Thiago Andrade Patente

Vias de Regulação Metabólicas em Células Dendríticas com Viés Tolerogênico

Tese apresentada ao Programa de Pós-Graduação em Imunologia do Instituto de Ciências Biomédicas da Universidade de São Paulo para obtenção do título de doutor em Ciências.

Área de Concentração: Imunologia

Orientador: José Alexandre Marzagão Barbuto

Co-orientadora: Maria Lúcia Cardillo Correa-Giannela

SÃO PAULO
2020

RESUMO

PATENTE, TA. **Vias de Regulação Metabólicas em Células Dendríticas com Viés Tolerogênico.** 2019. 182 f. Tese (Doutorado em Imunologia) – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2019.

O diabetes mellitus tipo 1 (DM1) é uma doença autoimune na qual células dendríticas (DC) desempenham um papel relevante. DC são células apresentadoras de antígenos, centrais para a diferenciação de células T $CD4^+$, incluindo células T reguladoras (Tregs). Quando o ambiente fornece sinais tolerogênicos, DC falham em induzir a proliferação de linfócitos T tendendo a induzir tolerância. Diferentes estímulos, como ácido retinóico (RA), dexametasona (Dex) e vitamina D3 (VitD3), são capazes de gerar DC tolerogênicas (tolDC). DC imunogênicas e tolDC diferem em expressão de moléculas co-estimulatórias, secreção de citocinas pró-inflamatórias, capacidade de gerar linfócitos T supressivos e perfil metabólico. Enquanto DC imunogênicas dependem da glicólise e de metabolismo anabólico, as vias metabólicas envolvidas na indução de Treg pelas tolDC são menos detalhados. AMPK é um sensor metabólico conhecido por antagonizar sinais anabólicos, promovendo catabolismo e estudos sugerem que tolDC sejam caracterizadas por um perfil catabólico. Entretanto, o papel da sinalização de AMPK na regulação metabólica e funcional de tolDC ainda não foi abordado. Ainda, a presença de VitD3 durante a diferenciação mo-DC, induz uma reprogramação metabólica inicial, dependente de glicose. Assim, o presente trabalho teve dois objetivos principais: (1) como a hiperglicemia é a principal característica do DM1, avaliou-se como a concentração de glicose afetaria a diferenciação de mo-DC tratadas com VitD3 (VitD-DC); (2) investigar como AMPK poderia controlar a diferenciação de tolDC induzida por VitD3, RA e Dex. Observou-se que, metabolicamente, VitD3 modula de maneira diferente mo-DC de controle e pacientes, induzindo tolDC em pacientes de maneira glicose independente. Em controles, VitD3 induziu aumento da glicólise e OXPHOS, que foram, pelo menos parcialmente, reduzidas em hiperglicemia, assim como a expressão de CD86, a secreção de TNF-α e a capacidade linfoestimulatória. Já em pacientes diabéticos, embora VitD3 reduziu tanto a expressão de CD86 quanto a secreção de TNF-α em hiperglicemia, o metabolismo das células não foi afetado, sugerindo que a reprogramação metabólica induzida pela VitD3 pode não depender da glicólise em pacientes. Na segunda parte do projeto, confirmamos que VitD3, Dex e RA induziram tolDC funcionais, já que estas tolDC diferenciaram células T $CD4^+$ supressoras. Entretanto, metabolicamente,

cada tolDC exibiu fenótipo distinto: VitD-DC aumentaram glicólise e OXPHOS, RA-DC reduziram a capacidade respiratória sobressalente e Dex-DC reduziram glicólise. A fosforilação de ACC, um alvo direto de AMPK, aumentou em VitD-DC e RA-DC, sugerindo aumento da atividade de AMPK. Coerentemente, o silenciamento de AMPK reverteu as alterações metabólicas induzidas por VitD3 e RA, mas não por Dex. Quando AMPK foi silenciada em RA-DC humana, tanto a atividade de ALDH (induzida pelo RA) como sua capacidade tolerogênica foram perdidas. Camundongos com DC deficientes em AMPK, apresentaram redução na atividade de ALDH e na frequência de DC $CD103^{+}CD11b^{+}$ intestinal, consideradas o equivalente *in vivo* das RA-DC. Isso sugere uma importância da sinalização de AMPK para a homeostase de DC tolerogênicas intestinais, promovendo ambiente anti-inflamatório via atividade de ALDH em DC $CD103^{+}CD11b^{+}$. Sendo assim, estes dados sugerem um papel fundamental da AMPK na homeostase intestinal e na regulação das propriedades metabólicas e tolerogênicas de RA-DC.

Palavras-chave: Células Dendríticas. Imunometabolismo. Diabetes tipo 1. AMPK. Tolerância.

ABSTRACT

PATENTE, TA. **Metabolic Regulatory Pathways in Tolerogenic Bias Dendritic Cells.** 2019. 182 f. Ph.D. Thesis (Immunology Department) – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2019.

Type 1 diabetes mellitus (T1D) is an autoimmune disease in which dendritic cells (DC) play a relevant role. DC are antigen presenting cells, central to $CD4^+$ T cell differentiation, including regulatory T cells (Tregs). When the environment provides tolerogenic signals, DC fail to induce T lymphocyte proliferation and are prone to induce tolerance. Different stimuli, such as retinoic acid (RA), dexamethasone (Dex) and vitamin D3 (VitD3), are capable of generating tolerogenic DC (tolDC). Immunogenic DC and tolDC differ in expression of costimulatory molecules, proinflammatory cytokine secretion, ability to generate suppressive T lymphocytes and metabolic profile. While immunogenic DC rely on glycolysis and anabolic metabolism to support their activity, the metabolic pathways involved in the induction of Treg by tolDC are less well defined. AMPK is a metabolic sensor known to antagonize anabolic signals, promoting catabolism and studies suggest that tolDC are characterized by a catabolic profile. However, the role of AMPK signaling in regulating tolDC metabolism and function has not been addressed. Moreover, the presence of VitD3 during mo-DC differentiation induces an initial glucose-dependent metabolic reprogramming. Thus, the present study had two main objectives: (1) as hyperglycemia is the main characteristic of T1D, we aimed to evaluate how glucose availability would impact the differentiation of mo-DC treated with VitD3 (VitD DC); (2) to investigate how and if AMPK could control the differentiation of tolDC induced by VitD3, RA and Dex. Metabolically, VitD3 differently modulates controls mo-DC and patients, inducing tolDC in patients in a glucose-independent manner. In controls, VitD3 induced increase in glycolysis and OXPHOS, which were, at least partially, reduced in hyperglycemia, as well as CD86 expression, TNF-α secretion and lymphostimulatory capacity. In diabetic patients, while VitD3 reduced both CD86 expression and TNF-α secretion in hyperglycemia, cell metabolism was not affected, suggesting that VitD3-induced metabolic reprogramming may not rely on glycolysis in patients. In the second part of the project, we confirmed that VitD3, Dex and RA induced functional tolDCs, since these tolDC induced suppressor $CD4^+$ T cells. Metabolically, however, each tolDC exhibited a distinct phenotype: VitD-DC had increased glycolysis and OXPHOS, RA-DC had reduced spare respiratory capacity and Dex-DC had reduced glycolysis. ACC phosphorylation, a direct downstream target of AMPK, was increased in VitD-DC and

RA-DC, suggesting increased AMPK activity. Consistently, AMPK silencing reverted the metabolic changes induced by VitD3 and RA, but not by Dex. When AMPK was silenced in human RA-DC, both ALDH activity (that was increased by RA treatment) and their tolerogenic capacity were lost. Mice with a deficiency in AMPK selectively in DC showed a reduction in ALDH activity and frequency of gut $CD103^{+}CD11b^{+}$ DC, considered to be the *in vivo* equivalent of RA-DC. This suggests that AMPK signaling is important for homeostasis of tolerogenic DC in the gut by promoting an anti-inflammatory status via regulation of ALDH activity specifically in $CD103^{+}CD11b^{+}$ DC. Taken together, these data point towards a key role for AMPK in regulating both the metabolic and tolerogenic properties of RA-DC and the homeostasis of the gut.

Keywords: Dendritic Cells. Immunometabolism. Type 1 Diabetes. AMPK. Tolerance.

1. INTRODUCTION

1.1. Diabetes

Diabetes mellitus (DM) is a syndrome characterized by hyperglycemia resulting from defects in insulin secretion associated or not with resistance to the action of this hormone. DM is one of the most common endocrine diseases in all populations, and its prevalence varies according to ethnic group and geographic region (FORLENZA; REWERS, 2011). According to the Multicenter Study on Prevalence of DM in Brazil (MALERBI; FRANCO, 1992), conducted from June 1986 to July 1988, the age-adjusted prevalence rate of DM in the Brazilian population aged 30 to 69 years ranged from 5.22% in Brasilia to 9.66% in São Paulo, with a national average of 7.66%. A study conducted between September 1996 and November 1997 in the city of Ribeirão Preto, with the same age range used in the multicenter study, showed that 12.1% of the resident population in this city (approximately 27,739 people) had DM and about 25% of then were diagnosed in the during the study (TORQUATO et al., 2003). Another study, conducted between February 2005 and June 2007, also at Ribeirão Preto, found an increased prevalence of diabetes, 15,02%, and about 15% of the subjects were diagnosed during the study (MORAES; FREITAS; GIMENO, 2010). According to data from the Ministry of Healthy (DATASUS), during 2011, the mortality rate from DM in Brazil was 30.1/100,000 inhabitants, representing 57,876 individuals who died specifically from this disease. More recent data from the United States, revealed that the prevalence of diabetes was 9.7% in 2016 and 2017 being more prevalent in men (XU et al., 2018).

In 2004, Wild et al. developed a study in which the prevalence of DM for the year 2000 and 2030 was estimated. For this, only populations diagnosed in studies that used the criteria used by the World Health Organization (blood glucose levels higher than 200 mg/dL two hours after ingestion of 75g of glucose) were used. In this study, it was estimated that about 171 million people would have DM in 2000 and about 366 million in 2030 (WILD et al., 2004). However, in 2015, the global number of adults with DM was estimated in 415 million, with projected increase to 642 million by 2040 (OGURTSOVA et al., 2017).

The clinical manifestations extremes and the pathogenesis are the basis for the classification in type 1 DM (T1D, an autoimmune disease with exuberant clinical manifestations resulting from almost complete insulin deficiency) and type 2 DM (T2D, oligo or asymptomatic patients whose insulin deficiency coexists with insulin resistance). The elevated blood glucose observed in the disease may be accompanied by other

biochemical changes and clinical manifestations whose severity depends on the degree of insulin deficit, environmental conditions and the evolution of chronic blood vessel complications (diabetic micro and macroangiopathy).

T1D corresponds to approximately 10% of DM cases and it is a complex autoimmune disease that by the time of diagnosis, has already affected most of the pancreatic islets (KLINKE, 2008). Although the most important associated HLA class II haplotypes have been known for decades (NERUP et al., 1974), the concordance rates between monozygotic twins suggests that other factors also play an important role in the pathogenesis of T1D (REDONDO et al., 2001). With the advent of genome wild association studies (GWAS) more than 60 different loci could be associated with the development and or progression of T1D (BAKAY et al., 2019), which highlights how complex this disease is. As an autoimmune disease, environmental factors, such as virus infections and diet habits, can also contribute to the initiation of T1D (PASCHOU et al., 2018). Yet, immunological factors involving both $CD8^+$ and $CD4^+$ T cells, as well as dendritic cells (DC) and other innate immune cells are also important and an extensive data is available describing how these mechanisms can influence islets beta cells destruction (LEHUEN et al., 2010). However, the precise mechanisms that trigger the initiation of T1D are not easy to unravel and are not completely understood. Endogenous ligands from programmed cell death of the pancreatic β cells, as well as infection with certain types of viruses, may initiate the process of insulitis, which generates more β-cell apoptosis, increased exposure of self-antigens and, by recruiting antigen presenting cells (APCs), such as DC, creates sensitization conditions of the immune system against islets (DOGUSAN et al., 2008; LIU, 2001; RASSCHAERT et al., 2003; 2005). In this context, it is believed that self-antigens from β-cell apoptosis are captured by DC that would migrate to the lymph node, where they would present these antigens to $CD4^+$ T lymphocytes, initiating the autoimmune adaptive immune response (CALDERON; CARRERO; UNANUE, 2014; TURLEY et al., 2003).

Data from the literature suggest that the development of T1D requires the collaboration of both $CD4^+$ and $CD8^+$T lymphocytes, since the transfer of only one of these cell subtypes from nonobese diabetic mice (NOD) , was unable to induce disease in immunocompromised mice (PHILLIPS et al., 2009). $CD4^+$ T lymphocytes may promote macrophage migration to the pancreatic islets through the production of chemokine C-C motif ligand 1 and 2 (CCL1 and CCL2, respectively) (CANTOR; HASKINS, 2007; MARTIN et al., 2008). In addition, $CD4^+$ T lymphocytes activate both B lymphocytes

and $CD8^+$ T lymphocytes, either by direct cytokine production (such as interleukin (IL) -21 (SUTHERLAND et al., 2009)), or by licensing APCs which promotes $CD8^+$ T cell activation during disease onset (BALASA et al., 1997). In this licensing, the interaction between CD40L-CD40 promotes an increased IL-7 production, which appears to be important for activation of $CD8^+$ T cells (CARRENO; BECKER-HAPAK; LINETTE, 2008) which, in turn, would lead to β cells death, recognized for exposing, in the context of class I molecules encoded by the major histocompatibility complex (MHC I), the antigens recognized by such effector cells.

DC and macrophages seem to be important for the onset of T1D. Macrophages comprise the most frequent myeloid cells present in the pancreatic islet (CARRERO et al., 2013) and macrophage's depletion by treatment with an antibody against the colony stimulating factor-1 (CSF-1) could prevent the diabetes onset if administered either at earlier time point (2-3 weeks of age) ort later time point (10 weeks of age) (CARRERO et al., 2017). DC also seem to play a pivotal role in T1D onset since the ablation of conventional DC (cDC) (specifically $CD11b^+$ DC) in nonobese diabetic (NOD) mice prevented the development of insulitis and subsequent T1D. Interestingly, while cDC were important in the induction of T1D, once the insulitis process is stablished, plasmacytoid DC (pDC) seem to be important to limit the progression of the disease, since the addition of pDC but not cDC, to mice with ongoing insulitis limited the progression of the disease (SAXENA et al., 2007). A role for the other subset of cDC (the $CD103^+$ DC) was also observed in NOD mice. The frequencies of $CD103^+$ DC was increase in NOD mice from 4-6 weeks of age and, concomitantly, the frequencies of intraislets $CD3^+$ T cells were also increased. The diabetes onset and the frequencies of intraislets $CD3^+$ T cells were abolished in mice lacking the Basic Leucine Zipper ATF-Like Transcription Factor-3 (Batf-3), the main transcription factor of $CD103^+$ DC, suggesting that this subset of cDC is also essential for the onset of T1D (FERRIS et al., 2014). It is still unclear which cell type is more important for the disease onset, if there is time-dependent process in which macrophages could be more prejudicial at the earlier stages while DC would be required once the insulitis process is starting or, yet, if macrophages and DC cooperate to initiate the recruitment of diabetogenic T cells into pancreatic islets.

1.2. Dendritic Cells

DC are specialized in capture, processing and presentation of antigens to T lymphocytes and are believed to be the most effective in activating naïve T lymphocytes (CROFT; BRADLEY; SWAIN, 1994). In general, DC have been functionally divided into immature DC (iDC) and mature DC (mDC) (BANCHEREAU et al., 2000; GUERMONPREZ et al., 2002). Since iDC are rich in molecules associated with antigen capture, they are normally located within various tissues, efficiently capturing antigens, and, once an homeostatic state is present within this tissue, they present these antigens to T lymphocytes inducing tolerance to them (ITANO; JENKINS, 2003). Thus, iDC contribute to the maintenance or establishment of a tolerant state by presenting self or non-self antigens to T lymphocytes (WALLET; TISCH, 2006), without, at the same time, providing the necessary costimulatory signals, usually dependent on molecules such as B7.1 (CD80) and B7.2 (CD86). Such presentation may lead to a condition called clonal anergy in T lymphocytes (LUTZ; SCHULER, 2002), or even to the differentiation of T lymphocytes into regulatory cells (Tregs) (TAI et al., 2011).

