Podcast Episode 17: Current Status of Rapamycin

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Teaser

Hey everyone! Welcome to the new episode of the Life Extension Podcast – technology & magic, society & business. Rapamycin is a drug with a mythical past and future at the same time. Listen to this episode if you are interested in Rapamycin, its origins, its application as a life-extending drug, and the underlying molecular mechanisms. Also learn about a scientist and a doctor who cooperate to administer Rapamycin to consumers as anti-aging drug despite a lack of regulatory approval.

Discovery

This episode is about the current status of Rapamycin, a drug for which some scientists, medical practitioners, and consumers have quite some expectations as it is supposed to slow down aging. Rapamycin was discovered by chance more than 50 years ago in a soil sample on the Polynesian island of Rapa Nui, also called the Easter Island. The island is famous for its remote location in the Pacific Ocean and for its giant statues, which used to be carved by Polynesians as part of their death rituals. Rapamycin is a compound which is naturally produced by a bacterium. The name Rapamycin is composed by Rapa from Rapa Nui, and by mycin referring to anti-fungus properties with which the compound was associated originally.

Later Rapamycin was found to have immunosuppressant and anti-growth effects in cells, resulting in a flow of studies, and ultimately in regulatory approvals as an anti-rejection drug after organ transplants, as well as against several cancers. During research about the mechanistic effects of Rapamycin, the mTOR signaling pathway has been discovered. The protein TOR, which means “Target Of Rapamycin”, was identified as a master-regulator in the response of eukaryote cells to nutrients, growth factors, and energy status. It was found that mTOR was hyperactivated in the presence of a variety of cancers and metabolic diseases like diabetes and obesity. The effect of Rapamycin is to inhibit the mTOR pathway and subsequently to improve or reverse certain disease conditions. Rapamycin and analogue compounds, together called Rapalogs, were found to have beneficial effects not only against cancer, but against a surprisingly wide range of age-related medical conditions. As a result, Rapamycin is the most promising candidate of becoming the first drug against aging itself.

Anti-aging effects of Rapamycin

As multiple studies have shown, the TOR pathway and Rapamycin as its inhibiting agent have significant effects on lifespans in model organisms incl yeast, the fly drosophila, and the roundworm. In 2009 it has been demonstrated for the first time, that Rapamycin significantly increases lifespans of mice, even when administered late in life (Harrison 2009). These experiments have been replicated many times on different genetic types of mice and with different doses. Results overwhelmingly confirm the life-

extending effect of Rapamycin, in some cases even dramatically so. At the same time mouse studies showed clear beneficial effects of Rapamycin against a wide range of age-related conditions, incl cancers, cardiac and vascular dysfunctions, and conditions of the central nervous system like e.g. dementia. It even improved age-related decline of cognition in healthy mice. Other studies have reported about Rapamycin protecting against infections. Vaccines provide better protection against infection when Rapamycin is taken. This effect has been tested not only on monkeys, but also on elderly humans who obtained vaccination against influenza. Rapamycin has also been tested on cell senescence, an important mechanism underlying aging. Numerous tests on humans and other animals have confirmed that Rapamycin reduces cell senescence (Selvarani 2021).

The majority of data derived from a large number of laboratory tests on Rapamycin confirms that Rapamycin significantly extends lifespans of mice, prevents or reverses age-related disease conditions, and even has beneficial effects on aging markers in otherwise healthy individuals, incl behavior.

Are there any side-effects? Experiences with Rapamycin taken by cancer patients or after organ transplants have confirmed that rapamycin is generally safe at least in short-term applications, while in some cases increased levels of blood sugar and blood fat (triglycerides) have been reported, but in other cases not. Anyway, such side-effects would mostly be deemed acceptable as trade-offs in cases of cancer or Alzheimer treatments. Side-effects in long-term administration by humans are not known yet. However in cases where Rapamycin is not taken against specific medical conditions, but rather for lifespan extension, dosage would be lower with no expected side effects, even in long-term administration (Green 2021).

Looking at the surprisingly wide range of age-related medical conditions against which Rapamycin has demonstrated beneficial effects, as well as the fact of effectively increasing lifespan in different animal species, it might also be assumed that Rapamycin as inhibitor of the mTOR pathway is actually acting against aging itself.

