RESEARCH REPORT OF THE UNIVERSITY OF GRAZ

A brief history of spermidine and the research on its geroprotective and potentially health-promoting effects

Why even unicellular organisms can plunge into cell death in a controlled manner - the success story of an unconventional scientist

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Foreword

This research report gives an overview of the history and the state of research on spermidine at the University of Graz as well as the international research landscape. The contents of the report represent significant milestones in the research of the cell protecting and potentially health-promoting effects of spermidine, however they have no claim on completeness of this very dynamic research area.

The effects shown were scientifically examined in the indicated preclinical and first clinical studies and in collaboration with the University of Graz and other international research groups. These findings currently serve as a basis for further clinical studies at renowned research institutes worldwide.

Disclaimer: In case of a disease, you should consult a physician. Self-medication with spermidine is not advised.

Contents

A brief history of spermidine and an exploration of its potentially health-promoting effects

Frank Madeo: From the dying unicellular organism to the renowned aging researcher

After studying biochemistry until 1994, Frank Madeo functioned as the head of a research group at the University of Tübingen for seven years. There he devoted himself to research on regulated cell death (apoptosis). For a long time, researchers assumed that this process does not take place in unicellular organisms (and this was also the way it was taught in textbooks).

Frank Madeo disregarded these assumptions and conducted a series of experiments that eventually challenged the textbook wisdom. Through this unconventional way of thinking, he managed to describe apoptosis in unicellular baker's yeast in 1997 [1]. This discovery has defined a new and separate field of research.

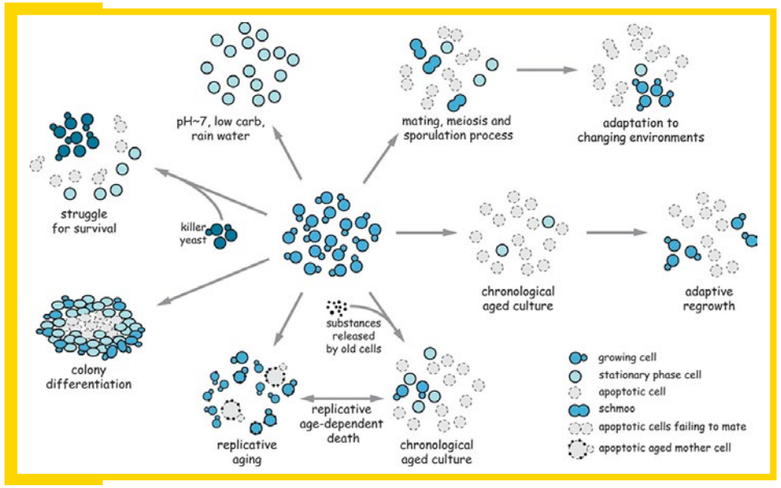

Figure 1: Different scenarios of yeast apoptosis. Growing yeast cells die in times of dwindling resources during chronological aging, after an attack of toxins, and due to unsuccessful mating (adapted from [2]).

Apoptosis is the regulated cell death by which an organism eliminates damaged cells. This suicide program of old, infertile, or defective cells gives also yeast populations an evolutionary advantage. Through factors such as a lack of food or the presence of toxins, weak and damaged cells die; however, some cells survive and enter a stage of survival. When the circumstances improve, these cells are reactivated and begin to grow again.

In 2002, Frank Madeo organized the first International Meeting on Yeast Apoptosis, where leading researchers in the field of cell death and aging research on the yeast organism meet to exchange the latest results. This event is now taking place regularly every 18 months, each time in different countries.

For his further work on regulated cell death in the yeast model and after his habilitation in physiological chemistry/biochemistry, Frank Madeo received one of the most renowned young researcher scholarships of the German Research Foundation, the Heisenberg Scholarship. In 2018, he was elected to the American Academy of Microbiology for his discovery of yeast apoptosis.

In 2004, Frank Madeo was appointed to the University of Graz to continue his research as professor for Cell Biology and Biochemistry at the Institute for Molecular Biosciences. There, he shifted his focus to aging and has since then been investigating the related processes in different organisms.

In 2009, Frank Madeo was awarded as best publishing scientist of the University of Graz and is also considered one of its most successful researchers. According to the German "Laborjournal", a journal for laboratory science, Frank Madeo was among the top fifty cited scientists in cell biology in the German-speaking region in the year 2013 and 2018. He is currently also the most cited biochemist in Austria and one of the most cited age researchers worldwide. Madeo was elected to the prestigious Academy for Health and Lifespan Research in 2022.

