DOI: 10.55522/jmpas.V13I1.6243 ISSN NO. 2320 – 7418

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Review article

Decoding the aging nexus: unravelling genetic networks and pharmacological strategies for lifespan extension and the methuselah paradox

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Received - 28-10-2023**, Revised** - 02-12-2023, **Accepted** - 08-02-2024 **(DD-MM-YYYY)**

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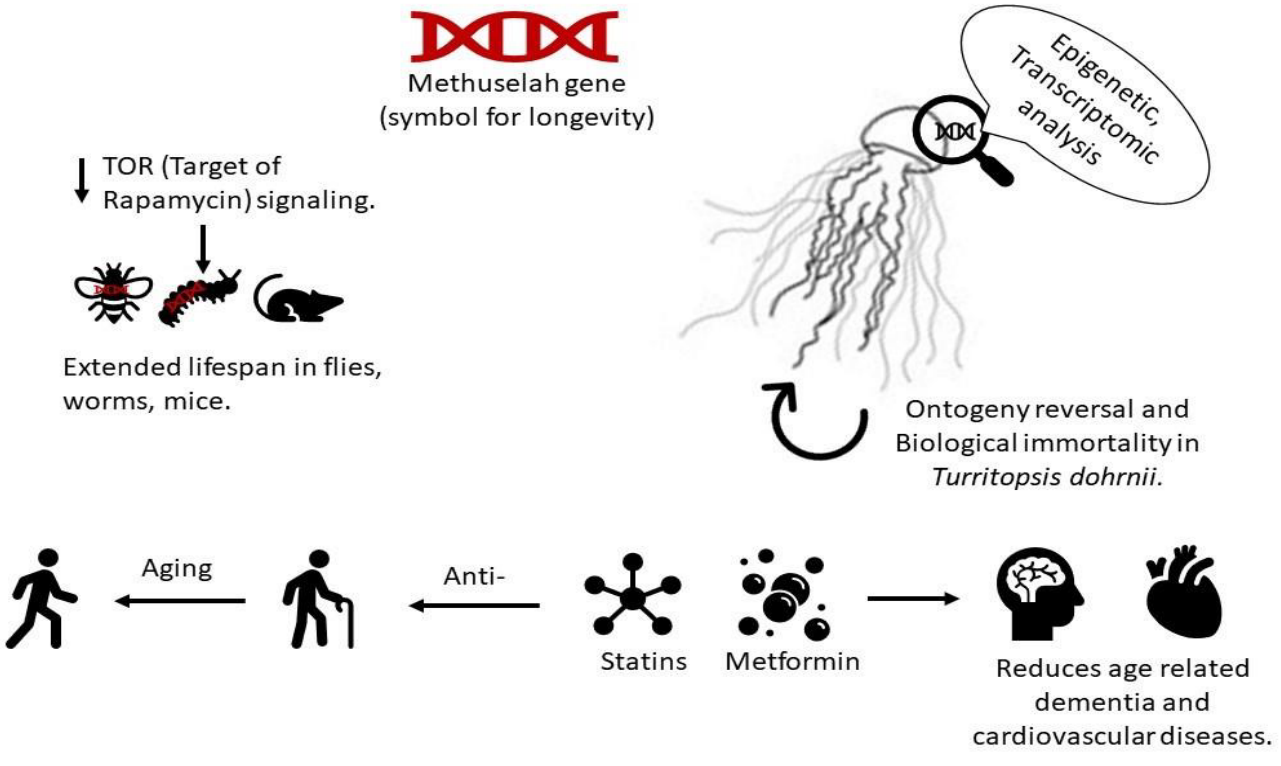
Anamitra Goswami, Nabanita Mukherjee, Moumita Sil, Ankita Ghosh, Prashant Ratnaparkhi, Arunava Goswami, Igor Polikarpov, 2024. Decoding the aging nexus: unravelling genetic networks and pharmacological strategies for lifespan extension and the methuselah paradox. Journal of medical pharmaceutical and allied sciences, V 13 - I 1, Pages - 6372 – 6376. Doi: https://doi.org/10.55522/jmpas.V13I1.6243.

