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The Centriolar Theory of Differentiation Explains the Biological Meaning of the Centriolar Theory of Organismal Aging

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Abstract

Centrioles, once thought to be simple structural components of the cell, have emerged as critical players in the aging process. This article reviews the existing theories linking centrioles to organismal aging, focusing on their roles in genomic stability, stem cell function, ciliary signaling, oxidative stress, and replicative Hayflick limit. Explored the evidence from model organisms, human studies, and clinical implications, highlighting the potential of centriole-targeted therapies to delay aging and prevent age-related diseases. By integrating findings from cellular biology, genetics, and clinical research, this article provides a comprehensive overview of the current understanding of centrioles in aging and outlines future directions for research and therapeutic development. The Centriolar Theory of Aging of the Organism is presented, which sees the accumulation of old, unrepairable centrioles in the organism as the main cause of the aging phenomenon. The biological meaning of this theory is explained by the Centriolar Theory of Differentiation, which links differentiation with centrioles. Thus, aging of the organism is not a separately programmed process or a separately stochastic process - both of these processes contribute. Aging of the organism is the result of the accumulation of old, unrepairable centrioles (stochastically accumulating defects) by the organism due to the implementation of differentiation programs (in the processes of development and then self-restoration).

Keywords: Centrioles, Aging, Genomic Instability, Senescence, Oxidative Stress, Stem Cell Dysfunction, Biogerontology.

Introduction

Aging is a complex biological process characterized by the progressive decline of cellular and organismal functions, leading to increased vulnerability to disease and death. While the molecular mechanisms underlying aging are multifaceted, recent research has highlighted the role of centrioles—microtubule-based organelles involved in cell division, signaling, and cellular organization—in the aging process. Centrioles are essential for the formation of centrosomes, which organize the mitotic spindle during cell division, and for the assembly of primary cilia, which act as sensory organelles in many cell types. Dysfunction in centrioles has been linked to a variety of age-related pathologies, including cancer, neurodegeneration, and tissue atrophy (Bettencourt-Dias & Glover, 2007; Nigg & Raff, 2009).

This article reviews the existing theories that link centrioles to organismal aging, focusing on their roles in genomic stability, stem cell function, ciliary signaling, cellular senescence, and oxidative stress. We also discuss evidence from model organisms, human studies, and clinical implications, as well as potential therapeutic interventions targeting centrioles to promote healthy aging.

Theories Linking Centrioles to Aging

Centrosome Amplification and Genomic Instability

Mechanism: Centriole overduplication leads to centrosome amplification, causing mitotic errors and aneuploidy. Centrosome amplification occurs when cells accumulate more than the typical two centrosomes, often due to defects in the regulation of centriole duplication. This can result in the formation of multipolar spindles during mitosis, leading to unequal chromosome segregation and aneuploidy—a condition characterized by an abnormal number of chromosomes (Nigg & Holland, 2018). Aneuploidy is a key driver of genomic instability, which is a hallmark of both aging and cancer (Gordon et al., 2012).

Evidence: Increased centrosome abnormalities have been observed in aged human cells and tissues, particularly in cancer cells. For example, studies have shown that aged fibroblasts and epithelial cells exhibit higher frequencies of centrosome amplification compared to younger cells (Prosser & Morrison, 2015). In cancer, centrosome amplification is a common feature of many tumor types, including breast, prostate, and lung cancers, and is associated with poor prognosis (Ganem et al., 2009). Additionally, research using mouse models has demonstrated that centrosome amplification can drive tumorigenesis by promoting chromosomal instability (Levine et al., 2017).

Implications: Genomic instability is a hallmark of aging and cancer, and centrosome amplification may contribute to both processes. In aging, the accumulation of centrosome abnormalities over time can lead to increased mitotic errors, cellular senescence, and tissue dysfunction (López-Otín et al., 2013). In cancer, centrosome amplification is a key contributor to tumor progression and metastasis, as it promotes chromosomal instability and genetic heterogeneity (Godinho & Pellman, 2014). Understanding the mechanisms underlying centrosome amplification and its role in genomic instability could provide new insights into the biology of aging and cancer, as well as potential therapeutic targets for age-related diseases and malignancies.

Stem Cell Dysfunction

Mechanism: Centriole defects impair asymmetric division in stem cells, leading to stem cell depletion. Stem cells rely on asymmetric cell division to maintain tissue homeostasis, a process in which one daughter cell retains stem cell properties while the other differentiates into a specialized cell type. Centrioles play a critical role in ensuring the fidelity of this process by organizing the mitotic spindle and ensuring proper segregation of cell fate determinants (Knoblich, 2010). Defects in centriole function, such as structural abnormalities or mislocalization, can disrupt asymmetric division, leading to an imbalance between stem cell self-renewal and differentiation. Over time, this imbalance results in stem cell depletion, reduced tissue regeneration, and accelerated aging (Gönczy, 2015).

Evidence: Studies in Drosophila and mammalian models have shown that centriole dysfunction is associated with impaired stem cell division and tissue regeneration. For example, in Drosophila, mutations in centriolar proteins such as SAS-4 disrupt centrosome function, leading to defective asymmetric division in neural stem cells and subsequent depletion of the stem cell pool (Basto et al., 2008). Similarly, in mammalian systems, centriole dysfunction in hematopoietic stem cells (HSCs) has been linked to impaired regenerative capacity and aging-related phenotypes (Yamashita et al., 2007). Additionally, research in mouse models has demonstrated that centriole defects in intestinal stem cells lead to disrupted tissue homeostasis and accelerated aging (Pineault et al., 2019).