At this stage of maturation, DC have a high density of receptors for immunocomplexes, cytokines and pattern recognition receptors (PRR), capable of recognizing pathogen-associated (PAMP) and damage-associated molecular patterns (DAMP) (STEINMAN et al., 2000). This set of receptors allows effective detection of homeostatic imbalances and their engagement leads DC to functional changes, characterized as maturation (MADDUR et al., 2010). DC maturation, thus, is triggered by the rupture of tissue homeostasis (CERBONI; GENTILI; MANEL, 2013; HEMMI; AKIRA, 2005) and turns on different metabolic, cellular, and gene transcription programs, allowing DC to migrate from peripheral tissues to T-dependent areas in secondary lymphoid organs, where T lymphocyte-activating antigen presentation may occur (ALVAREZ; VOLLMANN; ANDRIAN, 2008; DONG; BULLOCK, 2014; FRIEDL; GUNZER, 2001; HENDERSON; WATKINS; FLYNN, 1997; IMAI; YAMAKAWA; KASAJIMA, 1998; RANDOLPH; ANGELI; SWARTZ, 2005) (Figure 1).

Dendritic cells can be, also, anatomically divided into resident lymphoid tissue DC and migratory non-lymphoid tissue DC (HANIFFA; COLLIN; GINHOUX, 2013). They comprise heterogeneous populations with different subsets that can be distinguished by phenotypical markers and genetic profile. The first identification of a different population of DC arose from the observation that CD8 expression occurred on a subset

of mouse resident splenic and thymic DC (VREMEC, 1992). While the identification of mouse DC subpopulations is well advanced (MERAD et al., 2013; MILDNER; JUNG, 2014), mostly due to the facility of accessing a variety of tissues, the same is not true for human DC, where most studies that identified such subpopulations were performed in peripheral blood or skin. It is worth noting that recent studies have also characterized DC subpopulations in the human lung (GUILLIAMS et al., 2016) and intestine (GRANOT et al., 2017)

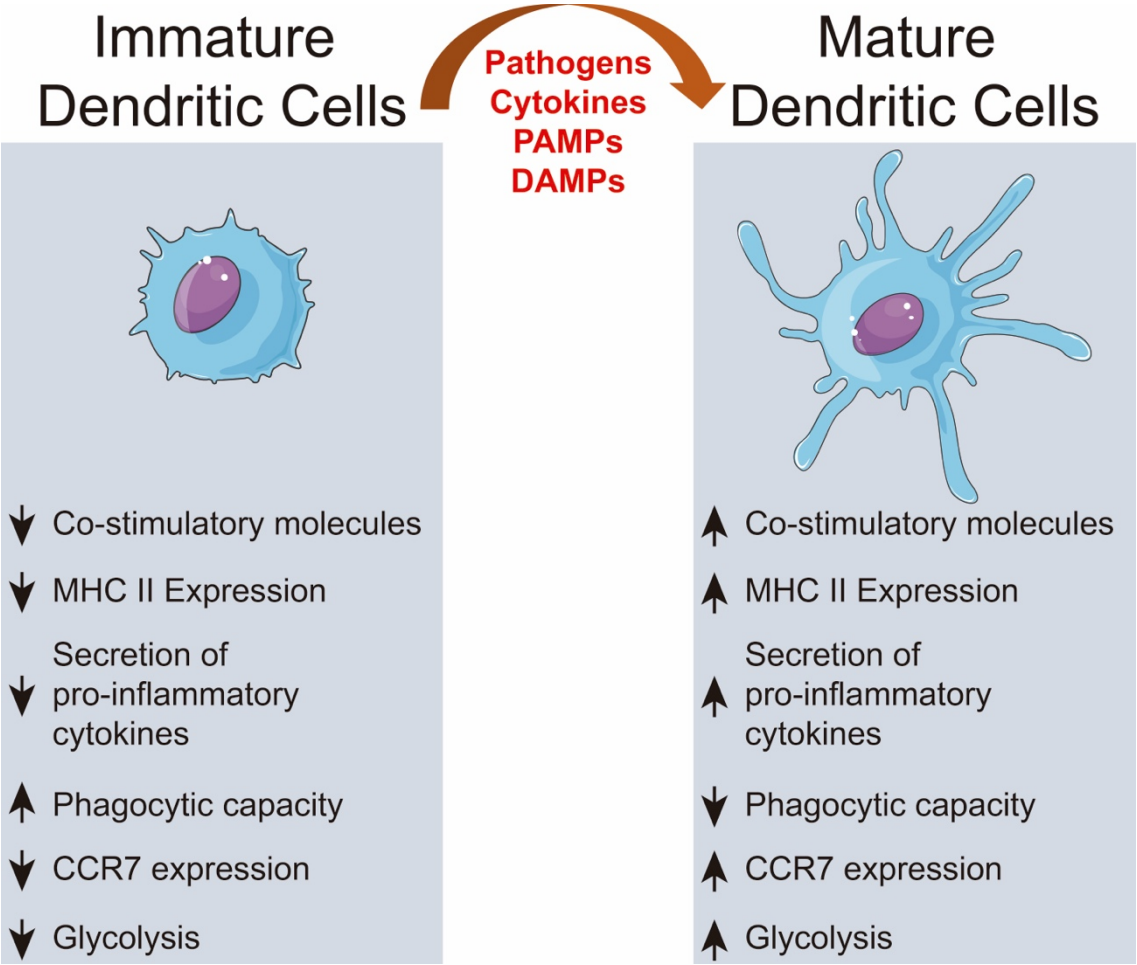

Figure 1: Dendritic cells activation. Extracellular signals, such as PAMPs or DAMPs, trigger alterations on immature DC leading to significant changes on surface proteins, intracellular pathways and metabolic activity. Adapted from Patente et. al, Front Immunol. 2019 Jan 21;9:3176.

In human blood, DC constitute a rare cell population that can be broadly divided into two subtypes: pDC and cDC. These subpopulations of DC can basically be distinguished by the expression of CD123 and CD11c, since pDC are $CD123^{+}CD11c^{-}$ and cDC are $CD123^{-}CD11c^{+}$ (BOLTJES; VAN WIJK, 2014; MERAD et al., 2013; O'KEEFFE; MOK; RADFORD, 2015; PATENTE et al., 2018). Additionally, cDC, can

be further subdivided into two other subsets of DC, namely cDC1 and cDC2 DC (GUILLIAMS et al., 2014). These subsets of cDC can be identified by the expression of CD141 in cDC1 and by the expression of CD1c in cDC2 (Figure 2). Genomic studies with emphasis on the subpopulations of monocytes and DC, could align the human peripheral blood $CD1c^+$ DC with the mouse $CD11b^+$DC and the human peripheral blood $CD141^+$ DC with the mouse $CD8\alpha^+/CD103^+$ DC respectively (ROBBINS et al., 2008; WATCHMAKER et al., 2013). New markers expressed by both human and mice DC could better define those subsets and the expression of XCR1 and CD172a are more commonly used to define cDC1 and cDC2, respectively. Nowadays, the nomenclature of cDC1 and cDC2 is well established and with new techniques, such as single cell RNA sequencing, new populations of DC (VILLANI et al., 2017), a better understanding of DC ontogeny (SEE et al., 2017), on how those subsets behave themselves in healthy and disease (DUTERTRE et al., 2019) and how specific transcription factors dictate the fate of each subset (DURAI et al., 2019) are starting to be unveiled.

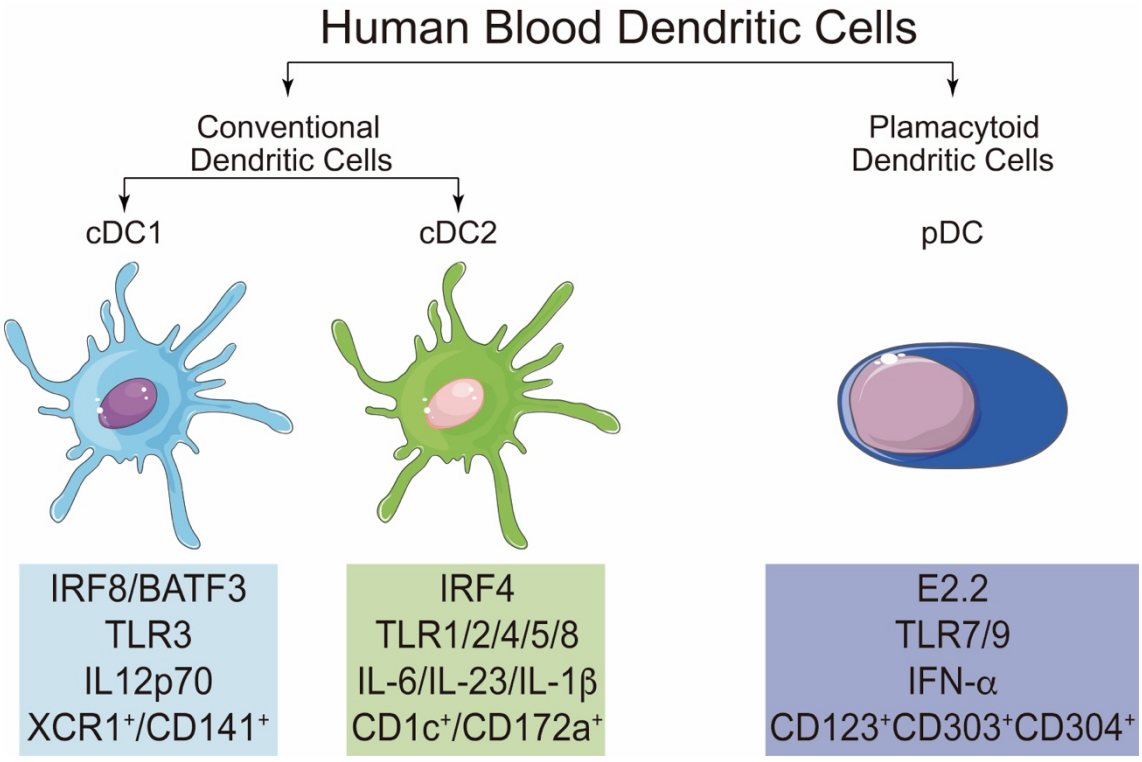

Figure 2: Main characteristics and differences of cDC1, cDC2 and pDC. In human blood, it is possible to find two main populations of DC: conventional DC (cDC) and plasmacytoid DC (pDC). cDC can be further subdivided in cDC1 and cDC2. Each subset of DC is characterized by its own transcription factors, functions and surface markers that helps to properly identify then in both mice and human. Adapted from Patente et. al, Front Immunol. 2019 Jan 21;9:3176.

Much of our understanding about human DC biology was possible due to *in vitro* experiments, in which monocytes isolated from the blood were differentiated to DC, the so called monocyte-derived DC (mo-DC), with the use of GM-CSF and IL-4(SALLUSTO; LANZAVECCHIA, 1994). However, they do not seem to be equivalent to the cDC we can find in the blood, since they arise from different precursors (GEISSMANN et al., 2010). It is still unclear to which subpopulation of DC, mo-DC are more closely related, but DC ontogeny data suggest that mo-DC are similar to the inflammatory DC (REYNOLDS; HANIFFA, 2015). Inflammatory DC are a heterogeneous subpopulation of DC, expressing higher levels of CD11c and MHCII. The firsts reports about inflammatory DC, were observed in the skin of atopic dermatitis patients (WOLLENBERG et al., 1996) and in the spleen of *Listeria* monocytogenes-infected mice (SERBINA et al., 2003). Recently, by gene signature analysis, inflammatory DC were more closely related to *in vitro* generated mo-DC than macrophages, cDC2, $CD16^+$ monocytes and $CD14^+$ monocytes, suggesting that inflammatory DC could be the counterparts of mo-DC (SEGURA et al., 2013).

1.3. Immunogenic *vs* tolerogenic DC

Initially, DC function was largely associated with its capacity to capture, process and present antigens to T cells in order to initiate T-cell mediated immunity (STEINMAN, 1991; STEINMAN; WITMER, 1978). However, it was soon becoming clear that those cells not only were important for the induction of immune response, but also for the induction of tolerance, either in the thymus, by helping to negatively select autoreactive T cells (BROCKER; RIEDINGER; KARJALAINEN, 1997), or in the periphery by probably inducing T cell anergy or deletion (FÖRSTER; LIEBERAM, 1996; KURTS, 1996). The balance between immunogenic and tolerogenic DC (tolDC) is crucial for the maintenance of tissue homeostasis helping to promote immunity or tolerance depending on the environment.

TolDC express less co-stimulatory molecules, secret less proinflammatory cytokines and upregulate the expression of inhibitory molecules, such as programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (GROHMANN et al., 2002; MANICASSAMY; PULENDRAN, 2011; MORELLI; THOMSON, 2007; SAKAGUCHI et al., 2010). Additionally, they are able to secrete anti-inflammatory cytokines (like IL-10) and are essential to prevent responses against healthy tissues (HAWIGER et al., 2001; IDOYAGA et al., 2013; MAHNKE et al., 2003;

STEINMAN et al., 2003; YATES et al., 2007; YOGEV et al., 2012). Among the numerous stimuli capable of generating tolDC, cytokines and interactions with other cell types (like mastocytes via PD-L1/PD-L2) seem to be important to induction of this state in DC (RODRIGUES et al., 2016; SVAJGER; ROZMAN, 2014). Among cytokines, IL-10, IL-6 and transforming growth factor beta (TGF-β) (TORRES-AGUILAR et al., 2010) have been described as capable of producing tolerogenic DC, with low expression of costimulatory molecules and MHC II, but capable of secrete high amounts of IL-10(LAN et al., 2006). Also, vitamin D3 (VitD3) (ADORINI, 2003; BAKDASH et al., 2014; FERREIRA et al., 2012; 2014; 2015), retinoic acid (RA) (BAKDASH et al., 2015), butyrate (KAISAR et al., 2017) and dexamethasone (Dex) (DÁŇOVÁ et al., 2015; MAGGI et al., 2016; NAVARRO-BARRIUSO et al., 2018) has been described as capable of inducing such condition, at least in vitro, on DC (Figure 3) and has been explored in animal models as a tool for the treatment of autoimmune diseases and prevention of transplant rejection (KLEIJWEGT et al., 2013; LAN et al., 2006).

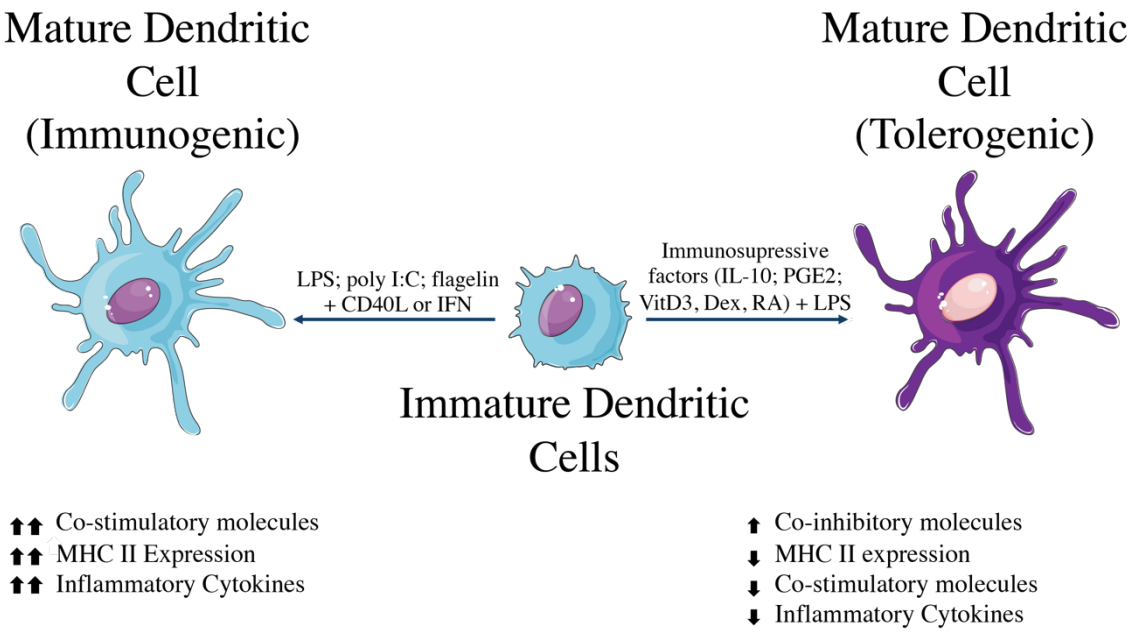

Figure 3: Immunogenic DC vs tolerogenic DC. Differents stimuli can engage differentiation of immature DC toward immunogenic of tolerogenic profile. Immunogenic DC are characterized by the ability to induce activation of T cells in order to stimulate an inflammatory response. On the other hand, tolerogenic DC can induce the differentiation of regulatory T cell (Tregs) in order to control inflammatory environments.

