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Mini-review

mTOR signaling in immune cells and its implications for cancer immunotherapy

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ABSTRACT

The realization that cellular metabolism dictates immune cell development, differentiation and function affords metabolic intervention as a potential venue for cancer immunotherapy. mTOR signaling, as a metabolic master regulator, controls immune cell biology in a cell type-specific and context dependent manner. Furthermore, mTOR activity needs to be fine-tuned to maintain proper immune function. These properties may be exploited for therapeutic purpose, yet caution should be taken against radical changes of mTOR activity. Here, the intricate and complex mTOR regulation in different immune cells is reviewed, highlighting latest discoveries and opportunities for cancer immunotherapy.

Introduction

Cancer immunotherapy aims to control and/or eradicate malignant tumor cells by manipulating patients' own, or HLA-matched donors', immune cells, instead of targeting tumor cells themselves. The recent success of checkpoint blockade therapy drastically intensifies the search for new immune regulatory targets. However, one can argue that real medical breakthroughs often come after extensive basic scientific research, just like the many years of investigation on the biological functions of PD-1 and CTLA4, two major inhibitory receptors on T cells, preceding the success of checkpoint blockade therapy on cancer patients [1]. The emergence of immunometabolism highlights the exquisite controls that cellular metabolism exerts over immune cell biology. For example, different stages of T cell differentiation are not merely associated with different modes of metabolism, they are actively shaped and directed by metabolic programing [2]. Thus, in principle, manipulating immune cell metabolism has the potential to join the growing cancer immunotherapy arsenal. Not surprisingly, as a central nexus that coordinates environmental cues and subsequent metabolic responses, the mechanistic target of rapamycin (mTOR) signaling pathway plays essential functions in a plethora of immune processes [3,4]. Although clinical utilization of mTOR inhibitors was originally intended to suppress immune system for organ transplant, later investigation revealed a much more diverse and nuanced effect of mTOR inhibition on different immune cells at different developmental stages, including an immune-enhancing effect on memory T cell formation. Given the prominent roles that the immune cells play in tumor surveillance and rejection, it is pivotal to understand the fundamental biology of mTOR mediated immune responses.

The fundamentals of mTOR signaling network has been extensively reviewed [3]. Briefly, mTOR, a serine/threonine protein kinase, forms catalytic subunit of two complexes, mTORC1 and mTORC2, which are distinguished by the scaffolding proteins Raptor and Rictor, respectively. mTORC2 controls cell survival and cytoskeletal remodeling by phosphorylating AKT and protein kinase C (PKC). It contributes to cell metabolism under specific conditions [5,6], which will be discussed below. Most of metabolic functions of mTOR are ascribed to mTORC1 (Fig. 1). mTORC1 drives anabolic metabolism, including amino acid metabolism and protein translation through its two best characterized targets, p70S6 kinase (S6K1) and eIF4E binding protein (4EBP). It also promotes lipid, nucleotide, amino acid, glutamine and glucose metabolism while suppressing autophagy, a form of catabolism [3,7]. Notably, mTORC1 can promote anabolic metabolism by either targeting broad range of enzymes in a metabolic pathway, including

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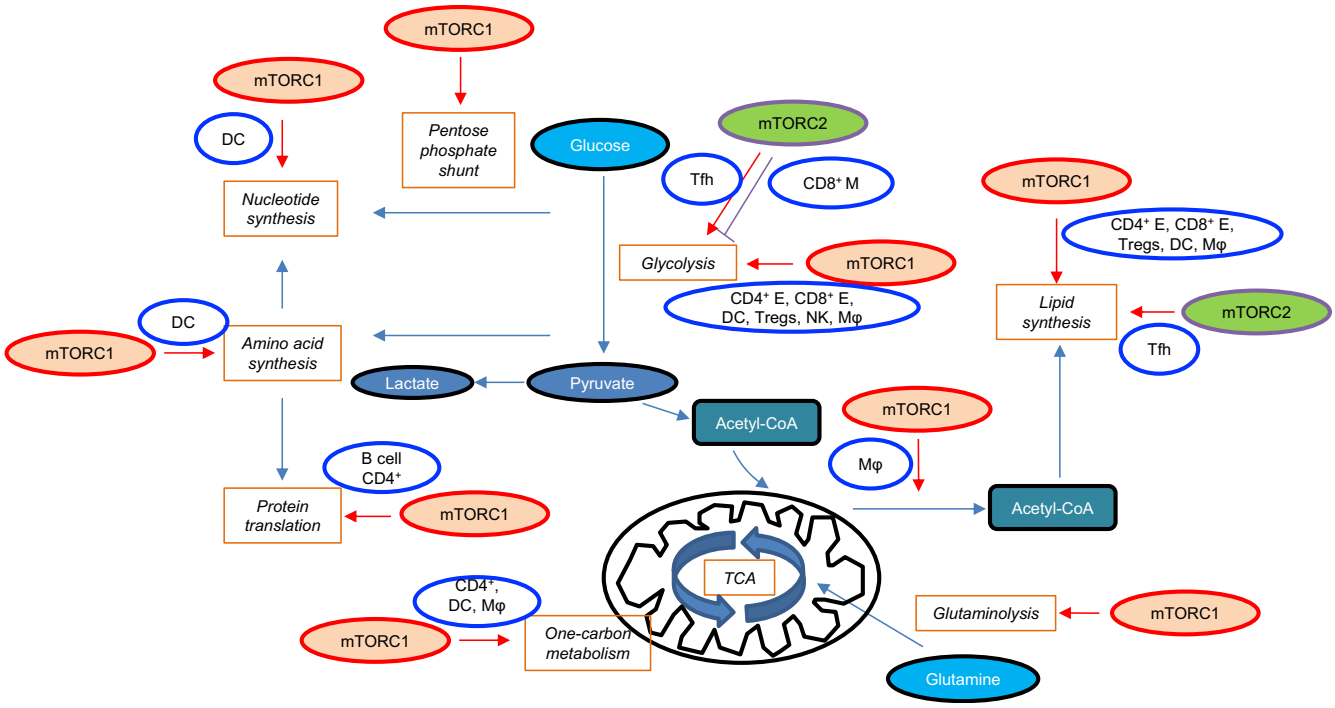

