



# The host mTOR pathway and parasitic diseases pathogenesis

Sajad Rashidi<sup>1</sup> · Reza Mansouri<sup>2</sup> · Mohammad Ali-Hassanzadeh<sup>3</sup> · Zahra Mojtahedi<sup>4</sup> · Reza Shafiei<sup>5</sup> · Amir Savardashtaki<sup>6</sup> · Nasrin Hamidizadeh<sup>7</sup> · Mohammadreza Karimazar<sup>1</sup> · Paul Nguewa<sup>8</sup> · Raúl Manzano-Román<sup>9</sup>

Received: 13 August 2020 / Accepted: 25 January 2021 / Published online: 3 February 2021  
© The Author(s), under exclusive licence to Springer-Verlag GmbH, DE part of Springer Nature 2021

## Abstract

The mechanistic (or mammalian) target of rapamycin (mTOR) is considered as a critical regulatory enzyme involved in essential signaling pathways affecting cell growth, cell proliferation, protein translation, regulation of cellular metabolism, and cytoskeletal structure. Also, mTOR signaling has crucial roles in cell homeostasis via processes such as autophagy. Autophagy prevents many pathogen infections and is involved on immunosurveillance and pathogenesis. Immune responses and autophagy are therefore key host responses and both are linked by complex mTOR regulatory mechanisms. In recent years, the mTOR pathway has been highlighted in different diseases such as diabetes, cancer, and infectious and parasitic diseases including leishmaniasis, toxoplasmosis, and malaria. The current review underlines the implications of mTOR signals and intricate networks on pathogen infections and the modulation of this master regulator by parasites. Parasitic infections are able to induce dynamic metabolic reprogramming leading to mTOR alterations in spite of many other ways impacting this regulatory network. Accordingly, the identification of parasite effects and interactions over such a complex modulation might reveal novel information regarding the biology of the abovementioned parasites and might allow the development of therapeutic strategies against parasitic diseases. In this sense, the effects of inhibiting the mTOR pathways are also considered in this context in the light of their potential for the prevention and treatment of parasitic diseases.

**Keywords** mTOR · Rapamycin · Parasites · Signaling · Modulation, · Therapies

## Introduction

Malaria, toxoplasmosis, and neglected tropical diseases including leishmaniasis and trypanosomiasis are deadly diseases in humans and a major global health challenge. Malaria is

endemic in 87 countries and causes approximately 219 million clinical cases and 435,000 deaths per year. Morbidity and mortality especially occurred in pregnant women and children living in the African Region (Gitta and Kilian 2020). Regarding leishmaniasis, approximately 1.5 to 2 million new

---

Section Editor: Kevin S.W. Tan

---

✉ Paul Nguewa  
panguewa@unav.es

✉ Raúl Manzano-Román  
rmanzano@usal.es

<sup>1</sup> Department of Parasitology and Mycology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>2</sup> Department of Immunology, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran

<sup>3</sup> Department of Immunology, School of Medicine, Jiroft University of Medical Sciences, Jiroft, Iran

<sup>4</sup> Department of Health Care Administration and Policy, School of Public Health, University of Nevada, Las Vegas, Las Vegas, NV, USA

<sup>5</sup> Vector-borne Diseases Research Center, North Khorasan University of Medical Sciences, Bojnurd, Iran

<sup>6</sup> Department of Medical Biotechnology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>7</sup> Molecular Dermatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>8</sup> ISTUN Instituto de Salud Tropical, Department of Microbiology and Parasitology, IdiSNA (Navarra Institute for Health Research), University of Navarra, c/ Irunlarrea 1, 31008 Pamplona, Spain

<sup>9</sup> Proteomics Unit, Cancer Research Centre (IBMCC/CSIC/USAL/IBSAL), 37007 Salamanca, Spain

cases are annually reported worldwide being 310 million people at risk. The mortality rate of leishmaniasis varies from 40,000 to 70,000 cases per year. The clinical manifestations of cutaneous leishmaniasis (CL) are mostly restricted to the skin lesions with different appearances, whereas visceral leishmaniasis (VL) is characterized by severe organic symptoms and might lead to death (Torres-Guerrero et al. 2017). Concerning toxoplasmosis, *Toxoplasma gondii* is its causative agent. It is an infectious zoonotic disease highly prevalent in humans in several regions including Brazil (77.5%), Sao Tome and Principe (75.2%), Iran (63.9%), Colombia (63.5%), and Cuba (61.8%) (Montazeri et al. 2020). Dealing with trypanosomes, these could cause African and American trypanosomiasis, whereas human African trypanosomiasis (sleeping sickness) is caused by *Trypanosoma brucei rhodesiense* and another chronic form occurring mostly in West and Central Africa, caused by *T. brucei gambiense*. In sleeping sickness, parasites initially can be detected in the bloodstream and interstitial spaces of several organs. After that, the parasites can potentially invade the central nervous system, indicating the start of the late stage (Rijo-Ferreira and Takahashi 2020). Another parasitic infectious disease, Chagas disease (American trypanosomiasis) is a chronic infection caused by *T. cruzi*. It is transmitted to human beings through the feces of infected triatomine bugs. The disease approximately affects 8 to 10 million people in the Americas, putting them at risk of developing life-threatening cardiac and gastrointestinal complications (Echeverria and Morillo 2019). These data clearly show the impact of the main parasitic diseases which may be at the molecular level mediated by the manipulation of key host signaling events. The mechanistic (previously referred as mammalian) target of rapamycin (mTOR) is a human serine–threonine kinase belonging to the phosphoinositide 3-kinase (PI3K)–related kinase family that tightly control gene expression, translation and at post-translational level, cell signaling, and function impacting essential physiological processes like the metabolism or autophagy with pathogenic insights (Bolourian and Mojtahedi 2020; Guertin and Sabatini 2007; Yeh and Yong 2020). Thus, mTOR plays a central function integrating signals and orchestrating their physiologic effects.

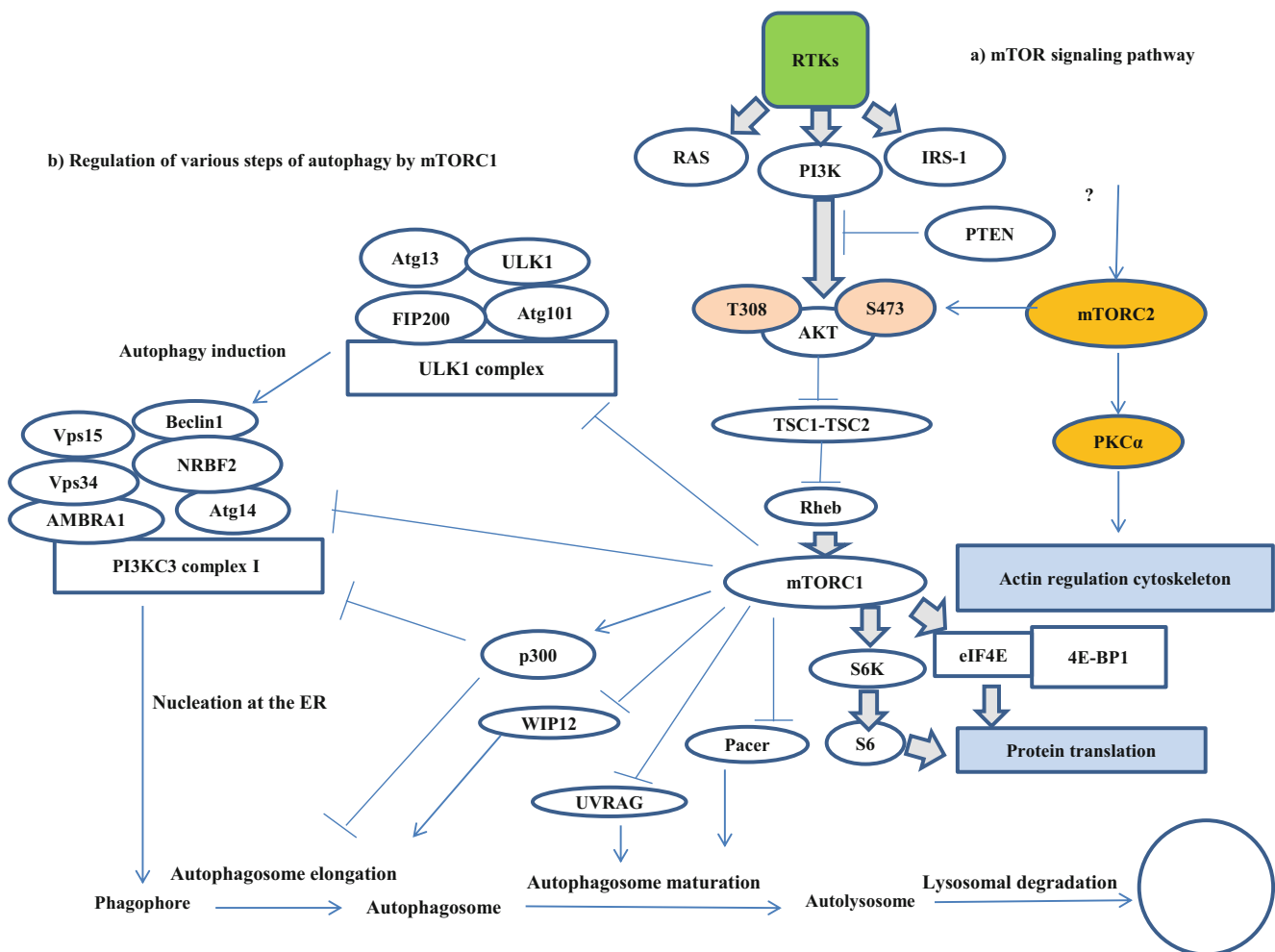
This master regulator binds to different groups of proteins and is composed by two distinct intracellular protein complexes, called mTOR1 (mTORC1) and mTOR2 (mTORC2) each of them having different subcellular localizations (mTORC1 is associated with endosomal and lysosomal membranes whereas mTORC2 is located at the plasma and ribosomal membranes) and specific subunits, thus exhibiting distinct functions and regulations. mTORC1 is rapamycin sensitive and mainly functions controlling protein synthesis, lipid metabolism, and organelle biogenesis. On the other hand, mTOR2 is rapamycin insensitive functioning as a regulator of the actin cytoskeleton, metabolism, and cell survival

(Tian et al. 2019). Ultimately, the signals orchestrate multiple and complex molecular responses tightly controlled by multi-step processes of activation determined by the stimulus, cell type, and the molecularly and spatially distinct mTOR pools (Sabatini 2017; Smith et al. 2020). As a major regulatory protein, mTORC1 controls cell growth, proliferation, and protein translation in response to signals from nutrients, growth factors, energy, and stress. Meanwhile, mTORC2 is relevant for the regulation of cellular metabolism and cytoskeletal structure (Betz and Hall 2013; Dimasuay et al. 2017a). A summary of different functions of mTORC1, mTORC2, and mTORC1 and its duty in regulation of different steps of autophagy has been depicted in Fig. 1, which makes this an attractive drug target. According to the critical role of mTOR pathway in vital cellular processes and diseases, mTOR inhibitors such as rapamycin and its analogues (rapalogues) have been newly applied to fight against cancers, rheumatoid arthritis, coronary restenosis, and organ transplantation (Santulli and Totary-Jain 2013).

mTOR signaling pathway integrates both intracellular and extracellular signals through multi-protein complexes. Each of these has several components acting as interacting proteins that basically regulate assembly of the complex, recruit substrates for mTOR, and ultimately control its functions. Due to the discovery of numerous mTOR-interacting proteins in different cells and diseases, further biochemical and molecular studies are needed to identify the exact role of such proteins in mTOR signaling and their possible involvements in diseases and health.

