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Efferocytosis creates a tumor microenvironment supportive of tumor survival and metastasis

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Abstract

Programmed cell death, or apoptosis, occurs in nearly all tissues of all multi-cellular organisms. In order to avoid leakage of intracellular contents, which could generate tissue damaging inflammation, apoptotic cells are cleared from tissues by phagocytes, which then dispatch the engulfed dying cell through the lysosomal pathway. Phagocytic clearance of apoptotic cells is referred to as efferocytosis. One key feature of efferocytosis is the production and release of wound healing cytokines by the phagocyte, which acts to resolve inflammation, and promote tissue repair. Phagocytic engulfment of apoptotic cells coupled with cytokine modulation aimed at immune suppression ensures that physiological programmed cell death does not induce inflammation and tissue damage. However, cytokines involved in wound healing and immune suppression are notorious for their role in the tumor microenvironment, increasing tumor cell motility and promoting evasion of anti-tumor immunity. Therefore, current and future studies aimed at targeting important players of efferocytosis should reveal new and efficacious therapeutic approaches for limiting cancer progression and relapse.

Keywords

efferocytosis; involution; tumor progression; immune function

Introduction

Physiological programmed cell death is a critical event in the development of multicellular organisms and tissue, and contributes to the normal turn-over of aging cells in healthy tissues, making room for younger healthy cells. In the mammary gland, for example, apoptosis allows for changes that occur during normal breast development. Apoptosis occurs in the ductal breast epithelium during puberty, forming hollow lumens in the ducts that initially develop as solid epithelial cords[1]. With each menstrual cycle in humans (estrous cycle in mice), the alveolar buds of the mammary epithelium undergo modest proliferation in preparation for pregnancy. In the event of a pregnancy, these epithelial growths continue

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Conflicts of Interest

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proliferating to generate the milk-producing epithelium, but in the absence of pregnancy, these alveolar buds will undergo apoptosis[2]. Following pregnancy and lactation, the alveolar mammary epithelium (which produces milk during lactation) undergoes widespread synchronized apoptosis, removing up to 90% of the mammary epithelium within only 7–10 days. This involution process returns the mammary epithelium to a quiescent state capable of future rounds of alveolar budding and pregnancy-induced expansion[3, 4]. While the mammary gland represents a rather dramatic example of physiological cell death, most tissues harbor some level of cell death at any given time. Some tissues produce dying cells with regular frequency, such as tissues with environmental exposures (epithelia of the skin, gut, lungs, retina). Other tissues generate dying cells with cyclical (endometrium, ovaries, testes) or diurnal (retina) frequency.

The idea that dying cells are removed from multicellular tissues is not a new idea. In fact, this idea was visited more than 100 years ago, when Metchnikoff discussed ‘physiological inflammation’ to describe the removal of dying cells from healthy tissues. Studies in nematodes demonstrated that cells were capable of engulfing their dying neighbors, but without inducing inflammation, requiring a revision of the term used to describe this phenomenon. The word efferocytosis, derived from the Latin root *effero*-meaning ‘to bury, or take to the grave,’ is relatively new, despite the long history of the concept it describes[5]. Coined in 2003, efferocytosis distinguishes itself from other sub-categories of phagocytosis (pinocytosis, micropinocytosis, etc.) through unique engulfment of dying cells via distinct signaling pathways to coordinate recognition, engulfment, and digestion of dying cells, and the concurrent modulation of cytokines produced by the phagocyte.

