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Changes in The Aging Cytoskeleton and How Metformin Plays a Role in Delaying Aging

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ABSTRACT

The cytoskeleton plays an important role in forming the cell framework and dynamics. The part that plays a role in supporting the spatial and mechanical functions of the cell is located in the cytoskeleton. Therefore, strategies to maintain the integrity and dynamics of the cytoskeleton have potential as therapies for age-related disorders. One thing that can be used to delay aging is metformin. Through AMPK activation, it can influence the cytoskeleton; namely, it can remodel the dynamics of the cytoskeleton by influencing structural changes in the actin cytoskeleton, which in turn will reduce the permeability of the filtration barrier in diabetic conditions and can increase insulin sensitivity, especially in old age, thereby delaying aging. In this review, we review the current understanding of the role played by the cytoskeleton in aging and review the opportunities and challenges for transitioning basic research into intervention development. Methods: Several major electronic databases, including PubMed, Scopus, and Cohcrane were used to select articles between April 2013 and April 2023. From the 8 existing literature, we present the activity of metformin as an aging delay. Cytoskeleton can change with age so it can affect the dynamics and structure of the cell. Metformin shows significant benefits, especially in delaying aging, through activation of the AMPK pathway so that it can increase the activity of mitochondria in producing ATP, which can affect the structure of the cytoskeleton. With this article on changes in the cytoskeleton with aging, it is hoped that insight into future research directions can be achieved.

Keywords: actin, aging cytoskeleton, delay aging, metformin, vimentin

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INTRODUCTION

With the advancement of medical technology, the average lifespan of people has steadily grown. However, the negative aspect of this health prosperity is the rising prevalence of aging. The World Health Organization (WHO) predicts that between 2015 and 2050, the proportion of individuals 60 and older will rise from 12% to 22% globally, comprising around 2 billion people.(WHO, 2022) A combination of genetic and environmental factors can influence the human aging process. Alterations in many cellular signaling pathways and metabolic activities can identify it. These include the generation of oxidative stress, the attrition of telomeres, epigenetic changes, disruptions in proteostasis and autophagy, and alterations in mitochondrial function.(Blackburn et al., 2015; Bonomini et al., 2015; Pal & Tyler, 2016; Picca et al., 2017) These factors collectively contribute to the aging process and can impact various cellular and organismal function aspects.

Aging is a complex phenomenon related to the gradual decline in the function of cells, tissues, and the whole organism throughout life, as cell structure and integrity changes. The structure and integrity of the cytoskeleton are associated with several cellular functions, such as migration, proliferation, degeneration, and mitochondrial bioenergy production, as well as chronic disorders. Cytoskeletal integrity is closely related to several functional activities of cells, such as aging, proliferation, degeneration, and mitochondrial bioenergy production.(Janikiewicz et al., 2018; Kim et al., 2022)

Any safe strategy that can delay or avoid aging can provide interesting results in preventing chronic diseases and can prolong a healthy life, namely diet, exercise, and using anti-aging agents. One of them is using metformin. Metformin has become the primary treatment for individuals with type 2 diabetes (T2DM) and is the most commonly prescribed drug for diabetes worldwide. Additionally, metformin may influence metabolic and cellular processes associated with age-related chronic conditions such as inflammation, fatty liver, oxidative damage, protein glycation, and cellular senescence. Moreover, metformin's role in reducing the production of reactive oxygen species (ROS) can be attributed to inhibiting the electron transport chain and inducing the expression of antioxidant genes through the SKN-1/Nrf2 transcription pathway. This mechanism provides insights into how metformin lowers ROS production. AMP-activated protein kinase (AMPK) is a vital energy status sensor that regulates the overall metabolic energy balance in the body. AMP-activated protein kinase (AMPK), a known regulator of cellular and systemic energy balance, is now recognized to control cell division, cell polarity, and cell migration, depending on the actin cytoskeleton.(Novelle et al., 2016)

