SciMedCentral

Journal of Immunology & Clinical Research

Review Article

mTOR Signaling and Dendritic Cell Biology

Yanyan Wang and Hongbo Chi*

Department of Immunology, St. Jude Children's Research Hospital, USA

*Corresponding author
Hongbo Chi. Department of Immunology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA. Phone: 901-595-6282; Fax: 901-595- 5766; E-mail: hongbo.chi@stjude.org

Submitted: 02 January 2014

Accepted: 20 January 2014

Published: 24 January 2014

Keywords

- Rapamycin
- mTOR
- Dendritic cell
- Tsc1
- Pten

Abstract

Dendritic cells (DCs), the most potent antigen-presenting cells in bridging innate and adaptive immunity, play a central role in orchestrating the decision between immunity and tolerance. The development, maturation and function of DCs are under the intricate control of various cellular and molecular mechanisms. Signaling via the mechanistic target of rapamycin (mTOR), a key kinase-mediated pathway in integrating cellular and environmental cues, has emerged as a crucial regulator of various aspects of DC biology. These studies have benefited from pharmacological inhibitors of mTOR, especially rapamycin, and genetic dissection of mTOR components and regulators such as Pten, Tsc1 and Raptor. Here we review the recent advances in understanding the functional significance and mechanistic basis of mTOR signaling in DC development and function.

INTRODUCTION

Dendritic cells (DCs) are a heterogeneous population of antigen-presenting cells (APCs) specialized to capture, process, and present antigens to T lymphocytes [1]. DCs develop from bone marrow (BM)-derived precursor populations, including monocyte and dendritic cell progenitors (MDPs) and common DC progenitors (CDPs) that subsequently give rise to plasmacytoid DCs (pDCs) and conventional DCs (cDCs). In the peripheral tissues, DCs encountering pathogens undergo maturational event through upregulation of co-stimulatory molecules (such as CD40, CD80 and CD86) and alteration of adhesion molecules. Antigen-bearing DCs then migrate to T cell areas of secondary lymphoid tissues, where they provide antigenic, co-stimulatory and cytokine signals to naïve T cells to initiate effector immune responses. In the absence of inflammatory or infectious signals, DCs present self-antigens in secondary lymphoid tissues to induce and maintain self-tolerance. Therefore, by bridging innate and adaptive immunity, DCs play a central role in orchestrating the decision between immunity and tolerance.

Whereas the research on DC development and function has traditionally focused on cellular pathways and ligand-receptor interactions, more recent studies highlight the key roles of molecular and signaling pathways in these processes. In particular, mTOR signaling has emerged as a crucial regulator of multiple aspects of DC biology, including the development, maturation and function of DCs. In this review, we discuss the recent advances in our understanding of the roles of mTOR signaling in the regulation of DC biology, and how pharmacological and genetic modulation of mTOR signaling impinges upon DC development and function and the outcome of immune responses.

mTOR signaling

The mechanistic target of rapamycin (mTOR, a serine/threonine kinase) is the catalytic unit of two distinct multi-protein complexes: mTOR complex 1 (mTORC1) and mTORC2 that are respectively defined by the scaffold proteins Raptor and Rictor (Figure 1) [2]. mTORC1 activity is dynamically regulated by environmental and intracellular signals, including immune, growth factor, and metabolic cues. Many upstream signals activate mTORC1 pathway through the small GTPase Rheb (Ras homologue enriched in brain). The tuberous sclerosis 1 (Tsc1) and Tsc2 form a complex that inactivates Rheb, thereby suppressing mTORC1 activity. Further upstream, the phosphoinositide 3-kinase (PI3K)-AKT pathway inactivates Tsc1/Tsc2 complex while AMP-activated protein kinase (AMPK) enhances its activity. The activity of PI3K-AKT pathway is also tightly controlled by negative regulators, with the most notable factor being the lipid phosphatase Pten. Deletion of Pten leads to the constitutive activation of PI3K-AKT signaling and is a common event in malignant transformation. S6K1 and 4E-BP1 are two best-characterized downstream targets of mTORC1 that regulate protein translation [2]. mTORC1 pathway also promotes anabolic metabolism such as glycolysis and lipid biosynthesis while inhibiting autophagy [3].