The process of phagocytosis (and efferocytosis) can be accomplished by most cells, but macrophages and dendritic cells are considered the professional phagocytes. Macrophages make up a key component of the innate immune system, but are not limited to the innate immune response as they are central orchestrators of the adaptive immune response as well. Regulation of cytokine and chemokine production is mediated by macrophages, with these cytokines and chemokines instructing the response of the cells in the adaptive immune system. Efferocytosis is critical to macrophage-mediated suppression of adaptive immune responses and resolution of inflammation[4, 6]. Efferocytosis resembles other categories of phagocytosis in many ways. For example, macrophages will digest engulfed materials and present them as antigens on their cell surface. When foreign bodies (e.g. pathogens) are ingested, macrophages will produce pro-inflammatory cytokines (e.g., type I interferons (IFNs), interleukin (IL)-12 that promote clonal expansion and activation of cytotoxic T-lymphocytes (CTLs). This ensures that foreign antigens will produce a cytotoxic immune response to kill invading pathogens and host cells infected by foreign pathogens. Conversely, engulfment of cells undergoing programmed cell death are likely to be derived from the host, and not likely to represent a pathogenic threat to the host. Therefore, macrophages are equipped to recognize a self-derived dying cell and engulf it, triggering a signaling cascade that suppresses pro-inflammatory cytokines, and at the same time induces the robust expression of anti-inflammatory (e.g., IL-10) and wound healing (e.g., transforming growth factor (TGF)-β) cytokines. When cells of the adaptive immune system (T-lymphocytes, B-lymphocytes) encounter these antigens presented by macrophages, the anti-inflammatory cytokines instruct the T- and B-lymphocytes to tolerate this antigen, and any cell expressing

this antigen, as it is a self-derived antigen. In this manner, efferocytosis results in suppression of adaptive immune response, promotion of immune tolerance, and wound healing/remodeling[5]. Interestingly, these same attributes that protect tissues from autoimmunity following programmed cell death can contribute to pathological events as well. Recent findings demonstrate that efferocytosis within the tumor microenvironment, a tissue with high levels of apoptotic cell death, exaggerates the immune suppressive microenvironment that characterizes aggressive cancers, contributing to evasion of anti-tumor immunity and increasing the potential for metastatic spread of tumor cells. Targeting efferocytosis in order to promote an anti-tumor immune response, yet limiting the negative outcome of tissue damage and auto-immunity, is the subject of current studies.

Efferocytosis: Important Players

Efferocytosis is carefully regulated at several levels. First, cells undergoing programmed cell death will secrete soluble factors that attract macrophages to the site of death, referred to as ‘find me’ signals, which include the chemokines CXCL1, CXCL14, CCL2, CCL6–8, and CCL11[7–9]. The dying cell will also mark its outer leaflet with the ‘eat me’ signal, allowing macrophages to recognize and bind to cells undergoing programmed cell death. Phosphatidlyserine (PS) exposed on the outer leaflet of the plasma membrane of an apoptotic cell is a hallmark of programmed cell death, and is the most widely recognized ‘eat me’ signal. Healthy cells actively retain PS on the inner leaflet of the plasma membrane. In contrast, at the onset of apoptosis, PS accumulates on the outer leaflet, marking the dying cell for engulfment[10–12]. In response to ‘find me’ signals, macrophages upregulate cell surface receptors and bridging molecules. These bridging molecules simultaneously bind to PS and macrophage cell surface receptors. Macrophages use several cell surface receptors to directly recognize PS, and several other receptors that bind to bridging molecules to indirectly bind PS on the apoptotic cell to the macrophage. For example, the PS receptor (PSR), brain angiogenesis inhibitor 1 (BAI1)[13–15], T cell immunoglobulin and mucin (TIM)-4, and Stabilin-2 are macrophage cell surface proteins that bind directly to PS and contribute to efferocytosis[16–23]. The bridging ligand MFG-E8 (MilkFat Globule Epidermal growth factor-like 8) simultaneously binds integrin $\alpha_v\beta_3$ and $\alpha_v\beta_5$ expressed on macrophages and PS on dying cells. The bridging ligands growth arrest specific-6 (Gas6) and protein S (ProS1) bind to receptor tyrosine kinases Tyro3, Axl, and MerTK[24, 25]. Engagement of the bridging molecules with both the dying cells (via PS) and the macrophage (through the receptor) induces Rac1-dependent cytoskeletal changes that drive apoptotic cell engulfment[26–28]. It is important to note that many of the receptors used by macrophages to recognize dying cells are also used by other phagocytes. For example, MerTK is used in retinal pigment epithelial cells (RPECs) and mammary epithelial cells (MECs) to ingest PS-flagged cells while MFG-E8, the PS-bridging ligand for integrin $\alpha_V\beta_3$ and $\alpha_V\beta_5$, is required in the mammary gland and in the retina for clearance of PS-labelled cells.