The use of tolDC to prevent the development or to treat autoimmune disease is a particular interesting research field. Clinical trials have already been performed for T1D (GIANNOUKAKIS et al, 2011), rheumatoid arthritis (BELL et al., 2017; BENHAM et al., 2015), multiple sclerosis (MS) (clinicaltrials.gov identifier: NCT02283671 and

NCT02618902) and Crohn's disease (JAUREGUI-AMEZAGA et al., 2015). The first phase I clinical trial with tolDC was performed by Giannoukakis et al. (GIANNOUKAKIS et al, 2011) in patients with T1D. In this trial, autologous DC were treated with antisense oligonucleotides for CD40, CD80 and CD86. And, even though no clinical improvement was reported, infusion of these tolDC was safe and well tolerated with no adverse effects reported by the patients. A second phase I study with tolerogenic DC was performed by Benham et al. in patients with rheumatoid arthritis in which tolDC were generated by the use of "signal inhibitor" of the nuclear factor kappa B (NF-κB) transcription factor (BENHAM et al., 2015). In this study, tolDC were pulsed with four citrullinated peptides, called Rheumavax, and reduction in effector T cell frequency with concomitant increase in Tregs frequency were observed. In the study performed by Jauregui-Amezaga et al., tolDC were administered intraperitoneally to Crohn's disease patients in different doses and time points. Again, no adverse effects were observed in the patients and decrease in the Crohn's Disease Activity Index (CDAI), Crohn's Disease Endoscopic Index of Severity (CDEIS) with increase in the numbers of circulating Tregs were observed.

Before the use in clinical trials tolDC have been studied in mouse models to prevent the onset of, for example, T1D in NOD mice (FERREIRA et al., 2014; MA et al., 2003; TAI et al., 2011). Both, genetically modified mice, expressing HLA-DQ8 on antigen-presenting cells and the human co-stimulatory molecule B7.1 on the islet-beta cells, which develop spontaneous diabetes and NOD mice, when treated with bone marrow-derived DC (BMDC) differentiated in the presence of IL-10, displayed reduced insulitis, increased numbers of Tregs in the spleen, suppression of diabetogenic T lymphocytes and did not develop T1D (TAI et al., 2011). It is worth noting that other treatments can also drive DC to a tolerogenic phenotype: immature GMDC from NOD mice, which have been shown to have higher CD80 and CD86 content compared to wild-type mouse BMDC, when treated with VitD3 displayed immunosuppressive properties (FERREIRA et al., 2014).

Although different methods were used for the generation of tolDC in the clinical trials tested so far, no adverse effects were observed, what, by itself, is already a positive observation. Thus, it is so far unclear, to what extent differences in methodology can change the effectiveness of the cells or can potentiate their beneficial effects. A common feature that seems to be shared by most of the tolDC tested is their ability to increase Tregs frequencies in the peripheral blood of the patients. However, each disease has its

own course, and this needs to be taken into consideration. For example, the window to treat T1D patients is tight and difficult to reach, since, normally, by the time of diagnosis, about 80% of the pancreatic islets have been already destroyed (KLINKE, 2008) and the tolDC-based therapy would not restore pancreatic islets.

Perhaps, the use of tolDC-based therapy in T1D would be more beneficial to prevent islet rejection, in the context of therapeutic transplantation. Although many studies in rodents have shown promising results with transfusion of modified tolerogenic DC in pancreatic islet transplantation models (HUANG et al., 2010; SUN et al., 2012; THOMAS et al., 2013; YANG et al., 2008), to date, no clinical trial results have been reported describing the effectiveness of tolDC in pancreatic islet transplantation or any other transplantation in humans. A study in primates, however, was able to demonstrate a significant increase in mean graft survival when VitD3 and IL-10 modified tolDC were administered seven days prior to kidney transplantation together with CTLA4-Ig (CD80/CD86 inhibitor), administered for a period of 2 or 9 weeks (EZZELARAB et al., 2013). These and other data in the literature highlight the potential of tolDC, both in transplantation and for the treatment of autoimmune diseases (OCHANDO et al., 2019).

1.4. Overview of metabolic pathways

Energy is necessary to execute any function, either in a complex organism or at a cellular level. Cells are constantly breaking down molecules to produce energy (a process called catabolism) or synthesizing molecules to either be stored or used immediately (a process called anabolism). Energy inside the cell is stored, mainly, in the form of adenosine triphosphate (ATP), which is constantly produced by the cell, mostly via two metabolic pathways: glycolysis and oxidative phosphorylation (OXPHOS). Glycolysis produces a limited amount of ATP but, in the presence of oxygen, it can fuel OXPHOS, via the tricarboxylic acid (TCA) cycle (MOOKERJEE et al., 2017), thus generating many more ATP molecules. The TCA cycle generates the reducing molecules, nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$), which serve as electron donors to the electron transport chain, fueling OXPHOS (PEARCE; PEARCE, 2013). Glycolysis is, of course, not the only metabolic pathway capable of fueling the TCA cycle. Other catabolic pathways like fatty acid oxidation (FAO) and glutaminolysis are also able to do so. Apart from catabolic pathways, anabolic pathways, like glycogenolysis, fatty acid synthesis and pentose phosphate pathway (PPP) are also

important in cells to regulate the bioenergetic status manage nutrients (O'NEILL; KISHTON; RATHMELL, 2016) (Figure 4).

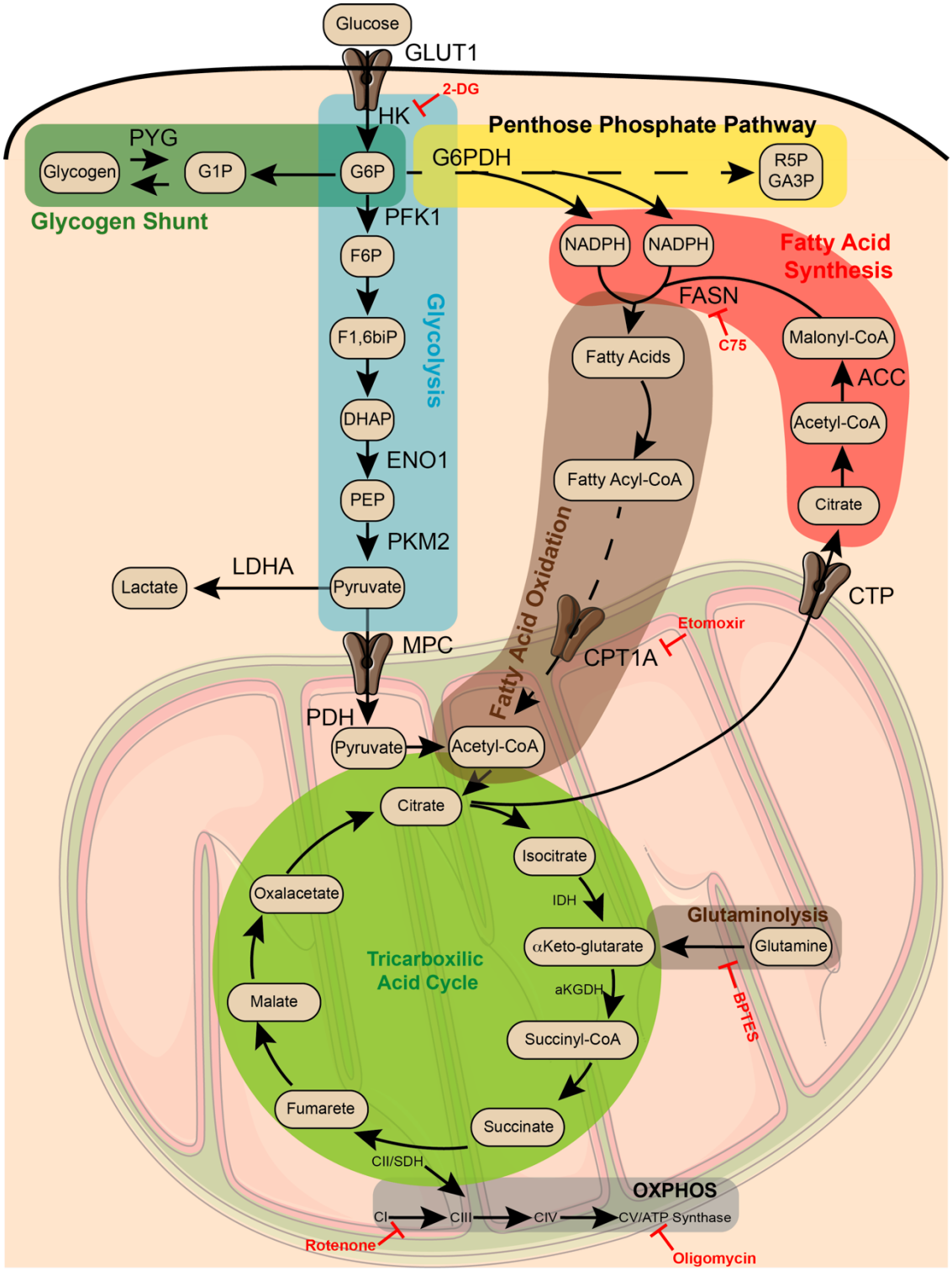

Figure 4: Overview of metabolic pathways. Frequently used metabolic inhibitors are indicated in red. 2-DG, 2-deoxy-D-glucose; ACC, acetyl-CoA carboxylase; αKGDH, α-ketoglutarate dehydrogenase; CoA, coenzyme A; CPT1, carnitine palmitoyltransferase 1, CTP, citrate transport protein; DHAP, dihydroxyacetone phosphate; DON, 6-Diazo-5-oxo-L-norleucine; ENO1, enolase 1; F1,6biP, fructose 1,6 biphosphate; F5P, fructose 5 phosphate; F6P, fructose 6 phosphate; FASN, fatty acid synthase; G6P,

glucose 6 phosphate; G6PDH, glucose 6 phosphate dehydrogenase; GA3P, glyceraldehyde 3 phosphate, GLUT1, glucose transporter 1; HK-II, hexokinase 2; IDH, isocitrate dehydrogenase; LDHA, lactate dehydrogenase A; MPC1, mitochondrial pyruvate carrier 1; NADPH, nicotinamide adenine dinucleotide phosphate; PDH, pyruvate dehydrogenase PDK1-4, pyruvate dehydrogenase kinase 1-4, PEP, phosphoenolpyruvate; PFK1, phosphofructokinase-1; PKM2, pyruvate kinase isozyme M2; R5P, ribose 5-phosphate; SDH, succinate dehydrogenase; TOFA, 5-(Tetradecyloxy)-2-furoic acid.

Glycolysis starts with the uptake of glucose from the extracellular space via specific glucose transporters (GLUT) that can be found in many isoforms, among which, GLUT1 is the main isoform expressed by immune cells(KNOTT; FORRESTER, 1995). Once inside the cells, glucose is rapidly phosphorylated into glucose 6-phospate (G6P), a process catalyzed by hexokinase (HK) that consumes ATP instead of producing it. A series of enzymatic reactions takes place in the cytosol to break down G6P and, ultimately, produce pyruvate that can either be reduced to lactate by lactate dehydrogenase (LDH) or carried into the mitochondria, by mitochondrial pyruvate carrier (MPC). Inside the mitochondria, pyruvate is converted to Acetyl-CoA that fuels the TCA. Glycolysis is a relatively poor pathway, for the production of ATP, since it produces only two molecules of ATP for each molecule of glucose. However, glycolysis is important to: (1) reduce NAD^+ to NADH, which is a cofactor for a series of enzymes; (2) provide biosynthetic intermediates, like G6P, for nucleotides (via PPP), 3-phosphoglycerate, for aminoacids (via the serine biosynthetic pathway) and citrate, derived from pyruvate in the TCA cycle, for fatty acids (DOMÍNGUEZ-AMOROCHO et al., 2019; O'NEILL; KISHTON; RATHMELL, 2016).

Experimentally, it is possible to inhibit glycolysis with 2-deoxy-d-glucose (2-DG) which is an analogous of glucose that is phosphorylated by HK, but whose end product, 2-deoxyglucose-phosphate (2-DG-P) cannot be used in the following steps of glycolysis, resulting in accumulation of 2-DG-P and inhibition of HK (SEO; CROCHET; LEE, 2013). The oxidation of glucose can be also blocked by a compound called UK-5099, which inhibits the activity of MPC, thus preventing the entrance of glucose-derived pyruvate into the mitochondria.

The PPP is a metabolic pathway that takes place in the cytosol and it is an offshoot of glycolysis. In the first step of PPP, G6P is dehydrogenated by glucose-6-phosphate dehydrogenase, generating 6-phosphogluconolactone. This molecule enters an oxidative branch of PPP that generates 2 equivalents of nicotinamide adenine dinucleotide phosphate (NADPH), which can be used for FAS, and ribulose-5-phosphate. This latter molecule may enter the non-oxidative branch of PPP, that starts with its conversion to ribose-5-phosphate (R5P), by the ribose-5-phosphate isomerase. R5P can serve as

substrate for the generation of 5-phosphoribosyl-1-pyrophosphate (PRPP) a key intermediate in the nucleotide biosynthesis, required for *de novo* synthesis of purine and pyrimidine nucleotides (BHAGAVAN; HA, 2015). Additionally, when G5P is in excess, ribulose-5-phospate can be converted to glyceraldehyde-3-phospahte (GA3P) or fructose-6-phosphate (F6P), refueling glycolysis.

In the FAO pathway fatty acids are converted into Acetyl-CoA that can be used, in the TCA, to generate NADH and $FADH_2$. The FAO pathway can be divided into two steps: the first one is the activation of the fatty acids that occurs in the cytosol; the second step is the β-oxidation and occurs inside the mitochondria. The activation step is the formation of a fatty acyl-CoA, a reaction catalyzed by acyl-CoA synthases, located in the outer membrane of the mitochondria. Short-chain fatty acyl-CoA, defined as having less than six carbons in the aliphatic tail, can diffuse into the mitochondria, while medium and long chain fatty acyl-CoA need to be conjugated with carnitine by the action of carnitine palmitoyl transferase I (CPT1). Once carnitine-conjugated fatty acyl-CoA are inside the mitochondrial matrix, CPT2 is responsible for the removal of carnitine, which is transferred back to the cytosol via carnitine-acylylcarnitine translocase. The next step in FAO is the oxidation of the acyl-CoA located at the β carbon of the molecule, the so called β-oxidation. This step involves the sequential action of 4 enzymes: acyl-CoA dehydrogenase, enoyl-CoA hydratase, β-hydroxyacyl-CoA dehydrogenase and 3-ketoacyl-CoA thiolase culminating with the production of acetyl-CoA, which can, now, fuel the TCA cycle to generate NADH and $FADH_2$, electron donors in the electron transport chain of OXPHOS (BHAGAVAN; HA, 2010; O'NEILL; KISHTON; RATHMELL, 2016). Experimentally, FAO can be partially blocked with etomoxir, a molecule that binds irreversibly to CPT1, thus preventing the entrance of fatty acyl-CoA in the mitochondria.

