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ВОЗМОЖНОСТЬ ПРИМЕНЕНИЯ ИНГИБИТОРОВ mTOR КАК СРЕДСТВ УВЕЛИЧЕНИЯ ПРОДОЛЖИТЕЛЬНОСТИ ЖИЗНИ

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POTENTIAL APPLICATION OF mTOR INHIBITORS IN EXTENDING LONGEVITY

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Резюме. Старение в широком смысле определяется как зависимое от времени ухудшение физиологических функций, затрагивающее большинство живых организмов. Многочисленные исследования показывают, что процесс старения в значительной степени зависит от различных внешних и внутренних факторов. Одним из ключевых звеньев в процессах, связанных со старением на клеточном уровне, является белок mTOR, который регулирует синтез белка, аутофагию, рост и пролиферацию клеток. Данная работа посвящена некоторым аспектам работы сигнального пути mTOR и ее ингибированию, вызывающему увеличение продолжительности жизни у некоторых модельных организмов.

Ключевые слова: mTOR, старение, продолжительность жизни, долгожительство, рапамицин.

Resume. Aging is broadly defined as the time-dependent functional decline that affects most living organisms. Multiple studies suggest that the process of ageing is considerably influenced by various external and internal factors. One of the key links in the processes associated with ageing at the cellular level is the protein mTOR which regulates protein synthesis, autophagy, cell growth and proliferation. This work focuses on some aspects of mTOR signaling and its inhibition which caused increase of the life span (LS) in several model organisms.

Keywords: mTOR, ageing, life span, longevity, rapamycin.

Relevance. The problems of ageing were topical at all times. The understanding of the work of mTOR signaling pathway lights the prospect of longevity and healthy ageing.

Aim: to present and review several significant publications on inhibitors of mTOR and members of its signaling pathway and estimate their potential applicability in extending human longevity.

Objectives:

1. Describing some aspects of mTOR signaling pathway and its inhibition; describing the application of medicines inhibiting mTOR or those having effect on the members of mTOR signaling pathway in order to trace the most perspective anti-ageing therapies.

2. To estimate possibility of the use of currently available mTOR inhibitors for extending human longevity.

Materials and methods. The materials for this review were obtained from available publications about ageing and the role of mTOR in this process and publications about application of mTOR inhibitors which extended the lifespan of model organisms.

Discussion. The mTOR is expanded as mechanistic (formerly mammalian) target of rapamycin. It is an evolutionary conserved serine-threonine kinase that senses and integrates a variety of environmental and intracellular signals, such as growth factors and nutrients to direct cellular and organismal responses. mTOR is a catalytic subunit in the protein complexes mTORC1 and mTORC2. The effects increasing the life span have been linked to inhibition of mTORC1. The mTORC1 consists of mTOR, Raptor, mLST8, and, in addition, DEPTOR and PRAS40 [1].

In experiments, mTOR inhibition prolonged the life of several model organisms such as Caenorhabditis elegans, Drosophila melanogaster, Saccharomyces cerevisiae, Mus musculus [1]. Hence, it is now accepted that the inhibition of mTOR extends lifespan.

The mechanisms through which mTOR inhibition increases lifespan is not yet well understood, though they must be associated with the effects on mRNA translation, autophagy and mitochondria, stem cell and immune function, regulation of senescence-associated secretory phenotype and cellular senescence [1, 2].

This effects correlate with many cellular and molecular hallmarks of aging identified in 2013 [3]. There are nine hallmarks which are generally considered to contribute to the aging process and together determine the aging phenotype. Among them are: loss of proteostasis, mitochondrial dysfunction, exhaustion of stem cells, cellular senescence, deregulated nutrient sensing [3].

Inhibition of mTORC1 can decrease protein synthesis because mTORC1 stimulates this process through several mechanisms such as ribosome biogenesis and regulation of initiation factors' activity. There are studies which suggest that ageing can be slowed due to a general decrease in mRNA translation caused by mTORC1 inhibition. The proposed explanation for this is reduction in the accumulation of proteotoxic and oxidative stress.