Discovery of the autophagy activating and cell protecting effect of spermidine

In collaboration with his doctoral student at that time, Tobias Eisenberg, Frank Madeo investigated possible factors that contribute to the activation or inhibition of cell death. With the help of a cell-biological screening method, an enzyme was found which breaks down so-called polyamines and thus initiates the process of apoptosis. This led the two researchers to treat aging yeast cells with the polyamine spermidine and to test whether this natural substance can stop age-induced cell death or at least delay it and thus extend the life span of yeast cells. The two researchers in that context discovered the protective effect of spermidine on aging cells – results that were published in a high-ranking journal of the "Nature Group" in 2009. This publication in turn founded a new field of research and has since then been cited over 1,000 times.

Spermidine is a polyamine that is naturally present in the body cells of all living organisms and that occurs in numerous food products. It is produced by the body's own cells and by the microbiome in the gut, but can especially be absorbed from food, in particular through wheat germ, nuts and mushrooms, among others.

Through further international collaboration, the two researchers and their team were able to trace the cell-protective effect of spermidine back to the autophagy promoting ability of spermidine. Autophagy is the process through which the cell removes old or defective cell tissue that accumulate during life. This self-cleaning leads to a cell renewal and thus prevents long-term damage that may be caused by these contaminated sites.

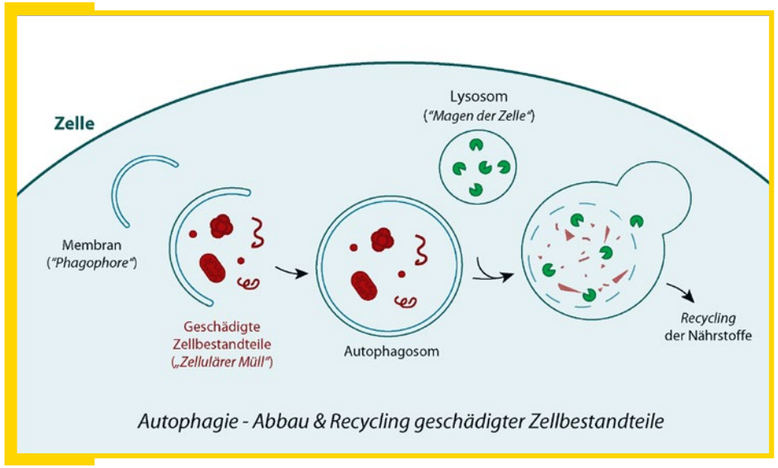

Figure 2: Damaged cell material is enclosed by a double membrane and forms a so-called autophagosome. By fusing with a lysosome, the cellular ‚waste' can be digested enzymatically and used for energy production (graphic adapted from [3]).

The discovery of spermidine-induced autophagy by Frank Madeo and Tobias Eisenberg in the yeast organism could subsequently also be transferred to fly, worm, rat and mouse models [4, 5] and has now also been demonstrated in human immune cells [6]. This finding has meanwhile stimulated numerous international research groups to investigate the cell-protective effects of spermidine in various disease models. Among other findings, the researchers discovered that mice with spermidine-rich nutrition exhibited an extended life span and that a spermidine-rich diet may be associated with reduced mortality and lower risk of certain age-associated diseases [5, 7, 8].

Fasting and decreased calorie consumption can activate the recycling process through autophagy, a cellular process that has shown essential for several of the spermidine-induced effects in model organisms. Spermidine accordingly acts as a „caloric restriction mimetic", thus it imitates certain effects of fasting, in particular, the activation of cellular self-cleaning [9].

Tobias Eisenberg was awarded the Promotion Prize of the province of Styria in 2011 for his research in spermidine. He is head of the NAWI Graz Central Lab Gracia, center for fluorescence- based cell analysis, as well as associate professor and group leader at the University of Graz in the field of autophagy research.

Heart-protecting effects of spermidine

In 2016, Frank Madeo and Tobias Eisenberg were able to present a further publication in collaboration with the research group around Simon Sedej from the Medical University of Graz in the renowned journal "Nature Medicine", that spermidine, by activating autophagy in cardiomyocytes, can slow down the age-related loss of heart function in mice [5]. Continuing this collaborative research effort, the two universities continue to investigate the protective effect of spermidine in rodent models of diastolic heart failure, an increasing age-related heart disease for which effective treatment options to date do not exist.

Tobias Eisenberg was awarded the Richard Pacher Prize of the Austrian Cardiological Society in 2018. In the same year, Frank Madeo was awarded the SENECA medal for his contribution to the research on aging.

