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Rapamycin Paradox Resolved

Katherine J. Hughes¹ and Brian K. Kennedy²

The goal of aging research is to extend healthspan, the period of life free of chronic disease. It has been known for decades that calorie restriction—a regime of reduced calorie consumption without malnutrition—extends the life span of mammals (1) and other model organisms. A primary effect of calorie restriction is to improve glucose homeostasis, which may underlie increased longevity. In the last few years, the focus has turned from characterizing genes and molecular mechanisms that drive aging (2) to small-molecule interventions, and in 2009, rapamycin was the first drug reported to extend the life span of mice—roughly 15% in females and 10% in males (3). Rapamycin has been proposed as a calorie restriction mimetic and, at least in mouse models, it is proving beneficial in preventing the onset of many age-related diseases (4). However, there is a fly in the ointment regarding its use (or that of rapalog derivatives) to extend healthspan. Rapamycin causes glucose intolerance and insulin resistance in mice and humans (5), effects that could outweigh longevity benefits. On page 1638 of this issue, Lamming et al. (6) identify a mechanism by which the drug confers insulin resistance, and show that rapamycin’s effect on glucose homeostasis and longevity can be uncoupled.

Discovered more than 40 years ago, rapamycin is now used clinically for a range of conditions, including cancer. It is a non-competitive and specific inhibitor of the nutrient-responsive mammalian target of rapamycin (mTOR) kinase (7). The mTOR protein is found in two protein complexes: mTORC1, which regulates pathways involved in mRNA translation, autophagy, and other cellular processes; and mTORC2, which regulates the cytoskeleton and insulin signaling. mTORC1 was originally identified as rapamycin sensitive, whereas mTORC2 was thought to be rapamycin insensitive. However, chronic rapamycin treatment inhibits mTORC2 in vitro and in mice (8). The longevity effects of rapamycin are thought to be mediated by blocking mTORC1 activity given many observations: the specificity of rapamycin; the extended life span of female mice lacking S6 kinase 1 (S6K1), a target of mTORC1 (9); and the role of mTORC1 in longevity in invertebrates (3, 10, 11). But interestingly, adult worms with reduced expression of the mTORC2 component Rictor live longer (12). Given this finding, the issue of which mTOR complex is linked to healthspan in mice has not been adequately resolved.

Using genetic mouse models to ablate mTORC1 or mTORC2 activity (by deleting Raptor for mTORC1 and Rictor for mTORC2) in zygote mice—animals expressing reduced amounts of mTOR and MLST8 (mTOR−−/−− mlst8−−/−−) because mice completely lacking mTOR, Raptor, or Rictor are inviable (13). Both proteins are present in mTOR1 and mTOR2 complexes. However, Lamming et al. observed that tissues from mtor−−/−− mlst8−−/−− mice had more pronounced defects in mTORC1 function. The authors speculate that these divergent effects on the two mTOR complexes may derive from preferential recruitment of the two proteins to mTORC2 when protein amounts are limiting. Similar to S6K1-deficient mice or mice treated with rapamycin, female mtor−−/−− mlst8−−/−− are long-lived. These findings strongly suggest that reduced mTORC1 function enhances longevity in mice.

Other mouse models of reduced mTORC1 function, such as Raptor−−/−− or mtor−−/−− Raptor−−/−−, were not long-lived, suggesting that the right amount of mTORC1 inhibition, or perhaps...
the right balance of mTORC1 to mTORC2 activity, must be attained for enhanced longevity. Also, the findings do not rule out a role for mTORC2 in aging. What Lamming et al. do achieve is a clear dissociation of impaired glucose homeostasis and enhanced longevity. Indeed, mtor<sup>-/-</sup> mice have normal glucose homeostasis and delayed aging derives from some other consequence(s) of mTORC1 inhibition. Considerable effort is being directed to identify new and better mTOR inhibitors. The results from Lamming et al. lead to some early predictions about the ability of such compounds to modulate longevity. For instance, high-sensitivity inhibitors that target the active site of mTOR, such as PP242 and Torin, have recently been developed (14). Although blocking both mTORC1 and mTORC2 function may be ideal for oncology and other conditions, these inhibitors may be less effective than rapamycin for increasing longevity and preventing age-associated diseases. The study by Lamming et al. may point the way toward such therapeutic approaches.

