Energy levels and growth are essential for organismal survival, yet are inversely related to longevity since a variety of interventions that reduce energy levels extend life span and delay aging (Kenyon, 2005). Most notable are genetic changes that reduce pro-growth pathways and also extend life span across species. In addition, caloric restriction (CR) increases life span in a wide range of species from yeast to mammals (Masoro, 2005). On the basis of these observations, a chemical intervention that diminishes cell growth pathways or restricts calories may also extend life span. Cell growth is an energy-taxing process necessary for cellular proliferation. To ensure successful cell growth, energy needs must be coordinated with energy levels and a favorable environment. Thus, RNA transcription and translation must be regulated based on energy and amino acid levels to ensure successful protein production. The target of rapamycin (TOR) pathway is key for this regulation (Tsang et al., 2007; Ma and Blenis, 2009); thus, it is a good therapeutic target for lifespan extension, but administration of TOR inhibitors may impart negative side effects, particularly if they are administered early in life at a time when growth is important for fitness. This notion is in accordance with evolutionary theories of aging which propose growth is essential for early life fitness that enables reproduction but may subsequently lead to age-related decline in health due to diminished selective pressure (Kirkwood and Austad, 2000).

Genetic or agent-induced inhibition of TOR signaling extends life span in a variety of species that include yeast, nematodes and flies (Kenyon, 2005). Even though inhibiting the TOR pathway extends life span in numerous species, such evidence has been lacking for mammals. However, a study recently published in Nature provides the long awaited evidence that rapamycin extends life span in mammals (Harrison et al., 2009). This study is a part of the National Institutes of Aging Interventions Testing Program (NIA-ITP) that evaluates a variety of agents on heterogeneous mice at three test sites. The rationale for using genetically heterogeneous mice and three test sites is to ensure diversity such that a broad spectrum of age-related maladies will be observed that are not unique to an isogenic strain or a single environment. These heterogeneous mice were generated by crossing four mouse strains such that each mouse is genetically unique. These test sites include the Jackson Laboratory, the University of Michigan and the University of Texas Health Science Center at San Antonio headed by the principal authors on the paper: Drs. David E. Harrison, Richard A. Miller and Randy Strong, respectively. In addition, Dr Z. Dave Sharp was the sponsor for rapamycin. The longer-lived rapamycin-fed mice appeared to have succumbed to the same life-threatening illnesses at the same proportion as the control mice, suggesting that rapamycin’s life-extending properties were not restricted to alleviating a subset of maladies as would be predicted by the experimental design. Interestingly, rapamycin extended life span even when chronic administration began in mice as old as 600 days (equivalent to 60 years in people). Thus, rapamycin or other mammalian TOR (mTOR) inhibitors may be efficacious for treating age-related illnesses in people without early or prolonged intervention; rapamycin may also be used as an aging prophylactic, assuming that chronic intervention is not toxic.

In order to understand the potential beneficial and toxic effects of chronic rapamycin treatment, a complete understanding of TOR signaling is necessary. The TOR signaling pathway is complicated being responsive to a wide range of stimuli and being interactive with numerous molecular mechanisms and cellular processes. There are several comprehensive reviews that highlight our current understanding of TOR signaling (Reiling and Sabatini, 2006; Tsang et al., 2007; Ma and Blenis, 2009). For its most basic function, TOR promotes cell growth by regulating protein synthesis in response to growth factors, levels of nutrients and amino acids, and various stress conditions that include energy levels, hypoxia, DNA damage, reactive oxygen species and mechanical stress (Figure 1). Thus, TOR...
ensures that protein synthesis occurs only when the conditions are right for cell growth. TOR, a protein kinase, enables protein generation by regulating translation of mRNA through phosphorylation of S6 kinase 1 (S6K1), which induces ribosome biogenesis that in turn increases protein translation (Tsang et al., 2007; Ma and Blenis, 2009). To test if rapamycin inhibited mTOR signaling at the dose given in the NIA mouse study, rapamycin-fed mice were shown to exhibit reduced levels of ribosomal protein S6 (a S6K1 substrate) phosphorylation; thus, supporting the notion that rapamycin’s life-extending properties are through inhibiting mTOR.

