Role of metabolic pathways and sensors in regulation of dendritic cell-driven T cell responses

Pelgrom, L.R.

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Dendritic cells are what they eat: how their metabolism shapes T helper cell polarization

Thiago A. Patente, Leonard R. Pelgrom, Bart Everts

Review
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Abstract

Dendritic cells (DCs) are professional antigen-presenting cells that play a crucial role in the priming and differentiation of CD4+ T cells into several distinct subsets including effector T helper (Th) 1, Th17 and Th2 cells, as well as regulatory T cells (Tregs). It is becoming increasingly clear that cellular metabolism shapes the functional properties of DCs. Specifically, the ability of DCs to drive polarization of different Th cell subsets may be orchestrated by the engagement of distinct metabolic pathways. In this review, we will discuss the recent advances in the DC metabolism field, by focusing on how cellular metabolism of DCs shapes their priming and polarization of distinct Th cell responses.

Introduction

Dendritic cells (DCs) are professional antigen-presenting cells that play a crucial role in the development of adaptive immune responses by governing the priming and maintenance of CD4+ and CD8+ T cell responses. Classically, DCs reside in a quiescent state in peripheral tissues acting as sentinels of the immune system. Upon capturing pathogen-derived antigens or detecting tissue- derived danger signals, DCs become activated and migrate to draining lymph nodes (LNs). Herein, processed antigens are presented to T cells to initiate an adaptive immune response. Depending on the DC subset involved and the nature of the activation signal received, DCs control the priming and differentiation of CD4+ T cells into several distinct subsets including effector T helper (Th) 1, Th17, and Th2 cells, as well as regulatory T cells (Tregs) [1].

It is becoming increasingly clear that immune cell activation and function, including that of DCs, are coupled to, and underpinned by, profound changes in cellular metabolism [2, 3]. There is a growing body of literature showing that acquisition of an immunogenic phenotype by DCs, characterized by enhanced migratory-capacity and overall T cell priming-capacity, is accompanied by, and dependent on a switch from oxidative phosphorylation (OXPHOS) to glycolysis [4-13]. In addition, more recent studies show that the ability of DCs to drive polarization of different Th cell subsets may be underpinned by engagement of distinct metabolic pathways. In this review, we will discuss these recent advances in the DCs metabolism field, by specifically focusing on how DC metabolism shapes the priming and polarization of distinct CD4+ T cell responses. For a discussion of the metabolic requirements of DCs to shape CD8+ T cell responses please refer to the following recent studies/ reviews [14-18].

Metabolic regulation of MHC II-mediated antigen presentation and costimulation

A prerequisite for priming of CD4+ T cell responses is antigen presentation in the context of MHC II. TLR-driven upregulation of surface expression of MHC II by murine DCs has been shown to depend on glycolysis [5, 9, 19]. DC activation involves acidification of the lysosomal compartment, which is required for efficient generation of peptides for loading into MHC II and that is dependent on activity of ATP-driven proton pumps [20]. In addition, TLR-driven surface expression of MHC II by DCs is primarily thought to arise from redistribution of molecules from endocytic compartments through an energy-dependent process called lysosome tubulation [21, 22]. Therefore, it is conceivable that glycolysis is required for efficient upregulation of surface expression of MHC II because it serves as a key source of ATP to support these two steps in antigen presentation (Figure 1). Mammalian target of rapamycin complex 1 (mTORC1)