PI3K also signals to mTORC2 in a process dependent upon the ribosome, although detailed mechanisms are not fully understood [4]. A signature activity of mTORC2 is the phosphorylation of AKT at Ser473, thereby contributing to full activation of AKT and the regulation of AKT downstream targets such as Foxo1 and Foxo3 [2].

Modulation of DC development, maturation and function by Rapamycin

The immunosuppressive property of rapamycin is traditionally ascribed to its potent activity to inhibit lymphocyte proliferation [5]. Recent studies have revealed that rapamycin impinges upon the differentiation, maturation and function of DCs, and these effects also contribute to its immunomodulatory property [6]. First, prolonged treatment with rapamycin *in vivo* decreases the numbers of DCs under steady state, as well as the expansion of DCs upon Flt3L treatment *in vivo* [7]. DC development can be recapitulated in BM culture supplemented with Flt3L or GM-CSF. Rapamycin strongly inhibits the generation of both pDCs and cDCs in Flt3L-supplemented culture, partly by blocking the proliferation of DC progenitors. In contrast, rapamycin does not prevent DC development in GM-CSF-supplemented BM culture [8].

Second, rapamycin impedes the maturation of DCs and instead, enhances their tolerogenic potential. Rapamycin inhibits the maturation of BM-derived DCs (BMDCs) as indicated by the decreased expression of co-stimulatory (CD80 and CD86) and MHC-Class II (MHC-II) molecules, even after exposure to potent inflammatory stimuli such as TLR and CD40 ligation [7,9,10]. Rapamycin-treated DCs are poor stimulators of T cell responses, by impairing T cell proliferation and IL-2 and IFNγ production [7,9] and inducing T cell anergy and apoptosis [9,10]. Instead, rapamycin-treated DCs enhance the generation of regulatory T cells [10]. *In vivo*, rapamycin-conditioned DCs prolong organ allograft survival [9,10] and reduce graft-versus-host disease [11]. Mechanistically, rapamycin impairs the expression of functional IL-4R and thus the responsiveness of DCs to the maturation-promoting signal IL-4 [7]. Additionally, rapamycin conditioning of DCs elicits the *de novo* production of IL-1β, which promotes the expression of the transmembrane protein IL-1R-like 1 (IL-1RL1, also known as ST2), a potent negative regulator of TLR signaling [12]. Thus, rapamycin-treated DCs undergo impaired maturation and promote immune tolerance by diminishing effector T cell responses and promoting regulatory T cell generation.

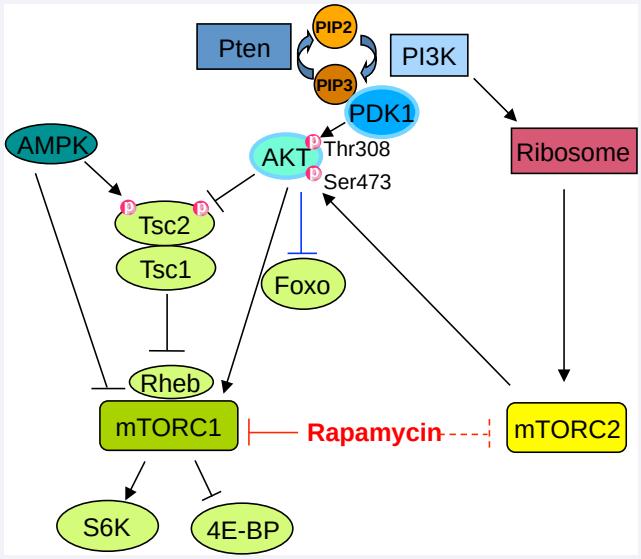

Figure 1 Components and regulators of mTOR signaling. mTOR is found in two distinct complexes, mTORC1 and mTORC2, and can be activated by multiple upstream signals. mTOR activity is also tightly controlled by negative regulators including Pten and the Tsc1-Tsc2 complex, which inactivate PI3K and Rheb activities, respectively. S6K and 4E-BP are two well-characterized downstream targets of mTORC1, whereas phosphorylation of AKT at Ser473 is the signature activity of mTORC2.

