen, Inflammation and its resolution in atherosclerosis: mediators and therapeutic opportunities, Nat. Rev. Cardiol. 16 (7) (2019) 389–406.
[4] A. Tajbakhsh, S.M. Gheibi Hayat, A.E. Butler, A. Sahebkar, Effect of soluble cleavage products of important receptors/ligands on efferocytosis: their role in inflammatory, autoimmune and cardiovascular disease, Ageing Res. Rev. 50 (2019) 43–57.
[5] Jr Yurdagul A, A.C. Doran, B. Cai, G. Fredman, I.A. Tabas Jr., Mechanisms and consequences of defective efferocytosis in atherosclerosis, Front Cardiovasc. Med. 4 (2017) 86.
[6] A.M. Grabiec, N. Denny, J.A. Doherty, K.E. Happonen, J. Hankinson, E. Connolly, M.E. Fife, T. Fujimori, N. Fujino, A. Goenka, S. Holden, G. Tavernier, R. Shah, P. C. Cook, A.S. MacDonald, R.M. Niven, B. Dahlbäck, S.J. Fowler, A. Simpson, T. Hussell, Diminished airway macrophage expression of the Axl receptor tyrosine kinase is associated with defective efferocytosis in asthma, J. Allergy Clin. Immunol. 140 (4) (2017) 1144–1146, e4.

[7] A. Tajbakhsh, M. Read, G.E. Barreto, M. Ávila-Rodriguez, S.M. Gheibi-Hayat, A. Sahebkar, Apoptotic neurons and amyloid-beta clearance by phagocytosis in Alzheimer's disease: pathological mechanisms and therapeutic outlooks, Eur. J. Pharmacol. 895 (2021), 173873.

[8] R.S. Magge, L.M. DeAngelis, The double-edged sword: neurotoxicity of chemotherapy, Blood Rev. 29 (2) (2015) 93–100.

[9] M. Benish, S. Ben-Eliyahu, Surgery as a double-edged sword: a clinically feasible approach to overcome the metastasis-promoting effects of surgery by blunting stress and prostaglandin responses, Cancers 2 (4) (2010) 1929–1951.

[10] T.L. Whiteside, The tumor microenvironment and its role in promoting tumor growth, Oncogene 27 (45) (2008) 5904–5912.

[11] Y. Chen, S. Zhang, Q. Wang, X. Zhang, Tumor-recruited M2 macrophages promote gastric and breast cancer metastasis via M2 macrophage-secreted CHI3L1 protein, J. Hematol. Oncol. 10 (1) (2017) 36.

[12] C.D. Gregory, M. Paterson, An apoptosis-driven 'onco-regenerative niche': roles of tumour-associated macrophages and extracellular vesicles, Philos. Trans. R. Soc. Lond. B Biol. Sci. 373 (1737) (2018), 20170003.

[13] C.D. Gregory, J.D. Pound, Cell death in the neighbourhood: direct microenvironmental effects of apoptosis in normal and neoplastic tissues, J. Pathol. 223 (2) (2011) 177–194.

[14] B. McDonald, K. Pittman, G.B. Menezes, S.A. Hirota, I. Slaba, C.C. Waterhouse, P. L. Beck, D.A. Muruve, P. Kubes, Intravascular danger signals guide neutrophils to sites of sterile inflammation, Science 330 (6002) (2010) 362–366.

[15] J.P. Smith, A.M. Lister, J.G. Tew, A.K. Szakal, Kinetics of the tingible body macrophage response in mouse germinal center development and its depression with age, Anat. Rec. 229 (4) (1991) 511–520.

[16] Y.S. Yi, Functional role of milk fat globule-epidermal growth factor VIII in macrophage-mediated inflammatory responses and inflammatory/autoimmune diseases, Mediat. Inflamm. 2016 (2016), 5628486.

[17] A.H. Wyllie, Apoptosis and the regulation of cell numbers in normal and neoplastic tissues: an overview, Cancer Metastas. Rev. 11 (2) (1992) 95–103.

[18] C.D. Gregory, J.D. Pound, Microenvironmental influences of apoptosis in vivo and in vitro, Apoptosis 15 (9) (2010) 1029–1049.

[19] I. Reiter, B. Krammer, G. Schwamberger, Cutting edge: differential effect of apoptotic versus necrotic tumor cells on macrophage antitumor activities, J. Immunol. 163 (4) (1999) 1730–1732.

[20] R.S. Cook, K.M. Jacobsen, A.M. Wofford, D. DeRyckere, J. Stanford, A.L. Prieto, E. Redente, M. Sandahl, D.M. Hunter, K.E. Strunk, D.K. Graham, H.S. Earp, MerTK inhibition in tumor leukocytes decreases tumor growth and metastasis, J. Clin. Investig. 123 (8) (2013) 3231–3242.

[21] J.C. Stanford, C. Young, D. Hicks, P. Owens, A. Williams, D.B. Vaught, M. M. Morrison, J. Lim, M. Williams, D.M. Brantley-Sieders, J.M. Balko, D. Tonetti, H.S. Earp, R.S. Cook, Efferocytosis produces a prometastatic landscape during postpartum mammary gland involution, J. Clin. Investig. 124 (11) (2014) 4737–4752.

[22] F.N. Soki, A.J. Koh, J.D. Jones, Y.W. Kim, J. Dai, E.T. Keller, K.J. Pienta, K. Atabai, H. Roca, L.K. McCauley, Polarization of prostate cancer-associated macrophages is induced by milk fat globule-EGF factor 8 (MFG-E8)-mediated efferocytosis, J. Biol. Chem. 289 (35) (2014) 24560–24572.

[23] A. Bondanza, V.S. Zimmermann, P. Rovere-Querini, J. Turnay, I.E. Dumitriu, C. M. Stach, R.E. Voll, U.S. Gaipl, W. Bertling, E. Pöschl, J.R. Kalden, A.A. Manfredi, M. Herrmann, Inhibition of phosphatidylserine recognition heightens the immunogenicity of irradiated lymphoma cells in vivo, J. Exp. Med. 200 (9) (2004) 1157–1165.

[24] M. Liu, R.S. O'Connor, S. Trefely, K. Graham, N.W. Snyder, G.L. Beatty, Metabolic rewiring of macrophages by CpG potentiates clearance of cancer cells and overcomes tumor-expressed CD47-mediated 'don't-eat-me' signal, Nat. Immunol. 20 (3) (2019) 265–275.

[25] F. Alciato, P.P. Sainaghi, D. Sola, L. Castello, G.C. Avanzi, TNF-alpha, IL-6, and IL-1 expression is inhibited by GAS6 in monocytes/macrophages, J. Leukoc. Biol. 87 (5) (2010) 869–875.

[26] H.A. Martinson, S. Jindal, C. Durand-Rougely, V.F. Borges, P. Schedin, Wound healing-like immune program facilitates postpartum mammary gland involution and tumor progression, Int. J. Cancer 136 (8) (2015) 1803–1813.

[27] Z. Li, Y. Li, J. Gao, Y. Fu, P. Hua, Y. Jing, M. Cai, H. Wang, T. Tong, The role of CD47-SIRPα immune checkpoint in tumor immune evasion and innate immunotherapy, Life Sci. 273 (2021), 119150.