ABSTRACT

We are all interested in knowing- whether genes and drugs can increase our life-span. As per Bible, Methuselah's lifespan lasted for a total of 969 years. Recent research has identified the Methuselah gene, a specific DNA segment that holds the potential to promote robust and healthy aging.



This discovery opens new avenues for the development of pharmaceutical interventions aimed at extending human lifespan. Aging, a complex process influenced by natural selection, has evolved over time, adapting to factors such as cellular senescence and genetic instability. Research on aging has extensively employed invertebrate models like cnidarians, worms, flies, and yeast. Utilizing genetic methodologies with these organisms has resulted in the identification of numerous aging genes. Remarkably, there is compelling evidence of evolutionary conservation within longevity pathways across diverse species, including mammals. In search of omic study, we would consider data from another set of experiments performed on Cnidarians and show that there has a great advanced on the `biology of aging' in an indirect way. Cnidarians, like *Turritopsis dohrnii*, showcase "ontogeny reversal," reverting to earlier stages, thus achieving biological immortality through repeated rejuvenation after reproduction. Alternatively, compounds like resveratrol and rapamycin, have been identified as having the ability to decelerate aging in model organisms. However, as of now, only rapamycin has demonstrated an impact on longevity in experiments on mice. The opportunity to postpone human aging currently exists, whether through established groups of tiny molecules or numerous emerging alternatives. In this context, we explore the approaches to convert findings from age-related research into pharmaceuticals.

Keywords: Biological immortality, Genomic exploration, Invertebrate models, Anti-aging drugs, Aging mechanisms

INTRODUCTION

Researchers have identified the Methuselah gene, a specific DNA fragment that grants individuals the potential for a robust and healthy old age. The methuselah gene mutation in *Drosophila melanogaster* extends lifespan by 35% and enhances stress resistance, potentially involving signal transduction pathways [1]. As creatures get older, the power of natural selection to influence their traits weakens, especially for qualities that matter before they have children. This means that harmful traits that only show up late in life don't get removed from the gene pool quickly [2]. As a result, the process of aging has changed over time by adjusting the characteristics associated with staying healthy as one gets older [3]. Additionally, aging has evolved by adapting to the factors that cause aging, such as cellular senescence or genetic instability. These factors can affect the capability of cells to transform into various cell types and their ability to regenerate [4]. Cnidarians have genes similar to more complex animals, showing how nature and aging are connected in fascinating ways. They share certain genomic structural characteristics and essential genes with bilaterians, shedding light on the intriguing interplay between evolutionary forces and the intricacies of aging and development [5-7]. Certain cnidarians display "ontogeny reversal," reverting to earlier stages, a phenomenon observed in *Turritopsis species*. The ground breaking research of Pascual-Torner et. al. (2022) showed that *Turritopsis dohrnii* uniquely achieves biological immortality by maintaining high rejuvenation capacity in post-reproduction. Studies also revealed the genomic sequencing of *T. dohrnii* and *Turritopsis rubra* (a species lacking rejuvenation). Comparative gene analysis, including DNA repair genes and aging, offers insights into *T. dohrnii's* extraordinary rejuvenation, emphasizing the need for whole-genome sequencing for comprehensive understanding [8-11].

The exploration of aging's intricacies traces back to Darwin's pondering, with initial theories proposing group selection. Evolutionary dynamics were shaped by limited life expectancy, largely due to infectious diseases, childbirth, and malnutrition. Recent centuries witnessed unprecedented demographic shifts, with global life expectancy surpassing 80. Aging, a primary risk element for prevalent diseases, now confronts societies with an aging populace beset by chronic ailments. Research on lengthening health span emerges as a potential solution, but aligning aging interventions with prevention proves challenging. Regulatory hurdles, the gradual nature of aging, and unclear efficacy post-disease onset pose complex questions for the integration of anti-aging drugs into healthcare strategies.

