TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 13
Number 2 *Spring 2020*

2020

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Abstract

Scientific and pharmaceutical advancements have revolutionized medicine. Many once- debilitating or fatal diseases can now be managed with medication. However, the search for a cure for the inevitable aging diseased state remained futile until recently. Rapamycin has been studied for its possible longevity effects, providing promising results for the development of anti-aging therapies. This paper evaluates the benefits and risks of rapamycin use. While rapamycin cannot be supported as a safe anti-aging drug, rapamycin studies have elucidated parts of the aging pathway, providing a breakthrough for anti-aging research.

Abbreviations

FKBP - FK506 Binding Protein
AKT – protein kinase B

Introduction

Hutchinson-Gilford Progeria Syndrome (progeria) is a rare genetic disease caused by a mutation on the LMNA gene which encodes for the Lamin-A protein. This causes a modified form of Lamin-A, known as progerin, which has an internal deletion of fifty amino acids (Graziotto et al. 2012). Wild-type Lamin A is the scaffolding of a cell, which holds the nucleus together. Researchers believe the variant Lamin-A leads to an unstable nucleus that causes the symptoms of progeria (The Progeria Research Foundation).

Children with progeria show early signs of aging, which include loss of body fat and hair, growth failure, stiffness of joints, aged looking skin, hip dislocation, cardiovascular disease, stroke, and generalized atherosclerosis. The lifespan of children with HGPS is fourteen years, with the common cause of death atherosclerosis (The Progeria Research Foundation).

The Progeria Research Foundation is currently conducting a clinical research trial to test a possible cure for Progeria. The trial is testing the combined use of Lonafarnib and Everolimus on HGPS patients. Lonafarnib is a farnesyltransferase inhibitor. By inhibiting the attachment of a farsenyl group to progerin, the progerin is unable to inhibit the cell function (The Progeria Research Foundation). Everolimus, a derivative of rapamycin, promotes the autophagy of the progerin (Graziotto et al. 2012).

Increased levels of progerin have been found in the skin and arteries of normal, aged individuals (McClintock et al. 2007, Olive et al. 2010). The correlation between increased progerin and the physiology of aging is seen in the rapid aging of HGPS patients with high levels of progerin and the decrease in age-associated symptoms upon autophagic degeneration of progerin. Thus, the correlation between HGPS and normal aging suggest rapamycin as a possible drug to promote longevity in the general population (Graziotto et al. 2012).

In 2009, a study showing that rapamycin extends the lifespan of mice was published. This was the first study to realize the anti-aging properties of rapamycin on mammals (Harrison et al. 2009). Since then, rapamycin has been explored as a possible anti-aging drug for humans.

Method

Articles sourced in this paper were obtained by searching Touro's database and Google Scholar. Some articles were referenced in review articles and the original articles were retrieved. Additionally, data was obtained from the Progeria Research Foundation and the lecture of Michael Hall who discovered and studies TOR.

Discussion

The Mechanism of Rapamycin

Rapamycin is a macrocyclic lactone secreted by the bacterium streptomyces hygroscopicus which was discovered on the Easter Island (Tee 2018). Is was originally intended for use as an antifungal. However, its immunosuppressive and anti- proliferative properties rendered it unsuitable as a safe antifungal treatment. Instead, these properties of rapamycin led to its development for other purposes, and rapamycin along with its derivatives are FDA approved for use as immunosuppressants and an anticancer agent (Lamming 2016).

Rapamycin combines with FKBP to inhibit the activity of the mechanistic target of rapamycin (mTOR), which is part of the phosphatidylinositol 3-kinase-related kinases family (Hall 2016). The mTOR protein forms two protein kinase complexes - mTORC1 and mTORC2, both balancing cell growth and metabolism with degradation. The mTOR pathways responds to favorable growth conditions, such as adequate nutrition, resources, and growth factors by stimulating anabolic processes (Kennedy, Lamming 2016, Laplante, Sabatini 2009). Conversely, stressful conditions in the cell inhibit the mTOR pathway, thereby inducing catabolic processes (Laplante, Sabatini 2009).

