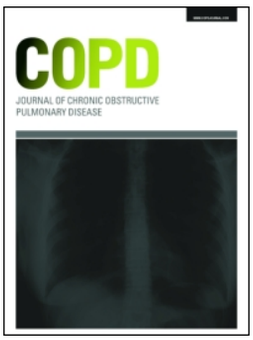

COPD: Journal of Chronic Obstructive Pulmonary Disease

ISSN: 1541-2555 (Print) 1541-2563 (Online) Journal homepage: https://www.tandfonline.com/loi/icop20

Mammalian Target of Rapamycin: Is It Relevant to COPD Pathogenesis or Treatment?

Evasio Pasini, Vincenzo Flati, Laura Comini, Adriana Olivares, Enrica Bertella, Giovanni Corsetti & Michele Vitacca

To cite this article: Evasio Pasini, Vincenzo Flati, Laura Comini, Adriana Olivares, Enrica Bertella, Giovanni Corsetti & Michele Vitacca (2019): Mammalian Target of Rapamycin: Is It Relevant to COPD Pathogenesis or Treatment?, COPD: Journal of Chronic Obstructive Pulmonary Disease

To link to this article: https://doi.org/10.1080/15412555.2019.1583726

Published online: 06 May 2019.

COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
https://doi.org/10.1080/15412555.2019.1583726

Mammalian Target of Rapamycin: Is It Relevant to COPD Pathogenesis or Treatment?

Evasio Pasini[a]*, Vincenzo Flati[b]*, Laura Comini[c], Adriana Olivares[c], Enrica Bertella[d], Giovanni Corsetti[e], and Michele Vitacca[d]

[a]Cardiac Rehabilitation of the Institute of Lumezzane, Istituti Clinici Scientifici Maugeri IRCCS, Brescia, Italy; [b]Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy; [c]Scientific Direction of the Institute of Lumezzane, Istituti Clinici Scientifici Maugeri IRCCS, Brescia, Italy; [d]Respiratory Rehabilitation of the Institute of Lumezzane, Istituti Clinici Scientifici Maugeri IRCCS, Brescia, Italy; [e]Division of Human Anatomy and Physiopathology, Department of Clinical & Experimental Sciences, University of Brescia, Brescia, Italy

ABSTRACT

The mammalian target of rapamycin (mTOR) signalling pathway regulates fundamental metabolic processes such as inflammation, autophagy and apoptosis, all of which influence cell fate. Recent experimental data suggest that mTOR signalling is involved in many diseases, including lung diseases, but with contrasting data. Overexpression of mTOR and its signalling proteins have been linked to lung cell senescence and development of emphysema, pulmonary hypertension and inflammation. On the other hand, mTOR inhibitors, as rapamycin and/or its derivatives, restore corticosteroid sensitivity in peripheral blood mononuclear cells from chronic obstructive pulmonary disease (COPD) patients, and overexpression of mTOR suppresses cigarette smoke-induced inflammation and emphysema, suggesting that induction of mTOR expression/activity might be useful to treat COPD. This apparent discrepancy is due to complex and heterogenic enzymatic pathway of mTOR. Translation of pre-clinical positive data on the use of mTOR inhibitors to COPD therapy needs a more in-depth knowledge of mTOR signalling.

ARTICLE HISTORY
Received 11 February 2019
Accepted 12 February 2019

KEYWORDS
COPD; health care; mTOR; metabolism; multi-protein complexes; inflammation

Introduction

The mammalian target of rapamycin (mTOR) has been identified as an intracellular downstream signal transducer. It plays an important role in regulating fundamental metabolic processes such as inflammation, autophagy, apoptosis, proteins synthesis and/or cytoskeleton organization which influence cell's survival or death, by integrating internal and external cell stimuli (1). mTOR is a highly conserved serine-threonine kinase (1), which belongs to the phosphoinositide 3-kinase-related protein kinase family, PIKK (2–4). It is found in two distinct protein kinase complexes: mTORC1 and mTORC2. They can act either synergistically, independently or even antagonistically, according to the prevalence of the various stimuli (2, 3).