How does rapamycin-induced mTOR inhibition extend life span? Rapamycin may have very general properties to extend life span, since mTOR coordinates cell growth in response to cellular stress and nutrient dynamics (Reiling and Sabatini, 2006). However, mTOR inhibition may also affect specific processes that extend life span (Tsang et al., 2007). Most important may be cancer progression. Rapamycin and other mTOR inhibitors appear to be antioncogenic for both mice and humans (Garber, 2001). These mTOR inhibitors may be especially effective for tumors with enhanced mTOR function that results from manipulation of the AKT pathway, since AKT up-regulates mTOR and S6K1 activity as part of a pro-growth response. mTOR inhibition also ameliorates cardiovascular hypertrophy and restenosis. In addition, mTOR inhibition may ameliorate some neurological disorders such as Huntington’s, Alzheimer’s and Parkinson’s disease possibly through improved autophagy that removes protein aggregates. Furthermore, mTOR inhibition may reduce obesity, since rapamycin reduces adipocyte differentiation and since S6K1 deletion reduces fat accumulation in mice.

Rapamycin, like CR, seems to ameliorate many aging characteristics. Since TOR promotes cell growth by regulating translation, TOR inhibitors might mimic CR. There is evidence that CR functions by inhibiting TOR signaling. For example, CR fails to extend life span in invertebrates defective for TOR signaling (Kaeberlein et al., 2005; Kenyon, 2005). However, unlike CR, the NIA-ITP study finds that rapamycin treatment does not reduce animal size. In addition, most mouse studies find CR fails to extend life span when initiated after 550 days (Masoro, 2005). Thus, the correlation between CR and TOR inhibition remains uncertain.

Could there be potential adverse side effects? This is a critical question to answer if mTOR inhibitors will be used to treat age-related diseases (especially if they are to be used prophylactically). One concern is that mTOR inhibitors may suppress the immune system. Rapamycin and other mTOR inhibitors have been used to prevent rejection of transplanted organs, since they are powerful immunosuppressants by reducing T-cell proliferation (Tsang et al., 2007). As a result, there is a history of using mTOR inhibitors in humans. At this time, organ transplant patients tolerate rapamycin at the doses given with minimal negative side effects. One of these side effects includes impaired glucose tolerance in kidney transplant patients. mTOR inhibitors may also prove valuable for treating autoimmune disease, since it is important for the survival of monocyte-derived dendritic cells and since rapamycin decreases MHC class II molecules on murine bone marrow-derived dendritic cells. Even though these immunosuppressant activities may have medical advantages, they may also have undesirable outcomes for people without the need to suppress their immune system, thus, limiting wide-spread prophylactic treatment.

These recently published results show that rapamycin-fed mice exhibit an extended life span when compared with control mice. The rapamycin-fed cohort exhibited the same spectrum of age-related diseases as the control cohort; thus, rapamycin seems to have a broad impact on ameliorating the aging process as opposed to resolving specific

Figure 1 The mTOR pathway regulates cell growth by enabling protein translation in response to signals. This pathway is important for cell mass and cell proliferation that are likely beneficial for early life fitness but perhaps at the expense of longevity. Cancer is one potential age-related disease that may be ameliorated by mTOR inhibition. GH, growth hormone; IGF-1, insulin-like growth factor-1.
life-threatening illness endemic to these genetically heterogeneous mice used by the NIA-ITP study. This life-extending property was realized even when rapamycin treatment was initiated late in life. On the basis of these results, rapamycin is a strong candidate for attenuating the aging process, even when first administered to individuals at advanced age. This could be a boon for extending health span. Still major questions must be addressed to understand just how mTOR inhibition ameliorates aging. Since mTOR has many functions, it might be desirable to target downstream proteins with a more specific action. Also it will be important to fully realize negative side effects to determine if rapamycin or other mTOR inhibitors should be administered as an aging prophylactic or as a treatment for specific age-related illnesses.

References