Implications: Reduced tissue regeneration and repair capacity contribute to the aging phenotype. Stem cell dysfunction is a key driver of age-related tissue degeneration, as it impairs the body's ability to replace damaged or senescent cells (Rando & Chang, 2012). This decline in regenerative capacity is observed in multiple tissues, including the skin, blood, and nervous system, and is associated with increased susceptibility to age-related diseases such as anemia, neurodegeneration, and impaired wound healing (Oh et al., 2014). Understanding the role of centrioles in stem cell maintenance and function could provide new strategies for enhancing tissue regeneration and delaying the onset of age-related pathologies.

Ciliary Dysfunction

Mechanism: Defective centrioles impair primary cilia, disrupting signaling pathways. Primary cilia are microtubule-based organelles that extend from the cell surface and function as sensory antennae, detecting extracellular signals and transducing them into intracellular responses. Centrioles serve as the basal bodies for primary cilia, anchoring them to the cell membrane and ensuring their structural integrity (Satir & Christensen, 2007). When centrioles are defective, cilia formation or function is compromised, leading to disruptions in critical signaling pathways such as Hedgehog, Wnt, and PDGFα, which are essential for cell proliferation, differentiation, and tissue homeostasis (Anvarian et al., 2019).

Evidence: Age-related ciliary dysfunction has been documented in renal, neural, and retinal tissues. In the kidneys, ciliary defects are associated with polycystic kidney disease (PKD), a condition characterized by the formation of fluid-filled cysts that impair renal function (Fliegauf et al., 2007). In the nervous system, ciliary dysfunction has been linked to neurodegenerative diseases such as Alzheimer's and Parkinson's, where impaired cilia-mediated signaling contributes to neuronal loss and cognitive decline (Hilgendorf et al., 2016). In the retina, ciliary defects are implicated in

age-related macular degeneration (AMD) and retinitis pigmentosa, leading to progressive vision loss (Wheway et al., 2018).

Implications: Ciliary dysfunction contributes to age-related diseases such as polycystic kidney disease and neurodegeneration. The loss of ciliary function disrupts cellular communication and homeostasis, leading to tissue degeneration and disease progression (Goetz & Anderson, 2010). For example, in PKD, defective cilia fail to sense fluid flow in renal tubules, resulting in abnormal cell proliferation and cyst formation (Harris & Torres, 2009). In neurodegenerative diseases, impaired ciliary signaling disrupts neuronal maintenance and repair, accelerating disease onset and severity (Guemez-Gamboa et al., 2014). Understanding the role of centrioles in ciliary function and dysfunction could provide new therapeutic targets for treating age-related diseases and improving tissue repair.

Cellular Senescence

Mechanism: Centriole abnormalities trigger cellular senescence through mitotic errors or DNA damage responses. Cellular senescence is a state of permanent cell cycle arrest that is induced by various stressors, including DNA damage, oxidative stress, and mitotic errors. Centrioles play a critical role in ensuring accurate chromosome segregation during cell division, and defects in centriole structure or function can lead to mitotic errors such as multipolar spindle formation, chromosome missegregation, and aneuploidy (Nigg & Holland, 2018). These errors can activate the DNA damage response (DDR) pathway, leading to the upregulation of tumor suppressors such as p53 and p16INK4a, which enforce cell cycle arrest and induce senescence (Funk et al., 2012). Additionally, centriole abnormalities can disrupt centrosome function, further contributing to genomic instability and senescence (Prosser & Morrison, 2015).

Evidence: Senescent cells with centrosome defects have been identified in aged tissues. Studies have shown that aged tissues, such as skin, liver, and lung, exhibit an increased prevalence of senescent cells with centrosome abnormalities (Rodier et al., 2011). For example, in aged human fibroblasts, centrosome amplification and structural defects are frequently observed, and these cells often display markers of senescence, such as senescence-associated β-galactosidase (SA-β-gal) activity and elevated expression of p16INK4a (Funk et al., 2012). Similarly, in mouse models of aging, centrosome dysfunction has been linked to the accumulation of senescent cells in various tissues, contributing to age-related tissue degeneration (Pineault et al., 2019).

Implications: The senescence-associated secretory phenotype (SASP) contributes to chronic inflammation and tissue degeneration. Senescent cells secrete a variety of pro-inflammatory cytokines, chemokines, and proteases, collectively known as the SASP, which can disrupt tissue architecture and promote chronic inflammation (Campisi, 2013). This low-grade, systemic inflammation, often referred to as "inflammaging," is a hallmark of aging and is implicated in the pathogenesis of numerous age-related diseases, including cancer, cardiovascular disease, and neurodegenerative disorders (López-Otín et al., 2013). Centriole dysfunction and the resulting cellular senescence may thus play a key role in driving inflammaging and age-related tissue dysfunction. Targeting senescent cells or modulating the SASP could provide new therapeutic strategies for mitigating the effects of aging and preventing age-related diseases.