Both mTORC1 and mTORC2 complexes have common subunits, i.e., mTOR catalytic subunit and mLST8 (also known as GβL), whereas other components distinguish them. For example:

- mTORC1 contains Raptor (regulator-associated protein of mTOR) and PRAS40 (5–7), while mTORC2 contains Rictor (rapamycin insensitive companion of mTOR), Protor (1 or 2 and acts as a Rictor-binding protein) and mSin1 (also called MAPKAP1) (8, 9).
- Both complexes are negatively influenced by Deptor, but both mTORC1 and mTORC2 negatively regulate Deptor expression as a means for their activity modulation (10).

mTOR is regulated by various external (i.e. nutrients and/or exercise) and internal (i.e. energy levels and/or stress signals) cell stimuli, which control eukaryotes growth, proliferation and metabolism. Indeed, nutrients availability trigger energy-consuming anabolic pathways or energy-producing catabolic pathways. In addition, the amount of cellular energy, sensed by AMP-activated protein kinase (AMPK), when high, stimulates mTOR, making possible protein synthesis and cell growth (11). Free amino acids (AA) are also essential for mTORC1 activation. Indeed, anabolic factors and other stimuli cannot activate mTOR if the AA concentration is limited. Particularly, the essential AAs, leucine and glutamine are crucial for mTOR signalling (12).

Another important point is that mTOR regulates physiological cell processes such as cell autophagy and this could be relevant for both development and therapy of chronic obstructive pulmonary disease (COPD) and other pathologies. Specifically, mTORC1 inhibits cell autophagy in the presence of nutrients. However, mTOR can also stimulate autophagy independently of mTORC1 through the mTORC2 complex

CONTACT Enrica Bertella enrica.bertella@icsmaugeri.it Istituti Clinici Scientifici Maugeri IRCCS, Via Salvatore Maugeri, 4, 27100 Pavia, Italy.
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/icop.
*These authors contributed equally to this study.

