Immunometabolism: Unveiling the Multifaceted Role During Efferocytosis

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Abstract. Chemotherapy and radiotherapy stand out as first-line therapeutic approaches for the treatment of different types of tumors. However, these antitumor therapies lead to an accumulation of apoptotic cells within the tumor microenvironment. The removal of apoptotic bodies in homeostatic situations and sterile inflammation is primarily performed by macrophages and Dendritic Cells (DCs), leading to the production of anti-inflammatory mediators and activation of Treg cells. Recent therapeutic approaches propose inhibition of efferocytosis as a promising alternative for tumor treatment. However, systemic blockade of efferocytosis may impact the clearance of dead cells in various tissues, favoring the release of DAMPs and the development of autoimmunities. Understanding the activation of metabolic pathways during the phagocytosis of apoptotic tumor cells could assist in reprogramming DCs towards an immunogenic profile, favoring the activation of antitumor response mediated by CD4+ and CD8+ T cells. This article reviews the interplay between tumor microenvironment, immunometabolism, and efferocytosis. Tumors exhibit rapid metabolic reprogramming, adapting to a hostile environment while evading immune surveillance. Metabolic plasticity allows tumors to redirect pathways and utilize by-products to support proliferation. The tumor microenvironment fosters immunosuppression, inhibiting immune cell functions and promoting an anti-inflammatory state. Efferocytosis, the clearance of apoptotic cells, induces metabolic alterations in phagocytes, influencing their activation. While apoptotic tumor cells promote a tolerogenic phenotype in phagocytes, inhibiting antitumor responses, blocking efferocytosis systemically presents challenges due to its physiological role in tissue homeostasis. Understanding the metabolic pathways activated during efferocytosis of apoptotic tumor cells represents a promising therapeutic approach. Reprogramming immune cells, such as DCs, towards an immunogenic state could enhance antitumor responses without compromising the clearance of non-tumor cells. This nuanced approach may offer novel strategies in cancer therapy, targeting immunometabolic pathways to bolster antitumor immunity while maintaining tissue homeostasis.

Keywords. Immunometabolism, tumor microenvironment, dendritic cells, phenotype.

1. Introduction

Chemotherapy and radiotherapy stand out as first-choice therapeutic approaches for the treatment of different types of tumors. However, these antitumor therapies lead to an accumulation of apoptotic cells within the tumor microenvironment [1]. It is known that the removal of apoptotic bodies in homeostatic situations and sterile inflammation is carried out primarily by macrophages and Dendritic Cells (DCs) and leads to the production of anti-inflammatory mediators and activation of Treg cells. Although recent therapeutic approaches propose the inhibition of efferocytosis as a promising alternative for the treatment of tumors. However, systemic blockade of efferocytosis can impact the clearance of these dead cells in different tissues, favoring the release of DAMPs and the development of autoimmunities [2]. Since several studies have shown the direct correlation between cellular metabolism and the activation of cells of the immune system, understanding the activation of metabolic pathways during the phagocytosis of apoptotic tumor cells could help in the reprogramming of DCs to an immunogenic profile, favoring the activation of

antitumor response mediated by TCD4+ and TCD8+ cells.

2. Bibliographic review

2.1 Tumors and the immune system

Tumors have a rapid reprogramming of metabolism, maintaining anabolic demands and creating an environment of hypoxia, acidification and absence of important nutrients [3]. They can change their energetic demands to adapt to this hostile environment while at the same time causing barriers to the body's immunosurveillance [4]. Vriens et al observed the desaturation of fatty acids to produce unusual chains, such as the biosynthesis of sapienate from palmitate in liver and lung tumor cells, highlighting the heterogeneity of fatty acid metabolism in cancers [5]. Aspartate metabolization – through an increase in the aspartate/glutamate transporter – can be used in the case of glutamine deprivation in the tumor environment as a metabolic alternative, as mentioned by Tajan et al [6].

Tumor metabolic plasticity allows the redirection of several metabolic pathways and the use of byproducts to support other routes, as in the case of the urea cycle, which is deregulated in tumor cells, producing excess ammonia [7][8]. The alteration in the urea cycle is used by tumors to generate mutations and increase cell proliferation, using the synthesis of pyrimidine and amino acids, sustaining tumor progression [9]; however, on the other hand, it generates biomarkers that can serve as a therapeutic target for immune checkpoint therapy (ICT) due to the high mutation rates. The tumor microenvironment (TME) turns out to be immunosuppressive, being capable of inhibiting the functions of immune cells, as occurs with the greater expression of PD-L1 in tumor memraban, which interacts with PD-1 of T cells, inhibiting them [10]. One way this occurs is through competition for glucose between immune cells and the tumor, in addition to the release of lactate by tumors, resulting from glucose metabolization (

Fig. **1**).

