Mtor kinase: physiological roles and interactions article review example

Health & Medicine, Cancer

Introduction:

Living organisms are equipped with robust machinery for executing a myriad of tasks to meet the day to day biological challenges. This machinery in turn relies on one or more interconnected pathways or networks composed of nucleic acid, proteins and other essential constituents. To say, it is the precise function of these components which determines the physiological well being organisms. Mammalian target of rapamycin (mTOR) kinases is one such known component that performs diverse physiological roles through its associations with the molecular machinery.

mTOR is a protein that responds to metabolism and ageing, intercellular stress to growth regulation, growth factors and nutrients (Durán & Hal, 2012). It is being regulated by small GTPases such as Ryh1, RalA, Rheb, Rag and Rac1.(mTOR) is also believed to possess structural complexity that enhances its functional competence. With the ever growing metabolic demands, mTOR kinases could require additional roles or a modification of its functions. It is not known fully whether mTOR kinase response to environmental stimuli and involvement in physiology is determined by various regulating mechanisms. In such context , the present description is concerned with high highlighting about mammalian target of rapamycin (mTOR) kinases and physiological roles and interactions.

About mTOR:

mTOR belongs to phosphoinositide -related kinase family. Its physiological importance comes into light due to the associated kinase activities (Yonezawa et al., 2004). Say, it is subject to phosphorylation on serine

residues in vivo and autophosphorylation in vitro. The autophosphorylation site was reported to be Ser2481 that is situated in a His-Ser-Phe motif close to the tail of conserved carboxyl-terminal mTOR. mTOR phosphoryates important substrates like p53, eIF4E-binding protein 1 (4E-BP1) , a 150-kDa raptor, STAT3, nPKCepsilon and nPKCdelta. The phosphorylation events of mTOR could initiate its journey in the physiology and signaling (Yonezawa et al., 2004). So, knowing about mTOR phosphorylation could be central.

In association with this, mTOR response to signaling is of primary importance. Signaling of mTOR is thought to be induced by amino acids and hormones like insulin (Proud, 2004).

This response is more towards intracellular amino acids instead of external amino acid levels.

As such, an association could exist between mToR response to internal secretions and phosphorylation at multiple sites (Proud, 2004). For instance, 4E-BP1 affects the function of mTOR when becomes phosphorylated at multiple sites. mTOR mediates the inactivation of kinase led phosphorylation and inhibition of elongation factor 2 (eEF2 kinase) . mTOR signaling becomes mandatory when insulin lowers the ability of eEF2 kinase to get bound with calmodulin (Proud, 2004). This could suggest that mTOR signaling and the need of novel phsohorylation sites becomes helpful when hormonal action alter kinase binding properties (Proud, 2004).

mTOR structure:

Yang et al (2013) described the structure –function aspects of mTOR kinases.

For this, they initially highlighted a typical mTOR–mLST8 complex that has a

crystal structure with1, 500-amino- acids and FAT, FRB, kinase and FATC domains. The mTOR–mLST8 possess a compact shape. Here, FAT domain, with helical repeats gives rise to C'-shaped a-solenoid that encircles kinase domain halfway and sits on it like a clamp. For a kinase domain structure, FATC domains appear integral. mTOR kinase domain is two lobe structure that is identical to canonical protein and PI3K kinase families (Yang etal., 2013). mTOR kinase domain has long ka1 helixthat is integral to a N- lobe as it is being packed in its concave surface in PI3Ks and mTOR. The domain has FRB insertion with a b-strand and two short helices fitted in the base of FRB (Yang etal., 2013).

Most importantly, the C-lobe of domain possesses four structural motifs in the PI3K core structure close to the catalytic cleft. These are FATC, ka9b, kaAL and LBE. These units give a spiny appearance on the on the activation loop that has a 30 residues which are involved in the protein kinases regulation. The activation loop structure is thought to be stabilized interaction between activation loop and FATC. The substrate binding siteis a MgF32 c-phosphate that projects to a highly conserved C- lobe grove. Overall, FRB domain serves to safeguard active site accessibility and ensures privileged substrates accessibility and for secondary motif through its binding (Yang etal., 2013).