Fig. 1. mTOR, cellular metabolism and immune cells. A simplified diagram depicting major metabolic pathways (italic fonts in red rectangle). mTORC1 positively controls most of them, including glycolysis, pentose phosphate shunt, nucleotide synthesis, amino acid synthesis, protein translation, one-carbon metabolism, glutaminolysis, and lipid biosynthesis. mTORC2 has both stimulating (in Tfh cells) and inhibitory functions (in memory $CD8^+$ T cells) on glycolysis. Blue circles denote immune cells where particular metabolic activity is found to be dependent on mTOR. $CD4^+$ E, effector $CD4^+$ T cells; $CD8^+$ E, effector $CD8^+$ T cells; $CD8^+$ M, memory $CD8^+$ T cells; Tfh, follicular helper T cells; Treg, regulatory T cells; DC, dendritic cells; NK, natural killer cells; Mφ, macrophages. Note, this figure shows that the particular metabolic pathways are associated with indicated immune cells and their functions; but it does not in any way indicate that they are the only or dominant metabolic pathways responsible for the immune function. See texts for more details.

glycolysis, pentose phosphate pathway and lipid biosynthesis [8], or by inducing expression of specific key enzymes. For example, mTORC1 promotes purine biosynthesis by inducing transcription of the mitochondrial tetrahydrofolate (mTHF) cycle enzyme methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) [9]. mTOR-mediated cellular metabolism is associated with many aspects of immunity in various immune cells (Fig. 1, also see below). However, given its pleiotropic effects on metabolism, it is so far unclear whether any specific metabolic pathways dominate mTOR-mediated immune function in a specific immune cell subset.

The original mTOR inhibitor, rapamycin, is a macrolide that preferentially targets mTORC1, but also targets mTORC2 under specific conditions in T cells [10]. mTORC1 senses numerous environmental signals, including many growth factors, energy, oxygen and nutrients, while mTORC2 is primarily activated by insulin and certain immune signals, such as ICOS ligation [5,11]. It is thought that both mTORC1 and mTORC2 are activated by PI3K-AKT pathway. PI3K, through AKT, inhibits the Tuberous Sclerosis Complex (TSC), composed of Tsc1 and Tsc2. TSC functions as a GTPase activating protein for the small GTPase Rheb, which is an essential activator of mTORC1. How PI3K-AKT activates mTORC2 is currently unclear [3]. However, there are PI3K-AKT independent pathways that activate mTOR in immune cells [12–14]. Thus, in this mini-review, I will mainly focus on the recent literature that directly examines mTOR signaling in immune cells and briefly discuss their implications for cancer immunotherapy.

mTOR and adaptive immune cells

$CD8^+$ T cells

Effector cytotoxic T lymphocytes (CTLs), derived from naïve $CD8^+$ T cells, are arguably the most prominent anti-tumor immune cells due to their ability to directly target and destroy tumor cells and maintain long-term memory response. A strong effector function of CTLs, including cytotoxic activity and effector cytokine production, is essential for effective anti-tumor activity. Furthermore, a durable immunotherapy necessitates a robust memory $CD8^+$ T cell formation. It is perhaps these dual requirements of efficient effector and memory responses that pose a challenge for manipulating mTOR activity for cancer immunotherapy.

Rapamycin was first shown to enhance memory $CD8^+$ T cell generation in an acute lymphocytic choriomeningitis virus (LCMV) infection model [15] and a *Listeria monocytonenes* infection model [16]. Later, a similar effect was reported in a xenograft thymoma model [17]. These unexpected findings indicate that mTORC1 negatively controls memory T cell formation. Consistent with this idea, over-activation of mTORC1, through Tsc1 or Tsc2 deletion, reduces memory $CD8^+$ T cell formation in a *Listeria monocytonenes* or vaccinia infection model [6,18]. Notably, direct manipulating mTOR-mediated metabolism is also capable of shifting effector vs memory T cell formation. Lower glycolytic rate, or lower mitochondrial membrane potential ($\Delta\Psi m$), which correlates with reduced mitochondrial OXPHOS and mTORC1 activity, is associated with enhanced memory $CD8^+$ T cell generation. Glycolysis inhibitor treatment, or sorting $CD8^+$ T cells with low $\Delta\Psi m$, enhances the anti-tumor activity of adoptively transferred $CD8^+$ T cells in a xenograft B16 melanoma model [19,20]. However, studies using genetic models caution against strong suppression of mTOR in T cells to treat tumor. Pollizzi et al. showed that Rheb deficiency, which significantly reduces mTORC1 activity, leads to reduced effector $CD8^+$ T cells and their function. Although Rheb-deficient T cells generate more memory T cells, consistent with negative regulation of memory T cell formation by mTORC1, they fail to respond to secondary immunization and control xenograft