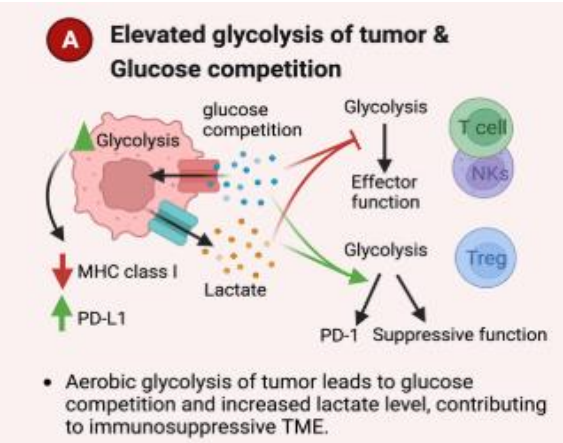

Fig. 1 - Competitive relationship between cells in the TME for glucose [11].

2.2 Immunometabolism during efferocytosis

Apoptosis is a mechanism of programmed cell death that occurs physiologically during tissue renewal and remodeling. However, in pathological events such as infectious processes and in the tumor environment, there is an intense accumulation of apoptotic cells in tissues [12]. During the beginning of the cell death process by apoptosis, cells begin to release soluble mediators, such as ATP, UTP, CXCL1, lysophosphatidylcholine, and sphingosine-1-phosphate, known as “find me” signals, which are responsible for attracting phagocytes present in the tissue to begin the phagocytosis process of these dead cells [13][14]. In addition to the “find me” signals, apoptotic cells also begin to express “eat me” signals on their membrane, mainly phosphatidylserine (PtdSer), a phospholipid that is found mainly at the internal interface of the plasma membrane of healthy cells, but which it is quickly exposed to the external portion of the membrane before the plasma membrane integrity is lost [15][16]. The recognition of apoptotic cells by phagocytes, through “eat me” signals, can occur through different receptors that allow direct interaction of PtdSer, such as TIM4, Stablin-2, and BAI1; or even, through receptors such as the TAM receptor family (Tyro-3, Axl and Mer), which require the help of bridge molecules, such as GAS6 and Protein S, to recognize PtdSer expressed by apoptotic cells [17][18][19]. In addition to the “find me” and “eat me” signals, cells undergoing apoptosis have a decrease in the expression of “don't eat me” signals, such as CD31 and CD47, which are molecules expressed by healthy cells to prevent their mistaken phagocytosis [20][21].

The internalization and digestion of dead cells is carried out both by professional phagocytes, such as macrophages and DCs, as well as by nonprofessional phagocytes, such as epithelial cells [22]. In this context, DCs stand out for being the main phagocytes capable of establishing the communication link between innate and adaptive immunity [23]. It is known that during an infectious process, the interaction and degradation of pathogenic agents by DCs make these cells have an immunogenic profile; that is, these cells increase the expression of molecules such as MHCII, CD80, CD86, and CCR7, as well as the production of inflammatory mediators, such as IL-1, IL-6, IL-8, IL-12p40 and TNF-α [24][25]. However, the interaction and degradation of apoptotic bodies leads to the differentiation of a tolerogenic profile in these cells, with low expression of MHCII, CD80, CD86, and CCR7, and the production of mediators with an anti-inflammatory profile, such as PGE2, TGF-β and IL-10 [26]. This tolerogenic microenvironment is essential for the maintenance of tissue homeostasis, as it favors the differentiation of T-regulatory lymphocytes (Treg) and prevents the recognition of self-antigens by autoreactive effector lymphocytes [27].

During the digestion of an apoptotic body, there is an accumulation of nutrients inside the