Nevertheless, recent research has investigated several metabolism-modifying drugs, including metformin, that have been found to inhibit the aging process. These drugs function as molecular agents, which may allow examination of the pathways and mechanisms involved in the aging process.(Barzilai et al., 2016) More recently, multiple studies using different cell lines and organismal models have shown metformin to have the potential to slow aging by targeting key molecules associated with aging. Research has also reported the role of metformin in inhibiting cellular aging through the modulation of cytoskeletal dynamics.(Szrejder et al., 2020) Researchers found that metformin was associated with a slight increase in intracellular ATP levels. It should be noted that the inhibition of mitochondrial function by metformin is concentration-dependent and only has an inhibitory effect at certain concentrations. In addition, low-dose metformin increased the activity of mitochondrial complex I in previous studies. Fenestration is dependent on actin remodeling, which requires ATP; therefore, any increase in ATP with metformin can increase fenestration formation. Thus, it can increase insulin sensitivity and ultimately can delay aging. So it can be concluded that metformin can influence AMPK, which can delay aging.(Hunt et al., 2020a) However, reviews on this topic still need to be improved.

RESEARCH METHOD

Search strategy

Our review encompassed a comprehensive literature search using keywords such as metformin, aging, cytoskeleton, and other related terms. Three primary electronic databases, including PubMed, Scopus, and Cochrane, were used to search for articles on metformin and its beneficial effects as an anti-aging agent. Studies conducted between August 2013 to August 2023 were included. No duplicate studies were found among the collected research articles.

Study selection

In the first stage, we screen and review articles by comparing criteria with abstracts and titles to see how well they fit. Inclusion criteria were established, including studies that evaluated the influence of metformin in delaying aging with a focus on its cytoskeletal effects. In addition to systematic reviews, we also included both in vitro and in vivo experimental investigations. Other study designs, such as theses and reviews without a specific focus, were excluded from the inclusion criteria. We verified the selected articles by checking their indexing in Scimago Journal and Country Rank (SJR) and scopus.

The next step involved determining exclusion criteria, such as studies on different populations or interventions. Information was taken from the chosen studies, including study populations, intervention details, outcomes, and critical findings. A qualitative approach was used to synthesize the data. Themes were identified across the studies, including the effectiveness of the interventions. The review was edited and revised for clarity, accuracy, and coherence. Additionally, the review was examined for errors and biases.

Data collection

Studies that meet the criteria will be summarized, and pertinent information, such as author names, countries, study aims, and key findings, will be retrieved. They will then be arranged in a table made in Microsoft Excel 2010 after that.

RESULTS AND DISCUSSION

After carefully searching databases, eliminating duplicates, and screening for inclusion criteria, we showed that metformin has an aging-delaying effect from the nine extant literature (Table 1). All of these results have been confirmed at SJR, as previously mentioned. Experts from the United States, The United Kingdom, and The Netherlands carried out most of the chosen studies.

Cytoskeleton

The cytoskeleton is one of the most complicated and functionally versatile structures, and it consists of 25 nm microtubules (α- and β-tubulin), 8-12 nm intermediate filaments (vimentin), and 5-9 nm microfilaments 9actin). Actin is a fundamental component of the cell's cytoskeleton and is crucial in providing structural stability and contributing to the cellular shape. It is the most abundant protein in most eukaryotic cells' cytoskeleton. Actin can be found in filamentous (F-actin) and monomeric (G-actin). The hydrolysis of nucleotides, the presence of ions, and the kind of actin-binding protein are some variables that control the transitions between these two states. This dynamic behavior of actin is essential for its involvement in a wide range of cellular functions. The filamentous actin cytoskeleton (F-actin) must be properly regulated to perform cell division, endocytosis, and migration.(Pollard & Goldman, 2018) The mechanical environment within cells plays a significant role in regulating these processes by connecting microtubules and microfilaments at the cell membrane and within the nucleus.