The two mTOR complexes have some shared components. They both contain the mTOR core, the regulatory protein Deptor, and mLST8/GβL to ensure complex assembly and stability (Kennedy, Lamming 2016).

In mTORC1, the mTOR protein kinase interacts with the scaffold protein Raptor, and the AKT substrate PRAS40 (Kennedy, Lamming 2016). As shown in in Figure 1, MTORC1 controls many processes, including protein synthesis, lipid synthesis, autophagy, mitochondrial metabolism, and biogenesis (Laplante, Sabatini 2009). Many of the functions of mTORC1 are inhibited by acute exposure to rapamycin which causes a decrease in biosynthesis and an increase in biodegradation (Tee 2018, Hall 2017).

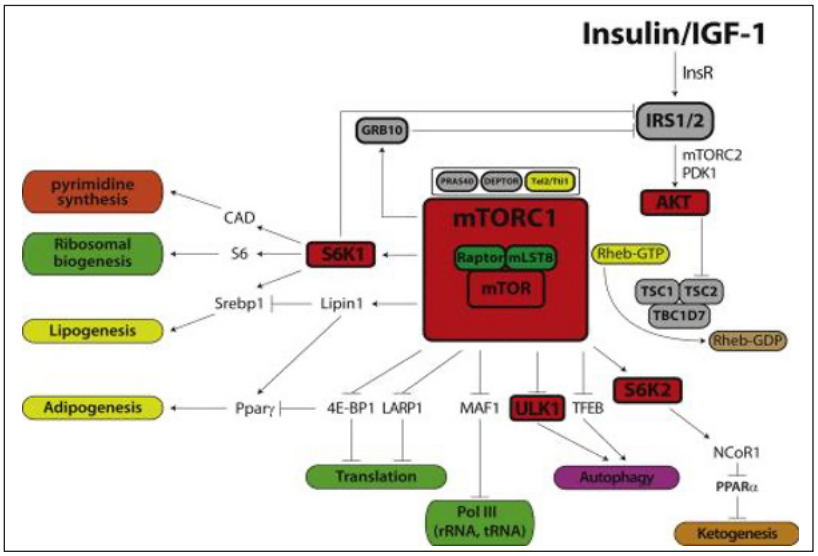

Figure 1. Diagram of the pathways involving mTORC1 (Kennedy, Lamming 2016)

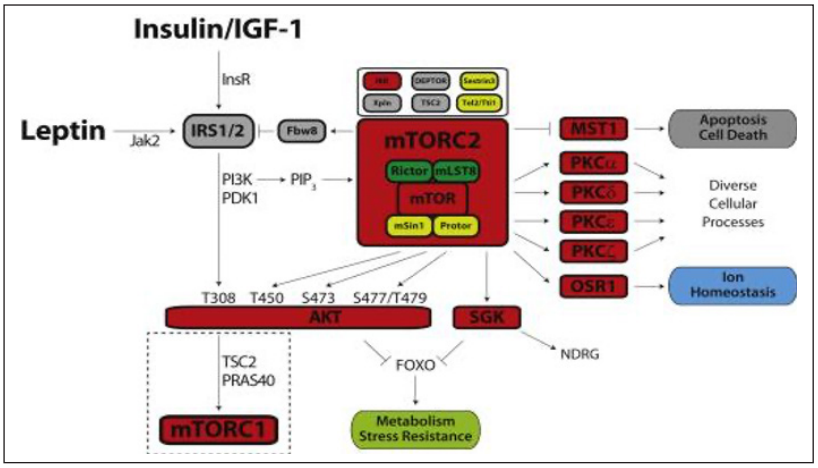

Figure 2. Diagram of the pathways involving mTORC2 (Kennedy, Lamming 2016)