Third, rapamycin exerts potent effects on DC functions and DC-mediated immune responses. An important mechanism is to shape the production of pro- and anti-inflammatory cytokines. However, as compared with the inhibitory effects of rapamycin on DC differentiation and maturation, the role of mTOR signaling in DC cytokine production is more complex. Weichhart et al reported that rapamycin promotes IL-12 but suppresses IL-10 production in DCs through regulation of transcription factors NF-κB and STAT3, respectively [13]. In an independent study, Ohtani also described the reciprocal effect of rapamycin on IL-12 and IL-10 expression in LPS-stimulated DCs. In this case, inhibition of IL-10 function reverses the enhancing effect of rapamycin on IL-12, indicating that rapamycin inhibits IL-12 expression indirectly via the autocrine action of IL-10 [14]. Further, the enhanced IL-12 production in DCs generated after chronic exposure to rapamycin has been ascribed to the failure to down-regulate GSK-3 activity [15]. Thus, rapamycin promotes IL-12 expression in DCs via distinct mechanisms in a context-dependent manner. Despite these observed positive effects on IL-12 production, rapamycin is also capable of suppressing IL-12 expression in human monocyte-derived DCs in response to LPS or CD40L stimulation [16], thereby highlighting the complex roles of mTOR in the regulation of IL-12 expression. Another surprising finding is that rapamycin promotes IL-1β secretion via caspase-1 activation [12,17]. As for other pro-inflammatory cytokines such as IL-6 and TNFα, mTOR inhibition has more variable and context-dependent effects. For instance, rapamycin has been shown to inhibit [17] or promote the expression of these cytokines [13], or have no strong effects [14].

Another important mechanism whereby mTOR signaling regulates DC functions is its requirement for the production of type I interferon (IFNα/β), especially in pDCs. In pDCs stimulated with TLR9, rapamycin treatment reduces the production of IFNα/β through disruption of the TLR9-MyD88 complex and subsequent impairment of phosphorylation and nuclear translocation of IFN regulatory factor 7 (IRF7). *In vivo* rapamycin treatment results in decreased IFNαβ in serum and in pDCs in response to stimulation with a TLR9 ligand or viral vaccine, leading to impaired immune responses [18]. A similar effect of rapamycin to inhibit TLR9-induced production of type I interferon has been observed in Flt3L-derived murine DCs and human PBMCs [17]. Consistent with these observations, inhibition of PI3K, especially PI3Kδ, impairs the ability of human pDCs to produce type I interferon but not other proinflammatory cytokines such as TNFα or IL-6 [19]. Aside from affecting cytokine and interferon production, rapamycin also regulates other cellular events in DCs to impinge upon DC functions [6]. For example, rapamycin has been shown to impinge upon DC survival [7,20,21], migration [11,22], antigen uptake [23, 24] and autophagy [25].

Overall, these results indicate that rapamycin exerts a

plethora of effects on DC development, maturation and functions. However, it is important to note that rapamycin is not an efficient inhibitor of mTORC1-mediated 4E-BP1 phosphorylation [26]. Additionally, rapamycin may inhibit mTORC2 activity with prolonged treatment and/or at a high dose [27, 28]. As a result, second-generation mTOR inhibitors have been developed that directly target the mTOR catalytic activity and thus have more specific and potent effects on mTOR [29]. Indeed, using these second-generation mTOR inhibitors, Rosborough et al recently reported that a rapamycin-insensitive mTORC1 signaling controls IL-10 and B7-homolog 1 (B7-H1) expression by DCs and the induction of regulatory T cells [30].

Inhibition of Flt3L-dependent CD8+ cDC development by Pten

Pten, an important signaling molecule in tumor suppression and immune regulation, is also critical for DC development and function (Figure 2). By using a tamoxifen-inducible Ptenflox/Pten-flox/flox; Rosa26-Cre-ER mouse strain, Sathaliyawala et al showed that acute Pten deletion in hematopoietic progenitors promotes the development of all DC subsets in the culture with Flt3L [8]. *In vivo* analysis demonstrates that the chimeras reconstituted with Pten-deficient BM cells contain increased numbers of CD8+ cDCs, but not CD8– cDCs or pDCs, indicating that Pten deletion in hematopoietic cells preferentially facilitates the development CD8+ cDCs. The authors further used Pten-flox/flox; CD11c-Cre+ mice that lack Pten in the CD11c-expressing DCs to investigate the specific role of Pten in mature DCs. In these animals, the number of splenic CD8+ cDCs is increased by 5-6 fold, and the competitive chimera system shows that this expansion is a cell-intrinsic effect. Cell developmental origin analysis demonstrates that the expansion of CD8+ cDCs in the absence of Pten originates at the immature CD8low differentiation stage. As the functional and developmental equivalent of CD8+ cDCs, the CD103+ cDC subset in tissues is also increased in Pten-flox/flox;CD11c-Cre+ mice. After DC-specific Pten loss, the control of *Listeria* infection is impaired, although antigen-specific T cell responses are mounted normally. Thus, Pten expression in DCs controls DC subset homeostasis that contributes to protection against bacterial infections. Consistent with the preferential effect of Pten deletion on CD8+ cDCs, such DC subset contains higher mTORC1 activity (p-S6) than CD8– cDCs under steady state and upon Flt3L treatment *in vivo*. Importantly, rapamycin treatment reverses the expansion of Pten-deficient DCs *in vitro* and *in vivo*. These results demonstrate that restriction of Flt3L-induced mTOR signaling by Pten ensures optimal DC pool size and subset composition [8].