[28] A. Tajbakhsh, P.T. Kovanen, M. Rezaee, M. Banach, S.A. Moallem, A. Sahebkar, Regulation of efferocytosis by caspase-dependent apoptotic cell death in atherosclerosis, Int. J. Biochem. Cell Biol. 120 (2020), 105684.

[29] A. Tajbakhsh, P.T. Kovanen, M. Rezaee, M. Banach, A. Sahebkar, Ca2+ Flux: searching for a role in efferocytosis of apoptotic cells in atherosclerosis, J. Clin. Med. 8 (12) (2019) 2047.

[30] D. Park, A.C. Tosello-Trampont, M.R. Elliott, M. Lu, L.B. Haney, Z. Ma, A. L. Klibanov, J.W. Mandell, K.S. Ravichandran, BAI1 is an engulfment receptor for apoptotic cells upstream of the ELMO/Dock180/Rac module, Nature 450 (7168) (2007) 430–434.

[31] A. Tajbakhsh, N. Farahani, S.M. Gheibihayat, A.M. Mirkhabbaz, A. Savardashtaki, M.R. Hamblin, H. Mirzaei, Autoantigen-specific immune tolerance in pathological and physiological cell death: Nanotechnology comes into view, Int. Immunopharmacol. 90 (2021), 107177.

[32] P.-A. Oldenborg, CD47: a cell surface glycoprotein which regulates multiple functions of hematopoietic cells in health and disease, ISRN Hematol. 2013 (2013), 614619.

[33] P.A. Oldenborg, A. Zheleznyak, Y.F. Fang, C.F. Lagenaur, H.D. Gresham, F. P. Lindberg, Role of CD47 as a marker of self on red blood cells, Science 288 (5473) (2000) 2051–2054.

[34] O. Per-Arne, Role of CD47 and signal regulatory protein alpha (SIRPalpha) in regulating the clearance of viable or aged blood cells, Transfus. Med. Hemother. 39 (5) (2012) 315–320.

[35] S.M.G. Hayat, et al., CD47: role in the immune system and application to cancer therapy, Cell. Oncol. (2019) 1–12.

[36] R. Hanayama, M. Tanaka, K. Miwa, A. Shinohara, A. Iwamatsu, S. Nagata, Identification of a factor that links apoptotic cells to phagocytes, Nature 417 (6885) (2002) 182–187.

[37] T.A. Werfel, R.S. Cook, Efferocytosis in the tumor microenvironment, Semin. Immunopathol. 40 (6) (2018) 545–554.

[38] D. Vyas, G. Laput, A.K. Vyas, Chemotherapy-enhanced inflammation may lead to the failure of therapy and metastasis, OncoTargets Ther. 7 (2014) 1015–1023.

[39] S. Reers, A.C. Pfannerstill, D. Rades, R. Maushagen, M. Andratschke, R. Pries, B. Wollenberg, Cytokine changes in response to radio-/chemotherapeutic treatment in head and neck cancer, Anticancer Res. 33 (6) (2013) 2481–2489.

[40] S. Ley, A. Weigert, B. Weichand, N. Henke, B. Mille-Baker, R.A. Janssen, B. Brüne, The role of TRKA signaling in IL-10 production by apoptotic tumor cell-activated macrophages, Oncogene 32 (5) (2013) 631–640.

[41] K.J. Poth, A.D. Guminski, G.P. Thomas, P.J. Leo, I.A. Jabbar, N.A. Saunders, Cisplatin treatment induces a transient increase in tumorigenic potential associated with high interleukin-6 expression in head and neck squamous cell carcinoma, Mol. Cancer Ther. 9 (8) (2010) 2430–2439.

[42] N. Casares, M.O. Pequignot, A. Tesniere, F. Ghiringhelli, S. Roux, N. Chaput, E. Schmitt, A. Hamai, S. Hervas-Stubbs, M. Obeid, F. Coutant, D. Métivier, E. Pichard, P. Aucouturier, G. Pierron, C. Garrido, L. Zitvogel, G. Kroemer, Caspase-dependent immunogenicity of doxorubicin-induced tumor cell death, J. Exp. Med. 202 (12) (2005) 1691–1701.

[43] I.K. Poon, C.D. Lucas, A.G. Rossi, K.S. Ravichandran, Apoptotic cell clearance: basic biology and therapeutic potential, Nat. Rev. Immunol. 14 (3) (2014) 166–180.

[44] C.D. Gregory, C.A. Ford, J.J. Voss, Microenvironmental effects of cell death in malignant disease, Adv. Exp. Med. Biol. 930 (2016) 51–88.

[45] G. Ichim, S.W. Tait, A fate worse than death: apoptosis as an oncogenic process, Nat. Rev. Cancer 16 (8) (2016) 539–548.

[46] G.S. Sarode, S.C. Sarode, N. Maniyar, N.K. Sharma, S. Patil, Carcinogenesis-relevant biological events in the pathophysiology of the efferocytosis phenomenon, Oncol. Rev. 11 (2) (2017) 343, 343-343.

[47] D.K. Graham, D. DeRyckere, K.D. Davies, H.S. Earp, The TAM family: phosphatidylserine sensing receptor tyrosine kinases gone awry in cancer, Nat. Rev. Cancer 14 (12) (2014) 769–785.

[48] D.B. Vaught, R.S. Cook, Clearance of dying cells accelerates malignancy, Oncotarget 6 (28) (2015) 24590–24591.

[49] D.B. Vaught, J.C. Stanford, R.S. Cook, Efferocytosis in the tumor microenvironment, in: Encyclopedia of Cell Biology, Elsevier Inc., 2015, pp. 374–378.

[50] D.B. Vaught, J.C. Stanford, R.S. Cook, Efferocytosis creates a tumor microenvironment supportive of tumor survival and metastasis, Cancer Cell Microenviron. 2 (1) (2015), e666.

[51] G. Lemke, C.V. Rothlin, Immunobiology of the TAM receptors, Nat. Rev. Immunol. 8 (5) (2008) 327–336.

[52] R.M. Linger, A.K. Keating, H.S. Earp, D.K. Graham, TAM receptor tyrosine kinases: biologic functions, signaling, and potential therapeutic targeting in human cancer, Adv. Cancer Res. 100 (2008) 35–83.

[53] K.Q. Nguyen, W.I. Tsou, D.A. Calarese, S.G. Kimani, S. Singh, S. Hsieh, Y. Liu, B. Lu, Y. Wu, S.J. Garforth, S.C. Almo, S.V. Kotenko, R.B. Birge, Overexpression of MERTK receptor tyrosine kinase in epithelial cancer cells drives efferocytosis in a gain-of-function capacity, J. Biol. Chem. 289 (37) (2014) 25737–25749.

[54] K.J. Png, N. Halberg, M. Yoshida, S.F. Tavazoie, A microRNA regulon that mediates endothelial recruitment and metastasis by cancer cells, Nature 481 (7380) (2011) 190–194.

[55] M. Aziz, A. Jacob, A. Matsuda, P. Wang, Review: milk fat globule-EGF factor 8 expression, function and plausible signal transduction in resolving inflammation, Apoptosis 16 (11) (2011) 1077–1086.

[56] A. Verma, S.L. Warner, H. Vankayalapati, D.J. Bearss, S. Sharma, Targeting Axl and Mer kinases in cancer, Mol. Cancer Ther. 10 (10) (2011) 1763–1773.

