Review Article

Cellular senescence perspective of mTOR in the delay of aging process

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ABSTRACT

Aging delay is an intricate thing that involves efforts of stress minimization and organism resilience enhancement so that homeostasis can be maintained in order to survive longer in healthy settings. Lately, metformin has become the most common drug used as a pharmacological intervention in both pre-clinical and clinical anti-aging research. Unfortunately, even though metformin research has progressed to clinical trials, the molecular mechanism behind metformin's impact in delaying aging and age-related diseases remains unknown. Countless hypotheses exist regarding the role of mTOR as a crucial gene in the emergence of aging, but there is no systematic explanation that can relate the gene's contribution to modest molecular processes such as cellular senescence, the aging process, and its association with the deceleration provided by metformin. This narrative review discusses the involvement of mTOR in the aging process. Understanding the core molecular pathway of metformin through its primary target gene will help determine the effective dose that provides the maximum slowing effect of aging along with the emphasis on minimum undesirable side effects, both short and long-term.

Keywords: Metformin, mTOR, Cellular senescence, Age-related disease, Aging

Introduction

mTOR or mechanistic target of rapamycin is a serine-threonine kinase that is composed of two distinct multiprotein complexes that differ functionally and structurally in their sensitivity to rapamycin. mTORC1 complex is made up of the regulatory-associated protein of mammalian target of rapamycin (RAPTOR); catalytic subunit; mammalian lethal with Sec13 protein8 (mLST8); DEP domain containing mTOR-interacting protein (Deptor) and the proline-rich Akt substrate 40 kDa (PRAS40), whereas the mTORC2 complex is made up of the rapamycin-insensitive companion of mTOR (RICTOR), mammalian stress-activated map kinase-interacting protein 1 (mSin1) and protein observed with Rictor 1 and 2 (Protor 1/2) [1, 2].

mTOR belongs to the PI3K-related kinase family that plays an important role in cellular responses through an immense number of external and internal cues perceivation and integration, amongst them are growth hormones also nutrition [3]. The landscape of mTOR signaling has broad to light that mTOR regulates mass accumulation and metabolism by altering important cellular activities such as protein integration and autophagy [4]. Due to the notability of these pathways in maintaining cellular and physiological equilibrium, mTOR signaling dysregulation is linked to metabolic diseases, neurodegeneration, cancer, and aging [5, 6].

Aging is a natural biomechanism that causes an unchangeable progressive decline throughout organism unit organs due to the accumulation of damage caused by a certain range of stresses [7]. Aging has contributed to several prolonged sicknesses in humans and also increased the risk of common diseases including but not limited to diabetes, Alzheimer's, Parkinson's, cardiovascular, pulmonary chronic obstruction, osteoporosis, and even osteoarthritis [8, 9]. Aging begins at the cellular level in the form of progressive loss of cell multiplication ability, as well as cellular

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function, throughout time [10]. This puts cellular senescence as a major causal element in the organismal aging process and facilitates aging-related diseases [11].

Metformin, the mTOR inhibitor other than rapamycin, has been authorized by the FDA as an anti-aging agent [12]. Many studies show the effect of metformin in slowing aging and the upgrowth of age-related diseases [13, 14]. Unfortunately, even though the molecular action mechanisms have been extensively researched, they were found to be complex and only partially understood. It made the major target point and the main pathway remains elusive [15]. To provide a better understanding through a comprehensive point of view, we offer a current perspective of mTOR contribution on aging deceleration through cellular senescence, the state when the cell lost its capability to build back cellular balance and loss the functional integrity after stress exposure.

Materials and Methods

The narration we made is based on the data collected from former experiments through the literature study approach. The journal articles that were found in Pubmed, Scopus, and Google Scholar using "metformin", "mTOR", "cellular senescence", "age-related disease", and "aging" keywords, were first filtered by the title and abstract. These keywords were used individually or in combination to establish a logical relationship between concepts. The articles were then refiltered by reviewing the complete content. The publication or article chosen must be a complete paper article in English published between 2017-2023, an experimental study, comprising in vivo, in vitro, and clinical experiments (not a review article).

Aging and homeostasis

Organisms, including humans, will survive when they can maintain internal stability that lies under a certain range of values, by putting back the general balance after disturbance from stress exposure. The successful self-regulated stability obtained from responding to the fluctuation of extrinsic circumstances is known as homeostasis. Homeostasis becomes a dynamic process due to the nature of external challenges [16]. At the organism level, homeostasis is the result of the total cumulation of organ systems homeostasis, each of which is composed of various tissues from different types of cells. Therefore, homeostasis in an organism is a projection of and built up by cellular homeostasis [17, 18].

The complex physiological process when humans naturally and progressively experience irreversible loss of the ability to re-establish equilibrium or homeostasis is known as aging. Aging brings clinical consequences for illness susceptibility since it reduces the human ability to maintain their health [8, 19, 20].