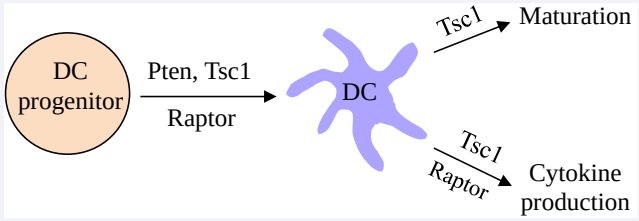

Figure 2 The roles of mTOR signaling in DC development, maturation and function. DC development and homeostasis are under the control of Pten, Tsc1 and Raptor. Tsc1 is also important for DC maturation and cytokine production, whereas Raptor controls IL-10 production in DCs. Although not depicted here, rapamycin treatment affects the development, maturation and cytokine production and functional activation of DCs.

Other studies using pharmacological inhibition or silencing of Pten also indicate a role of Pten in DC differentiation and function. Enhanced mTOR signaling via pharmacological inhibition of Pten or hyper-activation of AKT results in increased proportion and absolute number of human CD34+ cell-derived pDCs [31]. A small interfering RNA (siRNA) targeting Pten in DCs promotes their survival and maturation, including increased expressions of co-stimulatory molecules, which in turn facilities antigen-specific CD8+ T cell activation *in vitro* and *in vivo* [32].

Tsc1-mediated regulation of DC development and function

The tumor suppressor Tsc1 integrates upstream signals to suppress mTORC1 activity, and is also involved in modulating mTORC2 activity [2]. Our recent study demonstrates that Tsc1 is an important regulator of DC development [33]. We generated the Tsc1-flox/flox;Rosa26-Cre-ER genetic model and found that the ablation of Tsc1 after *in vivo* tamoxifen treatment impairs DC development. Loss of Tsc1 also inhibits the development of Flt3L-derived BMDCs *in vitro*. These defects are associated with diminished cell survival and proliferation. Moreover, Tsc1 deficiency causes DC spontaneous maturation, as indicated by the increased expression of co-stimulatory molecules, but a propensity to differentiate into other lineages. Moreover, Tsc1-deficient DCs produce decreased IL-12 and are impaired to mediate effector TH1 responses.

Mechanistically, Tsc1-deficient DCs exhibit increased activities of multiple metabolic pathways including glycolysis, mitochondrial respiration and lipid synthesis, as well as elevated expression of the transcription factor Myc, an established regulator of cell metabolism. Importantly, deletion of Myc in Tsc1-deficient cells partially blocks defective cell metabolism and DC survival and maturation, highlighting a key role of the Tsc1-Myc axis in metabolic programming of DC differentiation. Further, Tsc1 deficiency results in increased mTORC1 but decreased mTORC2 activity. Either rapamycin treatment or deletion of Rheb reverses the defective development of Tsc1-deficient DCs, but loss of mTORC2 alone does not have strong effects on DC development. Thus, aberrant activation of mTORC1 in the absence of Tsc1 largely accounts for the defective development. Our results demonstrate that the interplay between Tsc1-Rheb-mTORC1 signaling and Myc-dependent bioenergetic and biosynthetic activities constitutes a key metabolic checkpoint to orchestrate DC development [33].

