The role of the autophagy-inducer spermidine in cardiovascular ageing

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Abstract

Due to progressive degeneration of tissues with age, ageing has been recognised as a significant risk factor for the development of most chronic diseases, including cardiovascular diseases. Interventions – such as the addition of the polyamine spermidine to the diet – have been suggested to extend lifespan, as seen in a mouse model. This has partly been attributed to slowing down the negative effects of the ageing process on the cardiovascular system. Spermidine acts as a calorie restriction mimetic (CRM), which is naturally abundant in eukaryotic cells; however, the concentration of spermidine declines in cells with age. As spermidine is naturally found in several food sources, such as aged cheeses, fermented soybeans and wheatgerm, it is plausible to investigate the impact of dietary interventions on reducing the risk of age-related cardiovascular diseases. The data summarised in this paper indicates that the cardioprotective properties of spermidine can be partly attributed to its ability to promote autophagy in cardiac muscle, a vital process for the recycling of dysfunctional and potentially harmful cellular components, thus, preventing cardiomyopathies. Overall, the evidence presented in this review paper supports the use of spermidine as a promising candidate for delaying some of the age-related changes to the structure and function of the cardiovascular system.

Keywords: Spermidine, cardiac autophagy, increasing lifespan, slowing cardiovascular ageing, calorie restriction mimetic, spermidine and longevity, spermidine and autophagy induction

Introduction

The world's population is ageing, resulting in older persons making up a larger proportion of the population (United Nations, 2017). This has societal implications across a number of sectors including – but not limited to – goods and services, labour and healthcare (United Nations, 2017). The health challenges inherent in an ageing population will undoubtedly give rise to an increase in the rates of chronic diseases,

and thus the need to address this. Ageing is the main risk factor for the development of cardiovascular diseases (Niccoli and Partridge, 2012), equating to an increased risk in potential cases of myocardial infarction, stroke, heart failure and subsequent deaths (Niccoli and Partridge, 2012). The latest projections detailing the challenges of an ageing population within the United Kingdom show that there will be an additional 8.6 million people aged 65 and over by 2060 (Storey, 2018). This serves to place further strain on the publicly funded National Health Service (NHS; Storey, 2018), with cardiovascular diseases being the dominant cause of death (Majeed and Aylin, 2005)

A promising pharmacological candidate in addressing some of the problems associated with increased prevalence of cardiovascular diseases is the polyamine spermidine (Eisenberg *et al.*, 2016; Wang *et al.*, 2020). It has been suggested that decline in the levels of spermidine in cells is associated with an increased risk of the development of age-related cardiovascular diseases (Eisenberg *et al.*, 2009). Therefore, we aim to highlight some of the key physiological changes that occur as a result of ageing in the cardiovascular system and, more importantly, to collate the current research on the role and mechanism of the action of spermidine in delaying some of the observed age-associated cardiovascular diseases. We will also consider the potential of spermidine as a treatment and as a preventative tool for these challenges found in the ageing population.

Spermidine and autophagy

Spermidine is a member of the polyamine family and is naturally found in certain foods such as wheatgerm, fermented soybeans and aged cheeses (Madeo *et al.*, 2018a) Polyamines, such as spermidine, possess cations that interact with molecules such as lipids, proteins, DNA and RNA. These can have a negative charge, serving to stabilise them (Minois *et al.*, 2011). They therefore play various roles in cell proliferation, survival and growth by helping to mitigate DNA mutations and degradation along with delaying cell senescence and necrosis. This has implications for increasing longevity and reducing the incidence of age-related disease (Minois *et al.*, 2011).

Autophagy has been recognised as a vital process for lifespan extension and longevity (Rubinsztein *et al.*, 2011). Supplementation with spermidine has upregulated autophagy in yeast, worms, flies, human immune cells and mice, which subsequently led to lifespan extension (Eisenberg *et al.*, 2009). The same concept has been shown to hold true for cardiomyocytes, where spermidine promoted cardioprotective autophagy (Madeo *et al.*, 2018a; Eisenberg *et al.*, 2016). Autophagy plays a pivotal role in

maintaining optimal cellular environments by removing damaged organelles and toxic protein aggregates (Rubinsztein *et al.*, 2011). During ageing, damaged, misfolded and dysfunctional proteins accumulate, disrupting cellular environments and increasing risk of apoptosis induction (Escobar *et al.*, 2019). Therefore, discovering easily implementable methods of upregulating autophagy is of vital importance in tackling developments of cardiac pathophysiology.

