Published in final edited form as:
Cell Cycle. 2009 June 15; 8(12): 1820–1821.

Forever young, slim and fit:

Rapamycin to the rescue

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It is an indisputable fact that sustained dietary restriction increases lifespan of organisms, from yeast to mammals. Disputable, however, are mechanisms involved in this phenomenon. The dietary restriction-driven reduction of oxidative metabolism that leads to a decrease in production of reactive oxidants with DNA-damaging properties is one of the proposed mechanisms.[1] Whereas accumulation of oxidant-induced DNA damage progressing with age have been repeatedly demonstrated it is still debatable whether this is the only, or even the major cause of aging or lifespan limitation. The inconsistencies plaguing the reactive oxidant (ROS) theory of aging were persuasively presented in a recent review.[2] The dietary restriction-driven reduction of metabolic rate involves downregulation of the nutrient-sensor mammalian target of rapamycin (mTOR), the evolutionarily conserved serine/threonine protein kinase that is strongly implicated in stimulating cell growth.[3] TOR regulates two processes that can be accountable for the observed effect of dietary restriction on longevity. One of them is the rate of protein synthesis which is modulated by the effect of TOR on the ribosomal protein S6 kinase (S6K) and on the translation initiation factor 4E-binding protein (4E-BP).[4] Inhibition of protein synthesis e.g., through 4E-BP was shown e.g. to promote longevity of Drosophila.[5] It is therefore possible that inhibition of TOR just leads to reduction in the rate of protein synthesis and this is the mechanism of its effect prolonging longevity.[6] Inhibition of translation may shift cell metabolism to physiological state that favors maintenance and repair and this may lead to extension of lifespan.[4] However, regulation of autophagy is another process by which TOR may affect cell longevity. Autophagy can be induced by stress and also by dietary restriction. Inhibition of TOR elicits autophagy and prolongs life-span of *C. elegans*. However, because the latter effect requires the presence of DAF-16/DOXO transcription factor the induction of autophagy alone is inadequate to prolong these worms life.[3] The involvement of forkhead box class DAF-16 transcription factor in regulation of longevity was underscored in studies on Drosophila(dFOXO)[7,8] and *C. elegans* (FoxA)[9] in which an extension of lifespan was seen as a result of upregulation of this factor. It has been suggested that the FOXO and TOR pathways are antagonistic to each other and nutrients promote TOR and repress FOXO signaling, shortening lifespan.[9] It should be noted that the ROS- and TOR-associated mechanisms of aging are not mutually exclusive and interestingly, there are several points of their convergence.[2]

In this issue of *Cell Cycle*, Demidenko et al.,[10] present interesting observations that the mTOR inhibitor rapamycin attenuated the appearance of senescence of cells of several human and rodent cell lines, induced by their arrest in the cell cycle. In elegant experiments these authors demonstrate than ectopic expression of p21, p16 or treatment with n-butyrate (which elevates p21) causes senescence of these cells, with the classical features that include irreversible loss of cells ability to proliferation. Of importance, rapamycin was effective both, in delaying the appearance of senescence phenotype detected by various markers, and in preventing reproductive death, otherwise occurring as a result of prolonged arrest in the cell cycle. The data are convincing and the authors conclude on an optimistic note that “senescence can be pharmacologically suppressed.”

The in vitro induction of cell senescence by arrest in the cell cycle resembles the phenomenon observed over four decades ago and then defined as growth imbalance.[11] When progression through the cell cycle (replication) is halted and cell growth in terms of translation, transcription and protein accumulation continues the imbalance occurs and is reflected by cell enlargement, increased ratio of protein or RNA to DNA and expression of other markers currently considered characteristic of cell senescence. The function of the nutrient-sensor mTOR during the arrest is to stimulate cell growth thereby promoting the imbalance. Expectedly, growth inhibition by rapamycin whether by suppression of translation, enhancement of protein degradation by autophagy, or by both mechanisms, slows down the development of the imbalance (senescence) phenotype. Consistent with this mechanism is the earlier observation that growth stimulation during cell cycle arrest enhances senescence.[12] At organismal level the mTOR may be compared to the taste-sensor which by enhancing taste stimulates our appetite and may lead to obesity with all deleterious consequences such as type 2 diabetes. Rapamycin, in this analogy, curtails the desire to eat (feel hunger) keeping us slim and healthy. It certainly does it to individual cells.

Can we have the “magic pill” with the ability to keep us “forever young”? This is obviously too much to ask at present, but targeting mTOR appears to be the direction to follow to develop life prolonging and/or “rejuvenating” modalities.

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