Extension of life span by activating autophagy

Autophagy attacks cell-specific components that are defective or no longer required. These waste products, which are harmful to the organism in the long term, are digested by the cell and used for its own energy production. Thus, it can be shown that spermidine triggers the specific degradation of damaged mitochondria, the power plants of the cell, by autophagy (the so-called mitophagy). Damaged mitochondria can otherwise, if not disposed, lead to damage in the cell through the formation of reactive oxygen radicals.

By breaking down harmful substances within the cell, cellular stress resistance is improved and subsequently its life span is extended. Besides fasting and caloric restriction, spermidine-activated autophagy has also indicated to have a positive effect on longevity.

Organisms that, due to genetic modification, cannot perform autophagy or can only perform it to a very limited extent, do in fact not react to the life-prolonging effect of spermidine.

The results of a long-term study at the University of Innsbruck provide the first indications that the life-prolonging and health-promoting effects of spermidine could also be valid for humans. For a span of 20 years, more than 800 test subjects were asked about their daily eating habits. Those who consumed about 12 milligrams of spermidine per day within their daily nutrition (respectively those with a spermidine-rich diet) had a considerably increased life expectancy and showed a reduced risk of cardiovascular diseases, compared to those with a nutrition containing less spermidine [8].

The research group around Madeo has focused on fasting and its health-promoting effect on cells and organisms. Critical to this process is the energy-rich molecule Acetyl-CoA. With food intake, the concentration of this molecule in the cells increases or, if the nutrient supply is absent or reduced, it in turn decreases. Acetyl-CoA is therefore recognized as a biomarker, signaling nutrient presence within the cell. Madeo and his colleagues were able to show that the reduced concentration of acetyl-CoA activates autophagy [10, 11]. For these findings, Frank Madeo received the Archduke Johann Research Prize of the Province of Styria in 2015.

As a scientific public speaker, Frank Madeo holds numerous speeches around the topic of autophagy. In 2014, he gave a very successful lecture on the connection between nutrition and longevity at TEDxGraz. In addition, Tobias Eisenberg also speaks on autophagy and polyamines at international conferences and congresses.

In 2016, the Japanese researcher Yoshinori Ohsumi received the Nobel Prize for Medicine for his findings in relation to autophagy. His groundbreaking work laid the foundation for further research in this field. This was considered a breakthrough in understanding the process of cell renewal by autophagy, spawning research groups on the topic worldwide.

Further scientific information & selected literature

Spermidine, a natural substance for cell health

Spermidine is a polyamine that is naturally present in the cells of most living organisms and occurs in numerous food products. It is produced endogenously in the body and by the gut microbiome, but is especially absorbed from food, in particular through wheat germ, nuts and mushrooms, among other foods.

In addition to important cellular functions, such as the stabilization of DNA (the genetic information of a cell), an anti-oxidative and anti-inflammatory effect and the control of formation and function of certain proteins, spermidine can stimulate autophagy, a central recycling mechanism of the cell.

While produced endogenously, spermidine absorbed from foods may be particularly important with progressing age, as spermidine levels decline with age but can be counteracted through targeted food supply. This can be demonstrated by several interesting studies that deal with spermidine levels in humans in the context of aging.

Pekar T, et al. (2020). Spermidine in dementia: Relation to age and memory performance. Wien Klin Wochenschr. 132(1–2): 42–46. doi: 10.1007/s00508-019-01588-7.

The study of the FH Wiener Neustadt under the direction of Dr. Thomas Pekar in cooperation with Univ.-Prof. Dr. Reinhart Jarisch of the "FAZ-Floridsdorfer Allergiezentrum" suggests a connection between age and a decreasing spermidine content in the blood of humans.

Sánchez M, et al. (2023). Age-associated polyamines in peripheral blood cells and plasma in 20 to 70 years of age subjects. Amino Acids. doi: 10.1007/s00726-023-03269-2.

In this further study on the influence of aging on decreasing polyamine levels in humans, it was shown that especially white blood cells (so-called mononuclear cells, which mainly consist of immune cells, but also stem cells) are subject to age-related changes.

Soda et al. (2009). Long-term oral polyamine intake increases blood polyamine concentrations. J Nutr Sci Vitaminol. 55(4): 361–366. 19763038.

The study from Japan shows that the polyamine level in the human blood can be demonstrably increased by daily intake of spermidine-rich foods over a period of four weeks, thus underlining the relevance of oral intake of spermidine.

Pucciarelli S, et al. (2012). Spermidine and spermine are enriched in whole blood of nona/centenarians. Rejuvenation Res. 15(6): 590–595. doi: 10.1089/rej.2012.1349.