Another mechanism through which the inhibition of mTORC1 could slow aging is the stimulation of autophagy. The process of autophagy, which is known to be suppressed by mTORC1, might decline with age. This decline leads to accumulation of damaged proteins and damaged mitochondria. The reason of this phenomenon is not yet understood. Another link between mTOR and mitochondria is that mTORC1 participates in regulation of both functions of mitochondria and their biogenesis [1, 2, 4].

mTORC1 inhibition may preserve adult stem cell function in various tissues (Johnson et al, 2013). A decline in stem cell number and function might be a critical cause in age-related dysfunction of tissue homeostasis [1, 3, 4].

There are links between mTORC1 and cellular senescence which can be defined as a stable arrest of the cell cycle coupled to stereotyped phenotypic changes. This phenomenon is caused by telomere shortening, but there are other factors that trigger cellular senescence independently of telomere shortening. Because the number of senescent cells increases with aging, it has been widely assumed that senescence contributes to aging [3]. The senescent cells secrete proinflammatory mediators and this is now defined as senescence-associated secretory phenotype (SASP). It was identified that mTORC1 plays main role in SASP promotion (Laberge et al., 2015, Herranz et al; 2015) [1].

Caloric restriction, which is defined as a reduction in nutrient intake without malnutrition, is another intervention besides mTOR inhibitors that extends lifespan [1].

mTORC1 regulates many processes involved in the promotion of cell growth. This includes signaling integration of growth factors, energy status, oxygen and amino acids. The energy status of the cell is sensed by mTORC1 through AMP-activated protein kinase (AMPK). A strong signal that positively regulates mTORC1 is amino acids [2].

In the light of the above, the lifespan-enhancing effects of calorie restriction might be at least partly mediated by decreased mTORC1 signaling. The evidence for this speculation is that calorie restriction in yeast or worms with inhibited mTOR did not additionally lengthen their lifespan. Though, such additive effects were observed in experiments with in flies [1].

So far, the only known pharmacological substance, which prolongs lifespan in all studied model organisms, is rapamycin. Rapamycin was discovered as an antifungal medicine, later its immunosuppressive and anti-proliferative properties on mammalian cells were described. In clinics, rapamycin was mainly used as an immunosuppressant following transplant surgery [4, 5].

The inhibition of mTOR by rapamycin occurs when it forms a complex with the protein FKBP12 and then in this form inhibits the mTOR activity.

One study with mice suggests that rapamycin increased the median life span by 23% in males and by to 26% in females. This effect was dosage-dependent and such life span extending was observed at 42 ppm (figure 1). In general, the effect of rapamycin was stronger in females. The 4.7 ppm increased the median LS in females by 16% while in males it increased only by 3% [6]. The molecular mechanisms explaining this difference remain unclear. At 14 ppm the life span of males increased by 13% and 21% in males and females respectively.

