Rapamycin enhances lifespan: At last, an advantage for transplant recipients?*

Edward K. Geissler

Department of Surgery, University Hospital Regensburg, University of Regensburg, Franz-Josef-Strauss-Allee 11, Regensburg 93053, Germany

Correspondence and offprint requests to: Edward K. Geissler; E-mail: edward.geissler@klinik.uni-regensburg.de


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Summary of key findings of the article

A recently published article by Harrison and colleagues [1] confirms in mammals what has been known for several years in yeast, fruitflies and nematodes: the TOR inhibitor rapamycin extends lifespan. These extraordinary experiments were performed through The National Institute on Aging and Interventions Testing Program, which uses rigorous testing methods in genetically heterogeneous mice at three separate test sites to determine if ageing and lifespan are increased by specific agents. Remarkably, continuous rapamycin treatment extended not only the median lifespan in mice, but maximal lifespan was also significantly increased. Extended median and maximal lifespan were clearly evident at all three test sites in both female and male mice, and were generally on the order of a 10% or better improvement. Moreover, enhanced lifespan was demonstrated where feeding of rapamycin was initiated at either 270 or 600 days of age, suggesting that mid-life or late intervention has a positive effect, with no evidence for altered
disease patterns. Compared to other interventions aimed at increasing life expectancy in rodents, the rapamycin effect is impressively strong and worthy of further exploration.

Review of the field

For some time now it has been recognized that lifespan can be increased by reducing nutrient intake without causing malnutrition (‘dietary restriction’). Dietary restriction is thought to increase lifespan [2] via molecular pathways sensing nutrient status that couple nutrient availability to cellular metabolism. These pathways therefore serve to appropriately determine the need for cell growth versus somatic maintenance under various nutrient conditions. Most recently, a high-profile study of dietary restriction in rhesus monkeys has shown positive lifespan effects [3], although the significance of caloric restriction in primates remains highly controversial. Through integration of nutrient status with growth factor insulin/IGF signalling, TOR (mTOR in mammals) has emerged as a critical molecular control point that, when inactivated by drugs such as rapamycin or genetic interventions, mimics the low-intensity stress of dietary restriction. The effects of TOR inhibition during embryonic development result in retarded cell growth (e.g. in Drosophila: small, but otherwise normal, flies), but in adulthood appears to be more important for controlling processes like ageing.

There are a number of observations that support the contention that TOR is a vital link to lifespan. Kaeberlein et al. [4] have shown that a large-scale screen of 564 single-gene-deletion strains of yeast identified 10 genes that increase ‘replicative’ lifespan, which refers to the number of daughter cells yielded by a mother cell before senescence. Astonishingly, six of these genes were related to TOR signalling. In this study, lifespan could be increased via TOR-related gene mutations, but not by caloric restriction without TOR-related gene deletion, hinting that caloric restriction is directly linked to the TOR pathway. The TOR pathway in yeast has also been identified as important for increasing the time cells remain viable in a stationary phase (‘chronological’ life span), which reflects more upon ageing in post-mitotic tissues [5].

Studies conducted in fruitflies (Drosophila) add compelling evidence that TOR inhibition can significantly extend normal lifespan. To this effect, overexpression of the natural TOR pathway inhibitory signalling molecules TSC1 and TSC2, or dominant-negative forms of TOR itself, cause an extension of lifespan in Drosophila [6]. One explanation for this effect is that increased TOR signalling decreases the ability of an organism to inhibit stress associated with disease progression and ageing [7]. In C. elegans (nematodes), it has been shown that mutations in a key regulated-associated protein of TOR (raptor) extend the lifespan of adult organisms [8]; also, autophagy elicited by TOR inhibition enhances lifespan induced by dietary restriction [9]. Therefore, even metazoans demonstrate a convincing link between TOR signalling and lifespan (Figure 1).

Before the paper by Harrison et al. [1], there were hints in mammals that lifespan could be increased by mTOR inhibition. One of the most interesting findings concerns Snell and Ames dwarf mice, which have defects in (Pit1) [10] and Prop1 [11], respectively, linked to the TOR pathway [12]. These mice not only live longer than wild-type mice [13], they are also resistant to chemically induced cancer [14], raising the intriguing question of whether rapamycin extends lifespan or simply prevents death. We and others have published extensively on the anticancer effects of rapamycin [15,16], giving support for the latter observation. What is equally intriguing is that Ames dwarf mice consume even more food than normal-sized wild-type mice [17], suggesting a link to dietary restriction. This observation is substantiated by a recent report in humans that renal transplant recipients on rapamycin show a reduced body weight [18], although changes in body weight were not observed in the Harrison et al. mouse study [1].

Notwithstanding these observations, humans live much longer than mice, and therefore, must possess mechanisms that counteract ageing; these mechanisms likely complicate mTOR’s role in extending lifespan. Moreover, it is unreasonable to consider mTOR only a detriment to survival, since it has been naturally selected for regulating activities necessary for processes in long-lived animals, such as immune competence and tissue remodelling/angiogenesis/repair. Whether mTOR inhibition will lead to a longer lifespan in humans, therefore, remains unclear.

What is in it for the practising nephrologist

What about mTOR inhibitor use in transplantation? After reading the Harrison et al. article and considering the current literature, we must ask the obvious question: can transplant recipients actually expect some sort of a longevity advantage by taking rapamycin? This is a difficult question to answer, especially in the complicated context of organ transplantation. Unlike the mouse experiments where relatively short-lived animals were held under
specific pathogen-free conditions and did not enter the study with known organ failure, human renal transplant recipients living in an environment with pathogens are affected over a much longer period of time by potentially life-limiting underlying diseases, and face the likelihood that their transplant will eventually fail due to chronic rejection. Furthermore, side effects associated with rapamycin use are considerable, as are side effects with other immunosuppressants, and all too often lead to discontinued use. The balance of all these factors makes it impossible to foretell whether rapamycin treatment can provide a longevity benefit in this patient population, and furthermore, it is difficult to see how clinical trials could be designed to provide such evidence.

Nonetheless, perhaps we can look for some instruction from the work of Harrison et al. [1]. If we believe the concept that inhibiting mTOR can promote longevity, is it possible to extract this positive attribute for an overall benefit to transplant recipients? Balancing the ‘positives’ (e.g. anticancer effects, positive stress factors) and the ‘negatives’ (e.g. lipidaemia, proteinuria) may be most influenced by considering dosing. Interestingly, a continuous rapamycin dosing was applied in the Harrison et al. [1] experiments, which is very different from the bolus dosing used in transplant recipients. We have published a similar positive experience with continuous rapamycin dosing in food [19]. Therefore, perhaps, to get optimal performance out of mTOR inhibitors in clinical transplantation, it might be worth escalating research for a new vehicle to deliver mTOR inhibitors more continuously. If continuous dosing could provide effective immunosuppressive coverage, but yet allow for diet-restrictive-like positive attributes such as survival pathway activation (positive low-level stress response) and anticancer activities, an overall benefit to transplant recipients could be realized. In the meantime, it remains difficult to extrapolate the animal longevity data from Harrison et al. to meaningful practical advice for nephrologists treating transplant recipients.

**Take home message**

Although scientific evidence is strongly in favour of the premise that mTOR inhibition does extend lifespan in single cells, in multicellular organisms and in healthy animals, the pathological setting of human renal transplantation introduces a complex set of risks and benefits with mTOR inhibitor use that presently does not permit a reasonable estimation of a potential lifespan benefit to transplant recipients.

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**References**


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