is an important nutrient sensor that promotes glycolysis, anabolic metabolism and translation [23]. Consistent with a role for glycolysis in regulation of MHC II expression, mTORC1 is activated in DCs upon TLR stimulation [16] and is implicated in TLR-induced MHC II surface expression by DCs [19, 24], through its ability to promote lysosome acidification and tubulation [24, 25]. However, constitutive activation of mTORC1 in murine DCs has been shown to result in impaired MHC II expression, via mTORC1-driven suppression expression of complex transactivator (CIITA), a protein that directly drives the expression of MHC II [26]. In this scenario, as a consequence of constitutive mTORC1 activation, low CIITA expression already in immature DCs leads to reduced synthesis of MHC II molecules and thereby lower levels of the molecules on the surface on DCs following TLR stimulation, despite the promotion of lysosome acidification and tubulation [25]. Finally, mTORC1 may be involved in shaping the antigen repertoire loaded into MHC II. In immature DCs, autophagy – a process classically activated under bioenergetic stress that degrades cellular components to restore cellular energy levels – is thought to allow for cytosolic proteins to enter endosomes and thereby the MHC II-restricted presentation pathway [27]. Upon TLR stimulation, mTORC1 activity is increased and is likely to reduce basal levels of autophagy in activated DCs to limit endogenous but favor exogenous antigen presentation [28]. Together, this implicates glycolysis and mTOR signaling in the regulation of peptide-loading into, and surface expression of MHC II (Figure 1), although to what extent mTOR regulates these processes through control of glycolysis or other metabolic pathways is currently unclear.

In addition to antigen presentation in the context of MHC II, the upregulation of co-stimulatory molecules is also essential for efficient priming of Th cell responses by DCs. TLR-induced CD40 and CD86 expression has been shown to critically depend on glycolysis [5, 9]. In line with this observation, blocking glycolysis in TLR-activated DCs reduced their overall CD4+ T cell-priming capacity [5]. Mechanistically, it was found that increased glycolysis, by fueling the TCA cycle, supports *de novo* synthesis of fatty acids for the expansion of the endoplasmic reticulum (ER) and Golgi allowing for effective translation of those molecules [5]. This highlights the importance of anabolic metabolism fueled by glycolysis to support expression of costimulatory molecules by DCs that is required for effective priming of effector CD4+ T cell responses. Yet to what extent Th polarization by DCs is controlled by metabolism through regulation of expression of MHC II and costimulatory molecules is unclear at this point.

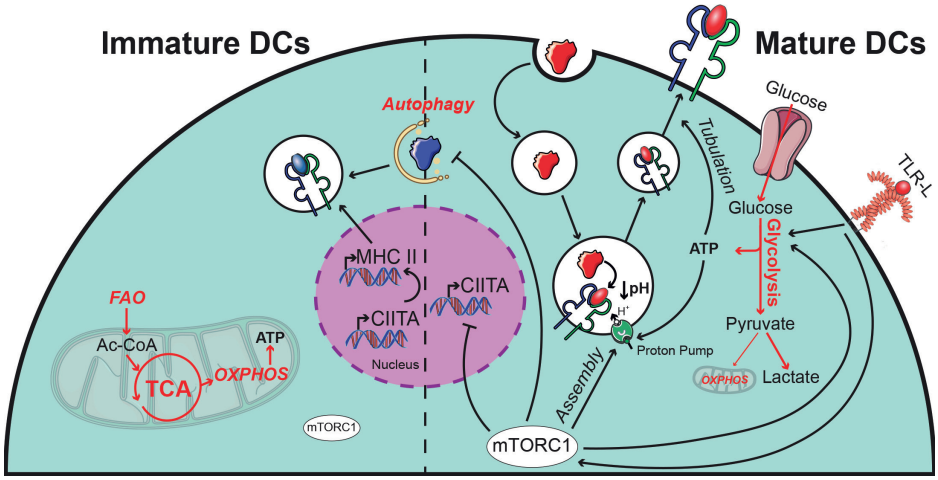

Figure 1. Role of mTOR and cellular metabolism in the regulation of MHC II-dependent antigen presentation by DCs.

Metabolic pathways and upstream signaling pathways regulating these are indicated in red and black, respectively. The left and the right sides of the figure depict how MHC II-dependent antigen presentation is metabolically regulated in unactivated (immature) and TLR-stimulated (mature) DCs, respectively.