MTORC2 contains the scaffold protein Rictor, the protein subunits mSIN1 and Protor-1/2 (Laplante 2009). Prolonged rapamycin use inhibits mTORC2 by binding to free mTOR and preventing it from forming the mTORC2 complex (Johnson et al. 2013, Sarbassov et al. 2006, Tee 2018). MTORC2 is stimulated by IGF-1, insulin, and leptin (Kennedy, Lamming 2016). MTORC2 regulates mTORC1 via the phosphorylation of AKT. AKT phosphorylates TSC2, which is part of the TSC complex. TSC2 promotes the conversion of Rheb-GTP, which activates mTORC1 to Rheb- GDP. Therefore, the phosphorylation of TSC2 inhibits this conversion process, allowing the Rheb-GTP complex to remain in its active form and activate mTORC1 (Manning, Toker 2017). AKT also phosphorylates PRAS40It, which is an inhibitor of mTORC1 in its unphosphorylated form (Sancak et al., 2007). The other regulatory functions of mTORC2 include regulating cell survival, metabolism, proliferation, and cytoskeleton organization (Laplante, Sabatini 2009). The pathways involving mTORC2 are outlined in Figure 2.

What Anti-Aging Effects does Rapamycin have on the Body?

MTORC1 controls many processes linked to aging. Therefore, the inhibition of these processes by rapamycin contribute to the drug's anti-aging effects (Johnson et al. 2013). The suggested mechanisms of reduced aging by mTORC1 inhibition are discussed in this section.

MTORC1 inhibition promotes autophagy, which is the recycling of amino acids and degradation of damaged macromolecules and organelles. Autophagy in the cells declines with age, and it is proposed that the accumulation of damaged particles contribute to cellular dysfunction of aged individuals (Cuervo 2008). MTROC1 inhibition promotes autophagic mediated longevity, as supported by studies on yeast and invertebrate (Johnson et al 2013).

Regulation of mRNA translation is another process that may contribute to the anti-aging benefits of rapamycin. Under favorable growth conditions, mTROC1 promotes mRNA translation and protein synthesis. Inhibition of mTORC1 reduces translation, and studies on yeast, nematodes, fruit flies, and mice provide evidence that regulation of mRNA translation increases lifespan (Kaeberlein, Kennedy 2011). A main reason for the increased lifespan accompanying global mRNA translation reduction is the differential protein translation of specific mRNA. Molecular evidence is seen in yeast; when mTORC1 is inhibited Gcn4 is preferentially translated and increased translation of Gcn4 increases lifespan. Similar mechanisms are seen in studies of nematodes and fruit flies (Johnson et al 2013).

Another function possibly contributing to the anti-aging benefit of rapamycin is reduced inflammation through mTORC1 inhibition. Hyperactivation of mTORC1 causes inflammation which is present in many age-related diseases such as kidney disease, vascular inflammation after angioplasty, atherosclerotic plaques, and lung infection. Therefore, rapamycin use reduces inflammation associated with these diseases. (Johnson et al 2013).

Additionally, studies on yeast link mTORC1 inhibition to

the activation of a stress response pathway. The increased stress resistance promotes lifespan extension. Also, regulation of mitochondrial function and enhanced stem cell function seem to contribute to the longevity effects of rapamycin (Johnson et al 2013).

Rapamycin Studies on Mammals

The 2009 study conducted by Harrison et al. on 1,901 mice provides evidence for the longevity effects of rapamycin on mammals. In comparison to the control group, rapamycin-fed female mice had a 13% lifespan extension, and male mice had a 9% lifespan extension. The average age of the mice was 600 days, which is the equivalence of 60 years in humans. Thus, the study demonstrates rapamycin's effectiveness when started late in the lifespan.

In 2019 Sills et al. studied the safety of rapamycin on 23 middle-aged marmosets who were fed rapamycin for nine months. The marmoset showed no significant side effects and only minor effects on hematological markers. Since marmosets are biologically similar to humans, the study suggest similar outcomes would occur in humans.