In this overview, we briefly address advancements in the exploration of immortality-related genes before shifting our focus to small molecules influencing aging. Our discussion will delve into the detailed examination of the two extensively researched compounds, rapamycin and resveratrol.

Unravelling the Molecular processes of *Turritopsis dohrnii*'s Biological Immortality and Rejuvenation: Genomic, Transcriptomic, and Functional Insights

The study delves into the genomic and transcriptomic exploration of *Turritopsis dohrnii*'s rejuvenation phenomenon, providing insights into endless vitality and challenging established aging paradigms. Pascual-Torner et al. (2022) present a comparative analysis of entire-genome assemblies between the non-immortal species *Turritopsis rubra* and *T. dohrnii*. The research uncovers genetic variants associated with key functions, including replication, telomere maintenance, DNA repair, redox regulation, stem cell dynamics, and cell-to-cell communication. During the life cycle reversal (LCR) procedure in *T. dohrnii*, there is a documented suppression of polycomb repressive complex 2 objectives and an activation of pluripotency-related targets, suggesting the involvement of these transcription factors in pluripotency induction. Another study focuses on oxidative stress responses and genomic stability in *T. rubra*and *T. dohrnii*, revealing genetic variations contributing to enhanced redox regulation and DNA repair mechanisms in *T. dohrnii*. Additional investigations explore variations in telomeric sequences,

shedding light on potential contributions to diminished telomere attrition and enhanced cellular adaptability [12-14]. The genetic insights into cellular adaptability and regeneration mechanisms highlight gene amplifications in *T. dohrnii*associated with apoptosis, neural system regulation, and microtubule function, providing valuable understanding of the species' extraordinary adaptability and regeneration capabilities [15-18]. Furthermore, the study on transcriptional regulation and epigenetic modifications reveals genetic variations affecting chromatin binding modulation and calcium binding sites, offering implications for cellular function and aging regulation [19-21]. The combined findings contribute significantly to unravelling the molecular intricacies underlying *Turritopsis dohrnii*'s pursuit of biological immortality and its unique capacity for rejuvenation [22-25].

Rapamycin: Unravelling a Journey from Easter Island to Aging Interventions

The narrative of rapamycin unfolds from a 1960s Canadian scientific expedition to Easter Island, where a soil sample yielded a potent activity capable of killing eukaryotic cells. This activity was later attributed to the discovery of rapamycin, a small molecule produced by bacteria [26]. Since its identification, rapamycin has undergone extensive research, with clinical trials investigating its applications in various disease conditions. Notably, rapamycin and its derivatives, known as rapalogs, have received approval for several disease indications despite significant side effects [27, 28]. A major breakthrough in the field occurred with the identification of the Target of Rapamycin (TOR) kinase, revealing insights into TOR signalling and its association with longevity. Reduced TOR signalling, particularly TORC1 activity, has been connected to extended lifespan in yeast, worms, flies, and mice [29, 30]. In mouse aging studies, rapamycin demonstrated remarkable longevity benefits, extending lifespan in both males and females [31]. The drug also exhibited potential in delaying age-associated pathologies, including neurodegenerative diseases and cardiac hypertrophy [32, 33]. However, chronic administration raised concerns, as it failed to address certain phenotypes and, in some cases, accelerated specific age-related conditions. Despite challenges and side effects, rapamycin's potential to delayed aging and delay age-related chronic diseases in humans remains a promising avenue, demonstrating proof-in-principle for interventions in the aging mechanisms.