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COMPUTER SCIENCE

How Smart Is Your Home?

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Individuals spend most of their time in their home or workplace; for many, these places are their sanctuaries. Over the course of the 20th century, technological advances have helped to enhance the comfort and shelter provided by our homes. Insights gained from capturing and modeling behavior in these places may be useful in making our environments more intelligent and responsive to our needs. Recent advances are bringing such “ambient intelligence” in the home closer to reality.

Since the miniaturization of microprocessors, computing power has been embedded in familiar objects such as home appliances and mobile devices; it is gradually pervading almost every level of society. Ambient intelligence extends the notion of computing to provide customized, automated support that is so gracefully integrated with our lives that it “disappears” (1). In the home, the idea is that computer software playing the role of an intelligent agent perceives the state of the physical environment and residents using sensors, reasons about this state using artificial intelligence techniques, and then takes actions to achieve specified goals, such as maximizing comfort of the residents, minimizing the consumption of resources, and maintaining the health and safety of the home and residents.

During perception, sensors embedded in the home generate readings while residents perform their daily routines (see the figure). The sensor readings are collected by a computer network and stored in a database that the intelligent agent uses to generate useful knowledge such as patterns, predictions, and trends. On the basis of this information, the intelligent agent selects an action and stores this selection in the database. The action is transmitted through the network to the physical components that execute the command. The action changes the state of the environment, triggering a new perception/action cycle.

Filling a home with sensors and controlling devices by a computer is not only possible, but it is simple and commonly found in homes today. Sensors are available off-the-shelf that localize movement in the home, provide readings for ambient light and temperature levels, and monitor usage of doors, phones, water, and appliances. Tiny, inexpensive sensors can be attached to objects to not only register their presence but also record histories of recent interactions. Such smart objects can harvest their own energy, and recent standards facilitate vendor-independent plug-and-play sensor design and modeling (2).

Proliferation of sensors in the home results in large amounts of raw data that must be analyzed to extract relevant information. Most smart-home data from environmental sensors such as infrared motion sensors and magnetic door sensors can be processed with a small computer. Once data are gathered from wearable sensors and smart phones (largely accelerometers and gyroscopes; sometimes adding camera, microphone, and physiological data), the amount of data may get too large to handle on a single computer, and cloud computing is appropriate. Cloud computing is also useful if data are collected for an entire community of smart homes to analyze community-wide trends and behaviors.

Currently, most users write rules by hand to interpret sensor data and to control devices. For example, home owners installing home automation equipment must write their own rules for when their lights turn on and off. Artificial intelligence (AI) plays a pivotal role in automating this process. AI and data-mining technologies seek useful information on resident behavior and the state of the home. Computer algorithms have been designed to predict and identify activities performed in the home and to recognize emotions, body mannerisms, and gestures (3, 4). These capabilities, as well as the abilities to recognize activities, identify trends, make assessments, and take action, are becoming more available and robust, but are not commonly found in actual homes.

The goal of much current research in ambient intelligence is to enable devices to interact with their peers and the networking infrastructure without explicit human control. The intelligent home must also be imbued with an awareness of the resident context (location, preferences, activities), physical context (lighting, temperature, house design), and time context (hour of day, day of week, season, year). Providing this type of context-aware reasoning makes it possible to design environments that provide, for example, customized lighting and temperature settings based on learned resident preferences; information retrieval and

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Technical advances are bringing intelligent homes that respond to residents’ needs and wishes within reach.

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