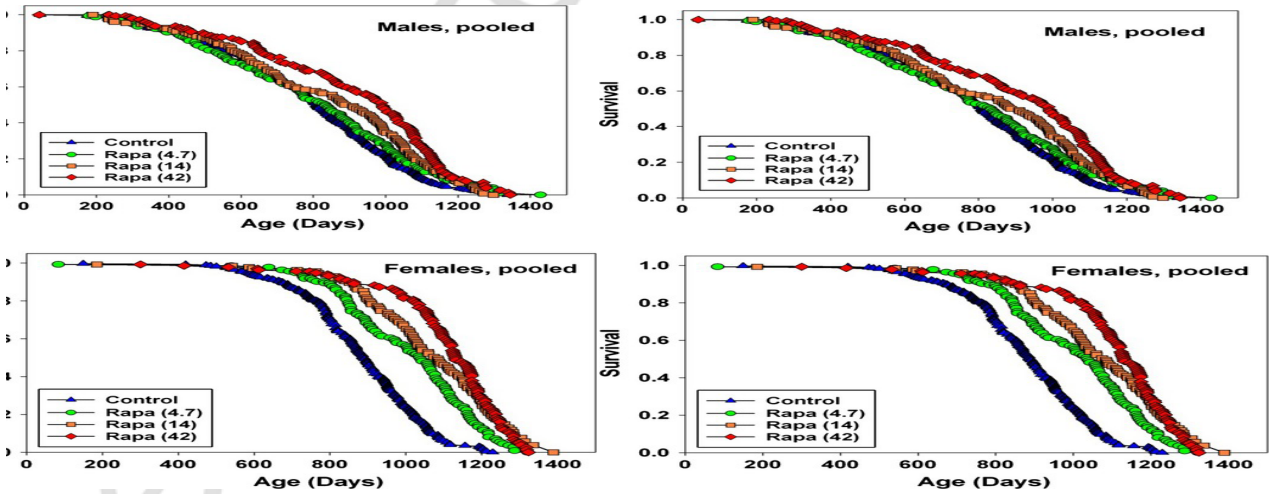

Fig. 1 – Survival curves at varying doses of rapamycin. The picture is taken from the cited article.

Although this increase in life span looks significant, the results of other works show lower effect of rapamycin on the life span of mice. In another study with rapamycin, the life span of male and female mice at 14 ppm increased by 11% and 16% [7].

Despite these data look encouraging, it is unlikely that rapamycin can be approved for use as a preventative measure in healthy individuals due to substantial side effects. One of the greatest concerns with rapamycin is its immunosuppressive effect. The studies with

mice have been performed in pathogen-free facilities. A carefully controlled study of the use of rapamycin in renal transplant recipients found that 34% of patients experienced viral infection, while 16% suffered from fungal infection. Hence, the long-term rapamycin treatment is associated with significant risks [4].

Other frequent negative effect associated with rapamycin includes dermatological adverse events. In renal transplant recipients, rapamycin was found to lead to edema in 60% of patients and aphthous ulcers in 55% of patients. Mucositis and rash have been observed in other patient populations. Rapamycin treatment has been associated with hair and nail disorders, with 90% of patients experiencing alopecia, and with loss of testicular function and reduced male fertility in both humans and mice [4].

Moreover, treatment with rapamycin causes significant metabolic changes, including hyperlipidemia, decreased insulin sensitivity, glucose intolerance, and an increased incidence of new-onset diabetes. On the other hand, these metabolic impairments caused by rapamycin might be a consequence of its "starvation-mimetic" action, so they might be required for its pro-longevity effect [8].

The mTORC1 signaling can be inhibited indirectly. Several researches shown that metformin, which is used as medication for the treatment of type 2 diabetes, increases the life span of model organisms such as C. elegans (Cabreir et al., 2013). The mechanism of action of metformin involves, at least in part, inhibition of the mitochondrial respiratory chain complex I. This, in turn, causes decreased ATP:ADP ratio, which activates AMPK. Metformin also increased the life span of mammals such as rats (Anisimov et al, 2003) and mice [9]. The mean lifespan of mice was increased by 5.83% by diet supplementation with 0.1% metformin. Further increase of the dosage (1%) was deleterious and reduced the life span of mice.

Life-extending effects on some model organisms were also found in resveratrol (Dario et al., 2006) and α ketoglutarate (Chin et al., 2014).

Some studies show that caffeine might increase life span of model organisms, and this effect might be linked with mTOR signaling (Lublin et al., 2011). One study suggests that caffeine extends life span, improves healthspan, and delays age-associated pathology in C. elegans. The highest mean life span extension (36.7%) was achieved at 15°C using 10 mM caffeine [10]. Although at first view this result is encouraging, we should not extrapolate this data on mammals. Multiple studies suggest that ageing in C. elegans might be genetically programmed and even increase its fitness (Labbadia et al., 2016; Lohr et al, 2019).

Conclusions:

1. Application of rapamycin significantly increases the life span of model organisms including mammals. The anti-ageing mechanism of rapamycin is complex, as the mTORC1 inhibited by this medicine regulates variety of diverse cell's processes mainly associated with metabolism, growth and proliferation. Signaling involving mTORC1 can be also inhibited in model organisms indirectly by other medicines such as metformin, resveratrol, alpha-ketoglutarate or caffeine.

2. The side effects of rapamycin make its prophylactic anti-ageing use scarcely acceptable by healthy individuals. Some methods of indirect mTORC1 inhibition might be perspective, but the therapies extending longevity and based on these methods are not yet

possible and require further researches. One of such methods which looks most promising is calorie restriction.

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