Cellular metabolism and the immune response control

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I. Introduction

Metabolism and immune system: The metabolic system was seen only as a system of power generation and metabolites for the functioning of cells. Today we know that changes in metabolic regulation may interfere directly in diseases that involve inflammatory processes. Thus, knowledge of the relationship between metabolism and cell signaling helps in understanding metabolic disorders, cancer, and also in the study of immune response (1, 2).

The relationship between metabolic and regulatory aspects of the immune system is not yet fully known. Even with major discoveries on the subject, the metabolism of many cells of the immune system is unknown (1, 2). The metabolic changes during phagocytosis of three types of immune cells from pigs, leukocytes and peritoneal exudate monocytes and alveolar macrophages. In this study it was observed that macrophages depend on oxidative phosphorylation to produce energy during phagocytosis, whereas the other two cells only use glycolysis to produce energy (3). Another study confirms the close relationship between immune system and metabolism, which showed that incubation of dendritic cells (differentiated in vitro) with LPS provides an increase in glucose consumption, increased formation of lactate and reduction in oxygen consumption. Furthermore, these changes also reflected in increased CD86 co-stimulatory molecule indicating a functional modulation of these cells (4). The need for metabolic resources to

build active components of the immune system, the messenger function of certain classes of metabolites and metabolites, and the intimate relationship between parasite and mammalian defense mechanism, which is probably immune regulatory events are reflected in the metabolism (5).

The metabolic profile of the cells of the immune system is also important to provide a tool that generates a systemic metabolic description induced by the parasite in the host, promoting a new direction of the immune response during infection by the parasite (5). In most biological systems, there is a stimulus that triggers an effector response, which usually makes the system back to the starting point. Although having different primary functions, the immune system and metabolic pathways are arranged in the same manner as in serum glucose levels in thermogenesis or bacterial infection, where the lipopolysaccharide stimulates TLR-4 receptor, which promotes the release of TNF-α, improving bactericidal activity and vascular permeability reducing infection (2).

Metabolism and associated pathways Akt/PI3K/mTOR: As well as the metabolic pathways generate energy, the means of regulation of protein synthesis involves several intracellular signaling pathways such as Akt as Akt (serine/threonine kinase), expressed in heart, lung, brain and skeletal muscle. Various stimuli, such as cytokines, growth factors and hormones, are responsible for the phosphorylation and activation of Akt, which is composed of three members, Akt1, Akt2 and Akt3 (6). The Akts proteins are recruited to the plasma membrane by PI3K, which acts as a lipid kinase. The Akt/PI3K pathway operates in promoting cell survival through evasion of apoptosis and cell proliferation through activation of mTOR in response to nutrient

availability and to stimulation by growth factors. The mTOR protein stimulates translation that is required for cell cycle progression (7).

mTORC1 activation is indirectly given when Akt phosphorylates TSC-2 one of the molecules of heterodimer TSC1 and TSC2, this activates the GTPase function of this heterodimer which reverses the inhibition of mTORC1, inhibiting RHEB to pass the ADP to ATP linked to this protein, by activation of cyclase function of the TSC heterodimer (8). Akt phosphorylation is important for neutralization and PRAS40, important for the activation and interactions mTOR1 and mTOR2 with their substrates (9). Thus, the mTOR pathway is also known as PI3K/Akt/mTOR. Despite the multiple substrates involved in this pathway. Additionally, Akt is not limited to this path and fulfills other functions at the cellular level.

Metabolism and mTOR: Mammalian Target of Rapamycin is a serine/threonine protein kinase involved in regulation of many cellular events, such growth, survival, function, metabolism, and differentiation. It is constitutively expressed, and its regulation occurs predominantly post-translationally (7). This protein was discovery from searches about target of Rapamycin, that was originally found as a growth inhibitor which have immunosuppressive and anticancer properties (10). Additionally, due to the ability of mTOR activation to regulate metabolism, it promotes a crucial link connecting metabolic demands and cellular function (7). This link is mediated through the control of key transcriptional regulators. (11).

mTOR fathers two functionally distinct signaling multi-protein complexes: mTORC1, which is composed of the scaffolding regulatory-associated protein

of mTOR (RAPTOR), DEP domain containing mTOR-interacting protein (DEPTOR), Proline-Rich Akt Substrate 40 kDa (PRAS40), and mammalian Lethal with Sec13 protein 8 (mLST8); and mTORC2, which is composed of RAPTOR-independent companion of TOR (RICTOR), protein observed with RICTOR (PROTOR), mSIN1 proteins, mLST8 and DEPTOR. The connection of mTOR with these adapter proteins has functional distinct consequences (3, 4).