Although Tsc1 plays a critical role in the development of Flt3L-derived DCs, it is not essential for the *in vitro* differentiation of GM-CSF-derived DCs [34]. Furthermore, deletion of Tsc1 via the CD11c-Cre system does not alter DC development [8], highlighting a context-dependent requirement of Tsc1 in DC development. Using GM-CSF-derived BMDCs, Pan et al. explored how the deletion of Tsc1 affects TLR-mediated activation and function of DCs [34]. Tsc1 deficiency results in increased

expression of TNFα and IL-6 but decreased IL-12p40 in response to LPS stimulation. Importantly, the absence of Tsc1 markedly impairs the expression of MHC-II as well as CIITA, a crucial transcription factor required for MHC-II expression, in DCs but not macrophages or B cells. Consequently, Tsc1-deficient BMDCs show impaired capacity for antigen presentation and activation of CD4+ T cells *in vitro* and *in vivo*. The defective MHC-II/CIITA expression in the mutant cells is associated with diminished expression of IRF4, and ectopic expression of IRF4 restores the CIITA/MHC-II expression. Moreover, Tsc1-deficient DCs have increased mTORC1 but decreased mTORC2 activity, and silencing of Raptor and rapamycin treatment indicate a crucial role of mTORC1 in regulating IRF4-CIITA-MHC-II expression. Together, these studies establish a crucial role of Tsc1-mTORC1 signaling in mediating IRF4-CIITA-MHC-II expression and DC functions [34].

Raptor in DC subset homeostasis and immune regulation

Raptor is the signature component of mTORC1 complex [2]. To study the role of mTORC1 in DC function, Ohtani et al developed mice with DC-specific deletion of Raptor Raptor-flox/flox;CD11c-Cre+ [35]. Loss of Raptor results in expansion of selective DC subsets such as CD8+ splenic cDCs and intestinal CD11c+CD11b+ DCs. Raptor deficiency diminishes the production of IL-10 and accordingly upregulates the expression of CD86 in intestinal CD11c+CD11b+ DCs. Furthermore, mice lacking Raptor in DCs are highly susceptible to dextran sodium sulfate-induced colitis. These results highlight an important role of mTORC1 in orchestrating DC subset homeostasis and anti-inflammatory programs in intestinal DCs [35].

Signaling via mTORC1 is also important for the homeostasis of the Langerhans cell (LC), a specialized DC population in the skin [36]. Using CD11c-Cre system to delete Raptor in LCs, Kellersch and Brocker reported that loss of mTORC1 activity results in an age-dependent progressive loss of LCs in the skin. This is ascribed to the impaired survival of Raptor-deficient LCs and more importantly, the increased emigration of these cells to leave the skin, an effect associated with altered expression of adhesion and migration molecules. In contrast to a crucial requirement of mTORC1, loss of mTORC2 via deletion of Rictor does not have strong effects on the homeostasis of LCs. Therefore, mTORC1 but not mTORC2 is crucial for the homeostasis of the sentinel DCs in the skin [36].

SUMMARY

DCs play a central role in directing the decision between immunity and tolerance and the outcome of immune responses. Although mTOR signaling is best characterized in T cells in the immune system, emerging evidence highlights the importance of mTOR in the regulation of various aspects of DC biology, including the development, homeostasis, maturation and function. These exciting advances have benefited from both pharmacological and genetic approaches to modulate mTOR activation. An important future direction is to develop and employ more advanced strategies such as second-generation mTOR inhibitors and spatially and temporally-controlled genetic deletion systems, to further dissect the functional impacts and mechanistic basis of mTOR signaling in DCs. Given the central roles of mTOR in integrating cellular and environmental cues, how mTOR is modulated by upstream signals in DCs, the key sentinel cell in the immune system, warrants further investigation. These studies may lead to the identification of innovative targets and strategies to modulate DC function for therapeutic intervention of immune-mediated disorders.

ACKNOWLEDGEMENTS

We acknowledge the large number of researchers who have contributed to this field whose work was not cited owing to space limitations. The authors' research is supported by US National Institutes of Health (AI101407, NS064599 and AI094089), National Multiple Sclerosis Society, and the American Lebanese Syrian Associated Charities (H.C.).