MerTK is required for efferocytosis by macrophages. Once MerTK is engaged by the dying cell via Gas6 or ProS1, MerTK undergoes dimerization, tyrosine kinase activation, and tyrosine phosphorylation, activating CRKII/DOCK180/ELMO signaling to the Rac GTPase,

which enables actin protrusions to completely surround and thus engulf the dying/apoptotic cell. Once consumed, the cell is processed by lysosomal degradation (Figure 1)[29–34].

In addition to engulfment and clearance of the apoptotic cell, MerTK signaling promotes expression and release of immune suppressive cytokines (IL-10, IL-13, IL-4 and TGFβ1), and repression of pro-inflammatory cytokines (IL-12, IFNγ). This promotes immune tolerance and tissue repair[35, 36]. Beyond the critical function of efferocytosis in tissue homeostasis, recent studies suggest that efferocytosis may support a more malignant tumor microenvironment, in part because of the cytokine signature associated with the process of efferocytosis[37–49]. Additionally, many of the receptors and ligands that facilitate the process of efferocytosis are overexpressed in cancer suggesting a specific role in tumorigenesis[36, 43, 50, 51].

Efferocytosis and Disease States

Dysfunction of efferocytosis is involved in several disease states such as atherosclerosis[52], retinal pigmentosa[53], chronic obstructive pulmonary inflammation[54], and type II diabetes[55]. While impaired clearance of apoptotic cells can promote disease states, intact efferocytosis can also lead to some pathophysiological states, primarily cancer. Tyro-3, Axl, MerTK and their PS-bridging ligand Gas6 and ProS1 are overexpressed in several cancer types, both in the tumor cells, per se, and in the tumor microenvironment (reviewed in[36] and[56]). Axl activation in tumor cells promotes proliferation and survival through the PI3K/Akt and MAPK/ERK signaling pathways, and it has been implicated in promoting the epithelial-to-mesenchymal transition[36, 57] Overexpression and/or activation of MerTK in tumor cells increases oncogenic PI3K/Akt, MAPK/ERK, JAK/STAT, and Src/FAK signaling, thus increasing tumor cell survival, proliferation and metastasis[36, 47]. MerTK expression within macrophages of the tumor microenvironment supports tumor metastasis and immune suppression through efferocytosis-induced production of wound healing, immune suppressive cytokines (IL-10, IL-13, IL-4 and TGFβ1) and repression of pro-inflammatory cytokines (IL-12, IFNγ)[35, 36]. Numerous studies indicate that targeted inhibition of MerTK or Axl would improve survival of cancer patients by limiting tumor growth, survival and metastasis, and/or by promoting an anti-tumor attack on the tumor cells. Studies of efferocytosis-mediated regulation of the tumor microenvironment is in its early stages, but results suggest that efferocytosis represents an immune checkpoint that is exploited by tumors to evade anti-tumor immunity.

Role of Immune Cell and Tumor Microenvironment in Tumor Progression

The efferocytosis receptor MerTK plays a critical role in the delicate balance of innate and adaptive immunity. Through efferocytosis and subsequent cytokine regulation, MerTK prevents immune reactions against self-antigens and long-term autoimmune disease[58]. Targeted genomic loss of MerTK in mice results in a hyper-inflammatory phenotype that progresses with age, resulting in lupus-like auto-immunity with moderate penetrance in aged mice[35]. Disease progression and penetrance is accelerated in the combined absence of MerTK, Axl, and Tyro3.