II. Metabolism and T cells differentiation

Such described previously, the mTOR ability to play a role in cellular differentiation occurs through the regulation of transcription regulators. Follow, some these regulators and its role in metabolic programs regulation.

HIF-1: The Hipoxia-inducible Factor is a hetrodimeric protein which regulates the expression of various genes crucial for cellular adaptation to a low-oxygen environment. This protein supports the differentiation of naïve CD4+ T cell to Th17 cell through the stabilization of the RORγt expression, as well as inhibits Treg differentiation through the inhibition of Foxp3, mediating its proteosomal degradation (3, 5).

Myc: The oncogenic transcription factor Myc regulates various metabolic pathways essentials for cellular growth and proliferation, such glycolysis, glutaminolysis, and fatty acid oxidation (14).

PPARα: The peroxisome proliferator-activated receptor α (PPARα) is a nuclear hormone receptor that regulates fatty acid metabolism and glucose homeostasis, playing a role as a intracellular sensor of endogenous fatty

acids. This receptor induces Treg differentiation and inhibits effector differentiation (11).

PPARγ: Like its homolog PPARα, PPARγ is a nuclear hormone receptor that regulates adipogenesis, lipid metabolism and glucose homeostasis in cells. This receptor plays the same role in T cell differentiation (11).

SREBP: The sterol regulatory element binding proteins (SREBP) plays a critical role in regulating cellular lipogenesis, facilitating the anabolic enzymes transcription, which is involved in cholesterol and fatty acid synthesis (11). This protein was found to associate with the IL17 promoter, where it interacts with and inhibits the activity of the aryl hydrocarbon receptor. This transcription factor is known to be important for expression of Th17-associated genes (5, 7).

Once the antigen is recognized, the integration of many factors from the microenvironment gives the effector fate of the naive CD4+ T cell. Until now, the T-cell subsets have been characterized only by their transcription factor expression and cytokine secretion profile. Nevertheless, it has currently proposed that each T-cell subset also hold a single metabolic profile and a corresponding set of signal requirements of mTOR complexes (11).

According this metabolic classification, the T-cell would present these features:

Th1 T cellsphenotype exhibit a strong glycolytic phenotype and express high levels in surface of the Glut1 glucose transporter. Its development is dependent on the mTORC1 signaling complex (3, 8).

Th2 Tcellsphenotype also express high levels in surface of the Glut1 glucose transporter and exhibits a high rate of lactate production and glucose uptake following stimulation. These cells can develop in absence of mTORC1 but are dependent on the mTORC2 signaling complex (3, 8).

Th17 cellsphenotype is the higher glycolytic T-cell subset. The IL-17-secreting CD4+ T cells development drastically decreases in T cells lacking mTOR, mTORC1 and treated with Rapamycin. Nevertheless, T cells lacking mTORC2 does not appear to have its development inhibited (3, 8).

Treg cellsphenotype exhibits an oxidative metabolic profile which uses mitochondrial respiration and fatty acid oxidation to achieve energy. The treatment with process of glycolysis inhibitor compounds in naive CD4+ T cells importantly enhance its development, what also occurs with culture conditions that conduces to a low mTOR signaling (3, 8).

III. Regulation of cell B by mTORC

The PI3K pathway to mTOR is required for B cell proliferation. Since the BCR is blocked by inhibition of mTOR. This was evidenced in mouse spleen cells, wherein inhibition of mTOR suppresses the proliferation and differentiation of B cells by CD40 (10, 11). In humans, Rapamycin suppresses B cell proliferation when is activated in the presence of CD40L and B cell inducing cytokines. Rapamycin prevents antibody-mediated apoptosis, generating a reduction of B cells that produce IgG and IgM, also suppresses the production of cytokines that induce proliferation of B cells and IgM, as IL-2 in inflammation conditions (18).

Some authors suggest that mTOR regulates IL-17, which is important in the proliferation of pro-B cells. Thus, if rapamycin in B-precursor acute lymphoblastic leukemia cell lines is evidence that IL-17 induces apoptosis in these cells is used. But when S1N1, an important element of mTORC2, is suppressed cell survival is increased possibly by the increased expression of IL-7R (20). In mature B cells, activation of TLRs and BCR induces activation of mTOR, even so, have been identified as Akt independently of mTOR regulates the BCR and this is accomplished by inactivating FoxO1 which is sequestered and degraded in cytoplasm after Akt is phosphorylated (21).