Ageing and the increased risk of cardiovascular dysfunction

There are a number of molecular mechanisms contributing to the development of cardiac pathology during the ageing process (Chiao and Rabinovitch, 2015). These include mitochondrial reactive oxygen species (ROS) production and dysfunction, calcium homeostasis impairment, extracellular matrix (ECM) remodelling, neurohormonal signalling, stem cell ageing, miRNA deregulation and altered nutrient and growth signalling (Chiao and Rabinovitch, 2015). The physiological processes responsible for the development of cardiovascular dysfunction are numerous, including altered left-ventricular diastolic filling, left-ventricular hypertrophy and increased aortic root diameter (Gerstenblith *et al.*, 1977) To compound this further, there are reductions in maximum heart rate and contractility along with a decline in cardioprotective and repair processes (Strait and Lakatta, 2012). Such repair processes are vital for protection against oxidative stress, the loss of proteostasis and mitochondrial dysfunction, which eventually culminate in cardiomyopathies (Strait and Lakatta, 2012). Spermidine has the potential to mitigate pathophysiological developments through inducing a number of cardiovascular changes (Figure 1). Autophagy is the principle mechanism by which benefits are conferred due to the upregulation of oxidative stress protection, recycling of dysfunctional proteins and mitochondrial biogenesis (LaRocca *et al.*, 2013; Minois *et al.*, 2011; Wang *et al.*, 2020).

Cardiac hypertrophy predominantly occurs due to the dysfunction of nutrient and growth signalling pathways, particularly involving mammalian target of rapamycin (mTOR) and insulin-like growth factor-1 (IGF-1) (Chiao and Rabinovitch, 2015). Studies in both *Drosophila* and mice have shown the importance of mTOR in cardiac-hypertrophy development with downregulation of mTOR signalling increasing resistance to cardiac ageing and upregulation impairing resistance to cardiac ageing (Chiao and Rabinovitch, 2015). Moreover, the insulin/IGF-1 pathway has been implicated in the development of cardiac disease with reduced activation of this pathway slowing cardiomyocyte dysfunction in mice and *Drosophila* (Li *et al.*, 2008; Wessels *et al.*, 2004). Spermidine works independently of the mTOR pathway to elicit

an anti-ageing effect via gene hypoacetylation as opposed to altering the phosphorylation status of mTOR (Minois, 2014). With regard to Insulin/IGF signalling, it has been demonstrated that reducing such signalling leads to glycine-N-methytransferase (Gnmt)-dependent spermidine level increase in *Drosophila,* resulting in increased lifespan (Tain *et al.*, 2020).

Additionally, mice over-expressing catalase in the mitochondria (mCAT) have shown slowed cardiac ageing, decreased hypertrophy and improved diastolic function (Dai *et al.*, 2009), whereas mice over-expressing mitochondrial polymerase – and hence increased mitochondrial mutation – have shortened lifespan and earlier onset of cardiac disease (Dai *et al.*, 2010). Subsequent mCAT mutations in these mice demonstrated reduced mitochondrial damage and cardiomyopathy (Trifunovic *et al.*, 2004; Dai *et al.*, 2010). Defective mitochondria play a pivotal role in age-related decline and cardiac dysfunction but can be targeted by spermidine through mitophagy induction (Madeo *et al.*, 2018a)

Changes in the ECM of cardiomyocytes as ageing progresses is also implicated in cardiac function decline. The cardiac ECM environment is comprised of collagen types I through to VI, elastin, laminin, fibrinogen and fibronectin, all generated by cardiac fibroblasts (DeQuach *et al.*, 2010). The ECM is responsible for aligning the cardiac myocytes and structurally supporting the heart. However, ECM components such as metalloproteinases, along with the quantity and quality of collagen deposition, can also contribute to diastolic heart failure depending on the individual's phenotype (Ouzounian *et al.*, 2008). While spermidine does not appear to impact the degree of collagen deposition in the ECM of cardiomyocytes in aged mice, it directly impacts cardiomyocytes through increased mitochondrial volumes and decreased sarcoplasmic volume. These changes were shown to increase myocardial compliance (Eisenberg *et al.*, 2016).

Although interventions in treating heart disease are relatively effective – mainly targeting cholesterol levels and blood pressure – they do not target the underlying mechanisms of cardiovascular disease development (Cabo and Navas, 2016). Spermidine, however, has demonstrated the potential to target these mechanisms in mouse models (Cabo and Navas, 2016). This is where the calorie restriction mimetic (CRM) spermidine may be extremely valuable in mitigating age-related cardiac pathologies.