[57] S. Farnworth-McHugh, N. Barth, L. Melville, M. Paterson, C. Lynch, P. Holland, I. Dransfield, C. Gregory, Potential oncogenic effect of the MERTK-dependent apoptotic-cell clearance pathway in starry-sky B-cell lymphoma, Front. Immunol. 11 (1759) (2020) 1759.

[58] K.V. Myers, S.R. Amend, K.J. Pienta, Targeting Tyro3, Axl and MerTK (TAM receptors): implications for macrophages in the tumor microenvironment, Mol. Cancer 18 (1) (2019) 94.

[59] X. Zhou, X. Liu, L. Huang, Macrophage-mediated tumor cell phagocytosis: opportunity for nanomedicine intervention, Adv. Funct. Mater. 31 (5) (2021), 2006220.

[60] T. Yokomizo, Leukotriene B4 receptors: novel roles in immunological regulations, Adv. Enzym. Regul. 51 (1) (2011) 59–64.

[61] T. Yokomizo, K. Kato, K. Terawaki, T. Izumi, T. Shimizu, A second leukotriene B (4) receptor, BLT2. A new therapeutic target in inflammation and immunological disorders, J. Exp. Med. 192 (3) (2000) 421–432.

[62] A. Sica, P. Larghi, A. Mancino, L. Rubino, C. Porta, M.G. Totaro, M. Rimoldi, S. K. Biswas, P. Allavena, A. Mantovani, Macrophage polarization in tumour progression, Semin. Cancer Biol. 18 (5) (2008) 349–355.