Other ways that immunity can be affected by the TAM family of receptors is through interactions with macrophages and how they are activated. Macrophages are functionally adaptable and alter their polarization state in response to different physiological conditions. The two major types of mΦs are M1 and M2, although other polarized states have been characterized[59]. "Classically-activated" M1 macrophages become activated by inflammatory mediators (GM-CSF and IFN-γ) which induce M1 polarization, produce Th1 pro-inflammatory cytokines (CXCL19 and CXCL10, IL-12, IFNγ), participate in antigen presentation, and promote an anti-tumor response[60, 61]. In MerTK knockout mice, LPS treatment leads to shock and death at lower levels than wildtype mice due to the increased cytokine release associated with M1 macrophage polarization[62]. However, mΦs that carry out efferocytosis are M2, more specifically M2c, polarized[63]. M2 macrophages produce Th2 cytokines (Il-10, IL13, IL4,TGFβ1, CCL17, CCL22 and CCL24), promote anti-inflammatory responses, and have pro-tumorigenic functions[61]. M2 polarized macrophages support tissue repair and angiogenesis through the production of VEGF or EGF thusly supporting the pro-tumorigenic designation[61]. Tumor associated macrophages are typically M2 polarized. They are pro-inflammatory and promote cell growth and recruitment through the production of IL6, TNFα, IL23 and may also promote tumor development through immune suppressive effects from the release of TGFβ and IL10[64–66].

Natural killer (NK) cells are important players of the innate immune system possessing potent cytotoxic activity. MerTK expression on NK cells dampens the maturation of NK cells into a cytotoxic state. Studies have demonstrated the anti-tumor ability of NK cells in colon, breast, and skin cancers, where NK cells block the seeding capacity of disseminated tumor initiating cells[67, 68]. Signaling through the efferocytosis receptors Axl and Tyro3 in dendritic cells activates suppressor of cytokine signaling (SOCS)1/3, dampening expression of pro-inflammatory cytokines, and inducing expression of anti-inflammatory cytokines[69, 70] [71], thus having a powerful immune suppressive effect akin to what is seen upon MerTK-mediated efferocytosis in macrophages[72].

Evasion and suppression of the host immune system plays an important role in malignant progression (reviewed in[73]). One way of achieving this is by stimulation of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs)[74]. MDSCs are functionally defined as immunosuppressive, immature myeloid cells that function in response to infection or stress to maintain normal tissue homeostasis[75]. They infiltrate developing tumors where they promote tumor vascularization[75] and disrupt major mechanisms of immunosurveillance which include antigen presentation by dendritic cells (DCs)[76] T cell activation[66, 76, 77] M1 macrophage polarization[78–80] and inhibition of NK cell cytotoxicity[81]. Factors robustly produced in response to efferocytosis, such as IL-10 and VEGF, affect the development and regulation of MDSCs, suggesting that this process may play a role in the immunosuppressive effects of MDSCs[82].

When CD8+ T cell responses are lessened or blunted, it correlates with a poorer patient prognosis; and recent studies demonstrated that MerTK signaling in the tumor microenvironment decreased CD8+ T-cells in tumors and tumor-draining lymph nodes[83, 84], providing one mechanism in which MerTK contributes to tumor growth and metastasis. Regulatory T (Treg) cells are another cell type that play a role in cancer[85, 86].

Under normal conditions, Treg cells regulate the expansion and activation of T and B cells[87]. There also exists a strong correlation between tumor progression and the frequency of Tregs in a variety of cancers[88–92]. However, increased levels of Tregs have been shown to be associated with increased survival in other cancer types, suggesting that, like the mΦ, this immune cell type has different phenotypes[93–95]. The diverse roles Tregs have on cancer is largely attributed to the dynamic effect TGFβ has in the generation and function of Tregs. TGFβ production is heavily dependent upon the surrounding microenvironment[96], and widespread clearance of apoptotic cells profoundly upregulates TGFβ1 within the local microenvironment, perhaps contributing to expansion of pro-metastatic and anti-inflammatory Tregs in the tumor microenvironment.

Inflammation is known to be a hallmark of cancer[97]. Tissues characterized by chronic inflammation generally exhibit a high cancer incidence[98]. This is probably due to the unresolved chronic immune response that mimics failed wound healing often seen in the tumor microenvironment where there are many cells with immunosuppressive activity[99] and the development of a pro-tumorigenic niche develops (reviewed in[100]). Tumors have often been likened to ‘wounds that do not heal’[101]. Expression signatures of chronic inflammation and expression signatures of wound healing are prominently expressed at developmental stages in which cell death and efferocytosis are prominent, such as the mammary gland during post-partum involution. Similarly, wound healing expression signatures are expressed in the most aggressive tumors.

