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Mini review

The interplay between central metabolism and innate immune responses

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ABSTRACT

A growing body of recent studies bring into light an important cross-talk between immune response and metabolism not only at the level of the organism as a whole, but also at the level of the individual cells. Cellular bioenergetics functions not only as a power plant to fuel up the cells, but the intermediate metabolites are shown to play an important role to modulate cellular responses. It is especially the pathways through which a cell metabolizes glucose that have been recently shown to influence both innate and adaptive immune responses, with oxidative phosphorylation used by resting or tolerant cells, while aerobic glycolysis (also termed 'Warburg effect') fueling activated cells. In this review we will address how the center metabolism shifts upon activation in the innate immune cells and how the intermediate metabolites modulate the function of immune cells.

1. Introduction

Cellular metabolism is a complex and delicate process that is regulated by different environmental cues, acting at the level of multiple layers of biochemical regulation. The importance of the central metabolism has been mostly appreciated from its role to maintain homeostasis and bioenergetics balance of an individual. However, recent evidence argues for an important cross-talk between immune system and metabolic regulation, bringing into the spotlight an unexpected layer of metabolic regulation of immune responses. In this review we will integrate the recent literature to present a systematic picture on the mechanisms through which central metabolism regulates the innate immune responses to the intruding pathogens.

Once a pathogenic microorganism breaches through the skin or mucosal barriers, it is immediately sensed by the innate immune cells such as Langerhans cell (dendritic cell) or tissue macrophages through germ-line encoded pattern recognition receptors (PRRs) including Toll-like receptors (TLRs), C-type lectin receptors (CLRs), NOD-like receptors (NLSs) or RigI-helicases. Subsequently, the activation of PRRs leads to either immediate phagocytosis of the pathogens or the secretion of soluble mediators such as pro-inflammatory cytokines or chemokines for the further recruitment of the effector cells to the site of infection. During this activation process, the metabolic state of innate immune cells has to switch rapidly in order to meet the heightened energy need from the basal resting state to a hyper active stage.

In the basal resting state, the cells use mainly the oxidative phosphorylation (OXPHOS) to generate ATP, process that takes place in the mitochondria through tricarboxylic acid cycle (TCA cycle) as the energy source, and accompanied by consumption of oxygen. However, upon immune activation the central metabolism shifts from OXPHOS to aerobic glycolysis to generate cellular ATP. Although glycolysis produces less ATP per glucose molecule compare to TCA cycle (2 versus 32 ATPs), less enzymatic steps are involved that can be easier enhanced, and therefore more ATP could be produced in a short time as compared to OXPHOS. This switch to aerobic glycolysis is called 'Warburg effect', after the first description of this process by Otto Warburg as a characteristic of cancer cell metabolism [1]. However, recent studies have demonstrated that the aerobic glycolysis is an important feature of the active immune metabolic signatures as well.

2. Metabolic shifts in innate immune cells after pathogen recognition

2.1. Oxidative phosphorylation

Oxidative phosphorylation (OXPHOS) takes place in the mitochondria and generates ATP through the electron transport

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chain. OXPHOS is the preferred bioenergetics pathway for the immune cells in their resting state. TCA cycle intermediate succinate and the metabolite NADH play major roles in the redox reaction for the production of ATP in the OXPHOS. Hence TCA cycle serves as a central hub in the mitochondrial OXPHOS. The major substrate of TCA cycle is acetyl-CoA, which could flux into the mitochondria through different pathways such as glycolysis, fatty acid oxidation, amino acids (via ketone bodies), depending on the substrate availability.

The role of OXPHOS during infections has been also shown by studies assessing the mitochondrial function in sepsis patients, that revealed that although the mitochondrial mass and proteins synthesis are not altered, the enzymatic activity of mitochondrial complex I, III and IV and oxygen consumption were significantly inhibited in sepsis. In addition, incubation of PBMCs from healthy donors with plasma from sepsis patients also reduces the oxygen consumption of healthy mitochondria [2], suggesting a plasma factor in the septic serum could modulate the mitochondrial oxygen consumption.

2.2. Aerobic glycolysis (Warburg effect)

In contrast to naïve or resting cells, immune activation leads to a shift of central metabolism of immune cells toward glycolysis. Aerobic glycolysis, also called "Warburg effect", was first described by Otto Warburg in 1923 who described that tumor cells produced lactate from glucose under normoxic condition [1]. The reason for this shift is the rapid growth of the tumor, with aerobic glycolysis serving on the one hand as a rapid source of ATP, and on the other hand as a way to generate the excess intermediate metabolites needed for the pentose phosphate pathway to synthesize nucleotides, the building blocks of tumor cell proliferation. Similarly, aerobic glycolysis is triggered in immune cells upon stimulation, resulting in a shift of the core metabolic pathways away from oxidative phosphorylation [3].

