These remarkable observations suggest that the remaining obstacles to fusion energy gain are now surmountable. These results also herald a new era in physics, that of high-energy-density science. It is truly fitting that this 21st-century frontier (*9*) can trace some of its origins back to the humble radiation cavity of the 19th century.

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CELL BIOLOGY

Burn Out or Fade Away?

A protein whose expression is turned on by stress delays the onset of age-related pathologies.

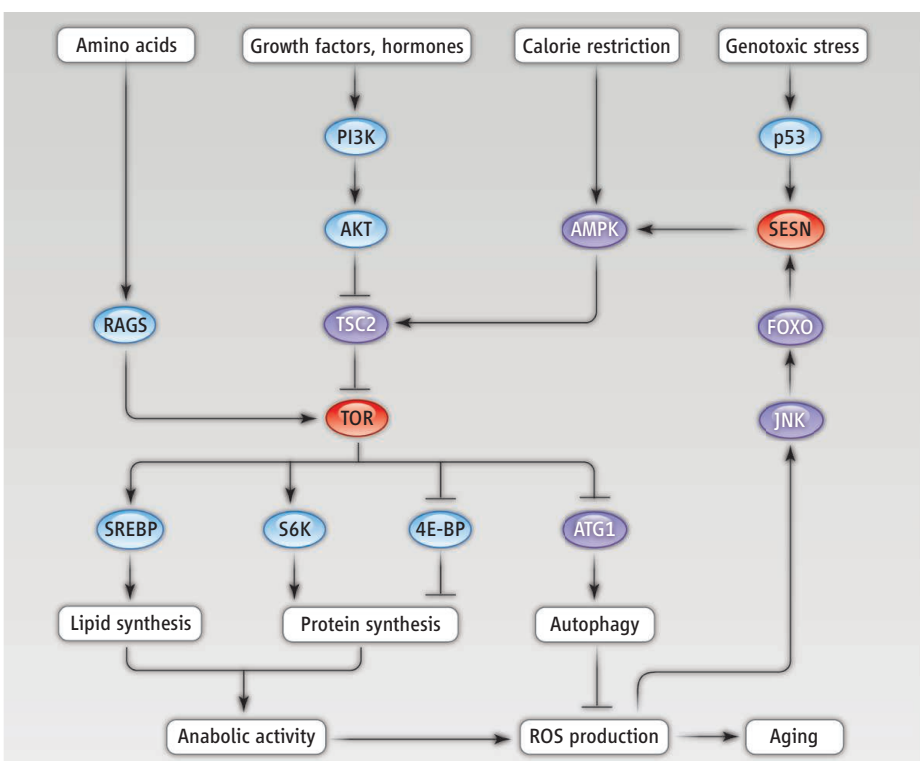
Ivan Topisirovic[1,2] and Nahum Sonenberg[1,2]

The target of rapamycin (TOR) kinase plays an evolutionarily conserved role, from yeast to human, in controlling metabolic activity in response to intracellular cues and extracellular stimuli (*1*). It stimulates anabolic processes that engender cell growth and proliferation by increasing protein synthesis and lipogenesis. TOR also inhibits autophagy, which is a major catabolic process. Persistent activation of TOR causes an imbalance between anabolic and catabolic processes, resulting in the accumulation of damaging reactive oxygen species (ROS), which favors the development of age-related disorders. Indeed, the inhibition of TOR by the drug rapamycin increases organism life span and reduces the incidence of age-related pathologies (*2*). On page 1223 of this issue, Lee *et al*. report that sestrin proteins prevent excessive TOR activation and delay the onset of age-related pathologies through a negative-feedback mechanism (*3*).

Sestrins are a family of highly conserved cytoplasmic proteins that contain a redox-active domain, and whose expression is induced by stress (*4*). There are three sestrins in mammals, but only one in the fly *Drosophila melanogaster*, making the latter an optimal model system for studying the physiological functions of sestrins. Activation of *Drosophila* TOR (dTOR) increases transcription of the gene encoding *Drosophila* sestrin (dSesn) through a signaling pathway that is not fully understood, but involves the enzyme c-Jun N-terminal kinase (JNK) and the forkhead box O (FOXO) transcription factor. In turn, increased abundance of dSesn inhibits dTOR signaling by activating adenosine monophosphate–activated protein kinase (AMPK) and tuberous sclerosis complex 2 (TSC2) proteins (see the figure).

Lee *et al*. report that the loss of dSesn results in chronic activation of dTOR, leading to the induction of anabolic processes and inhibition of autophagic degradation of dysfunctional mitochondria. This causes ROS accumulation and development of a variety of age-related pathologies in *Drosophila*, including muscle degeneration, cardiac arrhythmia, and lipid accumulation. Deletion of the gene encoding dSesn resulted in a 50% decrease in AMPK activity and a 50% increase in dTOR activity. Strikingly, feeding dSesn-deficient flies with pharmacological activators of AMPK (e.g., metformin), or the TOR inhibitor rapamycin, prevented the age-related phenotypes.

How does dSesn antagonize premature aging in flies? It has been proposed that aging is caused by the accumulation of stochastic molecular damage, which is mainly induced by mitochondrial ROS production (*5*). Treatment of flies lacking dSesn with the natural antioxidant vitamin E ameliorated most of the age-related pathologies, suggesting that they depend on ROS accumulation, and that the dSesn-induced negative feedback on TOR activity prevents ROS buildup. Although sestrins can eliminate ROS production in vitro (*4*), Lee *et al*. demonstrate that the intrinsic redox activity of dSesn is not critical for sup-



Metabolic network. Sestrins control the effects of TOR, in a complex network of pathways that regulate anabolism, catabolism, and the development of age-related pathologies. ATG1, authphagy-specific gene 1; P13K, phosphatidylinositol 3-kinase; RAGS, Ras-related GTP-binding protein; SREBP, sterol regulatory element-binding protein.