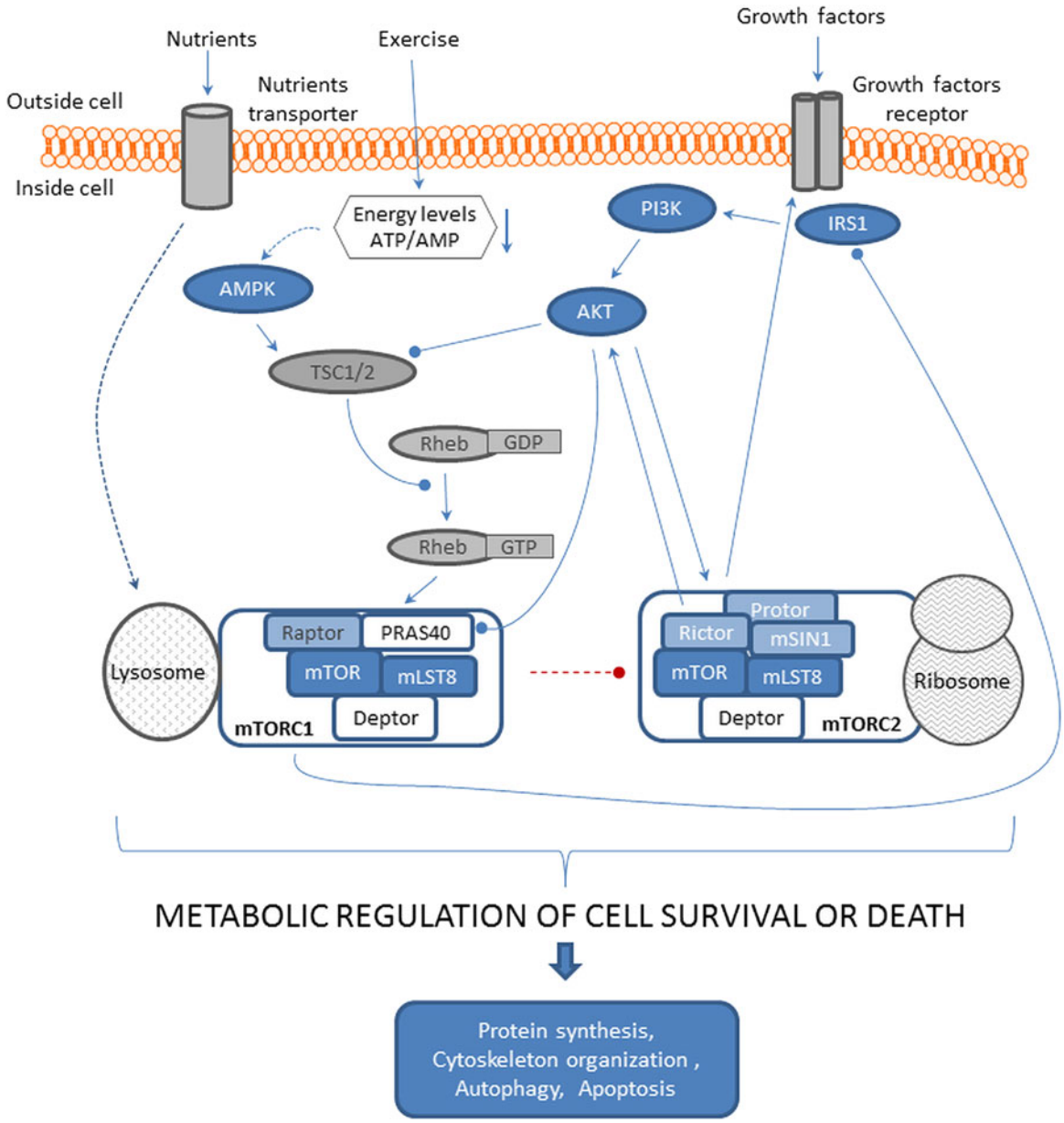

Figure 1. The mTOR machinery with all involved complexes and the relevant interaction lines. For further information see Ref. (1,2). The figure has been modified from that shown in Ref. (2) with the Author's permission. [AMPK: AMP-activated protein kinase; AKT (PKB): Protein kinase B; GDP: guanosine diphosphate; GTP: guanosine triphosphate; IRS1: insulin receptor substrate 1; mTORC1/2: mammalian target of rapamycin complex 1/2; PI3K: phosphoinositide 3-kinase; PRAS40: proline-rich Akt substrate of 40 kDa; TSC1/2: Tuberous sclerosis proteins 1 and 2; **Interrupted lines**: not yet clarified mechanisms; **Lines ending with an arrow**: activation; **Lines ending with a dot**: inhibition].

when nutrients are limited (13–15). Interestingly, the beginning of the autophagy process inhibits mTOR (12). However, when starvation is prolonged, mTOR is reactivated. Under these conditions, the role of mTORC1 shifts from being a repressor to being an activator of autophagy (15).

Data in the literature show that mTOR signalling is deregulated in many human diseases (16) so that its inhibition has been considered a novel therapy against many diseases, including cancers (17). However, considering the complex interplay between the two mTOR forms, it is intuitive that the sole inhibition of TORC1, such as by rapalogues, might not provide the desired therapeutic effect.

The complexity of the mTOR pathway is summarized in Figure 1 (1,2).

mTOR targeting in lung diseases

Recently, the use of mTOR inhibitors, such as rapamycin and its derivative, has been studied in lung diseases (18) such as idiopathic pulmonary fibrosis (IPF) and COPD (Table 1).

In vitro pre-clinical studies with mTOR inhibitors show contradictory results in pulmonary fibrosis. Indeed, in rats, rapamycin-reduced fibrosis (19); on the contrary, in mice, the same molecule caused disease worsening (20). Interestingly, a clinical trial with rapamycin worsens outcomes in IPF's human patients (21).

COPD is significantly correlated with inflammation and cell ageing that in turn is characterized by mTOR increased activity (22). Thus, mTOR inhibitors have also been tested in COPD. In fact, data on transgenic mice with mTOR

Table 1. mTOR in pulmonary disease.

Reference	Year	Type of study	Main message
Kennedy et al. (18)	2016	Experimental	Current knowledge of mTOR in lung pathology and potential explanation for its involvement in human diseases.
Jin et al. (19)	2014	Experimental	Alleviation of alveolitis and pulmonary fibrosis by rapamycin, with decreased expression of Matrix metalloproteinase 9 (MMP-9) and Tissue Inhibitor Metalloproteinase 1 (TIMP-1).
Madala et al. (20)	2011	Experimental	Increased expression of pro-fibrotic Th2 cytokine withamycin treatment.
Malouf et al. (21)	2011	Clinical	Association of everolimus with faster 3-year disease progression in surgically confirmed IPF.
Houssaini et al. (23)	2018	Experimental	Causal relationship between mTOR activation, lung cell senescence and lung alterations in COPD.
Mitani et al. (24)	2016	Experimental	Restored corticosteroid sensitivity by rapamycin.
Wang et al. (25)	2018	Experimental	Suppression of cigarette smoke-induced cell death, airway inflammation and emphysema by mTOR, likely through modulation of autophagy, apoptosis and necroptosis.
Duran et al. (26)	2014	Clinical	Current knowledge of drug-induced pneumonitis (mechanism, clinical impact and management) in cancer patients treated with mTOR inhibitors.

over-activity in lung vascular cells show rapid cell senescence with development of emphysema, pulmonary hypertension and inflammation. These results suggest that mTOR inhibition could be a potential therapeutic approach in COPD (23). Moreover, a study in humans shows that rapamycin restores corticosteroid sensitivity on isolated mononuclear cells from COPD patients suggesting its possible use in this disease (24).