Cellular homeostasis, cellular senescence, and mTOR

Cellular homeostasis is achieved when individual cells successfully cope with perturbation of intracellular stability which is related to cellular adaptation ability to stress. This ability also contributes to the organism's tremendous resilience as well as deterioration over time [21]. To maintain cellular homeostasis, cells characterize each trigger, receptor, signal transducer, effector, and adaptive response scheme from various stresses, in an outstanding molecular detail that will determine the appropriate cellular stress responses [16, 22]. Prolonged or severe homeostasis disruptions that cannot be managed by adaptive systems will result in cellular senescence, this state happens when a detrimental degree of stress exposure causes irreversible yet insufficient damage to cause elimination of stressed cells through regulated cell death [22].

A progressive shortening in telomere structure alteration, the signal from mitogen, oncogene, tissue damage, as well as cellular stress due to cellular oxidation, radiation, genotoxic and chemotherapy agent exposure, and last but not least epigenetic changes, chromatin disorganization, proteostasis disorders, mitochondrial dysfunction and nutritional deficiencies, are all examples of external and internal senescence catalyst [20, 23]. Senescence is a protective apparatus that limits the risk of oncogenic transformation of damaged cells through a tumor suppression mechanism. Senescence can be useful or harmful to organisms, depending on the setting [11, 24, 25]. Cells undergo senescence via two most studied major mechanisms [26-28]:

- *The p53/p21 pathway*

Telomere shortening, oncogenic stress, and oxidative stress will trigger DNA damage which activates p53. Activation of p53 regulates the expression of anti-proliferation gene p21. p21 is the part of Cip/Kip family together with p27 and p57 that encoded by CDKN1A (Cyclin-dependent kinases 1A). p21 inhibits kinase activity in the cyclin D-CDK 4/6 and cyclin E-CDK 1/2 complexes by binding to Cy1 and Cy2. This inhibition results in phosphorylation inhibition of the pRB family (RB1 (pRB), RBL1 (p107), and RBL2 (p130)), further related to pRB-E2Fs (protein Retinoblastoma-Eukaryotes Transcription Factors) or DREAM (Dimerization Partner, RB-like, E2F and multi-vulval class B) protein complex formation, results in cell cycle arrest. E2F was suspected able to activate TSC2 by inducing mTORC2 activation. HDACs (histone deacetylases) and SUV39H1 (histone methyltransferase) are the known factors that escalated this formation. While p21 can also be triggered independently from the p53 pathway, the only high levels and nucleic p21 that cause cellular senescence and induce cell cycle arrest.

- *The p16 pathway*

The INK4/ARF locus (Alternative Reading Frame) encodes CDKN (Cyclin-dependent kinase inhibitor) genes that contain CDKN2A (p16INK4A and p14ARF) and CDKN2B (p15INK4B). p16/p15 will bind to CDK4/6 which blocks the formation of the cyclin D-CDK4/6 complex, thus preventing RB protein phosphorylation and triggering the expression of E2F target genes in the form of the RB-E2F complex which ends in cell cycle arrest. p14 works by binding to MDM2/4 (Murine Double Minute) and inhibits its functions in destabilizing p53.

P53 is the dominant pathway of senescence due to replicative stress, the type of stress that most resembles the stages of natural aging. This was demonstrated by research data on the cells without p53 that are not experiencing senescence. The level of p53 activation which is affected by the spatiotemporal (length, type, and size) exposure of stressor on the cell, is a fundamental part of initiating cellular response determination (senescence, autophagy, atau regulated cell death). In addition to p53, senescence occurs when the cell's needs for proliferation are not met [29, 30]. The primary prerequisite for the cell to proliferate and differentiate properly, the cell must maintain a balance between increased protein, lipid, nucleotide production, and suppression of autophagic processes (since excess autophagy can end up in regulated cell death) [5, 31, 32]. The supreme regulator for this balance is mTOR (Mechanistic Target of Rapamycin), a serine/threonine protein kinase that coordinates the balance of the anabolic and metabolic response of cells when obtaining stress from the environment. mTOR is a versatile enzyme that consists of mTOR-Complex 1 and mTOR-Complex 2, both complexes of mTOR are defined by a diverse protein and specific substrates set [2, 4]. The mechanism of mTOR in doing so is by:

mTORC1

mTORC1 play the anabolic path by phosphorylates the hydrophobic spot (Thr389) of its main effector unit, S6K1 (P70S6-Kinase 1), that facilitates consecutive activation by PDK1 (3-Phosphoinositide-dependent kinase 1). The S6K1 activation followed by phosphorylation and activation of mRNA (messenger Ribo Nucleic Acid) translation induction substrates, such as eIF4B (Yeast Eukaryotic Initiation Factor 4B) also induction of eIF4B inhibitor, PDCD4 (Programmed Cell Death 4) to be degraded; increasing efficiency of mRNA translation through interaction with SKAR (S6K1 Aly/REF-like target), an element of the exon intersection complex. mTORC1 induces phosphorylation inhibition of elF4E Binding Protein (4EBP) to dissociate eIF4F so it can make eIF4F-5'cap complex dependent mRNA translation, occur. These events lead to protein synthesis. The activation of S6K1 also induces CAD (carbamoyl-phosphate synthetase) which enhances pyrimidine generation. Together with purine generation by activation of MTHFD2 (Methylenetetrahydrofolate dehydrogenase-2) through ATF4 (Activating Transcription Factor 4) induction phosphorylation, both support nucleotide synthesis. In cholesterol and fatty acid biosynthesis, mTORC1 acts as NADPH production booster through $C_6H_{12}O_6$ carbon units utilization by binding to SREBP (Sterol Responsive Element Binding Protein) and inducing PPP (pentose phosphate pathway) oxidation. mTORC1 also phosphorylates Lipin 1, the negative control of SREBP [3, 33].