Advances in understanding the complex signaling network upstream and downstream this molecule has led to a better knowledge of the mechanism of many diseases, including infectious and parasitic diseases. Actually, we know the intimate connectivity between parasites and host cell metabolism. For example, it was described that parasites may induce dynamic changes in the expression levels of host genes involved in catabolism that subsequently cause alterations in mTOR levels or states making mTOR a metabolic checkpoint kinase (Byles et al. 2013; Xu et al. 2019).

The current review attempts to update and describe the main related pathways and networks in which mTOR is involved in relation to pathogen infectious processes and the impact of parasite infections on these molecular signals and downstream effects. Such relevant interactions are mostly involved in the pathogenicity, immunopathology, survival, and proliferation of these parasites. This highly important multifaceted regulatory network upon infection is an attractive target for the control of these diseases. Thus, the role of important inhibitors of mTOR and autophagy activator that has been previously highlighted for the treatment of different diseases is reviewed herein pointing out the potential of these to underline some important molecular implications for the successful parasitic infectious processes. This knowledge may favor



**Fig. 1** **a** mTOR pathway: mTORC1 is activated by nutrients and mostly acts via the phosphorylation of two important effectors, 4EBP and p70S6 kinase 1 (S6K1). mTORC1 phosphorylates S6K1, which in turn phosphorylates and activates substrates included in mRNA translation initiation, such as eIF4B, a positive regulator of the 50 cap-binding eIF4F complex. mTORC1 phosphorylates 4EBP at different sites to induce its separation from eIF4E, triggering 50cap-dependent mRNA translation by the assembled eIF4F complex, **b** mTORC1 and its role in the regulation of autophagy: the activity of the unc-51-like kinase 1 (ULK1) complex is inhibited by phosphorylating autophagy-related gene 13 (ATG13) and ULK1. The nucleation stage of autophagy is inhibited through the phosphorylation of activating molecule in beclin-1-regulated

autophagy (AMBRA1), nuclear receptor-binding factor 2 (NRBF2), and Atg14 in the PI3KC3 complex I. Phosphorylation of WD-repeat domain phosphoinositide-interacting protein-2 (WIP12) and p300 and by mTORC1 inhibits VSP34 activity/LC3 lipidation and the recruitment of phosphatidylinositol phosphates along with the LC3 conjugation system for the autophagosome elongation. Eventually, mTORC1 negatively regulates the fusion of the autophagosome with the lysosome via the phosphorylation of pacer and UV radiation resistance-associated gene (UVRAG) that are essential for the lipid kinase activity of PI3KC3 complex II and the recruitment of the homotypic fusion and vacuole protein sorting (HOPS) tethering complex (Albert et al. 2010; Dossou and Basu 2019; Saxton and Sabatini 2017)

therapeutic and preventive actions directed to this key molecular mechanism for the treatment of important parasitic diseases.

### mTOR signaling networks: autophagy and immune responses

mTOR pathway regulate many essential cellular processes and physiological functions such as proliferation, metabolism, and autophagy—contributing to cellular homeostasis—among others. In addition, the mTOR pathway is also

involved in regulating directly—immune cell differentiation and effector function, or indirectly, immunometabolic signaling of T cells—the immune responses which show the essential regulatory networks in which is involved in (Saravia et al. 2020). Therefore, mutations in the components of the mTOR pathway frequently induce disorders like those detected in cancers. The regulatory role is basically achieved upon upstream signals through a cascade-mediated activity control mechanisms and/or by post-translational modifications of downstream or effector proteins in a temporal and spatial manner (Table 1) (Jiang et al. 2019; Qian et al. 2020; Tian et al.

**Table 1** Main mTOR signaling networks in relation with each of the molecular nodes (Laplante and Sabatini 2009; Tian et al. 2019)

Signal/pathway/stimuli/functions	mTOR1	mTOR2	Integration/origin (molecular pathway)
Growth factors	✓		I (insulin and Ras via PI3K/AKT and MAPK pathways)
Energy status	✓		I (AMP-activated protein kinase (AMPK))
Oxygen levels	✓		I (ATP/AMPK/TSC1/2)
Amino acids	✓		I (VPS34/GTPases)
Inflammatory mediators	✓		I (TSC1/2 complex)
Wnt ligand and PA	✓		I (TSC1/2 complex)
Phosphatidylinositol (3,4,5)-triphosphate (PIP3)	✓		I (AKT)
DNA damage	✓		I (p53, TSC2)
Energy exhaustion	✓		I (AMPK, TSC1/2)
Protein synthesis	✓		O (eukaryotic initiation factor 4E (eIF4E) and p70 ribosomal S6 kinase 1 (S6K1))
Autophagy	✓		O (unc-51-like kinase 1 (ULK1), autophagy-related gene 13 (ATG13), and focal adhesion kinase family–interacting protein of 200 kDa (FIP200))
Lipid synthesis	✓		O (sterol regulatory element–binding protein 1 (SREBP1), peroxisome proliferator–activated receptor-g (PPARg))
Mitochondrial metabolism and biogenesis	✓		O (PPARg coactivator 1 (PGC1-a))
Translation	✓		O (4EBP1 and S6K1)
Growth factors		✓	I (AKT)
Phosphatidylinositol (3,4,5)-triphosphate (PIP3)		✓	I (directly)
PI3K/Akt, mTORC1		✓	I (directly)
S6K1		✓	I (insulin receptor substrate (IRS))
Cell survival, metabolism, and proliferation		✓	O (AKT, FoxO1, SGK1, TSC1/2)
Cytoskeletal organization		✓	O (PKCa, paxillin, and GTP/RhoA and Rac1)
Cell survival, cytoskeleton reorganization, and cell movements		✓	O (serum and glucocorticoid kinase (SGK) and protein kinase C (PKC))

I, integration (pathway/molecule regulating the component); O, originated (pathway/molecule/effectors regulated by the component)

2019). In addition, the mTOR pathway is associated with other signaling pathways like the 5'-adenosine monophosphate-activated protein kinase (AMPK). These networks acting as molecular switchers can regulate other pathways or processes like autophagy impacting on immune system maintenance, and thus pointing out the complexity of these mTOR-dependent molecular circuits (Kim et al. 2011; Maiese 2020). mTOR normally acts as a nutrient sensor inhibiting autophagy—its phosphorylated form—but can be inhibited via stress (including pathogen infection) and nutrient starvation to initiate autophagy acting as a unique molecular intermediate that negatively regulates autophagy. The process may also be regulated via mTOR-independent pathways. Moreover, natural mTOR inhibitors like rapamycin and its derivatives act as autophagy activator both *in vitro* and *in vivo* having mTORC1 and mTORC2 important differences in their sensitivities to it.

Autophagy is a conserved cellular degradation process via the formation of double-membrane-bound autophagosomes. This phenomenon plays important roles in maintaining

homeostasis and preventing infection-mediated stresses between others. Furthermore, several distinct but related intracellular defense responses depend on autophagy-related genes which may be intertwined with pattern recognition receptor (PRR), inflammatory, and cell death pathways, and therefore can alter immune responses including inflammatory responses (Hu et al. 2015; Viret et al. 2018). On the other hand, autophagy is regulated by immunological and stress signals. The cross-talk between these signaling pathways helps to maintain homeostasis and physiological functions (Hua et al. 2019). The dysfunction of these regulatory networks is the cause of several diseases. Therefore, the dysfunction of autophagy has been linked to inflammatory diseases and defective immune responses against pathogens and may have pathological consequences including pathogen hyper-virulence (Jang et al. 2019). Additional functions and roles of autophagy detecting, cross-talking with, capturing and destroying invading pathogens have been described. Microorganisms have developed strategies to hijack selected sets of molecular mechanisms of the autophagic pathway to establish infection (Miller and Celli

2016). In spite of the complex regulatory process—with the potential of particular kinetics upon infections—and the dual outcomes of autophagy (anti-pathogens or favoring pathogen infections, even mixed responses, for example, favoring early during infections but becoming protective later in infections), parasites are also able to effectively evade and modulate host autophagy targeting mTOR which also impact on parasitic disease pathogenesis (Ghartey-Kwansah et al. 2020; Metz et al. 2015).

In addition, mTOR implications in the immune system are very relevant. The functional properties and the polarization states of the immune cells are dependent of conditions like hypoxia, pathogen-derived ligands, or lipid mediators, pointing out this molecule in sensing immune microenvironment and dictating the functions and differentiation of immune cells. However, it has recently been demonstrated that mTOR plays critical roles regulating CD4+ T cells, including not only T helper 1 (Th1), Th2 but also other Th cell subsets (critical in the immunity, inflammation and diseases) like Th9, Th17, regulatory T cells (Tregs) and forkhead box P3 (FOXP3), and *T follicular helper* (Tfh) cells (Wang et al. 2020). All these data highlight that mTOR is a key regulator of immune function impacting the immune cells maturation and differentiation and serving as a link between regulation of metabolism and function and activity of the cells of the immune system among others (Patsoukis et al. 2017). In sum, the mTOR-based modulatory and interconnected molecular events of essential and specialized host mechanisms in response to pathogen infections seems to be crucial for the control of infection and its therapeutic or prophylactic targeting might have significant clinical implications (Yang et al. 2020).

### mTOR signaling during pathogen infections

Years ago, many questions arose regarding the complex regulatory functions of this protein including the implications of their dysfunction or dysregulation in health and disease, mainly cancer. Given the previously detailed pivotal functions of mTOR on key host molecular responses it's not surprising the idea that pathogens modulate these pathways by targeting mTOR to further enhance their chances of survival. Thus, pathogens target mTOR complexes either directly or indirectly through for example interaction with upstream signals mediated by amino acids or with downstream signals transduced by lipids (Nouwen and Everts 2020). Pathogens may target other processes controlled by this kinase such as autophagy or translation, and finally promote immune evasion. Autophagy can be either inhibited or activated upon pathogen infection; to evade pathogen degradation and recognition or to support nutrients for replication, respectively (Le Sage et al. 2016; Wang et al. 2009a). Recently, it has been discovered that rickettsiae interfere in vitro with the autophagic response of endothelial cells activating mTOR and triggering an initial

autophagy response, thus allowing the establishment of an intracellular infection (Sahni et al. 2020).

