

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Aging — Lost in Translation?

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Extending the span of a healthy life has fascinated humanity ever since Gilgamesh failed to prevent his dying friend Enkidu from descending into the horrific netherworld, as described in the epic poem from ancient Iraq. Recent discoveries in the research on aging suggest that modern science is more adept at keeping aging at bay — at least temporarily and thus far only in worms, flies, and rodents¹ — than at halting it completely. A recent study by Selman and colleagues² has identified ribosomal protein S6 kinase 1 (S6K1) as a molecular player in the aging game. These investigators observed that deletion of the *S6k1* gene leads to an increased life span and resistance to age-related diseases in mice. As compared with their wild-type littermates, *S6k1*-deficient mice were protected against age-related declines in motor, bone, and immune function (but not against cancer) and had elevated sensitivity to insulin in old age.

Conserved genetic pathways modulate the life span in organisms such as yeast, worms, flies, and mice. Most prominent are the insulin and insulin-like growth factor 1 signaling (IIS) pathway and the target of rapamycin (now known as sirolimus) (TOR) pathway (Fig. 1). Because inhibition of these pathways has emerged as one of the most robust ways of increasing longevity across species, the identification of their downstream targets is critical in understanding the mechanisms that underlie life-span regulation.¹

How does the deletion of S6K1 extend the life span? S6K1 enhances messenger RNA translation during periods of high growth. It is a downstream target of the TOR pathway that acts to integrate nutrient and insulin signals. Worms and mice that lack S6K1 grow more slowly than their wild-type counterparts, and their body size is reduced.² How does this tie in with aging? Perhaps the reduction in protein synthesis itself may extend the life span, possibly by activating cellular defense systems against a variety of damaging agents. Consistent with this hypothesis is the idea that ag-

ing may be caused by an accumulation of somatic damage. Moreover, increased stress responses accompany life extension (in animal models) brought about by the inhibition of IIS or TOR activity.¹ Dampening growth could lead to a shift toward somatic maintenance.

An alternative but not mutually exclusive hypothesis — one that is favored by Selman et al. — is that the life extension brought about by abrogating S6K1 activity is effected through altered energy metabolism. This is the mechanism believed to underlie the life-extending effect of dietary restriction in multiple species. The similarity between the gene-expression profile of the liver in *S6k1*^{-/-} mice and that in mice subjected to dietary restriction is consistent with this hypothesis. Enhanced activity of AMP kinase (AMPK) in the hepatocyte is another “common denominator” for *S6k1*^{-/-} mice and mice subjected to dietary restriction. AMPK is a sensor of energy status and a downstream target of the TOR pathway (Fig. 1). Selman et al. also observed activation of AMPK in a long-lived strain of *Caenorhabditis elegans* deficient in the *C. elegans* *S6k1* orthologue. Using this mutant roundworm, the researchers went on to obtain evidence of AMPK activation (as opposed to modified translation) as the pivotal event that mediates the effect of *S6k1* on longevity. In this regard, it is noteworthy that metformin augments AMPK activation and extends the life of female mice.³ Regardless of the downstream mechanism, the effect of ablating *S6k1* on the longevity of female mice is in part consistent with the effect of administering sirolimus in older mice: the life span is extended in each case, although the effect of sirolimus is observed in both sexes.⁴

The current wave of experiments that reproducibly show an extension of the life span in mice with experimental modulation of conserved pathways has garnered attention. Conservation of the TOR pathway from plants to humans, as well as the fact that drugs targeting these pathways are already in clinical use, bodes well for the possibil-