Microfilaments, also called actin filaments, primarily consist of actin and form helical structures composed of two actin strands. These filaments have a slender diameter of approximately 7nm, making them the thinnest components of the cytoskeleton. Microfilaments serve diverse functions, including facilitating cytokinesis (cell division), promoting cell motility, and enabling the movement of cytosol throughout the cell to support nutrient and organelle transport. In addition, microfilaments play a critical role in muscle cells, where they, along with myosin, constitute the contractile elements responsible for muscle contraction. Actin and myosin are the primary components involved in muscle contraction.(Sliogeryte & Gavara, 2019; J. Wilson & Hunt, 2014)

Microtubules are prominent cytoskeleton components, forming hollow tubes with a diameter of approximately 23nm. They are composed α-, β-, and γ-tubulin dimers that polymerize. Microtubules have a variety of functions, including generating the flagella that help cells move forward and the mitotic spindle that separates chromatids during cell division and ensures they are distributed evenly to daughter cells. These extremely dynamic polar filaments are made of actively polymerizing and depolymerizing α/β-tubulin dimers, essential for cell survival and function.(Goodson & Jonasson, 2018) The cytoskeletal network of microtubules is dynamic and constantly undergoing repair.(J. Wilson & Hunt, 2014)

Intermediate filaments have a size range of approximately 8 to 12 nanometers, which positions them between the smaller (actin filaments) and larger microtubules. They have a variety of proteins, including keratin, vimentin, desmin, and lamin. Contrary to lamins, specifically found in the nucleus and support the nuclear envelope there, several intermediate filament proteins are distributed in the cytoplasm. The cytoplasmic intermediate filaments serve the purposes of providing structural support, providing tension, and maintaining cellular shape. They are dispersed throughout the cytoplasm and the nucleus's inner membrane. The proteins that make up intermediate filaments are fibrous, as opposed to the globular proteins that comprise actin and microtubules. They lack polarity, unlike actin and microtubules, but they possess flexibility, elasticity, and high tensile strength. Consequently, intermediate filaments are the most stable component of the cytoskeleton.(Lai & Wong, 2020)

Table 1

Studies of the aging cytoskeleton

Authors	Study Objective	Study Group	Type of Cytoskeleton	Principals Findings
Nicholas J. Hunt, Glen P. Lockwood, Sun Woo Kang, Tamara Pulpitel,	To see how metformin impacts the aging process and	The study was divided into 2 groups of young mice aged 3-4 months and old mice aged 18 months. Then divided into 4 groups each	Actin	Aging that occurs will change the structure of the actin cytoskeleton. Metformin, which is a delayer of aging, can increase transgelin expression and influence structural changes in the actin

Authors	Study Objective	Study Group	Type of Cytoskeleton	Principals Findings
Ximonie Clark, et al.	improves insulin resistance	with 5 μM, 50 μM, dan 100 μM metformin.		cytoskeleton, thereby increasing cell fenestration.
Gilberto Garcia, Raz Bar-Ziv, Maxim Averbukh, Nirmalya Dasgupta, Naibedya Dutta, Hanlin Zhang, Wudi Fan, et al.	To identify the bromodomain protein, BET-1, as a key regulator of actin function and longevity.	The study used a multipronged, cross-organismal screen combining a whole-genome CRISPR-Cas9 screen in human fibroblasts with in vivo Caenorhabditis elegans synthetic lethality screening.	Actin	The actin cytoskeleton is required for many cellular pathways, including cell division, autophagy, chaperone function, endocytosis, and exocytosis. Deterioration of this process manifests during aging and exposure to stress, caused in part by damage to the actin cytoskeleton. Overexpression of BET-1 preserves actin function in old age and increases lifespan.
Yuxuan Zheng, Michael L. Merchant, Tom J. Burke, Jeffrey D. Ritzenthaler, Ming Li, Adam E. Gaweda, et al.	To evaluate the effects of aging on the redox states of intracellular proteins and to examine whether Slc7a11 contributes to the age-dependent effects.	Primary lung fibroblasts were isolated from young (3 months) or old (24 months) female C57BL/6 mice.	Actin	In human skin fibroblasts, changes in the actin cytoskeleton result in disruption of the TGF-β signaling pathway followed by collagen production, thereby triggering skin aging. The actin cytoskeleton is believed to have an important role in fibroblast differentiation, myofibroblast contraction, formation of focal adhesion complexes, extracellular matrix remodeling, mechanical to biochemical signal transduction, and gene transcription.
Sam Dunkley, Binyam Mogessie.	To show that F-actin maintains chromatid association after cohesion deterioration in aged eggs.	Oocytes were isolated from the ovaries of 8- to 12-week CD1 or C57BL/6 (young) or 8 to 9 months CD1 or 13 to 14 months C57BL/6 (aged) mice, cultured, and microinjected with 6 to 8 pl of in vitro transcribed mRNA as decribed in detail recently.	Actin	The integrity of the actin cytoskeleton is critically affected by aging and may limit the rate of premature chromatid separation arising from loss of centromeric cohesion.
Maria Hernandez-Valladres, Elise Aasebo, Frode Berven, Frode Selheim, Oystein Bruserud.	To see biological characteristics of aging in human acute myeloid leukemia cells.	They compared AML cell proteomic and phosphoproteomic profiles for Group 1, elderly low-risk and younger low-risk patients with favorable genetic abnormalities; Group 2, high-risk patients with adverse genetic abnormalities and a higher median age against all low-risk patients with lower median age.	Actin, Microtubule	Cytoskeletal proteins can be viewed as part of the aging process and the relationship between age and changes in levels/phosphorylation of cytoskeletal proteins may reflect the impact of aging on AML.
Xiaodong Mu, Chieh Tseng, William S. Hambright, Polina Matre, Chic-Yi Lin, Palas Chanda, et al.	To observe that increased cytoskeletal stiffness and RhoA activation in progeria cells were directly coupled with increased nuclear blebbing, sun2 expression, and micronuclei-induced cGAS-Sting activation, part of the innate immune response.	The study used muscle-derived mesenchymal stromal/stem cells (MSCs) from the Zmpste24−/− (Z24−/−) mouse (a model for HGPS) and human HGPS fibroblasts.	Actin	Increased ECM stiffness and nuclear stiffness of progeria cells contribute to increased RhoA activation and cytoskeleton stiffness. Increased ROS production, inflammatory signals (NF-κB), and DNA damage in progeria cells can promote RhoA activation, thereby further increasing cytoskeleton stiffness.
Kristina Sliogeryte, Nuria Gavara.	To see how the biophysical changes impair the	Cells were derived from temple or labia tissue.	Vimentin	Increased vimentin assembly may underlay the aberrant biophysical properties progressively observed at the