Cells synthesize lipids by the FAS pathway, generating lipids needed for cell growth and proliferation. *De novo* synthesis of fatty acids takes place in the cytosol and has as the rate limiting enzyme the acetyl-CoA carboxylase (ACC). ACC is the enzyme responsible for the conversion of acetyl-CoA into malonyl-CoA. In this process, an important regulator of the ACC is citrate, that is deviated from the TCA to the cytosol via the mitochondria citrate transport (CTP) protein. Citrate is important for the FAS pathway for two reasons: (1) it binds to ACC promoting the assembly of its active polymeric form from its inactive protomer; (2) it provides carbon atoms for the FAS pathway by the

cytosolic generation of acetyl-CoA (citrate shuttle). The cytosolic acetyl-CoA is originated from the cleavage of citrate into acetyl-CoA and oxaloacetate by the action of ATP citrate lyase. The citrate shuttle is the main provider of cytosolic acetyl-CoA, since it cannot be transported from the mitochondria. After citrate is converted to acetyl-CoA in the cytosol, the polymeric ACC, whose assembly also depends on citrate, catalyzes the conversion of acetyl-CoA into malonyl-CoA which is then elongated by fatty acid synthetase (FASN), in a NADPH-dependent manner, producing mainly palmitate, a C_{16} fatty acid. Elongation of palmitate can occur in endoplasmic reticulum or in the mitochondria to generate long-chain fatty acids (LCFA) with C_{18}, C_{20}, C_{22} and C_{24} molecules. LCFA can be classified as monounsaturated (MUFA) or polyunsaturated (PUFA), depending on the number of double bonds between their carbon atoms. Malonyl-CoA is also an inhibitor of CPT1, a phenomenon that balances FAO and FAS in the cell. FAS can be blocked using a compound called C75, which inhibits FASN activity, thus preventing the synthesis of fatty acids from malonyl-CoA (BHAGAVAN; HA, 2010; BLANCO, 2017; O'NEILL; KISHTON; RATHMELL, 2016)

Another way cells can fuel the TCA cycle is via glutaminolysis, the process by which cells convert glutamine into TCA cycle metabolites. Initially glutamine is converted in glutamate, catalyzed by the enzyme glutaminase (GLS). Glutamate is, then, converted to α-ketoglutarate by the action of glutamate dehydrogenase enzyme and α-ketoglutarate can serve as an anaplerotic source to TCA cycle(YANG; VENNETI; NAGRATH, 2017). Glutaminolysis can be prevented by treating cells with a GLS inhibitor, like Bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide (BPTES). Glutamine metabolism seems to be especially important in tumor cells because they undergo a metabolic reprogramming that renders them highly dependent on glutaminolysis, believed to be mainly via the activation of the proto-oncogene *c-MYC* that increases the expression of high-affinity glutamine importers, like sodium-dependent neutral amino acid transporter type 2 (SLC1A5) (WISE et al., 2008).

1.5. Metabolic pathways in DC

While in the late 1920s, Otto Warburg described a mechanism present in tumor cells that became known as the Warburg effect, in which cells, even in the presence of oxygen to perform oxidative phosphorylation, "preferred" to use the glycolytic pathway to generate ATP (WARBURG; WIND; NEGELEIN, 1927), the influence of metabolism on immune cell function has only recently began to be investigated in depth. The first

reports of how metabolism could affect the immune cells functions date from the late 50's (ALONSO; NUNGESTER, 1956) and early 60's (OREN et al., 1963) showing differences in the metabolism of polymorphonuclear cells, basically by measurement of gas change in Warburg flasks or enzymatic activity. More recently, with advantage of more innovative techniques, it was possible to study in deep the changes orchestrated by metabolism in the function of immune cells.

A large data in the literature has focused in the metabolic changes that occurs in immunogenic DC, leading to the consensus that activation of immunogenic DC is accompanied by, and dependent on, a switch from OXPHOS to glycolysis (BASIT et al., 2018; EVERTS et al., 2012; 2014b; FLIESSER et al., 2015; JANTSCH et al., 2008; KRAWCZYK et al., 2010; MCKEITHEN et al., 2017; PANTEL et al., 2014; RYANS et al., 2017; THWE et al., 2017). It is becoming increasingly clear that immune cell activation and function, including that of DC, is coupled to, and underpinned by, profound changes in cellular metabolism (BUCK et al., 2017; O'NEILL; KISHTON; RATHMELL, 2016). Immature DC predominantly use OXPHOS to obtain energy; however, when stimulated by Toll-like Receptor ligands (TLRs), such as LPS, these cells rapidly increase the glycolytic pathway by consuming more glucose, which acts to fuel the TCA. Increased glucose flow, in fact, provides TCA intermediates, especially citrate and isocitrate, which are diverted to other pathways (such as FAS) (EVERTS et al., 2014b; KRAWCZYK et al., 2010). Recently, it was demonstrated that glycogen-derived carbon is used during this initial increase in the glycolytic pathway for citrate synthesis and that much of the extracellular glucose captured by DC is rapidly converted to glycogen(THWE et al., 2017). These modulations that occur in LPS-activated DC appear to be at least partially dependent on hypoxia inducible factor 1−alpha (HIF1α), since the silencing of this transcription factor was able to decrease the expression of the glucose transporters, such as GLUT-1, CD86 and the ability of these cells to stimulate the proliferation of T lymphocytes (JANTSCH et al., 2008). Additionally, long term LPS stimulation, increased the expression of mechanistic target of rapamycin (mTOR) which demonstrated to be important to stabilize HIF1α and sustain glycolytic activity in DC, with significant increasing expression of MHC II, CD80, CD86 and CD40 (GUAK et al., 2018).

While the metabolic basis of immunogenic DC is being largely explored, the metabolic alterations that drives tolerogenicity in DC are just starting to be unveiled (Figure 5). The generation of tolDC from monocytes in the presence of rapamycin, a

mTORC1 inhibitor (FISCHER et al., 2009), provided one of the first indications that blocking anabolic metabolism could favor acquisition of a tolerogenic phenotype in DC. Supporting this information, two recent studies aimed to characterize the metabolic properties of human mo-DC rendered tolerogenic with VitD3 alone (FERREIRA et al., 2015) or together with Dex (MALINARICH et al., 2015), and reported increased mitochondrial activity evidenced by heightened OXPHOS. In the latter study acquisition of tolerogenic phenotype by the DC was partly dependent on increased FAO (MALINARICH et al., 2015). Interestingly, VitD3-DC displayed increased mTOR/HIF1α-dependent glycolysis (FERREIRA et al., 2015) and this increased glycolysis was functionally relevant, since 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-DC treated with 2-DG(FERREIRA et al., 2015). Additionally, glycolysis inhibition limited their ability to suppress $CD4^+$ T cell proliferation. These cells showed an increased AMP-activated protein kinase (AMPK) activation (FERREIRA et al., 2015) and elevated glucose carbon tracing into the TCA cycle(VANHERWEGEN et al., 2018), suggesting that this increased glycolytic flux, in contrast to immunogenic DC, may primarily serve a catabolic role by fueling mitochondrial OXPHOS.

Consistent with these human DC data, a *in vivo* study focusing on the metabolic properties of DC in tumors (ZHAO et al., 2018), a microenvironment that is a well-known to promote tolDC (RAMOS et al., 2012), 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 it was dependent on β-catenin and peroxisome proliferator-activated receptor-γ (PPAR-γ) signaling. Importantly, blocking FAO in DC, abolished the increased Wnt5a-enhanced IDO activity as well as the induction of $FoxP3^+$ peripheral Treg (pTreg) differentiation leading to enhanced anti-tumor immunity *in vivo.* Interestingly, a similar β-catenin-PPAR-γ dependent pathway is required for the maintenance of tolDC in visceral adipose tissue (MACDOUGALL et al., 2018). This, together with the findings that tolDC in mucosal tissues depend on PPAR-γ signaling for ALDH expression and activity (HOUSLEY et al., 2009; KHARE et al., 2015), points towards a crucial role for PPAR-γ in supporting tolerogenic properties of DC. However, to what extent these PPAR-γ-driven effects are mediated by controlling lipid metabolism remains to be determined.

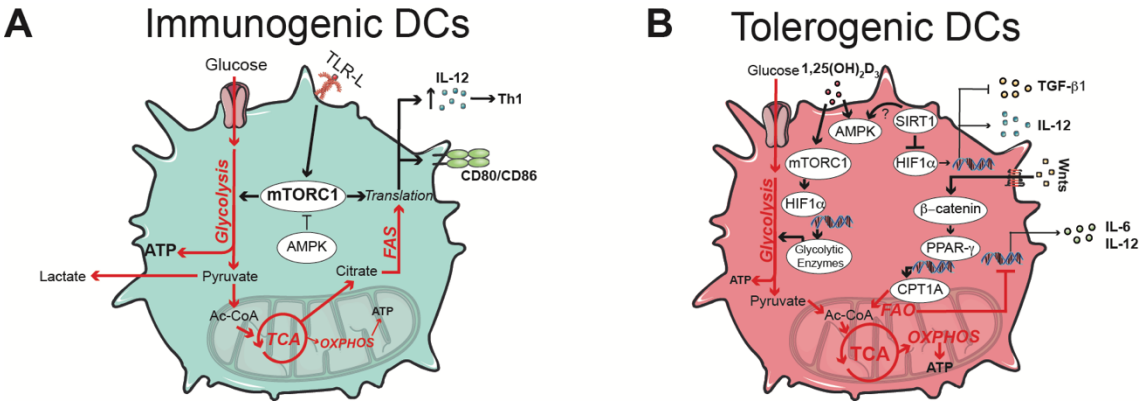

Figure 5: Metabolic characteristics of immunogenic and tolerogenic DC. Metabolic pathways and upstream signaling pathways regulating immunogenic (A) and tolerogenic (B) responses are indicated in red and black, respectively. Adenosine triphosphate (ATP); AMP-activated protein kinase (AMPK); carnitine palmitoyl transferase 1A (CPT1A); fatty oxidation (FAO); fatty synthesis (FAS); hypoxia inducible factor 1–alpha (HIF1α); mechanistic target of rapamycin complex 1 (mTORC1); oxidative phosphorylation (OXPHOS); peroxisome proliferator-activated receptor-γ (PPAR-γ); tricarboxylic acid (TCA); sirtuin-1 (SIRT1). Adapted from Patente et al. 2019.

A switch from OXPHOS towards aerobic glycolysis was observed in sirtuin-1 (SIRT1)-deficient DC by stabilization of HIF1α. As consequence, peripheral Treg (pTreg) differentiation was redirected towards Th1 priming T cells by enhanced IL-12 production and reduced TGF-β secretion by DC (LIU et al., 2015), providing further support for a key role in catabolic/oxidative metabolism in pTreg induction by DC. AMPK has a key role in promoting this type of metabolism and one could speculate that this kinase might be important in DC-driven induced Treg (iTreg) and pTreg polarization. The fact that SIRT1 can promote the activation of AMPK, through deacetylation of liver kinase B1 (LKB1) (CHEN et al., 2015), and that VitD3-treated human DC showed increased AMPK activation (FERREIRA et al., 2015), would be consistent with this idea and warrants a more direct assessment of the role of AMPK signaling in regulating the tolerogenic properties in DC.

1.6. AMPK: one metabolic sensor of the cells

Inside the cells, energy is measured by the levels of ATP produced, mainly, within the mitochondria. If ATP levels are low, catabolic process are triggered in order to break down molecules and uptake nutrients to restore the intracellular levels of ATP. In this sense, a protein that senses when ATP is low is crucial for the maintenance of cellular functions and homeostasis. The main sensor of cellular energy status, is AMPK which has the ability to sense increases in the AMP:ATP or ADP:ATP ratios and restores energy

homeostasis by inhibiting anabolic pathways that consumes ATP and promoting catabolic pathways that will have as end consequence the generation of ATP (GARCIA; SHAW, 2017).

AMPK is a heterotrimeric protein composed by an α-subunit, with catalytic activity, and a β– and γ-subunits with regulatory functions. All the subunits have more than one isoforms: (1) α1 and α2 subunits, encoded by the genes *PRKAA1* and *PRKAA2*; (2) β1 and β2 subunit, encoded by the genes *PRKAB1* and *PRKAB2* (THORNTON; SNOWDEN; CARLING, 1998); γ1, γ2 and γ3 subunits, encoded by the genes *PRKAG1* and *PRKAG2* and *PRKAG3* (CHEUNG et al., 2000). The AMPK complex is composed of one subunit of each and all the combinations can be found. The α–subunit is the most important one, since it contains the kinase domain and a threonine 172 (Thr172) residue that can be phosphorylated by LKB1 (HAWLEY et al., 2003) and calcium/calmodulin-dependent kinase kinase 2 (CAMKK2) (HAWLEY et al., 2005), the two main upstream kinases that activates AMPK.

The activation of AMPK can be regulated by a canonical nucleotide-dependent and a non-canonical nucleotide-independent mechanism (GARCIA; SHAW, 2017; HARDIE; ROSS; HAWLEY, 2012). In the canonical nucleotide-dependent regulation process, changes in AMP:ATP or ADP:ATP ratio promotes the binding of AMP or ADP to the γ-subunit of AMPK, which by itself promotes an allosteric activation of AMPK, especially the binding of AMP(GOWANS et al., 2013). AMP or ADP binding to the γ-subunit of AMPK also induces the phosphorylation of Thr172 by LKB1 (HAWLEY et al., 2003) and drives a conformational change in AMPK, protecting it from phosphatases actions, thus creating an activation loop (GOWANS et al., 2013; XIAO et al., 2011). On the other hand, the non-canonical nucleotide-independent regulation involves a series of cellular alterations that culminates with the phosphorylation of AMPK. Hormones and stress can induce increased levels in intracellular Ca^{2+} which induce the phosphorylation of Thr172 in AMPK by CAMKK2 (HAWLEY et al., 2005). Other mechanisms have been reported to also induce the activation of AMPK such as: (1) phosphorylation of AMPK in different sites by other kinases, like phosphorylation of Ser485 by cyclic-AMP-dependent protein kinase (PKA) in AMPKα1; (2) the localization of AMPK to the cellular membrane; (3) indirect (by increasing AMP levels) or direct activation by reactive oxygen species (ROS) and (4) DNA-damaging drugs that activate AMPK in a

LKB1-independent manner (revised in (GARCIA; SHAW, 2017; HARDIE; ROSS; HAWLEY, 2012)).