Postpartum Involution and the Pro-Metastatic Landscape: Potential Therapeutic Targets

During pregnancy, the mammary gland undergoes many changes which result in an expanded tissue capable of supporting milk production. While it is possible that the elevated growth hormone levels and enriched blood supply of the breast during pregnancy and lactation could provide a fertile environment for breast cancers to progress. However, breast cancers diagnosed during pregnancy do not correlate with a worse overall survival when compared to breast cancer diagnosed in age-matched women without a previous pregnancy[74]. In contrast, post-partum breast cancers (ppBCs), those diagnosed 2–5 years following a full-term pregnancy, are more invasive, more likely to be diagnosed as metastatic disease, and are associated with decreased disease free survival when compared to age matched women who have never been pregnant[102–104]. Collectively, these studies indicate that post-partum events within the breast are driving forces for the aggressive nature of ppBCs. Seminal studies by Schedin and colleagues demonstrated that human breast cancer cells grow and invade more rapidly within mammary fatpads of post-partum mice as compared to nulliparous mice. The post-partum mammary microenvironment was rich in cyclooxygenase 2 (COX-2) and fibrillar collagen. Importantly, inhibition of COX-2 using non-steroidal anti-inflammatory drugs (NSAIDs) reduced invasion and metastasis in a mouse model of ppBC[38, 45]. While NSAIDs have produced inconsistent results in studies examining breast cancer risk and relapse[105–108], postpartum status was not included as a variable in these studies.

The profound scale of efferocytosis occurring in the post-partum breast supports the idea that efferocytosis-induced expression of immune suppressive wound healing cytokines could amplify the pro-metastatic landscape of tumors existing therein. This notion was supported by results demonstrating that MerTK- dependent efferocytosis in the post-partum mammary gland promotes production of wound healing cytokines which stimulate tumor cell metastatic spread to the lungs. Genetic models of MerTK loss displayed impairment of efferocytosis during postpartum involution in mammary epithelia and in tumors existing therein[39], and a stark reduction in the levels of immune suppressive and wound healing cytokine signature seen during involution[39, 109]. Importantly, blockade of post-partum TGFβ1 reduced lung metastases in mouse models of ppBC to levels seen in tumor-bearing virgin mice. A similar study targeting IL-10 resulted in reduced tumor growth in postpartum mice when compared to nulliparous mice, although metastasis was not evaluated[110].

In considering the potential risks associated with blocking efferocytosis as a potential tumor treatment strategy, it is important to weigh the risks associated with necrotic cell lysis of dying cells, inflammation, tissue damage, and autoimmunity[39, 109]. As an illustration of this point, failure of post-partum efferocytosis in the mammary gland causes inflammation and scarring that interferes with future lactation[109]. With this in mind, it will be critical to identify the optimal therapeutic window for targeting for blockade of efferocytosis. Since blocking MerTK lowers expression levels of wound healing cytokines, similar to what is seen in the non-pregnant population, this would create an environment where the tumor cell is less likely to metastasize and escape immune targeting. Furthermore, MerTK promotes expression of programmed cell death ligand 1(PD-L1)[47], an immune checkpoint ligand commonly expressed on tumor cells to antagonize CD8+ T cells. Thus, blocking MerTK could also play a more direct role in promoting an anti-tumor immune attack by reversing the immunosuppressive capabilities of the tumor cell itself. Several MerTK inhibitors have been designed and show promise in treating diseases, including cancer. These drugs include UNC2025, UNC569, and UNC2881[111–113].

Future Directions & Concluding Remarks

While the postpartum mammary gland serves as an excellent model for studying the role of efferocytosis in tumor progression, it is limited as it primarily addresses the aggressive and metastatic nature of postpartum breast cancers. Nonetheless, this model has revealed that clearance of dying cells creates a tumor microenvironment that supports metastatic spread. Expanding this idea beyond the breast, it is plausible that the process of efferocytosis may reveal the limitations of using cytotoxic therapies, such as chemotherapy, to treat cancer. Since cytotoxic therapies result in widespread cell death and subsequent efferocytosis, it is possible that the immune response might support tumor recurrence and metastasis.

