STEMedicine

REVIEW ARTICLE

Magnesium in aging and aging-related disease

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Abstract

Magnesium (Mg^{2+}) is an essential divalent cation in human body. Its balance is tightly controlled via a balanced interplay among intestinal absorption, storage, and renal excretion, involving multiple transporters across cell membrane that regulate Mg^{2+} influx and efflux. Mg^{2+} is involved in a variety of physiological and pathological processes such as enzymatic reactions, energy metabolism, cell proliferation, apoptosis, oxidative stress, and inflammation. In particular, Mg^{2+} contributes to the molecular hallmarks of aging. Emerging evidence demonstrates that altered Mg^{2+} status has been associated with many aging-related diseases, including cancer, cardiovascular disease, neurodegenerative disease, musculoskeletal function, metabolic syndrome, and COVID-19. In this review, we focus on Mg^{2+} and its association with molecular hallmarks of aging. We also summarize recent findings supporting an important role of Mg^{2+} in aging-related disease including the COVID-19 pandemic.

Keywords: *magnesium*; *magnesium transporters*; *aging*; *human disease*

Received: 4 January 2022; Revised: 14 February 2022; Accepted: 21 February 2022; Published: 4 April 2022

Magnesium (Mg^{2+}) is the eighth most common element in the earth's crust (1). It is involved in various cellular activities, including signal transduction, ion transport, nucleic acid, protein synthesis, genomic stability, energy supply, and metabolic homeostasis (2). Due to its physiological significance, Mg^{2+} balance in human body and intracellular Mg^{2+} homeostasis needs to be tightly controlled via a dynamic interplay between intestinal absorption and renal excretion, involving multiple transporters across cell membrane that regulate Mg^{2+} influx and efflux (1). Mg^{2+} transporters include claudins, transient receptor potential melastatin 7 (TRPM7), TRPM6, solute carrier family 41 (SLC41), ancient conserved domain protein/cyclin M (CNNM), magnesium transporter 1 (MagT1), and mitochondrial RNA splicing 2 (Mrs2) (3, 4). Both hypomagnesemia and hypermagnesemia lead to human diseases. Chronic Mg^{2+} deficiency contributes to an increased risk of a variety of clinical disorders, such as cardiovascular diseases (CVDs), including hypertension and cardiac arrhythmias, stroke, type 2 diabetes, metabolic syndrome, depression, and neuropsychiatric disorders (5).

Aging is a progressive loss of physiological integrity and characterized by an increasing susceptibility to the development of multiple chronic diseases (6). The aging process involves various changes at the cellular, organ, and body levels. In general, aging encompasses multiple modes induced by DNA damage, oxidative stress, drug damage, mitochondrial dysfunction, paracrine secretion, or telomere shortening (7). Aging also leads to an increased incidence of numerous human diseases, such as CVDs, neurodegenerative diseases, immune disorders, respiratory diseases, cancers, and infections (8).

In this present review, we provide an illustrative overview of Mg^{2+} balance in human body and the underlying mechanisms involving various Mg^{2+} transporters. We also discuss the involvement of Mg^{2+} in molecular hallmarks of aging, with a focus on the important role of Mg^{2+} in aging-related human diseases.

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Citation: STEMedicine 2022, 3(2): e119 - http://dx.doi.org/10.37175/stemedicine.v3.i2.119

Mg^{2+} and human health

Mg^{2+} basics

Mg^{2+} is highly soluble and, therefore, readily available to living organisms (9). As the fourth most abundant cation in the body behind sodium, potassium, and calcium, Mg^{2+} is present in three forms, free, ionized (55–70%), protein-bound (20–30%), and forming complexes with anions such as phosphate, bicarbonate, and citrate (5–15%). In healthy individuals, serum concentration of total Mg^{2+} is maintained tightly within a range between 0.65 and 1.05 mmol/L (1). Bone functions as a large buffer pool contribute to the maintenance of serum Mg^{2+} concentrations (10). Total Mg^{2+} concentration in mammalian cells is in the 17–20 mM range, mostly located in mitochondria, nucleus, and endoplasmic reticulum (11). Within these organelles, Mg^{2+} is bound to phospholipid, proteins, nucleic acids, chromatin, and nucleotides. Cytoplasmic Mg^{2+} is the last and well detectable pool of intracellular Mg^{2+}, with the majority complexed with Adenosine Triphosphate (ATP) phosphonucleotides, and phosphometabolites (11, 12). With the application of novel Mg^{2+}-selective fluorescent probes and the development of new imaging techniques, cellular Mg^{2+} homeostasis awaits more accurate and dynamic evaluation (13). Mg^{2+} is an essential element for normal life activities, and Mg^{2+} homeostasis is precisely regulated to maintain functional stability of cells.