While for the catabolic, to support glycolysis domination more to oxidative phosphorylation metabolism, mTORC1 enhances HIFα (Hypoxia-Inducible Factors Subunit α) translation that induces the expression of several glycolytic enzymes such as PFK (Phospho-Fructo Kinase). mTORC1 also inhibits autophagy to some extent by phosphorylates ULK1 (Unc-51 Like Autophagy Activating Kinase 1); and inhibits autophagosome complexes of ULK1-ATG13 (Autophagy Related 13), FIP2000 (Fusion-inhibiting peptide 2000), and ATG101 (Autophagy Related 101) formation; inhibits TEFB (transcription factor EB) translocation into nucleus, therefore, inhibiting autophagy and lysosome biogenesis; and reduce protein ubiquitylation that makes degradation by 20 S proteosomes, decreased [2, 34].

mTORC2

mTORC2 works by phosphorylates its main substrates PKCα,δ,ε,ζ, γ as well as PKA, PKG, and SGK1, which belongs to the AGC protein kinase family that has accountability in the regulation of cytoskeletal remodeling, cell migration, and cell survival. mTORC2 activates the major effector in the insulin-PI3K signaling pathway, Akt/PKB (protein kinase B). An active Akt phosphorylates and inhibits key substrates such as the transcription factor Fox O1-3a (Forkhead box protein O1-3a), a metabolic regulator GSK3b (Glycogen synthase kinase-3 beta), and TSC2 (Tuberous Sclerosis Complex 2) a Rheb and raptor (mTORC1-inducing proteins) inhibitors. Akt activation on Ser473 along with phosphorylation via Thr308 by PDK1 will make Akt activation stronger. PDK1 activation facilitated by the activated SGK1. These, certainly strengthen mTORC1 activation [2, 33, 35].

There is evidence that p53 and mTOR cooperate in determining cell status as a response to stress exposure. p53 target genes such as REDD1 (Regulated in DNA Damage and Development 1), LKB1 (Liver Kinase B1), AMPKβ (AMP-Activated Protein Kinase Subunit β), TSC2, PTEN (coding phosphatase which inactivates the PI3K-AKT pathway by catalyzing PIP3 to PIP2), Sestri 1 and Sestrin 2 (activate AMPK and TSC2) are a series of mTORC1 inhibitor genes (the dominant mTOR subunit in determining cell proliferation). p53 can target some miRNAs as transcription objects that when these miRNAs attach to 3 UTR of mTOR results in repression of mTOR (miRNA 100) and mTOR downstream/upstream protein (miRNA 145,149,155) translation. p53 stimulates post-transcriptional miRNA maturation that when it binds to mTOR, ends up in mTOR cessation (miRNA 199a3p) due to elevation of degradation. On the other hand, the non-transcriptional pathway of p53 in regulating mTOR is through cytoplasmic translocation that induces ubiquitination degradation by MDM2, AMPK inhibition, and mTOR activation, all of which inhibits the autophagy process [36, 37].

Meanwhile, mTOR reciprocates p53 regulation via modulation of the p53 counter regulator protein, MDM2 (Mouse double minute 2 homolog). The main downstream of mTOR, S6K1 binds to MDM2 thereby inhibiting its work in degrading p53 when DNA damage occurs. In PTEN-deficient cells, mTOR competes with MDM2 to bind to p53 on Ser15 resulting in activation of p53 thereby triggering PICS (PTEN-loss induced cellular senescence) [38]. MDM2 also modulated by AKT via Ser166 and Ser 186 phosphorylation, triggers MDM2 translocation into the nucleus and results in the degradation of p53 while Ser367 phosphorylation makes MDM4 protected

from the proteolysis process and getting stabilized to inactivate p53. The stabilization of MDM4 is heightened due to deubiquitinization of USP2A (Ubiquitin-Specific Protease 2a). Other than that, under glucose deprivation, AMPK will phosphorylate p53 through Ser 15 and trigger cell cycle arrest. AMPK also triggers p53 phosphorylation indirectly via ULK1 (Unc51-Like Kinase 1) phosphorylation, ULK1 is an essential drive for autophagy. On excessive UV exposure, indirect activation of p53 through AMPK or direct phosphorylation through LKB1 via Ser15 and Ser392 followed by the activation of p21 transcription **(Figure 1)** [30, 37, 38].