[63] A. Shapouri-Moghaddam, S. Mohammadian, H. Vazini, M. Taghadosi, S. A. Esmaeili, F. Mardani, B. Seifi, A. Mohammadi, J.T. Afshari, A. Sahebkar, Macrophage plasticity, polarization, and function in health and disease, J. Cell Physiol. 233 (9) (2018) 6425–6440.
[64] A. Weigert, A.M. Johann, A. von Knethen, H. Schmidt, G. Geisslinger, B. Brüne, Apoptotic cells promote macrophage survival by releasing the antiapoptotic mediator sphingosine-1-phosphate, Blood 108 (5) (2006) 1635–1642.
[65] L.G. Lima, R. Chammas, R.Q. Monteiro, M.E. Moreira, M.A. Barcinski, Tumor-derived microvesicles modulate the establishment of metastatic melanoma in a phosphatidylserine-dependent manner, Cancer Lett. 283 (2) (2009) 168–175.
[66] Z.G. Fridlender, J. Sun, S. Kim, V. Kapoor, G. Cheng, L. Ling, G.S. Worthen, S. M. Albelda, Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN, Cancer Cell 16 (3) (2009) 183–194.
[67] K. Lauber, A. Ernst, M. Orth, M. Herrmann, C. Belka, Dying cell clearance and its impact on the outcome of tumor radiotherapy, Front. Oncol. 2 (2012) 116.
[68] H. Lei, M. Shi, H. Xu, S. Bai, X. Xiong, Q. Wei, L. Yang, Combined treatment of radiotherapy and immunotherapy for urological malignancies: current evidence and clinical considerations, Cancer Manag. Res. 13 (2021) 1719–1731.
[69] L. Apetoh, F. Ghiringhelli, A. Tesniere, M. Obeid, C. Ortiz, A. Criollo, G. Mignot, M.C. Maiuri, E. Ullrich, P. Saulnier, H. Yang, S. Amigorena, B. Ryffel, F.J. Barrat, P. Saftig, F. Levi, R. Lidereau, C. Nogues, J.P. Mira, A. Chompret, V. Joulin, F. Clavel-Chapelon, J. Bourhis, F. André, S. Delaloge, T. Tursz, G. Kroemer, L. Zitvogel, Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy, Nat. Med. 13 (9) (2007) 1050–1059.
[70] M.I. Koukourakis, A. Giatromanolaki, Tumor microenvironment, immune response and post-radiotherapy tumor clearance, Clin. Transl. Oncol. 22 (12) (2020) 2196–2205.
[71] Z. Asadzadeh, E. Safarzadeh, S. Safaei, A. Baradaran, A. Mohammadi, K. Hajiasgharzadeh, A. Derakhshani, A. Argentiero, N. Silvestris, B. Baradaran, Current approaches for combination therapy of cancer: the role of immunogenic cell death, Cancers 12 (4) (2020) 1047.
[72] J. Chang, S.S. Bhasin, D.R. Bielenberg, V.P. Sukhatme, M. Bhasin, S. Huang, M. W. Kieran, D. Panigrahy, Chemotherapy-generated cell debris stimulates colon carcinoma tumor growth via osteopontin, Faseb J. 33 (1) (2019) 114–125.
[73] S.H. Kim, S. Saeidi, X. Zhong, S.Y. Gwak, I.A. Muna, S.A. Park, S.H. Kim, H.K. Na, Y. Joe, H.T. Chung, K.E. Kim, W. Han, Y.J. Surh, Breast cancer cell debris diminishes therapeutic efficacy through heme oxygenase-1-mediated inactivation of M1-like tumor-associated macrophages, Neoplasia 22 (11) (2020) 606–616.
[74] S.H. Kim, et al., Reprograming of tumor-associated macrophages in breast tumor-bearing mice under chemotherapy by targeting heme oxygenase-1, Antioxidants (2021) 470.
[75] R.S. Kornbluth, The immunological potential of apoptotic debris produced by tumor cells and during HIV infection, Immunol. Lett. 43 (1–2) (1994) 125–132.
[76] J.K. Chan, J. Roth, J.J. Oppenheim, K.J. Tracey, T. Vogl, M. Feldmann, N. Horwood, J. Nanchahal, Alarmins: awaiting a clinical response, J. Clin. Investig. 122 (8) (2012) 2711–2719.
[77] A.O. Pisco, S. Huang, Non-genetic cancer cell plasticity and therapy-induced stemness in tumour relapse: 'What does not kill me strengthens me', Br. J. Cancer 112 (11) (2015) 1725–1732.
[78] R.B. Birge, S. Boeltz, S. Kumar, J. Carlson, J. Wanderley, D. Calianese, M. Barcinski, R.A. Brekken, X. Huang, J.T. Hutchins, B. Freimark, C. Empig, J. Mercer, A.J. Schroit, G. Schett, M. Herrmann, Phosphatidylserine is a global immunosuppressive signal in efferocytosis, infectious disease, and cancer, Cell Death Differ. 23 (6) (2016) 962–978.
[79] K. Chen, Z. Bao, W. Gong, P. Tang, T. Yoshimura, J.M. Wang, Regulation of inflammation by members of the formyl-peptide receptor family, J. Autoimmun. 85 (2017) 64–77.
[80] M. Pasparakis, P. Vandenabeele, Necroptosis and its role in inflammation, Nature 517 (7534) (2015) 311–320.
[81] M.J. Gough, A.A. Melcher, A. Ahmed, M.R. Crittenden, D.S. Riddle, E. Linardakis, A.N. Ruchatz, L.M. Emiliusen, R.G. Vile, Macrophages orchestrate the immune response to tumor cell death, Cancer Res. 61 (19) (2001) 7240–7247.
[82] M.S. Kindy, J. Yu, H. Zhu, M.T. Smith, S. Gattoni-Celli, A therapeutic cancer vaccine against GL261 murine glioma, J. Transl. Med. 14 (2016) 1.
[83] C.C. Shan, L.R. Shi, M.Q. Ding, Y.B. Zhu, X.D. Li, B. Xu, J.T. Jiang, C.P. Wu, Cytokine-induced killer cells co-cultured with dendritic cells loaded with the protein lysate produced by radiofrequency ablation induce a specific antitumor response, Oncol. Lett. 9 (4) (2015) 1549–1556.
[84] J. Unga, M. Hashida, Ultrasound induced cancer immunotherapy, Adv. Drug Deliv. Rev. 72 (2014) 144–153.
[85] A.D. Garg, D.V. Krysko, T. Verfaillie, A. Kaczmarek, G.B. Ferreira, T. Marysael, N. Rubio, M. Firczuk, C. Mathieu, A.J. Roebroek, W. Annaert, J. Golab, P. de Witte, P. Vandenabeele, P. Agostinis, A novel pathway combining calreticulin exposure and ATP secretion in immunogenic cancer cell death, EMBO J. 31 (5) (2012) 1062–1079.
[86] J. Deng, Y. Zhang, J. Feng, F. Wu, Dendritic cells loaded with ultrasound-ablated tumour induce in vivo specific antitumour immune responses, Ultrasound Med. Biol. 36 (3) (2010) 441–448.
[87] R.A. Maldonado, U.H. von Andrian, How tolerogenic dendritic cells induce regulatory T cells, Adv. Immunol. 108 (2010) 111–165.
[88] J.E. Talmadge, D.I. Gabrilovich, History of myeloid-derived suppressor cells, Nat. Rev. Cancer 13 (10) (2013) 739–752.
[89] C. Mauri, A. Bosma, Immune regulatory function of B cells, Annu. Rev. Immunol. 30 (2012) 221–241.