Authors	Study Objective	Study Group	Type of Cytoskeleton	Principals Findings
	cellular function of human dermal fibroblasts.	Neonatal and adult age 62, adult age 21, and age 47.		cellular level in the course of human ageing.
Danila Bobkov, Anastasia Polyanskaya, Anastasia Musorina, Ekaterina Lomert, Sergey Shabelnikov, Galina Poljanskaya.	To see changes in cell motility and organization of the contractile apparatus of the human umbilical cord Wharton's jelly mesenchymal stem cells (MSCWJ-1) in the process of replicative senescence.	MSCWJ-1 is a human mesenchymal stem cell line obtained from Wharton's jelly of the human umbilical cord. In each independent experiment: one vial with cells was thawed from the cryobank; cells were passaged; and at selected passages, cells were prepared in accordance with the following procedures.	Actin	The higher the passage, there is an increase in the structural integrity of the actin cytoskeleton, a significant reduction in nuclear RhoA levels; and decreased cell velocity.

Changes in Cytoskeletal Integrity as Mediators of Aging

Apart from actin expression, age-related disturbances have been reported in the actin cytoskeleton. The mechanisms by which the actin cytoskeleton is involved in the aging process mainly revolve around three pillars: chaperonin-assisted folding, interaction with actin-binding proteins, and Post-Translational Modifications (PTMs).(Balchin et al., 2018; Pollard, 2016) Disruptions in these three pillars during the aging process can hinder cellular function. In addition to somatic cells, stem and progenitor cells may operate improperly due to modifications in the actin cytoskeleton.(Lai & Wong, 2020) As explained in Table 1, the aging process carried out on cell cultures taken from the human umbilical cord carried out passage up to passage 38, this process affects the integrity of the cytoskeleton, especially actin in passages 15 to 38 with the result that actin integrity increases.(Bobkov et al., 2020)

