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Guest Editorial

Intermittent mTOR Inhibition Reverses Kidney Aging in Old Rats

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Summary

Short-term administration of the rapamycin analogue RAD001 (everolimus), already approved for clinical use for different human disorders, has been found to counter-regulate age-related transcriptomic changes and kidney pathology in rats. The study offers a step forward in establishing a safer rapalog dosing regimen for the treatment of age-related diseases.

The quest for therapies that slow aging and increase healthy life span is rapidly expanding, with a few compounds showing early promise in reaching this goal. The discovery that rapamycin, an inhibitor of mechanistic target of rapamycin (mTOR), can extend the life span of several model organisms, including yeasts, worms, flies, and mice, has elicited major interest in aging research by providing a molecular target for a potential pharmacological antiaging intervention in humans. Rapamycin-based therapy has shown benefits for patients in a range of clinical applications by acting as an immunosuppressant to prevent rejection of kidney and liver transplants, and in the treatment of autoimmune disorders, certain types of cancers and lymphangioleiomyomatosis (a rare, progressive lung disease). However, the use of rapamycin as an antiaging molecule is unlikely to be approved for healthy individuals due to considerable side effects related to its ability to suppress the immune system (1). Moreover, rapamycin has been found to promote glucose intolerance, insulin resistance, and hyperlipidemia in mice and rats (2,3), and predispose transplant patients to new-onset diabetes mellitus (4). A number of other adverse events associated with rapamycin-based therapy has also been reported (5). mTOR is a protein serine/threonine kinase that is found in two distinct protein complexes, mTOR complex 1 (mTORC1) and mTORC2. It is now accepted that the beneficial effects of rapamycin are largely mediated by the inhibition of mTORC1, which is acutely sensitive to rapamycin, while many of the negative side effects of the drug stem from the inhibition of mTORC2 after long-term exposure to rapamycin in a cell- and tissue-specific manner. Several derivatives of rapamycin (known as rapalogs) with improved pharmacokinetics have been developed (6); some of these have been shown to have reduced metabolic side effects in mice, likely due to decreased disruption of mTORC2 due to their pharmacokinetics (7). Different dosing schedules have been tested that minimize side effects while providing a safer strategy that may enable the translation of rapamycin-based therapies to the clinic (7).

The development of a pro-longevity drug is hampered by difficulties in defining physiological parameters that are true indicators of aging and by the amount of time required to evaluate the drugs's ability to extend human life. One of the approaches used to overcome the limitation of lengthy clinical trials has been to test whether short-time intervention with putative pro-longevity drugs can slow down phenotypic changes associated with the aging process. A recent clinical trial demonstrated that treatment for 6 weeks with the rapamycin analogue RAD001 (everolimus) ameliorated immuno-senescence and improved the response of elderly humans to influenza vaccination (8).

In this issue, Shavlakadze et al. (9) evaluated the outcome of an intermittent administration of RAD001, initiated at 22.5 months of age in rats (roughly equivalent to a 60-year-old person), at doses and treatment duration similar to those previously used in humans (8). The authors compared the transcriptional profiles in liver, skeletal muscle, and kidney between young and old rats on RAD001, and found a striking (37%) reversal in the expression of age-regulated genes in the kidney, many of which linked to inflammation and fibrosis, together with a reduction in the severity of nephropathy lesions in aged rats (9). Under these conditions, the expression of age-regulated genes in liver and gastrocnemius of RAD001-treated rats was minimally altered despite lower activating phosphorylation of two surrogate markers of mTORC1 activity. Additional studies are needed to establish the presence of alternative RAD001-dependent mechanisms in the control of the liver and gastrocnemius transcriptome. RAD001 (at a dose of 1 mg/kg once a week for 6 weeks) was well-tolerated by old rats, with no significant changes in fasting blood glucose and body weight trajectories

compared to controls. The authors attribute the safe metabolic profile to a "fairly selective effect" of this low-dose and short-term treatment paradigm on gene expression in the kidney, a tissue in which mTORC2 signaling is strongly resistant to rapamycin (10). These findings reinforce the idea that selective mTORC1 inhibition might be a safe and effective strategy to counteract age-related kidney pathology.

How does inhibition of TOR activity influence aging? The authors report the role of c-Myc as a possible target of mTORC1 and point at a mechanism whereby RAD001 may suppress the age-dependent increase in the expression of c-Myc downstream target genes. The c-Myc proto-oncogene functions as a transcriptional regulator modulated by the mTORC1-CREB2 pathway. A recent study reports on the fact that Myc haploinsufficiency (Myc+/–) confers extended life span and health span in mice resulting from changes in multiple cellular processes such as those implicated in nutrient and energy sensing pathways (eg, AKT, TOR, and S6K) (11). It is unclear whether administration of RAD001 will counteract age-related kidney pathology in this longevity mouse model. In this issue, Shavlakadze and coworkers further demonstrate in HEK293 cells that RAD001 may affect c-Myc protein turnover by promoting its degradation; however, the fact that c-Myc protein was below detectable levels in the kidney puts into question the relevance of this observation in vivo. Nonetheless, this study helps define a therapeutic window in which rapalogs confer beneficial antiaging effects and guard against age-related diseases through mTORC1 inhibition while minimizing mTORC2-related side effects. Are rapalogues suitable antiaging drugs for people? Further research is needed to determine whether intermittent mTOR inhibition will promote human longevity and protect against age-related diseases.

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Conflict of Interest

None reported.

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