Now, we know that many pathogens affect host cell pathways including mTOR and autophagy to develop the infection processes in their hosts (Nouwen and Everts 2020). Viruses target mTOR pathway with diverse approaches and at specific levels to achieve mRNA translation and modulate apoptosis and autophagy. Viruses have different targeting strategies between vertebrates and arthropod vectors and some like dengue virus serotype-2 (DENV-2) and ZIKA viruses obtain relevant benefits of arthropod TOR autophagy inhibition (Brackney et al. 2020; Le Sage et al. 2016; Patel and Hardy 2012). In this sense, the inhibition of the PI3K-AKT-mTOR pathway affects the autophagic reaction induced by pathogen infections (Yang et al. 2020). Therefore, autophagy and mTOR have a close relationship acting as a multi-use bridge in pathogen infections and host cells, especially taking into account its immune signaling involvement on innate and adaptive immune responses. Several viruses modulate mTOR activity by subverting the mTORC1 signaling network targeting upstream points like PI3K, protein kinase B (Akt), or tuberous sclerosis complex-2 (TSC-2), although others also act downstream the mTOR node or via lysosomal signaling. In addition, the application of multiple strategies to interact with and have the control over mTOR signaling is normal in viruses (Le Sage et al. 2016).

The host translation by mTOR is also modulated by pathogens with several aims: (i) to promote the translation of their mRNAs, (2) to liberate amino acids, or (3) to inhibit cytokine responses (De Leon et al. 2017; Joubert et al. 2015). Lastly, the control of host anti-inflammatory responses via interleukin 10 (*IL-10*) production may also be achieved by pathogens upon selective signaling through PI3K-Akt-mTOR since cytokine production is dependent on mTOR signaling. Pro-inflammation can be also promoted by the cross-talk between PI3K/Akt/mTOR and toll like receptor/ nuclear factor kappa-light-chain-enhancer of activated B cells (TLR/NF- $\kappa$ B) signaling pathways upon bacterial infection (Li et al. 2018; Peres et al. 2015). All these point out the multiple facets of PI3K/Akt/mTOR in inflammatory regulation constituting thus important strategies to minimize the extent of host damage and immunopathology. Moreover, the activation of mTOR also has the ability to promote immune cell effector function—as in the case of virus-natural killer (NK)-infected cells, coupling the metabolic sensing, and immune responses. In this sense, an IL-18-dependent molecular mechanism drive proliferative NK cell responses upon viral infections and the IL-18-dependent upregulation of amino acid transporters induce mTORC1 activation by amino acids, an important stimuli for the mTOR-dependent regulation of innate and adaptive immune response during *Trypanosoma cruzi* infection (Cerbán et al. 2020; Nandagopal et al. 2014; Zimmer et al. 2019). Considering the important role of IL-18 in the

activation and differentiation of various T cell populations and the pivotal role of mTOR on dendritic cells and macrophage function, it can be mentioned that mTOR and associated pathways may regulate pathogen infection activity and serve as potential anti-pathogenic and inflammatory modulatory targets (Maiese 2020; Nouwen and Everts 2020). In this regard, it is highly relevant to highlight the potential use of mTOR inhibitors for immune modulation. An illustration is the inhibition of Middle East respiratory syndrome coronavirus (MERS-CoV) propagation *in vitro* and their potential to prevent coronavirus disease (COVID-19) severity via AMPK activation and mTOR inhibition derived signals (Kindrachuk et al. 2015; Maiese 2020; Zheng et al. 2020). Targeting this master regulator seems to be a potential approach to prevent the consequences of microorganism infections.

### The impact of parasitic diseases on mTOR signaling

Protozoan parasites can manage host signaling pathways, including the mTOR pathway, being *Leishmania*, *Toxoplasma*, and *Plasmodium* spp., excellent examples showing the ability of parasites to manage host mTOR pathway and consequently allowing their survival and growth in infected host cells (Chakraborty et al. 2017). mTOR inhibitors have been used for the treatment of cancer and certain immune system-mediated disorders in humans (Fruman et al. 2017; Hillmann and Fabbro 2019). Therefore, the selective inhibition of mTOR activity might come into the focus as molecular target to prevent parasitic diseases. Growing evidence suggests that targeting this pathway may provide important information about the susceptibility of different species, the specific biological significance of this, and the rationale for clinical trials. Herein, we present mainly in protozoan parasites evidences of the importance of this host signaling pathway during the infection process (Table 2 and Fig. 2).

### *Leishmania* parasites and host mTOR

The therapeutic efficacy of mTOR inhibitors including GSK-2126458, rapamycin, and KU-0063794 has been evaluated in *L. major*-infected mice (García-Martínez et al. 2009; Khadir et al. 2018; Knight et al. 2010). Interestingly, GSK-2126458 and rapamycin decreased the parasite load and the footpad swelling of infected mice. However, the administration “*in vitro*” of a wide range of rapamycin doses, selected based on IC<sub>50</sub> values could not allow the elimination of promastigotes which emphasizes the complexity to correlate “*in vivo*” and “*in vitro*” drug conversions and effects and the need to proper dose-dilution inhibitory assays and screenings (Phan et al. 2020). Immunoassay experiments indicated a higher significant increase in the ratio of interleukin (IL)-4 and IFN- $\gamma$ /IL-4 in splenocytes of infected mice treated with rapamycin. Therefore, these cytokine profiles supported the

remarkable polarization towards Th1 immune response. Furthermore, the increased level of CD69, as an early activation marker, was observed on splenic and lymph CD4+ and CD8+ T cells in rapamycin-treated mice (Khadir et al. 2018). It seems that, in addition to the therapeutic efficacy of mTOR inhibitors, the immunomodulatory properties and adjuvanticity of such inhibitors might suggest novel insights in vaccination strategies against leishmaniasis (Khadir et al. 2018). In 2019, a similar study confirmed the healing property of intraperitoneally injection of rapamycin (10.2  $\mu$ g/dose) and the reduction of parasite burden in *L. tropica* infected-BALB/c mice (Khadir et al. 2019).

Other mTOR/PI3K inhibitors have been found useful against visceral leishmaniasis (VL). The half-maximal effective concentration (EC<sub>50</sub>) levels of such compounds were reported to be 0.14 up to 13.44  $\mu$ M for amastigote forms of *L. donovani* (Phan et al. 2020). The treatment of experimental VL with mTOR/PI3K inhibitors including dactolisib (BEZ235, NVP-BEZ235), torin 2, and NVP-BGT226 also reduced the rate of *Leishmania* parasites by 53%, 35%, and 54% respectively, in infected livers (Phan et al. 2020). Moreover, there are other inhibitors like miransertib (ARQ 092) that potentiate mTOR-dependent autophagy in *Leishmania*-infected macrophages and “*in vivo*” (Nandan et al. 2018).

Regarding “*in vitro*” studies, macrophages infected by *Leishmania* parasites show alteration of its proteome (Hassani and Olivier 2013). The results of several “*in vitro*” proteomic studies on infected macrophages indicated that leishmanial-glycoprotein 63 (GP63) cleaves mTOR and inhibits (inactivates) the production of the mTORC1 (Chaparro et al. 2020; Matte and Descoteaux 2011; Shapira and Zinoviev 2011; Shertz and Cardenas 2011). The degradation of important components of the Akt/mTOR axis, containing mTOR, Akt, and the tuberous sclerosis complex-2 (TSC-2) has been implicated in that process (Matte and Descoteaux 2011). The cleavage induced in mTOR leads to the phosphorylation (activation) of 4E (eIF4E)-binding protein 1 (4E-BP1) (suppressing translation in host cell) and propagation of *Leishmania* parasites (Shapira and Zinoviev 2011). In parallel to mTOR cleavage and 4E-BP1 activation, the expression of type I IFN (a defensive factor against parasite) was decreased in macrophages. Rapamycin suppressed the aforementioned processes and finally the parasite replication. Interestingly, another study declared that the pharmacological activation of 4E-BPs by rapamycin increased the parasite proliferation (Jaramillo et al. 2011; Shertz and Cardenas 2011); however, genetic knockout of 4E-BP1/2 decreased the burden of *Leishmania* parasites in macrophages. Since the innate immune cell function is regulated by mTOR (Weichhart et al. 2015); therefore, *Leishmania* parasites by subverting and controlling the host translational system (through the induction of cleavage in mTOR) are able to evade the host immune system

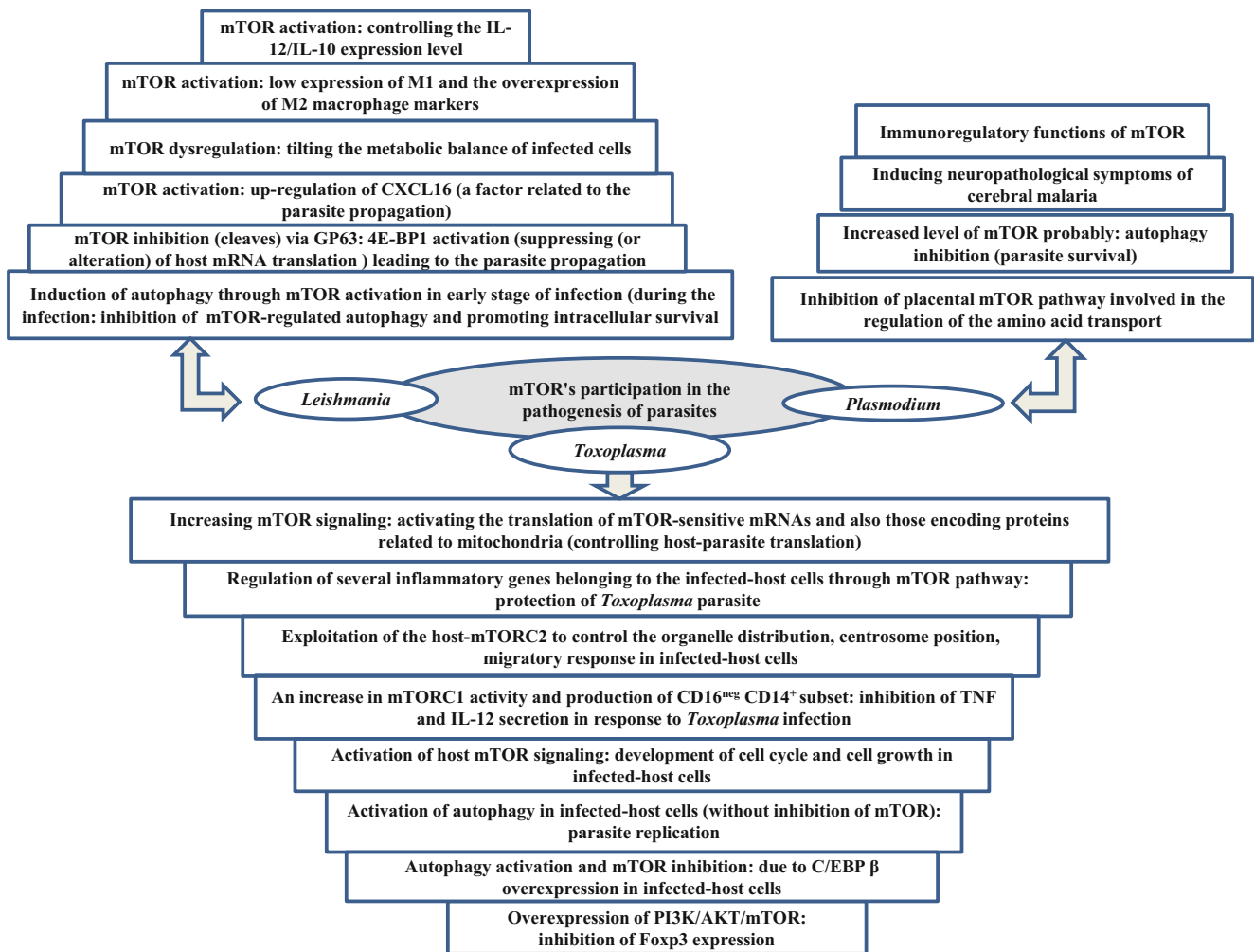
**Table 2** Importance and/or outcomes when suppressing mTOR signals on other parasitic infections