Mg^{2+} transporters and Mg^{2+} homeostasis

Mg^{2+} is absorbed mainly in the small intestine (mainly in the jejunum and the ileum), stored in bone mineral, and excreted through urine and feces (14). In the small intestine, paracellular absorption is driven by higher luminal Mg^{2+} concentrations (1.0–5.0 mmol/L) and accounts for 80–90% of Mg^{2+} uptake (15). The kidneys regulate serum Mg^{2+} concentrations through excretion and reabsorption. Mg^{2+} excretion follows a circadian rhythm and only 3–5% of serum Mg^{2+} is excreted, and the thick ascending limb of the loop of Henle reabsorbs 60–70% of the filtered Mg^{2+}, with about 10% reabsorbed in the distal tubule (3, 16). Under physiological conditions, the tightly regulated balance of Mg^{2+} intestinal uptake, intracellular storage, and renal excretion is achieved through a specialized transport system consisting of Mg^{2+} transporters across biological membranes (Fig. 1).

Biological function of Mg^{2+}

Mg^{2+}, as a cofactor, has been involved in more than 600 enzymatic reactions and exerts critical effects in a variety of cellular biological activities (11, 17). Mg^{2+} is indispensable for major cellular processes, including energy metabolism, apoptosis, and proliferation. Mg^{2+} acting as an allosteric modulator or as a cofactor in the form of Mg-ATP modulates the activity of enzymes implicated in glycolysis, the Krebs cycle, and the respiratory chain, core processes of energy metabolism (18). Mechanisms whereby Mg^{2+} regulates cell proliferation involve the cell cycle inhibitor p27 and p53, and other negative modulators of cell proliferation such as Jumonji and numblike (18, 19). Evidence for the role of Mg^{2+} in cell apoptosis remains inconclusive. In many experimental models, Mg^{2+} deprivation induced cell death by apoptosis, and dietary Mg^{2+} restriction accelerated apoptosis (18, 20, 21).

X-ray crystal structure analysis reveals that Mg^{2+} specifically binds to the major and minor grooves of DNA (22, 23). Mg^{2+} stabilizes the DNA conformation by electrostatic force or hydrogen bonds and contributes to the secondary and tertiary structure of DNA (24, 25). DNA aggregation study showed that DNA fragments strongly aggregated on Mg^{2+}-treated glass and in Mg^{2+} solution in a concentration-dependent manner (26). Thus, the maintenance of intracellular Mg^{2+} at a physiological level is important for DNA stability. Additionally, abnormal Mg^{2+} concentrations can also lead to oxidative stress and damage to the double-stranded structure, thus weakening the DNA stability (27, 28). Moreover, Mg^{2+} is required for a variety of enzymes involved in DNA repair pathways, such as nucleotide excision repair (NER), base excision repair (BER), and mismatch repair (MMR), indicating the important role of Mg^{2+} in maintaining genome stability (29–31).

Both in vitro and in vivo experiments have demonstrated that a decreased level of Mg^{2+} affects the behavior of leukocytes and vascular endothelial cells and activates the production of inflammatory factors in acute inflammation (32). The underlying mechanisms involve the upregulation of stress proteins and Nuclear Factor -kappa B (NF-kB) pathways, and the impairment of Ca^{2+} dynamics (33). Increased reactive oxygen species (ROS) and altered Ca^{2+} dynamics induced by low Mg^{2+} further lead to impaired mitochondrial function (34). In chronic diseases, Mg^{2+} inhibits oxygen free radical production and mast cell degranulation, protects epithelial cells, and alleviates the inflammatory and oxidative damage to cells and blood vessels (35). Moreover, reduced Mg^{2+} has been observed in a variety of diseases, such as CVD, asthma, preeclampsia, osteoporosis, inflammatory bowel disease, mental health disorders, and neurodegenerative disease (36–38).

Mg^{2+} and aging

Aging is a progressive reduction of the body's physiological and psychological adaptability to the environment, leading to increased vulnerability to death. Studies have linked aging to molecular cross-linking, free radicals-induced damage, changes in immune function, telomere shortening, and the presence of senescence genes in DNA (7, 39). However, there is not a single theory that can completely explain the aging process, indicating that it is

