

## Putting mammalian target of rapamycin on track

Mammalian target of rapamycin (mTOR) is the target protein of rapamycin, a bacterial metabolite in *Streptomyces hygroscopicus* primarily found in the soil sample from Easter Island in South America thirty years ago. Since mTOR was discovered in 1994, the explosive research progress in this field has greatly enhanced our understanding of the role and cellular functions through which mTOR control cellular processes, such as protein synthesis, cell structure organization, cell proliferation, and cell survival. Combined with several other proteins, mTOR constitutes two protein complexes: mTOR complex 1 or mTOR complex 2, through which mTOR exerts its biological functions. The activity of mTOR is mainly regulated through phosphorylation. Growth factors, nutrient, amino acids, and other signaling pathways can modulate the activity of mTOR by using very complicated process.

Given the important roles of mTOR in the regulation of apoptosis and autophagy, which are implicated in the development of neurodegenerative diseases, ischemic stroke, cardiovascular diseases, metabolic diseases, autoimmune diseases, and tumors, manipulating the activity of mTOR may offer a novel opportunity to fight against these disorders

The role of mTOR in the body is complicated and its activity needs to be tightly regulated to achieve benefit in a specific pathological condition. For example, the activation of mTOR is potentially involved in the tumorigenesis, tumor growth, and invasion, mTOR inhibitors have been developed as therapeutic agents for many types of cancer. However, in non-tumor diseases, such as neurodegenerative and cardiovascular diseases, whether the activation of mTOR benefit the progression of these diseases is variable and the alteration of mTOR activity might be just one of pathophysiological changes of these diseases. This is why loss of mTOR balance, over activation or loss of activity, can result in one pathophysiological process, not another. To define the signaling pathways that mTOR mediated in different pathological conditions and to develop modulators for a specific mTOR bioactivity may pave the way to the treatment of a variety of diseases.

The feedback regulation of mTOR activation maintains the balance of mTOR activity in cells to avoid over inhibition or over activation. For example, mTOR induces the phosphorylation and activation of its target protein p70S6K, which can phosphorylate insulin receptor substrate 1 (IRS1). Insulin mediates a strong activating pathway for mTORC1. However, the phosphorylation of IRS1 then negatively regulates insulin induced activation mTOR. In some scenarios with aberrant mTOR activity, the intrinsic feedback regulation may not be enough to control the activity of mTOR and the pathological conditions ensue. Excessive activation of mTOR may cause uncontrolled cell growth and proliferation, leading to atherosclerosis or tumor formation, while diminished activity of mTOR may predispose to degenerative diseases. To maintain the activity of mTOR at the physiological levels appears to be crucial.

However, it is a tough task to balance the activity in the body practically. Firstly, to modulate the activation of mTOR, the researchers are currently focusing on the development of mTOR inhibitors

only. Secondly, due to the broad nature of mTOR activities and ubiquitous expression of mTOR in the body, it is difficult to separate its beneficial effect from possible side effects when mTOR inhibitors are used to target one type of disease or an organ of the body. To avert the possible side effects, localized application of more specific mTOR modulators should be considered.

Further understanding the bioactivities of mTOR in the body will help us get insight into the roles of mTOR in the development and progression of a variety of diseases. More refined mTOR regulators will lead to their practical application in the treatment of systemic diseases.

## **Publication**

[mTOR: A Novel Therapeutic Target for Diseases of Multiple Systems.](#)

Chong ZZ

*Curr Drug Targets. 2015*