Connection between PETN pathway and mTORC1:

mTORC1 pathway is much susceptible to activation by PTEN-phosphoinositide 3-kinase (PI3K) signaling (Carracedo & Pandolfi , 2008). This serves as a important for controlling cell growth, metabolism and

survival. The PI3K family is divided into class I, II an III. PTEN–PI3K pathway is regulated at multiple levels. However, the downstream components of mTORC1 play pivotal role in regulating PI3K in a negative feedback mechanism. The cross talk that occurs during pathway signaling was being exploited by researchers in designing mTOR kinase-PI3K inhibitors that could target both upstream and downstream of the PI3K pathways. Ultimately the researchers would like to inhibit PTEN/PI3K pathway from mTORC2 to mTORC1(Carracedo & Pandolfi , 2008).

mTOR regulation by GTP ases:

Durán & Hal (2012) described that mTOR regulation is influenced by GTP ases. They added insights on the localization of TOR in TORC1 and TORC2 complexes. Cellular processes such as autophagy, nutrient uptake, ribosome biogenesis and protein synthesis are regulated by TORC1. Whereas, lipid synthesis, cell survival and actin cytoskeleton organization are controlled by TORC2 (Durán & Hal, 2012). As revealed from studies in Drosophila, RAB family members play vital role in regulating TORC1 and TORC2 thus enriching the TOR pathway . The interaction between small GTPases and mTOR has been exploited well in the cancer therapy

Say, GTPases when become altered contribute to cell transformation and cancer development. by involving in the mTOR pathway. It was described that GTPases when targeted by specific inhibitors, could become functionally altered that might affect various cancer progression events.

This has shed light on significance of GTP ase interaction with TORs and their impact on the TOR pathway (Durán & Hal, 2012).

Action of Rapamycin:

Rapamaycin was isolated from Streptomyces hygroscopicus and is better known with other names like zotarolimus, umirolimus and sirolimus. It is applied for inhibiting restenosis following angioplasty and as a treating various cancer forms. The target of rapamycin genes TOR1 and TOR2 have a potential to mediate the growth inhibitory effects of rapamycin.

mTORC1 is inhibited by rapamycin by attaching to FK506-binding protein FKBP12 which on interacting with the complex decreases its activity. Rapamycin insensitive mTORC2 on chronic exposure to rapamycin contributes to sequestration of mTOR from mTORC2. Such action on mTORC2 could lead to chronic rapamycin treatment driven metabolic complications, abnormal lipid profile and glucose intolerance.

mTOR in aging phenomenon:

Recently, researchers described the significance of mTORs and related pathways with regard to age related disabilities. They described that mTOR plays important role in aging regulation . This came into light when gene encoding yeast orthologue of S6K — SCH9 in S. cerevisiae was deleted and yeast chronological lifespan was doubled later (Johnson, Rabinovitch,& Kaeberlein, 2013). Subsequently, it was found that longevity was being affected by mTORC1 when the lifespan in the nematode Caenorhabditis elegans was extended by a the mTORC1 component raptor (daf-15) or RNA interference (RNAi) knockdown of mTOR (let-363). In addition, mutations in mTORC1 pathway were also found to extend the lifespan in yeast replicative ageing models and fruitfly Drosophila mela- nogaster, mice and fruitflies.

mTOR complexes, mTORC1 and mTORC were thought to possess distinct constituent proteins for executing a spectrum of downstream processes. Say, mTORC1 has TTI1–TEL2, mTOR, mLST8, raptor, PRAS40, deptor and mTORC2 is made of TTI1–TEL2, mTOR, mSIN1, rictor, protor, deptor, and mLST8. Increased longevity from mTORC2 could occur when it inhibits FOXO3a through S6K1 and AKT.

So, mTOR also interacts with other longevity pathways . As a part of this, it responds to good number of environmental stimuli that involve longevity contributing factors (Johnson, Rabinovitch,& Kaeberlein, 2013).

For instance, longevity in mice, fruitflies, nematodes is increased by IGF-1-like signaling (IIS) or low insulin levels. Here, the activity of mTOR was described to linked through various routes

mTOR exerts its action by interacting through mTORC2 to represses FOXO1 and FOXO3 which have regulatory effect on mTORC1. mTORC1 plays role in hypoxic responses that influences longevity. Say, in mammals, early hypoxic response in activated by TORC1 through translation and stabilization of HIF-1 and translation of HIF-1 target genes like vascular endothelial growth factor (VEGF).

mTORC1 is down regulated by prolonged hypoxia. Longevity is positively and negatively regulated by HIF-1 in C. elegans. Lifespan of animals is thought to be extended on deletion of HIF-1 (Johnson, Rabinovitch & Kaeberlein, 2013)

Scientists have reported that it is feasible to retard the development of age-related diseases as certain molecular changes are connected to aging . On these grounds, it was speculated that inhibition of mTORC1 could posiitvley impact age-related pathologies in mice and humans mTORC1 could

modulate the onset of age related diseases like type 2 diabetes, autoimmune disease, heart disease, deterioration of cognitive and immune system, alzheiers disease , kidney disease and cancer. On these grounds, it was speculated that inhibition of mTORC1 could posiitvley impact age-related pathologies in mice and humans . mTOR executes longevity through mechanisms like mRNA translation, authophagy, mitochondrial biognenesis, inflammation, enhanced stress response and rejuvenation of stem cell function(Johnson, Rabinovitch,& Kaeberlein, 2013).

