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EDITORIAL

Disrupted calcium homeostasis: a hidden driver of cellular aging

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Abstract

Calcium is a critical second messenger in cellular signaling and has increasingly been recognized as an important regulator of aging. Calcium fluxes influence electrochemical gradients across cellular membranes, ligand binding, enzyme activity, and other processes associated with age-related cellular changes. In particular, calcium plays a pivotal role in driving cells toward senescent phenotypes, including cell cycle arrest and the development of the senescence-associated secretory phenotype (SASP). Modulation of calcium signaling has therefore emerged as a potential molecular strategy to regulate the burden of senescent cells. A deeper understanding of how calcium channels, mitochondrial calcium handling, and intracellular calcium dynamics contribute to senescence may reveal new opportunities for therapeutic interventions targeting age-related diseases.

Keywords: Calcium, cell, senescence, aging

Calcium is a vital second messenger in cells. Over time, calcium signaling—the movement of calcium ions within and between cells—has been increasingly recognized as an important process involved in aging. These calcium fluxes influence electrochemical gradients across cellular membranes and regulate ligand binding, enzyme activity, and other mechanisms associated with aging [1]. Such processes contribute to age-related changes, including cellular senescence, declines in muscle performance, and osteoarthritis [2], alterations in mitochondrial metabolism [3], and cardiac dysfunction [4]. Calcium signaling also affects cellular senescence, which is now widely recognized as a central hallmark of aging and age-related diseases [5]. While classical drivers of aging, such as DNA damage, cell death, and mitochondrial dysfunction have been extensively studied, the role of calcium signaling as a potential integrator of these pathways remains poorly understood.

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As cells age, their regulatory mechanisms progressively shift toward senescent patterns. Senescent cells permanently exit the cell cycle and stop dividing. However, these cells continue secreting soluble factors referred to as the senescence-associated secretory phenotype (SASP) [5, 6]. The release of these factors promotes cellular stress and contributes to chronic inflammation. Calcium plays a pivotal role in these processes, acting as a key second messenger that regulates cell proliferation, secretion, migration, and cell death.

The accumulation of intracellular calcium in senescent cells can arise from influx across the plasma membrane or from the release of calcium stored in the endoplasmic reticulum (ER), often linked to mitochondrial dysfunction. For example, the expression of calbindin 1 (CALB1) is upregulated in response to several senescence-inducing stresses in human mammary epithelial cells (hMECs) [6]. Similarly, the calcium channel transient receptor potential melastatin 7 (TRPM7) is elevated during skin keratinocyte senescence and aging, promoting calcium transfer from the ER to the mitochondria [7]. In contrast, transient receptor potential channel 1 (TRPC1), an ER-associated calcium channel, has been shown to exert protective effects by maintaining calcium homeostasis and preventing cellular senescence-associated cartilage breakdown under mechanical and inflammatory stress [2].

Calcium channels located in the plasma membrane and ER directly influence mitochondrial interactions and cell death pathways. In several experimental models, cellular senescence was suppressed through repression

of miRNA-129, which controls a signaling cascade involving intracellular calcium regulation, mitochondrial membrane potential (MMP), reactive oxygen species (ROS) generation, DNA damage, and senescence through inositol 1,4,5-trisphosphate receptor type 2 (ITPR2) [8, 9]. Another study reported that the expression of the mitochondrial calcium uniporter (MCU) and its regulatory subunit MCU1 declines with age in macrophages. Both human and mouse models demonstrated that altered mitochondrial calcium uptake contributes to inflammation [10]. However, excessive mitochondrial calcium overload can determine whether cells undergo senescence or cell death. Transient release of mitochondrial calcium through the mitochondrial permeability transition pore (mPTP) contributes to calcium overload in senescent cells. Inhibition of mPTP or blockade of the mitochondrial Na^+/Ca^{2+} exchanger (NCLX) further increases mitochondrial calcium levels, driving cells toward cell death. Interestingly, inhibition of poly (ADP-ribose) polymerase 1 (PARP1) prevented cell death despite elevated mitochondrial calcium, shifting the cellular response toward senescence. These findings highlight potential molecular targets for manipulating the balance between cellular senescence and cell death [11].

Only a few therapeutic strategies have been proposed that target calcium modulation to prevent or eliminate senescent cells. For instance, resveratrol, a natural polyphenol, has been shown to further increase calcium levels in senescent cells, triggering their death and representing a potential senolytic strategy [11]. In addition, a clinical trial in older adults (55-85 years old) demonstrated that individuals consuming a vegetable- and calcium-rich diet exhibited an anti-inflammatory gut microbiome and improved markers of brain health compared with those not following the same diet [12]. Another study showed that TRPM7 regulates keratinocyte senescence by modulating intracellular calcium signaling [7].

Increasing evidence indicates that alterations in calcium homeostasis influence several factors, including the balance between senescence and cell death. Although many classical drivers of aging have been extensively investigated, calcium signaling may represent an important integrative mechanism linking these pathways. Understanding how calcium channels, mitochondrial calcium handling, and intracellular calcium dynamics contribute to senescence could open new opportunities for therapeutic interventions. Future studies integrating calcium imaging, metabolic profiling, and senescence models will be critical to determine whether targeting Ca^{2+} homeostasis can reshape the landscape of geroscience interventions.

Declarations

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