Oxidative Stress and Centriole Damage

Mechanism: Reactive oxygen species (ROS) damage centriolar proteins and microtubules. ROS are highly reactive molecules generated as byproducts of cellular metabolism, particularly in mitochondria. While ROS play important roles in cellular signaling, excessive ROS levels can cause oxidative damage to cellular components, including proteins, lipids, and DNA (Schieber & Chandel, 2014). Centrioles, which are composed of microtubules and associated proteins, are particularly vulnerable to oxidative damage due to their structural complexity and critical role in cell division and cilia formation. ROS can modify centriolar proteins, disrupt microtubule dynamics, and impair centrosome function, leading to defects in mitosis, ciliogenesis, and cellular organization (Funk et al., 2012).

Evidence: Increased oxidative damage to centrosomes has been observed in aged cells. Studies have shown that aged cells exhibit higher levels of oxidative stress markers, such as protein carbonylation and lipid peroxidation, which correlate with centrosome abnormalities (Funk et al., 2012). For example, in aged fibroblasts, oxidative damage to centrosomal proteins has been linked to centrosome amplification and mitotic defects (Prosser & Morrison, 2015). Additionally, experimental induction of oxidative stress in cultured cells results in centrosome fragmentation and impaired cilia formation, further supporting the role of ROS in centriole dysfunction (Pihan, 2013).

Implications: Cumulative damage to centrioles leads to impaired cell division and ciliary function. Oxidative damage to centrioles can disrupt their ability to organize the mitotic spindle, resulting in chromosome missegregation, aneuploidy, and genomic instability (Finkel & Holbrook, 2000). These defects contribute to cellular senescence, tissue degeneration, and increased cancer risk. Furthermore, oxidative damage to centrioles can impair the formation and function of primary cilia, disrupting critical signaling pathways such as Hedgehog and Wnt, which are essential for tissue development and homeostasis (Anvarian et al., 2019). Over time, the accumulation of oxidative damage to centrioles and centrosomes may play a significant role in the decline of cellular and tissue function observed during aging.

Centrosome Aging Hypothesis

Mechanism: Cumulative damage to centrosomes limits replicative potential (Hayflick limit). The centrosome aging hypothesis proposes that centrosomes, like other cellular components, accumulate damage over time, leading to a decline in their function and contributing to the finite replicative capacity of cells, known as the Hayflick limit (Hayflick & Moorhead, 1961). Centrosomes are essential for organizing the mitotic spindle and ensuring accurate chromosome segregation during cell division. Over time, oxidative stress, DNA damage, and protein misfolding can impair centrosome function, leading to mitotic errors, genomic instability, and eventual cell cycle arrest (Nigg & Holland, 2018). This progressive decline in centrosome function is thought to play a key role in cellular aging and the loss of tissue regenerative capacity.

Evidence: Reduced centrosome function has been observed in senescent cells. Studies have shown that senescent cells, which have reached their replicative limit, often exhibit centrosome abnormalities such as fragmentation, overduplication, and mislocalization (Hinchcliffe & Sluder, 2001). For example, in aged human fibroblasts, centrosome dysfunction is associated with increased levels of p16INK4a, a marker of cellular senescence, and reduced ability to

form functional mitotic spindles (Funk et al., 2012). Additionally, experiments in model organisms, such as Drosophila and mice, have demonstrated that centrosome defects accelerate aging phenotypes, including tissue atrophy and reduced lifespan (Basto et al., 2008; Pineault et al., 2019).

Implications: Centrosome dysfunction contributes to tissue atrophy and aging. As centrosomes play a critical role in cell division and tissue homeostasis, their decline in function can lead to impaired tissue regeneration and repair. This is particularly evident in tissues with high turnover rates, such as the skin, blood, and intestinal epithelium, where centrosome dysfunction can result in stem cell depletion and reduced regenerative capacity (Rando & Chang, 2012). Furthermore, centrosome abnormalities can promote the accumulation of senescent cells, which secrete pro-inflammatory factors that contribute to chronic inflammation and tissue degeneration, a hallmark of aging (Campisi, 2013). Understanding the role of centrosome aging in cellular and organismal aging could provide new insights into the mechanisms of aging and potential strategies for promoting healthy aging.

Evolutionary and Maintenance Theories

Mechanism: Lack of selective pressure on centriole maintenance post-reproduction. Evolutionary theories of aging suggest that the force of natural selection declines with age, as traits that affect survival and reproduction late in life have less impact on an organism's fitness (Medawar, 1952). Centrioles, which are essential for cell division, cilia formation, and cellular organization, are subject to this principle. Early in life, centriole function is critical for development, growth, and reproduction, and thus is under strong selective pressure. However, after reproductive age, the maintenance of centriole function becomes less critical for evolutionary fitness, leading to a gradual decline in the mechanisms that repair and maintain centrioles (Kirkwood & Austad, 2000). This lack of selective pressure allows for the accumulation of centriole damage and dysfunction in later life.

Evidence: Antagonistic pleiotropy in centriole-related genes. Antagonistic pleiotropy is a concept in evolutionary biology where genes that confer benefits early in life may have detrimental effects later in life (Williams, 1957). For example, genes that promote rapid cell division and tissue growth during development may also contribute to genomic instability and cellular senescence in later life. Studies have identified centriole-related genes, such as PLK4 and CEP152, that are essential for centriole duplication and function during development but may contribute to centrosome amplification and mitotic errors in aging cells (Nigg & Holland, 2018). This trade-off between early-life benefits and late-life costs supports the idea that centriole dysfunction in aging is a byproduct of evolutionary processes.