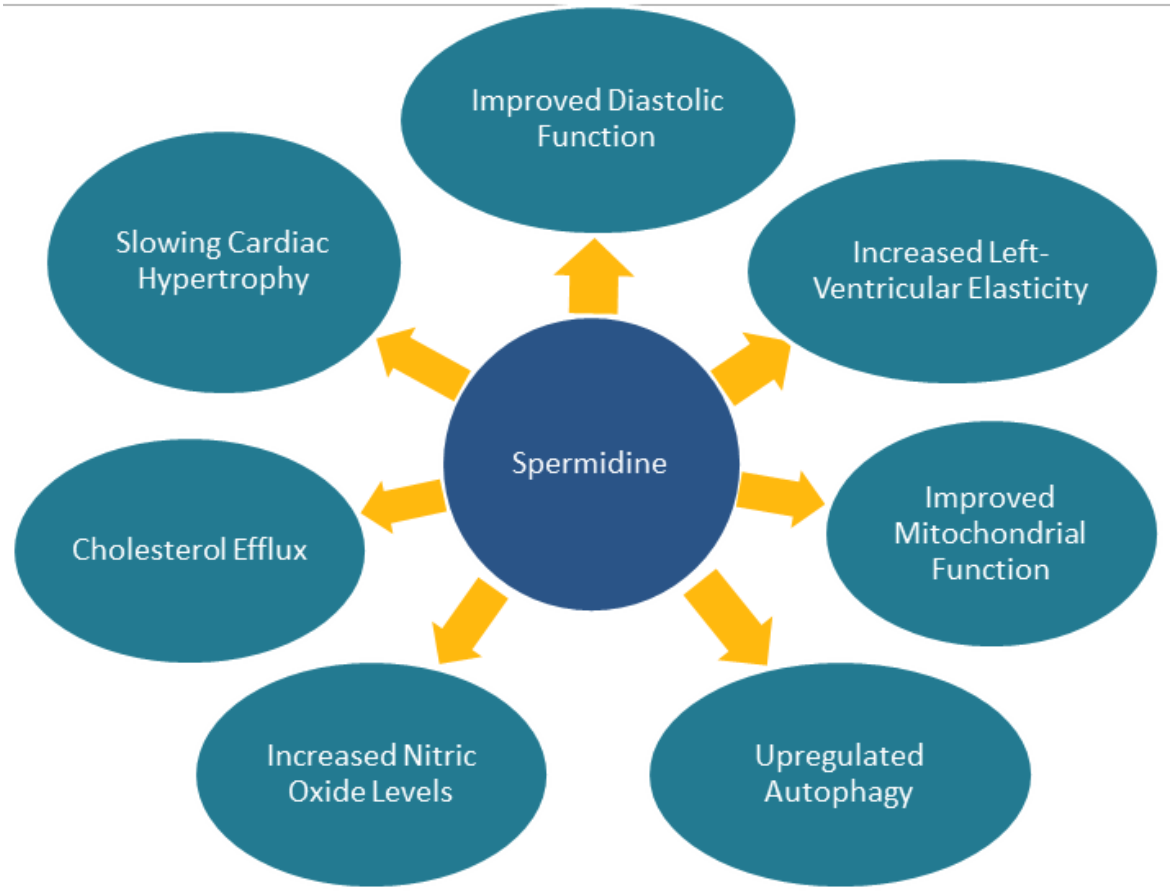

Figure 1: Cardioprotective effects of spermidine

Mechanism of spermidine in inducing autophagy

It has been shown that the beneficial effects of spermidine are due to its ability to induce autophagy (Eisenberg *et al.*, 2009). Model organisms such as yeast, worms and flies, with deficient machinery to induce autophagy, acquired no life-extension benefits from the introduction of spermidine. Such studies suggest that effective machinery to induce autophagy is necessary for spermidine to be effective (Eisenberg *et al.*, 2009). It has also been demonstrated that spermidine-induced paraquat resistance is markedly reduced in *Drosophila* that have defective machinery for autophagy compared to those without deficits (Minois *et al.*, 2012). Spermidine inhibits the activity of certain histone acetyltransferases (HATs) resulting in H3 hypoacetylation (Eisenberg *et al.*, 2009). This confers gene transcription regulation favouring the induction of autophagy and apoptosis as opposed to inflammatory necrotic cell death (Eisenberg *et al.*, 2009).