The observational study examined the polyamine levels in the blood of healthy people over 90 years of age as well as centenarians from the region of central Italy. In comparison to control persons aged 60–80 years, the elder group showed a clearly higher spermidine level in the blood. Surprisingly, the spermidine levels of healthy centenarians were similar to those of a much younger comparison group with an average age of 46 years. The extent to which these differences can be attributed to a diet or genetic or other cellular causes will have to be examined in further studies.

Due to the health-promoting effects of spermidine in animal models, two independent teams of renowned aging researchers have selected this natural substance among the top candidates for the most promising anti-aging substances [12, 13]. The reason for the life-prolonging effect of spermidine in several model organisms is due to its autophagy-promoting effect that appears to be evolutionarily maintained up to mammals (shown in the example of the mouse) [5, 9, 14].

Eisenberg T, et al. (2009). Induction of autophagy by spermidine promotes longevity. Nat Cell Biol. 11(11): 1305–1314. doi: 10.1038/ncb1975.

In 2009, with the help of recognized model organisms of aging (yeast, flies, worms), Frank Madeo and his team were already able to demonstrate the life-prolonging effect of spermidine and causally link it to the activation of autophagy. It is also demonstrated that organisms that are unable to perform autophagy or due to genetic defects are only able to perform autophagy to a limited extent, lose the ability to prolong life through spermidine.

Viltard M, et al. (2019). The metabolomic signature of extreme longevity: naked mole rats versus mice. Aging (Albany NY). 11(14): 4783–4800. doi: 10.18632/aging.102116.

Naked mole-rats are colloquially considered to be nearly immortal, as they have a life expectancy nearly ten times that of other rodent species. An equivalent life expectancy in humans would equate to around 1,000 years of age. This interesting study recognizes the lack of a decline in spermidine levels in naked mole rats to be a unique biological finding, suggesting that maintaining spermidine levels may be a factor contributing to an increased lifespan.

Kiechl S, et al. (2018). Higher spermidine intake is linked to lower mortality: a prospective population- based study. The American Journal of Clinical Nutrition. 108(2): 371–380. doi: 10.1093/ajcn/nqy102.

The first indications that the life-prolonging effect of spermidine could also be conserved in humans comes from epidemiology (an observational study). The team around Prof. Dr. Stefan Kiechl of the Medical University of Innsbruck was able to link a spermidine-rich diet to a longer life expectancy. People from the small town of Bruneck in Northern Italy, who were identified to maintain the most spermidine-rich diet over a period of 20 years, showed lower mortality than those who belonged

to the group with lower spermidine intake. The authors of the study calculated the life-prolonging effect statistically to equate to approximately 5 years of increased life.

Neurodegeneration/dementia

In an aging society, age-related neurodegenerative diseases such as Parkinson's and Alzheimer's, as well as other dementias, are a critical point of study. With increasing age, memory performance decreases.

Autophagy is an important factor in the pathogenesis of serious neurodegenerative diseases. In Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis and other diseases, impairment of autophagy leads to the accumulation of pathogenic proteins and damaged cell organelles [15]. Spermidine could potentially provide a promising new therapeutic approach by activating autophagy in these diseases, but also during the known physiological decline in cognitive performance during aging. First results could already be demonstrated in that area, especially when talking about prevention in early stages or from preclinical research.

Wirth M, et al. (2018). The effect of spermidine on memory performance in older adults at risk for dementia: A randomized controlled trial. Cortex. 109: 181–188. doi: 10.1016/j.cortex.2018.09.014.

In older adults with early signs of cognitive impairment, promising results were obtained in a pilot human study (SMARTAGE) at the "Charité Berlin", led by Prof. Dr. Agnes Flöel. A positive effect on memory performance was shown after 3 months of supplementing with a spermidine-rich wheat germ extract. In particular the mnemonic ability to distinguish seemed to be improved by the supplementation of spermidine.

The possible neuroprotective effect of spermidine was also established by an association of dietary spermidine intake with structural parameters of the brain in subjects of the SMARTAGE study. More spermidine in the diet was shown to be associated with greater hippocampal volume and more prominent cortex in brain regions central to memory performance [16]. In a follow-up study to SMARTAGE, these results are shown to be confirmed in a longer observation period (one year) and a larger cohort of at least men over 70 years of age, while the overall cohort showed no significant improvement in memory [17]. Moreover, this study brought to light a new and perhaps important finding: In the overall cohort, a key inflammatory marker was lowered after ingestion of the spermidine-rich extract. This could be significant because chronic inflammation is an important causal driver of both memory decline and aging in general.

