The Mammalian Target of Rapamycin: A Cell Key Modulator of Ageing

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ABSTRACT | The target of rapamycin is a key modulator of ageing in different organisms, ranging from yeast to rodents, and it is likely that this function has been conserved also in humans (mTOR, mammalian target of rapamycin). The signaling pathway of mTOR senses and integrates a variety of environmental inputs to regulate not only the organismal growth but also its homeostasis. This pathway regulates many important cellular processes that are implicated in the appearance of age-related diseases including cancer, obesity, type 2 diabetes, and neurodegeneration in late life.

INTRODUCTION

Ageing is said to be the result of different factors, which act as regulators and / or modulators and are encoded in the genetic material. The thought there might be genes responsible for ageing, did change the established dogma and since then research has focused on identifying these genes in order to delay ageing and prolong life expectancy.

Caloric restriction extends the maximum life span in some species such as yeast and mice. It can be seen that the metabolic energy investment, which is normally used in anabolic processes, is then used in somatic maintenance and catabolic processes to ensure cell survival (Holliday, 1989). For this, the cell must have a kind of sensor sensitive to the nutritional status of the cell as well as to different growth factors that may be around. One candidate which can perform this function in mammals is the target of rapamycin (TOR).

METHODS

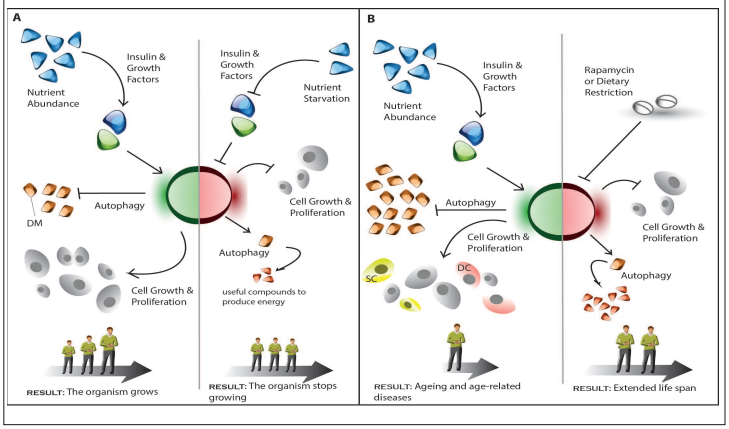
Research of relevant literature focused on three aspects was done: 1) Ageing process, 2) current knowledge about the pathway of mTOR and 3) information about the role of mTOR along life. At first a total of 20 articles were selected.

After reading each one, the important aspects were written on a summary table. Some of the first articles are not included in the final review due to they were repetitive in content. While doing more research, specific articles were found and used to adquire more knowledge about the subject. This research was carried out using information databases such as PubMed and Science Direct. Furthermore, the review is divided into three key points that match the search criteria literature: The mTORC1 signaling network, ageing modulation and the effect of rapamycin.

RESULTS

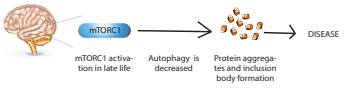
The mTORC1 molecule has two faces along life

(A) In early life it has a positive stage, in which the mammalian target of rapamycin complex 1 (mTORC1) acts as a sensor of nutritional status and its activation promotes cell growth and proliferation. (B) The second stage, or negative stage, refers to mTORC1 action in late life. In order to extend life span, mTORC1 function must be inhibited or at least decreased.



Relationship between mTORC1 and age-related diseases

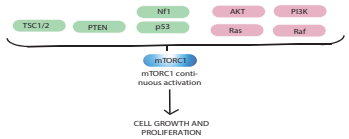
•Neurodegenerative diseases: mTORC1 is an important regulator of autophagy and its continuous activation result in the deposition of protein aggregates in cells.



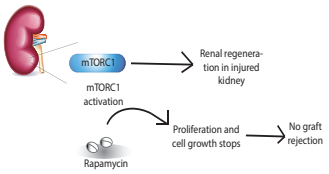
•Type 2 diabetes: S6K, one of the effectors of mTORC1, has a substrate-inactivating function of the insulin receptor (IRS1), responsible for activating the PI3K pathway in the presence of insulin and insulin-like growth factors (IGF-1). The continuous mTORC1 signaling pathway involves a long-term sensibilization to insulin by the cells (Um et al., 2004).

•Heart disease: mTORC1 complex plays a key role due to it has been seen that inhibition by rapamycin, has shown to attenuate cardiac hypertrophy (Shioi et al., 2003).

•Cancer: Mutations in the tumor supressor genes (green) encoding TSC1, TSC2, PTEN and Nf1 are some examples and all of them result in activation of mTORC1. Furthermore, loss of p53 promotes the activation of mTORC1 complex (Guertin and Sabatini, 2007). Mutations in oncogens (red) such as Akt and PI3K can stimulate cell growth and proligeration through mTORC1 activation.



•Kidney disease: mTORC1 is necessary for renal regeneration and repair and inhibition of mTORC1 by rapamycin has been shown to prolong delayed graft rejection in humans who have received a kidney transplant (Liu, 2006).



CONCLUSIONS

- mTORC1 is essential in early life for the development in many species. Inhibition of this pathway during late life extends life span.
- The mTORC1 behaviour is consistent with the predictions of the theory of antagonistic pleiotropy.
- It is far unknown the possible cross talk of mTORC1 with other ageing pathways. Another challenge is to describe the contribution of each of the effectors of mTORC1 and the different inputs that have a great influence in determining life span across species.
- Rapamycin antagonizes and/or modulates the mTORC1 effects on the organism.
- Side effects of rapamycin are the reason why this compound is not used in humans due to it increases blood cholesterol levels, cause anemia and delayed wound healing, within other alterations.

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SYNTHESIS

In 1972 rapamycin was purified and in the early two-thousands it was shown to extend life span in mice. The comprehensive study of rapamycin led to different centers to be set in an ancient mechanism that regulates ageing in different species in which the target of rapamycin (TOR) is involved.

The signaling network of the mammalian target of rapamycin (mTOR) was studied to know its role in ageing. It was seen that life expectancy was increased by removing the cell growth and proliferation, one of the effects of mTOR.

The development of drugs able to slow ageing could be used as preventive medicine to postpone common diseases of ageing. They would provide us a time of life-quality and prolong the period of vitality before the body starts to weak and die.