Changes in Actin Expression during Aging

Actin filaments can affect the shape and stiffness of cells and influence cellular movement.(Lai & Wong, 2020) When a cell interacts with its surrounding cells or the Extracellular Matrix (ECM), its direction and degree of movement can be observed.(Svitkina, 2018) By binding with the protein myosin, actin filaments play a crucial role in activating essential processes such as cytokinesis during cell division and muscle contraction.(Chou & Pollard, 2019) The actin cytoskeleton generates internal forces that play a critical role in numerous cellular processes, such as cell division, cell motility, muscle contraction, cytokinesis, and intracellular transport.(Pollard, 2016) Disruptions in the dynamic behavior of actin, which can occur due to mutations in actin or actin-binding proteins or the administration of actin-binding drugs, can lead to significant changes in cellular structure and function.(Kawaguchi & Asano, 2022) An increase in the turnover of F-actin may contribute to cellular senescence, while a decrease in actin turnover can lead to cell death via pathways like apoptosis.(Tang et al., 2019) Actin turnover also plays a role in reducing the number of senescent cells.(Kawaguchi & Asano, 2022) Age-related diseases can result from the aging process, which can alter actin expression in the cytoskeleton and disturb the dynamics and organization of the actin cytoskeleton. Factors contributing to altered actin expression with aging include hormonal changes, nutrition, and actin polymerization activity within the cytoskeleton.(Lai & Wong, 2020) Cytoskeleton expression, especially actin, was seen in research conducted using the human umbilical cord during the aging process; seen from the proteins that bind to actin, namely myosin-9 and α-actinin-4, the expression of actin will change with age.(Bobkov et al., 2020)

Actin Damage by Reactive Oxygen Species (ROS) in the Aging Process

The signaling network of the actin cytoskeleton consists of a diverse range of proteins, such as kinases, phosphatases, integrins, GTPases, ion channels, and transporters. These proteins can directly regulate actin's arrangement, organization, and function within the cytoskeleton. Additionally, they can indirectly impact cell growth and survival.(Q. Xu et al., 2017) Reactive oxygen species (ROS) must be present at optimal levels for cellular processes, including calcium homeostasis, ion channel kinetics, and cytoskeletal remodeling to occur usually.(C. Wilson & González-Billault, 2015) But dysregulation of actin and microtubule dynamics can occur when chemical reduction and oxidation are not balanced.(Kawaguchi & Asano, 2022) Microtubule polymerization capacity is decreased, and actin filaments are disrupted due to the oxidation of specific amino acid residues in microtubules and actin filaments. Conversely, inhibiting ROS production can lead to abnormal actin polymerization and impaired cellular function.(C. Wilson & González-Billault, 2015) Although ROS production may increase with aging, it is unknown if ROS damage causes aging.(Roy et al., 2017) Oxidative stress can harm the reorganization of the actin cytoskeleton through direct modifications of actin itself or actin regulatory proteins. These modifications can disrupt cytoskeletal dynamics and the ability of G-actin to polymerize. Additionally, reactive oxygen species (ROS) can impact the actin cytoskeleton signaling process by oxidizing actin regulatory proteins or altering pertinent proteins' expression.(Kim et al., 2022) In other studies, metformin can rearrange the disorganized cytoskeleton of the trabecular meshwork (TM) both in vivo and in vitro and significantly inhibits tert-butyl hydroperoxide (tBHP) induced ROS production and activation of integrin/Rho-associated protein kinase (ROCK) signaling in human TM cells (HTMCs). Thus, metformin can reduce IOP elevation in steroid-induced OHT rat models and exert a protective effect against oxidative injury by regulating cytoskeleton remodeling via the integrin/ROCK pathway.(Xu et al., 2023)

Changes in Intermediate Filaments during Aging

Intermediate filaments have a significant impact on the regulation of cellular signaling pathways that are involved in cell survival and proliferation. They also contribute to tissue repair and regrowth following injury. The composition and organization of the intermediate filament network are altered due to tissue damage, which impacts the viscoelastic characteristics of cells. This is important for regenerated cells to migrate to the injury site as efficiently as possible.(Kim et al., 2022) Intermediate filament proteins present in focal adhesions also participate in integrin-based mechanical transduction, particularly in response to extracellular matrix (ECM) stiffness, which can indicate aging.(Langlois et al., 2017) Changes to the structure of actin and intermediate filaments can negatively impact chondrocytes' elastic modulus and viscoelastic properties. The connection between intermediate filaments and actin in chondrocytes is established through the involvement of lectins, which link different components of the cytoskeleton pectin and play a role in determining the mechanical characteristics of individual cells. Minor disturbances in the intermediate filaments can compromise this interaction, leading to structural modifications in the actin cytoskeleton.(Ndiaye et al., 2022) In previous research, referring to Table 1, changes occurred in vimentin, namely that as the cells got older, the amount of vimentin increased, and the shape also became shorter and thicker.(Sliogeryte & Gavara, 2019)