Based on the mTOR molecular action mechanism for cell cycle continuity, mTOR contributes to the process of cellular senescence not only by directly affecting the senescence inductor genes (p53, p21, p16) but also by conditioning the conduciveness of the environment through the availability of essential things to support the development of senescence. mTOR is considered the major regulator of the quiescence/senescence state of cel1 [1, 39].

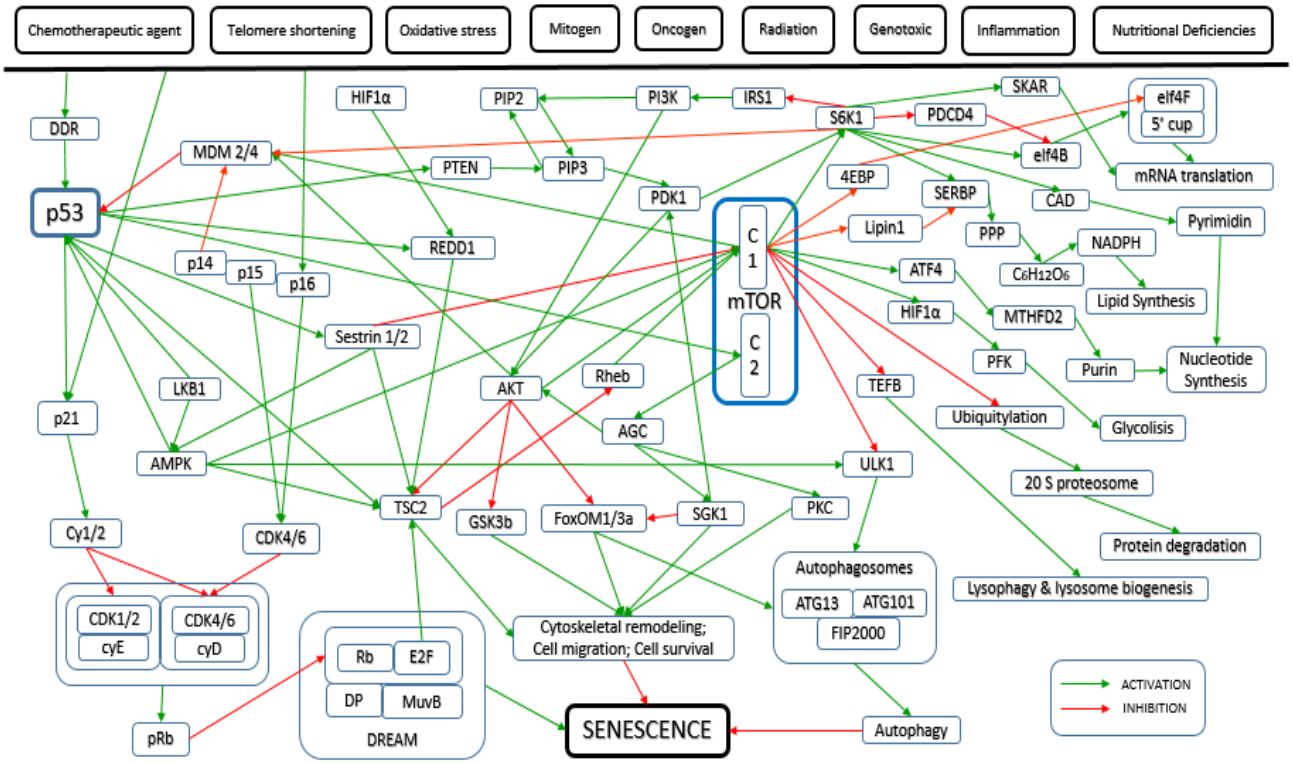

Figure 1. The mTOR contribution to the process of senescence cellular. The fundamental ways mTOR regulates the senescence of cells are through modulation of genes involved in cell cycle progression and prevention of a decent cellular metabolism required for the cell cycle.

Cellular senescence and age-related disease

Senescent cells that undergo the cellular senescence process, have certain characteristics such as apoptosis resistance and, an increase in protein synthesis, along with changes in metabolism that include elevated glycolysis, reduced fatty acid oxidation, elevated production of reactive oxygen species, and the development of a secretory phenotype linked with senescence (SASP) [40]. The SASP involves the release of pro-inflammatory mediators such as cytokines, bradykines, prostenoids, miRNAs, damage-associated molecular pattern proteins (DAMPs), and chemokines that draw in immune cells. These substances all help to remove senescent cells. The SASP also induces stem cell dysfunction factors such as activin A, hemostatic factors such as PAI-1, pressors, and extracellular matrix-damaging molecules. Inflammaging, a persistent low-grade systemic inflammation that develops beyond any pathogenic episodes is also sustained and exacerbated by the SASP. SASP factors can cause secondary senescence in both proximal and distal directions, spreading and increasing the senecent load. When the senescence load exceeds the capacity of tissue, it causes age-related pathological alterations that eventually lead to illness, cancer, and death **(Figure 2)**. Among those illnesses are: osteoporosis, osteoarthritis, frailty, cardiovascular, pulmonary fibrosis, renal, and other neurodegenerative disease [41-43].