When is deleted TSC1 or TSC2, is inhibited the maturation of cells B, contrary to what happened when Akt was active, in where B cells were significantly reduced in the marginal zone (MZ). But when rapamycin was fed this phenomenon was corrected, and once again the importance of mTOR is displayed in the control populations of B cells in MZ. Despite all the evidence to date is known that the PI3K pathway is a major regulatory functions and populations of B cells through regulating FoxO1. But do not have enough information to indicate the direct role of mTOR in the control and regulation of B cells, which is still under study and demonstration (22).

IV. Metabolism and APCs Regulation

Dendritic Cells (DC): crucial regulators of both cellular activation and tolerance in adaptive immune responses. The function which DC will perform depends on their activation and differentiation status (23).

The DC activation occurs through PAMP stimulation of TLR, what leads a metabolic transition in the resting immature DC, which is characterized by a

conversion from mitochondrial b-oxidation of lipid and OXPHOS to aerobic glycolysis (9, 10).

Once exposed to TLR agonists, in an early phase, the lacking of glucose in culture medium leads to critical faults in DC activation, such production of IL-12p40 and surface expression of CD40 and CD86. Afterwards, DCs activated by TLR signals are highly dependent on glucose for survival, becoming more sensitive to apoptosis by nutrient limitation. Thus, for full DC activation is essential initiating glycolysis at the time (9, 10).

Differently than OXPHOS, glycolytic pathway may be requested due to the necessity to produce substrates which will be used during DC activation. As an option, glycolytic pathway components can control protein translation and can be responsible to regulate the translation of crucial proteins for DC activation (24).

Macrophagues: Macrophages can be classified into two major groups M1 (inflammatory) and M2 (anti-inflammatory). And each type of macrophage used different metabolic pathways, M1 uses energy mainly anaerobic glycolysis, mediated by HIF-1α, while M2 employs FAO mediated PPARÉ¤ and PGC-1β (26). Evidencing with this, the relationship with of the metabolic function and and the population of macrophages. This regulation may be mediated by mTOR, which is an important nutrient sensor / power as processes such as protein synthesis, autophagy, glycolysis and regulation of immune response, de novo lipogenesis, among others. (27)

Natural killer cells (NK cells): The NK cells rapamycin inhibits proliferation by blockade of the cell cycle in G1 phase in rat. Nevertheless, rapamycin does

not affect interferon production by NK cells. When mTOR is inhibited in vitro, the death of T-cell YEC-1mediated by NK cells decreases slightly. In vivo, rapamycin reduces the number of NK cells in rat liver allografts (10).

Neutrophils: Human neutrophil is inhibited the chemotaxis and chemokinesis induced by GM-CSF, when rapamycin is delivered. The same way, the response to IL-8. Rapamycin reduces polymerization of actin, important for leukocyte migration. mTORC1 is linked in activation of neutrophils and acute lung injury in association with TLR2 and TLR4 (18).

V. Mitochondrial metabolism and regulation of immune response

Effect Warburg: Is a termination used to describe a mechanism of some cancer cells to metabolize glucose via glycolysis, where the conversion of glucose to lactate with oxygen available to obtain energy with rapid generation but less efficient pathway for obtaining ATP (20, 21). Carbon precursors necessary for the synthesis of nucleic acids, phospholipids, fatty acids, cholesterol and porphyrins can be provides by glycolysis (28). Glycolysis in normal tissues is the metabolism of 6-carbon glucose to 3-carbon pyruvate and the energy in the form of ATP occur via oxidative phosphorylation in mitochondria (30).

Hexocinase-2 (HK-2) is an isoform over-expressed in many cancer cells and is located on the external mitochondrial membrane protein VDAC (voltage-dependent anion channel). HK-2 has preferential access to mitochondrial generated ATP via the mitochondrial adenine nucleotide translocator (ANT), and protection from inhibition by its product G-6-P. Cancer cells have overproduced HK-2 and making the reaction between ATP and the incoming

glucose to produce G-6-P at a high rate (30). Studies suggest a link between cancer cells and Hif-1a, where high Hif-1a activity is demonstrated to mediate the Warburg effect. HIF-1a is able to produce enzymes hexokinase 2, triosephosphate isomerase, isomerase, glucose 6-phosphate, and pyruvate kinase M2 (PKM2) in glycolysis (31). HIF-1 is a transcription factor responsible for the change of gene expression during cellular response to low oxygen conditions. Amplifies HIF-1 transcription of genes encoding glucose transporters and glycolytic enzymes (32).