Changes in Microtubule Expression with Aging

Changes in the mechanical properties of human skin are a major characteristic of aging. In addition to changes in collagen and elastin organization and ECM density, dermal fibroblasts from aged donors were 60% stiffer than those from younger donors. The increased stiffness of older fibroblasts is due to increased actin polymerization, leading to increased levels of actin filaments. In addition, the research shows a possible correlation between increased cell stiffness and higher microtubule cytoskeleton. An increase in the number of microtubules will affect the main function of the microtubules themselves, namely in connection with mitochondria. So that in the aging process, ATP production will decrease.(Kim et al., 2022; Sliogeryte & Gavara, 2019)

Metformin's Anti-Aging Effects

Metformin Delays Aging through the Insulin/Insulin-like Growth Factor-1 Signaling (IIS) Elevated blood sugar levels (hyperglycemia) and excessive insulin levels (hyperinsulinemia) contribute to accelerated aging, and the insulin/insulin-like growth factor signaling (IIS) pathway regulates both of these conditions. The porosity of the fenestrations of the hepatic sinusoidal endothelial cells explicitly affects the liver's sensitivity to insulin.(Mohamad et al., 2016) In experiments involving mice, the administration of metformin over nine months increased porosity and frequency of fenestrations in the liver, leading to improved insulin sensitivity and an extended lifespan. (Hu et al., 2021) Other studies have also demonstrated that long-term treatment with metformin improves physical performance, enhances insulin sensitivity, and increases lifespan.(Novelle et al., 2016)

Metformin Reduces Accumulation of AGEs

Advanced Glycation End-products (AGEs) buildup is associated with aging and serves as a marker of aging. AGEs are formed when glucose combines with other proteins. High glucose levels can lead to the functional loss of normal proteins, converting them into senescent proteins. By encouraging the use of glucose in tissues, the drug metformin, which is frequently prescribed to treat type 2 diabetes, might lessen the buildup of AGEs. This process can strengthen the interaction between AGEs and their RAGE receptor. After binding, nuclear factor- κB signaling and intracellular oxidative stress are induced, which regulates the transcriptional levels of tumor necrosis factor-alpha (TNF- α) and endothelin-1. These regulatory processes may ultimately contribute to delaying cellular senescence.(Haddad et al., 2016)

Metformin Delays Aging by Regulating ROS Levels

Metformin can decrease the generation of reactive oxygen species (ROS) within mitochondria by reversing the electron flow from mitochondrial respiratory chain complex I. This mechanism plays a crucial role in extending cellular lifespan. By reducing mitochondrial potential and ROS levels, metformin effectively inhibits cellular aging processes.(Y. Xu et al., 2018) Long-term administration of low-dose metformin can lead to an increase in glutathione peroxidase 7 localized in the endoplasmic reticulum (ER). This increase may potentially safeguard human cells from premature aging.(Fang et al., 2018) It's worth noting that while metformin generally reduces intracellular ROS, it can also have the opposite effect on ROS production. For instance, the author found that metformin can increase ROS levels, which activates the transcription of SKN-1, a factor known to prolong longevity in worm cells, De Haes *et al*.(De Haes et al., 2014)

Indeed, metformin has been found to stimulate the production of physiological levels of reactive oxygen species (ROS) to activate SKN-1, a factor associated with delaying aging. Metformin can also alleviate oxidative stress by enhancing the levels of SIRT3 within mitochondria. Through the activation of AMPK, metformin promotes H3K79 methylation and increases SIRT3 levels, ultimately attenuating senescence in endothelial cells.(Karnewar et al., 2018) In summary, ROS at physiological levels can activate SKN-1 to impede aging processes, whereas excessive ROS can induce oxidative stress and cause cellular damage.