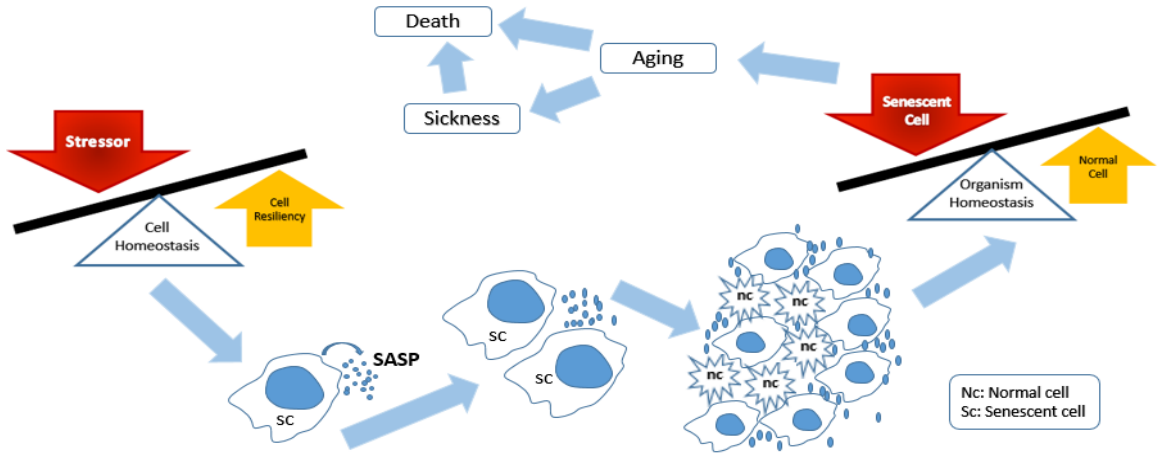

Figure 2. The mechanism of cellular senescence induced aging and age-related disease that eventually led to death. A problem is conducted by senescent cells when its accumulation reaches an organism's intolerable range.

Metformin action mechanism and mTOR involvement

Metformin works primarily through the OCT (Organic Cationic Transporters-1, -2, -3) and MATEs (Multidrug And Toxin Extrusion Transporters). Alternative metformin action mechanisms are through direct binding to mGPDH (Mitochondrial Glycerol 3-Phosphate Dehydrogenase) on the outer layer of the mitochondria inner membrane thereby inhibiting its function in glycerol-phosphate uptake process to reduce NADH and regenerate NAD+ cytosol. This inhibition will lower the Cytoplasmic NAD+/NADH ratio and affect the synthesis of glucose from lactate and glycerol in mitochondria [44]. As a result of ATP depletion, the cell's relative energy decreases, and the ratio of AMP (Adenosine Monophosphate)/ATP (Adenosine Triphosphate) increases. AMP inhibits fructose-1,6-bisphosphatase-1 (an enzyme that regulates the rate of gluconeogenesis) and triggers AMPK activation (5' AMP-activated Protein Kinase), the primary detector of the cellular metabolic state that is capable of switching anabolic pathways to catabolic energy generation pathways [14, 45].

As a consequence, AMPK activation leads to phosphorylation of raptors and mTORC1 substrates, namely S6K1 and 4E-BP1 thus reducing translation and inhibiting the action of mTORC1; PGC1-a (Peroxisome roliferator-activated receptor Gamma Coactivator-1 alpha) activation and mitochondrial biogenesis; activation of SIRT-1 (Sirtuin-1) and other nutrient-sensing pathways; Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-kB) and proinflammatory cytokines inhibition that also inhibits of AGE (advanced glycation end products) formation; and autophagy induction via ULK1 activation [46]. At the same time, Metformin accesses the Non-AMPK pathway through direct inhibition of mTORC1 via Rag-GTPase or indirectly through upregulation of REDD1 (Regulated in DNA Damage and Development 1) which triggers TSC2 phosphorylation and reducing insulin-IGF1 levels leading to the decrease of IRS (Insulin Receptor Substrate) phosphorylation and PI3K(Phosphoinositide 3-Kinases) inactivation, these, will inhibit PIP2 (Phosphatidylinositol-4,5-Bisphosphate) transformation to PIP3 (Phosphatidylinositol-3,4,5-Trisphosphate), as a result, inhibition of PDK1 (Phosphoinositide-Dependent Kinase-1) uptake and Akt activation. When Akt is not activated, TSC inhibits Rheb and further inhibits mTORC1 activation (mTORC1 must bind to Rheb) [45, 47].