Metabolic regulation of DC-driven Th1 polarization

A key Th1-polarizing cytokine produced by DCs is IL-12 [29]. IL-12 expression by DCs has been shown to critically depend on glycolysis by supporting the *de novo* synthesis of fatty acids for the expansion of the endoplasmic reticulum (ER) and Golgi required for effective translation [5]. Concordantly, inhibition of glycolysis in murine LPS-activated DCs impaired their ability to promote IFN-γ secretion by CD4+ T cells. Moreover, type 1 conventional DCs (cDC1s), the primary DC subset that produces IL-12 and drives Th1 responses *in vivo* [30, 31], are more glycolytic than cDC2s [15]. Despite the importance of mTORC1 in driving glycolytic metabolism and translation, interfering with mTORC1 signaling has been shown to augment IL-12 secretion [32-34]. In line with this, hyperactivation of mTORC1 in CD11c+ cells, by ablation of its negative regulator tuberous sclerosis 1 (TSC1), resulted in downregulation of *il12a* and consequently in impaired Th1 priming by BMDCs generated with FLT3L [35]. Presumably this suppressive effect of mTORC1 signaling on IL-12 production is mediated by a an mTORC1-driven negative feedback loop involving IL-10 [33, 36]. Nonetheless, favoring anabolic metabolism, by inactivation of AMP-activated kinase (AMPK), which normally promotes OXPHOS and catabolic metabolism in part by suppressing mTOR activity, increases IL-12 production by DCs [9, 37]. This points toward an important role for anabolic metabolism supported by glycolysis in supporting the ability of DCs to promote Th1 differentiation (Figure 2a).

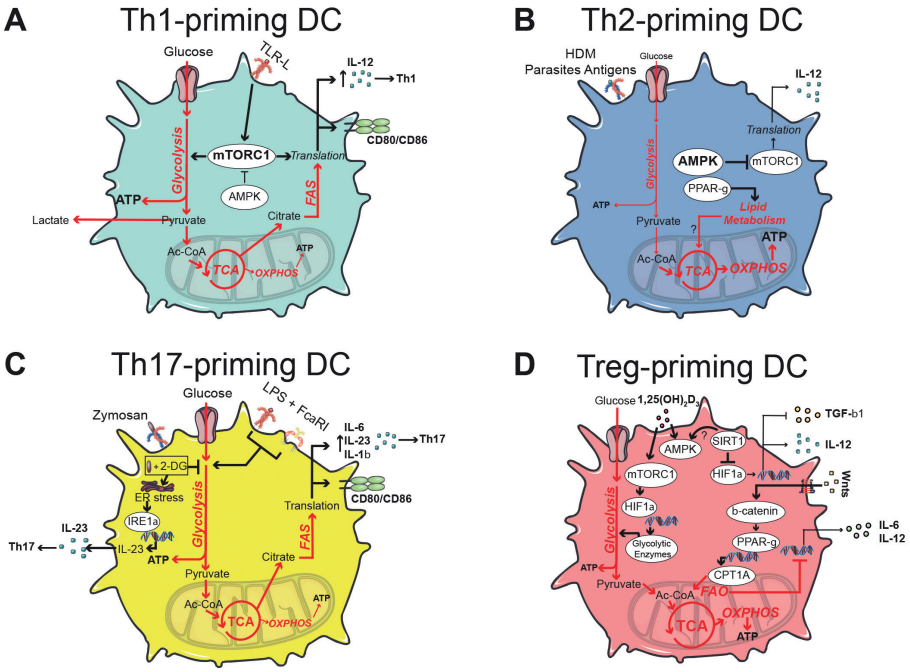

Figure 2. Metabolic characteristics of DCs that prime different Th cells.

Metabolic pathways and upstream signaling pathways regulating these in DCs that prime Th1 (a), Th2 (b), Th17 (c) and Treg (d) responses are indicated in red and black, respectively.

Metabolic regulation of DC-driven Th2 polarization

Despite the evidence that DCs are crucially important for induction of Th2 responses, the nature of the polarizing signals derived from DCs to drive these responses are not fully understood, although reduced TCR signal strength, absence of IL-12 and secretion of type 2 cytokines by other innate type 2 immune cells have been suggested [38, 39]. Likewise, the metabolic properties of Th2-priming DCs are not well defined.