Metformin Regulates Protein Homeostasis

According to previous studies, metformin treatment has been associated with a decrease in global progerin expression in human breast carcinoma cells. Progerin is a mutated form of lamin A, a nuclear envelope protein that can accelerate cellular aging. Metformin is believed to reduce the translation of progerin protein, thereby contributing to the delay of aging processes. Additionally, metformin has been shown to promote the clearance of progerin protein through the activation of autophagy, which can ultimately extend the lifespan of cells.(Park & Shin, 2017)

Furthermore, metformin can inhibit aging by stimulating the production of specific proteins related to aging. For example, it can increase the expression of glutathione peroxidase 7 (GPx7), which protects against oxidative stress and contributes to the extension of cellular lifespan.(Fang et al., 2018)

Metformin Maintains Telomere Stability

Research conducted by Garcia-Martin *et al*.(Kreutzenberg et al., 2015) has demonstrated that metformin may stop the telomere erosive process in the placenta. The metformin-treated group exhibited significantly longer telomeres compared to the placebo group.(Kreutzenberg et al., 2015) Furthermore, metformin activates RAG1, an endonuclease that promotes DNA cleavage and translocation, ultimately leading to telomerase activation. This activation of telomerase helps in stabilizing chromosomes.(Finley, 2018) In addition, metformin can also activate the telomere transcription process via SIRT1.(Zheng et al., 2020) The active forces of the cytoskeleton regulate nuclear and chromatin dynamics, which in turn can affect the spatiotemporal regulation of genomic processes and influence cell behavior. With the cytoskeleton physically linked to the nucleoskeleton, these extracellular mechanical signals can mediate changes in chromatin structure. Active cytoskeletal forces can mediate mechanotransduction to the nucleus, reorganizing chromosome organization and the permissiveness of chromatin structure by regulatory molecules. Cytoskeletal junctions to the nucleus are also crucial for maintaining quiescent euchromatin and the more repressive condensed chromatin, namely heterochromatin assembly. The connections between the actin cytoskeleton and the nuclear membrane stabilize heterochromatin.(Makhija et al., 2016) Overall, metformin can slow down the aging process by preserving telomere length.

Effect of metformin on the cytoskeleton

Metformin can not only reduce the accumulation of AGEs, and regulate ROS levels but also cause increased transgelin expression and structural changes in the actin cytoskeleton. In conclusion, metformin ameliorated age-related changes in liver sinusoidal endothelial cells through AMPK and endothelial nitric oxide pathways, which may improve insulin sensitivity in the liver, especially in old age. Metformin may also delay aging through its effects on nutrient-sensing pathways, specifically by activating AMPK. Through calorie restriction, Metformin can prevent defenestration, which can cause insulin resistance and pseudocapillary changes.(Hunt et al., 2020) Previous studies revealed metformin's beneficial and protective effects on centrosome amplification through modulating AKT/TOR signaling to inhibit centrosome amplification caused by age and oxidative stress. Where the centrosome itself contains many microtubule cytoskeleton components.(Na et al., 2015)

CONCLUSION

The cytoskeleton, which serves as a support for cells, plays a vital role in cell aging. Actin is thought to play a direct role in aging, especially on 3 pillars: chaperonin-assisted folding, interaction with actin-binding proteins, and Post-Translational Modifications (PTMs). ROS production may increase with age, but it is unknown whether damage to ROS causes aging. Oxidative stress can harm actin cytoskeleton reorganization through direct modification of actin itself or actin regulatory proteins. These modifications can impair cytoskeletal dynamics and the ability to polymerize. Age-related diseases can occur due to the aging process, which can alter actin expression in the cytoskeleton and disrupt the dynamics and organization of the cytoskeleton. Metformin, a type 2 diabetes mellitus drug, has shown many significant benefits, especially in delaying aging by activating the AMPK pathway to increase mitochondrial activity in producing ATP, which can then affect the structure of the cytoskeleton. ROS can also be inhibited by metformin, resulting in remodeling of the cytoskeleton via the ROCK pathway. With this article on changes in the cytoskeleton with aging, it is hoped that insights into future research directions can be achieved.

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