Parasite/study	mTOR signaling in host cells	Overall impact	Molecular impact	References
<i>T. cruzi</i> in vitro	Regulation of invasion, differentiation and replication	Decreased parasite load	Increased IL-12, IL-6, TNF and IL-1 $\beta$ production. Reduced arginase-1 activity and expression, and IL-10 production. Decreased iNOS expression and activity	(Cerbán et al. 2020; Ohtani et al. 2008; Rojas Márquez et al. 2018)
	Host cell susceptibility to trypomastigotes and lysosomal exocytosis	Perinuclear lysosome accumulation and lysosome biogenesis, reduced invasion by metacyclic trypomastigotes (gp82-mediated and lysosome-dependent), and increased invasion by tissue culture trypomastigotes (lysosome-independent)	Nuclear translocation of transcription factor EB (TFEB), a mTOR-associated lysosome biogenesis regulator	(Cortez et al. 2016)
		Host cell invasion by metacyclic trypomastigotes (gp82-mediated and lysosome-dependent) increased under nutritional stress	Actin cytoskeleton disruption and lysosome mobilization to the cell periphery that culminates in exocytosis	(Martins et al. 2011)
	Lysosome-dependent entry of tissue culture-derived trypomastigotes to the cells	Favored colonization of parasites	Actin cytoskeleton organization with F-actin re-arrangements at the focal adhesion sites	(Liu et al. 2008; Romano et al. 2009)
	Regulation of gene expression and protein synthesis	Metabolic modeling contributing to pathology	Inhibition of mTORC1 phosphorylation and the induced increase in the maximal respiration and spare reserve capacity	(Libisch et al. 2018)
	Angiogenesis regulation	Anti-angiogenic effects	No elevation of VEGF-A induced by <i>T. cruzi</i> infection upon AKT phosphorylation inhibition	(Penas et al. 2020)
	Regulation of immune T cells responses	Allow the parasites to establish the chronic disease	Reduced IL-2 production, prevention of Otub-1 protein expression and increased CTLA-4 and GRAIL expression which inhibits T cell proliferation	(Stempin et al. 2017)
<i>T. brucei</i> in vitro and in vivo	Regulation of cell cycle progression	Decrease in parasitemia: potent trypanocide	Altered cytokinesis and cell size/cell cycle arrest.	(Diaz-Gonzalez et al. 2011)
<i>Echinococcus granulosus</i> in vitro	Regulate macrophage differentiation in response to helminth infection	Induces the alternative activation of macrophages		(Hallowell et al. 2017; Wang et al. 2019)
<i>Brugia malayi</i> in vitro	Metabolic modulation of dendritic cells to influence the regulation of the host immune response	Inhibits mTOR pathway by downregulating the phosphorylation of mTOR and its regulatory proteins, p70S6K1 and 4E-BP1 resulting in increased autophagy	Increased phosphorylation of beclin1 and induced the conversion of LC3II (microtubule-associated protein light chain 3) to LC3I and decreased levels of p62	(Narasimhan et al. 2016)
<i>Clonorchis sinensis</i> in vitro and in vivo	Regulation of cellular function and inflammation	Apoptosis suppression, migration, inflammation and autophagy promotion	Declined trend of p-mTOR/mTOR expression ratio and decreased p-AKT	(Shang et al. 2020)
<i>Schistosoma japonicum</i> in vitro	Metabolism regulation	Dynamic changes in the expression levels of genes involved in catabolism and anabolism suppression	Increased levels of phosphorylated AMPK, AKT, and mTORC1	(Xu et al. 2019)

GRAIL, E3 ubiquitin ligase; CTLA-4, cytotoxic T lymphocyte-associated protein 4

and survive. Furthermore, the dysregulation of mTORC1 pathway can tilt the metabolic balance of cells and may be associated with a number of pathological conditions (Yeh and

Yong 2020). *Leishmania* parasites may control the metabolism of host cells in a coordinated way altering the transcription/translation rates of genes for its survival. The



**Fig. 2** mTOR's participation (activation and inhibition) in the pathogenesis of *Leishmania*, *Toxoplasma* and *Plasmodium* parasites

absence in myeloid cells of resistance factors against experimental VL-like hypoxia-inducible factor-1 alpha (HIF-1 $\alpha$ ) finally results in mTOR activation by *B-cell lymphoma 2* (BCL2)–interacting protein 3 (BNIP3) which subsequently leads to lipid synthesis through nuclear translocation of activated SREBP-1c (Mesquita et al. 2020). This subsequently led to the induction of lipogenic gene transcripts resulting in a dysregulated lipid metabolism “in vivo” with lipid accumulation that favors parasite multiplication.

Another study investigated the role of *Leishmania* parasites in the alteration of host mRNA translation in favor of the infection. Such translational modifications mostly target central cellular functions by overexpressing proteins involved in RNA metabolism and chromatin remodeling and by inhibiting the expression of proteins relevant to antigen presentation and intracellular trafficking (Chaparro et al. 2020). In silico analyses related to such a discovery identified poly (A)-binding protein cytoplasmic 1 (PABPC1) via mTOR-activated translation and growth factor-beta (TGF- $\beta$ ) through activated translation depending on RNA helicase eIF4A during

leishmaniasis infection. Interestingly, the use of specific inhibitors including torin-1 or rapamycin (mTOR inhibitors) and silvestrol (eIF4A-inhibitor) decreased the expression of PABPC1 and TGF- $\beta$ , respectively, without affecting PABPC1 and TGF- $\beta$  transcript levels (Chaparro et al. 2020). In addition, those data revealed that leishmaniasis infection–related changes during the translation of eIF4A- and mTOR-sensitive mRNAs participate in the modulation of immune responses and mRNA metabolism which are useful for the parasite reproduction (Chaparro et al. 2020).

In the early stages of *Leishmania* infection in macrophages, parasites inhibit the induction of autophagy processes through the activation of the Akt (or PI3K-Akt) pathway. Interestingly 1-day post infection, *Leishmania* parasites induce autophagy but later during the infection they inhibit the mTOR-regulated autophagy promoting, thus intracellular survival in a compensatory and time-dependent manner (Thomas et al. 2018).

The function of mTOR has been investigated in the regulation of M2 macrophage polarization for the management of innate immune homeostasis and survival of *Leishmania*



parasites in host macrophages (Byles et al. 2013). Parasites activate the host mTOR pathway through phosphorylation of mTOR, 4E-BP1, and ribosomal protein S6 kinase beta-1 (S6K1 or p70S6K) (Byles et al. 2013). The activation of mTOR in *Leishmania* infection leads to the low expression of M1 macrophage markers (ROS, NO, NOX-1, iNOS, TNF- $\alpha$ , IL-12, and IL-1 $\beta$ ), and the overexpression of M2 macrophage markers (arginase-1, TGF- $\beta$ , IL-10, CD163, and CD206) (Biswas et al. 2012; Kumar et al. 2018; Martinez et al. 2013). In addition, the inhibition of mTOR in *Leishmania* infection enhances the translocation of NF- $\kappa$ B to the nucleus and the deactivation of STAT-3 (signal transducer and activator of transcription 3). Therefore, the inhibition of M2 macrophage polarization reduces the survival rate of *Leishmania* parasites inside macrophages.

*L. donovani* is able to escape from immune responses through the induction of the IL-10 production and the inhibition of IL-12 release by infected macrophages (Bhattacharya and Ali 2013). It is also known that *L. donovani* binds to the TLR-2 and other possible receptors involved in the phagocytosis, then driving to the modulation of IL-12/IL-10 cytokines (the decrease of IL-12 and increase of IL-10) (Cheekatla et al. 2012). Consequently, such processes activate mTOR through both PI3K-dependent and -independent mechanisms (Cheekatla et al. 2012; Fukao et al. 2002; Martin et al. 2003). These data highlighted the role of mTOR and PI3K in controlling the IL-12/IL-10 expression level in *Leishmania* infection. The inhibition of mTOR by rapamycin reversed the *Leishmania*-modulated IL-10 and IL-12 in human monocytes and THP-1-derived macrophages (the upregulation of IL-12 through PI3K/Akt pathway and decrease of IL-10) (Cheekatla et al. 2012; Harizanov and Kaftandjiev Iskren 2014). Taken together, the blockade of the mTOR pathway with rapamycin inhibits the cytokine level deviation induced by *Leishmania* and increases the host immune responses. It might be an attractive strategy to be developed for the treatment of leishmaniasis in the future.

CXCL16 is considered as a multifunctional chemokine that is expressed by immune cells such as macrophages in response to pathogens. However, its role remains unknown in parasitic infections (Veinotte et al. 2016). It has been recently shown that the presence and propagation of *L. donovani* parasites in infected bone marrow-derived macrophages (BMDM) lead to upregulation of CXCL16 in these cells (Chaparro et al. 2019). Although the link between CXCL16 and *Leishmania* pathogenicity needs to be investigated, it was observed that leishmanial-lipophosphoglycan (LPG) plays a critical role in the induction of CXCL16 expression. Surprisingly, the upregulation of CXCL16 in BMDM by *L. donovani* is dramatically affected by the activity of AKT/mTOR (Chaparro et al. 2019). More investigations should be performed to clarify the

possible interactions of CXCL16, LPG, and mTOR in the pathogenicity of *Leishmania* parasites.

### **Toxoplasma parasite and host mTOR**

Targeting host cell processes is an important strategy in *T. gondii* to manage the progression of infection in host cells (Hakimi et al. 2017). In vitro experiments on murine macrophages revealed that this apicomplexan parasite can reprogram the host cell transcriptome (Leroux et al. 2018). Remarkably, the translation of transcripts encoding proteins belonging to metabolic pathways and components of the translation machinery was activated during the infection. It seems that *T. gondii* infection activate the translation of mTOR-sensitive mRNAs and the preferential translation of transcripts with 5'-oligopyrimidine tracts and also those encoding proteins related to mitochondria to promote infection (Leroux et al. 2018). In addition, the host-parasite translational control has been determined by changes in mRNA levels of proliferating host cells, driven by gene expression changes that are consistent with mTOR activation and may serve to follow the host-parasite dynamic (Holmes et al. 2019).

The effect of *T. gondii* intracellular replication on the activation of host mTOR pathway has been previously studied (Wang et al. 2009b). Those results revealed that the activation of host mTOR signaling leads to the development of cell cycle and cell growth in infected host cells, independent from the growth-promoting effectors (eIF4E and S6K1). Moreover, it has been shown that *Toxoplasma* induces and activates autophagy in infected host cells to promote replication and such a mechanism does not produce mTOR inhibition, and it even occurs in host cells with hyperactive mTOR signaling (Orlofsky 2009; Wang et al. 2009a).