[90] Jr da Silva IA, R. Chammas, A.P. Lepique, S. Jancar Jr., Platelet-activating factor (PAF) receptor as a promising target for cancer cell repopulation after radiotherapy, Oncogenesis 6 (1) (2017) 296.
[91] P.M. Gunjal, G. Schneider, A.A. Ismail, S.S. Kakar, M. Kucia, M.Z. Ratajczak, Evidence for induction of a tumor metastasis-receptive microenvironment for ovarian cancer cells in bone marrow and other organs as an unwanted and underestimated side effect of chemotherapy/radiotherapy, J. Ovarian Res. 8 (2015) 20.
[92] L. Revesz, Effect of tumour cells killed by x-rays upon the growth of admixed viable cells, Nature 178 (4547) (1956) 1391–1392.
[93] P. Chalasani, M. Marron, D. Roe, K. Clarke, M. Iannone, R.B. Livingston, J. S. Shan, A.T. Stopeck, A phase I clinical trial of bavituximab and paclitaxel in patients with HER2 negative metastatic breast cancer, Cancer Med. 4 (7) (2015) 1051–1059.
[94] R. Digumarti, P.P. Bapsy, A.V. Suresh, G.S. Bhattacharyya, L. Dasappa, J.S. Shan, D.E. Gerber, Bavituximab plus paclitaxel and carboplatin for the treatment of advanced non-small-cell lung cancer, Lung Cancer 86 (2) (2014) 231–236.
[95] P. DeRose, P.E. Thorpe, D.E. Gerber, Development of bavituximab, a vascular targeting agent with immune-modulating properties, for lung cancer treatment, Immunotherapy 3 (8) (2011) 933–944.
[96] C.M. Stach, X. Turnay, R.E. Voll, P.M. Kern, W. Kolowos, T.D. Beyer, J.R. Kalden, M. Herrmann, Treatment with annexin V increases immunogenicity of apoptotic human T-cells in Balb/c mice, Cell Death Differ. 7 (10) (2000) 911–915.
[97] B. Frey, P. Schildkopf, F. Rödel, E.M. Weiss, L.E. Munoz, M. Herrmann, R. Fietkau, U.S. Gaipl, AnnexinA5 renders dead tumor cells immunogenic–implications for multimodal cancer therapies, J. Immunotoxicol. 6 (4) (2009) 209–216.
[98] L.E. Munoz, B. Frey, F. Pausch, W. Baum, R.B. Mueller, B. Brachvogel, E. Poschl, F. Rödel, K. von der Mark, M. Herrmann, U.S. Gaipl, The role of annexin A5 in the modulation of the immune response against dying and dead cells, Curr. Med. Chem. 14 (3) (2007) 271–277.
[99] A.W. Beck, T.A. Luster, A.F. Miller, S.E. Holloway, C.R. Conner, C.C. Barnett, P. E. Thorpe, J.B. Fleming, R.A. Brekken, Combination of a monoclonal anti-phosphatidylserine antibody with gemcitabine strongly inhibits the growth and metastasis of orthotopic pancreatic tumors in mice, Int. J. Cancer 118 (10) (2006) 2639–2643.
[100] J. He, Y. Yin, T.A. Luster, L. Watkins, P.E. Thorpe, Antiphosphatidylserine antibody combined with irradiation damages tumor blood vessels and induces tumor immunity in a rat model of glioblastoma, Clin. Cancer Res. 15 (22) (2009) 6871–6880.
[101] Y. Yin, X. Huang, K.D. Lynn, P.E. Thorpe, Phosphatidylserine-targeting antibody induces M1 macrophage polarization and promotes myeloid-derived suppressor cell differentiation, Cancer Immunol. Res. 1 (4) (2013) 256–268.
[102] A.R. Patil, C.J. Thomas, A. Surolia, Kinetics and the mechanism of interaction of the endoplasmic reticulum chaperone, calreticulin, with monoglucosylated (Glc1Man9GlcNAc2) substrate, J. Biol. Chem. 275 (32) (2000) 24348–24356.
[103] R.G. Spiro, Q. Zhu, V. Bhoyroo, H.D. Söling, Definition of the lectin-like properties of the molecular chaperone, calreticulin, and demonstration of its copurification with endomannosidase from rat liver Golgi, J. Biol. Chem. 271 (19) (1996) 11588–11594.
[104] M. Michalak, J. Groenendyk, E. Szabo, L.I. Gold, M. Opas, Calreticulin, a multi-process calcium-buffering chaperone of the endoplasmic reticulum, Biochem. J. 417 (3) (2009) 651–666.
[105] J. Nangalia, C.E. Massie, E.J. Baxter, F.L. Nice, G. Gundem, D.C. Wedge, E. Avezov, J. Li, K. Kollmann, D.G. Kent, A. Aziz, A.L. Godfrey, J. Hinton, I. Martincorena, P. Van Loo, A.V. Jones, P. Guglielmelli, P. Tarpey, H.P. Harding, J.D. Fitzpatrick, C.T. Goudie, C.A. Ortmann, S.J. Loughran, K. Raine, D.R. Jones, A.P. Butler, J.W. Teague, S. O'Meara, S. McLaren, M. Bianchi, Y. Silber, D. Dimitropoulou, D. Bloxham, L. Mudie, M. Maddison, B. Robinson, C. Keohane, C. Maclean, K. Hill, K. Orchard, S. Tauro, M.Q. Du, M. Greaves, D. Bowen, B. Huntly, C.N. Harrison, N. Cross, D. Ron, A.M. Vannucchi, E. Papaemmanuil, P. J. Campbell, A.R. Green, Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2, N. Engl. J. Med. 369 (25) (2013) 2391–2405.
[106] M. Kielbik, I. Szulc-Kielbik, M. Klink, Calreticulin-multifunctional chaperone in immunogenic cell death: potential significance as a prognostic biomarker in ovarian cancer patients, Cells 10 (2021) 1.
[107] A. Schcolnik-Cabrera, B. Oldak, M. Juárez, M. Cruz-Rivera, A. Flisser, F. Mendlovic, Calreticulin in phagocytosis and cancer: opposite roles in immune response outcomes, Apoptosis 24 (3–4) (2019) 245–255.
[108] Y.C. Lu, C.N. Chen, B. Wang, W.M. Hsu, S.T. Chen, K.J. Chang, C.C. Chang, H. Lee, Changes in tumor growth and metastatic capacities of J82 human bladder cancer cells suppressed by down-regulation of calreticulin expression, Am. J. Pathol. 179 (3) (2011) 1425–1433.
[109] M. Feng, J.Y. Chen, R. Weissman-Tsukamoto, J.P. Volkmer, P.Y. Ho, K. M. McKenna, S. Cheshier, M. Zhang, N. Guo, P. Gip, S.S. Mitra, I.L. Weissman, Macrophages eat cancer cells using their own calreticulin as a guide: roles of TLR and Btk, Proc. Natl. Acad. Sci. USA 112 (7) (2015) 2145–2150.
[110] K. Ni, T. Luo, A. Culbert, M. Kaufmann, X. Jiang, W. Lin, Nanoscale metal-organic framework co-delivers TLR-7 agonists and anti-CD47 antibodies to modulate macrophages and orchestrate cancer immunotherapy, J. Am. Chem. Soc. 142 (29) (2020) 12579–12584.
[111] N.R. Vandchali, F. Moadab, E. Taghizadeh, A. Tajbakhsh, S.M. Gheibi-Hayat, CD47 functionalization of nanoparticles as a poly(ethylene glycol) alternative: a novel approach to improve drug delivery, Curr. Drug Targets (2021).