Pekar T, et al. (2021). The positive effect of spermidine in older adults suffering from dementia. Wien Klin Wochenschr. 133(9): 484-491. doi: 10.1007/s00508-020-01758-y.

After studying the connection between age and a sinking spermidine level in the blood of humans [18], conducted under the direction of Dr. Thomas Pekar (FH Wiener Neustadt), in the further course of the study, the influence of a targeted spermidine-rich diet, especially in subjects with mild dementia, an improvement in memory performance could be achieved. The cognitive performance of elderly subjects was measured. Initial analyses of spermidine content in comparison with cognitive performance (measured using the standardized mini-mental state examination score (MMSE), among others) show a reciprocal correlation at the start of the study. This means that subjects with less spermidine in their blood showed lower cognitive performance on average, which improved by around 2 points in the group with mild dementia on a high spermidine diet in this pilot study.

Gupta VK, et al. (2013). Restoring polyamines protects from age-induced memory impairment in an autophagy-dependent manner. Nat Neurosci. 16(10): 1453–1460. doi: 10.1038/nn.3512.

In flies (the fruit fly Drosophila is an important and recognized model organism of aging) the learning ability of the flies decreases with increasing age. Additionally, spermidine levels are shown to decrease with age. Targeted supplementation of aging flies with spermidine can compensates for the age-related decline in the learning ability; an effect that depends on the autophagy competence of the fly cells. Spermidine has a positive effect on the functionality (more precisely the dynamic flexibility) of the fly's neuronal synapses [19].

Schroeder S, et al. (2021). Dietary spermidine improves cognitive function. Cell Reports. 35(2): 108985. doi: 10.1016/j.celrep.2021.108985.

The results originally obtained in the fly model were confirmed in a mouse model of aging in the course of a study at the University of Graz. The work of the researchers around Schroeder et al. points in particular to the importance of so-called mitophagy, the autophagic degradation of defective mitochondria and thus improved quality management and maintenance of healthy mitochondrial function. Again, using the fly model, the researchers showed that targeted prevention of mitophagy leads to loss of the neuroprotective effect of spermidine.

Further studies in different disease models also indicate a neuroprotective effect of spermidine in Alzheimer's disease and Parkinson's disease [20, 21].

Sleep

In addition to an increased risk of dementia, sleep disorders occur more frequently in old age. Disturbed sleep rhythms, but also sleep deprivation, have been shown to promote dementia and thus pose an additional risk factor of these age-associated diseases. First indications showed already in the last years that spermidine and other polyamines seemed to be closely linked to the control of circadian processes, which are central for the regulation of normal sleep behavior [22].

Huang S, et al. (2022). A brain-wide form of presynaptic active zone plasticity orchestrates resilience to brain aging in Drosophila. PLOS Biology. 20(12): e3001730. doi: 10.1371/journal.pbio.3001730.

In the study by Huang et al., researchers from the working group led by Prof. Stephan Sigrist at Charité Berlin and Freie Universität Berlin were able to demonstrate a sleep-promoting effect of spermidine using the fly model. While aged flies show disturbed sleep behavior compared to young flies, spermidine supplementation at least partially prevented these age-related changes. Similarly, spermidine-treated flies were more robust to sleep deprivation, subsequently catching up on sleep more quickly and effectively.

Heart function

The risk of suffering from a cardiovascular disease increases with age. Arterial aging is characterized by stiffening of large, elastic arteries and arterial endothelial dysfunction. It also leads to stiffening of the heart muscle and to varying degrees of partly systolic (contractile), but also diastolic (relaxation phase of the heart) dysfunction. A further risk factor of cardiovascular diseases is high blood pressure, which also increases with age.

LaRocca TJ, et al. (2013). The autophagy enhancer spermidine reverses arterial aging. Mechanisms of Ageing and Development. doi: 10.1016/j.mad.2013.04.004.

In older mice, loss of elasticity in arteries was observed and associated with a reduced endothelial function. In addition, an increase in oxidative stress was observed in aortas of the older mice. Supplementation with spermidine restored arterial elasticity to normal levels, normalized endothelial function and prevented oxidative stress in the treated mice.

Eisenberg T, et al. (2016). Cardioprotection and lifespan extension by the natural polyamine spermidine. Nature Medicine. 22(12): 1428–1438. doi: 10.1038/nm.4222.