In 2018, an interesting study investigated the role of PI3K/Akt or mTOR pathway in the regulation of several inflammatory genes on *Toxoplasma*-infected host cells (Zhou et al. 2018). This study found that *Toxoplasma* parasite induced the overexpression of several genes: glutamate-cysteine ligase (GCL), glutathione S-transferase (GST), PH domain and leucine-rich repeat protein phosphatases 2 (PHLPP2), vascular endothelial growth factor (VEGF), NAD(P)H: quinone oxidoreductase (NQO1), and casein kinase2 $\beta$  (CK2 $\beta$ ). Those results also confirmed the downregulation of pigment epithelium-derived factor (PEDF) and PH domain and leucine-rich repeat protein phosphatases 1 (PHLPP1). The use of inhibitors of PI3K and mTOR showed that the regulation of most of the aforementioned genes was depending on the activation of mTOR or PI3K/Akt. Therefore, it was suggested that the protection of *Toxoplasma* parasite in infected host cells is probably related to the modulation of gene expression from such cells through mTOR pathway.

*T. gondii* excretory secretory antigens (TgESAs) can induce fetal teratogenesis or spontaneous abortion in pregnant mice infected with *Toxoplasma* via the dysfunction of Tregs (Chen et al. 2013; Chen et al. 2017). The inhibitory function of TgESAs on Foxp3 expression may lead to the induction of adverse pregnancy consequences in *Toxoplasma*-infected mice. In fact, Tregs are considered critical cells in sustaining immune tolerance of pregnancy (Guerin et al. 2009), whereas Foxp3 regulates the differentiation and functions of Tregs (Ono 2020). Current data support that TgESAs increase the gene/protein expression of the PI3K/AKT/mTOR pathway in EL4 cells (mouse ascites lymphoma lymphoblast) and therefore inducing the loss of Foxp3 (inhibition of Foxp3 expression through overexpression of PI3K/AKT/mTOR) (Chen et al. 2019). Overall, this information highlighted the critical role of TgESAs in reducing not only the expression of Foxp3 and the dysfunction of Tregs but also the occurrence of adverse pregnancy consequences in *Toxoplasma*-infected mice.

IL-12 and TNF are produced in primary human monocytes against *T. gondii* tachyzoites through a mechanism requiring tachyzoite phagocytosis. In contrast to the CD16<sup>+</sup> CD14<sup>+</sup> subset, CD16<sup>neg</sup> CD14<sup>+</sup> subset is not able to secrete TNF and IL-12 in response to *T. gondii* exposure (Amancio et al. 2018). This deficiency of the CD16<sup>neg</sup> CD14<sup>+</sup> subset is due to an increase of the mTORC1 activity and can be overcome directly through the rapamycin administration or indirectly via the stimulation of mTORC2 by IFN $\gamma$  priming. Indeed, the inhibition of mTORC1 activity is essential for the IL-12p40 response of CD16<sup>neg</sup> CD14<sup>+</sup> subset to *T. gondii* (Amancio et al. 2018).

In 2010, it was postulated that *T. gondii* may exploit host mTORC2 to control the organelle distribution, centrosome position, migratory response in infected host fibroblasts (Wang et al. 2010). Further experiments remarkably clarified that a continual signaling via host cell mTORC2-Akt was essential to maintain the centrosome position and the homogeneous distribution of mitochondria and lysosomes near the parasitophorous vacuole (PV) in *Toxoplasma*-infected host cells (Wang et al. 2010). The migratory response in fibroblasts is deeply affected by centrosome reorientation (Gomes et al. 2005). Surprisingly, the centrosome reorientation and migratory response were suppressed by *Toxoplasma* in infected cells (Wang et al. 2010). Therefore, *Toxoplasma* parasite activates the abovementioned mechanisms to reorganize and induce useful changes in the *Toxoplasma*-infected host cell to facilitate the pathogenesis process.

Azathioprine, a drug against the inflammatory bowel disease (IBD), is able to induce autophagy through the downregulation of mTORC1 (Hooper et al. 2019). In contrast, *Toxoplasma* enhances the activation of mTORC1 to reduce the activation of autophagy. Such mechanisms (mTORC and autophagy) are also induced by *Toxoplasma* parasite to escape from the immune system (Mirjalali et al. 2019; Wang et al.

2009b). On the other hand, the effect of *Toxoplasma* on the activation of mTORC1 might affect the azathioprine's mechanism of action in patients with IBD (Mirjalali et al. 2019). This might give warning concerning the prescription of drugs used to treat IBD such as azathioprine in patients with both IBD and toxoplasmosis.

Host cells increase their autophagic activity to fight against toxoplasmosis. In contrast, *T. gondii* recruits and manages the host cell–autophagic machinery to induce and maintain its pathogenicity (Gao et al. 2014). Rottlerin is a natural polyphenol that is able to increase the host cell–autophagic properties against toxoplasmosis diminishing *Toxoplasma* growth in infected host cells (Ietta et al. 2017). Autophagy can be synergistically increased by *Toxoplasma* in combination with rottlerin treatment. However, the use of autophagy-specific inhibitor (chloroquine) elucidated that the anti-parasitic effect of rottlerin is autophagy-independent and probably induced by the converging inhibitory effect of *Toxoplasma* and this compound in host protein translation which is mediated by eIF2 $\alpha$  phosphorylation and mTOR inhibition, respectively (Ietta et al. 2017; Torricelli et al. 2015). Altogether, these events led to increase both autophagy and the inhibition of protein synthesis, finally inducing a disruption in *Toxoplasma* replication. It seems that the inevitable occurrence of protein translation inhibition that is induced in concomitance with autophagy induction are important mechanisms allowing the reduction of parasite growth. This is especially observed when treatment induced inhibition of autophagy is synergistically increased by *Toxoplasma* infection through mTORC1/4EBP (Ietta et al. 2017).

On the other hand, the exact mechanism of autophagy activation in non-hematopoietic cells infected by *Toxoplasma* remains unknown. The expression of CCAAT/enhancer-binding protein  $\beta$  (C/EBP  $\beta$ ) has been correlated with autophagy regulation in non-hematopoietic cells (Yu et al. 2017). These authors demonstrated that C/EBP  $\beta$  inhibition decreased the elimination rate of *Toxoplasma* in non-hematopoietic cells, whereas the overexpression of C/EBP  $\beta$  increased the autophagy and death of parasites in infected cells. In addition, C/EBP  $\beta$  overexpression and C/EBP  $\beta$  inhibition reduced and increased mTOR activity respectively. Taken together, the results suggested that the overexpression of C/EBP  $\beta$  in *Toxoplasma*-infected non-hematopoietic cells might be associated with autophagy activation and mTOR inhibition in such cells. The mTOR activator phosphatidic acid blocked the rise of the elimination rate of parasites induced by C/EBP  $\beta$  upregulation, reinforcing the potential of this strategy for drug intervention against toxoplasmosis (Yu et al. 2017).

### **Plasmodium parasites and host mTOR**

The anti-malaria properties of rapamycin have been highlighted previously showing that PfkfBP35 (an immunophilin

FK506-binding protein) is a unique *Plasmodium falciparum* target protein for this compound (Bianchin et al. 2015; Monaghan et al. 2017). However, the mTOR inhibitory effect of rapamycin had been more largely investigated for the treatment of malaria. Atovaquone, another anti-malaria drug, also targets Akt/AMPK/mTOR pathway (mTOR inhibition) through the induction of the mitochondrial dysfunction (Ke et al. 2018).

In addition to the rapamycin therapy (as mTOR inhibitor) against *Plasmodium* parasites, several investigations have focused on the relations of the host mTOR pathway and the physiopathology and immunopathology of malaria infection. It was shown that *P. yoelii* sporozoites invasion can upregulate mTOR signaling and downregulate Bcl-2 and p53, which inhibit autophagy, apoptosis, and cell cycle progression, respectively as immune evasion strategies (Belachew 2018; Zheng et al. 2014).

Placental *P. falciparum* malaria might produce a local inflammatory reaction which is known as intervillitis—with impaired amino acid transport to the fetus—and low birthweight is a related symptom (Dimasuay et al. 2017a). The mTOR pathway has an important role in the regulation of the amino acid transport and the inhibition of this mechanism in placental malaria—correlated intervillitis (Dimasuay et al. 2014; Dimasuay et al. 2017a). It seems that by restituting the placental mTOR pathway, neonatal survival and birthweight may improve. Surprisingly, the presence of a dysregulated autophagy in placental malaria—associated intervillitis can impair transplacental amino acid transport (Dimasuay et al. 2017b). Therefore, a novel therapeutic strategy based on the mTOR pathway against placental malaria might be explored.

Cerebral malaria (CM) is a common form of severe malaria caused by *P. falciparum* and *P. vivax* associated with high mortality. Although the pathogenesis of CM remains unclear, it seems that parasite features and the host's immune responses are involved in this process (Dorovini-Zis et al. 2011; Gordon et al. 2015; Milner Jr et al. 2014; Sierro and Grau 2019). The administration of rapamycin in infected mice with CM blocked the breakdown of the blood–brain barrier, reduced the brain hemorrhage, and increased the survival rate of infected mice demonstrating the immunoregulatory functions of mTOR as well as the therapeutic properties of rapamycin in CM. In addition, such a treatment diminished the influx of T cells (CD4 and CD8) into the brain and reduced the accumulation of infected erythrocytes in the brain of infected mice with CM (Gordon et al. 2015; Mejia et al. 2017). Moreover, leukocyte trafficking to the brain and leukocyte proliferation in the brain was blocked in infected mice treated by rapamycin (Gordon et al. 2015).

In 2017, a similar study revealed the protective properties of rapamycin in experimental CM. This study indicated that rapamycin induced the reduction of neuropathology and death

via the regulation of host responses to CM infection (Mejia et al. 2017). After the treatment with rapamycin, the parasite cytoadherence was inhibited through the downregulation of CD36 in peripheral organs such as white adipose tissue. In addition, the alteration of splenic immune response by decreasing activated T cells with migratory phenotype and enhancing the local cytotoxic T cell activation were observed after the administration of rapamycin in CM cases. Furthermore, the levels of ICAM-1 (intercellular adhesion molecule 1) from the brain endothelial and brain pathology were reduced. All the aforementioned alterations led to parasite elimination while decreasing CD8 T cell migration in the infected brain. Overall, the induced vascular activation, pleiotropic effects on host immune responses, and the parasite sequestration might further suggest the clinical use of rapamycin in the treatment of CM.

AMPK is a vital metabolic sensor that plays a major role in maintaining energy homeostasis in both normal physiological and pathological conditions. In addition, this enzyme is correlated with autophagy, a process that is observed during pathologic conditions and metabolic stress (Weisová et al. 2011; Williams et al. 2011). In 2018, the results of an interesting study identified that levels of genes encoding AMPK catalytic subunits  $\alpha 1$  and  $\alpha 2$  were downregulated, and there was also a decrease in protein levels of activated AMPK in infected brains with CM. Surprisingly, this study suggested that the use of AMPK-activating drugs might reduce morbidity related to CM (Apoorv et al. 2018). As previously explained in this review, mTOR is able to inhibit autophagy and AMPK may inhibit mTOR to boost autophagy. Most probably, the AMPK upstream regulatory function over mTOR in T cells finally impact CM consequences (Gordon et al. 2015). More investigation regarding the relationships between autophagy, mTOR, and AMPK might provide more information for the development of effective AMPK-activating drugs against CM.