Recent studies show Warburg effect have many mechanisms: tumor microenvironment and stabilization of HIF, oncogene activation and loss of tumor suppressor genes, mitochondrial dysfunction in cancer cells, nuclear DNA mutations, epigenetic changes, miRNA, glutamine metabolism, and post-translational modifications (28).

Metabolic pathways and importance in the differentiation and function of immune cells: The response, proliferation, polarization or action of immune cells requires the supply of nutrients and high energy consumption, for this reason the contribution of ATP for these functions comes from differential form of the various metabolic pathways, from glycolysis, to pyruvate until lactate production or acyl-CoA, to enter the tricarboxylic cycle acid (TCA); or through of the fatty acids oxidation (FAO). Producing enough electrons (NADH and FADH2) to activate of the electron transport chain to fuel oxidative phosphorylation (OXPHOS) (1).

It is also already considered that myeloid cells such as granulocytes, dendritic cells, macrophages, B cells and T cells mainly use glycolysis as a

source of ATP via anaerobic when they present an effector or inflammatory profile (Figure XX)(1, 2). This is evidenced by neutrophils that have few mitochondria and consume little oxygen (34). Under these conditions the Warburg effect is generated. Producing lactate and NADPH, an essential cofactor for the NADPH oxidase for the production of important microbicidal product H_2O_2 (35). Some authors suggest that eosinophils and basophils are metabolically similar to neutrophils (36)

As with neutrophils, macrophages are important in the immune response and are distributed in all organs and tissues. Playing an important role in innate immunity and adopt different states of activation. Interferon-É¤ (IFN-É¤), in combination with TLR agonists, induces M1 (inflammatory), while IL-4 and IL-13 cytokines induces M2 (regulators) (37). M1 macrophages secrete IL-12, IFN-gamma promotes, thus inducing NK cells and T cells, addition of TNF-α, that activate other immune cells, and NO. Contrary M2 macrophages, secret anti-inflammatory molecules and stimulate tissue repair. Activation of M1 and M2 is characterized by the use of different metabolic pathways (38). M1 using arginine as a substrate to produce iNOS occurs only in the M1, and not in M2. M2 using arginine as a substrate for Arginase1 expressed only in the M2, and not in M1(37). The M1 macrophages possess a glycolytic metabolism. Similar to the different types of activated cells such as dendritic cells and granulocytes. (Figure XX). The Macrophage M1 has higher basal mitochondrial oxygen consumption, the other macrophages. M2 macrophages inducing the mitochondrial OXPHOS through of IL-4 and FAO. in such a way, metabolism M2 is strongly biased towards the use of FAO and mitochondrial respiration to meet their energy needs (Figure XX) (39).

DCs derived from cultured bone marrow stimulated with colony-stimulating factor granulocyte-macrophage, are a model of production of TNF-α and inducible nitric oxide synthase (iNOS). At rest, the DCs oxidize glucose in the mitochondria, by OXPHOS, with little lactate production. But, once stimulated with TLR agonists, become dependent on Warburg metabolism to subsistence (40). PI3K and Akt are important in the activation of glycolytic metabolism (41); play an important role in the duration of glycolysis in DCs activated. As evidenced by DCs activated by more than 12 hours which increases glucose consumption and TCA and mitochondrial oxygen consumption cease (40), increasing lactate production, and the cells survive only by aerobic glycolysis (Fig. XX). The high production NO gas by iNOS from arginine, inactive mitochondrial respiration in these cells. So the activation of glycolytic metabolism in activated DCs induces the expression of iNOS and production of NO thus inhibits OXPHOS. This subsistence mechanism is vital for the rapid production of ATP in the absence of machinery for the production of mitochondrial ATP (42).

As the cells of the innate immune system, the T and B cells activated Warburg metabolism used at the time of the proliferation. In contrast to most of innate cells, which use Warburg metabolism after activation but not proliferate (1). Contrary to activated effector T cells, memory T and B cells do not use aerobic glycolysis but if they use mitochondrial FAO for their development and persistence, maintain or adopt a catabolic metabolism (Figure XX) (43). Once an antigen recognized by naive T cells and with adequate costimulation, this growth rapid, proliferation, and acquisition of specialized effector functions is initiated. This requires of the T cell a

metabolic reprogramming and energetic. This pass of a catabolic metabolism to an anabolic metabolism, changes the cell is not in a state of maintenance and homeostasis (1).