From all the possible alternative pathways of metformin in delaying the process of aging and age related disease mentioned above, the underlining part of the explanation is that every of these pathways are ponting to the same thing and emphasize the major contribution of mTOR in senescence progression. It's as well shown through the result from the former researches among them are the intervention using metformin in osteoarthritis mice model by Li *et al*. giving the attenuation of osteoarthritis symptom through senescence modulation which is supported by the reduction of p21, p16, and mTOR in molecular level. This finding are corroborate by Feng *et al*. research that served the data about cartilage degeneration attenuation in osteoarthritis mice model under metformin intervention followed by the reduction of p16INK4a and mTOR. Another research using multiple myeloma model by Wang *et al.* giving the fact that metformin excert anti-cancer effects through senescence induction in cancer cells projected by the rise of p21, p27 and the decrease of mTOR level so the proliferation of the cancer cells were inhibited. While those data confirming metformin impact in age related diseases progression, Chen *et al*. brings the evidence of mitophagy supression and cellular senescence inhibition on the UVA induced skin aging process by metformin through dimming p53, p16, p21 and mTOR action. And last but not least, the research by Zang confirms the evidence of senescence alleviation following metformin intervention on

human dental pulp stem cells through the decrease of p53, p21, p16 and mTOR concentration **(Table 1)**.

Table 1. Studies of metformin with mTOR involvement on cellular senescence

Subject	Dosage	Result	Mechanism of senescence modulation	Ref
Mice ADSC	100 µM and 200 µM	OA symptom attenuation	↓ p21 ↓ p16 ↓ mTOR	[48]
C57BL/6 mice	10 µL per joint			
C57BL/6 mice	100 and 200 mg/kg-weight			
Mice articular chondrocytes	4 mM and 5 mM	OA amelioration	↓ p16INK4a ↓ mTOR	[49]
Mice cartilage explants	4 mM and 8 mM			
Kunming mice	10mg/kg-weight	Attenuation of UVA-induced skin aging	↓ p53, ↓ p16, ↓ p21 ↓ mTOR	[50]
HFF	100 µM			
Murine	250mg/kg weight/day	MM cell growth inhibition	↑ p21, ↑ p27, ↓ mTOR	[51]
Human MM RPMI8226 & U266 cell lines	5 mM and 20 mM			
Human DPSCs	100 µM	Alleviation of DPSCs senescence	↓ p53, ↓ p21, ↓ p16 ↓ mTOR	[52]

Met = metformin; Px = participants; ↑ = increase; ↓ = decrease; mTOR = mechanistic target of rapamycin; ADSCs = Adipose-derived mesenchymal stem cells; OA = osteoarthritis; HFF = human foreskin fibroblast; UVA = ultraviolet A; MM = Multiple myeloma; DPSCs = Dental pulp stem cells

Conclusion

The collected studies provide significant scientific evidence of metformin's impact on aging and the progression of age-related diseases with the most molecular action mechanism observed in these studies involving the mTOR pathway. The chronological mechanism of human aging on a cellular level and the importance of mTOR contribution to cellular stress response support the builds of the perspective that metformin helps the organism's homeostasis maintenance through modulating mTOR in cellular homeostasis management. It is noteworthy that stressing the topic review on mTOR helps to determine the major pathway of metformin action mechanisms along with the advantages of minimizing the possible unwanted effect of the drug as well as confronts the challenges of finding a certain range of therapeutic window dose that effectively works on mTOR modulation.

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References

1. Weichhart T. mTOR as regulator of lifespan, aging, and cellular senescence: A mini-review. Gerontology. 2018;64(2):127-34. doi:10.1159/000484629
2. Kim J, Guan KL. mTOR as a central hub of nutrient signalling and cell growth. Nat Cell Biol. 2019;21(1):63-71. doi:10.1038/s41556-018-0205-1
3. Kezic A, Popovic L, Lalic K. mTOR inhibitor therapy and metabolic consequences: Where do we stand? Oxid Med Cell Longev. 2018;2018:1-8. doi:10.1155/2018/2640342
4. Liu GY, Sabatini DM. mTOR at the nexus of nutrition, growth, ageing and disease. Nat Rev Mol Cell Biol. 2020;21(4):183-203. doi:10.1038/s41580-019-0199-y
5. Cayo A, Segovia R, Venturini W, Moore-Carrasco R, Valenzuela C, Brown N. mTOR activity and autophagy in senescent cells, a complex partnership. IJMS. 2021;22(15):8149. doi:10.3390/ijms22158149
6. Stallone G, Infante B, Prisciandaro C, Grandaliano G. mTOR and aging: An old fashioned dress. IJMS. 2019;20(11):2774. doi:10.3390/ijms20112774
7. Manole F, Marian P, Mekeres GM, Voiţă-Mekereş F. Systematic review of the effect of aging on health costs. Arch Pharm Pract. 2023;14(3):58-61.
8. Li Z, Zhang Z, Ren Y, Wang Y, Fang J, Yue H, et al. Aging and age-related diseases: From mechanisms to therapeutic strategies. Biogerontology. 2021;22(2):165-87. doi:10.1007/s10522-021-09910-5
9. Benhamú B, Martín-Fontecha M, Vázquez-Villa H, López-Rodríguez ML, Ortega-Gutiérrez S. New trends in aging drug discovery. Biomedicines. 2022;10(8):2006. doi:10.3390/biomedicines10082006
10. Alhazmi SMA, Alabbas FMA, Alyami HSA, Alharbi EME, Alilwit AOF, Ghamri MS, et al. Sexual dysfunction related to multiple sclerosis: Literature review. Int J Pharm Res Allied Sci. 2022;11(1):6-10.
11. Von Kobbe C. Cellular senescence: A view throughout organismal life. Cell Mol Life Sci. 2018;75(19):3553-67. doi:10.1007/s00018-018-2879-8