It has been shown that the immunometabolic modulation via dietary restriction (DR) in infected mice with CM inhibits neuropathology in severe malaria. DR can reduce parasite accumulation in the brain and enhance parasite clearance in the spleen in CM-infected mice although DR does not affect parasite growth (Mejia et al. 2015). Leptin, a host-derived adipokine involved in appetite signaling, is essential for CM pathology in experimental models being immunomodulation and control of the energy balance possible functions of leptin (Lago et al. 2008; Mejia et al. 2015). In this sense, DR reduces the level of leptin and the activity of mTORC1 in T cells (Mejia et al. 2015). Regarding T cells, very recently it has been shown that CD4+ T cell led to exhaustion during malaria which is associated with reduced mTOR activity (Villegas-Mendez et al. 2020). Interestingly, leptin administration abrogates the reduction of mTORC1 activity in T cells so the administration of leptin signaling inhibitors and rapamycin

reduce the cerebral pathology of infected mice experimentally. Therefore, it seems that mTORC1 and leptin can provide an important link between nutrition, immunometabolism, and experimental CM pathology. These highlight the clinical importance of the interplay between the nutrient/energy sensor mTORC1 and leptin.

Before starting the *Plasmodium*-intraerythrocytic stage and clinical manifestations, such parasites replicate in the liver stage affecting different signaling pathways in the infected hepatocytes (Kaushanskya et al. 2013). These authors demonstrated that the downregulation of the pro-death protein p53 in *P. yoelii* infected hepatocytes was induced by the propagation of the parasite and facilitated the *P. yoelii* survival. Those interesting results also indicated the increased level of anti-apoptotic signaling proteins p-Bcl-2 and p-PI3K-Akt, and the pro-proliferative phosphorylated states of mTOR, as other signaling pathways altered in *P. yoelii* infected hepatocytes. Such data suggest that the increased level of mTOR probably leads to autophagy inhibition which consequently favors parasite survival.

Finally, it is also imperative to point out the important and similar impact of other parasite infections on mTOR pathway and its inhibition, showing the broad regulatory functions of this kinase on the majority of the mammalian parasitic infections (Table 2).

### The target of rapamycin in parasites

The target of rapamycin pathway is also present in parasites themselves with high similarities between mTOR and parasite TORs which makes mTOR/PI3K inhibitors highly effective against parasites both “in vivo” and “in vitro” (Diaz-Gonzalez et al. 2011; Phan et al. 2020). In parasites, there are orthologues with different regulatory functions including cell cycle regulation and protein synthesis or cell polarization and cytokinesis (Barquilla et al. 2008; Barquilla and Navarro 2009). It has been shown that *Leishmania* TOR3 is essential for acidocalcisome biogenesis and the development of leishmaniasis in animals. TOR3-mutant *Leishmania* parasites were not able to survive and propagate in macrophages. The disability of this strain to cause leishmaniasis in animal models confirmed that the lower infectivity was due to a defective formation of acidocalcisome (Da Silva and Beverley 2010). Additionally, TOR3-*Leishmania* mutants exhibited defects in osmoregulation and were highly sensitive to glucose starvation. Additionally, TOR4 has been reported in *T. brucei* and is associated with an Armadillo domain-containing protein (TbArmtor), an important vault protein, and LST8 (lethal with sec-13 protein 8) to compose a unique TOR complex, TbTORC4. The inhibition of TbTOR4 led to the irreversible differentiation of the *Trypanosome* parasite into the quiescent form (Barquilla et al. 2012; Saldivia et al. 2013). According to the aforementioned roles of TORs in parasites, the inhibition

of TOR kinase functions in trypanosomatids might be further exploitable for innovative treatments.

### Conclusions and future directions

The current review attempted to provide information regarding manipulations of host mTOR signaling networks mainly by *Leishmania*, *Toxoplasma*, and *Plasmodium* but highlighting a global targeting by parasites. It appears clear that the survival, propagation, and pathogenicity progress of the protozoan parasites are deeply dependent on the alteration of host vital signaling and connected pathways such as mTOR and autophagy. Parasites have developed sophisticated strategies to target the metabolism of the immune cells to subvert potential deleterious immune responses acting on metabolic pathways controlled by this master regulator. These and the roles of mTOR in regulating the development and differentiation of cell subsets of the innate and adaptive immune response make that therefore, targeting such pathways might further open new venues in the treatment of parasitic diseases. Accordingly, the mTOR inhibitory function of rapamycin served as a strategy to deeper understand complex signaling and modulatory molecular events that parasites alter to successfully achieve infection. Overall, research on new non-toxic compounds with ample inhibitory properties and/or combinational kinase inhibitor treatments against different species of parasites might facilitate novel insights and developments towards their clinical usage. Thus, further investigations are needed to explore more biological functions of the mTOR signaling pathway in different cells and host-parasite relationships. The promising host mTOR modulation support that checking out more details regarding functions of mTORC2, cooperation and integration of mTORC1 and mTORC2, other upstream or downstream potential regulators and the effect of dysfunction or dysregulation of such components in health and parasitic diseases. It might be useful to understand a number of sensing stimuli/stresses and the underlying molecular cascades and checkpoints with the aim of developing highly selective novel intervention strategies targeting pathways that regulate host and parasite metabolism. Finally, the key functions of parasite TORs and their high similarities with mTOR can further facilitate this goal.

**Acknowledgements** PN thanks La Fundación La Caixa (LCF/PR/PR13/11080005), Fundación Caja Navarra, Gobierno de Navarra-Salud (12/2017), Fundación Roviralta, Ubesol, Government of Navarre, Laser Ebro, Inversiones Garcilaso de la Vega and COST Actions CA18217 and CA18218 for their support.

### Declarations

**Competing interests** The authors declare that they have no conflict of interest.

## References

- Albert S, Serova M, Dreyer C, Sablin M-P, Faivre S, Raymond E (2010) New inhibitors of the mammalian target of rapamycin signaling pathway for cancer. *Expert Opin Investig Drugs* 19(8):919–930
- Amancio AMT, Mittereder L, Carletti A, Sher A, Jankovic D (2018) Inhibition of mTORC1 activity is required for the IL-12p40 response of classical CD16neg CD14+ primary human monocytes to *Toxoplasma gondii*. *J Immunol* 200(1 Supplement):50.10
- Apoorv TS, Karthik C, Babu PP (2018) AMP-activated protein kinase (AMPK) is decreased in the mouse brain during experimental cerebral malaria. *Neurosci Lett* 662:290–294
- Barquilla A, Navarro M (2009) *Trypanosome* TOR complex 2 functions in cytokinesis. *Cell Cycle* 8:697–699
- Barquilla A, Crespo JL, Navarro M (2008) Rapamycin inhibits trypanosome cell growth by preventing TOR complex 2 formation. *Proc Natl Acad Sci U S A* 105(38):14579–14584
- Barquilla A et al (2012) Third target of rapamycin complex negatively regulates development of quiescence in *Trypanosoma brucei*. *Proc Natl Acad Sci U S A* 109(36):14399–14404
- Belachew EB (2018) Immune response and evasion mechanisms of *Plasmodium falciparum* parasites. *J Immunol Res* 2018:652968
- Betz C, Hall MN (2013) Where is mTOR and what is it doing there? *J Cell Biol* 203(4):563–574
- Bhattacharya P, Ali N (2013) Involvement and interactions of different immune cells and their cytokines in human visceral leishmaniasis. *Rev Soc Bras Med Trop* 46(2):128–134
- Bianchin A, Allemand F, Bell A, Chubb AJ, Guichou J-F (2015) Two crystal structures of the FK506-binding domain of *Plasmodium falciparum* FKBP35 in complex with rapamycin at high resolution. *Acta Crystallogr Sect F Struct Biol Cryst Commun* 71(6):1319–1327
- Biswas SK, Chittezhath M, Shalova IN, Lim J-Y (2012) Macrophage polarization and plasticity in health and disease. *Immunol Res* 53(1–3):11–24
- Bolourian A, Mojtahedi Z (2020) Obesity and COVID-19: the mTOR pathway as a possible culprit. *Obes Rev* 9:e13084
- Brackney DE, Correa MA, Cozens DW (2020) The impact of autophagy on arbovirus infection of mosquito cells. *PLoS Negl Trop Dis* 14:e0007754
- Byles V, Covarrubias AJ, Ben-Sahra I, Lamming DW, Sabatini DM, Manning BD, Horng T (2013) The TSC-mTOR pathway regulates macrophage polarization. *Nat Commun* 4:1–11
- Cerbán FM, Stempin CC, Volpini X, Silva EAC, Gea S, Motran CC (2020) Signaling pathways that regulate *Trypanosoma cruzi* infection and immune response. *Biochim Biophys Acta Mol Basis Dis* 1866(5):165707
- Chakraborty S, Roy S, Mistry HU, Murthy S, George N, Bhandari V, Sharma P (2017) Potential sabotage of host cell physiology by apicomplexan parasites for their survival benefits. *Front Immunol* 8:1261
- Chaparro V, Leroux L-P, Zimmermann A, Jardim A, Johnston B, Descoteaux A, Jaramillo M (2019) *Leishmania donovani* lipophosphoglycan increases macrophage-dependent chemotaxis of CXCR6-expressing cells via CXCL16 induction. *Infect Immun* 87:e00064–e00019
- Chaparro V et al (2020) Translational profiling of macrophages infected with *Leishmania donovani* identifies mTOR- and eIF4A-sensitive immune-related transcripts. *PLoS Pathog* 16:e1008291
- Cheekatla SS, Aggarwal A, Naik S (2012) mTOR signaling pathway regulates the IL-12/IL-10 axis in *Leishmania donovani* infection. *Med Microbiol Immunol* 201(1):37–46
- Chen JL, Y-y G, Zhang J, X-y Q, J-f Q, Wu J-p, Wang Y (2013) The dysfunction of CD4+ CD25+ regulatory T cells contributes to the abortion of mice caused by *Toxoplasma gondii* excreted-secreted antigens in early pregnancy. *PLoS One* 8(7):e69012
- Chen J et al (2017) Chinese 1 strain of *Toxoplasma gondii* excreted-secreted antigens negatively modulate Foxp3 via inhibition of the TGFβRII/Smad2/Smad3/Smad4 pathway. *J Cell Mol Med* 21(9):1944–1953
- Chen J, Hu L, Wang J, Cao Y, Zhu D, Chen L, Duan Y (2019) *Toxoplasma gondii* excreted-secreted antigens suppress Foxp3 via PI3K-AKT-mTOR signaling pathway. *J Cell Biochem* 120(9):16044–16051
- Cortez C, Real F, Yoshida N (2016) Lysosome biogenesis/scattering increases host cell susceptibility to invasion by *Trypanosoma cruzi* metacyclic forms and resistance to tissue culture trypomastigotes. *Cell Microbiol* 18(5):748–760
- Da Silva LM, Beverley SM (2010) Expansion of the target of rapamycin (TOR) kinase family and function in *Leishmania* shows that TOR3 is required for acidocalcisome biogenesis and animal infectivity. *Proc Natl Acad Sci U S A* 107(26):11965–11970
- De Leon JA et al (2017) Positive and negative regulation of the master metabolic regulator mTORC1 by two families of *Legionella pneumophila* effectors. *Cell Rep* 21(8):2031–2038
- Diaz-Gonzalez R et al (2011) The susceptibility of trypanosomatid pathogens to PI3/mTOR kinase inhibitors affords a new opportunity for drug repurposing. *PLoS Negl Trop Dis* 5:e1297
- Dimasuay G, Glazier J, Rogerson S, Jansson T, Boeuf P (2014) Inhibition of placental mTORC1 signalling may explain decreased placental nutrient transport and contribute to restricted fetal growth in placental malaria. *Placenta* 35(9):A62
- Dimasuay KG et al (2017a) Inhibition of placental mTOR signaling provides a link between placental malaria and reduced birthweight. *BMC Med* 15(1):1
- Dimasuay KG et al (2017b) Impaired placental autophagy in placental malaria. *PLoS One* 12(11):e0187291
- Dorovini-Zis K et al (2011) The neuropathology of fatal cerebral malaria in malawian children. *Am J Pathol* 178(5):2146–2158
- Dossou AS, Basu A (2019) The emerging roles of mTORC1 in macromanaging autophagy. *Cancers* 11(10):1422
- Echeverria LE, Morillo CA (2019) American trypanosomiasis (Chagas disease). *Infect Dis Clin* 33(1):119–134
- Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT (2017) The PI3K pathway in human disease. *Cell* 170(4):605–635
- Fukao T et al (2002) PI3K-mediated negative feedback regulation of IL-12 production in DCs. *Nat Immunol* 3(9):875–881
- Gao D et al (2014) Autophagy activated by *Toxoplasma gondii* infection in turn facilitates *Toxoplasma gondii* proliferation. *Parasitol Res* 113(6):2053–2058
- García-Martínez JM, Moran J, Clarke RG, Gray A, Cosulich SC, Chresta CM, Alessi DR (2009) Ku-0063794 is a specific inhibitor of the mammalian target of rapamycin (mTOR). *Biochem J* 421(1):29–42
- Gharthey-Kwansah G et al (2020) Autophagy in the control and pathogenesis of parasitic infections. *Cell Biosci* 10:101
- Gitta B, Kilian N (2020) Diagnosis of malaria parasites *Plasmodium* spp. in endemic areas: current strategies for an ancient disease. *Bioessays* 42:1900138
- Gomes ER, Jani S, Gundersen GG (2005) Nuclear movement regulated by Cdc42, MRCK, myosin, and actin flow establishes MTOC polarization in migrating cells. *Cell* 121(3):451–463
- Gordon EB et al (2015) Inhibiting the Mammalian target of rapamycin blocks the development of experimental cerebral malaria. *MBio* 6:e00725–e00715
- Guerin LR, Prins JR, Robertson SA (2009) Regulatory T-cells and immune tolerance in pregnancy: a new target for infertility treatment? *Hum Reprod Update* 15(5):517–535
- Guertin DA, Sabatini DM (2007) Defining the role of mTOR in cancer. *Cancer Cell* 12(1):9–22

