Rapamycin: Extending Health Span and Life Span

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Rapamycin is the most effective life extension drug ever discovered. More than 6400 citations are listed in PubMed with "rapamycin" in the title. Pfizer is the drug company that holds the patent on rapamycin under the brand name Rapamune®; the generic name for rapamycin is sirolimus. From research into rapamycin's mechanisms of action, 2 important themes have emerged.

Theme #1 is the story of rapamycin and its ability to slow down the onset of age-related diseases, which results in increased health span and life span.

Theme #2 is the story of mTOR and autophagy, which has resulted in the discovery of a previously unknown fundamental process in cells that regulates metabolism, health and the aging process. This discovery is ushering in a revolution in the science of life extension.

Revolutionary Breakthrough in Life Extension

This article will explain how research on rapamycin, mTOR and autophagy has resulted in a new understanding of the mechanisms that regulate cellu metabolism, health and the aging process in all living organisms. Research on rapamycin, mTOR and autophagy has resulted in one of the most important breakthroughs in the science of life extension that have ever occurred.

Rapamycin treatment has increased life span by 25% to 60% in most species it has been tested on.[1] When rapamycin was given to 20-month (elderly) mice, females lived 14% longer and males lived 9% longer.[2] This is equal to an increase of approximately 7 years in the life span. These results suggest that rapamycin started late in life may also improve health and extend life span in elderly humans.

Discovery of Rapamycin

In 1964, a team of scientists embarked on a scientific expedition to Easter Island, which is famous for the large stone statues that were built during the 13th to the 16th centuries. The purpose of the expedition was to search for compounds that might express antifungal and/or antibiotic properties. Analysis of soil samples from that expedition revealed a strain of bacteria called *Streptomyces rapamycinicus*, which produced a compound that scientists named rapamycin. The name rapamycin was based on Rapa Nui, which is the name the indigenous people called their island.

Rapamycin initially exhibited strong antifungal properties, but efforts to develop it as an antifungal drug were discontinued when it was discovered to have potent immunosuppressive activity. However, people who receive an organ transplant need to take immunosuppressive drugs to prevent the rejection of their new organ. Consequently, in September 1999, rapamycin received FDA approval as a drug to prevent organ rejection in patients who had received a kidney transplant.[3] Since 1999, rapamycin has been taken safely by millions of people.

Rapamycin's Mechanism of Action

In 1994, several scientists independently discovered different aspects of rapamycin's mechanism of action.[4] When rapamycin crosses a cell membrane and enters a cell, it binds with an enzyme that David Sabatini named mTOR, which stands for the **mechanistic target of rapamycin.** In doing so, rapamycin partially inhibits mTOR activity, which enables the activation of autophagy. Rebalancing the mTOR/autophagy ratio is proving to result in remarkable improvements in health and delayed onset of aging, which explains why rapamycin is ushering in a revolution in life extension.

mTOR

mTOR is a key regulator of cellu metabolism that has stimulated a great deal of scientific interest. Now, 25 years after its discovery, more than 11 000 papers have been published on mTOR.

When nutrients are available to a cell, mTOR initiates signals that activate cell metabolism, telling the cell to use the available nutrients to build new proteins, build new enzymes and other cell components. mTOR is a key sensor of nutrient availability. When nutrients are available,

mTOR activates cell anabolic (building) processes of growth and proliferation.

Autophagy

Autophagy is a process within all cells that counterbalances mTOR's activities. In 2016, Japanese scientist Yoshinori Ohsumi was awarded the Nobel Prize in physiology and medicine for discovering the mechanism of autophagy.[5] Autophagy is the process in which damaged proteins, enzymes, and other cell components are selectively broken down for reuse or elimination.

Autophagy has also been referred to as the cellular housekeeping process or cellular trash removal. Over time, some cell components become damaged and become increasingly dysfunctional. When cell waste products build up, cells begin to malfunction and eventually die.[6] When mTOR is over-functioning, which is most of the time in most people, activation of autophagy is minimal. The cells might not die, but the increased amount of cellular "trash" begins to increasingly hinder many aspects of cell function.

When autophagy is activated, damaged and dysfunctional cell components are selectively broken down for reuse, recycling or removal. Thus, it is important to realize that by removing cellular waste, and damaged cellular components, autophagy is a critical detoxification process in all cells.[7] PubMed now contains more than 30 000 citations with the term "autophagy" in the title, which indicates the level of scientific interest in this topic.