Sirtuins, Resveratrol and Small Molecules: Deciphering Longevity Pathways in Yeast to Mice

This passage delves into the intricate world of Sirtuins, a class of protein deacetylases, and their implications for longevity across various organisms [34]. Beginning with yeast, where Sirtuins, particularly Sir2, have been connected to enhanced replicative lifespan through mechanisms like suppressing rDNA recombination, the narrative extends to worms and flies, exploring controversial findings on the impact of Sirtuin orthologs on aging [35]. In mice, the focus shifts to SIRT1 and resveratrol, uncovering tissue-specific effects and their potential roles in enhancing longevity [36, 37]. The section also delves into the controversial nature of resveratrol and Sirtuin Activating Compounds (STACs), detailing their in vitro and in vivo effects on SIRT1 activity [38-40]. Despite conflicting data on their ability to extend mouse lifespan, these small molecules open avenues for clinical applications. The passage highlights the complexity of unravelling Sirtuin functions, emphasizing the need for further studies to unlock the total spectrum of their roles in aging and potential clinical benefits.

Metformin and Statins: Examining Widely Used Drugs in the Aging Context

This passage delves into the potential anti-aging effects of two commonly used drugs: metformin and statins. Metformin, traditionally prescribed for type II diabetes, has appeared as a candidate for modulating aging, with recent studies showcasing an approximately 5% increase in male mouse median and maximum lifespan [41]. Given its safety profile in human administration, metformin is notably considered a dietary restriction mimetic, activating AMP kinase in response to cellular energy deficits [42]. The drug's positive impact extends to age-related diseases, lowering the risk of heart-related disease and cancer, as suggested by clinical studies [43, 44]. The discussion on statins explores their inhibition of HMG-CoA reductase, leading to reduced LDL-associated cholesterol levels [45, 46]. While simvastatin did not show longevity benefits in the NIA Intervention Testing Program, statins have demonstrated protective effects against age-related diseases, including dementia and certain cancers, in human clinical trials [47]. However, caution is advised due to manageable side effects in some patients, inconsistent protective effects in clinical studies, and debates about the efficacy of statins for cardiovascular disease in individuals over 80. The passage emphasizes the need for further studies before conclusively categorizing statins as anti-aging drugs.

CONCLUSION

In conclusion, the exploration of vitality and aging mechanisms has witnessed remarkable strides in recent research. From the identification of the Methuselah gene, offering potential for robust aging, to the genomic and transcriptomic insights into the biological immortality of *T. dohrnii*, the pursuit of understanding aging has taken intriguing directions. The evolutionary dynamics of aging, shaped by natural selection and adapting to factors such as cellular aging, have been uncovered through diverse models, including invertebrates and cnidarians.

The discussion on small molecules like rapamycin and resveratrol has unveiled promising possibilities for extending lifespan, with rapamycin demonstrating notable longevity benefits in mouse studies. Sirtuins, particularly SIRT1 and SIRT6, have been involved in

longevity pathways across species, showcasing the complexity of their roles in aging. Additionally, widely used drugs like metformin and statins have emerged as potential modulators of aging, with metformin showing positive effects on mouse lifespan.

As the quest to decipher the molecular intricacies of aging continues, the integration of findings into pharmaceutical interventions becomes a crucial focus. The potential to postpone human aging through small molecules or established drugs opens new avenues for anti-aging strategies. However, challenges such as regulatory hurdles, the gradual nature of aging, and uncertainties post-disease onset pose complex questions for the practical implementation of anti-aging drugs in healthcare. In this dynamic landscape of aging research, further studies are essential to validate and refine the potential interventions. The complex interaction between genetic, molecular, and environmental factors necessitates a comprehensive understanding to develop effective and safe approaches for extending health span. The journey from Methuselah to modern genomic exploration signals a promising era for aging research, with the potential to transform how we perceive and address the challenges of a growing elderly demographic.

Conflict of interests: Declare None.

ACKNOWLEDGMENT

The authors are thankful to the technical assistant Mr. Ashim Dhar for his assistance in technical work.

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