Hypoacetylation of histones has been shown to promote longevity in yeast cells also, particularly through the activation of Sir2 and NAD+-dependent histone deacetylases

and is therefore considered a potential key event in healthy ageing (Imai *et al.*, 2000) This provides further evidence that hypoacetylation may be key in promoting longevity, which is a key mechanism of spermidine.

Additionally, spermidine acts as an acetyltransferase inhibitor in E1A-associated protein p300 (EP300) through competitive inhibition of the EP300 protein with Acetyl-CoA (Pietrocola *et al.*, 2015). It has been demonstrated that when Acetyl-CoA levels are depleted in human and murine cell lines, deacetylation of cytoplasmic proteins occurs stimulating autophagy in heart and muscle cells (Mariño *et al.*, 2014). However, when Acetyl-CoA levels are maintained during starvation, autophagy induction is inhibited (Mariño *et al.*, 2014).

Another pathway in which the action of spermidine is critical involves the polyamine-eIF5A-hypusine axis (Puleston, Buck and Pearce, 2019). Spermidine promotes autophagy in B cells and macrophage activation through the hypusination of a conserved lysine residue in the eIF5A protein (Zhang, Alsaleh, Feltham and Sun, 2019) (Puleston *et al.*, 2019). Activation of eIF5A subsequently triggers the expression of mitochondrial proteins involved in the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (Puleston *et al.*, 2019). In B cells, post-translational modification of the eIF5A protein stimulates the production of autophagy transcription factor TFEB, which has the potential to reverse immune cell senescence (Zhang *et al.*, 2019).

Induction of autophagy for cardiac protection by spermidine

Spermidine is synthesised *in vivo* via the conversion of arginine to ornithine, which is then converted to polyamines putrescine, spermidine and spermine mediated by ornithine decarboxylase (Figure 2) (Minois, 2014).

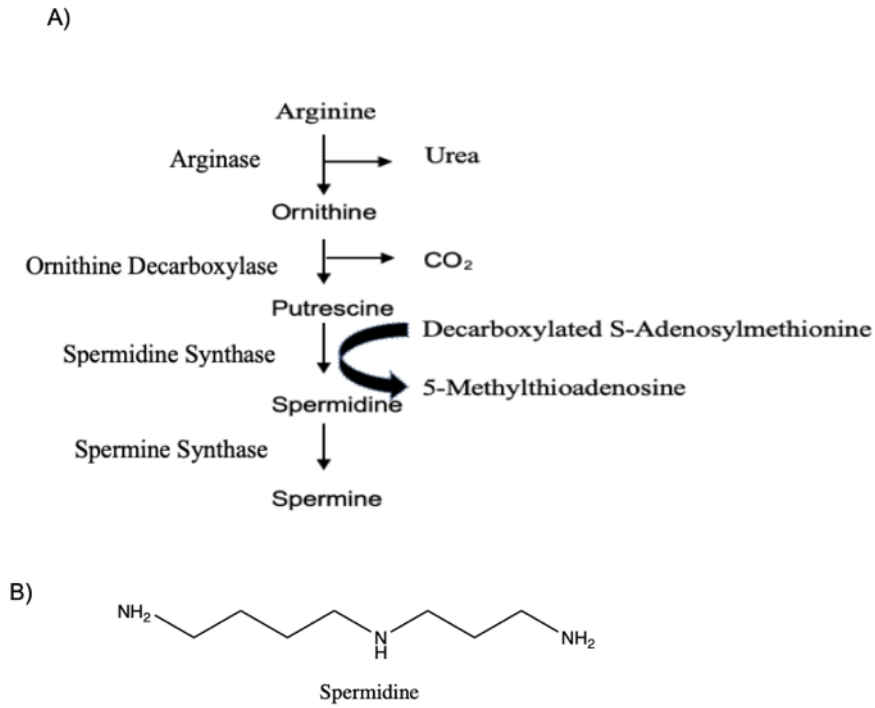

Figure 2: A) Biosynthetic pathway of polyamine spermidine via ornithine decarboxylase; B) Chemical structure of spermidine

Spermidine is acquired in a number of ways including cellular biosynthesis, microbiota generation and through oral uptake (Madeo *et al.*, 2018a). It is well established that spermidine levels decline in humans as we age with concentrations of cellular spermidine being determined by dietary intake, cellular biosynthesis, rates of catabolism and urinary excretion (Madeo *et al.*, 2018a). However, increased dietary intake of polyamines has been shown to increase the blood concentration of polyamines in both mice and humans (Soda *et al.*, 2009). Polyamine levels in this study were determined through centrifugation of blood samples and subsequent high-performance liquid chromatography analysis, which showed statistically significant blood concentration increases (Soda *et al.*, 2009). The transport mechanism of polyamines into the intracellular environment is currently poorly understood with only three competing models, none of which fully explain the transport process (Nowotarski *et al.*, 2013).