It is evident that understanding all aspects of the immune response will be important for finding innovative and effective ways to prevent, treat, and cure cancer. Efferocytosis will need to be considered as immunotherapies are expanded and utilized.

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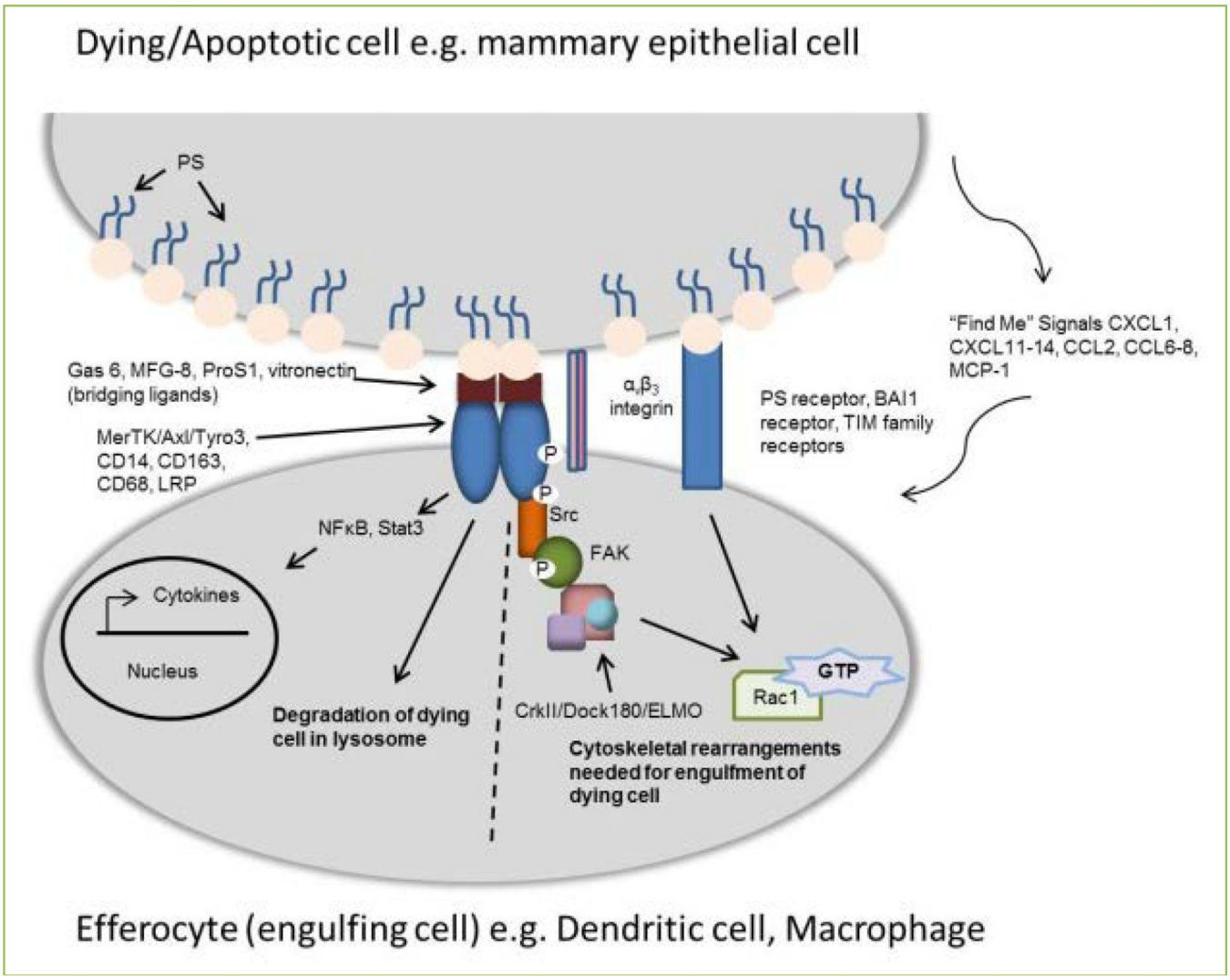

Figure 1.
Important players in efferocytosis.