Implications: Late-life centriole dysfunction is a byproduct of evolution. The decline in centriole function with age contributes to the aging phenotype by impairing cell division, cilia formation, and tissue homeostasis. This decline is not actively selected against because it occurs after the reproductive period, when the force of natural selection is weak (Kirkwood & Austad, 2000). As a result, centriole dysfunction becomes a hallmark of aging, leading to increased genomic instability, cellular senescence, and tissue degeneration. Understanding the evolutionary basis of centriole aging provides insights into why aging occurs and highlights the challenges of developing interventions to delay or reverse age-related decline.

Centriolar Theory of Organismal Aging

Mechanism: In cells, processes for detecting and repairing defects are constantly active, ensuring the maintenance of cellular integrity. These mechanisms encompass a wide range of cellular components, including molecules, structures, organelles, and organoids. Moreover, during asymmetric divisions of human stem cells, new molecules, structures, organelles, and organoids are selectively segregated into the valuable sibling stem cell, while old molecules, structures, organelles, and organoids are preferentially directed into the expendable sibling cell, which embarks on the path of differentiation. However, centrioles stand as a remarkable exception. Unlike other cellular structures, damaged centrioles are not subject to repair. Even minor structural changes in centrioles can lead to severe consequences for the tissue. These consequences include cell cycle exit, resulting in cellular senescence, or uncontrolled division leading to tumorigenic transformation (Bettencourt-Dias & Glover, 2007; Nigg & Stearns, 2011). It is easy to imagine what happens over time in an organism filled with non-repairable centrioles.

Evidence: Research has shown that centrioles retain their structure throughout the cell cycle, yet over time, they accumulate damage. This damage accumulates every second, contributing to cellular dysfunction and, as a result, the aging of the organism (Piel, Nordberg, Euteneuer, & Bornens, 2001).

Disruptions in centriole function are associated with chromosomal instability—a hallmark of cancer. The loss of centriole integrity can lead to the formation of an abnormal mitotic spindle, resulting in aneuploidy and tumorigenic transformation of cells (Ganem, Godinho, & Pellman, 2009).

Experimental interference with centriole structure can trigger cellular senescence—a state of permanent cell cycle arrest. This underscores the critical role of centrioles in maintaining the proliferative capacity of cells (Mikule, Pitluk, & Buster, 2007).

Consequences: The inability to repair centrioles has serious implications for tissue homeostasis and organismal aging. Over time, accumulated centriole damage can lead to:

- Enhanced cellular senescence, which contributes to tissue degeneration and the aging process.
- Increased cancer risk due to chromosomal instability caused by defective centrioles.
- Reduced regenerative potential of tissues, as cells with damaged centrioles exit the mitotic cycle.

Many terminally differentiated cells eliminate the centriole, effectively reducing their entropy to nearly zero. Unicellular organisms and plant cells function well without centrioles. However, they lack true tissues and irreversible differentiation. It is likely that non-repairable centrioles, which accumulate entropy and thereby drive organismal aging, are primarily necessary for complex processes of irreversible differentiation. Organismal aging appears to be the price paid for irreversible differentiation.

Centriolar Theory of Differentiation and Proliferative Cellular Aging

Mechanism: During embryogenesis of multicellular animals, as zygotic progeny cells lose their totipotency, it is hypothesized that two distinct sets of irreversible differentiation inducers form based on nuclear and mitochondrial DNA. These sets of inducers double with each subsequent cell division. The irreversible differentiation inducer sets associate with centrioles (except in species with unlimited regeneration). Each pair of inducer sets is linked to one of the centrioles. During cell division, these sets double and bind to newly formed corresponding centrioles in parallel with centriole duplication.

During asymmetric divisions, one irreversible differentiation inducer separates from the inducer set. There are two systems of asymmetric division:

1. Old (maternal) centrioles accumulate in sibling cells that are undergoing differentiation.
2. Old (maternal) centrioles accumulate in sibling stem cells.

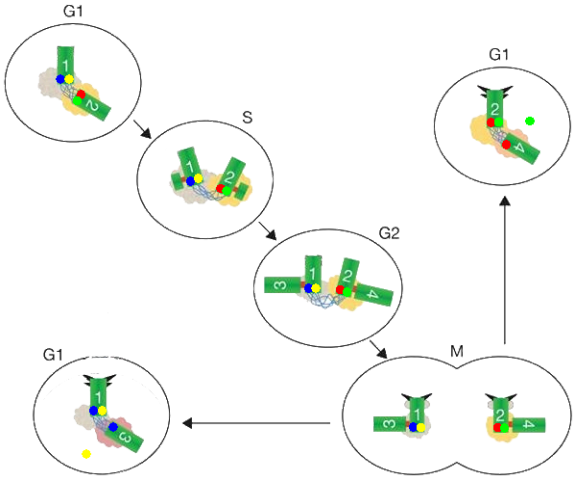
The choice of system depends on whether the irreversible differentiation inducer detaches from the old or young centriole. In the first system, the inducer detaches from the set attached to the old centriole, leaving the old centriole in the non-stem sibling cell. In the second system, the inducer detaches from the set attached to the young centriole, leaving the old centriole in the stem cell. It is likely that organisms can alternate between these two systems of asymmetric division. Studies have shown that centrioles exhibit age-dependent asymmetry during stem cell division. In Drosophila germline stem cells, the maternal centriole is preferentially retained in the stem cell, while the daughter centriole is passed on to the differentiating cell. This asymmetry plays a critical role in maintaining the identity and function of stem cells (Yamashita et al., 2007).