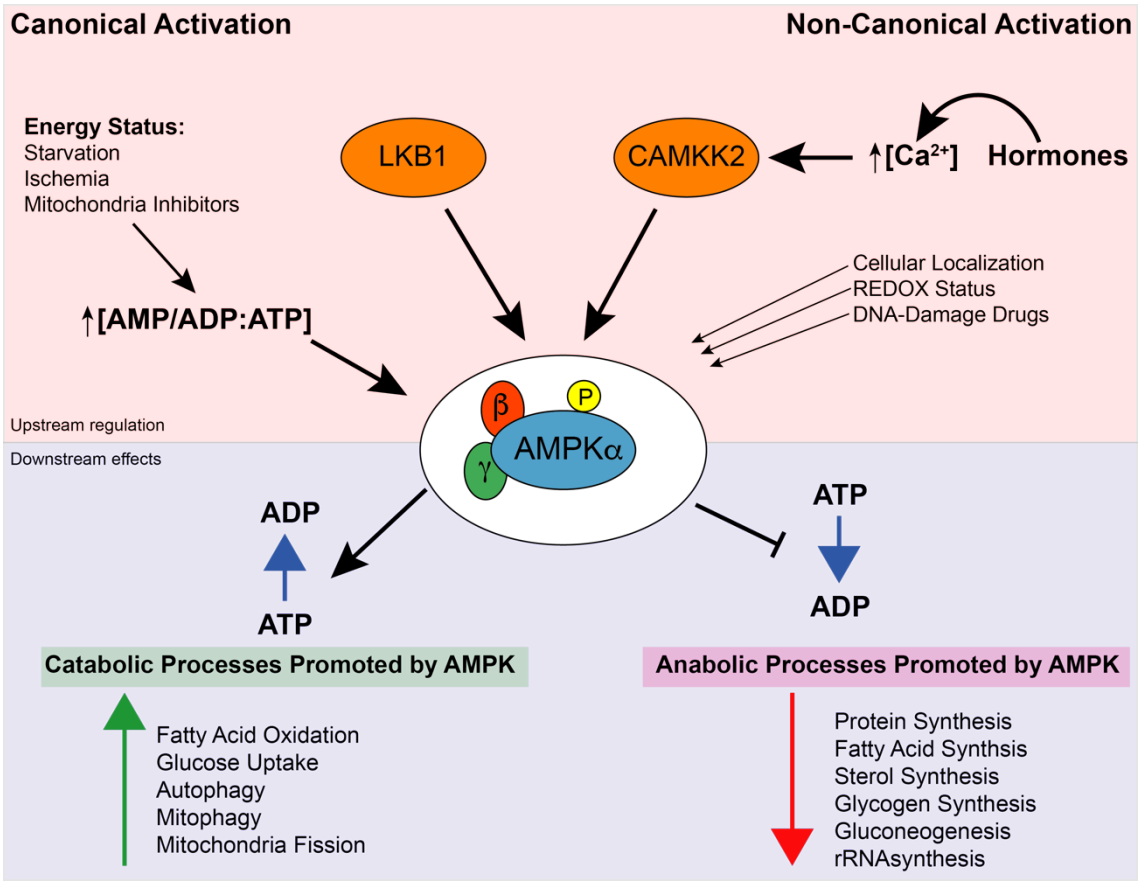

Figure 6: AMPK activation in mammalian cells. Canonical and non-canonical pathways can activate AMPK, mainly altering the AMP/ADP:ATP ratio. However, increases in Ca^{2+} concentration, localization of AMPK within the cells, redox status and DNA-damage drugs might activate AMPK that has as main characteristic the activation of catabolic processes while inhibiting anabolic processes. Adapted from Garcia, D. and Shaw, R.J., Molecullar Cell, 2017

As already discussed, AMPK activation has as main goal, the restoration of energy homeostasis, by promoting the generation of ATP, via catabolic pathways, and preventing the consumption of ATP by inhibiting anabolic pathways. As consequence, AMPK activation has a direct impact in the overall cellular metabolism affecting lipid, glucose and protein metabolism. Additionally, AMPK activation has an important role in regulating mitochondria dynamics: promoting mitochondrial biogenesis, fission and mitophagy. This apparently contradictory effects of AMPK, promoting mitophagy and mitochondrial fission while promoting, also, mitochondrial biogenesis, suggests that AMPK favors the segregation of damaged and dysfunctional mitochondria and, at the same time, induces the synthesis of new mitochondria to replace the mitochondrial mass, lost by mitophagy (GARCIA; SHAW, 2017; HARDIE; ROSS; HAWLEY, 2012).

AMPK promotes glucose uptake by phosphorylating the thioredoxin interacting protein (TXNIP) (WU et al., 2013a), TBC1 domain family member 1 (TBC1D1) (PEHMØLLER et al., 2009) and histone deacetylase 5 (HDAC5) (MCGEE et al., 2008) and therefore, by different mechanisms, increasing GLUT1 (TXNIP) and GLUT4 (TBC1D1 and HDAC5) translocation to the membrane, and, thus, glucose uptake, leading to the normalization of AMP:ATP ratio (WU et al., 2013b). AMPK is also a central regulator of lipid metabolism, since it promotes the phosphorylation of ACC1 and ACC2 leading to inhibition of FAS and promotion FAO by an indirect activation of CPT1, since the production of malonyl-CoA, inhibitor of CPT1, is reduced (O'NEILL; KISHTON; RATHMELL, 2016; PEARCE; PEARCE, 2017; WANG et al., 2016). Protein metabolism, which is largely regulated by mTOR, especially mTORC1 (JONES; PEARCE, 2017), is also affected by AMPK, since it can inhibit mTORC1 activity by two different mechanisms: (1) phosphorylation and activation of upstream mTORC1 inhibitor tuberous sclerosis 2 (TSC2) (INOKI; ZHU; GUAN, 2003) and (2) phosphorylation with consequent inhibition of the regulatory-associated protein of mTOR (Raptor) (GWINN et al., 2008), a scaffold subunit of mTORC1 that recruits downstream substrates. AMPK has also been linked with the direct phosphorylation of eukaryotic elongation factor 2 kinase (eEF2K) (LEPRIVIER et al., 2013), a negative protein elongator that is inhibited by mTORC1 (FALLER et al., 2014), reinforcing the importance of correct balance of these two important metabolic sensors and further demonstrating how these two proteins work, counteracting the actions of each other.

6. CONCLUSIONS

6. CONCLUSIONS

- Metabolic reprogramming induced by VitD3 in diabetic patients' monocytes is different from that induced in healthy donors' monocytes;

- Extracellular glucose levels had little effect upon VitD3-induction of functional tolDC in both T1D patients and healthy donors;

- Blood DC from T1D patients are more glycolytic and are characterized by higher secretion of TNF-α, which might indicate that these cells have a pro-inflammatory phenotype.

- VitD3, RA and Dex induce different metabolic changes in tolDC, which are, however, are equally capable to induce functional suppressive T cells;

- VitD3 treated DC were affected by extracellular glucose levels, which had no effect on RA- and Dex-induced DC;

- AMPK is required for various immunosuppression-related in vivo and in vitro activities of RA-DC, but not for VitD DC and Dex-DC, though its activity was also elevated on Vit DC;

- LCFA pathway might be a common feature for VitD3-, RA- and Dex-induced tolDC;

7. REFERENCES

7. REFERENCES

ADORINI, L. Tolerogenic dendritic cells induced by vitamin D receptor ligands enhance regulatory T cells inhibiting autoimmune diabetes. v. 987, p. 258–261, 1 abr. 2003.

ALLEN, J. S. et al. Plasmacytoid dendritic cells are proportionally expanded at diagnosis of type 1 diabetes and enhance islet autoantigen presentation to T-cells through immune complex capture. **Diabetes**, v. 58, n. 1, p. 138–145, jan. 2009.

ALONSO, D.; NUNGESTER, W. J. Comparative study of host resistance of guinea pigs and rats. V. The effect of pneumococcal products on glycolysis and oxygen uptake by polymorphonuclear leucocytes. **Journal of Infectious Diseases**, v. 99, n. 2, p. 174–181, set. 1956.

ALTINOZ, M. A. et al. Erucic acid, a nutritional PPARδ-ligand may influence Huntington's disease pathogenesis. p. 1–9, 15 out. 2019.

ALTINOZ, M. A.; OZPINAR, A. PPAR-δ and erucic acid in multiple sclerosis and Alzheimer's Disease. Likely benefits in terms of immunity and metabolism. **International immunopharmacology**, v. 69, p. 245–256, 7 fev. 2019.

ALVAREZ, D.; VOLLMANN, E. H.; ANDRIAN, VON, U. H. Mechanisms and consequences of dendritic cell migration. **Immunity**, v. 29, n. 3, p. 325–342, 19 set. 2008.

ANGELIN, A. et al. Foxp3 Reprograms T Cell Metabolism to Function in Low-Glucose, High-Lactate Environments. **Cell Metabolism**, p. 1–20, 10 abr. 2017.

ANGELINI, F. et al. Altered phenotype and function of dendritic cells in children with type 1 diabetes. **Clinical and Experimental Immunology**, v. 142, n. 2, p. 341–346, 1 nov. 2005.

AUTISSIER, P. et al. Evaluation of a 12-color flow cytometry panel to study lymphocyte, monocyte, and dendritic cell subsets in humans. **Cytometry Part A**, v. 9999A, p. NA–NA, 2010.

BACHEM, A. et al. Superior antigen cross-presentation and XCR1 expression define human CD11c +CD141 +cells as homologues of mouse CD8 +dendritic cells. **Journal of Experimental Medicine**, v. 207, n. 6, p. 1273–1281, 7 jun. 2010.

BAKAY, M. et al. The Genetic Contribution to Type 1 Diabetes. **Current Diabetes Reports**, v. 19, n. 11, p. 55–14, 4 nov. 2019.

BAKDASH, G. et al. Vitamin D3 metabolite calcidiol primes human dendritic cells to promote the development of immunomodulatory IL-10-producing T cells. **Vaccine**, v. 32, n. 47, p. 6294–6302, 29 out. 2014.

BAKDASH, G. et al. Retinoic acid primes human dendritic cells to induce gut-homing, IL-10-producing regulatory T cells. **Mucosal Immunology**, v. 8, n. 2, p. 265–278, mar. 2015.

BALASA, B. et al. CD40 ligand-CD40 interactions are necessary for the initiation of insulitis and diabetes in nonobese diabetic mice. **Journal of immunology (Baltimore, Md. : 1950)**, v. 159, n. 9, p. 4620–4627, 1997.

BANCHEREAU, J. et al. Immunobiology of dendritic cells. **Annual Review of Immunology**, v. 18, n. 1, p. 767–811, 2000.

BARTHELS, C. et al. CD40-signalling abrogates induction of RORγt+ Treg cells by intestinal CD103+ DCs and causes fatal colitis. p. 1–13, 2 mar. 2017.

BASIT, F. et al. Human Dendritic Cell Subsets Undergo Distinct Metabolic Reprogramming for Immune Response. **Frontiers in immunology**, v. 9, p. 2489, 2018.

BEKIARIS, V.; PERSSON, E. K.; AGACE, W. W. Intestinal dendritic cells in the regulation of mucosal immunity. **Immunological reviews**, v. 260, n. 1, p. 86–101, jul. 2014.

BELL, G. M. et al. Autologous tolerogenic dendritic cells for rheumatoid and inflammatory arthritis. **Annals of the rheumatic diseases**, v. 76, n. 1, p. 227–234, jan. 2017.

BENHAM, H. et al. Citrullinated peptide dendritic cell immunotherapy in HLA risk genotype-positive rheumatoid arthritis patients. **Science translational medicine**, v. 7, n. 290, p. 290ra87–290ra87, 3 jun. 2015.

BHAGAVAN, N. V.; HA, C. E. **Chapter 25. Nucleotide Metabolism**. Traducao. [s.l.] Elsevier Inc, 2015. p. 465–488

BHAGAVAN, N. V.; HA, C.-E. **Lipids I: Fatty Acids and Eicosanoids**. Traducao. First Edition ed. [s.l.] Elsevier Inc, 2010. p. 191–207

BLANCO, B. 8. **Chapter 15 - Lipid Metabolism**. Traducao. [s.l.] Elsevier Inc, 2017. p. 325–365

BOLTJES, A.; VAN WIJK, F. Human dendritic cell functional specialization in steady-state and inflammation. **Frontiers in immunology**, v. 5, p. 131, 2014.

BROCKER, T.; RIEDINGER, M.; KARJALAINEN, K. Targeted Expression of Major Histocompatibility Complex (MHC) Class II Molecules Demonstrates that Dendritic Cells Can Induce Negative but Not Positive Selection of Thymocytes In Vivo. **Journal of Experimental Medicine**, v. 185, n. 3, p. 541–550, 3 fev. 1997.

BUCK, M. D. et al. Mitochondrial Dynamics Controls T Cell Fate through Metabolic Programming. **Cell**, v. 166, n. 1, p. 63–76, 30 jun. 2016.

BUCK, M. D. et al. Metabolic Instruction of Immunity. **Cell**, v. 169, n. 4, p. 570–586, 4 maio 2017.

CALDERON, B.; CARRERO, J. A.; UNANUE, E. R. The central role of antigen presentation in islets of Langerhans in autoimmune diabetes. **Current opinion in immunology**, v. 26, p. 32–40, fev. 2014.

CANTOR, J.; HASKINS, K. Recruitment and Activation of Macrophages by Pathogenic CD4 T Cells in Type 1 Diabetes: Evidence for Involvement of CCR8 and CCL1. **Journal of immunology (Baltimore, Md. : 1950)**, v. 179, n. 9, p. 5760–5767, 18 out. 2007.

CAPPA, M. et al. A mixture of oleic, erucic and conjugated linoleic acids modulates cerebrospinal fluid inflammatory markers and improve somatosensorial evoked potential in X-linked adrenoleukodystrophy female carriers. **Journal of Inherited Metabolic Disease**, v. 35, n. 5, p. 899–907, 22 dez. 2011.

CARRENO, B. M.; BECKER-HAPAK, M.; LINETTE, G. P. CD40 regulates human dendritic cell-derived IL-7 production that, in turn, contributes to CD8+ T-cell antigen-specific expansion. **Immunology and Cell Biology**, v. 87, n. 2, p. 167–177, 11 nov. 2008.

CARRERO, J. A. et al. Defining the Transcriptional and Cellular Landscape of Type 1 Diabetes in the NOD Mouse. **PLoS ONE**, v. 8, n. 3, p. e59701–14, 26 mar. 2013.

CARRERO, J. A. et al. Resident macrophages of pancreatic islets have a seminal role in the initiation of autoimmune diabetes of NOD mice. **Proceedings of the National Academy of Sciences of the United States of America**, v. 114, n. 48, p. E10418–E10427, 28 nov. 2017.

CARROLL, K. C.; VIOLLET, B.; SUTTLES, J. AMPKα1 deficiency amplifies proinflammatory myeloid APC activity and CD40 signaling. **Journal of leukocyte biology**, v. 94, n. 6, p. 1113–1121, dez. 2013.

CASTRO, L. F. C.; TOCHER, D. R.; MONROIG, O. Long-chain polyunsaturated fatty acid biosynthesis in chordates: Insights into the evolution of Fads and Elovl gene repertoire. **Progress in lipid research**, v. 62, p. 25–40, 1 abr. 2016.

CERBONI, S.; GENTILI, M.; MANEL, N. Diversity of pathogen sensors in dendritic cells. **Advances in immunology**, v. 120, p. 211–237, 2013.

CHEN, X. et al. Type 1 diabetes patients have significantly lower frequency of plasmacytoid dendritic cells in the peripheral blood. **Clinical Immunology**, v. 129, n. 3, p. 413–418, 1 dez. 2008.

CHEN, X. et al. Intercellular interplay between Sirt1 signalling and cell metabolism in immune cell biology. **… immunology**, v. 145, n. 4, p. 455–467, 3 jun. 2015.

CHEUNG, P. C. et al. Characterization of AMP-activated protein kinase gamma-subunit isoforms and their role in AMP binding. **The Biochemical journal**, v. 346 Pt 3, n. Pt 3, p. 659–669, 15 mar. 2000.

COLEMAN, M. M. et al. Alveolar Macrophages Contribute to Respiratory Tolerance by Inducing FoxP3 Expression in Naive T Cells. **American journal of respiratory cell and molecular biology**, v. 48, n. 6, p. 773–780, 3 jun. 2013.

COOMBES, J. L. et al. A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. **Journal of Experimental Medicine**, v. 204, n. 8, p. 1757–1764, 6 ago. 2007.

COOPER, M. A. et al. Human natural killer cells: a unique innate immunoregulatory role for the CD56(bright) subset. **Blood**, v. 97, n. 10, p. 3146–3151, 15 maio 2001.

CROFT, M.; BRADLEY, L. M.; SWAIN, S. L. Naive versus memory CD4 T cell response to antigen. Memory cells are less dependent on accessory cell costimulation and can respond to many antigen-presenting cell types including resting B cells. **Journal of immunology (Baltimore, Md. : 1950)**, v. 152, n. 6, p. 2675–2685, 15 mar. 1994.

DAHLÉN, E. et al. Dendritic cells and macrophages are the first and major producers of TNF-alpha in pancreatic islets in the nonobese diabetic mouse. **Journal of immunology (Baltimore, Md. : 1950)**, v. 160, n. 7, p. 3585–3593, 1 abr. 1998.

DAHLÉN, E.; HEDLUND, G.; DAWE, K. Low CD86 Expression in the Nonobese Diabetic Mouse Results in the Impairment of Both T Cell Activation and CTLA-4 Up-Regulation. **Journal of immunology (Baltimore, Md. : 1950)**, v. 164, n. 5, p. 2444–2456, 1 mar. 2000.

DÁŇOVÁ, K. et al. NF-κB, p38 MAPK, ERK1/2, mTOR, STAT3 and increased glycolysis regulate stability of paricalcitol/dexamethasone-generated tolerogenic dendritic cells in the inflammatory environment. **Oncotarget**, v. 6, n. 16, p. 14123–14138, 10 jun. 2015.