12. Alshammari QT, Alsubaie AN, Alkayyat AA, Qazaq AM, Alnukhali AA, Alrefaei MG, et al. Magnetic resonance imaging of chronic low back pain: Correlation between pain, disability, and disc herniation. Arch Pharm Pract. 2023;14(1):87-91.
13. Valencia WM, Palacio A, Tamariz L, Florez H. Metformin and ageing: Improving ageing outcomes beyond glycaemic control. Diabetologia. 2017;60(9):1630-8. doi:10.1007/s00125-017-4349-5
14. Piskovatska V, Stefanyshyn N, Storey KB, Vaiserman AM, Lushchak O. Metformin as a geroprotector: Experimental and clinical evidence. Biogerontology. 2019;20(1):33-48. doi:10.1007/s10522-018-9773-5
15. Mohammed I, Hollenberg MD, Ding H, Triggle CR. A critical review of the evidence that metformin is a putative anti-aging drug that enhances healthspan and extends lifespan. Front Endocrinol. 2021;12:718942. doi:10.3389/fendo.2021.718942
16. Billman GE. Homeostasis: The underappreciated and far too often ignored central organizing principle of physiology. Front Physiol. 2020;11:200. doi:10.3389/fphys.2020.00200
17. Mohamad Kamal NS, Safuan S, Shamsuddin S, Foroozandeh P. Aging of the cells: Insight into cellular senescence and detection Methods. Eur J Cell Biol. 2020;99(6):151108. doi:10.1016/j.ejcb.2020.151108
18. de Magalhães JP, Passos JF. Stress, cell senescence and organismal ageing. Mech Ageing Dev. 2018;170:2-9. doi:10.1016/j.mad.2017.07.001
19. Rhinn M, Ritschka B, Keyes WM. Cellular senescence in development, regeneration and disease. Development. 2019;146(20):dev151837. doi:10.1242/dev.151837
20. Pomatto LCD, Davies KJA. The role of declining adaptive homeostasis in ageing. J Physiol. 2017;595(24):7275-309. doi:10.1113/JP275072
21. Promislow D, Anderson RM, Scheffer M, Crespi B, DeGregori J, Harris K, et al. Resilience integrates concepts in aging research. iScience. 2022;25(5):104199. doi:10.1016/j.isci.2022.104199
22. Galluzzi L, Yamazaki T, Kroemer G. Linking cellular stress responses to systemic homeostasis. Nat Rev Mol Cell Biol. 2018;19(11):731-45. doi:10.1038/s41580-018-0068-0
23. Gorgoulis V, Adams PD, Alimonti A, Bennett DC, Bischof O, Bishop C, et al. Cellular senescence: Defining a path forward. Cell. 2019;179(4):813-27. doi:10.1016/j.cell.2019.10.005
24. Calcinotto A, Kohli J, Zagato E, Pellegrini L, Demaria M, Alimonti A. Cellular senescence: Aging, cancer, and injury. Physiol Rev. 2019;99(2):1047-78. doi:10.1152/physrev.00020.2018
25. Paramos-de-Carvalho D, Jacinto A, Saúde L. The right time for senescence. eLife. 2021;10:e72449. doi:10.7554/eLife.72449
26. Roger L, Tomas F, Gire V. Mechanisms and regulation of cellular senescence. IJMS. 2021;22(23):13173. doi:10.3390/ijms222313173
27. Herranz N, Gil J. Mechanisms and functions of cellular senescence. J Clin Investig. 2018;128(4):1238-46. doi:10.1172/JCI95148
28. Kumari R, Jat P. Mechanisms of cellular senescence: Cell cycle arrest and senescence associated secretory phenotype. Front Cell Dev Biol. 2021;9:645593. doi:10.3389/fcell.2021.645593
29. Mijit M, Caracciolo V, Melillo A, Amicarelli F, Giordano A. Role of p53 in the regulation of cellular senescence. Biomolecules. 2020;10(3):420. doi:10.3390/biom10030420
30. Wu D, Prives C. Relevance of the p53–MDM2 axis to aging. Cell Death Differ. 2018;25(1):169-79. doi:10.1038/cdd.2017.187
31. Fujimaki K, Li R, Chen H, Della Croce K, Zhang HH, Xing J, et al. Graded regulation of cellular quiescence depth between proliferation and senescence by a lysosomal dimmer switch. Proc Natl Acad Sci USA. 2019;116(45):22624-34. doi:10.1073/pnas.1915905116
32. Wang Z. Regulation of cell cycle progression by growth factor-induced cell signaling. Cells. 2021;10(12):3327. doi:10.3390/cells10123327
33. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell. 2017;168(6):960-76. doi:10.1016/j.cell.2017.02.004
34. Deleyto-Seldas N, Efeyan A. The mTOR–Autophagy axis and the control of metabolism. Front Cell Dev Biol. 2021;9:655731. doi:10.3389/fcell.2021.655731
35. Sun Y, Wang H, Qu T, Luo J, An P, Ren F, et al. mTORC2: A multifaceted regulator of autophagy. Cell Commun Signal. 2023;21(1):4. doi:10.1186/s12964-022-00859-7
36. Lindström MS, Bartek J, Maya-Mendoza A. p53 at the crossroad of DNA replication and ribosome biogenesis stress pathways. Cell Death Differ. 2022;29(5):972-82. doi:10.1038/s41418-022-00999-w
37. Cui D, Qu R, Liu D, Xiong X, Liang T, Zhao Y. The cross talk between p53 and mTOR pathways in response to physiological and genotoxic stresses. Front Cell Dev Biol. 2021;9:775507. doi:10.3389/fcell.2021.775507
38. Jung SH, Hwang HJ, Kang D, Park HA, Lee HC, Jeong D, et al. mTOR kinase leads to PTEN-loss-induced cellular senescence by phosphorylating p53. Oncogene. 2019;38(10):1639-50. doi:10.1038/s41388-018-0521-8
39. Saoudaoui S, Bernard M, Cardin GB, Malaquin N, Christopoulos A, Rodier F. mTOR as a senescence manipulation target: A forked road. In: Advances in Cancer Research. Vol 150. Elsevier; 2021:335-63. doi:10.1016/bs.acr.2021.02.002
40. Kaur J, Farr JN. Cellular senescence in age-related disorders. Transl Res. 2020;226:96-104. doi:10.1016/j.trsl.2020.06.007
41. Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F. Cellular senescence in ageing: From mechanisms to therapeutic opportunities. Nat Rev Mol Cell Biol. 2021;22(2):75-95. doi:10.1038/s41580-020-00314-w