- Hakimi M-A, Olias P, Sibley LD (2017) *Toxoplasma* effectors targeting host signaling and transcription. *Clin Microbiol Rev* 30(3):615–645
- Hallowell R et al (2017) mTORC2 signalling regulates M2 macrophage differentiation in response to helminth infection and adaptive thermogenesis. *Nat Commun* 8:14208
- Harizanov RN, Kaftandjiev Iskren T (2014) Interactions between parasite and host in human visceral leishmaniasis. *J Cytol Tissue Biol* 1:001
- Hassani K, Olivier M (2013) Immunomodulatory impact of *Leishmania*-induced macrophage exosomes: a comparative proteomic and functional analysis. *PLoS Negl Trop Dis* 7(5):e2185
- Hillmann P, Fabbro D (2019) PI3K/mTOR pathway inhibition: opportunities in oncology and rare genetic diseases. *Int J Mol Sci* 20(22):5792
- Holmes MJ, Shah P, Wek RC, Sullivan WJ (2019) Simultaneous ribosome profiling of human host cells infected with *Toxoplasma gondii*. *MSphere* 4(3):e00292–e00219
- Hooper KM et al (2019) The inflammatory bowel disease drug azathioprine induces autophagy via mTORC1 and the unfolded protein response sensor PERK. *Inflamm Bowel Dis* 25(9):1481–1496
- Hu B et al (2015) Binding of the pathogen receptor HSP90AA1 to avibirnavirus VP2 induces autophagy by inactivating the AKT-mTOR pathway. *Autophagy* 11(3):503–515
- Hua F, Li K, Shang S, Wang F, Hu Z (2019) Immune signaling and autophagy regulation. *Adv Exp Med Biol* 1206:551–593
- Ietta F et al (2017) Rottlerin-mediated inhibition of *Toxoplasma gondii* growth in BeWo trophoblast-like cells. *Sci Rep* 7(1):1–9
- Jang YJ, Kim JH, Byun S (2019) Modulation of autophagy for controlling immunity. *Cells* 8(2):138
- Jaramillo M et al (2011) *Leishmania* repression of host translation through mTOR cleavage is required for parasite survival and infection. *Cell Host Microbe* 9(4):331–341
- Jiang Y, Su S, Zhang Y, Qian J, Liu P (2019) Control of mTOR signaling by ubiquitin. *Oncogene* 38:3989–4001
- Joubert P-E, Stapleford K, Guivel-Benhassine F, Vignuzzi M, Schwartz O, Albert ML (2015) Inhibition of mTORC1 enhances the translation of chikungunya proteins via the activation of the Mnk/eIF4E pathway. *PLoS Pathog* 11(8):e1005091
- Kaushanskya A et al (2013) Interrogation of infected hepatocyte signaling reveals that suppression of host p53 is critical for *Plasmodium* liver stage infection. *Cell Rep* 3(3):630–637
- Ke F et al (2018) The anti-malarial atovaquone selectively increases chemosensitivity in retinoblastoma via mitochondrial dysfunction-dependent oxidative damage and Akt/AMPK/mTOR inhibition. *Biochem Biophys Res Commun* 504(2):374–379
- Khadir F et al (2018) Therapeutic control of leishmaniasis by inhibitors of the mammalian target of rapamycin. *PLoS Negl Trop Dis* 12:e0006701
- Khadir F et al (2019) Antileishmanial effect of rapamycin as an alternative approach to control *Leishmania tropica* infection. *Vet Parasitol* 276:108976
- Kim J, Kundu M, Viollet B, Guan K-L (2011) AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat Cell Biol* 13(2):132–141
- Kindrachuk J et al (2015) Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome coronavirus infection as identified by temporal kinome analysis. *Antimicrob Agents Chemother* 59(2):1088–1099
- Knight SD et al (2010) Discovery of GSK2126458, a highly potent inhibitor of PI3K and the mammalian target of rapamycin. *ACS Med Chem Lett* 1(1):39–43
- Kumar A et al (2018) *Leishmania* infection activates host mTOR for its survival by M2 macrophage polarization. *Parasite Immunol* 40(11):e12586
- Lago R, Gómez R, Lago F, Gómez-Reino J, Gualillo O (2008) Leptin beyond body weight regulation-current concepts concerning its role in immune function and inflammation. *Cell Immunol* 252(1-2):139–145
- Laplane M, Sabatini DM (2009) mTOR signaling at a glance. *J Cell Sci* 122(Pt 20):3589–3594
- Le Sage V, Cinti A, Amorim R, Mouland AJ (2016) Adapting the stress response: viral subversion of the mTOR signaling pathway. *Viruses* 8(6):152
- Leroux L-P et al (2018) The protozoan parasite *Toxoplasma gondii* selectively reprograms the host cell translome. *Infect Immun* 86(9):e00244–e00218
- Li B, Xi P, Wang Z, Han X, Xu Y, Zhang Y, Miao J (2018) PI3K/Akt/mTOR signaling pathway participates in *Streptococcus uberis*-induced inflammation in mammary epithelial cells in concert with the classical TLRs/NF- $\kappa$ B pathway. *Vet Microbiol* 227:103–111
- Libisch MG, Faral-Tello P, Garg NJ, Radi R, Piacenza L, Robello C (2018) Early *Trypanosoma cruzi* infection triggers mTORC1-mediated respiration increase and mitochondrial biogenesis in human primary cardiomyocytes. *Front Microbiol* 9:1889
- Liu L, Chen L, Chung J, Huang S (2008) Rapamycin inhibits F-actin reorganization and phosphorylation of focal adhesion proteins. *Oncogene* 27(37):4998–5010
- Maiese K (2020) The mechanistic target of rapamycin (mTOR): novel considerations as an antiviral treatment and possibilities for COVID-19. *Curr Neurovasc Res* 17(3):332–337
- Martin M, Schifferle RE, Cuesta N, Vogel SN, Katz J, Michalek SM (2003) Role of the phosphatidylinositol 3 kinase-Akt pathway in the regulation of IL-10 and IL-12 by *Porphyromonas gingivalis* lipopolysaccharide. *J Immunol* 171(2):717–725
- Martinez FO et al (2013) Genetic programs expressed in resting and IL-4 alternatively activated mouse and human macrophages: similarities and differences. *Blood* 121(9):e57–e69
- Martins RM, Alves RM, Macedo S, Yoshida N (2011) Starvation and rapamycin differentially regulate host cell lysosome exocytosis and invasion by *Trypanosoma cruzi* metacyclic forms. *Cell Microbiol* 13(7):943–954
- Matte C, Descoteaux A (2011) Disruption of the AKT/mTOR pathway by *Leishmania major* promastigotes. *BMC Proc* 5(Suppl 1):P44
- Mejia P et al (2015) Dietary restriction protects against experimental cerebral malaria via leptin modulation and T cell mTORC1 suppression. *Nat Commun* 6:6050
- Mejia P, Treviño-Villarreal JH, Reynolds JS, De Niz M, Thompson A, Marti M, Mitchell JR (2017) A single rapamycin dose protects against late-stage experimental cerebral malaria via modulation of host immunity, endothelial activation and parasite sequestration. *Malar J* 16(1):455
- Mesquita I et al (2020) The Absence of HIF-1 $\alpha$  Increases Susceptibility to *Leishmania donovani* Infection via Activation of BNIP3/mTOR/SREBP-1c Axis. *Cell Rep* 30(12):4052–4064
- Metz P et al (2015) Dengue virus inhibition of autophagic flux and dependency of viral replication on proteasomal degradation of the autophagy receptor p62. *J Virol* 89(15):8026–8041
- Miller C, Celli J (2016) Avoidance and subversion of eukaryotic homeostatic autophagy mechanisms by bacterial pathogens. *J Mol Biol* 428(17):3387–3398
- Milner DA Jr et al (2014) The systemic pathology of cerebral malaria in African children. *Front Cell Infect Microbiol* 4:104
- Mirjalali H, Shahrokh S, Asadzadeh Aghdaei H, Zali MR (2019) Letter to the Editor: Activated *Toxoplasma* may attenuate the effect of azathioprine and deteriorate the symptoms in IBD patients via mTORC1 manipulation. *Inflamm Bowel Dis* 25(11):e137–e137
- Monaghan P, Leneghan DB, Shaw W, Bell A (2017) The antimalarial action of FK506 and rapamycin: evidence for a direct effect on FK506-binding protein PfkFBP35. *Parasitology* 144(7):869–876
- Montazeri M et al (2020) The global serological prevalence of *Toxoplasma gondii* in felids during the last five decades (1967–