The centriole serves as a structure for transporting, distributing, and releasing irreversible differentiation inducers. It is clear that any crude interference with such a structure would disrupt the finely tuned mechanism of differentiation. Therefore, centrioles are not repaired and are neither removed nor inactivated before terminal differentiation.

Evidence: Research indicates that centriole dysfunction accumulates with age, leading to impaired cell division and tissue homeostasis. For instance, in mammals, aging centrioles exhibit structural defects that disrupt mitotic spindle formation, promoting cellular senescence and tissue degeneration (Piel et al., 2001). In neural progenitor cells, asymmetric centriole inheritance is observed, where the maternal centriole is retained in the progenitor cell while the daughter centriole is passed to the differentiating cell. This process ensures the maintenance of the progenitor cell pool while allowing simultaneous tissue differentiation (Wang et al., 2009). Centriole defects are linked to chromosomal instability and cancer development.

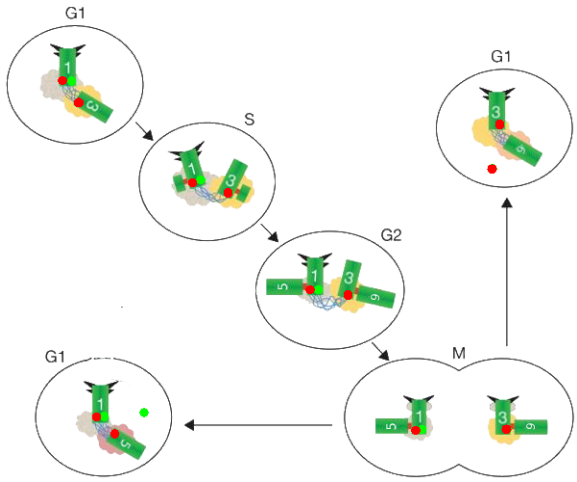
Dysfunctional centrioles can lead to improper chromosome segregation, resulting in aneuploidy and tumorigenic transformation. This highlights the importance of centriole structural integrity in preventing oncogenic processes (Ganem et al., 2009). In stem cells, the accumulation of aging centrioles is associated with a decline in regenerative capacity. For example, in aging hematopoietic stem cells, centriole dysfunction leads to reduced proliferation and differentiation potential, impairing tissue repair (Loncarek & Bettencourt-Dias, 2018).

Picture 1. Asymmetric distribution of hypothetical inducers of irreversible differentiation. A possible scenario in asymmetric division systems is shown, where an old centriole selectively enters the descendant stem cell.



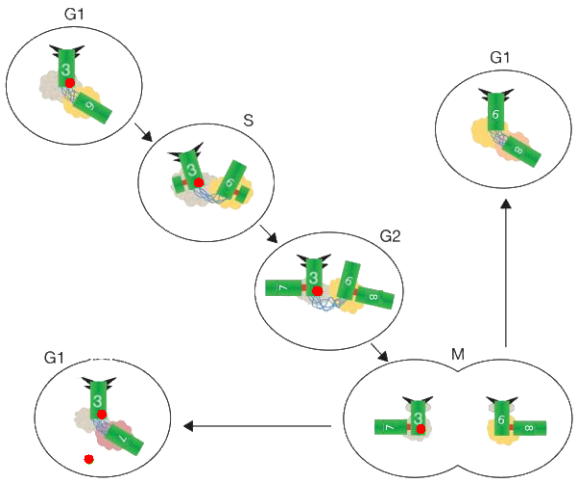
The upper left part shows a pluripotent blast in the G1 phase, in which the de novo assembled centrioles are numbered "1" and "2". For ease of perception, only two inducers of irreversible differentiation are shown quantitatively. Each de novo assembled centriole has a corresponding set of inducers attached to it - for ease of perception, only two inducers in each set are taken. Inducers in/on centriole 1 are marked in blue and yellow. Inducers in/on centriole 2 are marked in red and green. When a progenitor cell divides, descendant cells receive different centrioles with corresponding (different) inducers. The sets of inducers are duplicated in the daughter cells together with the centrioles. During an asymmetric division, one inducer is split off from the set of inducers. Depending on the system of asymmetric divisions, it is either from the new or from the old centriole. Once released, the irreversible differentiation inducer switches off the active gene network and switches on another gene network corresponding to this specific irreversible differentiation inducer.

Picture 2.



The upper left shows a multipotent cell in G1 phase in which the gene network was switched as a result of a previous asymmetric division, which irreversibly switched off the totipotency gene network and determined the fate of subsequent daughter cell differentiations. This occurred due to the fact that one inducer detached from centriole 3 and now only red inducer is in/onto centriole 3. And in/on centriole 1 there is a complete set (both green and red). Subsequent asymmetric division results in subsequent detachment of the inducer from centriole 5 and centriole 6. One daughter cell (centriole 1 and centriole 5) is identical in the set of inducers to the ancestor cell centriole 1 and centriole 3). The release of the green inducer once again involves the gene network, characterizing the cell- progenitor. In this way a pool of stem cells of appropriate potency is maintained. Price ago- accumulation of old irreparable centrioles. The second cell-descendant (centriole 3 and centriole 6) has from cell- ancestor corresponding centriole 3 red inducer. Its detachment from the newer centriole 6 will cause the incorporation of a corresponding gene network different from that of the progenitor cell - irreversible differentiation will occur.