42. Kirkland JL, Tchkonia T. Cellular senescence: A translational perspective. EBioMedicine. 2017;21:21-8. doi:10.1016/j.ebiom.2017.04.013
43. Zhang L, Pitcher LE, Yousefzadeh MJ, Niedernhofer LJ, Robbins PD, Zhu Y. Cellular senescence: A key therapeutic target in aging and diseases. J Clin Investig. 2022;132(15):e158450. doi:10.1172/JCI158450
44. Elssayed A, AlRgaiba RI, AlZalbani MK, Hassan MRJ, AlMalki KH, AlGhannam AA, et al. Review on diagnosis and management approach of multiple sclerosis. Int J Pharm Res Allied Sci. 2023;12(1):100-5.
45. Kulkarni AS, Gubbi S, Barzilai N. Benefits of metformin in attenuating the hallmarks of aging. Cell Metab. 2020;32(1):15-30. doi:10.1016/j.cmet.2020.04.001
46. Yousif E, Loaz O, Almohiy H, Algahtani M, Alelyani M, Salih M, et al. Clinical evaluation and standardization of image quality and technical protocols for special radiological procedures. Int J Pharm Res Allied Sci. 2023;12(1):116-22.
47. Hu D, Xie F, Xiao Y, Lu C, Zhong J, Huang D, et al. Metformin: A potential candidate for targeting aging mechanisms. Aging Dis. 2021;12(2):480. doi:10.14336/AD.2020.0702
48. Li Z, Liu L, Yang Y, Zheng H, Cai Y, Ma Y, et al. Metformin ameliorates senescence of adipose-derived mesenchymal stem cells and attenuates osteoarthritis progression via the AMPK-Dependent autophagy pathway. Oxid Med Cell Longev. 2022;2022:1-17. doi:10.1155/2022/4620254
49. Feng X, Pan J, Li J, Zeng C, Qi W, Shao Y, et al. Metformin attenuates cartilage degeneration in an experimental osteoarthritis model by regulating AMPK/mTOR. Aging. 2020;12(2):1087-103. doi:10.18632/aging.102635
50. Chen Q, Zhang H, Yang Y, Zhang S, Wang J, Zhang D, et al. Metformin attenuates UVA-Induced skin photoaging by suppressing mitophagy and the PI3K/AKT/mTOR Pathway. IJMS. 2022;23(13):6960. doi:10.3390/ijms23136960
51. Wang Y, Xu W, Yan Z, Zhao W, Mi J, Li J, et al. Metformin induces autophagy and G0/G1 phase cell cycle arrest in myeloma by targeting the AMPK/mTORC1 and mTORC2 pathways. J Exp Clin Cancer Res. 2018;37(1):63. doi:10.1186/s13046-018-0731-5
52. Zhang S, Zhang R, Qiao P, Ma X, Lu R, Wang F, et al. Metformin-Induced MicroRNA-34a-3p downregulation alleviates senescence in human dental pulp stem cells by targeting CAB39 through the AMPK/mTOR signaling pathway. Stem Cells Int. 2021;2021:1-13. doi:10.1155/2021/6616240