[112] B. Binnington, L. Nguyen, M. Kamani, D. Hossain, D.L. Marks, M. Budani, C. A. Lingwood, Inhibition of Rab prenylation by statins induces cellular glycosphingolipid remodeling, Glycobiology 26 (2) (2015) 166–180.
[113] C.P. Zambirinis, E. Levie, S. Nguy, A. Avanzi, R. Barilla, Y. Xu, L. Seifert, D. Daley, S.H. Greco, M. Deutsch, S. Jonnadula, A. Torres-Hernandez, D. Tippens, S. Pushalkar, A. Eisenthal, D. Saxena, J. Ahn, C. Hajdu, D.D. Engle, D. Tuveson, G. Miller, TLR9 ligation in pancreatic stellate cells promotes tumorigenesis, J. Exp. Med. 212 (12) (2015) 2077–2094.
[114] B.R. Lokesh, M. Wrann, Incorporation of palmitic acid or oleic acid into macrophage membrane lipids exerts differential effects on the function of normal mouse peritoneal macrophages, Biochim. Biophys. Acta 792 (2) (1984) 141–148.
[115] B. Ha, Z. Lv, Z. Bian, X. Zhang, A. Mishra, Y. Liu, 'Clustering' SIRPα into the plasma membrane lipid microdomains is required for activated monocytes and macrophages to mediate effective cell surface interactions with CD47, PLoS One 8 (10) (2013) 77615.
[116] N.G. Sosale, T. Rouhiparkouhi, A.M. Bradshaw, R. Dimova, R. Lipowsky, D. E. Discher, Cell rigidity and shape override CD47's "self"-signaling in phagocytosis by hyperactivating myosin-II, Blood 125 (3) (2015) 542–552.
[117] K. Asano, M. Miwa, K. Miwa, R. Hanayama, H. Nagase, S. Nagata, M. Tanaka, Masking of phosphatidylserine inhibits apoptotic cell engulfment and induces autoantibody production in mice, J. Exp. Med. 200 (4) (2004) 459–467.
[118] Y.Y. Chen, C.F. Lo, T.Y. Chiu, C.Y. Hsu, T.K. Yeh, C.P. Chen, C.L. Huang, C. Y. Huang, M.H. Wang, Y.C. Huang, H.H. Ho, Y.S. Chao, J.C. Shih, L.K. Tsou, C. T. Chen, BPRDP056, a novel small molecule drug conjugate specifically targeting phosphatidylserine for cancer therapy, Transl. Oncol. 14 (1) (2021), 100897.
[119] N. Prevete, F. Liotti, A. Amoresano, P. Pucci, A. de Paulis, R.M. Melillo, New perspectives in cancer: Modulation of lipid metabolism and inflammation resolution, Pharmacol. Res. 128 (2018) 80–87.
[120] R. Avni, B. Cohen, M. Neeman, Hypoxic stress and cancer: imaging the axis of evil in tumor metastasis, NMR Biomed. 24 (6) (2011) 569–581.
[121] Q.T. Le, N.C. Denko, A.J. Giaccia, Hypoxic gene expression and metastasis, Cancer Metastas. Rev. 23 (3–4) (2004) 293–310.
[122] S.M. Evans, C.J. Koch, Prognostic significance of tumor oxygenation in humans, Cancer Lett. 195 (1) (2003) 1–16.
[123] A.J. Majmundar, W.J. Wong, M.C. Simon, Hypoxia-inducible factors and the response to hypoxic stress, Mol. Cell 40 (2) (2010) 294–309.
[124] C. Koumenis, B.G. Wouters, "Translating" tumor hypoxia: unfolded protein response (UPR)-dependent and UPR-independent pathways, Mol. Cancer Res. 4 (7) (2006) 423–436.
[125] N.B. Hao, M.H. Lü, Y.H. Fan, Y.L. Cao, Z.R. Zhang, S.M. Yang, Macrophages in tumor microenvironments and the progression of tumors, Clin. Dev. Immunol. 2012 (2012), 948098.
[126] Y.K. Han, G.Y. Park, M.J. Bae, J.S. Kim, W.S. Jo, C.G. Lee, Hypoxia induces immunogenic cell death of cancer cells by enhancing the exposure of cell surface calreticulin in an endoplasmic reticulum stress-dependent manner, Oncol. Lett. 18 (6) (2019) 6269–6274.
[127] L. Sun, Y. Wang, L. Wang, B. Yao, T. Chen, Q. Li, Z. Liu, R. Liu, Y. Niu, T. Song, Q. Liu, K. Tu, Resolvin D1 prevents epithelial-mesenchymal transition and reduces the stemness features of hepatocellular carcinoma by inhibiting paracrine of cancer-associated fibroblast-derived COMP, J. Exp. Clin. Cancer Res. 38 (1) (2019) 170.
[128] M.M. Gilligan, A. Gartung, M.L. Sulciner, P.C. Norris, V.P. Sukhatme, D. R. Bielenberg, S. Huang, M.W. Kieran, C.N. Serhan, D. Panigrahy, Aspirin-triggered proresolving mediators stimulate resolution in cancer, Proc. Natl. Acad. Sci. USA 116 (13) (2019) 6292–6297.
[129] S. Ran, P.E. Thorpe, Phosphatidylserine is a marker of tumor vasculature and a potential target for cancer imaging and therapy, Int. J. Radiat. Oncol. Biol. Phys. 54 (5) (2002) 1479–1484.
[130] S. Polavarapu, B.S. Dwarakanath, U.N. Das, Differential action of polyunsaturated fatty acids and eicosanoids on bleomycin-induced cytotoxicity to neuroblastoma cells and lymphocytes, Arch. Med. Sci. 14 (1) (2018) 207–229.
[131] X. Huang, M. Bennett, P.E. Thorpe, A monoclonal antibody that binds anionic phospholipids on tumor blood vessels enhances the antitumor effect of docetaxel on human breast tumors in mice, Cancer Res. 65 (10) (2005) 4408–4416.
[132] M.J.W. Peeters, A. Rahbech, P. Thor Straten, TAM-ing T cells in the tumor microenvironment: implications for TAM receptor targeting, Cancer Immunol. Immunother. 7 (9) (2019) 1472–1484.
[133] V. Davra, S. Kumar, K. Geng, D. Calianese, D. Mehta, V. Gadiyar, C. Kasikara, K. C. Lahey, Y.J. Chang, M. Wichroski, C. Gao, M.S. De Lorenzo, S.V. Kotenko, T. Bergsbaken, P.K. Mishra, W.C. Gause, M. Quigley, T.E. Spires, R.B. Birge, Axl and Mertk receptors cooperate to promote breast cancer progression by combined oncogenic signaling and evasion of host anti-tumor immunity, Cancer Res. 81 (3) (2020) 698–712.
[134] P. Aehnlich, et al., TAM receptor inhibition-implications for cancer and the immune system, Cancers (2021) 6.
[135] R. Cabezón, E.A. Carrera-Silva, G. Flórez-Grau, A.E. Errasti, E. Calderón-Gómez, J.J. Lozano, C. España, E. Ricart, J. Panés, C.V. Rothlin, D. Benítez-Ribas, MERTK as negative regulator of human T cell activation, J. Leukoc. Biol. 97 (4) (2015) 751–760.
[136] J.D. Jones, B.P. Sinder, D. Paige, F.N. Soki, A.J. Koh, S. Thiele, Y. Shiozawa, L. C. Hofbauer, S. Daignault, H. Roca, L.K. McCauley, Trabectedin reduces skeletal prostate cancer tumor size in association with effects on M2 macrophages and efferocytosis, Neoplasia 21 (2) (2019) 172–184.