Aging mice fed with spermidine showed an increased autophagy rate and improved mitochondrial respiration of heart muscle cells in the study by Frank Madeo and Tobias Eisenberg in collaboration with Assistant Professor Dr. Simon Sedej at the Medical University of Graz. Spermidine thus led to an improved elasticity of the heart muscle cells, which ultimately improved the diastolic functionality of the heart and provided preventive protection against the development of so-called diastolic dysfunction. In a salt-sensitive rat model, a model for hypertension-induced heart failure that received an increased salt intake with the diet, spermidine feeding not only reduced systemic hypertension, but also delayed the development of heart failure.

In collaboration with the team around Prof. Dr. Stefan Kiechl of the Medical University of Innsbruck, the researchers discovered hints of an association between nutritional spermidine intake and cardiac health in humans in the course of the BRUNECK study: In test persons part of this observational study, a high dietary spermidine intake correlated with lower blood pressure and a significantly reduced risk of suffering from cardiovascular diseases and related deaths in direct comparison to test persons with a lower spermidine intake.

Yan J, et al. (2019). Spermidine-enhanced autophagic flux improves cardiac dysfunction following myocardial infarction by targeting the AMPK/mTOR signalling pathway. Br J Pharmacol. 176(17): 3126– 3142. doi: 10.1111/bph.14706.

In a rat heart attack model, spermidine was shown to prevent the death of cardiomyocytes through necrosis. Similarly, spermidine administration led to a reduction in infarct size and improved cardiac function in these rats in response to cell-protective autophagy activation. In addition, spermidine supplementation reduced oxidative damage and had anti-inflammatory effects by decreasing the production of pro-inflammatory cytokines.

Matsumoto M, et al. (2019). Endothelial Function is improved by Inducing Microbial Polyamine Production in the Gut: A Randomized Placebo-Controlled Trial. Nutrients. 11(5). doi: 10.3390/nu11051188.

Intestinal microbiota bacteria can increase the production of putrescine, a spermidine precursor, in the intestine. For a period of 12 weeks, the participants were fed a yogurt mixed with polyamine-producing probiotics. Afterwards, the arterial tone, a marker for endothelial function, was measured. As compared to the placebo group, an improved endothelial function could be found.

Restricted endothelial function is associated with the development of arteriosclerosis. The authors of the study therefore speculate that the consumption of polyamine-producing bacteria could reduce the risk of arteriosclerosis, results that are in line with preclinical research in mice [23].

Immune defense and immune system

One of the main features of aging is a weakening of the immune response of the adaptive immune system. As a result, one has a reduced B-cell function and a declining vaccination efficiency in old age. Additionally, the ability of certain T-cells to support the immune defense in old age decreases. The autophagy activity of these immune cells also decreases with age. Thus, older adults have a higher risk for infectious diseases and respond more poorly to vaccinations.

Zhang H, et al. (2019). Polyamines Control eIF5A Hypusination, TFEB Translation, and Autophagy to Reverse B Cell Senescence. Mol Cell. 76(1): 110-125.e9. doi: 10.1016/j.molcel.2019.08.005.

In this study of the team of Prof. Dr. Katharina Simon at the renowned Oxford University, it was examined whether the induction of autophagy by the supply of spermidine leads to improved B-immune cell response. Additionally, they investigated the response to immunization, a process that is required in vaccinations to protect against infectious agents. In older mice fed with spermidine, it was shown that the response of the B-immune cells (or more precisely of a subgroup of the B-immune cells, the so-called "memory cells" of the immune system) was rejuvenated and had increased response to vaccination. This process was dependent on the B-immune cells preliminarily restored by spermidine-induced autophagy.

Alsaleh G, Panse I, Swadling L, Zhang H, Richter FC, Meyer A, Lord J, Barnes E, Klenerman P, Green C, and Simon AK (2020). Autophagy in T cells from aged donors is maintained by spermidine and correlates with function and vaccine responses. Elife. 9. doi: 10.7554/eLife.57950.

In a further in vitro study conducted by Katharina Simon, the concepts of the study of aging B cells published in 2019 [24] could be transferred to human T-immune cells. T-cells – taken from older human donors – showed lower spermidine levels and reduced autophagy competence compared to T-cells from younger subjects. Treatment of these cells in spermidine cultures was able to restore autophagy and functional ability of the T-cells. In the future, these findings may be used to improve vaccination success in aging humans.

Al-Habsi M, et al. (2022). Spermidine activates mitochondrial trifunctional protein and improves antitumor immunity in mice. Science. 378(6618): eabj3510. doi: 10.1126/science.abj3510.