Furthermore, a very elegant and recent study on isolated airway epithelium of human COPD and in mouse lung chronically exposed to cigarette smoke shows that activation of mTOR and/or inhibition of autophagy may be a new mechanism of cigarette smoke-induced COPD (25).

However, transplant recipients or cancer patients treated with rapamycin derivatives have increased non-infectious drug-induced pneumonitis (26) with increased inflammatory cytokines production (27) and consequent worsening of lung functions.

The apparent discrepancy between pro-disease and anti-disease activity of mTOR in the lung may be explained by the multiple activities exerted by mTOR through multi-protein complexes (TORC1 and TORC2) which may work synergistically, independently or antagonistically. Both complexes are influenced by internal and external cell stimuli (2, 3). Thus, the contradictory results obtained by using mTOR inhibitors and nowadays presented in the scientific literature are probably context-dependent and possibly influenced by many factors such as the species tested, the experimental model, age and animals used, the presence of concomitant diseases, the genotype/phenotype of lung disease studied, etc. (18).

Notably, and also of particular interest for a COPD possible treatment, the dosages of rapalogues used in clinical settings, partially inhibit only mTORC1 but not mTORC2 (28). So the signalling mediated by mTORC2 can still be active and capable of mediating its effects, including the activation of Akt. Furthermore, mTORC2 activation can promote autophagy, a process known to mediate resistance to therapeutic interventions such as cancer chemotherapy. Thus, the efficacy of rapalogues treatment may be hindered by their lack of efficacy versus mTORC2 (at least at the doses used in the clinical setting). This suggests that inhibition of mTOR, by allosteric inhibitors of the rapalogues family, activates different metabolic pathways cross talks, as a result of the very intricate manner in which the mTOR pathway works.

Conclusion

We believe that, in order to successfully translate the use of mTOR inhibitors in pulmonary diseases such as COPD, we need more in-depth knowledge of the mTOR signalling. As in all complex processes that involve opposite results, is important to be informed in order to evaluate the final effect of a new therapy in a new field such as COPD. This is necessary to avoid repeating previous optimistic approaches, where *in vivo* positive pre-clinical data, when translated to a clinical setting, did not show the expected health improvements for patients.

Acknowledgments

We would like to thank Robert Coates (*Centro Linguistico*, Bocconi University, via Sarfatti, Milano, Italy), medical writer and editor, for his linguistic revision.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors contributions

EP and VF had concept, designed the study and drafted the manuscript. EB, GC and MV revised the manuscript. LC and AO performed the literature search, drafted the manuscript and gave technical assistance. All the authors critically reviewed and approved the manuscript.

ORCID

Enrica Bertella http://orcid.org/0000-0001-8178-3112

References

1. Shimobayashi M, Hall MN. Making new contacts: the mTOR network in metabolism and signalling crosstalk. Nat Rev Mol Cell Biol. 2014;15(3):155–162. doi:10.1038/nrm3757.