Recently discovered is the ability of spermidine to improve cardiac function in rats through activation of the AMPK/mTOR pathway and through slowing cardiac hypertrophy (Yan *et al.*, 2019). Investigations in rat models fed a high salt diet with simultaneous spermidine administration show similar results (Eisenberg *et al.*, 2016).

Delayed hypertension onset, decreased cardiac hypertrophy and increased diastolic functioning were shown while renal injury due to increases in blood pressure was reduced (Eisenberg *et al.*, 2016). This has been demonstrated in both rats and mice with spermidine significantly improving markers of cardiac ageing such as left-ventricular hypertrophy and stiffness while mitigating diastolic dysfunction (Eisenberg *et al.*, 2016). Expression of LC3-II – an autophagy marker – was reduced in aortas of older mice, whereas p62 – an autophagy substrate marker – was increased relative to younger mice (LaRocca *et al.*, 2013). Addition of spermidine restored the LC3-II expression and reduced p62 in older mice, but did not have an effect in younger mice. Moreover, H3 histone acetylation was decreased and Atg3 – an autophagy protein – was upregulated in both old and young mice (LaRocca *et al.*, 2013). It has been shown that the induction of autophagy in mice through exogenous supplementation with spermidine stimulates cholesterol efflux (Michiels *et al.*, 2016). This inhibits lipid accumulation and necrotic core formation in vascular smooth muscle cells, hinting at a potential to prevent vascular disease (Michiels *et al.*, 2016).

Expression of the Atg5 protein has also been observed and is vital for the induction of autophagy in cardiomyocytes as demonstrated in Atg5-deficient mice (Nakai *et al.*, 2007). Loss of this protein was shown to induce cardiomyopathy in mice, producing hypertrophy, left-ventricular dilatation, contractile dysfunction and increased ubiquitination (Nakai *et al.*, 2007). In addition, it was seen that contractile tissue was preserved, an improvement in mitochondrial function was noted along with improved inflammation suppression mechanisms (Nakai *et al.*, 2007). The most likely explanation for this effect is the increased bioavailability of nitric oxide (NO) acting as a vasodilator, reducing arterial blood pressure (Van Faassen *et al.*, 2009). In old mice, endothelial dilation functions are approximately 25 per cent lower compared to young mice and also approximately 20 per cent increase in arterial stiffness in old mice hypothesises to be due to decreased NO bioavailability (LaRocca *et al.*, 2013). This poses the question of whether the NO pathways and autophagy are independent mechanisms or can only work in conjunction with each other (Madeo *et al.*, 2018a).

Conclusion

Spermidine has demonstrated promising results for promoting longevity and improving health span in various research models, particularly through the polyamine's ability to induce autophagy (Madeo *et al.*, 2018a). Cardioprotective effects are also apparent through the induction of nitric-oxide synthesis by spermidine; however, this mechanism needs to be elucidated further to identify therapeutic

molecular targets (Madeo *et al.*, 2018a). Although one survey-based study linked increased consumption of spermidine rich foods to lower rates of cardiovascular disease in humans (Kiechl *et al.*, 2018), more research is needed to ascertain whether the effects seen in mice are translatable to humans with respect to longevity and the extent of benefits to cardiac health. For example, levels of blood spermidine concentrations needed to maintain optimal cardiovascular health in humans are not known. Nonetheless, noting that spermidine levels reduce in ageing individuals (Madeo *et al.*, 2018a) and blood concentrations of the polyamine can be increased through dietary intake (Soda *et al.*, 2009) provides a promising basis for the potential use of spermidine as a supplement.

These findings represent an important step in establishing treatment targets and discovering precise molecular pathways implementable in preventing age-related disease. However, minimum dosages will need to be determined that could be potentially therapeutic. It will also need to be determined whether the potential effects are translatable to the majority of the population (Madeo *et al.*, 2018b). There have been conflicting results with respect to how supplementation of spermidine impacts blood levels of the compound, with some studies demonstrating an increase and others having no impact (Brodal *et al.*, 1999. Soda *et al.*, 2009; Schwarz *et al.*, 2018). However, the differences observed in these studies are likely to be associated with the concentrations of spermidine administered. Spermidine is also being investigated for treatment surrounding intrauterine growth restriction in newborns and reducing the impact of oxidative stress caused by hypoxia on the heart (Chai *et al.*, 2019).