Picture 2.



The upper left part shows a unipotent cell in the G1 phase. Centriole 3 has only one differentiation inducer. And centriole 6 has no differentiation inducers. During asymmetric division, one descendant cell, containing an older centriole 3 with one inducer, produces a daughter centriole 7, containing an inducer identical to the ancestor cell, which splits off from centriole 7. The second descendant cell does not have a differentiation inducer and therefore does not split off any inducers - as a result, neither it nor its descendants differentiate. In some generations, programmed apoptosis will be activated.

Experimental studies demonstrate that disruption of centriole structure or function can induce cellular senescence or apoptosis. For example, laser ablation of centrioles in cultured cells results in cell cycle arrest, emphasizing the critical role of centrioles in maintaining cellular viability (Mikule et al., 2007).

Consequences: Organismal aging is the price of being a multicellular organism with true tissues composed of irreversibly differentiated, highly specialized cells. In both differentiation systems, aging is driven by the accumulation of non-repairable old centrioles.

- First system: The oldest centrioles accumulate in terminally differentiated cells, directly impairing the organism's function.
- Second system: The oldest centrioles accumulate in stem cells, leading to a decline in regeneration rates and a gradual accumulation of increasingly aged centrioles (due to delayed replacement) in all cells. This
- impairs the function of non-stem cells by extending their lifespan, ultimately disrupting the organism's functionality.

Most likely, both asymmetric division systems—and consequently, both systems of accumulating non-repairable old centrioles—coexist within organisms, ensuring the inheritance of both old and new centrioles. However, regardless of where old centrioles accumulate, their inability to be repaired leads to the relentless rise of entropy and the accumulation of defects. As a result, cells, tissues, and ultimately the entire organism inevitably age.

Evidence from Model Organisms

C. elegans

Role of SAS-4 and other centriolar proteins in lifespan regulation: In the nematode Caenorhabditis elegans, centriolar proteins such as SAS-4 play a critical role in regulating lifespan. Studies have shown that mutations in SAS-4 and other centriole-associated genes disrupt normal cell division and cilia formation, leading to reduced lifespan and accelerated aging phenotypes (Kirkwood et al., 2005). These findings highlight the importance of centriole integrity in maintaining cellular and organismal homeostasis.

Centriole dysfunction and its impact on germline stem cells: Centriole dysfunction in C. elegans has been shown to impair the division and maintenance of germline stem cells, leading to reduced fertility and premature aging (Pelletier et al., 2006). For example, mutations in centriole duplication genes result in defective spindle formation and chromosome missegregation, which compromise the regenerative capacity of germline stem cells and contribute to age-related decline.

Drosophila

Centrosome loss in intestinal stem cells and its effect on tissue homeostasis: In Drosophila melanogaster, the loss of centrosomes in intestinal stem cells disrupts tissue homeostasis and accelerates aging. Studies have demonstrated that centrosome loss leads to defective asymmetric cell division, resulting in stem cell depletion and impaired tissue regeneration (Basto et al., 2008). This disruption in stem cell function contributes to the decline in tissue integrity and organismal lifespan.

Centriole defects in Drosophila have been linked to a shortened lifespan. For instance, mutations in centriole-associated genes such as DSAS-4 result in abnormal centrosome function, mitotic errors, and increased cellular senescence (Yamashita et al., 2007). These findings underscore the role of centrioles in maintaining cellular and organismal health.

Mice

Centriole dysfunction in aged tissues and its contribution to age-related diseases: In mice, centriole dysfunction has been observed in aged tissues and is associated with the development of age-related diseases. For example, aged mice exhibit increased centrosome abnormalities in tissues such as the liver, kidney, and brain, which correlate with impaired tissue function and increased susceptibility to diseases such as cancer and neurodegeneration (Prosser & Morrison, 2015). These observations suggest that centriole dysfunction is a key contributor to the aging process.

Genetic models of centriole-associated aging in mice have provided valuable insights into the role of centrioles in aging. For instance, mutations in centriole duplication genes such as PLK4 and CEP152 result in centrosome amplification, mitotic errors, and accelerated aging phenotypes (Nigg & Raff, 2009). These models have helped elucidate the molecular mechanisms linking centriole dysfunction to age-related tissue degeneration.

Human Studies and Clinical Implications

Centriole Dysfunction in Age-Related Diseases

Centrosome amplification, a hallmark of many cancers, is driven by centriole overduplication and dysfunction. This leads to mitotic errors, chromosomal instability, and aneuploidy, which are key drivers of tumor progression and metastasis (Ganem et al., 2009). For example, in breast and prostate cancers, centrosome amplification is associated with aggressive tumor behavior and poor prognosis. Understanding the role of centrioles in cancer biology provides potential targets for therapeutic interventions aimed at stabilizing centrosome function and reducing genomic instability.