In contrast to activation with LPS, stimulation of DCs with house dust mite extract (HDM), an antigen mixture known to promote DC-dependent Th2 responses in the lung resulting in allergic asthma, was recently found to induce only a mild increase in glycolysis with no loss of OXPHOS over time [19]. This suggests a more catabolic metabolic state of Th2-priming DCs, similar to what has been implied for other cells involved in type 2 immune responses [40]. Consistent with this, increased phosphorylation of AMPK was found in CD11b+ lung cDC2s of mice infected with hookworm that promotes strong Type 2 immune responses in the lung [37]. Moreover, mice with a specific deletion of AMPKα1 in CD11c-expressing cells fail to mount protective Th2 responses

against this parasitic worm infection, suggesting AMPK-driven catabolic metabolism in DCs may be functionally relevant for Th2 priming. This would be supported by the observations that acute mTOR inhibition potentiates Th2 priming by human DCs *in vitro* [41] and that mice with a DC-specific deletion of mTOR have higher circulating titers of type 2 cytokine-dependent antibodies IgE and antigen-specific IgG1, in a model of allergic asthma, although this is not mirrored by an enhanced Th2 response in the lungs [42].

Lipid metabolism, regulated by PPAR-γ, may also play an important role in Th2 priming by DCs. Mice with a deletion of PPAR-γ in CD11c-expressing cells are resistant to induction of allergic asthma [43]. In contrast, stimulation of DCs with PPAR-γ activator rosiglitazone, ameliorates airway inflammation in a mouse model of asthma [44]. In agreement with this, deletion of Sirtuin-1 (SIRT1) in DCs restricts an allergen-induced Th2 response in the lung by activating PPAR-γ [45]. This may indicate that a certain level of PPAR-γ activity is required for Th2 priming by DCs, but strong activation may interfere with this, possibly by rendering DCs tolerogenic [46, 47]. Taken together, these studies provide a first indication that Th2-priming DCs, have a more oxidative metabolic profile dependent on AMPK and low PPAR-γ signaling (Figure 2b). One could hypothesize that this oxidative/catabolic metabolic profile limits high expression of IL-12 and MHC II, thereby favoring Th2 polarization by DCs. However, this link remains to be experimentally addressed.

Metabolic regulation of DC-driven Th17 polarization

The polarization of naïve CD4+ T cells into Th17 cells is driven by TGF-β and IL-6, while IL-23 and IL-1β play a prominent role in the expansion and survival of Th17 cells [48, 49]. Little is known about the metabolic regulation of TGF-β production by DCs. However, both the secretion of IL-6 by murine DCs in response to TLR stimulation [6, 50] and the secretion of IL-23 and IL-1β by human DCs following the combined engagement of TLRs and FCαR [51, 52] seem to be dependent on anabolic metabolism characterized by *de novo* fatty acid synthesis fueled by glycolysis. However, another study found that blocking glycolysis during TLR stimulation increased IL-23 expression by human DCs due to enhanced expression of the ER stress sensor IRE1α [53]. Consistent with this latter observation, treatment of murine DCs with glycolysis inhibitor 2-deoxyglucose (2-DG) can enhance their Th17-priming potential [5] (Figure 2c). These opposing may suggest that the metabolic requirements for cytokine production can be context specific and depend on the DC subset and type of stimulus involved, as has been demonstrated for different TLR ligands in monocytes [54].

The metabolic pathways involved in Th17 differentiation by DCs *in vivo* are not well defined. Mice with a defect in mTORC1 in CD11c-expressing cells, show a