[137] M.R. Crittenden, J. Baird, D. Friedman, T. Savage, L. Uhde, A. Alice, B. Cottam, K. Young, P. Newell, C. Nguyen, S. Bambina, G. Kramer, E. Akporiaye, A. Malecka, A. Jackson, M.J. Gough, Mertk on tumor macrophages is a therapeutic target to prevent tumor recurrence following radiation therapy, Oncotarget 7 (48) (2016) 78653–78666.
[138] W. Leconet, C. Larbouret, T. Chardès, G. Thomas, M. Neiveyans, M. Busson, M. Jarlier, N. Radosevic-Robin, M. Pugnière, F. Bernex, F. Penault-Llorca, J. M. Pasquet, A. Pèlegrin, B. Robert, Preclinical validation of AXL receptor as a target for antibody-based pancreatic cancer immunotherapy, Oncogene 33 (47) (2014) 5405–5414.
[139] G. Moody, B. Belmontes, S. Masterman, W. Wang, C. King, C. Murawsky, T. Tsuruda, S. Liu, R. Radinsky, P.J. Beltran, Antibody-mediated neutralization of autocrine Gas6 inhibits the growth of pancreatic ductal adenocarcinoma tumors in vivo, Int. J. Cancer 139 (6) (2016) 1340–1349.
[140] A. Kirane, K.F. Ludwig, N. Sorrelle, G. Haaland, T. Sandal, R. Ranaweera, J. E. Toombs, M. Wang, S.P. Dineen, D. Micklem, M.T. Dellinger, J.B. Lorens, R. A. Brekken, Warfarin blocks Gas6-mediated axl activation required for pancreatic cancer epithelial plasticity and metastasis, Cancer Res. 75 (18) (2015) 3699–3705.
[141] S.G. Kimani, S. Kumar, N. Bansal, K. Singh, V. Kholodovych, T. Comollo, Y. Peng, S.V. Kotenko, S.G. Sarafianos, J.R. Bertino, W.J. Welsh, R.B. Birge, Small molecule inhibitors block Gas6-inducible TAM activation and tumorigenicity, Sci. Rep. 7 (2017) 43908.
[142] S.K. Smart, et al., The emerging role of TYRO3 as a therapeutic target in cancer, Cancers (2018), E474.
[143] E. Thorp, D. Cui, D.M. Schrijvers, G. Kuriakose, I. Tabas, Mertk receptor mutation reduces efferocytosis efficiency and promotes apoptotic cell accumulation and plaque necrosis in atherosclerotic lesions of apoe-/- mice, Arterioscler. Thromb. Vasc. Biol. 28 (8) (2008) 1421–1428.
[144] T.A. Werfel, D.L. Elion, B. Rahman, D.J. Hicks, V. Sanchez, P.I. Gonzales-Ericsson, M.J. Nixon, J.L. James, J.M. Balko, P.A. Scherle, H.K. Koblish, R.S. Cook, Treatment-induced tumor cell apoptosis and secondary necrosis drive tumor progression in the residual tumor microenvironment through MERTK and IDO1, Cancer Res. 79 (1) (2019) 171–182.
[145] D.H. Munn, M.D. Sharma, T.S. Johnson, P. Rodriguez, IDO, PTEN-expressing Tregs and control of antigen-presentation in the murine tumor microenvironment, Cancer Immunol. Immunother. 66 (8) (2017) 1049–1058.
[146] M. Sandahl, D.M. Hunter, K.E. Strunk, H.S. Earp, R.S. Cook, Epithelial cell-directed efferocytosis in the post-partum mammary gland is necessary for tissue homeostasis and future lactation, BMC Dev. Biol. 10 (2010) 122.
[147] Y. Chen, C. Liu, S. Zhu, X. Liang, Q. Zhang, X. Luo, L. Yuan, L. Song, PD-1/PD-L1 immune checkpoint blockade-based combinational treatment: immunotherapeutic amplification strategies against colorectal cancer, Int. Immunopharmacol. 96 (2021), 107607.
[148] S. Christoph, D. Deryckere, J. Schlegel, J.K. Frazer, L.A. Batchelor, A. Y. Trakhimets, S. Sather, D.M. Hunter, C.T. Cummings, J. Liu, C. Yang, D. Kireev, C. Simpson, J. Norris-Drouin, E.A. Hull-Ryde, W.P. Janzen, G.L. Johnson, X. Wang, S.V. Frye, H.S. Earp, D.K. Graham, UNC569, a novel small-molecule mer inhibitor with efficacy against acute lymphoblastic leukemia in vitro and in vivo, Mol. Cancer Ther. 12 (11) (2013) 2367–2377.
[149] W. Zhang, A.L. McIver, M.A. Stashko, D. DeRyckere, B.R. Branchford, D. Hunter, D. Kireev, M.J. Miley, J. Norris-Drouin, W.M. Stewart, M. Lee, S. Sather, Y. Zhou, J.A. Di Paola, M. Machius, W.P. Janzen, H.S. Earp, D.K. Graham, S.V. Frye, X. Wang, Discovery of Mer specific tyrosine kinase inhibitors for the treatment and prevention of thrombosis, J. Med. Chem. 56 (23) (2013) 9693–9700.
[150] W. Zhang, D. DeRyckere, D. Hunter, J. Liu, M.A. Stashko, K.A. Minson, C. T. Cummings, M. Lee, T.G. Glaros, D.L. Newton, S. Sather, D. Zhang, D. Kireev, W. P. Janzen, H.S. Earp, D.K. Graham, S.V. Frye, X. Wang, UNC2025, a potent and orally bioavailable MER/FLT3 dual inhibitor, J. Med. Chem. 57 (16) (2014) 7031–7041.
[151] G.M. Schroeder, Y. An, Z.W. Cai, X.T. Chen, C. Clark, L.A. Cornelius, J. Dai, J. Gullo-Brown, A. Gupta, B. Henley, J.T. Hunt, R. Jeyaseelan, A. Kamath, K. Kim, J. Lippy, L.J. Lombardo, V. Manne, S. Oppenheimer, J.S. Sack, R.J. Schmidt, G. Shen, K. Stefanski, J.S. Tokarski, G.L. Trainor, B.S. Wautlet, D. Wei, D. K. Williams, Y. Zhang, Y. Zhang, J. Fargnoli, R.M. Borzilleri, Discovery of N-(4-(2-amino-3-chloropyridin-4-yloxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (BMS-777607), a selective and orally efficacious inhibitor of the Met kinase superfamily, J. Med. Chem. 52 (5) (2009) 1251–1254.
[152] C.-J. Chen, Y.-P. Liu, MERTK inhibition: potential as a treatment strategy in EGFR tyrosine kinase inhibitor-resistant non-small cell lung cancer, Pharmaceuticals 14 (2) (2021) 130.
[153] R. Bulla, C. Tripodo, D. Rami, G.S. Ling, C. Agostinis, C. Guarnotta, S. Zorzet, P. Durigutto, M. Botto, F. Tedesco, C1q acts in the tumour microenvironment as a cancer-promoting factor independently of complement activation, Nat. Commun. 7 (2016) 10346.
[154] S. Winslow, K. Leandersson, A. Edsjö, C. Larsson, Prognostic stromal gene signatures in breast cancer, Breast Cancer Res. 17 (1) (2015) 23.
[155] C. Agostinis, R. Vidergar, B. Belmonte, A. Mangogna, L. Amadio, P. Geri, V. Borelli, F. Zanconati, F. Tedesco, M. Confalonieri, C. Tripodo, U. Kishore, R. Bulla, Complement protein C1q binds to hyaluronic acid in the malignant pleural mesothelioma microenvironment and promotes tumor growth, Front. Immunol. 8 (2017) 1559.
[156] H. Huang, M. Tan, L. Zheng, G. Yan, K. Li, D. Lu, X. Cui, S. He, D. Lei, B. Zhu, J. Zhao, Prognostic implications of the complement protein C1Q and its correlation with immune infiltrates in osteosarcoma, OncoTargets Ther. 14 (2021) 1737–1751.
[157] D. Bertheloot, E. Latz, HMGB1, IL-1alpha, IL-33 and S100 proteins: dual-function alarmins, Cell Mol. Immunol. 14 (1) (2017) 43–64.