Ciliary dysfunction in Alzheimer's and Parkinson's diseases: Primary cilia, which are anchored by centrioles, play critical roles in neuronal signaling and

maintenance. Dysfunction of cilia has been implicated in neurodegenerative diseases such as Alzheimer's and Parkinson's. For instance, defective cilia disrupt Hedgehog and Wnt signaling pathways, which are essential for neuronal survival and function (Goetz & Anderson, 2010). This disruption contributes to the progressive loss of neurons and cognitive decline observed in these diseases.

Renal and Cardiovascular Diseases: Role of primary cilia in tissue homeostasis: Primary cilia are essential for maintaining tissue homeostasis in renal and cardiovascular systems. In the kidneys, cilia act as mechanosensors, detecting fluid flow and regulating cell proliferation and differentiation. Dysfunction of cilia, often due to centriole defects, is a key feature of polycystic kidney disease (PKD), a condition characterized by the formation of fluid-filled cysts that impair renal function (Fliegauf et al., 2007). Similarly, in the cardiovascular system, ciliary dysfunction contributes to hypertension and atherosclerosis, highlighting the importance of centriole integrity in maintaining tissue health.

Biomarkers of Centriole Aging

Centrosome abnormalities, such as overduplication, fragmentation, and mislocalization, have been proposed as biomarkers of cellular aging. These abnormalities are frequently observed in aged tissues and are associated with increased cellular senescence and tissue dysfunction (Hinchcliffe & Sluder, 2001). For example, centrosome amplification in skin fibroblasts and epithelial cells correlates with age-related decline in tissue regenerative capacity.

Advances in imaging and molecular techniques have enabled the development of diagnostic tools for detecting centriole dysfunction. For instance, high-resolution microscopy and immunofluorescence staining can be used to visualize centrosome abnormalities in patient samples (Funk et al., 2012). Additionally, molecular markers such as p16INK4a and SA-β-gal, which are associated with cellular senescence, can be used to assess centriole-related aging phenotypes. These tools have the potential to improve early diagnosis and monitoring of age-related diseases.

Therapeutic Interventions

Centrioles have emerged as promising targets for interventions aimed at delaying aging and preventing age-related diseases. By addressing centriole dysfunction, it may be possible to mitigate the cellular and tissue-level declines associated with aging. For example, stabilizing centrosome function could reduce mitotic errors, genomic instability, and cellular senescence, all of which contribute to aging and age-related pathologies (Kirkwood, 2005). Additionally, restoring ciliary function could improve signaling pathways critical for tissue homeostasis, offering potential benefits for diseases such as neurodegeneration, polycystic kidney disease, and cardiovascular disorders.

Several strategies are being explored to target centrioles and centrosomes for therapeutic purposes. Small molecule inhibitors, such as those targeting Polo-like kinase 4 (PLK4), have shown promise in reducing centrosome amplification and restoring normal cell division in cancer cells (Nigg & Raff, 2009). Similarly, gene therapies aimed at correcting mutations in centriole-associated genes, such as CEP152 and SAS-6, could help restore centriole function and improve tissue regeneration. For example, CRISPR-Cas9-based gene editing has been

used to correct centriole defects in experimental models, demonstrating the potential for precision medicine approaches in treating centriole-related disorders (Doudna & Charpentier, 2014).

Furthermore, antioxidant therapies that reduce oxidative stress could help protect centrioles from damage, thereby preserving their function and delaying age-related decline (Finkel & Holbrook, 2000). For instance, compounds such as N-acetylcysteine (NAC) and coenzyme Q10 have been shown to reduce oxidative damage to centrosomes and improve cellular function in aged tissues. These approaches highlight the potential for centriole-targeted therapies to promote healthy aging and prevent age-related diseases.

Future Directions

Hypothesis

Hypothesis 1: Aging Due to Increased Proportion of Aged Centrioles

The presence of old centrioles in the body correlates with elevated markers of age-related cellular dysfunction, reduced regenerative capacity, and accelerated aging rates. Aged centrioles lose structural integrity, impairing their role in microtubule organization and cell division.

Hypothesis 2: Rejuvenation via Increased Proportion of New Centrioles

New centrioles correlate with reduced aging markers, enhanced regeneration, and slower aging. Fresh centrioles improve cytoskeletal dynamics and ensure accurate mitotic spindle formation, critical for maintaining genomic stability.

Hypothesis 3: Cytoskeletal Disorganization

Dysfunctional aged centrioles disrupt microtubule networks, impairing intracellular transport, organelle migration, and cell shape maintenance. This exacerbates oxidative stress and reduces cellular resilience 41115. For example, centrioles regulate actin filaments and microtubules essential for cellular architecture 15.

Hypothesis 4: Autophagy Impairment

Aged centrioles may fail to participate in phagophore cup formation, leading to accumulation of damaged organelles and proteins—a hallmark of age-related pathologies like neurodegeneration. New centrioles enhance autophagy, improving cellular clearance.

Hypothesis 5: Epigenetic Alterations

Age-related replication errors in centrioles (e.g., during S-phase duplication) disrupt gene expression linked to the cell cycle and DNA repair. Maternal centrioles carry additional proteins (e.g., tubulins) that influence transcriptional regulation, creating a feedback loop that accelerates aging.

Hypothesis 6: Loss of Cell Polarity and Migration

Aged centrioles impair cellular polarity, critical for tissue regeneration (e.g., in epithelial or stem cells). This reduces wound healing efficiency and tissue renewal. New centrioles restore microtubule organization, enhancing cell migration.