switch toward Th17 instead of Th2 polarization in response to HDM-induced asthma, that is accompanied by changes in the frequency and metabolic profile of lung DCs [42]. This was found to be mediated by inflammatory DCs, that expressed higher levels of IL-23, IL-6, and IL-1β, which the authors postulated to be due to enhanced fatty acid oxidation in these cells. However, it is conceivable that loss of mTORC1-driven IL-10 secretion, that could otherwise suppress expression of these pro-inflammatory cytokines, also contributes to this phenotype [33, 36]. Of note, susceptibility to develop Th17-driven experimental autoimmune encephalomyelitis (EAE), a murine model for multiple sclerosis, was not increased, implying that mTOR in DCs restricts Th17 responses in a tissue-specific manner [42]. Furthermore, DCs in which cholesterol accumulated as a consequence of deletion of ATP binding cassette transporters A1 and G1 (ABCA1 and ABCG1), two transporters responsible for cholesterol efflux, displayed increased secretion of IL-23, IL-6, and IL-1β and a potentiated ability to drive Th17 polarization [55]. The known stimulating effect of cholesterol on pro-inflammatory TLR signaling and inflammasome activation is likely to explain these effects [56]. However, whether cholesterol synthesis and/or regulation of its efflux is a metabolic process general employed by DCs to prime Th17 responses such as following exposure to Th17-priming pathogens is unknown and warrants further investigation.

Metabolic regulation of DC-driven Treg polarization

DCs are also key regulators of maintenance of immune tolerance by governing the development of regulatory T cells (Tregs). Tregs can be induced in the thymus, referred to as thymic-derived Tregs (tTregs), as well as in the periphery (pTregs) or *in vitro* (iTregs) from naïve T cells [57]. A diverse set of mechanisms has been identified through which pTreg and iTreg differentiation from naïve T cells can be induced by DCs, including low costimulatory signal strength, increased expression of IL-10 and TGF-β and enhanced activity of retinaldehyde dehydrogenase (RALDH) and indoleamine 2,3-dioxygenase (IDO) [58, 59]. Now, the metabolic characteristics of tolerogenic DCs and requirements for their tolerogenic phenotype leading to pTreg and iTreg differentiation are also starting to be elucidated.

It has long been appreciated that differentiation of human monocytes toward DCs in the presence of mTORC1 inhibitor rapamycin, generates tolerogenic DCs [60], providing a first indication that inhibition of anabolic metabolism could favor acquisition of a tolerogenic DC phenotype. Consistent with this notion, two recent studies characterizing the metabolic properties of human moDCs rendered tolerogenic with $1,25(OH)_2D_3$ (VitD3) alone [61] or together with dexamethasone [62], reported increased mitochondrial activity evidenced by heightened OXPHOS. In the latter study, acquisition of tolerogenic phenotype

by the DCs was partly dependent on increased FAO [62]. Interestingly, VitD3–DCs additionally displayed increased mTOR/hypoxia induced factor (HIF)-1α-dependent glycolytic rates [61]. This increased glycolysis was functionally relevant as several markers of a tolerogenic phenotype (i.e. reduced expression of costimulatory molecules CD86 and CD80 and increased production of IL-10) was lost by VitD3–DCs in which glycolysis was inhibited [61]. Concordantly, glycolysis inhibition limited their ability to suppress CD4+ T cell proliferation. Interestingly, the observations that these cells show an increased AMPK activation [61] and elevated glucose carbon tracing into the TCA cycle [63], suggest that this increased glycolytic flux, in contrast to immunogenic DCs, may primarily serve a catabolic role by fueling mitochondrial OXPHOS.

Largely consistent with these human DC data, a recent *in vivo* study focusing on the metabolic properties of DCs in tumors [64], a microenvironment that is a well-known to render DCs tolerogenic [65], revealed that these cells displayed increased FAO-dependent OXPHOS. This metabolic shift as well as IDO activity was driven by tumor cell-derived Wnt5a and dependent on β-catenin and PPAR-γ signaling. Importantly, when FAO was blocked in DCs, Wnt5a failed to enhance IDO activity in these cells as well as to instruct them to promote FoxP3+ pTreg differentiation and as a consequence enhanced anti-tumor immunity *in vivo*. Interestingly, a similar β-catenin-PPAR-γ-dependent pathway is required for the maintenance tolerogenic DCs in visceral adipose tissue [66]. This, together with the findings that tolerogenic DCs in mucosal tissues depend on PPAR-γ signaling for RALDH expression and activity [46, 47], points toward a crucial role for PPAR-γ in supporting tolerogenic properties of DCs in various settings (Figure 2d). However, to what extent these PPAR-γ-driven effects are mediated by controlling lipid metabolism remains to be determined.