The mTOR/Autophagy Ratio

Throughout 99.9% of human evolution, people did not begin their day by opening the refrigerator and fixing breakfast. The vast majority of people who have ever lived did not eat 3 meals per day. They had to hunt or forage for their food every day. However, the following 2 innovations have played a major role in changing how much and how often people eat: (1) refrigeration and (2) rapid advances in food processing and packaging. These 2 innovations have enabled modern humans to severely upset their mTOR/autophagy ratio, which has resulted in serious health consequences.

The Household Refrigerator Revolution

The electric refrigerator was invented in 1913, and within a few years, companies began the mass production and marketing of home refrigerators. Throughout the 1930s and 1940s, the household refrigerator gained widespread acceptance. Today, government data indicate that 99.9% of American households have a refrigerator.

Food Packaging & Food Processing

Following World War II, revolutions in food processing and food packaging occurred. This resulted in better preservation and extended shelf life. These 2 innovations make food easily available all the time.

mTOR Syndrome

Because food is easily available 24/7 these days, modern humans spend far more time consuming and digesting food than our ancient ancestors. Today, many people have breakfast, lunch, dinner, between-meal snacks, dessert, and evening cocktails. Consequently, modern humans spend about 16 hours per day consuming and digesting food, compared to our ancient ancestors, who often ate only once per day and spent about 4 hours digesting their food. This results in the constant overexpression of mTOR and a severe deficiency in the activation of autophagy. I call this imbalance ***mTOR Syndrome.***

When cells are constantly receiving mTOR's growth signals, they eventually become stressed and various cell components become damaged because autophagy's recycling, rejuvenation, detoxification and renewal processes are not being activated.

Dysregulation of mTOR and Autophagy

Most Americans are suffering from one or more age-related diseases. The United States is currently experiencing an epidemic of epidemics. We have an epidemic of cancer, heart disease, diabetes, obesity, osteoporosis, Alzheimer's disease, ADHD, autism and opioid addiction, to name a few. The overexpression of mTOR (mTOR Syndrome) is increasingly being recognized as a fundamental mechanism underlying the onset of some of the most common age-related diseases such as cancer, neurodegenerative diseases, and type 2 diabetes.[8]

Benefits of Taking Rapamycin

Most cells contain hundreds of mTOR sites. When rapamycin is taken, it enters cells and binds to some of the mTOR sites. This results in partial inhibition of mTOR and the activation of autophagy, which promotes a wide range of health benefits in people who are constantly over-activating mTOR (most people).

Inhibiting mTOR and activating autophagy allows all cells in the body to detoxify more effectively and undergo revitalization and renewal. Results from animal models suggest that partially inhibiting mTOR with rapamycin will help improve symptoms for virtually all chronic degenerative diseases. This includes metabolic syndrome and type 2 diabetes, neurological diseases such as Parkinson's and multiple sclerosis, inflammatory conditions like rheumatoid arthritis and systemic lupus erythematosus, macular degeneration, glaucoma, obesity, hearing loss, periodontal disease, cognitive decline and Alzheimer's disease.[9]

Rapamycin: A New Treatment for Obesity?

Obesity is an escalating global health crisis with direct links to metabolic syndrome and cardiovascular disease. Because rapamycin inhibits mTOR, it mimics calorie restriction. In animal models, rapamycin therapy has been

shown to decrease appetite, and decrease body weight, and fat mass.[10] Because of these results, rapamycin is being considered a potential therapy for the treatment of obesity.[11]

Rapamycin, Mitochondria and Energy

Mitochondria are organelles within cells that are responsible for energy production in the form of adenosine triphosphate (ATP). Mitochondria are also where the greatest number of free radicals are generated in the body. Consequently, over time, mitochondria experience oxidative damage and a decline in function.[12]

Mitochondrial dysfunction is one of the hallmarks of biological aging. There is increasing evidence that autophagy in mitochondria (mitophagy) is significantly impaired in some of the most common human age-related diseases.[13] It has also been proposed that oxidative damage to mitochondrial DNA (mtDNA) is strongly associated with the decline in energy in aging individuals.[14] These results are consistent with the theory that rapamycin increases longevity by increasing autophagy and lowering levels of free radical damage in mitochondria.[15]

Obstacles to Rapamycin's Acceptance as a Life Extension Drug

Although rapamycin is an FDA-approved drug, most doctors are either not familiar with it or only know it as a drug to treat cancer or to prevent organ transplant rejection. Consequently, most doctors are not familiar with rapamycin as a life extension drug.