Hypothesis 7: Signaling Pathway Disruption

Centrioles modulate pathways like Wnt/Notch, regulating proliferation and

differentiation. Aged centrioles activate pro-inflammatory pathways (e.g., NF-κB), promoting chronic inflammation—a key aging driver. New centrioles suppress senescence-associated secretory phenotype (SASP).

Hypothesis 8: Genomic Instability

Defective centrioles cause mitotic errors (e.g., aneuploidy), accelerating organismal aging, particularly in highly proliferative tissues (e.g., skin, gut). New centrioles reduce genomic instability risks.

Hypothesis 9: Mitochondrial Interaction

Aged centrioles disrupt mitochondrial transport along microtubules, reducing energy metabolism efficiency and increasing reactive oxygen species (ROS). New centrioles improve mitochondrial distribution, supporting metabolic health.

Hypothesis 10: Role in Intercellular Communication

Centrioles influence cilia formation, which mediates signaling (e.g., Hedgehog). Aged centrioles impair ciliary function, reducing cellular responsiveness. New centrioles restore cilia, enhancing tissue coordination.

Hypothesis 11: Post-Translational Modifications

Aged (maternal) centrioles accumulate modifications (e.g., acetylation, polyglutamylation) and distinct proteins. Suppression of centriolar deacetylases (e.g., HDAC6) may mimic age-related changes by hyperacetylating tubulin.

Unanswered Questions

While significant progress has been made in understanding the role of centrioles in aging, establishing direct causal links between centriole dysfunction and aging in humans remains a critical challenge. Most studies have relied on model organisms or in vitro systems, and further research is needed to determine whether centriole dysfunction is a primary driver of aging or a secondary consequence of other aging processes (López-Otín et al., 2013). Longitudinal studies in human populations, combined with advanced genetic and molecular analyses, could help clarify the role of centrioles in human aging.

Centrioles are traditionally studied in the context of cell division, but their roles in non-dividing cells and post-mitotic tissues, such as neurons and muscle cells, are less well understood. In these cells, centrioles are essential for the formation and function of primary cilia, which play critical roles in sensory and signaling processes (Kirkwood & Austad, 2000). Investigating how centriole dysfunction contributes to age-related declines in post-mitotic tissues could provide new insights into the biology of aging and age-related diseases.

Emerging Technologies

Advances in imaging technologies, such as super-resolution microscopy and live-cell imaging, have revolutionized the study of centriole dynamics. These techniques allow researchers to visualize centriole structure and function in real time, providing unprecedented insights into how centrioles change with age (Hinchcliffe & Sluder, 2001). For example, super-resolution microscopy has revealed age-related changes in centrosome architecture and microtubule organization, shedding light on the mechanisms underlying centriole dysfunction.

CRISPR-Cas9 gene editing has emerged as a powerful tool for studying centriole

function and its role in aging. By creating targeted mutations in centriole-associated genes, researchers can investigate the effects of centriole dysfunction on cellular and organismal aging (Doudna & Charpentier, 2014). Additionally, CRISPR-based approaches hold promise for developing gene therapies to correct centriole defects and restore normal cellular function in age-related diseases.

Translational Research

Translating basic research on centrioles into clinical applications is a key goal for the future. Potential therapeutic strategies include small molecule inhibitors to stabilize centrosome function, gene therapies to correct centriole defects, and antioxidant treatments to protect centrioles from oxidative damage (Campisi, 2013). These approaches could help delay aging and prevent age-related diseases by maintaining centriole integrity and function.

Centriole research should be integrated into broader studies of aging to better understand how centriole dysfunction interacts with other hallmarks of aging, such as genomic instability, mitochondrial dysfunction, and cellular senescence (Kirkwood, 2005). This integrative approach could provide a more comprehensive understanding of the aging process and identify new targets for interventions to promote healthy aging.

Conclusion

Centrioles, once considered mere structural components of the cell, are now recognized as key players in the aging process. Their roles in maintaining genomic stability, stem cell function, and cellular signaling make them critical to understanding the biology of aging. Centrioles ensure accurate chromosome segregation during cell division, support the regenerative capacity of stem cells, and facilitate the formation and function of primary cilia, which are essential for cellular communication and homeostasis (Nigg & Holland, 2018; Goetz & Anderson, 2010). Dysfunction in these processes contributes to the hallmarks of aging, including genomic instability, tissue degeneration, and chronic inflammation (López-Otín et al., 2013).

By elucidating the mechanisms linking centrioles to aging, we can develop novel interventions to promote healthy aging and prevent age-related diseases. For example, targeting centriole dysfunction through small molecule inhibitors, gene therapies, or antioxidant treatments could help restore cellular function and delay the onset of age-related pathologies (Kirkwood, 2005; Nigg & Raff, 2009). Additionally, understanding the evolutionary and maintenance theories of centriole aging provides insights into why centriole dysfunction occurs and how it can be mitigated.

Future research should focus on translating these findings into clinical applications, offering hope for extending healthspan and improving quality of life in an aging population. This includes developing biomarkers for early detection of centriole dysfunction, advancing therapeutic strategies to stabilize centriole function, and integrating centriole research into broader studies of aging (Campisi, 2013; Hinchcliffe & Sluder, 2001). By bridging the gap between basic science and clinical practice, we can unlock the potential of centriole-targeted therapies to enhance healthy aging and address the growing burden of age-related diseases.

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