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Review

The impact of metabolic reprogramming on dendritic cell function

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ABSTRACT

Dendritic cells (DCs) are antigen-presenting cells with the ability to activate naïve T cells and direct the adaptive cellular immune response toward a specific profile. This is important, as different pathogens demand specific "profiles" of immune responses for their elimination. Such a goal is achieved depending on the maturation/activation status of DCs by the time of antigen presentation to T cells. Notwithstanding this, recent studies have shown that DCs alter their metabolic program to accommodate the functional changes in gene expression and protein synthesis that follow antigen recognition. In this review, we aim to summarize the data in the literature regarding the metabolic pathways involved with DC phenotypes and their functions.

1. Introduction

Dendritic cells (DCs) play a pivotal role in the maintenance of immune system functioning, as they are specialized antigen-presenting cells (APCs) that regulate the activation and upkeep of T lymphocyte responses [1–3]. After binding with pathogen-associated molecular pattern molecules (PAMPs), damage-associated molecular pattern molecules (DAMPs) and pattern recognition receptors (PRRs), such as toll-like receptors (TLRs) [4], a range of signaling pathways is activated. Additionally genetic changes occur, leading to cytokine and chemokine production. Hence, DCs express Major Histocompatibility Complex (MHC) class I or II and costimulatory molecules, in addition to producing cytokines that lead to adaptive immune responses [5–7].

TLR signaling - one of the main pathways for DC activation - for example, stimulates metabolic reprogramming that is essential for the complete DC maturation and the perfect performance of its functions. This metabolic reprogramming happens through switching over mitochondrial oxidative phosphorylation (OXPHOS) to aerobic glycolysis [8]. After switching to glycolytic metabolism, TLR-activated DCs become more dependent on glucose for their survival and functioning. Thus, it is possible that this metabolic pathway also plays a crucial role in the lifespan of DCs [8]. Hence, the activation of protein kinase mammalian target of rapamycin (mTOR) in TLR-activated DCs reduces DC survival due to a glucose consumption limitation [9]. Furthermore, mTOR inhibits autophagy in DCs, contributing to its antigen presentation function [10].

Abbreviations: AGE, advanced glycation end products; AICAR, 5-Aminoimidazole-4-carboxamide ribonucleotide; AMPK, 5′ adenosine monophosphate-activated protein kinase; APC, antigen-presenting cell; Atg7, autophagy-related gene 7; ATP, adenosine triphosphate; ATRA, all-trans retinoic acid; BMDC, bone marrow-derived dendritic cells; CCR7, C-C motif chemokine receptor 7; CD, cluster of differentiation; COX-2, cyclooxygenase-2; CTL, cytotoxic T lymphocyte; DAMPs, damage-associated molecular pattern molecules; DC, dendritic cell; DHA, docosahexaenoic acid; EAE, experimental autoimmune encephalomyelitis; E-FABP, epidermal-type fatty acid binding protein; ER, endoplasmic reticulum; GLUT, glucose transporter; GM-CSF, granulocyte-macrophage colony-stimulating factor; GSK3, glycogen synthase kinase 3; HDL, high density lipoprotein; HIF1α, hypoxia inducible factor 1 alpha; IL, interleukin; LDL, low density lipoprotein; iNKT cells, Invariant natural killer T; ILT, Immunoglobulin-like transcript; LPS, lipopolysaccharide; mDCs, myeloid dendritic cells; MMDCs, monocyte-derived dendritic cells; mTOR, protein kinase mammalian target of rapamycin; mTORC1, mammalian/mechanistic target of rapamycin complex 1; mTORC2, mammalian/mechanistic target of rapamycin complex 2; NADPH, glyceraldehyde-3-phosphate dehydrogenase; NF-kB, nuclear factor kappa B; NKT, natural killer T cell; Nrf2, Nfe2l2 tm1Ywk; OXPHOS, oxidative phosphorylation; PAMPs, Pathogen-Associated Molecular Patterns; PBMC, peripheral blood mononuclear cells; PFKFB, 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K/AKT, phosphatidylinositol 3′-kinase-protein kinase B; PPARγ, peroxisome proliferator-activated receptor gamma; PRR, pattern recognition receptors; RALDH, retinaldehyde dehydrogenase; RAPA, rapamycin; SIRT1, sirtuin 1; T2DM, type 2 diabetes mellitus; shRNA, short hairpin RNA; siRNA, short interfering RNA; TLR, toll like receptor; TNF-α, tumor necrosis factor-alpha; α-GalCer, α-galactosyl-ceramid