phagolysosome, leading to changes in the cellular metabolism of macrophages. Recently, it was demonstrated that arginine, derived from apoptotic cell digestion, appears to play a key role in actin polymerization, which is known to be necessary for the internalization of subsequent apoptotic cells [28]. Furthermore, it was demonstrated that the production of PGE2, as well as cytokines, such as TGF-β1, IL-10, and IL-13, during the efferocytosis of these apoptotic bodies by macrophages, is directly related to the increase in lipid content resulting from the digestion of apoptotic body [29]. Furthermore, it is known that the internalization of apoptotic cells leads to an increase in the expression of the transmembrane protein SLC2A1 (solute carrier 2A1), the carrier responsible for glucose uptake [30]. The positive regulation of this transporter, SLC2A1, leads to an increase in glucose uptake, favoring the activation of glycolytic metabolism, resulting in an increase in lactate production, which together with other mediators polarizes macrophages towards an anti-inflammatory profile, M2 [30]. On the other hand, Zhang and colleagues correlated the tolerogenic profile of macrophages, after efferocytosis of apoptotic cells, with the activation of the β-oxidation pathway and mitochondrial respiration [31]. As a result of the activity of these metabolic pathways, the authors showed that there is an increase in NAD+ production, one of the precursors for the production of IL-10, which has an anti-inflammatory profile and is involved in tissue repair [31]. However, to date, little is known about the impact of efferocytosis on the metabolism of DCs and how metabolic activation sustains the tolerogenic profile of this phagocyte after the internalization and digestion of apoptotic bodies in the tumor microenvironment.

2.3 Efferocytosis in the tumor microenvironment and immunometabolism

Tumor cells have several mechanisms to escape the immune system, such as evasion of recognition by immune cells and modifications in the transcription and translation process of anti-apoptotic proteins, such as Bcl-2 and BCL-xL [32]. Regarding metabolic changes in phagocytes in the tumor microenvironment (TME), it has been demonstrated that Wnt5a secretion by murine melanoma cells is capable of inducing the production of anti-inflammatory mediators by DCs and Treg activation [33]. Treatment of these DCs with etomoxir, a Cpt1a (Carnitine palmitoyl transferase I) blocker that inhibits β-oxidation, resulted in the reversal of the tolerogenic profile of these DCs, leading to an increase in the production of inflammatory mediators, activation of CD8+ T lymphocytes and a decrease in tumor mass [33].

Despite the ability of tumor cells to evade the immune system, the therapeutic options available for the treatment of tumors, such as chemotherapy and radiotherapy, act by inducing different patterns of death in these cells, such as apoptosis, necrosis, necroptosis or pyroptosis [34]. Although some of these chemotherapy drugs are capable of inducing an immunogenic death pattern, such as necrosis, most therapeutic approaches act by inducing apoptosis of tumor cells [35]. The efferocytosis of these apoptotic tumor cells by phagocytes promotes a tolerogenic microenvironment, with high production of IL-4, IL-10, IL-13, TGF-β, and PGE2, which prevents an efficient antitumor response [36]. Since DCs play a crucial role in the interface between innate and adaptive immunity, the immunosuppressive profile acquired after efferocytosis of apoptotic tumor cells may cause a reduction in the antigen-presenting capacity of this phagocyte and, consequently, reduce the activation of antitumor T cells. Given this, blocking the recognition of apoptotic cells by phagocytes in the TME has proven to be an interesting therapeutic option [37]. Kang and colleagues demonstrated that blocking efferocytosis using annexin V is capable of increasing tumor immunogenicity using an experimental cervical carcinoma cancer tumor model [38]. Furthermore, another study demonstrated that blocking the efferocytosis of prostate tumor cells, using anti-PtSer antibodies, promotes the activation of tumor-associated macrophages, in an inflammatory profile (M1 macrophages), in addition to favoring the maturation of DCs and activation of CD8+ T cells in the TME [39].

However, this approach becomes challenging since blocking efferocytosis using systemic administration can compromise the physiological removal of apoptotic bodies in different tissues, leading to the progression of cell death, with the release of intracellular contents, inflammation, and, consequently, the development of autoimmunities [40]. Therefore, understanding the metabolic pathways activated during the efferocytosis of apoptotic tumor cells may be a promising therapeutic approach, as it enables the reprogramming of tolerogenic DCs to an immunogenic profile, making them capable of inducing an anti-tumor response mediated by T lymphocytes. , without affecting the clearance of apoptotic cells in different tissues.

3. Conclusion

In summary, the tumor microenvironment is immunosuppressive and tumors have several mechanisms to suppress immune cells, either through the secretion of anti-inflammatory compounds or through nutritional competition. Immune cells, in turn, when efferocytosing a tumor cell, have their metabolism shaped to maintain a tolerogenic profile supported by specific metabolic pathways, as in the case of β-oxidation and glycolytic metabolism for macrophages. Cells in this state express soluble molecules and mediators that reduce their activation capacity.

As some of the treatment alternatives, we can talk about the possibility of blocking

phosphatidylserine, to avoid the efferocytosis of tumor bodies or the metabolic reprogramming of immune cells - such as DCs (bridge between innate and adaptive immunity) - to change them into an immunogenic state, which would be the most appropriate as it involves the subsequent activation of T lymphocytes, without blocking the efferocytic process of non-tumor cells.

4. References

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