Future research with spermidine is currently being centred around safety and tolerability of the compound with one study demonstrating this it is safe and well tolerated in mice and older adults with subjective cognitive decline (Schwarz *et al.*, 2018) leading the way for longer exposure studies to be conducted. That being said, spermidine is naturally abundant in all eukaryotic cells so is unlikely to be poorly tolerated if acquired from exogenous food sources.

A larger number of studies will need to be completed to determine any possible side effects and utility of spermidine in human populations with more epidemiological studies taking into consideration any confounding factors. If successful, the compound has the potential clinical application of targeting specific mechanisms responsible for the onset of cardiovascular diseases.

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Glossary

Acetylation Introduction of an acetyl (O=C-R) functional group into a chemical compound

Acetyl CoA A molecule involved in many biochemical reactions, mainly the tricarboxylic acid cycle for energy production

Ageing The occurrence of structural and functional changes that occur over time

Apoptosis Controlled cell death as part of an organism's normal growth process

Autophagy Cell regulatory mechanism that removes dysfunctional or unnecessary components

Biogenesis Synthesis of substances by a microorganism

Calorie restriction mimetic Molecule mimicking the anti-ageing effects of calorie restriction

Cardiovascular Relating to the heart and blood vessels

Cardiomyocytes Cells comprising heart muscle

Cardiomyopathy Disease of the heart muscle

Catabolism The break-down of molecules through metabolic pathways

Cations Positively charged ions

Cell necrosis Death of cells due to injury, disease or lack of blood supply

Chronic disease A health condition lasting for longer than three months

Compound A substance formed when two or more chemical elements are combined

Diastolic Relaxation phase of the heart

Eukaryotic cell Cells found in animals, plants and fungi

Exogenous From an outside source

Extracellular matrix Network of proteoglycans, water, minerals and fibrous proteins that form structural and biochemical support to surrounding cells

Fibroblasts Principle active cell in connective tissue that synthesises the extracellular matrix and collagen

Glycine-N-methyltransferase Catalyses the methylation of glycine from S-adenosylmethionine

Histone Proteins in eukaryotic cell nuclei that package and order the DNA into structural units called nucleosomes

Histone acetyltransferases Enzymes that transfer acetyl groups to acetylate lysine amino acids on histone proteins

Homeostasis Maintenance of an equilibrium

Hypertension Persistently raised arterial blood pressure not within healthy limits

Hypertrophy Enlargement of an organ or tissue due to increase in cellular size

Hypoacetylation Insufficient acetylation causing gene inactivation

Hypoxia A lack of oxygen supply

Hypusination Addition of the amino acid hypusine, which is only found in eukaryotic translation initiation factor 5A (eIF5A) and archaebacteria

In Vivo Within a living organism

Metalloproteinase Any protease enzyme with a metal involved in its catalytic mechanism

Microbiota Communities of microorganisms

MiRNA Micro RNA functioning in RNA silencing and post-transcriptional regulation

Mitochondria An organelle responsible for respiration and energy production

Mitochondrial Polymerase Mitochondrial replication machinery

Mitophagy Degradation of mitochondria by autophagy

mTOR Mammalian Target of Rapamycin is a protein kinase involved in a number of cellular processes (ageing in this case).

Oxidative phosphorylation The process of ATP formation through the transfer of electrons from NADH or $FADH_2$ to Oxygen forming H_2O

Paraquat A chemical herbicide that is highly toxic

Pathophysiology Abnormal functioning associated with disease or injury

Polyamine A carbon containing compound comprising of more than two amino ($-NH_2$) groups

Pharmacological Uses, effects and modes of action of drugs

Proteostasis Biological pathways in cells that regulate biogenesis, folding, trafficking and protein degradation

Sarcoplasmic volume Amount of cytoplasm of striated muscle cells

Senescence Deterioration with age

Systolic Contraction phase of the heart

Tricarboxylic acid cycle The second stage of cellular respiration occurring in the mitochondria, involved in energy production.

Ubiquitination The process of adding a ubiquitin protein to a protein tagging the protein for degradation

Vasodilator Increasing the diameter of a blood vessel

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