2. Flati V, Corsetti G, Pasini E, et al. Nutrition, nitrogen requirements, exercise and chemotherapy-induced toxicity in cancer patients. A puzzle of contrasting truths? Anticancer Agents Med Chem. 2016; 16(1):89–100. doi:10.2174/1871520615666150824152900.
3. Kim YC, Guan KL. mTOR: a pharmacologic target for autophagy regulation. J Clin Invest. 2015;125(1):25–32. doi:10.1172/JCI73939.
4. Foster KG, Fingar DC. Mammalian target of rapamycin (mTOR): conducting the cellular signaling symphony. J Biol Chem. 2010;285(19):14071–14077. doi:10.1074/jbc.R109.094003.
5. Hara K, Maruki Y, Long X, et al. Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action. Cell. 2002; 110(2):177–189.
6. Carracedo A, Ma L, Teruya-Feldstein J, et al. Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer. J Clin Invest. 2008; 118(9):3065–3074. doi:10.1172/jci34739.
7. Garber K. Targeting mTOR: something old, something new. J Natl Cancer Inst. 2009;101(5):288–290. doi:10.1093/jnci/djp034.
8. Sarbassov DD, Ali SM, Kim DH, et al. Rictor, a novel binding partner of mTOR, defines a rapamycin-insensitive and raptor-independent pathway that regulates the cytoskeleton. Curr Biol. 2004;14(14):1296–1302. doi:10.1016/j.cub.2004.06.054.
9. Jacinto E, Facchinetti V, Liu D, et al. SIN1/MIP1 maintains rictor-mTOR complex integrity and regulates Akt phosphorylation and substrate specificity. Cell. 2006;127(1):125–137. doi:10.1016/j.cell.2006.08.033.
10. Yang Y, Bardeleben C, Frost P, et al. DEPTOR is linked to a TORC1-p21 survival proliferation pathway in multiple myeloma cells. Genes Cancer. 2014;5(11–12):407–419. doi:10.18632/genesandcancer.44.
11. Mihaylova MM, Shaw RJ. The AMPK signalling pathway coordinates cell growth, autophagy and metabolism. Nat Cell Biol. 2011;13(9):1016–1023. doi:10.1038/ncb2329.
12. Averous J, Lambert-Langlais S, Carraro V, et al. Requirement for lysosomal localization of mTOR for its activation differs between leucine and other amino acids. Cell Signal. 2014;26(9): 1918–1927. doi:10.1016/j.cellsig.2014.04.019.
13. Vlahakis A, Graef M, Nunnari J, et al. TOR complex 2-Ypk1 signaling is an essential positive regulator of the general amino acid control response and autophagy. Proc Natl Acad Sci USA. 2014; 111(29):10586–10591. doi:10.1073/pnas.1406305111.
14. Bernard M, Dieudé M, Yang B, et al. Autophagy fosters myofibroblast differentiation through MTORC2 activation and downstream upregulation of CTGF. Autophagy. 2014;10(12): 2193–2207. doi:10.4161/15548627.2014.981786.
15. Gurusamy N, Lekli I, Mukherjee S, et al. Cardioprotection by resveratrol: a novel mechanism via autophagy involving the mTORC2 pathway Cardiovasc Res. 2010; 86(1):103–112. doi: 10.1093/cvr/cvp384.
16. Boutouja F, Stiehm CM, Platta HW. mTOR: a cellular regulator interface in health and disease. Cells. 2019;8(1):pii: E18. doi: 10.3390/cells8010018.
17. Faivre S, Kroemer G, Raymond E. Current development of mTOR inhibitors as anticancer agents. Nat Rev Drug Discov. 2006;5(8):671–688. doi:10.1038/nrd2062.
18. Kennedy BK, Pennypacker JK. Mammalian target of rapamycin: a target for (lung) diseases and aging. Ann Am Thorac Soc. 2016;13(5 Suppl.):S398–S401. doi:10.1513/AnnalsATS.201609-680AW.
19. Jin X, Dai H, Ding K, et al. Rapamycin attenuates bleomycin-induced pulmonary fibrosis in rats and the expression of metalloproteinase-9 and tissue inhibitors of metalloproteinase-1 in lung tissue. Chin Med J (Engl). 2014;127(7):1304–1309.
20. Madala SK, Maxfield MD, Davidson CR, et al. Rapamycin regulates bleomycin-induced lung damage in SP-C-deficient mice. Pulm Med. 2011;2011:653524. doi:10.1155/2011/653524.
21. Malouf MA, Hopkins P, Snell G, et al. Everolimus in IPF study investigators. An investigator-driven study of everolimus in surgical lung biopsy confirmed idiopathic pulmonary fibrosis. Respirology. 2011; 16(5):776–783. doi:10.1111/j.1440-1843.2011.01955.x.
22. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244–254.
23. Houssaini A, Breau M, Kebe K, et al. mTOR pathway activation drives lung cell senescence and emphysema. JCI Insight. 2018; 3(3):pii: 93203. doi:10.1172/jci.insight.93203.
24. Mitani A, Ito K, Vuppusetty C, et al. Restoration of corticosteroid sensitivity in chronic obstructive pulmonary disease by inhibition of mammalian target of rapamycin. Am J Respir Crit Care Med. 2016; 193(2):143–153. doi:10.1164/rccm.201503-0593OC.
25. Wang Y, Liu J, Zhou JS, et al. MTOR suppresses cigarette smoke-induced epithelial cell death and airway inflammation in chronic obstructive pulmonary disease. J Immunol. 2018;200(8): 2571–2580. doi:10.4049/jimmunol.1701681.
26. Duran I, Goebell PJ, Papazisis K, et al. Drug-induced pneumonitis in cancer patients treated with mTOR inhibitors: management and insights into possible mechanisms. Expert Opin Drug Saf. 2014;13(3):361–372. doi:10.1517/14740338.2014.888056.
27. Buron F, Malvezzi P, Villar E, et al. Profiling sirolimus-induced inflammatory syndrome: a prospective tricentric observational study. PLoS One. 2013;8(1):e53078. doi:10.1371/journal.pone.0053078.
28. Thoreen CC, Sabatini DM. Rapamycin inhibits mTORC1, but not completely. Autophagy. 2009;5(5):725–726. doi:10.4161/auto.5.5.8504.