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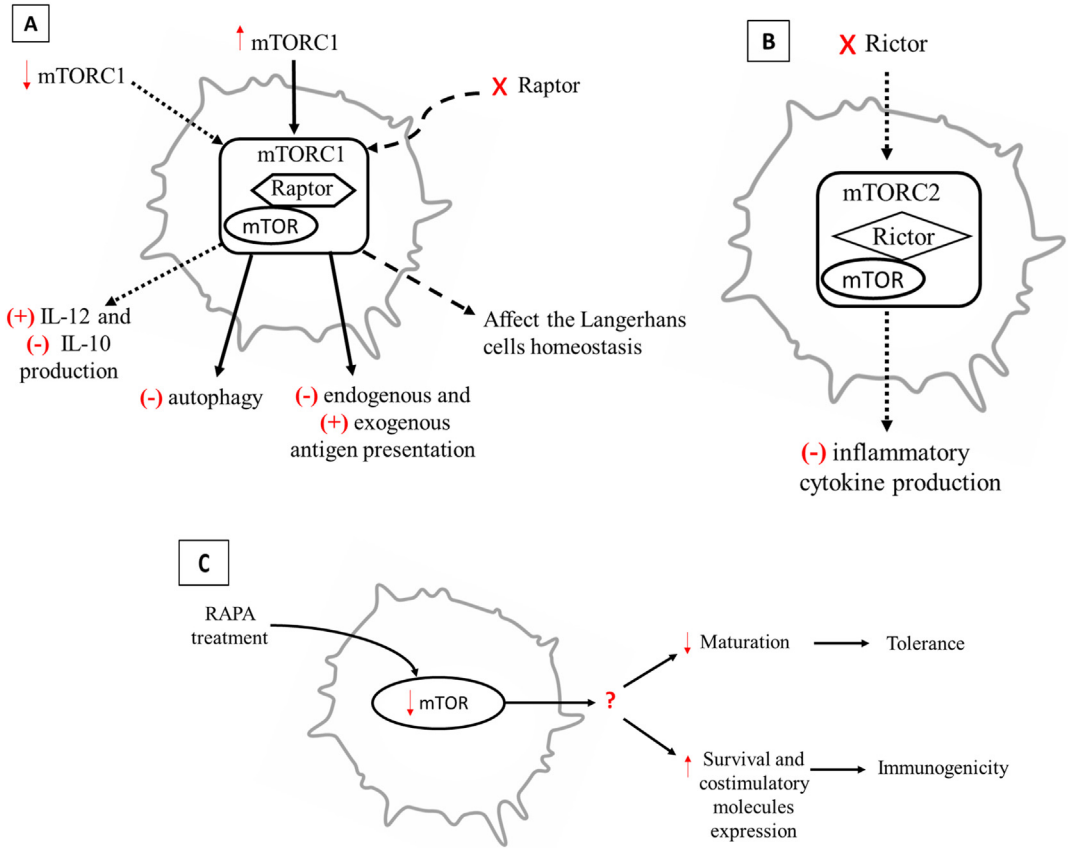

Fig. 1. mTOR signaling pathway is involved with different aspects of DC functioning, which consists of two complexes – mTORC1 and mTORC2. (A) The inhibition of mTORC1 by RAPA promotes an alteration in DC cytokine production. In contrast, the stimulation of mTORC1 activity results in decreased autophagy and control of antigen processing. In addition, the deletion of Raptor component affects mouse Langerhans cell homeostasis (B) The deletion of Rictor – the component of mTORC2 – on DCs lead to decreased inflammatory cytokines. (C) The RAPA-treatment of DCs inhibits mTOR, resulting in either the induction of tolerogenic DCs due to impaired maturation or augmented immunogenicity due to an increase in DC survival and costimulatory molecules expression. ↑ Indicates increased function/activity; ↓ indicates decreased function/activity; x indicates deletion; (+) indicates stimulation and (−) indicates impairment.

Thus, DC survival and development depend on a complex network of metabolic pathways that readily respond to intrinsic and extrinsic signals. In addition, changes in such pathways lead to the production of different molecules that are necessary for cell activation and immune responses [11]. Moreover, the manipulation of DC metabolism could become a therapeutic strategy, as long as the immunogenic DC profile can be controlled [12].

In the first part of this review, we concentrate on the data in the literature regarding four metabolic pathways in DCs: mTOR signaling; autophagy; glucose metabolism; and fatty acid metabolism. Then, to understand and interpret the importance of metabolism to DC functions, we approach its modulation through the control of the metabolism. Such modulations could contribute to the development of new drugs.

2. Dendritic cells metabolism

In this section of the review, we will discuss four metabolic pathways critical to DC activation. The findings described here provide a better understanding of how these mechanisms control DC functions.

2.1. mTOR signaling in DCs

In order to go from inactive/resting cells to functional antigen presenting cells, DCs experience serious structural and metabolic modifications. These processes are mainly orchestrated by the mTOR [13]. All functions coordinated by the mTOR network are divided between two complexes, mTORC1 and mTORC2, depending on with what proteins mTOR interacts [14]. mTORC1 and mTORC2 functions depend on the key components of Raptor and Rictor, respectively [15].

After the encounter with PAMPs, cytokines like FMS-related tyrosine kinase 3 ligand (Flt3L), when bound to the appropriate receptors on DCs, activate a cascade of signaling pathways resulting in activated mTOR. This activation promotes protein synthesis and cell growth. In plasmacytoid DCs and $CD8^+$ DCs, Flt3L is favored over other cytokines to induce cell development. Rapamycin (RAPA), a natural antifungal metabolite with immunosuppressive attributes [16], can inhibit the effect of Flt3L [17].

In some intriguing reports, RAPA-treated-DCs/APCs induced $CD4^+$ $CD25^+$ $Foxp3^+$ regulatory T cell expansion and were unable to stimulate $CD4^+$ $CD25^-$ T cell expansion [18]. Similarly, RAPA decreased the expression of costimulatory molecules in bone marrow-derived DC (BMDCs) [19–21] and prevented maturation of these cells, even after anti-CD40 stimulation [22]. However, rapamycin could also induce DC immunogenicity. Amiel et al. (2012) demonstrated that TLR-activated-DCs treated with RAPA exhibited increased survival and expressed high levels of costimulatory molecules for a longer time period compared to DCs activated in the absence of the mTOR inhibitor [9].

In mice, deficiency of mTORC1-component Raptor resulted in an increased number of splenic $CD8^+$ DCs and intestinal $CD11c^+CD11b^+$ DCs. The weakened function of mTORC1 on intestinal DCs led to an anti-inflammatory intestinal environment [23]. In addition, Raptor deletion affected Langerhans cell homeostasis and induced reduction of their number in mouse skin [15]. Interestingly, the inhibition of mTORC1 by RAPA increased IL-12 production and decreased IL-10 production by myeloid DCs (mDCs) [24]. The inhibition of mTORC2