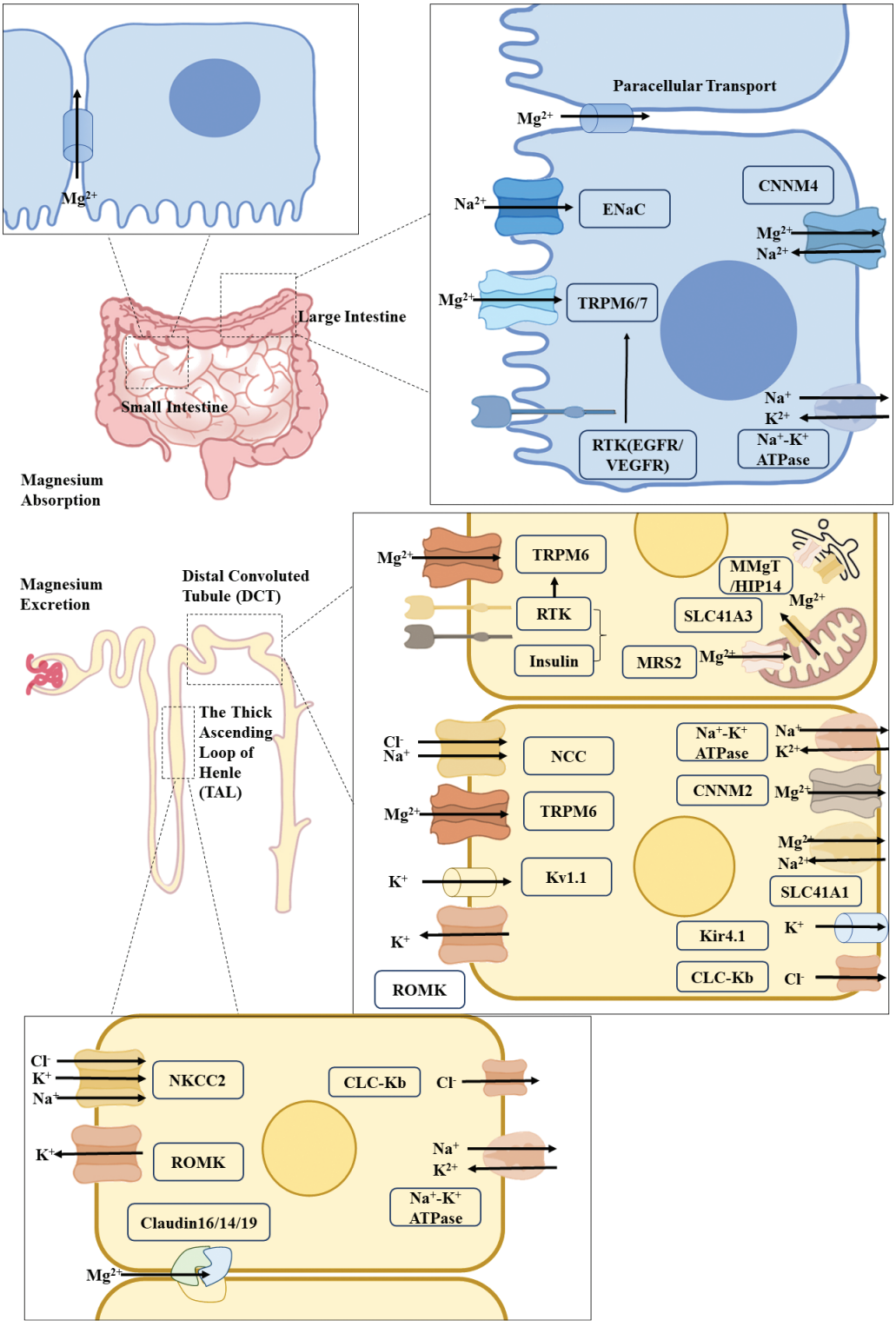

Fig. 1. Mechanism of Mg^{2+} balance in the body. Mg^{2+} is absorbed mainly in the intestine and excreted through the kidney. Claudin-16, Claudin-19, TRPM6/7, Mrs2, SLC41A1/3, and CNNM2/4 are transporters of Mg^{2+}. Receptor tyrosine kinase (RTK) and its ligands such as epidermal growth factor (EGF) influence Mg^{2+} homeostasis by regulating Mg^{2+} transporters.

a complicated process regulated by multiple factors at the genetic and cellular levels, and by the environment and society. Previous studies have demonstrated several cellular and molecular hallmarks of aging, including telomere attrition, mitochondrial dysfunction, genome instability, epigenetic alterations, a loss of proteostasis, dysregulated

nutrient sensing, cellular senescence, stem cell exhaustion, and altered intracellular communication (Fig. 2) (40). In this review, we focus on several hallmarks of aging, which have been closely associated with Mg^{2+}.