DÁŇOVÁ, K. et al. Tolerogenic Dendritic Cells from Poorly Compensated Type 1 Diabetes Patients Have Decreased Ability To Induce Stable Antigen-Specific T Cell Hyporesponsiveness and Generation of Suppressive Regulatory T Cells. **The Journal of Immunology**, v. 198, n. 2, p. 729–740, 15 jan. 2017.

DEL RIO, M.-L. et al. Development and functional specialization of CD103+ dendritic cells. **Immunological reviews**, v. 234, n. 1, p. 268–281, mar. 2010.

DENNING, T. L. et al. Functional Specializations of Intestinal Dendritic Cell and Macrophage Subsets That Control Th17 and Regulatory T Cell Responses Are Dependent on the T Cell/APC Ratio, Source of Mouse Strain, and Regional Localization. **Journal of immunology (Baltimore, Md. : 1950)**, v. 187, n. 2, p. 733–747, 6 jul. 2011.

DHAR, A. K.; BARTON, D. A. Depression and the Link with Cardiovascular Disease. **Frontiers in Psychiatry**, v. 7, n. 1, p. 130–9, 21 mar. 2016.

DINICOLANTONIO, J. J.; O'KEEFE, J. H. Importance of maintaining a low omega–6/omega–3 ratio for reducing inflammation. **Open Heart**, v. 5, n. 2, p. e000946–4, 26 nov. 2018.

DOGUSAN, Z. et al. Double-Stranded RNA Induces Pancreatic -Cell Apoptosis by Activation of the Toll-Like Receptor 3 and Interferon Regulatory Factor 3 Pathways. **Diabetes**, v. 57, n. 5, p. 1236–1245, 1 maio 2008.

DOMINGUEZ, L. J.; BARBAGALLO, M. **Chapter 3. Not All Fats Are Unhealthy**. Traducao. [s.l.] Elsevier Inc, 2017. p. 35–58

DOMÍNGUEZ-AMOROCHO, O. et al. Immunometabolism: A target for the comprehension of immune response toward transplantation. **World Journal of Transplantation**, v. 9, n. 2, p. 27–34, 20 jun. 2019.

DONG, H.; BULLOCK, T. N. J. Metabolic influences that regulate dendritic cell function in tumors. **Frontiers in immunology**, v. 5, p. 24, 2014.

DOTTA, F. et al. Coxsackie B4 virus infection of beta cells and natural killer cell insulitis in recent-onset type 1 diabetic patients. **PNAS**, v. 104, n. 12, p. 5115–5120, 20 mar. 2007.

DRAPER, E. et al. Omega-3 fatty acids attenuate dendritic cell function via NF-κB independent of PPARγ. **The Journal of Nutritional Biochemistry**, v. 22, n. 8, p. 784–790, 1 ago. 2011.

DUAN, W.; CROFT, M. Control of Regulatory T Cells and Airway Tolerance by Lung Macrophages and Dendritic Cells. **Annals of the American Thoracic Society**, v. 11, n. Supplement 5, p. S306–S313, dez. 2014.

DURAI, V. et al. Cryptic activation of an Irf8 enhancer governs cDC1 fate specification. **Nature immunology**, v. 462, p. 1–31, 17 ago. 2019.

DUTERTRE, C.-A. et al. Single-Cell Analysis of Human Mononuclear Phagocytes Reveals Subset-Defining Markers and Identifies Circulating Inflammatory Dendritic Cells. **Immunity**, v. 51, n. 3, p. 573–589.e8, 17 set. 2019.

DZIONEK, A. et al. BDCA-2, BDCA-3, and BDCA-4: three markers for distinct subsets of dendritic cells in human peripheral blood. **Am Assoc Immnol**, v. 165, n. 11, p. 6037–6046, 1 dez. 2000.

ESTERHÁZY, D. et al. Classical dendritic cells are required for dietary antigen-mediated induction of peripheral Treg cells and tolerance. **Nature immunology**, v. 17, n. 5, p. 545–555, maio 2016.

ESTERHÁZY, D. et al. Compartmentalized gut lymph node drainage dictates adaptive immune responses. **Nature Publishing Group**, v. 569, n. 7754, p. 126–130, maio 2019.

EVERTS, B. et al. Commitment to glycolysis sustains survival of NO-producing inflammatory dendritic cells. **Blood**, v. 120, n. 7, p. 1422–1431, 16 ago. 2012.

EVERTS, B. et al. TLR-driven early glycolytic reprogramming via the kinases TBK1-IKKε supports the anabolic demands of dendritic cell activation. **Nature immunology**, v. 15, n. 4, p. 323–332, abr. 2014b.

EVERTS, B.; PEARCE, E. J. Metabolic control of dendritic cell activation and function: recent advances and clinical implications. **Frontiers in Immunology**, v. 5, p. 203, 2014.

EZZELARAB, M. B. et al. Regulatory Dendritic Cell Infusion Prolongs Kidney Allograft Survival in Nonhuman Primates. **American Journal of Transplantation**, v. 13, n. 8, p. 1989–2005, 11 jun. 2013.

FALLER, W. J. et al. mTORC1-mediated translational elongation limits intestinal tumour initiation and growth. **Nature Publishing Group**, p. 1–16, 5 nov. 2014.

FENG, T. et al. Generation of Mucosal Dendritic Cells from Bone Marrow Reveals a Critical Role of Retinoic Acid. **Journal of immunology (Baltimore, Md. : 1950)**, v. 185, n. 10, p. 5915–5925, 3 nov. 2010.

FERREIRA, G. B. et al. Differential protein pathways in 1,25-dihydroxyvitamin d(3) and dexamethasone modulated tolerogenic human dendritic cells. **Journal of proteome research**, v. 11, n. 2, p. 941–971, 3 fev. 2012.

FERREIRA, G. B. et al. 1,25-Dihydroxyvitamin D3 Promotes Tolerogenic Dendritic Cells with Functional Migratory Properties in NOD Mice. **Journal of immunology (Baltimore, Md. : 1950)**, v. 192, n. 9, p. 4210–4220, 18 abr. 2014.

FERREIRA, G. B. et al. Vitamin D3 Induces Tolerance in Human Dendritic Cells by Activation of Intracellular Metabolic Pathways. v. 10, n. 5, p. 711–725, 10 fev. 2015.

FERRIS, S. T. et al. A Minor Subset of Batf3-Dependent Antigen-Presenting Cells in Islets of Langerhans Is Essential for the Development of Autoimmune Diabetes. **Immunity**, v. 41, n. 4, p. 657–669, 16 out. 2014.

FILGUEIRAS, L. R. et al. Leukotriene B4-mediated sterile inflammation promotes susceptibility to sepsis in a mouse model of type 1 diabetes. **Science signaling**, v. 8, n. 361, p. ra10–ra10, 27 jan. 2015.

FISCHER, R. et al. Use of rapamycin in the induction of tolerogenic dendritic cells. **Handbook of experimental pharmacology**, v. 188, n. 188, p. 215–232, 2009.

FLIESSER, M. et al. Hypoxia-inducible factor 1α modulates metabolic activity and cytokine release in anti-Aspergillus fumigatus immune responses initiated by human dendritic cells. **International journal of medical microbiology : IJMM**, v. 305, n. 8, p. 865–873, dez. 2015.

FORLENZA, G. P.; REWERS, M. The epidemic of type 1 diabetes. **Current Opinion in Endocrinology, Diabetes and Obesity**, v. 18, n. 4, p. 248–251, ago. 2011.

FÖRSTER, I.; LIEBERAM, I. Peripheral tolerance of CD4 T cells following local activation in adolescent mice. **European journal of immunology**, v. 26, n. 12, p. 3194–3202, dez. 1996.

FRIEDL, P.; GUNZER, M. Interaction of T cells with APCs: the serial encounter model. **Trends in Immunology**, v. 22, n. 4, p. 187–191, abr. 2001.

GARCIA, D.; SHAW, R. J. AMPK: Mechanisms of Cellular Energy Sensing and Restoration of Metabolic Balance. **Molecular Cell**, v. 66, n. 6, p. 789–800, 15 jun. 2017.

GEISSMANN, F. et al. Development of monocytes, macrophages, and dendritic cells. **Science (New York, N.Y.)**, 2010.

GIANNOUKAKIS et al. Phase I (Safety) Study of Autologous Tolerogenic Dendritic Cells in Type 1 Diabetic Patients. **Diabetes Care**, v. 34, n. 9, p. 2026–2032, 25 ago. 2011.

GOWANS, G. J. et al. AMP Is a True Physiological Regulator of AMP-Activated Protein Kinase by Both Allosteric Activation and Enhancing Net Phosphorylation. **Cell Metabolism**, v. 18, n. 4, p. 556–566, 1 out. 2013.

GRANOT, T. et al. Dendritic Cells Display Subset and Tissue-Specific Maturation Dynamics over Human Life. **Immunity**, v. 46, n. 3, p. 504–515, 21 mar. 2017.

GROHMANN, U. et al. CTLA-4-Ig regulates tryptophan catabolism in vivo. **Nature immunology**, v. 3, n. 11, p. 1097–1101, nov. 2002.

GROUX, H. et al. A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. **Nature**, v. 389, n. 6652, p. 737–742, 16 out. 1997.

GUAK, H. et al. Glycolytic metabolism is essential for CCR7 oligomerization and dendritic cell migration. **Nature communications**, v. 9, n. 1, p. 1–12, 15 jun. 2018.

GUERMONPREZ, P. et al. Antigen presentation and T cell stimulation by dendritic cells. **Annual Review of Immunology**, v. 20, p. 621–667, 2002.

GUILLIAMS, M. et al. Dendritic cells, monocytes and macrophages: a unified nomenclature based on ontogeny. **Nature reviews. Immunology**, v. 14, n. 8, p. 571–578, ago. 2014.

GUILLIAMS, M. et al. Unsupervised High-Dimensional Analysis Aligns Dendritic Cells across Tissues and Species. **Immunity**, v. 45, n. 3, p. 669–684, 20 set. 2016.

GUTIÉRREZ, S.; SVAHN, S. L.; JOHANSSON, M. E. Effects of Omega-3 Fatty Acids on Immune Cells. **International Journal of Molecular Sciences**, v. 20, n. 20, p. 5028–21, out. 2019.

GWINN, D. M. et al. AMPK Phosphorylation of Raptor Mediates a Metabolic Checkpoint. **Molecular Cell**, v. 30, n. 2, p. 214–226, abr. 2008.

HANIFFA, M.; COLLIN, M.; GINHOUX, F. Ontogeny and functional specialization of dendritic cells in human and mouse. v. 120, p. 1–49, 2013.

HARDIE, D. G.; ROSS, F. A.; HAWLEY, S. A. AMPK: a nutrient and energy sensor that maintains energy homeostasis. **Nature reviews. Molecular cell biology**, v. 13, n. 4, p. 251–262, 22 mar. 2012.

HAWIGER, D. et al. Dendritic cells induce peripheral T cell unresponsiveness under steady state conditions in vivo. **Journal of Experimental Medicine**, v. 194, n. 6, p. 769–779, 17 set. 2001.

HAWLEY, S. A. et al. Complexes between the LKB1 tumor suppressor, STRAD alpha/beta and MO25 alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. **Journal of biology**, v. 2, n. 4, p. 28–16, 2003.

HAWLEY, S. A. et al. Calmodulin-dependent protein kinase kinase-beta is an alternative upstream kinase for AMP-activated protein kinase. **Cell Metabolism**, v. 2, n. 1, p. 9–19, jul. 2005.

HEMMI, H.; AKIRA, S. TLR signalling and the function of dendritic cells. **Chemical immunology and allergy**, v. 86, p. 120–135, 2005.

HENDERSON, R. A.; WATKINS, S. C.; FLYNN, J. L. Activation of human dendritic cells following infection with Mycobacterium tuberculosis. **Journal of immunology (Baltimore, Md. : 1950)**, v. 159, n. 2, p. 635–643, 15 jul. 1997.

HOUSLEY, W. J. et al. PPARgamma regulates retinoic acid-mediated DC induction of Tregs. **Journal of leukocyte biology**, v. 86, n. 2, p. 293–301, ago. 2009.

HOVING, L. R. et al. GC-MS Analysis of Medium- and Long-Chain Fatty Acids in Blood Samples. In: **Toll-Like Receptors**. Methods and Protocols. Traducao. New York, NY: Springer New York, 2018. v. 1730p. 257–265.

HUANG, Y. et al. Kidney-Derived Mesenchymal Stromal Cells Modulate Dendritic Cell Function to Suppress Alloimmune Responses and Delay Allograft Rejection. **Transplantation**, v. 90, n. 12, p. 1307–1311, dez. 2010.

HUANG, Y.-S. et al. Eicosadienoic acid differentially modulates production of pro-inflammatory modulators in murine macrophages. **Molecular and Cellular Biochemistry**, v. 358, n. 1-2, p. 85–94, 19 jun. 2011.

IDOYAGA, J. et al. Specialized role of migratory dendritic cells in peripheral tolerance induction. **Journal of Clinical Investigation**, v. 123, n. 2, p. 844–854, fev. 2013.

ILIEV, I. D. et al. Human intestinal epithelial cells promote the differentiation of tolerogenic dendritic cells. **Gut**, v. 58, n. 11, p. 1481–1489, nov. 2009.

IMAI, Y.; YAMAKAWA, M.; KASAJIMA, T. The lymphocyte-dendritic cell system. **Histology and histopathology**, v. 13, n. 2, p. 469–510, abr. 1998.

INAGAKI, K. et al. Identification and expression of a rat fatty acid elongase involved in the biosynthesis of C18 fatty acids. **Bioscience, biotechnology, and biochemistry**, v. 66, n. 3, p. 613–621, mar. 2002.

INNES, J. K.; CALDER, P. C. Omega-6 fatty acids and inflammation. **Prostaglandins, leukotrienes, and essential fatty acids**, v. 132, p. 41–48, maio 2018.

INOKI, K.; ZHU, T.; GUAN, K.-L. TSC2 mediates cellular energy response to control cell growth and survival. **Cell**, v. 115, n. 5, p. 577–590, 26 nov. 2003.

IP, W. K. E. et al. Anti-inflammatory effect of IL-10 mediated by metabolic reprogramming of macrophages. **Science (New York, N.Y.)**, v. 356, n. 6337, p. 513–519, 5 maio 2017.

ITANO, A. A.; JENKINS, M. K. Antigen presentation to naive CD4 T cells in the lymph node. **Nature immunology**, v. 4, n. 8, p. 733–739, ago. 2003.

JAKOBSSON, A.; WESTERBERG, R.; JACOBSSON, A. Fatty acid elongases in mammals: their regulation and roles in metabolism. **Progress in lipid research**, v. 45, n. 3, p. 237–249, maio 2006.

JANTSCH, J. et al. Hypoxia and Hypoxia-Inducible Factor-1 Modulate Lipopolysaccharide-Induced Dendritic Cell Activation and Function. **Journal of immunology (Baltimore, Md. : 1950)**, v. 180, n. 7, p. 4697–4705, 19 mar. 2008.

JAUREGUI-AMEZAGA, A. et al. Intraperitoneal Administration of Autologous Tolerogenic Dendritic Cells for Refractory Crohn's Disease: A Phase I Study. **Journal of Crohn's & colitis**, v. 9, n. 12, p. 1071–1078, 27 nov. 2015.

JONES, R. G.; PEARCE, E. J. MenTORing Immunity: mTOR Signaling in the Development and Function of Tissue-Resident Immune Cells. **Immunity**, v. 46, n. 5, p. 730–742, 16 maio 2017.

KAISAR, M. M. M. et al. Butyrate Conditions Human Dendritic Cells to Prime Type 1 Regulatory T Cells via both Histone Deacetylase Inhibition and G Protein-Coupled Receptor 109A Signaling. **Frontiers in immunology**, v. 8, p. 13–14, 30 out. 2017.