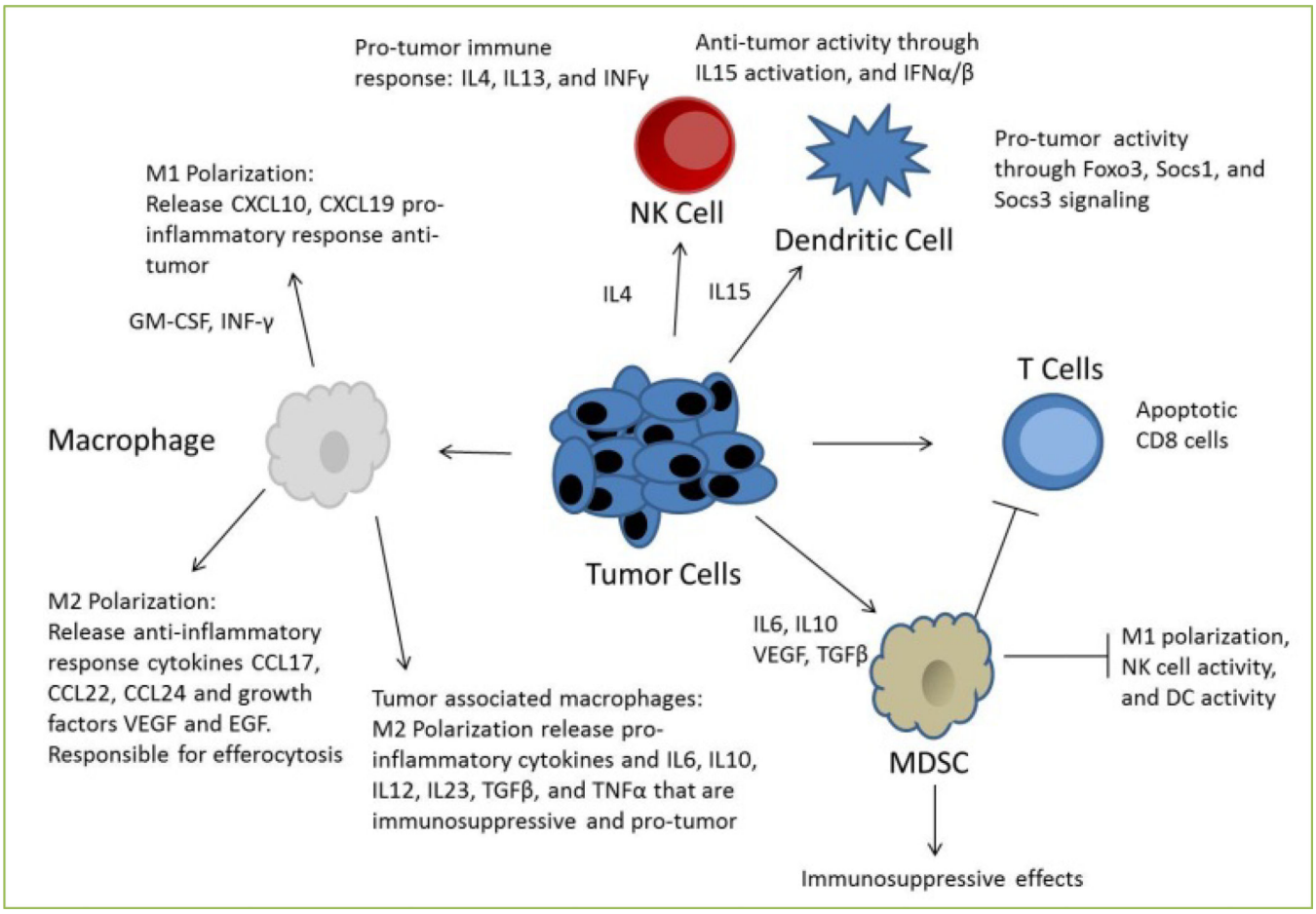

Figure 2.
Immune cells in tumor progression.