Mg^{2+} and telomere attrition

Telomere consists of a 6-bp repeat sequence, TTAGGG. It is located at the ends of chromosomes, which shortens gradually with each cell division and ultimately limits cellular proliferative capacity (41). Telomeric chromatin structure and integrity are influenced by Mg^{2+}. Telomere (>50%) is localized in the nuclear laminae, and their trailing lamin-binding proteins are dependent on the presence of Mg^{2+} (42). In addition to maintaining the telomere structure, Mg^{2+} also contributes to the regulation of telomerase; the enzyme catalyzes the addition of guanine-rich repetitive sequences to maintain telomeres (43). Telomerase reverse transcriptase (TERT) is the catalytic component of telomerase (44). TERT is known to exerts its biological effects through an interaction with the mammalian target of rapamycin (mTOR) pathway, which is sensitive to changes of Mg^{2+} status (45). Liu et al. found that Mg^{2+} can activate the mTOR signaling, which consequently protects against the age-related decline in muscle regenerative potential and muscle mass (46). Additionally, circadian fluctuation of mTOR is regulated through Mg^{2+} oscillations in a

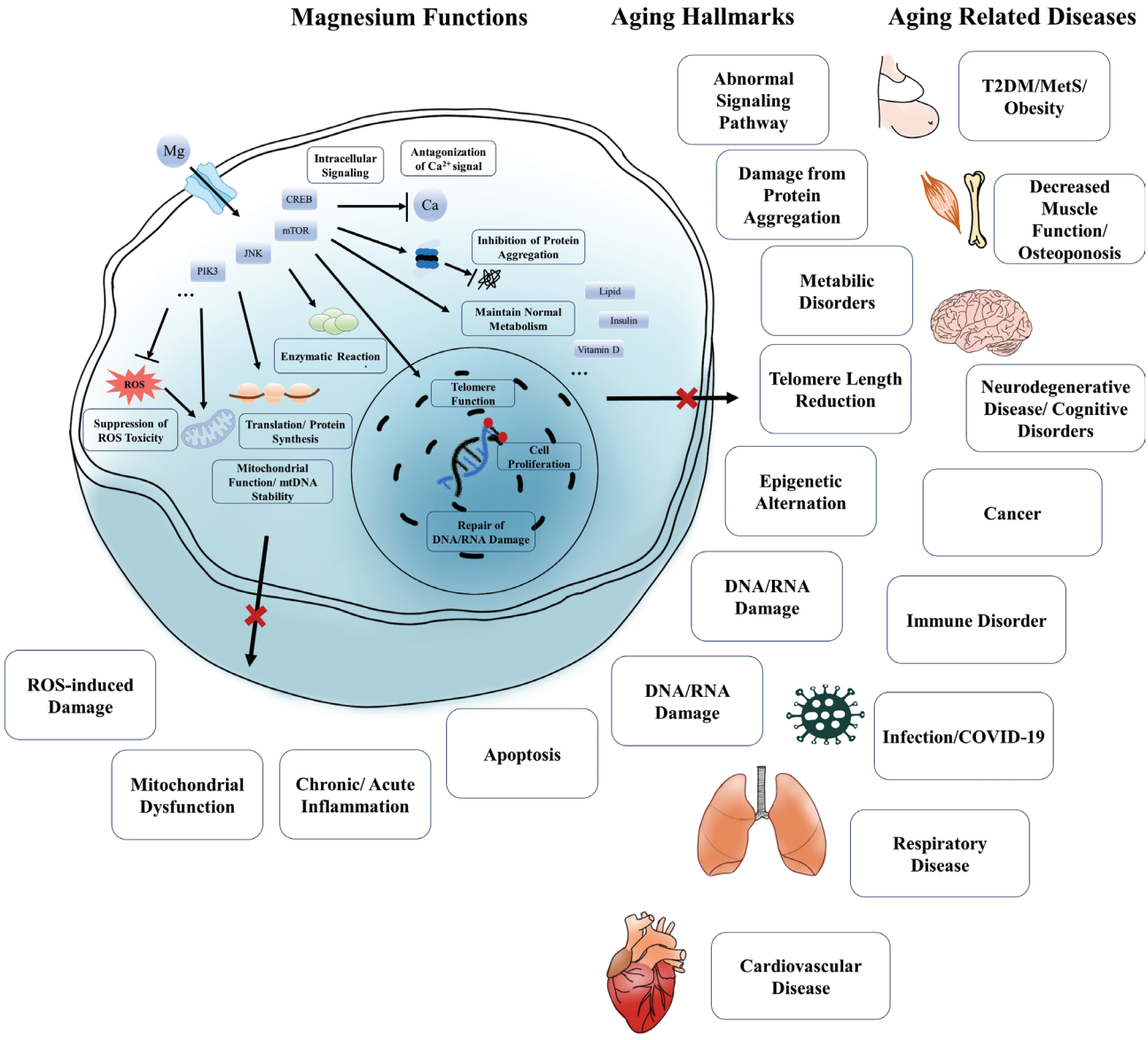

Fig. 2. The role of Mg^{2+} in cell physiology, aging, and aging-related disease. Mg^{2+} contributes to the regulation of intracellular environment, signaling pathways, cation concentration, and mitochondrial function. Mg^{2+} is critically linked to molecular hallmarks of aging and is involved in the development of aging-related disease.