- 2017): a systematic review and meta-analysis. *Parasit Vectors* 13(1): 82
- Nandagopal N, Ali AK, Komal AK, Lee S-H (2014) The critical role of IL-15-PI3K-mTOR pathway in natural killer cell effector functions. *Front Immunol* 5:187
- Nandan D, Zhang N, Yu Y, Schwartz B, Chen S, Kima PE, Reiner NE (2018) Miransertib (ARQ 092), an orally-available, selective Akt inhibitor is effective against *Leishmania*. *PLoS One* 13:e0206920
- Narasimhan PB et al (2016) Microfilariae of *Brugia malayi* inhibit the mTOR pathway and induce autophagy in human dendritic cells. *Infect Immun* 84(9):2463–2472
- Nouwen LV, Everts B (2020) Pathogens MentORing macrophages and dendritic cells: manipulation of mTOR and cellular metabolism to promote immune escape. *Cells* 9(1):161
- Ohtani M et al (2008) Mammalian target of rapamycin and glycogen synthase kinase 3 differentially regulate lipopolysaccharide-induced interleukin-12 production in dendritic cells. *Blood* 112(3): 635–643
- Ono M (2020) Control of regulatory T-cell differentiation and function by T-cell receptor signalling and Foxp3 transcription factor complexes. *Immunology* 160(1):24–37
- Orlofsky A (2009) *Toxoplasma*-induced autophagy: a window into nutritional futile cycles in mammalian cells? *Autophagy* 5(3):404–406
- Patel RK, Hardy RW (2012) Role for the phosphatidylinositol 3-kinase-Akt-TOR pathway during sindbis virus replication in arthropods. *J Virol* 86:3595–3604
- Patsoukis N, Weaver JD, Strauss L, Herbel C, Seth P, Boussiotis VA (2017) Immunometabolic regulations mediated by coinhibitory receptors and their impact on T cell immune responses. *Front Immunol* 8:330
- Penas FN et al (2020) Pyridinecarboxylic Acid derivative stimulates pro-angiogenic mediators by PI3K/AKT/mTOR and inhibits reactive nitrogen and oxygen species and NF- $\kappa$ B Activation through a PPAR $\gamma$ -dependent pathway in *T. cruzi*-infected macrophages. *Front Immunol* 10:2955
- Peres AG et al (2015) Uncoupling of pro-and anti-inflammatory properties of *Staphylococcus aureus*. *Infect Immun* 83:1587–1597
- Phan T-N, Baek K-H, Lee N, Byun SY, Shum D, No JH (2020) In vitro and in vivo activity of mTOR kinase and PI3K inhibitors against *Leishmania donovani* and *Trypanosoma brucei*. *Molecules* 25(8): 1980
- Qian J, Su S, Liu P (2020) Experimental approaches in delineating mTOR signaling. *Genes* 11(7):738
- Rijo-Ferreira F, Takahashi JS (2020) Sleeping sickness: a tale of two clocks. *Front Cell Infect Microbiol* 10:525097
- Rojas Márquez JD, Ana Y, Baigorri RE, Stempin CC, Cerban FM (2018) Mammalian target of rapamycin inhibition in *Trypanosoma cruzi*-infected macrophages leads to an intracellular profile that is detrimental for infection. *Front Immunol* 9:313
- Romano PS, Arboit MA, Vázquez CL, Colombo MI (2009) The autophagic pathway is a key component in the lysosomal dependent entry of *Trypanosoma cruzi* into the host cell. *Autophagy* 5(1):6–18
- Sabatini DM (2017) Twenty-five years of mTOR: uncovering the link from nutrients to growth. *Proc Natl Acad Sci U S A* 114(45):11818–11825
- Sahni A, Narra HP, Sahni SK (2020) Activation of mechanistic target of rapamycin (mTOR) in human endothelial cells infected with pathogenic spotted fever group rickettsiae. *Int J Mol Sci* 21(19):7179
- Saldivia M, Barquilla A, Bart J-M, Diaz-González R, Hall MN, Navarro M (2013) Target of rapamycin (TOR) kinase in *Trypanosoma brucei*: an extended family. *Biochem Soc Trans* 41(4):934–938
- Santulli G, Totary-Jain H (2013) Tailoring mTOR-based therapy: molecular evidence and clinical challenges. *Pharmacogenomics* 14(12): 1517–1526
- Saravia J, Raynor JL, Chapman NM, Lim SA, Chi H (2020) Signaling networks in immunometabolism. *Cell Res* 30(4):328–342
- Saxton RA, Sabatini DM (2017) mTOR signaling in growth, metabolism, and disease. *Cell* 168(6):960–976
- Shang M et al (2020) In vivo and in vitro studies using *Clonorchis sinensis* adult-derived total protein (Cs TP) on cellular function and inflammatory effect in mouse and cell model. *Parasitol Res* 119(5):1641–1652
- Shapira M, Zinoviev A (2011) *Leishmania* parasites act as a Trojan horse that paralyzes the translation system of host macrophages. *Cell Host Microbe* 9(4):257–259
- Shertz CA, Cardenas ME (2011) Exploiting and subverting Tor signaling in the pathogenesis of fungi, parasites, and viruses. *PLoS Pathog* 7: e1002269
- Sierro F, Grau GE (2019) The ins and outs of cerebral malaria pathogenesis: immunopathology, extracellular vesicles, immunometabolism, and trained immunity. *Front Immunol* 10:830
- Smith SF, Collins SE, Charest PG (2020) Ras, PI3K and mTORC2-three's a crowd? *J Cell Sci* 133(19):jcs234930
- Stempin CC, Marquez JDR, Ana Y, Cerban FM (2017) GRAIL and otubain-1 are related to T cell hyporesponsiveness during *Trypanosoma cruzi* infection. *PLoS Negl Trop Dis* 11(1):e0005307
- Thomas SA, Nandan D, Kass J, Reiner NE (2018) Countervailing, time-dependent effects on host autophagy promote intracellular survival of *Leishmania*. *J Biol Chem* 293(7):2617–2630
- Tian T, Li X, Zhang J (2019) mTOR signaling in cancer and mTOR inhibitors in solid tumor targeting therapy. *Int J Mol Sci* 20(3):755
- Torres-Guerrero E, Quintanilla-Cedillo MR, Ruiz-Esmerjand J, Arenas R (2017) Leishmaniasis: a review. *F1000Res* 6:750
- Torricelli C et al (2015) Phosphorylation-independent mTORC1 inhibition by the autophagy inducer Rottlerin. *Cancer Lett* 360(1):17–27
- Veinotte L, Gebremeskel S, Johnston B (2016) CXCL16-positive dendritic cells enhance invariant natural killer T cell-dependent IFN $\gamma$  production and tumor control. *Oncoimmunology* 5(6):e1160979
- Villegas-mendez A et al (2020) exhausted cd4+ t cells during malaria exhibit reduced mTORc1 activity correlated with loss of T-bet expression. *J Immunol* 205(6):1608–1619
- Viret C, Rozières A, Faure M (2018) Autophagy during early virus-host cell interactions. *J Mol Biol* 430(12):1696–1713
- Wang Y, Weiss LM, Orlofsky A (2009a) Host cell autophagy is induced by *Toxoplasma gondii* and contributes to parasite growth. *J Biol Chem* 284(3):1694–1701
- Wang Y, Weiss LM, Orlofsky A (2009b) Intracellular parasitism with *Toxoplasma gondii* stimulates mammalian-target-of-rapamycin-dependent host cell growth despite impaired signalling to S6K1 and 4E-BP1. *Cell Microbiol* 11(6):983–1000
- Wang Y, Weiss LM, Orlofsky A (2010) Coordinate control of host centrosome position, organelle distribution, and migratory response by *Toxoplasma gondii* via host mTORC2. *J Biol Chem* 285(20): 15611–15618
- Wang H et al (2019) Thioredoxin peroxidase secreted by *Echinococcus granulosus* (sensu stricto) promotes the alternative activation of macrophages via PI3K/AKT/mTOR pathway. *Parasit Vectors* 12(1):542
- Wang P, Zhang Q, Tan L, Xu Y, Xie X, Zhao Y (2020) The regulatory effects of mTOR complexes in the differentiation and function of CD4+ T cell subsets. *J Immunol Res* 2020:3406032
- Weichhart T, Hengstschlager M, Linke M (2015) Regulation of innate immune cell function by mTOR. *Nat Rev Immunol* 15(10):599–614
- Weisová P, Dávila D, Tuffy LP, Ward MW, Concannon CG, Prehn JH (2011) Role of 5'-adenosine monophosphate-activated protein kinase in cell survival and death responses in neurons. *Antioxid Redox Signal* 14(10):1863–1876
- Williams T, Courchet J, Viollet B, Brenman JE, Polleux F (2011) AMP-activated protein kinase (AMPK) activity is not required for neuronal development but regulates axogenesis during metabolic stress. *Proc Natl Acad Sci U S A* 108(14):5849–5854

- Xu Z-P, Chang H, Ni Y-Y, Li C, Chen L, Hou M, Ji M-J (2019) *Schistosoma japonicum* infection causes a reprogramming of glycolipid metabolism in the liver. *Parasit Vectors* 12(1):388
- Yang B et al (2020) Autophagy induction by the pathogen receptor NECTIN4 and sustained autophagy contribute to peste des petits ruminants virus infectivity. *Autophagy* 16(5):842–861
- Yeh H-S, Yong J (2020) mTOR-coordinated post-transcriptional gene regulations: from fundamental to pathogenic insights. *J Lipid Atheroscler* 9(1):8–22
- Yu Y, Zhao N, An J, Zhang X (2017) CCAAT/enhancer-binding protein  $\beta$  mediates the killing of *Toxoplasma gondii* by inducing autophagy in nonhematopoietic cells. *DNA Cell Biol* 36(3):212–218
- Zheng H, Tan Z, Xu W (2014) Immune evasion strategies of pre-erythrocytic malaria parasites. *Mediat Inflamm* 2014(6):362605
- Zheng Y, Li R, Liu S (2020) Immunoregulation with mTOR inhibitors to prevent COVID-19 severity: a novel intervention strategy beyond vaccines and specific antiviral medicines. *J Med Virol* 99(9):1495–1500
- Zhou W, Quan J-H, Gao F-F, Ismail HAAH, Lee Y-H, Cha G-H (2018) Modulated gene expression of *Toxoplasma gondii* infected retinal pigment epithelial cell line (ARPE-19) via PI3K/Akt or mTOR signal pathway. *Korean J Parasitol* 56(2):135–145
- Zimmer CL et al (2019) NK cells are activated and primed for skin-homing during acute dengue virus infection in humans. *Nat Commun* 10(1):3897

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.