Building on the findings of Oxford University, a Japanese researcher team demonstrated enhanced immune system antitumor responses following restoration of an age-induced reduction in immune cell spermidine levels, achieved by spermidine supplementation. In aged mice stimulated by PD-L1 monoclonal antibody therapy, administration of spermidine improved the function of cytotoxic T-cells directed against tumor cells. Spermidine appeared to directly influence T-cell function by increasing fatty acid oxidation through stimulation of mitochondrial activity. These results are consistent with the protective effect of spermidine against metabolic disease through enhanced fat catabolism (see chapters on type 2 diabetes, metabolic disease, and obesity).

The efficiency enhancing function of spermidine in the context of immunity directed against tumor cells [25, 26], but also a tumor suppressive effect through spermidine-mediated autophagy [14] have also been shown in previous studies in mouse models. Yang Q, et al. (2016). Spermidine alleviates experimental autoimmune encephalomyelitis through inducing inhibitory macrophages. Cell Death Differ. 23(11): 1850–1861. doi: 10.1038/cdd.2016.71.

Further research of the immune-modulating effect of spermidine come from preclinical research in a mouse model of experimental autoimmune mediated encephalitis, a mouse model of multiple sclerosis. The inhibitory effect of spermidine on pro-inflammatory macrophages, and the stimulation of anti-inflammatory macrophages, could be used to slow down the progression of multiple sclerosis-like degeneration of neurons. The anti-inflammatory macrophages prevented the migration of cytotoxic T-cells into brain tissue and thus an autoimmune reaction. Future studies will have to clarify to what extent the results are transferable to humans.

Intestinal health

Carriche GM, et al. (2020). Regulating T cell differentiation through the polyamine spermidine. Journal of Allergy and Clinical Immunology. doi: 10.1016/j.jaci.2020.04.037.

Spermidine is found in the intestinal tract along with other polyamines. According to the study by Carriche, et al. spermidine can promote the differentiation of T-cells into so-called regulatory T-cells (Tregs), an important subclass of immune cells that are particularly necessary for a balanced immune system. Supplementation of spermidine in mice with induced intestinal inflammation (colitis) led to an increased production of regulatory T-cells and to the relief of intestinal inflammation.

Muscles and bones

The risk of developing osteoarthritis increases with age. It is suspected that the decreasing autophagy with increasing age is responsible for this process to some extent. If the regulation of bone-degrading osteoclasts and bone-building osteoblasts is out of balance, various diseases can occur, including osteoporosis.

Yamada T, et al. (2019). Daily intake of polyamine-rich Saccharomyces cerevisiae S631 prevents osteoclastic activation and bone loss in ovariectomized mice. Food Science and Biotechnology. 28. doi: 10.1007/s10068-019-00561-4.

For this study, mice were fed daily with a special polyamine-rich yeast, which also contains a high concentration of spermidine, thus reducing bone loss mainly by reducing osteoclast activation. The data confirm previous findings after the administration of pure spermidine [27].

Damaged cell organelles are crucial for myopathies, i.e. diseases that manifest themselves through degeneration and decline of muscle tissue. It is therefore suspected that autophagy may play a central role in offsetting the decline of muscle tissue and in model organisms, it has been shown that the administration of spermidine could be beneficial by activating or reactivating protective autophagy in muscle tissue [28].

Fan J, et al. (2017). Spermidine coupled with exercise rescues skeletal muscle atrophy from D-gal- induced aging rats through enhanced autophagy and reduced apoptosis via AMPK-FOXO3a signal pathway. Oncotarget. 8(11): 17475–17490. doi: 10.18632/oncotarget.15728.

In aging rats, spermidine supplementation was able to reduce age-related atrophy, i.e., skeletal muscle atrophy, by upregulating autophagy and reducing apoptosis of myocytes (skeletal muscle cells). This effect was further enhanced by physical exercise of the animals.

Chrisam M, et al. (2015). Reactivation of autophagy by spermidine ameliorates the myopathic defects of collagen VI-null mice. Autophagy. 11(12): 2142–2152. doi: 10.1080/15548627.2015.1108508.

Mice with a genetic muscle defect were able to regain muscle strength through spermidine supplementation. In this model system, spermidine was not only able to activate autophagy in muscle cells, but also led to structural improvement of muscle fibers and cellular structures (myofibrils) responsible for the contraction of muscle cells.

Further promising research fields of spermidine

Type-2-Diabetes, metabolic diseases and obesity

Recent studies have also shown a possible protective effect of spermidine in cases of overweight, obesity and certain metabolic diseases (including diabetes and the so-called metabolic syndrome). Liao C-Y, et al. (2021). The Autophagy Inducer Spermidine Protects Against Metabolic Dysfunction During Overnutrition. J Gerontol A Biol Sci Med Sci. 76(10): 1714–1725. doi: 10.1093/gerona/glab145.