MgATP-sensitive manner (45). Altered circadian rhythms affect the expression of TERT mRNA and accelerate the aging process, and fluctuations in Mg^{2+} are critically implicated in the modulation of cellular clock and play a role in aging-related diseases (47).

Mg^{2+} and mitochondrial dysfunction

Intracellular Mg^{2+} deficiency has been shown to affect coupled respiration, increase ROS production, and inhibit the antioxidant defense systems, including superoxide dismutase (SOD), catalase, and glutathione, leading to the disruption of mitochondrial function (48). A reduction in intracellular Mg^{2+} also disturbs mitochondrial Mg^{2+} homeostasis through modulating mitochondrial RNA splicing 2 (Mrs2), a Mg^{2+} transporter specifically involved in mitochondrial Mg^{2+} influx and promoting mitochondrial Mg^{2+} efflux via the 41st family of solute carrier member 3 (SLC41A3) (49). The regulation of mitochondrial Mg^{2+} by Mrs2 has significantly influenced cellular energy status and cellular vulnerability. Mrs2 knockdown induces loss of electron transport chain complex I, decreases cellular and nuclear ATP levels, depolarizes $\Delta\Psi m$, and renders cells sensitive to oxidative stress inducers and apoptotic stimuli (48). In line with this, the overexpression of Mrs2 enhances cellular resistance to apoptosis-inducing drugs (50).

SLC41A3 is a novel transporter important for mitochondrial Mg^{2+} efflux, and its mRNA expression was increased under Mg^{2+}-deficient conditions (51). Intriguingly, intracellular ATP levels were reduced in cells with SLC41A3 overexpression, indicating that the transporter contributes to mitochondrial ATP production (52). Studies based on obesity models show that during ischemia and hypoxia, the increase of extracellular Mg^{2+} was associated with decreased ATP levels and TRPM7 inhibition, leading to exacerbated cell damage (53, 54). Moreover, reduced intake of Mg^{2+} and consequent low serum Mg^{2+} level induce oxidative stress injury through decreasing antioxidant enzyme activity, activating the inflammatory pathways, lipid peroxidation, and endothelial dysfunction (55). Dietary Mg^{2+} supplementation in a mouse model of premature aging has been shown to enhance the mitochondrial membrane potential and consequently increase H^+-coupled mitochondrial NADPH and ATP productions, leading to an extended life expectancy (56).

Mg^{2+} in genomic instability and epigenetic alterations

As early as 1976, it was shown that Mg^{2+} in DNA polymerase is essential for the fidelity of DNA replication (57). Acting as an essential cofactor for the DNA damage repair process, Mg^{2+} contributes to the stabilization of the chromatin structure during the cell cycle (58). However, in cells undergoing apoptosis, intracellular levels of free Mg^{2+} are increased, constituting an early event in the process of apoptosis (59). At the protein level, Ca^{2+}- and Mg^{2+}-dependent endonucleases have been implicated in DNA breaks during apoptosis (60). Furthermore, Mg^{2+} has been linked to epigenetics, and DNA methylation is associated with chromatin compaction and gene silencing.

In the offspring of Mg^{2+}-deficient dams, 11β-hydroxysteroid dehydrogenase-2 (Hsd11b2) CpG promoters displayed substantial hypermethylation, contributing to downstream down-regulated gene expression (61). In pregnant rats, Mg^{2+} deficiency induced by a low Mg^{2+} diet is able to affect the methylation of specific cytosines in the hepatic glucocorticoid genes and consequently cause metabolic complications in the neonatal offspring (62). In addition, even a short-term deprivation of dietary Mg^{2+} has been shown to greatly upregulate neutral-sphingomyelinase (N-SMAse) and p53 in cardiomyocytes, which is associated with genomic changes that are important in the development of aging (63).