Conversely, a switch from OXPHOS toward aerobic glycolysis by stabilization of hypoxia induced factor (HIF)-1α, as seen in SIRT1-deficient DCs, redirects pTreg toward Th1 priming by enhancing IL-12 production and reducing TGF-βeta expression [67], providing further support for a key role in catabolic/oxidative metabolism in pTreg induction by DCs. Given the key role for AMPK signaling in promoting this type of metabolism it is tempting to speculate that this kinase is important in DC-driven iTreg and pTreg polarization. The fact that SIRT1 can promote the activation of AMPK, through deacetylation of LKB1 [68], and that VitD3-treated human DCs showed increased AMPK activation [61], would be consistent with this idea and warrants a more direct assessment of the role of AMPK signaling in regulating the tolerogenic properties in DCs. The aforementioned studies have focused on the metabolic requirements for DCs to promote iTreg or pTreg differentiation. To what extent these observations,

can be extrapolated to DC-driven tTreg differentiation in the thymus remains an open question.

Concluding remarks

Ever since the appearance of the first studies focusing on the role of cellular metabolism in DC function about a decade ago, this field has rapidly grown and has provided key novel insights into the metabolic pathways that shape the functional properties of DCs. As reviewed here, a picture is emerging that the metabolic requirements for DCs to drive Th1 and Th17 polarization share similarities in which glycolysis and mTOR-driven anabolic metabolism play a central role. In contrast, Th2 and Treg induction by DCs seem to rely on more oxidative lipid metabolism driven by AMPK and PPAR-γ signaling (Figure 2). This shared dependency on anabolic metabolism by Th1-priming and Th17-priming DCs, and on catabolism by DC-driven Th2 and Treg priming, largely correspond with the respective strong and more muted activation profiles of these DCs. Yet, whether there are specific additional metabolic cues that underpin or instruct DCs to either prime a Th1 versus Th17 response or a Th2 versus Treg response is still poorly understood. It is conceivable that this polarizing instruction is primarily provided by external cues such as cytokines, pathogen or danger signals that through classical signaling cascades drive expression of certain combination of polarizing cytokines by DCs. In this scenario, metabolic sensors, such AMPK and mTOR, integrate signals from these external stimuli with nutrient availability to engage a metabolic program tailored to the bioenergetic and bio-synthetic requirements for DC activation that is needed to prime a specific Th cell response. In this context, certain changes in cellular metabolism would have an essential supportive function, yet not in itself be sufficient for providing instructive signals that shape Th cell polarization by DCs. However, primarily based on studies with T cells and macrophages, the growing realization that certain external stimuli can coopt specific metabolic pathways, enzymes or promote production of particular metabolites in order to dominantly regulate expression of certain cytokines, makes it tempting to speculate that such metabolic regulatory mechanisms are also operational in DCs to actively promote or repress expression of proteins that shape Th cell polarization. More in-depth functional comparison of the upstream metabolic regulators and metabolic pathways in different Th cell-priming DCs will be needed, to determine whether there are unique metabolic programs that underpin and truly drive the ability of DCs to prime distinct Th cell responses both *in vitro* and *in vivo*. In addition, such studies will help to better understand the relative contribution of, and interplay between, intracellular metabolic and signaling pathways in shaping Th cell polarization by DCs. Finally, to what extent the metabolic characteristics and thereby Th cell-polarizing properties of DC subsets are determined by their ontogeny

versus the micro-environment they reside is an intriguing question that remains to be answered. Addressing these issues, will contribute to a more complete understanding of the multifaceted role of cellular metabolism in Th cell priming by DCs, and will reveal whether directed targeting of metabolic pathways in DCs could hold promise as novel approach to direct Th cell polarization that can be exploited in DC-based immunotherapy for the treatment of various types of immune-mediated disease.

Conflicts of interest statement
Nothing declared.

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