Rapamycin Side Effects in Humans

Although rapamycin has been found to increase the lifespan of flies, mice, and marmosets, few studies have tested its anti-aging effect on humans (Graziotto et al. 2012). This section will review negative side effects of rapamycin treatment and the evidence to support the drug as an anti-aging therapy for humans.

Many studies on rapamycin have been conducted on immunocompromised patients. Side effects of renal and heart transplant patients taking rapamycin for its immunosuppressive property include delayed wound healing, interstitial pneumonitis, anemia, high cholesterol and triglyceride levels, infection, edema, and gastrointestinal symptoms. (Baur et al. 2011, Ekberg et al. 2010, Graziotto et al. 2012). Long term side effects of rapamycin include glucose intolerance, decreased insulin sensitivity, and increased risk of new onset diabetes (Johnston et al. 2008, Lamming 2016). While these reported side effects may seem to outweigh the potential benefits of rapamycin, it is important to consider that the adverse effects may be influenced by the patients' underlying condition or drug interactions (Kraig et al. 2018).

A small-scale study found that short term everolimus treatment boosted the immune response of normal, elderly individuals to the flu vaccine. This suggests that rapamycin improves immunosenescence, one characteristic of aging. Since rapamycin is also known for its immunosuppressive properties, its effects on the immune system seem to be dependent on disease, age, and/or antigen (Mannick et al. 2014).

Another small-scale study of a similar population found rapamycin use safe for elderly individuals with stabilized medical conditions. This population did not show a significant change in plasma glucose, insulin, and insulin sensitivity, which contrasts with the increased risk of diabetes seen with transplant patients. Additionally, there was no significant elevation in triglyceride levels, which was also a concerning side effect seen in previous studies. The side-effects reported in the study group were limited to a facial rash and GI symptoms. However, the study did not reveal any change in cognitive functioning, physical performance, or immune parameters. While these results do not support the anti-aging benefits of rapamycin, the limited side-effects on normal individuals support the safety of rapamycin use for further clinical testing (Kraig et al. 2018).

Despite the promising results of life extension seen in mammals, only a limited number of clinical trials with small sample sizes were conducted on humans. Therefore, rapamycin must undergo further studies to determine its efficacy.

Conclusion/Further Research

The substantial side-effects associated with rapamycin use in transplant patients makes it difficult for it to be approved as a preventative aging treatment. However, the discovery of life extension by inhibiting mTOR provides a basis for the search of other anti-aging treatments that work by a similar mechanism. One suggestion is MTORC1 specific- inhibition, which is sufficient to extend lifespan and may have reduced side effects. Studies have demonstrated the importance of mTORC2 in human physiology and metabolism (Lamming et al. 2016). For example, mTORC2 plays an important role in B-Cells, T-cell and macrophages (Byles et al. 2013, Festuccia et al. 2014). Additionally, prolonged ex-vivo exposure to rapamycin inhibits lipogenesis in rat hepatocyte which can be attributed to the disruption of mTORC2 (Brown et al. 2007, Kennedy, Lamming 2016).

Kennedy and Lamming found that while chronic exposure to FKBP12-rapamycin complex inhibits mTORC2, chronic exposure to the rapamycin-FKBP51 complex does not inhibit mTORC2. The binding affinity of rapamycin with FBPK51 has an inverse relationship with the inhibition of mTROC2. Therefore, a rapamycin analog with a strong affinity for FKPB51 should be studied as a mTORC1 specific inhibitor (2016).

Another possibility, which is not well-studied, is to harness the benefits of rapamycin by eating a low-protein diet. Amino acids are one of the stimuli for mTORC1, but not mTROC2 (Lamming 2016). Studies show leucine consumption affects mTORC1 activity in humans, and a short-term protein-free diet reduces mTORC1 signaling

(Moberg et al. 2014, Harputlugil et al. 2014). The branch-chain amino acids - leucin, isoleucine and valine – enhance the mTORC1 activity in skeletal muscle, liver, pancreas and adipose tissue in rodents. Therefore, a diet with limited proteins or specific amino acids may provide a more natural approach to reduce aging (Lamming 2016).

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