Mg^{2+} and metabolic disturbances

Many studies have demonstrated metabolic characteristics of aged animals, such as glucose intolerance, insulin resistance, decreased fatty acid oxidation, mitochondrial biosynthesis, and impaired oxidative phosphorylation (64). Mg^{2+} exerts its significant impact on the metabolic state through functioning as a cofactor of critical enzymes in mitochondria, where Mg^{2+} binds to ATP and forms Mg-ATP complex to regulate the glycolytic enzymes (65). Mg^{2+} contributes to the activation of mitochondrial dehydrogenases that are important in energy metabolism, including pyruvate dehydrogenase complex (PDH) (66), isocitrate dehydrogenase (IDH), and 2-oxoglutarate dehydrogenase complex (OGDH), rate-limiting enzymes of the Krebs cycle (67, 68). Mg^{2+} also functions as a second messenger in the regulation of insulin secretion and release, influencing insulin downstream signaling pathways (69–71). Calorie restriction (CR) is known to improve lifespan and age-associated deteriorations by changing metabolic state (72). Studies have found that Mg^{2+} mediates the beneficial effects of CR via R-loops suppressors Rnh1/201 and Pif1, and Mg^{2+} supplementation protects against the accumulation of R-loops (RNA–DNA hybrids), which contributes to genomic instability and lifespan-shortening (73). It has been shown that CR increases intracellular Mg^{2+} by upregulating Mg^{2+} transporter TRPM7, while disruption of the transporter reduces environmental Mg^{2+} levels and compromises CR-induced repression of the lifespan-shortening formation of RNA-DNA hybrids (73).

Mg^{2+}, protein stability, and intracellular communication

Low levels of Mg^{2+} have been observed in the brain tissue of patients with neurological disorders, such as migraine, epilepsy, and Parkinson's and Alzheimer's diseases (AD). Underlying mechanisms of these diseases might include an abnormal aggregation of extracellular amyloid

β-protein (Aβ), tau phosphorylation, and neuroinflammation characterized by increased TNF-α and IL-1β expressions (74). It was observed that at the cellular level and in animal models, Mg^{2+} was able to downregulate TNF-α and IL-1β and reduce the accumulation of amyloid β precursor protein in the brain (75, 76). In addition, Mg^{2+} was documented to promote Aβ clearance, through participating in the proteasomal degradation pathway and decreasing the permeability of blood–brain barrier (77).

Mg^{2+} and its transporters are crucial modulators of the communication between intracellular signaling pathways. The N-methyl-D-aspartate (NMDA) receptor is involved in excitatory neurotransmission, neuroplasticity, neuroexcitotoxicity, and memory and circadian clock rhythm, important process associated with aging (78). Mg^{2+} is able to inhibit NMDA receptors, and a decrease in extracellular Mg^{2+} depolarizes the membrane potential, leading to hyperexcitability (79). The ability of TRPM7 to act as a kinase also suggests that it is able to influence intracellular signaling. Several TRPM7 kinase substrates have been identified, including annexin-1, myosin IIA heavy chain, and calpain, supporting a role for TRPM7 in cell function, such as contraction, dilation, growth, migration, apoptosis, cell adhesion, and anti-inflammatory responses (80–83). In lymphocytes, Mg^{2+} influx through TRPM7 contributes to the functioning of the phosphoinositide 3-kinase (PI3K)/Akt/mTOR signaling pathway, which is critical to prevent axonal overgrowth and induce cellular response to membrane stretch and fluid shear force (2, 84). In addition, the overexpression of SLC41A1, a Na^+/Mg^{2+} exchanger responsible for Mg^{2+} efflux, was observed to remarkably weaken the phosphorylation of Akt/PKB on Thr308 and Ser473, and ERK1/2 on Thr202/Tyr204 (85).

Mg^{2+} and aging-related diseases

Aging is one of the primary risk factors associated with the development of multiple human diseases, including cancer, CVD, neurodegenerative disease, osteoporosis, musculoskeletal disorders, and COVID-19 (86). The prevalence of these diseases is remarkably increased in the elderly, significantly affecting the life expectancy. For examples, approximately 80 million people in the United States have at least one form of CVD, with almost one-half aged ≥60 years (87). As of today, the majority of new cancers occur in susceptible populations aged 55 years or older, and the incidence is still rapidly increasing as compared to younger adults (88). An epidemiological study in France shows that deaths specifically related to cancer patients aged over 65 account for 75.3% from all cancers (89). Similar epidemiological data are also observed for other aging-related disease. In this review, we will throw light on the critical role of Mg^{2+} in these common human diseases based on recent experimental and epidemiological data.

Mg^{2+} and cancer

It has been shown that elevated intracellular Mg^{2+} concentrations favor tumor proliferation, due to its involvement in the regulation of tumor-associated telomerase and protein phosphatase 1D, a Mg^{2+}-dependent enzyme (90). Mg^{2+} deficiency impairs cell migration and growth by inducing cell cycle arrest. Upon Mg^{2+} restriction, cancer cells undergo cell cycle arrest in the G0/G1 through the up-regulation of p27, p21, and p16 (91, 92). Additionally, Mg^{2+} selectively enhanced the stability G-quadruplex of oncogene promoters and consequently impacts transcription of target genes, which provides a new insight on the observation that Mg^{2+} deficiency promotes the occurrence of cancers (93).