The study, conducted at the renowned Buck Institute for Research on Aging, Novato, California, USA, under the direction of aging researcher Brian Kennedy, was able to show in aging mice that the daily administration of spermidine can protect against obesity. Spermidine prevented the development of obesity in mice fed a particularly high-fat diet. The authors attributed the effect of spermidine to increased lipolysis in visceral adipose tissue, i.e. the breakdown of storage fat.

Monelli E et al. (2022). Angiocrine polyamine production regulates adiposity. Nat Metab. doi: 10.1038/s42255-022-00544-6.

In line with the study by Liao et al, another group of researchers was able to show that daily administration of spermidine can reduce obesity as a result of a high-fat diet. The study, published in the renowned journal Nature Metabolism, showed increased lipolysis of fat cells triggered by genetic stimulation of a local production of polyamines spermidine in neighboring blood vessel cells. This so-called paracrine effect was shown in the mouse model. However, the researchers were also able to show that adipose tissue taken from obese people has a lower spermidine level than that from non-obese individuals. This is a first indication of the transferability of the results to humans.

Zhou J, et al. (2022). Spermidine-mediated hypusination of translation factor EIF5A improves mitochondrial fatty acid oxidation and prevents non-alcoholic steatohepatitis progression. Nat Commun. 13(1): 5202. doi: 10.1038/s41467-022-32788-x.

Recent studies also indicate a liver-protective effect of spermidine in a mouse model of unhealthy (high fat and fructose) diet-induced non-alcoholic hepatitis/steatohepatitis (NASH), which describes an advanced form of non-alcoholic fatty liver disease. In this study, treatment with spermidine significantly protected against fatty liver disease and improved mitochondrial function of liver cells.

The above studies confirm previous experiments with mice, which, in addition to weight reduction by spermidine, also showed less liver fat, higher glucose tolerance, and improved insulin sensitivity [29]. Administration of spermidine showed a direct impact on fat metabolism by inhibiting genes responsible for new lipid formation. At the same time, signals important for fatty acid oxidation were shown to be upregulated [29]. These mechanisms, coupled with the enhancement of lipolysis activity, could contribute to the improvements in metabolic status. Similar effects were observed after injection of spermidine in mice fed a high-calorie diet based on sugar consumption [30].

Further research, including human clinical trials, will be needed to further elucidate the potential of spermidine in the context of diabetes, obesity and metabolic syndrome.

Hair growth & psoriasis

The supplementation of spermidine leads to a lengthening of the hair shaft, as well as to a stimulation of hair growth of human hair follicles in an organ culture. Furthermore, spermidine has been demonstrated to be an important factor in human epithelial stem cells [31]. Spermidine prolongs anagenesis, the growth phase of the hair cycle, and in a first pilot study in humans after the supply of a spermidine-containing supplement, the proliferation of hair follicles was increased. These findings could provide the basis for a therapy of hair loss [32]. Additionally, spermidine inhibits symptoms such as redness, swelling and inflammation of the skin disease psoriasis in mice [33].

In addition, a group of researchers was able to show that spermidine improves the structure and functional properties of old and UV-stressed skin cells that are important for the skin's barrier function. Spermidine prevented the senescence of human skin cells and promoted the expression of genes of important skin proteins such as collagen and fibronectin. As a consequence, spermidine-treated old cells showed properties that were almost comparable to young, healthy cells [34].

Depression

Coumarylspermidine, found in safflower, is a derivative of spermidine that is quickly converted into spermidine in the body. Rats suffering from depression due to constant stress were demonstrated to have decreased symptoms of depression when supplemented with the ingredient coumarylspermidine contained in a food extract [35].

Fertility

Initial evidence suggests that spermidine plays a role in supporting fertility. Roundworms that are unable to produce spermidine in their cells due to a genetic defect lay fewer eggs and thus show a reproductive problem that can be corrected through spermidine supplementation [36]. In humans, the spermidine content of the male seminal fluid correlates with spermatogenesis and sperm motility, an important criterion for functionality [37]. A connection between polyamines and the formation of female egg follicles is also suspected in mice [37] and the administration of spermidine reduced signs of aging in female germline cells in response to oxidative stress through activation of cell-protective autophagy [38].. In a first pilot study on the impact of a spermidine-rich dietary supplement, a possible improvement in the hormones important for fertility has been described [39]. These data are interesting, but have to be investigated and confirmed in future clinical trials.

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