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Mitochondria: A new member involved in stem cell senescence. An extended commentary on "Mitochondria pleiotropism in stem cell senescence: Mechanisms and therapeutic approaches by Mas-Bargues C. [Free Radic. Biol. Med. (2023) Nov 1;208:657–671. doi:10.1016/j.freeradbiomed.2023.09.019]

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Mitochondria are subcellular organelles with double membranes that are found in most eukaryotic cells. They perform multiple functions that are essential for homeostasis maintenance, mainly in energy production, but also in cell metabolism, calcium homeostasis, and reactive oxygen species (ROS) regulation, as highlighted by Mas-Bargues in a recent review [1]. Due to these reasons, mitochondria were considered the "powerhouses of the cells" in 1957 by Siekevitz; however, years later, Pagliarini and Rutter (2013) [2] also noticed that “mitochondria might spend their days as the “powerhouses of the cell” but clearly moonlight in an array of other activities”, therefore, we will highlight in this commentary the meaning of that sentence.

Generally, the number of mitochondria in a cell depends on the organism, the tissue, and the cell type. Approximately in our bodies, we have 500 times more mitochondria than cells [3,4]. Moreover, it is well known that there are between 1000 and 2000 mitochondria per cell, representing approximately 25 % of cell volume. This amount is higher in some organs, such as the muscles, brain, heart, and liver, because these organs have a higher metabolic activity [3,4]. The mitochondria found in stem cells differ in number, size, and appearance, and these differences depend on cellular metabolism. Therefore, stem cells with a higher metabolism exhibit greater mitochondrial activity. Stem cells undergo changes in energy metabolism during different biological processes, and mitochondria can regulate the function of stem cells by altering their energetic and metabolic pathways [5]. This indicates that mitochondria in stem cells play a crucial role in regulating cell energy production.

Stem cells rely heavily on mitochondria because oxygen consumption, ATP production, and mitochondrial localization patterns dictate stem cell fate [6]. It is worth mentioning that during stem cell asymmetric division, mitochondria are also asymmetrically distributed among the progeny. In hematopoietic stem cells (HSCs), an asymmetric distribution of organelles (lysosomes and mitochondria) upon cell

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division is related to distinct metabolic profiles and cell fates [7]. Recently, researchers described “old” and “new” mitochondria according to their morphology and OXPHOS activity. Interestingly, “old” mitochondria are selectively distributed to the daughter cell that will enter the differentiation pathway, whereas “new” mitochondria are reserved for the daughter cells that will ensure stem cell self-renewal [8].

Since their discovery, mitochondria have attracted the attention of scientists, particularly in recent decades.

1. Mitochondria as critical mediators in pathologies

In a review, Green and Reed (1998) [9] described for the first time that mitochondria also play an important role in programmed cell death, including the release of caspase activators, changes in membrane potential, alterations in cellular oxidation-reduction, and activation/inhibition of pro- and anti-apoptotic proteins. Altogether, these data confirm that “Mitochondria might spend their days as the “powerhouses of the cell” but clearly moonlight in an array of other activities”. Unsurprisingly, mitochondrial dysfunction has been linked to numerous human diseases because of the central role of mitochondria in cells. More than 200 mutations in the mitochondrial DNA (mtDNA) have been associated with disorders and premature aging [10]. Therefore, in more detail, the study is about the failure of normal mitochondrial function (mitochondrial dysfunction), which can be involved in multiple diseases/pathologies involving cell death and aging.

Moreover, one of the more critical links between mitochondrial dysfunction and disease is the overproduction of ROS due to aerobic metabolism (Krebs cycle and electronic transport chain) [1,4]. Mitochondria typically generate waste in the form of free radicals (ROS) during ATP production. The cell contains protective enzymes that convert ROS to less harmful forms, thereby preventing extensive damage. However, in cases of high ROS production, cells cannot defend themselves. These toxic species accumulate over time and, therefore, cause extreme injury and stress to cells, leading to senescence and cell death. Overproduction of ROS in cells is frequently observed in patients with chronic diseases associated with premature aging [1,4].

However, two mechanisms are essential for the regular function of the mitochondria and, therefore, in mitochondrial dynamics to renew the bioenergetic machinery. During fission, mitochondria are divided and damaged elements are degraded by mitophagy. However, during fusion, the mitochondria are linked to other mitochondria to regenerate mitochondrial function, including ATP production. In fact, during nutrient deprivation, the fusion rate increases and the fission rate decreases [4], maintaining the equilibrium between fission and fusion, and, finally, mitophagy. When mitochondria are defective, fission is similar to mitochondrial dysfunction as well as defects in mitochondrial fusion, despite their opposite function in regulating the mitochondrial dynamics [11]. The loss of equilibrium between fission and fusion leads to the accumulation of damaged mitochondria.