In addition to Mg^{2+} itself, Mg^{2+} transporters are also importantly implicated in the development of cancer. Many studies have already shown that the Mg^{2+} transporter TRPM7 exerts important effects on cellular proliferation, survival, cell cycle progression, migration, and invasion in various cell lines of cancer. An aberrant expression of TRPM7 has been observed in different types of cancer, especially pancreatic adenocarcinoma. The TRPM7 expression in the tissue of human pancreatic adenocarcinoma was positively correlated with the primary tumor size, stage, and progression (94). In line with this, the down-regulation of TRPM7 in human pancreatic cancer cells inhibits cell proliferation, effect that could be diminished by Mg^{2+} supplementation (95). In breast cancer tissues, the CNNM3 expression is increased and promotes Mg^{2+} entry into cells through binding to the phosphatase of regenerating liver 2 (PRL-2), consequently contributing to oncogenesis (96).

Mg^{2+} and cardiovascular disease

Mild to moderate Mg^{2+} deficiency associates with an increased risk of atherosclerosis, ischemic heart disease, and congestive heart failure (HF), while severe Mg^{2+} deficiency can cause ventricular arrhythmias that might lead to even sudden cardiac death (97). Mg^{2+} is important in regulating membrane potential and contractility of cardiomyocytes and autoregulatory cells (98). Severe Mg^{2+} loss may induce a prolongation of QT interval and the widening of QRS waves, resulting in ventricular arrhythmias (99). In the vasculature, Mg^{2+} is known to exert vasoprotective effects through regulating vascular tone and cytosolic Ca^{2+} (100). Epidemiological and experimental data show that Mg^{2+} has an inverse association with blood pressure, and the Mg^{2+} supplement may decrease peripheral vascular resistance and blood pressure (101). A meta-analysis of 34 randomized clinical trials involving 2028 participants shows that daily intake of 300 mg Mg^{2+} for 1 month is sufficient to elevate serum Mg^{2+} and reduce blood pressure (102). It is worth noting that TRPM7, acting as a vascular Mg^{2+} regulator, is critically implicated in hypertension. In

a mouse model of TRPM7 deficiency, angiotensin II (Ang II)-induced blood pressure elevation was exaggerated, and the deteriorate effects on cardiac remodeling and left ventricular dysfunction were also amplified (103).

Mg^{2+} was found to influence the development of atherosclerosis by regulating the production of prostacyclin and NO (104–106). Low Mg^{2+} status might promote the expression of proinflammatory and prothrombotic factors, such as interleukin-1β (IL-1β), IL-6, and vascular cell adhesion molecule 1 (VCAM-1), important molecules for the progress of atherosclerosis (107). Vascular calcification is one of the main features of atherosclerosis (108). Mg^{2+} regulated by TRPM7 increases the expression of inhibitors of calcification such as matrix Gla protein, osteopontin, and bone morphogenetic protein (BMP7) and reduces the formation of osteogenic VSMCs and vascular calcification (109). Moreover, clinical studies have confirmed that low serum Mg^{2+} levels are found in patients with coronary artery disease (CAD), an atherosclerotic disease that typically affects the heart (110).

Mg^{2+} and neurodegenerative disease

Mg^{2+} abundance in cerebrospinal fluid is higher than that in blood and is positively correlated with cognitive function (2, 111). In an in vitro blood–brain barrier model, TRPM7 and MagT1 are functionally active and involved in the transport of Mg^{2+} (77). Neuronal growth depends on changes of the cytoskeleton in the growth cone (112). High TRPM7 expression was observed in the tips of the growth cone, which mediates Mg^{2+} influx to fulfil the energy requirements of the neuronal network (113). In addition, Mg^{2+} promotes the differentiation of neural stem cells into neurons, and TRPM7 was able to influence astrocyte proliferation and migration by regulating extracellular regulated protein kinase (ERK) and c-Jun N-terminal kinase (JNK) activities (114).

Mg^{2+} deficiency causes emotional memory impairment and worsens the symptoms presented in AD (115). Mg^{2+} protects neuronal function in AD by reducing the TNF-α expression in glial cells with mechanisms involving PI3K/Akt and nuclear factor-kappa B (NF-κB) (76). In an animal model of Parkinson's disease (PD), the expression level of SLC41A1 was reduced contributing to apomorphine (APO)-induced rotational behavior, while Mg^{2+} supplement significantly improved the behavior (116). Additionally, function loss of Mrs2 transporter important for mitochondrial Mg^{2+} homeostasis was observed in rats with demyelinating mutations. (117). It is believed that the disruption of mitochondrial Mg^{2+} dynamic dysregulates ATP production, leading to abnormal cell metabolism, thus triggering demyelination and neurological dysfunctions (49). Furthermore, neurological diseases such as migraine, seizures, anxiety, depression, and stroke have also been associated with a low Mg^{2+} abundance in serum and cerebrospinal fluid (49, 118, 119). However, further well-designed Randomized Controlled Trial (RCT) studies are still needed to confirm whether Mg^{2+} supplementation can improve the prognosis of these diseases.