Another obstacle is that many doctors also work in large group practices, which have standard-of-care or practice guidelines that prohibit doctors from prescribing a drug like rapamycin.

Rapamycin Breakthrough

When rapamycin is taken daily by people who have received an organ transplant, it does suppress the immune system. However, an important breakthrough occurred with the publication of a human clinical trial titled ***mTOR inhibition improves immune function in the elderly***.[16]

In this human study, it was discovered that when elderly humans take rapamycin once weekly rather than daily, they gained a substantial increase in the functioning of their immune system. The results of this study suggest that partially inhibiting mTOR and activating autophagy by taking rapamycin once weekly can strengthen the immune system and delay the onset of age-related diseases.

New Blockbuster Rapamycin Study

Long-lived animals are known to have genes in common that negatively and positively affect life span. Dr. Vera Gorbunova, who is Co-Director of the Rochester Aging Research Center in New York, examined 10 prominent life extension therapies in mice and assessed how each intervention affected the genes associated with maximum lifespan.[17] The interventions evaluated were rapamycin, 17-alpha-estradiol, pituitary-specific positive transcription Factor 1 (PiT1), growth hormone, rilmenidine, ascorbyl-palmitate, acarbose, calorie restriction, methionine restriction and protandim.

RAPAMYCIN WINS: The results from Dr. Gorbunova's study revealed that **r**apamycin had the greatest effect in reducing the activity of genes that have a negative effect on maximum life span AND, rapamycin had the greatest effect on promoting the activity of genes that have a positive effect on maximum life span. This study confirms that rapamycin is a life extension drug that is ushering in a revolution in life extension and healthy aging.

Rapamycin: Dosing and Side Effects

Because mTOR is a key regulator of growth, rapamycin should not be taken by children or adolescents as these are periods of rapid growth. Generally, rapamycin is not prescribed for people younger than 30 years of age.

Groundbreaking Human Clinical Trial

Dr. Joan Mannick devised a human clinical trial using the drug RAD001 (also known as everolimus), which is a rapalog with effects very similar to rapamycin.

The 218 subjects in this trial were elderly people older than 65 years of age. Elderly people were selected for this trial because the immune system in elderly people is generally significantly weaker compared with immune system function in younger individuals.

The subjects for this 6-week trial were randomly divided into the following 4 groups:

Group 1: Subjects received 0.5 mg of RAD001 daily
Group 2: Subjects received 5.0 mg of RAD001 once weekly
Group 3: Subjects received 20 mg of RAD001 once weekly
Group 4: Placebo subjects

After 6 weeks, there was a 2-week drug-free washout period. Then, all subjects were administered the seasonal flu vaccine. Antibody titers to various strains of influenza virus were measured before the administration of the flu vaccine, and again at 4 weeks after administration of the flu vaccine.

The results revealed that elderly people who took 5 mg once weekly had the best outcomes. The subjects who took a 5-mg dose once weekly gained, on average, a 20% enhancement in their immune system's response to the flu vaccine.

The Mannick trial was important for 2 reasons. First, it revealed that partial inhibition of mTOR could provide health benefits in elderly individuals, without adverse events. Second, this study revealed that taking 5 mg once weekly provided superior benefits compared with either daily dosing or a higher dose given once weekly. Consequently, 5

mg to 6 mg of rapamycin taken once weekly is the dose that is most frequently prescribed in patients who are interested in life extension and healthy aging.

When rapamycin is taken once weekly as a life extension drug, it has proven to be a VERY safe drug. Occasionally, some people develop painful mouth ulcers, which usually resolve quickly by lowering the dose. If rapamycin is taken too frequently or if the dose is too high, it can result in immunosuppression and excessive loss of body fat, muscle and bone density. However, these adverse events seldom occur when rapamycin is only taken once weekly.

Who Can Benefit from Rapamycin?

Virtually everyone. The results from animal studies (mostly in mice) reveal that most age-related diseases respond favorably to rapamycin therapy at doses that partially inhibit mTOR.

These days, most adult humans have one or more age-related diseases. Although there are some exceptions, most adult humans alive today can benefit from taking rapamycin. Improving health and slowing the onset of age-related diseases will benefit everyone.

Intermittent Fasting or Time-Restricted Eating

In my book, I present a number of natural alternatives for individuals who have difficulty getting a prescription for rapamycin. However, for this article, I am just going to discuss the most important method to correct the out-of-balance mTOR/autophagy ratio that exists in most people, which is intermittent fasting or time-restricted eating.