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pressing the observed age-related phenotypes, which are almost exclusively mediated through dSesn-AMPK-TSC2 signaling pathway that inhibits dTOR. This is consistent with the previously established role for mammalian sestrins 1 and 2 in blocking mammalian TOR (mTOR) signaling (and aging phenotypes) in reponse to genotoxic stress through a pathway that involves the tumor suppressor protein p53 and the same Sesn-AMPK-TSC2 cascade (*6*).

Caloric restriction blunts aging and delays the onset of age-related pathologies in many organisms (*7*). The TOR pathway has emerged as a prime candidate for mediating these effects. Lee *et al*. underscore TOR's role in aging by uncovering a feedback mechanism that keeps dTOR activity in check, thereby maintaining the integrity of mitochondria, a major ROS source. Several targets of TOR have been implicated in affecting mitochondrial function. For example, in response to caloric restriction in *Drosophila*, the eIF4E-binding protein (d4E-BP) can prolong life span by promoting the translation of messenger RNAs (mRNAs) that encode components of the mitochondrial electron transport chain (thus boosting mitochondrial functional capacity) (*8*). In mammalian cells, a complex of proteins containing mTOR (mTORC1) stimulates mitochondrial biogenesis and oxidative metabolism by promoting the association of two proteins, peroxisome proliferator-activated receptor–γ coactivator 1–α and yin-yang 1 (*9*). Thus, sestrins would presumably keep this association in check.

In addition to the effect of sestrins on mitochondria, TOR also controls two cellular processes that affect mitochondrial function and integrity and are intimately linked to aging: protein synthesis (mRNA translation) and autophagy. Inhibition of autophagy abates life-span extension by caloric restriction in the nematode *Caenorhabditis elegans* (*10*) and decreases longevity in yeast (*11*). TOR stimulates mRNA translation by inhibiting 4E-BPs and activating S6 kinases (S6K) (*1*). Reduced S6K activity extends life span in the nematode (*12*), the fruit fly *Drosophila melanogaster* (*13*), and mice (*14*). Depletion of an eIF4E isoform (eIF4E is a protein inhibited by 4E-BPs) extends life span in *C. elegans* (*15*), and loss of d4E-BP reduces longevity in flies (*8*).

Lee *et al*. demonstrate that sestrins and TOR act as central nodes of the complex regulatory network that controls aging by linking genotoxic and oxidative stress with the control of metabolic activity. Although it remains to be determined whether this pathway is evolutionarily conserved, recent findings that the FOXO transcription factor increases Sesn3 abundance in mammalian cells (*16*) implies that a similar mechanism functions in mammals. Accordingly, aberrant mTOR activity underlies several human age-related disorders, including diabetes, obesity, heart disease, muscle degeneration, and cancer. As sestrins appear to amend the age-related effects of excessive TOR signaling, developing molecular mimics of sestrin could open new therapeutic avenues to target age-related pathologies.

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CLIMATE CHANGE

How Stable Is the Methane Cycle?

Ship and satellite data help to elucidate how methane emissions from sources such as wetlands may change in a warming climate.

Martin Heimann

Methane is, after water vapor and carbon dioxide, the third most important greenhouse gas in the atmosphere. Its concentration in the atmosphere has more than doubled since preindustrial times. Human energy production and use, landfills and waste, cattle raising, rice agriculture, and biomass burning are considered responsible for this increase (*1*). However, ~40% of current global methane sources are natural. Most natural emissions come from anaerobic decomposition of organic carbon in wetlands, with poorly known smaller contributions from the ocean, termites, wild animals, wildfires, and geological sources. Two observational studies now shed light on how these natural sources are changing in today's changing climate (*2*, *3*).

Ice core studies have shown that the natural methane sources must have changed substantially during the glacial cycles. How stable are they under global warming? Wetlands and permafrost soils, including the sub-sea permafrost under the Arctic Ocean, contain at least twice the amount of carbon that is currently in the atmosphere as carbon dioxide. Release of a sizable fraction of this carbon as carbon dioxide and/or methane would lead to warmer atmospheric temperatures, causing yet more methane to be released. It would thus create a positive feedback loop that amplifies global warming. However, observational evidence for such release on regional and global scales has been elusive.

On page 1246 of this issue, Shakhova *et al*. (*2*) report convincing evidence of methane outgassing from the Arctic continental shelf off northeastern Siberia (Laptev and East Siberian Sea), based on painstaking repeated surveys using Russian ice breakers between 2003 and 2008. In this region, the relatively shallow continental shelf extends up to 1000 km north of the coastline. The seabed consists of relict permafrost from the last glaciation (*4*), when sea levels were considerably lower than today. The permafrost layer contains substantial amounts of organic carbon and also traps methane seeping up from underneath. In the permafrost, the methane forms relatively stable methane hydrates, but warming of the seawater or a decrease in pressure by a reduction in sea level will destabilize the hydrates, releasing methane into the ocean waters (*5*).

Shakhova *et al*. now document large areas with surface waters that are highly supersaturated in methane; in some places, methane concentrations are more than 100 times as high as expected in equilibrium with the ambient atmosphere. Based on their extensive data set, the authors estimate an annual outgassing to the atmosphere of ~8×10^{12} grams of carbon (8 Tg C) as methane from the East Siberian Arctic Shelf waters. Consistent with this, concurrent atmospheric concentration measurements on the ship and with a helicopter document methane levels up to four times as high as recorded elsewhere in the Arctic basin.

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