Mammalian Target of Rapamycin
MasTOR Mediator of Cellular Changes in Pathological States?

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M ore than 30 years ago, a soil sample from Easter Island was found to contain a bacterial strain that produced a potent antifungal metabolite later named rapamycin. In addition to its antifungal properties, rapamycin was found to possess antiproliferative and immunosuppressant properties.1 The intracellular target of this intriguing compound is known as TOR, for target of rapamycin, which is the central component of 2 macromolecular complexes, TORC1 and TORC2 (Figure), having distinct protein components and functional roles. TOR-mediated events have been demonstrated in cancer, metabolic disorders, angiogenesis, and cardiac hypertrophy, as well as memory and learning.

TOR is a serine/threonine kinase that is highly conserved among species.1 Mammalian TOR is known as mTOR. mTORC1 contains core components mTOR, raptor, and mLST8 and is rapamycin sensitive. mTORC2 contains mTOR, rictor, and mLST8 and is believed to be rapamycin insensitive, although prolonged exposure to rapamycin may disrupt mTORC2 assembly.2 On entering the cell, rapamycin binds to an intracellular cofactor, the peptidyl-prolyl cis/trans-isomerase FKBP12 (FK506-binding protein). This complex then binds to and inhibits mTORC1. mTORC1 controls several pathways that regulate cell mass, and mTORC2 controls the actin cytoskeleton, thereby modulating the shape of the cell.

A number of activating and inhibitory signals converge on the TOR-dependent signaling pathways. These include a variety of growth factors, hypoxia, hormones, nutrients, and osmotic and mechanical stress.3 Growth factors act via the phosphoinositide 3-kinase pathway. For example, growth factor binding leads to the recruitment and phosphorylation of the insulin receptor substrate, followed by the recruitment of phosphoinositide 3-kinase. This interaction leads to the conversion of the membrane phospholipid phosphatidylinositol-4,5-phosphate to phosphatidylinositol-3,4,5 phosphate; a process that can be interrupted by the lipid phosphatase and tensin homologue. Phosphatidylinositol-3,4,5 phosphate then corecruits phosphoinositide-dependent kinase 1 and Akt (also known as protein kinase B), which results in Akt phosphorylation and activation. Next in this pathway, the tuberous sclerosis complex (TSC1/2) heterodimer is phosphorylated by Akt. Phosphorylation of TSC2 disrupts the TSC1/2 complex and leads to mTORC1 activation. Amino acids stimulate mTORC1 activity via inhibition of TSC1/2 or stimulation of Rheb.

The energy status of the cell is sensed through AMP-activated protein kinase in response to the cellular ATP:AMP ratio. If energy levels are low, the AMP levels increase, and AMP-activated protein kinase is activated, which activates TSC2, thereby inhibiting mTORC1. Similarly, hypoxia leads to a reduction in protein synthesis via 2 distinct mechanisms, first, via a decrease in mTORC1 activity by regulated in the development and DNA damage response 1–mediated activation of TSC1/2 and, second, by inhibition of a translation initiation factor.

Downstream effectors of TOR signaling targets include, but are not limited to, the translation regulators ribosomal S6 kinase 1 and eukaryotic initiation factor 4E binding protein 1. mTOR1 associates with ribosomal S6 kinase 1 and eukaryotic initiation factor 4E binding protein 1 via raptor and leads to phosphorylation of these modulatory proteins. Eukaryotic initiation factor 4E binding protein 1 acts as a translational repressor of eIF4E, phosphorylation of eukaryotic initiation factor 4E binding protein 1 relieves this inhibition, and translational initiation ensues. Phosphorylation of ribosomal S6 by ribosomal S6 kinase 1 leads to an increase in translation of ribosomal proteins and other translation regulators, ultimately leading to enhanced protein synthesis. In addition, phosphorylated ribosomal S6 kinase 1 mediates feedback inhibition by phosphorylating insulin receptor substrate and promoting its degradation. The net result of this interaction attenuates Akt signaling.

mTORC2 upstream regulators and functions are less well defined; however, mTORC2 is known to phosphorylate Akt and protein kinase C-α.4 One possible link is TSC1/2 complex activation of mTORC2,4 which could link the Akt-dependent feedback loop.

Cardiac hypertrophy is an abnormal increase in heart muscle mass and results either from a physiological adaptive remodeling attributed to an increased demand during prolonged exercise or pathological adaptation in response to hemodynamic stress attributed to volume or pressure overload on the heart.5 With sustained hemodynamic overload, a variety of compensatory mechanisms are activated that maintain a working hemodynamic range. With time, these mechanisms lead to end-organ damage within the ventricle, further remodeling and eventually decompensated heart failure. Given the involvement of mTOR in cell growth, it is not surprising that mTOR-related signaling has received attention as a potential mechanism in the progression toward heart failure.

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The therapeutic potential of rapamycin and its analogs is promising. Indeed, rapamycin is already used to prevent organ rejection in transplant surgery, in clinical trials for the treatment of certain types of cancer, and to prevent in-stent restenosis. An emerging and exciting potential therapeutic use for these compounds is in the treatment of hypertrophic heart disease.

In this issue, Soesanto et al present further evidence for the importance of the mTOR pathway in pathological cardiac hypertrophy. Using the spontaneously hypertensive rat model, Soesanto et al demonstrate that administration of rapamycin attenuated the inevitable cardiac hypertrophy that develops in this model. This finding is particularly striking because the underlying hypertrophic stimulus, high blood pressure, persisted and was even enhanced in the treated animals. The reason for the enhanced blood pressure is unclear. Of note, however, is that common adverse effects in humans treated with rapamycin are hyperlipidemia and thrombocytopenia and not altered blood pressure. Given the fact that rapamycin treatment worsened the hypertrophy in the spontaneously hypertensive rat, further studies are required where rapamycin is given in conjunction with anti-hypertensive agents.

Although an intriguing study, this work leaves many unanswered questions. What was the cause of weight loss in these animals? What is the optimal dosage and length of time of treatment and at what point treatment should begin? What is the involvement of cardiac fibroblasts and the effect of rapamycin on matrix reorganization? What is the effect of rapamycin once the decompensation phase ensues many months after hypertension develops? What is the interaction of mTOR in this spontaneously hypertensive rat model with the many other pathways that have been implicated in cardiac hypertrophy, such as the protein kinase C-dependent pathway and the Ras/rapidly growing fibrosarcoma oncogene/mitogen-activated protein kinase/extracellular signal-regulated protein kinase pathway? A major therapeutic benefit of disruption of the mTOR signaling pathway could be regression of pre-existing hypertrophy, as found in mice with ascending aortic constriction–induced pressure overload. Thus, finally, can rapamycin revert cardiac remodeling to a normal/near-normal morphology and, potentially, function in the clinically relevant spontaneously hypertensive rat model?

Disclosures

None.

References

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