Intermittent fasting and time-restricted eating don't limit what you eat or how much you eat, they limit WHEN you eat. These programs recommend consuming all your daily food/caloric intake in a shorter period of time, which allows more time for the activation of autophagy. There are numerous protocols for intermittent fasting and time-restricted eating. However, the 16:8 protocol is the most popular regime, in which food is consumed within an 8-hour period (noon to 8 PM), which leaves 16 hours without food intake, or fasting. Another version is called the 5:2 protocol, in which an individual eats normally for 5 days per week but does a complete 24-hour fast on 2 non-consecutive days. For example, fasting days might be Monday and Thursday on the 5:2 protocol.

Intermittent fasting and time-restricted protocols are successful in providing more time for autophagy to be activated. However, many people don't have the discipline to adhere to these programs. Enter rapamycin, a proven method of partially inhibiting mTOR and activating autophagy, without dieting or engaging in intermittent fasting. However, the benefits of intermittent fasting are so profound (inhibiting mTOR and activating autophagy), I now encourage everyone to engage in intermittent fasting. Taking rapamycin and engaging in intermittent fasting will simply accelerate improvements in health.

Monitoring Your Rapamycin Therapy

Although taking rapamycin at lower doses once weekly has been shown to be quite safe, it is advisable to monitor your progress. The main metrics to track are the following:

- How do you feel, how is your overall energy?
- Your body weight. Many people taking rapamycin lose some weight. However, rapid weight loss or losing too much weight could be a sign of rapamycin toxicity or over-inhibition of mTOR.
- Serum triglycerides. If they fall too low, your dose of rapamycin could be too high, or you could be taking it too frequently.[18]
- Iron and hemoglobin levels. Kidney transplant patients taking rapamycin/sirolimus occasionally develop anemia, and low levels of iron and hemoglobin.[19] It is advisable to monitor these lab values when taking rapamycin.

My new book, ***Rapamycin, mTOR, Autophagy & Treating mTOR Syndrome*** contains links to important scientific studies, podcasts and interviews with key rapamycin scientists. In writing this book, one of my primary goals was to organize and provide scientific documentation that confirms that rapamycin is a safe and effective life extension drug. In addition to educating yourself about rapamycin, I encourage you to use this information to educate your physician about the benefits and safety of rapamycin therapy, which hopefully will convince your doctor to write you a prescription for rapamycin.

The Dog Aging Project

Animals get many of the same age-related diseases that humans get. Organizers of the *Dog Aging Project* plan to follow tens of thousands of companion (pet) dogs in a multi-year study to track their health and identify factors that can increase their lifespan.

In one arm of the Dog Aging Project, approximately 500 dogs will be administered rapamycin to explore and document rapamycin's ability to improve the health span and life span of dogs. To nominate a dog for inclusion in the Dog Aging Project, go to: www.dogagingroject.org.

Rapamycin News

Rapamycin News is an online forum for people interested in anti-aging drugs. They list physicians who prescribe rapamycin, information about purchasing rapamycin from online pharmacies, and information about obtaining rapamycin from foreign generic pharmaceutical companies without a prescription. The web address for *Rapamycin News* is: https://www.rapamycin.news/.

The Age Reversal Network

A not-for-profit group called the ***Age Reversal Network*** maintains a list of physicians who are knowledgeable about rapamycin and more likely to prescribe it for anti-aging

purposes. You can access their physician's referral list at: https://age-reversal.net/physician-directory/.

The Age Reversal Network may also make referrals to telehealth physicians who can assist people in obtaining a prescription for rapamcyin and other medications that have demonstrated anti-aging properties. I suggest you join the Age Reversal Network **(www.age-reversal.net),** which is free, so they can keep you updated about new developments in the field of human longevity.

Rapamycin: A New Era in Life Extension

Most people alive today suffer from mTOR Syndrome; the over-activation of mTOR and insufficient activation time for autophagy. This is where rapamycin can help, because it suppresses mTOR and activates autophagy, thereby helping to correct the mTOR/autophagy imbalance that most people suffer from.

When autophagy is activated for longer periods of time, the processes of cellular detoxification, renewal and recycling function more efficiently and for longer periods of time. This enables every cell in the body to function better, which improves overall health and slows down the onset of age-related diseases.

Rapamycin is opening a new era for humans to experience substantial increases in health span and life span.

My new book titled ***Rapamycin, mTOR, Autophagy and Treating mTOR Syndrome*** can be ordered from: www.lifeextension.com

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