Some molecules such P13K, Akt, Myc, and HIF are associated with immune and metabolic signals for the activation, function, development and upkeep of T cells. So the metabolic pathways induce a T helper subsets (1). As was evidenced in Treg cells mainly use mitochondrial OXPHOS and FAO for their development and subsistence (17) or in Th17 cells where glycolysis is primarily required (44). In activated T cells the IL-12 induce an increase in the glucose transporter and glycolytic metabolism. Besides glycolysis in maintaining the activity of active effector T cells, exist other pathways involved, as via the pentose phosphate and glutaminolysis as well as the use of key molecules such as citrate and malate (Figure XX) (1). It is important to consider the available nutrients, substrates, or other resources that can create an imbalance in the environment of immune cells, affecting the metabolism of cell function and fate of immune cells.

Mitochondria in the production of iNOS and inflammation: All metabolic process to generate ATP by OXPHOS generates ROS, which are involved in oxidative stress of the mitochondria. Production of O2- in excess, induces activation of factors of redox-sensitive transcription, such as NF-kB, and thus an increase of cytokines, chemokines, inducible nitric oxide synthase (iNOS), eicosanoids, and adhesion molecules (45). Some of these superoxide anions combine with nitric oxide (NO) to produce peroxynitrite (ONOO-), a powerful oxidant. These ROS oxidize proteins, membrane lipid and mtDNA; damaging mitochondrial integrity (46). Being mitochondria, the inducer of the pro-

inflammatory action by the action of innate immunity using redox sensitive or direct inflammasome activation molecules. Progression that result in the immediate activation of caspase-1, and subsequent activation of the inactive precursor of IL-1β and IL-18 (47).

DAMPs activate the same receptors that detect PAMPs, such as TLRs and cytoplasmic NOD and NLRs (46). Once activated, NLRP3 this is depolymerized and induces the recruitment of the adapter protein ASC and caspase-1 (and her cleavage), and other cytoskeletal proteins, glycolytic enzymes and caspase-7. This group of proteins called inflammasome. This complex induces pro-inflammatory, such as IL-1β and IL-18.(47).

Elevated levels of ROS generated by the mitochondria activate NLRP3 inflammasome. Interestingly, the humidity and the myth-AMPS can activate APCs, as well as other non-immune cells including mesenchymal stem cells and astrocytes. Additionally, IL-1β pro-inflammatory IL-6, MCP-1 and TNF is induced by degradation of mtDNA in mouse primary astrocytes. (48). This activation of the inflammasome can activate NF-kB, increasing even more pro-inflammatory cytokines duration of the inflammatory response. This summation of events can be a clear explanation to the high deterioration of mitochondria (46).

Biogenesis of mitochondria: The availability of nutrients and oxygen can determine the function of a time cell proliferate and differentiate. Under normal conditions the cell has high level out of ATP/ADP/AMP. Thus, an increase in AMP activates AMPK, activating ATP production by activating TSC 1 and 2 which blocks mTOR (7). After ATP levels are increased activated

Akt/PKB promotes mitochondrial biogenesis by phosphorylation and nuclear translocation of NRF-1 and nuclear translocation with increased mitochondrial hexokinase (HK), using glycolysis coupled to OXPHOS with uptake mitochondrial ATP, especially in order to allow cell survival and maintenance of cell functions (49). An important protein in the biogenesis of mitochondria is BAD, which is involved in the initiation of a protein complex that catalyzes the first step of glycolysis by deHK-4 activation. But absent BAD gives a restriction of respiration in the presence of glucose and in the absence of glucose dephosphorylated BAD and induces apoptosis(50). This interaction between energy metabolism and the regulation of apoptosis, is important in mitochondrial biogenesis, and any imbalance can lead to mitochondrial failure and loss problems inducing pathological cell survival (51).

Thus, the whole process of inflammation, oxidation and apoptosis, requires a high rate of mitochondrial replacement to allow the restoration of damaged mitochondria continuously and cell survival, which may serve as a signal that stimulates the production of mediators anti-inflammatories such as the IL-10. This is evidenced by the increased immune tolerance during periods of mitochondrial biogenesis may be a risk for recurrent or secondary infections evidencing with them a close relationship between immunosuppression and the regeneration of the mitochondria, this period of immunosuppression may be greater depending the damage level of the mitochondria involved in the initial inflammatory process.(49).

VI. References

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