Mg^{2+} and musculoskeletal function

Mg^{2+} is important for skeletal muscle energy metabolism as a cofactor for enzymes related to ATP synthesis, and Mg^{2+} deficiency is associated with fibromyalgia, a condition characterized by chronic widespread musculoskeletal pain (120). In healthy older women, daily Mg^{2+} supplementation over 12 weeks significantly improved physical performance assessed by Short-Physical Performance Battery (SPPB) score and a 4-m walking test, suggesting that Mg^{2+} may serve as a complementary treatment for aging-related physical deconditioning (121). In addition, Mg^{2+} enhances the activity of vitamin D and is involved in osteoblast proliferation and bone mineralization, and Mg^{2+} deficiency leads to reduced parathyroid hormone (PTH) synthesis and secretion, causing low Ca^{2+} (122). Therefore, Mg^{2+} supplement might be promising in the prevention of age-related osteoporosis.

Mg^{2+} and abnormal metabolism

Mg^{2+} has been found to modulate the activation of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, lipoprotein lipase, and lecithin-cholesterol acyltransferase, enzymes critically implicated in lipid metabolism (123). Mg^{2+} is also required to regulate genes that are involved in adipogenesis, lipolysis, and inflammation, such as PPAR-γ (124). Animal studies have shown that Mg^{2+} decreases lipid accumulation in hepatocytes by regulating enzymatic activities and transcriptional genes related to lipid metabolism (125). In type 2 diabetic patients, reduced serum Mg^{2+} levels were observed, and Mg^{2+} is believed to mediate the development of diabetes through insulin resistance (126). The effects of Mg^{2+} on glucose, lipids, and blood pressure suggest a role of Mg^{2+} in metabolic syndrome, and in line with this, Mg^{2+} supplementation was reported to be effective in treating metabolic syndrome in patients with comorbid hypomagnesemia (127).

Mg^{2+} and COVID-19

COVID-19 is one type of zoonotic epidemic exploded in late December in 2019, which shares a high degree of homology with Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) (128). COVID-19 is more prevalent in the elderly, and elderly patients are more likely to develop severe or critical pneumonia, with a high mortality rate (129, 130). Intriguingly, more and more clinical evidence showed that some aspects of COVID-19 pathogenesis are similar with the symptoms presented in Mg^{2+} deficiency (131). It has been demonstrated that up to 60% of critically ill patients in the ICU present with some degree of Mg^{2+} deficiency (132). In

addition, people with hypertension, CVD, diabetes, and obesity are at high risk of developing COVID-19 (133). It is well known that these aging-related diseases are all characterized by hypomagnesemia and are associated with low-grade inflammation. Low Mg^{2+} status is believed to stimulate granulocyte oxidative burst, activate endothelial cells, and upregulate the production of cytokines, thus promoting inflammation that might lead to diseases (33). Mg^{2+} also leads to increased plasminogen activator inhibitor-1 (PAI-1) production and the inhibition of fibrinolysis, which may be associated with the elevated D-D dimer observed in COVID-19 (134). Moreover, COVID-19 could directly infect endothelial cells via ACE2 receptor, which induces cytokine storm, thus increasing permeability, vasoconstriction, and fostering thrombogenesis, while Mg^{2+} is significant in maintaining endothelial function and vascular integrity (135, 136). Collectively, a low Mg^{2+} status might accelerate the progression of COVID-19 from mild to serve stages, and Mg^{2+} supplementation might be one of the feasible treatment modalities, especially in severe patients (137).

Conclusion and perspectives

Mg^{2+} is an indispensable cation in human body regulating a variety of physiological and pathological processes. Under normal conditions, intracellular and extracellular Mg^{2+} levels are tightly controlled through a complicated Mg^{2+} transport system, and dynamic Mg^{2+} homeostasis is critical for human health. However, altered Mg^{2+} status also contributes to the molecular hallmarks of the aging process. Emerging evidence indicates that Mg^{2+} plays an important role in multiple aging-related diseases including the COVID-19 pandemic. The modulation of Mg^{2+} status might be a promising therapeutic option for human disease, which deserved further investigation.

Conflict of interest and funding

The authors declare no conflict of interest. This research was funded by the National Natural Science Foundation of China (81873504 and 82170379), the National Key Research and Development Program of China (2018YFC1312802), and Shanghai Pujiang Program (21PJD039).

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