Nothing is simple however in molecular biology, and although the mTOR pathway is considered a master-regulator of cell metabolism, downstream negative feedback loops or compensatory mechanisms are sometimes counter-acting the expected effects. So it happens that Rapamycin can have both positive and negative effects on sugar and fat levels in blood, or other metabolic factors. Or that Rapamycin stops cell growth of some cancer types in some organisms, and in other cases not, or is effective for a certain duration of treatment but not afterwards. A solution to deactivate such compensatory pathways or feedback loops has been suggested in using Rapamycin in combination with other pharmacological treatments (Li 2014). Other research trying to understand mechanisms of aging has looked directly at DNA and found connections between an organism's longevity, TOR pathway activation levels, and the presence of histones, an important factor in DNA folding and gene expression in the nucleus of gut cells (Partridge 2021).

Research on Rapamycin as an inhibitor of the mTOR signalling pathway and as treatment option against disease conditions is ongoing, and more regulatory approvals for use in human patients can be expected over time. However, regulatory approval as treatment against aging itself is not to be expected anytime soon, first because aging is not officially recognized as a disease yet, and second because human lifespans cannot be tested within the lifespan of existing individuals. Trials results would only be available after trial subjects have died.

Blagosklonny

One scientist who is perhaps the most active promoter of Rapamycin as anti-aging drug is Mikhail Blagosklonny. In his hyperfunction theory he claims that growth-promoting pathways in cells such as TOR, are driving age-related diseases, when unnecessarily activated. According to this theory, aging is the continuation of an organism's developmental growth in younger years. Taking aging as manifestation of age-related diseases, Blagosklonny claims that Rapamycin as inhibitor of the mTOR growth-promoting pathway in cells could act as anti-aging drug. Inhibiting growth, which used to be important in younger but not in older years, would therefore slow down aging – or so the theory goes. According to Blagosklonny, Rapamycin is today the only known compound qualifying as life-extension drug. In comparison, anti-oxidants, NAD boosters, Resveratrol, and most other compounds discussed in anti-aging medicine do not actually extend lifespans.

Steve Horvath, known for his contribution to the epigenetic clock, has found recently that Rapamycin slows down epigenetic aging (Horvath 2019). Blagosklonny is therefore not the only scientist recognizing life-extension properties of Rapamycin, considering the available robust data derived from research on mice, as well as preliminary data on humans. But he is perhaps more radical than others, when recommending that longevity clinics start to administer Rapamycin to human patients. Although not approved as anti-aging drug, Rapamycin is already approved for a number of cancers, which makes it available as prescription drug, if medical practitioners play along. After all, Blagosklonny writes, "we have one life to live, and cannot wait for results from others, if we want to live longer ourselves. …… Now is the time for longevity clinics. This is the last chance for the current generation to live longer." (Blagosklonny 2021). Blagosklonny has found at least one medical practitioner who listened to his call. Alan Green's practice in New York is actively administering Rapamycin as a preventive anti-aging drug (Blagosklonny 2019) based on Blagosklonny's advice. Green has started to take Rapamycin himself in 2016 and since then has treated more than 600 individuals. According to his blog all are doing well without side-effects. He claims that side-effects mentioned in the medical literature are all based on administration of Rapamycin in transplant medicine, where dosage is much higher (Green 2021). Unfortunately the way how Green promotes the use of Rapamycin as anti-aging drug on his website is not much different from providers of life-extension magic throughout millennia of various human cultures. The consumer can hardly verify his claims of health improvements, although safety has apparently been established by various regulatory approvals for other medical conditions. Green has based his practice mainly on the theories and scientific support of Blagosklonny, and according to his blog he is the only medical practice in the US doing so. Therefore, even if Rapamycin does actually work as longevity drug for humans, the range of scientific support and clinical experience is still much too narrow to properly evaluate efficacy. So far the consumer is still stuck with the logic of all life-extension magic: by taking this drug you risk wasting your time or losing some money. But by not taking it you definitely lose the potential benefits of additional years of health and lifespan.

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