REFERENCES

1. Merad M, Sathe P, Helft J, Miller J, Mortha A. The dendritic cell lineage: ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting. Annu Rev Immunol. 2013; 31: 563-604.
2. Laplante M, Sabatini DM. mTOR signaling in growth control and disease. Cell. 2012; 149: 274-293.
3. Zeng H, Chi H. mTOR and lymphocyte metabolism. Curr Opin Immunol. 2013; 25: 347-355.
4. Zinzalla V, Stracka D, Oppliger W, Hall MN. Activation of mTORC2 by association with the ribosome. Cell. 2011; 144: 757-768.
5. Chi H. Regulation and function of mTOR signalling in T cell fate decisions. Nat Rev Immunol. 2012; 12: 325-338.
6. Thomson AW, Turnquist HR, Raimondi G. Immunoregulatory functions of mTOR inhibition. Nat Rev Immunol. 2009; 9: 324-337.
7. Hackstein H, Taner T, Zahorchak AF, Morelli AE, Logar AJ, Gessner A, et al. Rapamycin inhibits IL-4--induced dendritic cell maturation in vitro and dendritic cell mobilization and function in vivo. Blood. 2003; 101: 4457-63.
8. Sathaliyawala T, O'Gorman WE, Greter M, Bogunovic M, Konjufca V, Hou ZE, et al. Mammalian target of rapamycin controls dendritic cell development downstream of Flt3 ligand signaling. Immunity. 2010; 33: 597-606.
9. Taner T, Hackstein H, Wang Z, Morelli AE, Thomson AW. Rapamycin-treated, alloantigen-pulsed host dendritic cells induce ag-specific T cell regulation and prolong graft survival. Am J Transplant. 2005; 5: 228-236.
10. Turnquist HR, Raimondi G, Zahorchak AF, Fischer RT, Wang Z, Thomson AW. Rapamycin-conditioned dendritic cells are poor stimulators of allogeneic CD4+ T cells, but enrich for antigen-specific Foxp3+ T regulatory cells and promote organ transplant tolerance. J Immunol. 2007; 178: 7018-31.
11. Reichardt W, Dürr C, von Elverfeldt D, Jüttner E, Gerlach UV, Yamada M, et al. Impact of mammalian target of rapamycin inhibition on lymphoid homing and tolerogenic function of nanoparticle-labeled dendritic cells following allogeneic hematopoietic cell transplantation. J Immunol. 2008; 181: 4770-9.
12. Turnquist HR, Sumpter TL, Tsung A, Zahorchak AF, Nakao A, Nau GJ, et al. IL-1beta-driven ST2L expression promotes maturation resistance in rapamycin-conditioned dendritic cells. J Immunol. 2008; 181: 62-72.
13. Weichhart T, Costantino G, Poglitsch M, Rosner M, Zeyda M, Stuhlmeier KM, et al. The TSC-mTOR signaling pathway regulates the innate

inflammatory response. Immunity. 2008; 29: 565-577.

14. Ohtani M, Nagai S, Kondo S, Mizuno S, Nakamura K, Tanabe M, et al. Mammalian target of rapamycin and glycogen synthase kinase 3 differentially regulate lipopolysaccharide-induced interleukin-12 production in dendritic cells. Blood. 2008; 112: 635-43.

15. Turnquist HR, Cardinal J, Macedo C, Rosborough BR, Sumpter TL, Geller DA, et al. mTOR and GSK-3 shape the CD4+ T-cell stimulatory and differentiation capacity of myeloid DCs after exposure to LPS. Blood. 2010; 115: 4758-4769.

16. Haidinger M, Poglitsch M, Geyeregger R, Kasturi S, Zeyda M, Zlabinger GJ, et al. A versatile role of mammalian target of rapamycin in human dendritic cell function and differentiation. J Immunol. 2010; 185: 3919-3931.

17. Schmitz F, Heit A, Dreher S, Eisenächer K, Mages J, Haas T, et al. Mammalian target of rapamycin (mTOR) orchestrates the defense program of innate immune cells. Eur J Immunol. 2008; 38: 2981-92.

18. Cao W, Manicassamy S, Tang H, Kasturi SP, Pirani A, Murthy N, et al. Toll-like receptor-mediated induction of type I interferon in plasmacytoid dendritic cells requires the rapamycin-sensitive PI(3)K-mTOR-p70S6K pathway. Nat Immunol. 2008; 9: 1157-1164.

19. Guiducci C, Ghirelli C, Marloie-Provost MA, Matray T, Coffman RL, Liu YJ, et al. PI3K is critical for the nuclear translocation of IRF-7 and type I IFN production by human plasmacytoid predendritic cells in response to TLR activation. J Exp Med. 2008; 205: 315-322.

20. Woltman AM, van der Kooij SW, Coffer PJ, Offringa R, Daha MR, van Kooten C. Rapamycin specifically interferes with GM-CSF signaling in human dendritic cells, leading to apoptosis via increased p27KIP1 expression. Blood. 2003; 101: 1439-1445.