KHARE, A. et al. Cutting Edge: Dual Function of PPARγ in CD11c +Cells Ensures Immune Tolerance in the Airways. **Journal of immunology (Baltimore, Md. : 1950)**, v. 195, n. 2, p. 431–435, 2 jul. 2015.

KLEIJWEGT, F. S. et al. Critical Role for TNF in the Induction of Human Antigen-Specific Regulatory T Cells by Tolerogenic Dendritic Cells. **Journal of immunology (Baltimore, Md. : 1950)**, v. 185, n. 3, p. 1412–1418, 21 jul. 2010.

KLEIJWEGT, F. S. et al. Tolerogenic dendritic cells impede priming of naïve CD8(+) T cells and deplete memory CD8(+) T cells. v. 43, n. 1, p. 85–92, 1 jan. 2013.

KLINKE, D. J. Extent of Beta Cell Destruction Is Important but Insufficient to Predict the Onset of Type 1 Diabetes Mellitus. **PLoS ONE**, v. 3, n. 1, p. e1374–10, 2 jan. 2008.

KLOCPERK, A. et al. Changes in innate and adaptive immunity over the first year after the onset of type 1 diabetes. **Acta Diabetologica**, p. 1–11, 27 set. 2019.

KNOTT, R. M.; FORRESTER, J. V. Role of glucose regulatory mechanisms in diabetic retinopathy. **The British journal of ophthalmology**, v. 79, n. 11, p. 1046–1049, nov. 1995.

KRAWCZYK, C. M. et al. Toll-like receptor-induced changes in glycolytic metabolism regulate dendritic cell activation. **Blood**, v. 115, n. 23, p. 4742–4749, 10 jun. 2010.

KURTS, C. Constitutive class I-restricted exogenous presentation of self antigens in vivo. **Journal of Experimental Medicine**, v. 184, n. 3, p. 923–930, 1 set. 1996.

LAMPEN, A. et al. Metabolism of vitamin A and its active metabolite all-trans-retinoic acid in small intestinal enterocytes. **Journal of Pharmacology and Experimental Therapeutics**, v. 295, n. 3, p. 979–985, dez. 2000.

LAMPROPOULOU, V. et al. Itaconate Links Inhibition of Succinate Dehydrogenase with Macrophage Metabolic Remodeling and Regulation of Inflammation. **Cell Metabolism**, v. 24, n. 1, p. 158–166, 12 jul. 2016.

LAN, Y. Y. et al. "Alternatively Activated" Dendritic Cells Preferentially Secrete IL-10, Expand Foxp3+CD4+ T Cells, and Induce Long-Term Organ Allograft Survival in Combination with CTLA4-Ig. **Journal of immunology (Baltimore, Md. : 1950)**, v. 177, n. 9, p. 5868–5877, 18 out. 2006.

LEHUEN, A. et al. Immune cell crosstalk in type 1 diabetes. v. 10, n. 7, p. 501–513, jul. 2010.

LEPRIVIER, G. et al. The eEF2 Kinase Confers Resistance to Nutrient Deprivation by Blocking Translation Elongation. **Cell**, v. 153, n. 5, p. 1064–1079, 23 maio 2013.

LI, Q. et al. Interferon-alpha initiates type 1 diabetes in nonobese diabetic mice. **Proceedings of the National Academy of Sciences of the United States of America**, v. 105, n. 34, p. 12439–12444, 26 ago. 2008.

LIU, D. Double-Stranded Ribonucleic Acid (RNA) Induces -Cell Fas Messenger RNA Expression and Increases Cytokine-Induced -Cell Apoptosis. **Endocrinology**, v. 142, n. 6, p. 2593–2599, 1 jun. 2001.

LIU, G. et al. Dendritic cell SIRT1-HIF1α axis programs the differentiation of CD4+ T cells through IL-12 and TGF-β1. v. 112, n. 9, p. E957–E965, 17 fev. 2015.

LUTZ, M. B.; SCHULER, G. Immature, semi-mature and fully mature dendritic cells: which signals induce tolerance or immunity? **Trends in Immunology**, v. 23, n. 9, p. 445–449, set. 2002.

MA, L. et al. Prevention of Diabetes in NOD Mice by Administration of Dendritic Cells Deficient in Nuclear Transcription Factor-κB Activity. **Diabetes**, v. 52, n. 8, p. 1976–1985, 1 ago. 2003.

MACDOUGALL, C. E. et al. Visceral Adipose Tissue Immune Homeostasis Is Regulated by the Crosstalk between Adipocytes and Dendritic Cell Subsets. **Cell Metabolism**, v. 27, n. 3, p. 588–601.e4, 6 mar. 2018.

MADDUR, M. S. et al. Dendritic Cells in Autoimmune Diseases. v. 3, n. 1, p. 1–7, 12 jan. 2010.

MAGGI, J. et al. Dexamethasone and Monophosphoryl Lipid A-Modulated Dendritic Cells Promote Antigen-Specific Tolerogenic Properties on Naive and Memory CD4+ T Cells. **Frontiers in immunology**, v. 7, n. 8, p. 1473–12, 19 set. 2016.

MAHNKE, K. et al. Induction of CD4+/CD25+ regulatory T cells by targeting of antigens to immature dendritic cells. **Blood**, v. 101, n. 12, p. 4862–4869, 15 jun. 2003.

MALERBI, D. A.; FRANCO, L. J. Multicenter study of the prevalence of diabetes mellitus and impaired glucose tolerance in the urban Brazilian population aged 30-69 yr. The Brazilian Cooperative Group on the Study of Diabetes Prevalence. **Diabetes Care**, v. 15, n. 11, p. 1509–1516, nov. 1992.

MALINARICH, F. et al. High mitochondrial respiration and glycolytic capacity represent a metabolic phenotype of human tolerogenic dendritic cells. **The Journal of Immunology**, v. 194, n. 11, p. 5174–5186, 1 jun. 2015.

MANICASSAMY, S.; PULENDRAN, B. Dendritic cell control of tolerogenic responses. **Immunological reviews**, v. 241, n. 1, p. 206–227, maio 2011.

MARCHETTI, D. P. et al. Inflammatory profile in X-linked adrenoleukodystrophy patients: Understanding disease progression. **Journal of Cellular Biochemistry**, v. 119, n. 1, p. 1223–1233, 23 ago. 2017.

MARTIN, A. P. et al. Increased expression of CCL2 in insulin-producing cells of transgenic mice promotes mobilization of myeloid cells from the bone marrow, marked insulitis, and diabetes. **Diabetes**, v. 57, n. 11, p. 3025–3033, nov. 2008.

MCGEE, S. L. et al. AMP-activated protein kinase regulates GLUT4 transcription by phosphorylating histone deacetylase 5. **Diabetes**, v. 57, n. 4, p. 860–867, abr. 2008.

MCKEITHEN, D. N. et al. The emerging role of ASC in dendritic cell metabolism during Chlamydia infection. **PLoS ONE**, v. 12, n. 12, p. e0188643–18, 7 dez. 2017.

MEHTA, L. R.; DWORKIN, R. H.; SCHWID, S. R. Polyunsaturated fatty acids and their potential therapeutic role in multiple sclerosis. **Nature Clinical Practice Neurology**, v. 5, n. 2, p. 82–92, fev. 2009.

MERAD, M. et al. The Dendritic Cell Lineage: Ontogeny and Function of Dendritic Cells and Their Subsets in the Steady State and the Inflamed Setting. **Annual Review of Immunology**, v. 31, n. 1, p. 563–604, 21 mar. 2013.

MILDNER, A.; JUNG, S. Development and function of dendritic cell subsets. **Immunity**, v. 40, n. 5, p. 642–656, 2014.

MILLS, E. L. et al. Succinate Dehydrogenase Supports Metabolic Repurposing of Mitochondria to Drive Inflammatory Macrophages. **Cell**, v. 167, n. 2, p. 457–461.e14, 6 out. 2016.

MISHARIN, A. V. et al. Flow Cytometric Analysis of Macrophages and Dendritic Cell Subsets in the Mouse Lung. **American journal of respiratory cell and molecular biology**, v. 49, n. 4, p. 503–510, out. 2013.

MOCKING, R. J. T. et al. Ala54Thr Fatty Acid-Binding Protein 2 (FABP2) Polymorphism in Recurrent Depression: Associations with Fatty Acid Concentrations and Waist Circumference. **PLoS ONE**, v. 8, n. 12, p. e82980–10, 10 dez. 2013.

MOLLAH, Z. U. A. et al. Abnormal NF-kappa B function characterizes human type 1 diabetes dendritic cells and monocytes. **Journal of immunology (Baltimore, Md. : 1950)**, v. 180, n. 5, p. 3166–3175, 1 mar. 2008.

MONTANI, M. S. G. et al. High glucose and hyperglycemic sera from type 2 diabetic patients impair DC differentiation by inducing ROS and activating Wnt/β-catenin and p38 MAPK. **BBA - Molecular Basis of Disease**, v. 1862, n. 4, p. 805–813, 1 abr. 2016.

MOOKERJEE, S. A. et al. Quantifying intracellular rates of glycolytic and oxidative ATP production and consumption using extracellular flux measurements. **The Journal of biological chemistry**, v. 292, n. 17, p. 7189–7207, 28 abr. 2017.

MOON, Y. A. et al. Identification of a mammalian long chain fatty acyl elongase regulated by sterol regulatory element-binding proteins. **The Journal of biological chemistry**, v. 276, n. 48, p. 45358–45366, 30 nov. 2001.

MORAES, S. A.; FREITAS, I.; GIMENO, S. Diabetes mellitus prevalence and associated factors in adults in Ribeirão Preto, São Paulo, Brazil, 2006: OBEDIARP Project. **Cadernos de Saúde …**, v. 26, n. 5, p. 929–941, 2010.

MORELLI, A. E.; THOMSON, A. W. Tolerogenic dendritic cells and the quest for transplant tolerance. **Nature Reviews Immunology**, v. 7, n. 8, p. 610–621, 13 jul. 2007.

NAGY, K.; TIUCA, I.-D. Importance of Fatty Acids in Physiopathology of Human Body. In: **Fatty Acids**. Traducao. [s.l.] InTech, 2017. p. 1–21.

NAVARRO-BARRIUSO, J. et al. Comparative transcriptomic profile of tolerogenic dendritic cells differentiated with vitamin D3, dexamethasone and rapamycin. **Scientific Reports**, v. 8, n. 1, p. 14985, 8 out. 2018.

NELSON, J. R.; RASKIN, S. The eicosapentaenoic acid:arachidonic acid ratio and its clinical utility in cardiovascular disease. **Postgraduate Medicine**, v. 131, n. 4, p. 268–277, 14 maio 2019.

NERUP, J. et al. HL-A antigens and diabetes mellitus. **Lancet (London, England)**, v. 2, n. 7885, p. 864–866, 12 out. 1974.

NIEVES, W. et al. Myeloid-Restricted AMPKα1 Promotes Host Immunity and Protects against IL-12/23p40–Dependent Lung Injury during Hookworm Infection. **Journal of immunology (Baltimore, Md. : 1950)**, v. 196, n. 11, p. 4632–4640, 20 maio 2016.

O'NEILL, L. A. J.; KISHTON, R. J.; RATHMELL, J. A guide to immunometabolism for immunologists. **Nature reviews. Immunology**, v. 16, n. 9, p. 553–565, set. 2016.

OCHANDO, J. et al. Tolerogenic Dendritic Cells in Organ Transplantation. **Transplant International**, p. tri.13504–31, 31 ago. 2019.

OGURTSOVA, K. et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. **Diabetes Research and Clinical Practice**, v. 128, p. 40–50, jun. 2017.

ONODERA, T. et al. Eicosapentaenoic acid and 5-HEPE enhance macrophage-mediated Treg induction in mice. **Scientific Reports**, v. 7, n. 1, p. 1821–11, 4 jul. 2017.

OREN, R. et al. Metabolic patterns in three types of phagocytizing cells. **The Journal of cell biology**, v. 17, n. 3, p. 487–501, jun. 1963.

O'KEEFFE, M.; MOK, W. H.; RADFORD, K. J. Human dendritic cell subsets and function in health and disease. **Cellular and Molecular Life Sciences**, v. 72, n. 22, p. 1–17, 4 ago. 2015.

PANTEL, A. et al. Direct type I IFN but not MDA5/TLR3 activation of dendritic cells is required for maturation and metabolic shift to glycolysis after poly IC stimulation. **PLoS biology**, v. 12, n. 1, p. e1001759, jan. 2014.

PASCHOU, S. A. et al. On type 1 diabetes mellitus pathogenesis. **Endocrine Connections**, v. 7, n. 1, p. R38–R46, 17 jan. 2018.

PATENTE, T. A. et al. Human Dendritic Cells: Their Heterogeneity and Clinical Application Potential in Cancer Immunotherapy. **Frontiers in immunology**, v. 9, p. 3176, 2018.

PEARCE, E. J.; EVERTS, B. Dendritic cell metabolism. **Nature Reviews Immunology**, v. 15, n. 1, p. 18–29, 1 jan. 2015.

PEARCE, E. J.; PEARCE, E. L. Immunometabolism in 2017: Driving immunity: all roads lead to metabolism. **Nature reviews. Immunology**, v. 18, n. 2, p. 1–2, 11 dez. 2017.

PEARCE, E. L.; PEARCE, E. J. Metabolic Pathways in Immune Cell Activation and Quiescence. **Immunity**, v. 38, n. 4, p. 633–643, 18 abr. 2013.

PEHMØLLER, C. et al. Genetic disruption of AMPK signaling abolishes both contraction- and insulin-stimulated TBC1D1 phosphorylation and 14-3-3 binding in mouse skeletal muscle. **American Journal of Physiology-Endocrinology and Metabolism**, v. 297, n. 3, p. E665–E675, set. 2009.

PELGROM, L. R. et al. LKB1 expressed in dendritic cells governs the development and expansion of thymus-derived regulatory T cells. **Cell research**, p. 1–14, 27 mar. 2019.

PENG, R. et al. Abnormal Peripheral Blood Dendritic Cell Populations in Type 1 Diabetes. **Annals of the New York Academy of Sciences**, v. 1005, n. 1, p. 222–225, 1 nov. 2003.

PEREIRA, D. M. et al. Anti-Inflammatory Effect of Unsaturated Fatty Acids and Ergosta-7,22-dien-3-ol from Marthasterias glacialis: Prevention of CHOP-Mediated ER-Stress and NF-κB Activation. **PLoS ONE**, v. 9, n. 2, p. e88341–9, 13 fev. 2014.

PHILLIPS et al. Type 1 Diabetes Development Requires Both CD4+ and CD8+ T cells and Can Be Reversed by Non-Depleting Antibodies Targeting Both T Cell Populations. **The Review of Diabetic Studies**, v. 6, n. 2, p. 97–103, 2009.

QAISAR, N. et al. A Critical Role for the Type I Interferon Receptor in Virus-Induced Autoimmune Diabetes in Rats. **Diabetes**, v. 66, n. 1, p. 145–157, jan. 2017.

QUENTIN, T. et al. Different expression of the catalytic alpha subunits of the AMP activated protein kinase--an immunohistochemical study in human tissue. **Histology and histopathology**, v. 26, n. 5, p. 589–596, maio 2011.

RAMALHO, T. et al. Leukotriene-B4 modulates macrophage metabolism and fat loss in type 1 diabetic mice. **Journal of Leukocyte Biology**, v. 106, n. 3, p. 665–675, 22 jul. 2019.

RAMOS, R. N. et al. Monocyte-derived dendritic cells from breast cancer patients are biased to induce CD4+CD25+Foxp3+ regulatory T cells. **Journal of leukocyte biology**, v. 92, n. 3, p. 673–682, set. 2012.

RANDOLPH, G. J.; ANGELI, V.; SWARTZ, M. A. Dendritic-cell trafficking to lymph nodes through lymphatic vessels. **Nature Reviews Immunology**, v. 5, n. 8, p. 617–628, ago. 2005.

RASSCHAERT, J. et al. Global profiling of double stranded RNA- and IFN-?-induced genes in rat pancreatic beta cells. **Diabetologia**, v. 46, n. 12, p. 1641–1657, 1 dez. 2003.