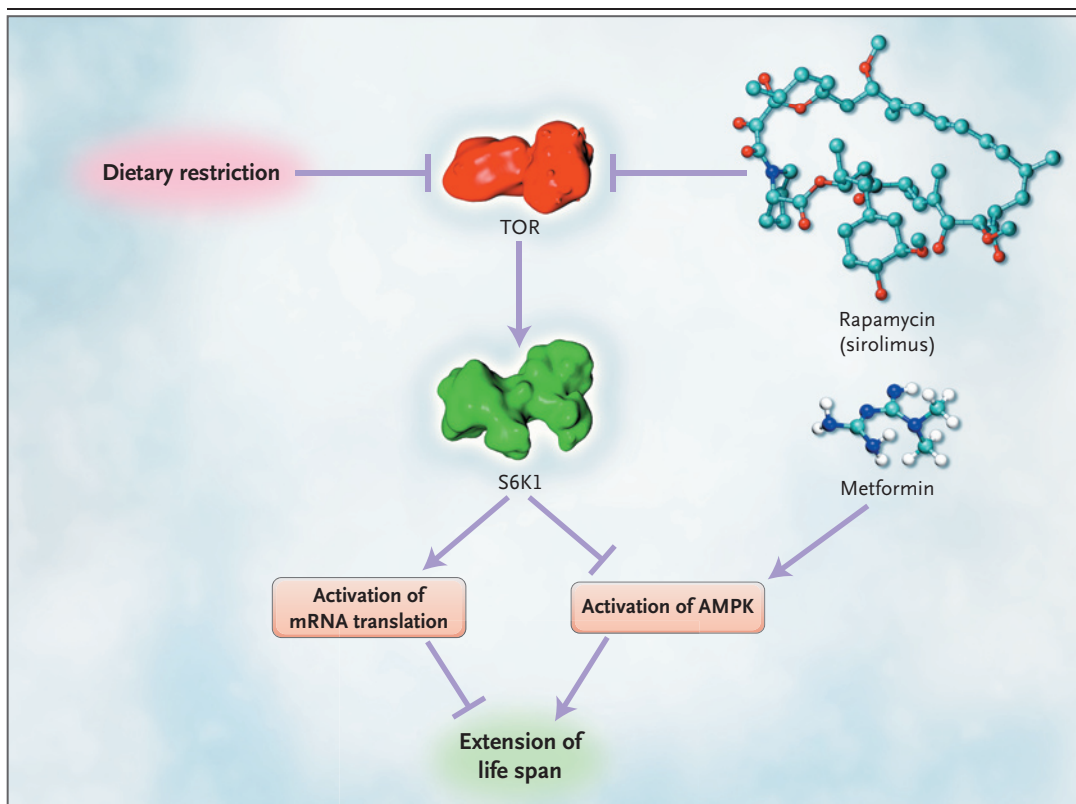


Figure 1. Longevity Pathways.

The conserved target of rapamycin (now known as sirolimus) (TOR) pathway is emerging as a mediator of life span through dietary restriction in multiple species. Inhibiting S6 kinase (S6K) (a downstream target of TOR) has been shown to extend the life span of yeast, flies, worms, and now mice (as described in the recent report by Selman et al.²). The activation of messenger RNA (mRNA) translation and the activation of AMP kinase (AMPK) occur downstream of S6K1 activation and are believed to be critical for life-span–extension phenotypes. Drugs that target the TOR pathway, such as sirolimus and metformin, have been shown to extend the life span of mice.

ity of pharmacologic intervention in aging. That said, many questions must be addressed before one can envisage a clinical trial of such an intervention. Not least among them is the question of long-term effects of drugs that target the TOR pathway — whether these drugs are currently in use (e.g., sirolimus or metformin) or eventually to be developed. There is also the question of the extent to which the mouse model, on a molecular level, mimics the aging process in humans. The fact that cancer developed in the *S6k1*-deficient mice at the same rate as it did in the control mice is in contrast to the therapeutic effect of sirolimus on cancer in humans and points to differences in the species' molecular mechanisms. That *S6k1* deficiency has a sex-specific effect is also curious. What is its basis?

These questions notwithstanding, further work

in this area is warranted. Extension of a healthful life span would probably lead to a reduction in health care costs by providing protection against diseases for which aging is a risk factor.

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