The first hints for an important role of metabolic shifts for immune cell activation were provided by the studies on the metabolic regulation in T cells [4–6]. The active T cells, as compared to quiescent naïve T cells, have greater bioenergetic and biosynthetic needs to cope with the massive clonal expansion and its active functionality. To meet these needs, the metabolic rewiring shifts the core metabolism of T-cells from mainly mitochondrial oxidative phosphorylation (OXPHOS) at the resting stage, to aerobic glycolysis upon activation. The CD28/PI3K/Akt pathway has been suggested to be responsible for the increased glycolytic activity in T cell activation [7]. Upon TCR and CD28 signaling in the active T cells, stimulation of PI3K and Akt signaling pathways further activate mTOR (mammalian target of rapamycin), which plays a central role in cell proliferation and protein translation [8].

AMPK (AMP-activated protein kinase) and mTOR are two evolutionary conserved signaling molecules modulating the sensing of cellular metabolic state and directing the cell functional fate [9]. mTOR forms two distinct multi-protein complexes: mTORC1 (mTOR complex 1) and mTORC2 (mTOR complex 2). mTORC1 is regarded as a master regulator of cell growth and metabolism [10]. AMPK functions as barometer of cellular energy level. When cellular ATP level is low, AMPK is activated and phosphorylates TSC2, subsequently inhibiting the mTORC1 activity [11]. mTOR is also demonstrated to play a pivotal role in integrating the environment cues and determine the functional fate of T cell [6]. Growth factor signals upstream of mTORC1 converges on TSC1/TSC2 degradation through the PI3K/Akt pathway [12]. AMPKα-deficient $CD8^+$ T cells have higher glycolytic activity and produce more proinflammatory cytokines in vitro, and AMPK is dispensable for T cell proliferation and the cytotoxic function of $CD8^+$ T cell in vivo [13]. AMPK and mTOR therefore play antagonistic roles in regulating the function of T cells.

HIF-1α (hypoxia inducible transcription factor-1) is the key transcription factor responsible for the transcription of enzymes involved in glycolysis. It is a heterodimeric helix-loop-helix transcription factor composed of α and β subunits and is known to regulate the expression of genes involved in a plethora of host stress responses triggered by hypoxia. HIF-1α is implicated in most aspects of hypoxia-induced gene expression and it is essential for hypoxia-induced increases in glycolysis and angiogenesis in tumor cells, as well as normal tissues [14]. HIF-1α is hydroxylated by HIF prolyl-hydroxylases in normoxia and the hydroxylated HIF-1α is subsequently recognized and ubiquitinized by the VHL E3 ubiquitin ligase. The ubiquitinated HIF-1α is degraded then by the proteasome [15]. The prolyl-hydroxylase is inhibited by hypoxia and leads to HIF-1α stabilization and activation of the downstream pathways including glycolysis.

In addition to oxygen tension, many additional endogenous or exogenous factors have been shown to stabilize HIF-1α in the myeloid innate immune cells. Endogenous factors such as growth factors can stabilize HIF-1α via PI3K/Akt pathway, which in addition to a hypoxic environment at the tissue level can also up-regulate the HIF-1α regulated genes in the immune cells [16]. A number of exogenous ligands such as LPS and other TLR ligands could induce HIF-1α stabilization in the myeloid innate immune cells, including DCs [17], monocytes [18] and macrophages [19]. The stabilization of HIF-1α is an important step for the immune cells, insuring the up-regulation of the glycolysis and the energy needs of the activated leukocytes.

2.3. Dendritic cells

Dendritic cells (together with tissue macrophages) are the sentinels of the immune system at the tissue level. DCs are a highly heterogeneous group of cells, consisting of different cell types depending on the specific tissue locations [20]. DCs function as a bridge between innate and adaptive immunity by sensing the intruder and instructing the adaptive immunity through antigen presentation. Resting DCs are mainly fueled by oxidative phosphorylation in the mitochondria via β-oxidation of lipids. Upon activation by TLR agonists, a profound metabolic transition to aerobic glycolysis occurs in DCs. It has been demonstrated that the shift toward aerobic glycolysis induced in DCs by TLR stimulation is driven by the PI3K/Akt pathway. In turn, this process is antagonized by AMPK [17] (Fig. 1). The upregulated aerobic glycolysis insures the energy need of DC activation, and supports the de novo synthesis of fatty acids for the expansion of the endoplasmic reticulum and Golgi for the production and secretion of the effector proteins such as cytokines [21]. The commitment to glycolysis was also demonstrated to sustain the survival of the activated DCs by down-regulating the TCA cycle in the mitochondria [22].

2.4. Monocytes and macrophages

Monocytes and macrophages are both important myeloid innate immune cells, standing at the first line of defense against pathogens. Monocytes circulate in the bloodstream where a constantly high oxygen tension is present, while macrophages locate in the tissue or at the site of inflammation where oxygen tension is generally considerably lower. It is therefore not surprisingly to find that macrophages possess higher HIF-1α activity. HIF-1α activation is associated with macrophages differentiation [23], while macrophage-colony stimulating factor (M-CSF) as well as hypoxia are demonstrated to enhance monocyte survival by increasing glycolysis pathway [24], presumably via

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