The mTOR role in aging has been explored well by the researchers with the goal of developing novel drugs that target mTOR pathway. Especially, the novel focus is on ATP-competitive inhibitors that block phosphorylation of mTORC1 and mTORC2.

It was reported that lifespan could be extended from dietary restriction . However, dietary restriction could lessen TORC1 mTORC1 activity in mammalian tissues and invertebrate organisms(Johnson, Rabinovitch,& Kaeberlein, 2013).. Under conditions of non-dietary restriction. disrupting mTORC1 genetically or pharmacologically was shown to increase life . On these grounds, it was been evidenced that mTORC1 could exert its action downstream . This came into light when dietary restriction failed prolong a replicative lifespan when genes encoding the mTOR and S6K homologues were deleted. Further, this effect was also found when RNAi knockdown of mTOR was united with dietary restriction . Similarly, in a nutrient-dependent manner, dominant-negative alleles of mTOR were able to prolong lifespan. Many, studies have focused on processes that are mTORC1-regulated like induction of autophagy and decreased mRNA translation to prolong lifespan

from dietary restriction in different organisms. Collectively, these experiments seem to lessen mTORC1 signaling with the goal of promoting longevity (Johnson, Rabinovitch,& Kaeberlein, 2013). This could indicate that the association between mTOR and other factors might advance our understanding on mechanisms that could slow down aging.

Differential control of mTORC1 on mRNA translation

Thoreen et al., (2013) explored the differential control of mTORC1 in view of mRNA translation. Their emphasis was on Torin , a ATP-competitive inhibitors of mTOR that

alters pro liferation and protein synthesis than rapamycin to a much extent. In this regard, the effects of Torin 1 was tested from several perspectives Say, Torin was capable of blocking mTORC1-dependent events like 4E-BP1 and S6K1 phosphorylation in cells mouse embryonic fibroblasts (MEF) and suppressing 35S-Cys/Met incorporation into protein.

Further, Torin 1 was able to inhibit several 5’ terminal oligopyrimidine(TOP) mRNA translational efficiencies (Thoreen et al., 2012).

TOP mRNAs constitute those mRNAs that possess a cytidine after the 5’ cap followed by continuous stretch of 4–14 pyrimidines. They also encode translation associated proteins

Torin 1 was also reported to suppress as TOP motifs that were previously undefined. In this context, researchers have found mTOR inhibition sensitive 85 mRNAs that possess unrecognized TOP-like motif. The basis for regulating TOP mRNA translation by mTOR was attributed to 4E-BP phosphorylation to which the translation of mRNAs with TOP and TOP-like motifs was highly

sensitive (Thoreen et al., 2012).

So, 4E-BPs appear central for mTOR signaling as it mediates mTOR inhibition of mRNAsThis could indicate that there may be several TOP and TOP-like motifs and mTOR could appear very important for translation of several mRNAs. So, Torin 1exhbits great range in its suppressing action on TOP mRNAs . Many unknown TOP mRNAs play pivotal role in protein synthesis similar to already known TOP mRNAs (Thoreen et al., 2012).

However, the inhibitory action of mTOR on all these mRNAs was described well.

Thus, mTOR appears as special kinase in its mode of interactions with various factors.

Its function role in physiology appears to begin with the presence of reliable structural site domains that provide accessibility for substrates.

Much of the research on mTOR kinases was on inhibiting its action and understanding its responses to environmental stimuli. Its involvement in signaling pathways became apparent due to interaction with PTEN/PI3K pathway. Its association with the biological process like protein synthesis autophagy, lipid synthesis through TORC1 and TORC2 complexes has made it a important kinase for cancer studies. Especially, with the discovery of Rapamycin, research on mTORC kinases has been accelerated to much extent on TOR1 and TOR2.

Further, mTOR has been proved to be very important for aging phenomenon. Experimental studies have added much insights on the longevity increasing potential of mTORC1/2. mTOR appears to be the in fighting against age related diseases by relying on several mechanisms . Its effect on mRNA

trnanslation program was evidenced by Torins that prevents mTORC1-dependent events.

Conclusion:

It can be concluded that mTOR kinases constitute one of the important kinases. They appear to possess multiple responding properties when presented with several environmental cues or factors. This feature is believed to be associated with mechanisms that either control or regulate mTOR kinases. The outcome of such interaction could be either beneficial or detrimental depending on the tasks of internal environment. Research is in progress to exploit the networks/pathways of mTOR kinases to further understand the basic biology, longevity in relation to diet restriction and target diseases like cancer. Hence, mTOR kinase response to environmental stimuli and involvement in physiology is determined by various regulating mechanisms.

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