[158] A. Tajbakhsh, M. Rezaee, G.E. Barreto, S.A. Moallem, N.C. Henney, A. Sahebkar, The role of nuclear factors as "Find-Me"/alarmin signals and immunostimulation in defective efferocytosis and related disorders, Int. Immunopharmacol. 80 (2020), 106134.
[159] S.J. He, J. Cheng, X. Feng, Y. Yu, L. Tian, Q. Huang, The dual role and therapeutic potential of high-mobility group box 1 in cancer, Oncotarget 8 (38) (2017) 64534–64550.
[160] R. Kang, Q. Zhang, H.J. Zeh, M.T. Lotze, D. Tang, HMGB1 in cancer: good, bad, or both? Clin. Cancer Res. 19 (15) (2013) 4046–4057.
[161] Y. Suzuki, K. Mimura, Y. Yoshimoto, M. Watanabe, Y. Ohkubo, S. Izawa, K. Murata, H. Fujii, T. Nakano, K. Kono, Immunogenic tumor cell death induced by chemoradiotherapy in patients with esophageal squamous cell carcinoma, Cancer Res. 72 (16) (2012) 3967–3976.
[162] J. Fucikova, P. Kralikova, A. Fialova, T. Brtnicky, L. Rob, J. Bartunkova, R. Spísek, Human tumor cells killed by anthracyclines induce a tumor-specific immune response, Cancer Res. 71 (14) (2011) 4821–4833.
[163] M. Michaud, I. Martins, A.Q. Sukkurwala, S. Adjemian, Y. Ma, P. Pellegatti, S. Shen, O. Kepp, M. Scoazec, G. Mignot, S. Rello-Varona, M. Tailler, L. Menger, E. Vacchelli, L. Galluzzi, F. Ghiringhelli, F. di Virgilio, L. Zitvogel, G. Kroemer, Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice, Science 334 (6062) (2011) 1573–1577.
[164] S.P. Cartland, S.W. Genner, G.J. Martínez, S. Robertson, M. Kockx, R.C. Lin, J. F. O'Sullivan, Y.C. Koay, P. Manuneedhi Cholan, M.A. Kebede, A.J. Murphy, S. Masters, M.R. Bennett, W. Jessup, L. Kritharides, C. Geczy, S. Patel, M. M. Kavurma, TRAIL-expressing monocyte/macrophages are critical for reducing inflammation and atherosclerosis, iScience 12 (2019) 41–52.
[165] Y. Luo, Y. Chihara, K. Fujimoto, T. Sasahira, M. Kuwada, R. Fujiwara, K. Fujii, H. Ohmori, H. Kuniyasu, High mobility group box 1 released from necrotic cells enhances regrowth and metastasis of cancer cells that have survived chemotherapy, Eur. J. Cancer 49 (3) (2013) 741–751.
[166] R. Kang, D. Tang, N.E. Schapiro, K.M. Livesey, A. Farkas, P. Loughran, A. Bierhaus, M.T. Lotze, H.J. Zeh, The receptor for advanced glycation end products (RAGE) sustains autophagy and limits apoptosis, promoting pancreatic tumor cell survival, Cell Death Differ. 17 (4) (2010) 666–676.
[167] H. Kazama, J.E. Ricci, J.M. Herndon, G. Hoppe, D.R. Green, T.A. Ferguson, Induction of immunological tolerance by apoptotic cells requires caspase-dependent oxidation of high-mobility group box-1 protein, Immunity 29 (1) (2008) 21–32.
[168] S. Chiba, M. Baghdadi, H. Akiba, H. Yoshiyama, I. Kinoshita, H. Dosaka-Akita, Y. Fujioka, Y. Ohba, J.V. Gorman, J.D. Colgan, M. Hirashima, T. Uede, A. Takaoka, H. Yagita, M. Jinushi, Tumor-infiltrating DCs suppress nucleic acid-mediated innate immune responses through interactions between the receptor TIM-3 and the alarmin HMGB1, Nat. Immunol. 13 (9) (2012) 832–842.
[169] M. Ciampricotti, C.S. Hau, C.W. Doornebal, J. Jonkers, K.E. de Visser, Chemotherapy response of spontaneous mammary tumors is independent of the adaptive immune system, Nat. Med. 18 (3) (2012) 344–346.
[170] J.F. Curtin, N. Liu, M. Candolfi, W. Xiong, H. Assi, K. Yagiz, M.R. Edwards, K. S. Michelsen, K.M. Kroeger, C. Liu, A.K. Muhammad, M.C. Clark, M. Arditi, B. Comin-Anduix, A. Ribas, P.R. Lowenstein, M.G. Castro, HMGB1 mediates endogenous TLR2 activation and brain tumor regression, PLoS Med. 6 (1) (2009) 10.
[171] S. He, J. Cheng, L. Sun, Y. Wang, C. Wang, X. Liu, Z. Zhang, M. Zhao, Y. Luo, L. Tian, C. Li, Q. Huang, HMGB1 released by irradiated tumor cells promotes living tumor cell proliferation via paracrine effect, Cell Death Dis. 9 (6) (2018) 648.
[172] H. Roca, J.D. Jones, M.C. Purica, S. Weidner, A.J. Koh, R. Kuo, J.E. Wilkinson, Y. Wang, S. Daignault-Newton, K.J. Pienta, T.M. Morgan, E.T. Keller, J.E. Nör, L. D. Shea, L.K. McCauley, Apoptosis-induced CXCL5 accelerates inflammation and growth of prostate tumor metastases in bone, J. Clin. Investig. 128 (1) (2018) 248–266.
[173] J. Zhu, Y. Zhou, L. Wang, J. Hao, R. Chen, L. Liu, J. Li, CXCL5/CXCL8 is a promising potential prognostic and tumor microenvironment-related cluster in hepatocellular carcinoma, J. Gastrointest. Oncol. 11 (6) (2020) 1364–1380.
[174] B. Ma, H. Cheng, C. Mu, G. Geng, T. Zhao, Q. Luo, K. Ma, R. Chang, Q. Liu, R. Gao, J. Nie, J. Xie, J. Han, L. Chen, G. Ma, Y. Zhu, Q. Chen, The SIAH2-NRF1 axis spatially regulates tumor microenvironment remodeling for tumor progression, Nat. Commun. 10 (1) (2019) 1034.
[175] J.W. Kim, I. Tchernyshyov, G.L. Semenza, C.V. Dang, HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia, Cell Metab. 3 (3) (2006) 177–185.
[176] E. Reznik, M.L. Miller, Y. Şenbabaoğlu, N. Riaz, J. Sarungbam, S.K. Tickoo, H. A. Al-Ahmadie, W. Lee, V.E. Seshan, A.A. Hakimi, C. Sander, Mitochondrial DNA copy number variation across human cancers, eLife 5 (2016), e10769.
[177] X. Zhao, A. Cai, Z. Peng, W. Liang, H. Xi, P. Li, G. Chen, J. Yu, L. Chen, JS-K induces reactive oxygen species-dependent anti-cancer effects by targeting mitochondria respiratory chain complexes in gastric cancer, J. Cell. Mol. Med. 23 (4) (2019) 2489–2504.
[178] J.M. Mates, F.M. Sanchez-Jimenez, Role of reactive oxygen species in apoptosis: implications for cancer therapy, Int. J. Biochem. Cell Biol. 32 (2) (2000) 157–170.
[179] H.U. Simon, A. Haj-Yehia, F. Levi-Schaffer, Role of reactive oxygen species (ROS) in apoptosis induction, Apoptosis 5 (5) (2000) 415–418.
[180] H. Deng, W. Yang, Z. Zhou, R. Tian, L. Lin, Y. Ma, J. Song, X. Chen, Targeted scavenging of extracellular ROS relieves suppressive immunogenic cell death, Nat. Commun. 11 (1) (2020) 4951.
[181] J.P. Thiery, J.P. Sleeman, Complex networks orchestrate epithelial-mesenchymal transitions, Nat. Rev. Mol. Cell Biol. 7 (2) (2006) 131–142.
[182] J.P. Thiery, H. Acloque, R.Y. Huang, M.A. Nieto, Epithelial-mesenchymal transitions in development and disease, Cell 139 (5) (2009) 871–890.
[183] D. Ribatti, R. Tamma, T. Annese, Epithelial-mesenchymal transition in cancer: a historical overview, Transl. Oncol. 13 (6) (2020), 100773.
[184] S. Lamouille, J. Xu, R. Derynck, Molecular mechanisms of epithelial-mesenchymal transition, Nat. Rev. Mol. Cell Biol. 15 (3) (2014) 178–196.
[185] N. Dave, S. Guaita-Esteruelas, S. Gutarra, À. Frias, M. Beltran, S. Peiró, A.G. de Herreros, Functional cooperation between Snail1 and twist in the regulation of ZEB1 expression during epithelial to mesenchymal transition, J. Biol. Chem. 286 (14) (2011) 12024–12032.
[186] M.J. Wheelock, Y. Shintani, M. Maeda, Y. Fukumoto, K.R. Johnson, Cadherin switching, J. Cell Sci. 121 (Pt 6) (2008) 727–735.
[187] D.M. Toivola, G.Z. Tao, A. Habtezion, J. Liao, M.B. Omary, Cellular integrity plus: organelle-related and protein-targeting functions of intermediate filaments, Trends Cell Biol. 15 (11) (2005) 608–617.
[188] Y.-S. Yoon, Y.J. Lee, Y.H. Choi, Y.M. Park, J.L. Kang, Macrophages programmed by apoptotic cells inhibit epithelial-mesenchymal transition in lung alveolar epithelial cells via PGE2, PGD2, and HGF, Sci. Rep. 6 (2016) 20992, 20992-20992.
[189] Y.B. Kim, Y.H. Ahn, J.H. Jung, Y.J. Lee, J.H. Lee, J.L. Kang, Programming of macrophages by UV-irradiated apoptotic cancer cells inhibits cancer progression and lung metastasis, Cell. Mol. Immunol. 16 (11) (2019) 851–867.
[190] A. Bahrami, M. Majeed, A. Sahebkar, Curcumin: a potent agent to reverse epithelial-to-mesenchymal transition, Cell. Oncol. 42 (4) (2019) 405–421.
[191] L.S. Carstensen, O. Lie-Andersen, A. Obers, M.D. Crowther, I.M. Svane, M. Hansen, Long-term exposure to inflammation induces differential cytokine patterns and apoptosis in dendritic cells, Front. Immunol. 10 (2019) 2702.
[192] M. Hansen, M.H. Andersen, The role of dendritic cells in cancer, Semin. Immunopathol. 39 (3) (2017) 307–316.
[193] I. Piotrowski, K. Kulcenty, W. Suchorska, Interplay between inflammation and cancer, Rep. Pract. Oncol. Radiother. 25 (3) (2020) 422–427.
[194] G. Solinas, G. Germano, A. Mantovani, P. Allavena, Tumor-associated macrophages (TAM) as major players of the cancer-related inflammation, J. Leukoc. Biol. 86 (5) (2009) 1065–1073.
[195] M.J. Waldner, M.F. Neurath, Mechanisms of immune signaling in colitis-associated cancer, Cell. Mol. Gastroenterol. Hepatol. 1 (1) (2015) 6–16.
[196] G. Stasiłojć, A. Nagel, P. Koszałka, J.J. Bigda, Defective apoptosis of U937 cells induced by benzyl isothiocyanate (BITC), Acta Biochim. Pol. 66 (4) (2019) 401–407.