21. Amiel E, Everts B, Freitas TC, King IL, Curtis JD, Pearce EL, et al. Inhibition of mechanistic target of rapamycin promotes dendritic cell activation and enhances therapeutic autologous vaccination in mice. J Immunol. 2012; 189: 2151-2158.

22. Sordi V, Bianchi G, Buracchi C, Mercalli A, Marchesi F, D'Amico G, et al. Differential effects of immunosuppressive drugs on chemokine receptor CCR7 in human monocyte-derived dendritic cells: selective upregulation by rapamycin. Transplantation. 2006; 82: 826-34.

23. Hackstein H, Taner T, Logar AJ, Thomson AW. Rapamycin inhibits macropinocytosis and mannose receptor-mediated endocytosis by bone marrow-derived dendritic cells. Blood. 2002; 100: 1084-1087.

24. Monti P, Mercalli A, Leone BE, Valerio DC, Allavena P, Piemonti L. Rapamycin impairs antigen uptake of human dendritic cells. Transplantation. 2003; 75: 137-145.

25. Jagannath C, Lindsey DR, Dhandayuthapani S, Xu Y, Hunter RL Jr, Eissa NT. Autophagy enhances the efficacy of BCG vaccine by increasing peptide presentation in mouse dendritic cells. Nat Med. 2009; 15: 267-276.

26. Choo AY, Yoon SO, Kim SG, Roux PP, Blenis J. Rapamycin differentially inhibits S6Ks and 4E-BP1 to mediate cell-type-specific repression of mRNA translation. Proc Natl Acad Sci U S A. 2008; 105: 17414-17419.

27. Sarbassov DD, Ali SM, Sengupta S, Sheen JH, Hsu PP, Bagley AF, et al. Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. Mol Cell. 2006; 22: 159-168.

28. Delgoffe GM, Pollizzi KN, Waickman AT, Heikamp E, Meyers DJ, Horton MR, et al. The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2. Nat Immunol. 2011; 12: 295-303.

29. Benjamin D, Colombi M, Moroni C, Hall MN. Rapamycin passes the torch: a new generation of mTOR inhibitors. Nat Rev Drug Discov. 2011; 10: 868-880.

30. Rosborough BR, Raïch-Regué D, Matta BM, Lee K, Gan B, DePinho RA, et al. Murine dendritic cell rapamycin-resistant and rictor-independent mTOR controls IL-10, B7-H1, and regulatory T-cell induction. Blood. 2013; 121: 3619-3630.

31. van de Laar L, van den Bosch A, Boonstra A, Binda RS, Buitenhuis M, Janssen HL, et al. PI3K-PKB hyperactivation augments human plasmacytoid dendritic cell development and function. Blood. 2012; 120: 4982-4991.

32. Kim JH, Kang TH, Noh KH, Kim SH, Lee YH, Kim KW, et al. Enhancement of DC vaccine potency by activating the PI3K/AKT pathway with a small interfering RNA targeting PTEN. Immunol Lett. 2010; 134: 47-54.

33. Wang Y, Huang G, Zeng H, Yang K, Lamb RF, Chi H. Tuberous sclerosis 1 (Tsc1)-dependent metabolic checkpoint controls development of dendritic cells. Proc Natl Acad Sci U S A. 2013; 110: E4894-4903.

34. Pan H, O'Brien TF, Wright G, Yang J, Shin J, Wright KL, et al. Critical role of the tumor suppressor tuberous sclerosis complex 1 in dendritic cell activation of CD4 T cells by promoting MHC class II expression via IRF4 and CIITA. J Immunol. 2013; 191: 699-707.

35. Ohtani M, Hoshii T, Fujii H, Koyasu S, Hirao A, Matsuda S. Cutting edge: mTORC1 in intestinal CD11c+ CD11b+ dendritic cells regulates intestinal homeostasis by promoting IL-10 production. J Immunol. 2012; 188: 4736-4740.

36. Kellersch B, Brocker T. Langerhans cell homeostasis in mice is dependent on mTORC1 but not mTORC2 function. Blood. 2013; 121: 298-307.

Cite this article

Wang Y, Chi H (2014) mTOR Signaling and Dendritic Cell Biology. J Immunol Clin Res 2(1): 1015.