RASSCHAERT, J. et al. Toll-like receptor 3 and STAT-1 contribute to double-stranded RNA+ interferon-gamma-induced apoptosis in primary pancreatic beta-cells. v. 280, n. 40, p. 33984–33991, 7 out. 2005.

REDONDO, M. J. et al. Heterogeneity of type I diabetes: analysis of monozygotic twins in Great Britain and the United States. **Diabetologia**, v. 44, n. 3, p. 354–362, mar. 2001.

REWERS, M. J. et al. Assessment and monitoring of glycemic control in children and adolescents with diabetes. **Pediatric Diabetes**, v. 15, n. S20, p. 102–114, 3 set. 2014.

REYNOLDS, G.; HANIFFA, M. Human and Mouse Mononuclear Phagocyte Networks: A Tale of Two Species? **Frontiers in immunology**, v. 6, p. 330, 2015.

ROBBINS, S. H. et al. Novel insights into the relationships between dendritic cell subsets in human and mouse revealed by genome-wide expression profiling. **Genome biology**, v. 9, n. 1, p. R17, 24 jan. 2008.

RODRIGUES, C. P. et al. Tolerogenic IDO+ Dendritic Cells Are Induced by PD-1-Expressing Mast Cells. **Frontiers in immunology**, v. 7, p. 111–17, 25 jan. 2016.

RUDENSKY, A. Y. Regulatory T cells and Foxp3. **Immunological reviews**, v. 241, n. 1, p. 260–268, 1 maio 2011.

RYANS, K. et al. The immunoregulatory role of alpha enolase in dendritic cell function during Chlamydia infection. **BMC immunology**, v. 18, n. 1, p. 27, 19 maio 2017.

SAKAGUCHI, S. et al. FOXP3+ regulatory T cells in the human immune system. **Nature reviews. Immunology**, v. 10, n. 7, p. 490–500, 18 jun. 2010.

SALLUSTO, F.; LANZAVECCHIA, A. Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor alpha. **Journal of Experimental Medicine**, v. 179, n. 4, p. 1109–1118, 1 abr. 1994.

SALOMON, B. et al. B7/CD28 costimulation is essential for the homeostasis of the CD4+CD25+ immunoregulatory T cells that control autoimmune diabetes. **Immunity**, v. 12, n. 4, p. 431–440, abr. 2000.

SANDERSON, P. et al. Dietary fish oil diminishes the antigen presentation activity of rat dendritic cells. **Journal of Leukocyte Biology**, v. 62, n. 6, p. 771–777, 1 dez. 1997.

SARGENT, J. R.; COUPLAND, K.; WILSON, R. Nervonic acid and demyelinating disease. **Medical Hypotheses**, v. 42, n. 4, p. 237–242, abr. 1994.

SASSA, T. et al. Lorenzo's oil inhibits ELOVL1 and lowers the level of sphingomyelin with a saturated very long-chain fatty acid. **Journal of Lipid Research**, v. 55, n. 3, p. 524–530, mar. 2014.

SAWADA, Y. et al. Resolvin E1 inhibits dendritic cell migration in the skin and attenuates contact hypersensitivity responses. **Journal of Experimental Medicine**, v. 212, n. 11, p. 1921–1930, 19 out. 2015.

SAXENA, V. et al. The countervailing actions of myeloid and plasmacytoid dendritic cells control autoimmune diabetes in the nonobese diabetic mouse. **Journal of immunology (Baltimore, Md. : 1950)**, v. 179, n. 8, p. 5041–5053, 15 out. 2007.

SEDLMAYR, P. et al. Severely depressed natural killer cell activity of patients with adrenoleukodystrophy under treatment with Lorenzo's oil. **Journal of Inherited Metabolic Disease**, v. 18, n. 1, p. 101–102, 1995.

SEE, P. et al. Mapping the human DC lineage through the integration of high-dimensional techniques. **Science (New York, N.Y.)**, v. 66, p. eaag3009, 4 maio 2017.

SEGURA, E. et al. Human Inflammatory Dendritic Cells Induce Th17 Cell Differentiation. **Immunity**, v. 38, n. 2, p. 336–348, 21 fev. 2013.

SEO, M.; CROCHET, R. B.; LEE, Y.-H. **Chapter 14 – Targeting Altered Metabolism—Emerging Cancer Therapeutic Strategies**. Traducao. Second Edition ed. [s.l.] Elsevier, 2013. p. 427–448

SERBINA, N. V. et al. TNF/iNOS-Producing Dendritic Cells Mediate Innate Immune Defense against Bacterial Infection. **Immunity**, v. 19, n. 1, p. 59–70, jul. 2003.

SIMOPOULOS, A. An Increase in the Omega-6/Omega-3 Fatty Acid Ratio Increases the Risk for Obesity. **Nutrients**, v. 8, n. 3, p. 128–17, mar. 2016.

SIMOPOULOS, A. P. Importance of the ratio of omega-6/omega-3 essential fatty acids: evolutionary aspects. **World review of nutrition and dietetics**, v. 92, p. 1–22, 2003.

SITKIN, S. et al. P852 A metabolomics approach to discover biomarkers of chronic intestinal inflammation associated with gut microbiota dysbiosis in ulcerative colitis and Celiac. **Journal of Crohn's & colitis**, v. 12, n. supplement_1, p. S547–S548, 16 jan. 2018.

SITKIN, S.; POKROTNIEKS, J. Alterations in Polyunsaturated Fatty Acid Metabolism and Reduced Serum Eicosadienoic Acid Level in Ulcerative Colitis: Is There a Place for Metabolomic Fatty Acid Biomarkers in IBD? **Digestive diseases and sciences**, p. 1–2, 5 jul. 2018.

SOROOSH, P. et al. Lung-resident tissue macrophages generate Foxp3+ regulatory T cells and promote airway tolerance. **Journal of Experimental Medicine**, v. 210, n. 4, p. 775–788, 8 abr. 2013.

STEINMAN, R. M. The dendritic cell system and its role in immunogenicity. **Annual Review of Immunology**, v. 9, n. 1, p. 271–296, 1991.

STEINMAN, R. M. et al. The induction of tolerance by dendritic cells that have captured apoptotic cells. **Journal of Experimental Medicine**, v. 191, n. 3, p. 411–416, 2000.

STEINMAN, R. M. et al. Dendritic cell function in vivo during the steady state: a role in peripheral tolerance. **Annals of the New York Academy of Sciences**, v. 987, p. 15–25, abr. 2003.

STEINMAN, R. M.; WITMER, M. D. Lymphoid dendritic cells are potent stimulators of the primary mixed leukocyte reaction in mice. **PNAS**, v. 75, n. 10, p. 5132–5136, 1 out. 1978.

SUMMERS, K. L. et al. Reduced IFN-α secretion by blood dendritic cells in human diabetes. **Clinical Immunology**, v. 121, n. 1, p. 81–89, out. 2006.

SUN, G. et al. Adoptive Infusion of Tolerogenic Dendritic Cells Prolongs the Survival of Pancreatic Islet Allografts: A Systematic Review of 13 Mouse and Rat Studies. **PLoS ONE**, v. 7, n. 12, p. e52096, 18 dez. 2012.

SUN, X. et al. Fatty Acid Metabolism is Associated With Disease Severity After H7N9 Infection. **EBioMedicine**, v. 33, n. C, p. 218–229, 1 jul. 2018.

SUTHERLAND, A. P. R. et al. Interleukin-21 is required for the development of type 1 diabetes in NOD mice. **Diabetes**, v. 58, n. 5, p. 1144–1155, maio 2009.

SVAJGER, U.; ROZMAN, P. Tolerogenic dendritic cells: molecular and cellular mechanisms in transplantation. **Journal of Leukocyte Biology**, v. 95, n. 1, p. 53–69, 2 jan. 2014.

SWAIN, S. et al. CD103 (αE Integrin) Undergoes Endosomal Trafficking in Human Dendritic Cells, but Does Not Mediate Epithelial Adhesion. **Frontiers in immunology**, v. 9, p. 208–15, 21 dez. 2018.

TAI, N. et al. IL-10-conditioned dendritic cells prevent autoimmune diabetes in NOD and humanized HLA-DQ8/RIP-B7.1 mice. **Clinical Immunology**, v. 139, n. 3, p. 336–349, 1 jun. 2011.

TAMURA, K. et al. Novel lipogenic enzyme ELOVL7 is involved in prostate cancer growth through saturated long-chain fatty acid metabolism. **Cancer Research**, v. 69, n. 20, p. 8133–8140, 15 out. 2009.

TEAGUE, H. et al. Dendritic cell activation, phagocytosis and CD69 expression on cognate T cells are suppressed by n-3 long-chain polyunsaturated fatty acids. **… immunology**, v. 139, n. 3, p. 386–394, 13 jun. 2013.

THOMAS, D. C. et al. Protection of Islet Grafts Through Transforming Growth Factor-β–Induced Tolerogenic Dendritic Cells. **Diabetes**, 2013.

THORNTON, C.; SNOWDEN, M. A.; CARLING, D. Identification of a novel AMP-activated protein kinase beta subunit isoform that is highly expressed in skeletal muscle. **The Journal of biological chemistry**, v. 273, n. 20, p. 12443–12450, 15 maio 1998.

THWE, P. M. et al. Cell-Intrinsic Glycogen Metabolism Supports Early Glycolytic Reprogramming Required for Dendritic Cell Immune Responses. **Cell Metabolism**, v. 26, n. 3, p. 558–567.e5, 5 set. 2017.

TORQUATO, M. T. et al. Prevalence of diabetes mellitus and impaired glucose tolerance in the urban population aged 30-69 years in Ribeirão Preto (São Paulo), Brazil. **Sao Paulo medical journal = Revista paulista de medicina**, v. 121, n. 6, p. 224–230, 6 nov. 2003.

TORRES-AGUILAR, H. et al. IL-10/TGF-beta-treated dendritic cells, pulsed with insulin, specifically reduce the response to insulin of CD4+ effector/memory T cells from type 1 diabetic individuals. **Journal of Clinical Immunology**, v. 30, n. 5, p. 659–668, set. 2010.

TURLEY, S. et al. Physiological Cell Death Triggers Priming of Self-reactive T Cells by Dendritic Cells in a Type-1 Diabetes Model. **Journal of Experimental Medicine**, v. 198, n. 10, p. 1527–1537, 10 nov. 2003.

VANHERWEGEN, A.-S. et al. Vitamin D controls the capacity of human dendritic cells to induce functional regulatory T cells by regulation of glucose metabolism. **The Journal of steroid biochemistry and molecular biology**, v. 187, p. 134–145, 24 nov. 2018.

VILLANI, A.-C. et al. Single-cell RNA-seq reveals new types of human blood dendritic cells, monocytes, and progenitors. **Science (New York, N.Y.)**, v. 356, n. 6335, p. eaah4573–14, 20 abr. 2017.

VREMEC, D. The surface phenotype of dendritic cells purified from mouse thymus and spleen: investigation of the CD8 expression by a subpopulation of dendritic cells. **Journal of Experimental Medicine**, v. 176, n. 1, p. 47–58, 1 jul. 1992.

VUCKOVIC, S. et al. Decreased blood dendritic cell counts in type 1 diabetic children. **Clinical Immunology**, v. 123, n. 3, p. 281–288, jun. 2007.

WALLET, M. A.; TISCH, R. Type 1 diabetes, inflammation and dendritic cells. **Drug Discovery Today: Disease Mechanisms**, v. 3, n. 3, p. 373–379, set. 2006.

WANG, H. et al. ω-3 Polyunsaturated fatty acids affect lipopolysaccharide-induced maturation of dendritic cells through mitogen-activated protein kinases p38. **Nutrition**, v. 23, n. 6, p. 474–482, jun. 2007.

WANG, L. et al. The elevated glutaminolysis of bladder cancer and T cells in a simulated tumor microenvironment contributes to the up-regulation of PD-L1 expression by interferon-&gamma. **OncoTargets and Therapy**, v. Volume 11, p. 7229–7243, 2018.

WANG, M.-D. et al. HBx regulates fatty acid oxidation to promote hepatocellular carcinoma survival during metabolic stress. **Oncotarget**, v. 7, n. 6, p. 6711–6726, 9 fev. 2016.

WARBURG, O.; WIND, F.; NEGELEIN, E. THE METABOLISM OF TUMORS IN THE BODY. **The Journal of general physiology**, v. 8, n. 6, p. 519–530, 7 mar. 1927.

WATCHMAKER, P. B. et al. Comparative transcriptional and functional profiling defines conserved programs of intestinal DC differentiation in humans and mice. **Nature immunology**, v. 15, n. 1, p. 98–108, 1 dez. 2013.

WHEAT, W. et al. Increased NF-kappa B activity in B cells and bone marrow-derived dendritic cells from NOD mice. **European journal of immunology**, v. 34, n. 5, p. 1395–1404, maio 2004.

WILD, S. et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. **Diabetes Care**, v. 27, n. 5, p. 1047–1053, maio 2004.

WISE, D. R. et al. Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. **Proceedings of the National Academy of Sciences of the United States of America**, v. 105, n. 48, p. 18782–18787, 2 dez. 2008.

WOLLENBERG, A. et al. Immunomorphological and Ultrastructural Characterization of Langerhans Cells and a Novel, Inflammatory Dendritic Epidermal Cell (IDEC) Population in Lesional Skin of Atopic Eczema. **Journal of Investigative Dermatology**, v. 106, n. 3, p. 446–453, 1 jan. 1996.

WU, N. et al. AMPK-Dependent Degradation of TXNIP upon Energy Stress Leads to Enhanced Glucose Uptake via GLUT1. **Molecular Cell**, v. 49, n. 6, p. 1167–1175, 28 mar. 2013a.

WU, N. et al. AMPK-dependent degradation of TXNIP upon energy stress leads to enhanced glucose uptake via GLUT1. **Molecular Cell**, v. 49, n. 6, p. 1167–1175, 28 mar. 2013b.

XIAO, B. et al. Structure of mammalian AMPK and its regulation by ADP. **Nature Publishing Group**, v. 472, n. 7342, p. 230–233, 4 abr. 2011.

XU, G. et al. Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population based study. **BMJ**, v. 362, p. k1497, 4 set. 2018.

YANG, D.-F. et al. CTLA4-Ig-modified dendritic cells inhibit lymphocyte-mediated alloimmune responses and prolong the islet graft survival in mice. **Transplant Immunology**, v. 19, n. 3-4, p. 197–201, jul. 2008.

YANG, L.; VENNETI, S.; NAGRATH, D. Glutaminolysis: A Hallmark of Cancer Metabolism. **Annual Review of Biomedical Engineering**, v. 19, n. 1, p. 163–194, 21 jun. 2017.

YATES, S. F. et al. Induction of regulatory T cells and dominant tolerance by dendritic cells incapable of full activation. **Journal of immunology (Baltimore, Md. : 1950)**, v. 179, n. 2, p. 967–976, 15 jul. 2007.

YOGEV, N. et al. Dendritic cells ameliorate autoimmunity in the CNS by controlling the homeostasis of PD-1 receptor(+) regulatory T cells. **Immunity**, v. 37, n. 2, p. 264–275, 24 ago. 2012.

ZAPATA-GONZALEZ, F. et al. Human dendritic cell activities are modulated by the omega-3 fatty acid, docosahexaenoic acid, mainly through PPARγ:RXR heterodimers: comparison with other polyunsaturated fatty acids. **Journal of Leukocyte Biology**, v. 84, n. 4, p. 1172–1182, 16 jul. 2008.

ZENG, H. et al. Type 1 regulatory T cells: a new mechanism of peripheral immune tolerance. **Cellular and Molecular Immunology**, v. 12, n. 5, p. 566–571, 8 jun. 2015.

ZEYDA, M. et al. Polyunsaturated Fatty Acids Block Dendritic Cell Activation and Function Independently of NF-κB Activation. **The Journal of biological chemistry**, v. 280, n. 14, p. 14293–14301, 1 abr. 2005.

ZHAO, F. et al. Paracrine Wnt5a-β-Catenin Signaling Triggers a Metabolic Program that Drives Dendritic Cell Tolerization. **Immunity**, v. 48, n. 1, p. 147–160.e7, 16 jan. 2018.