2. Mitochondrial dysfunction and aging

During aging, mitochondria become more fragmented and disconnected due to reduced mitochondrial biogenesis and to alterations in mitochondrial dynamics. Moreover, a larger population of dysfunctional mitochondria, which should have been recycled through mitophagy, enters a hibernation-like state termed "mitochondrial zombies". These zombie mitochondria release proinflammatory signals, contributing to inflammation and loss of function in the neighboring tissues. Decreased mitophagy with aging disrupts the recycling cycle, resulting in impaired creation of new mitochondria, reduced mitochondrial growth and fusion, and excessive increase in mitochondrial fission. This leads to a smaller, less connected, and less functional population of mitochondria [4,11,12]. The accumulation of dysfunctional mitochondria with aging leads to excessive ROS production causing oxidative damage, and an enhanced mitochondria-mediated apoptosis, which contributes to an increased percentage of apoptotic cells [13]. Interestingly, senescent cells that accumulate with aging have been described to display an increased mitochondrial mass. In fact, several *in vitro* models of cellular senescence demonstrate that mitochondrial dynamics are impaired [14,15]. Mitochondria of senescent cells are found to be elongated, enlarged, swollen, and hyperfused. It has been suggested that this hyperfused mitochondrial networks could be the underlying mechanism of apoptosis resistance of senescent cells [16].

Aging is a complex biological process characterized by a gradual decline in cellular and tissue functions, ultimately affecting the entire organism. Recently, Mas-Bargues (2023) [1] reported that stem cells, essential for tissue maintenance and repair, play a vital role in aging. Moreover, the review showed emerging data that present mitochondria as a significant contributor to aging, stem cell function, and age-related tissue dysfunction. Notably, the review highlighted mitochondrial pleiotropy, which is the ability of mitochondria to influence various cellular processes. In the realm of mitochondrial pleiotropy, these encompass the mechanisms by which mitochondria affect stem cell fate decisions, including energy production, metabolic regulation, ROS signaling, and epigenetic modifications, and how mitochondria alterations drive stem cell senescence and contribute to biological aging and age-related diseases. Understanding how the mitochondria influence this process has significant implications for understanding aging and developing therapeutic strategies.

3. Anti-aging mitotherapies

Targeting mitochondrial health (mito-therapy) represents a promising tool to prevent stem cell senescence, and can be considered as a potential anti-aging therapy [1].

Taurine (or 2-aminoethane-sulfonic acid) is an endogenous and natural compound, sulfur-containing amino acid. Taurine is synthesized in the human liver from cysteine and methionine, although at a low rate, as the primary source of taurine is dietary. Seafood, particularly mussels, clams, and shellfish, is rich in taurine. Significant amounts of taurine have also been identified in turkey and dark chicken meat [17]. Moreover, recently some supplements are developed with taurine such as energetic drinks [18]. Upon ingestion, taurine is taken up by the digestive system and is transported to the liver via the portal vein. There, it is distributed throughout the body, including in the heart, retina, and developing brain, where it exists in its free form. The process of cellular uptake of taurine is facilitated by specialized transporters that are highly responsive to the concentration of intracellular taurine [17]. Taurine, a predominantly unbound amino acid, enters the mitochondria through a putative taurine transporter. Once inside, it functions as a radical scavenger, offering protection against mitochondrial dysfunction [19]. Several clinical studies have explored the therapeutic potential of taurine, with a particular focus on its capacity as an antioxidant that enhances mitochondrial function [20]. Finally, excess plasma taurine is mostly excreted via urine [20].

Recent studies have demonstrated that taurine plays a critical role in aging because taurine supplementation increases the health and lifespan of mice and monkeys [20,21]. Mechanistically, taurine exhibits various beneficial effects, including reducing cellular senescence, protecting against telomerase deficiency, suppressing mitochondrial dysfunction, decreasing DNA damage, and attenuating inflammaging [21].

Taurine suppresses mitochondrial dysfunction by two main mechanisms. On the one hand, taurine modulates calcium channels [18], thereby preventing calcium overload to maintain energy production and to avoid the collapse of the mitochondrial membrane potential. On the other hand, taurine increases the antioxidative capacity, thereby reducing ROS accumulation. Taurine also mediates mitochondrial biogenesis, as briefly described below [21]. Thus, taurine might play a beneficial role against dysfunctional mitochondria-associated aging (Fig. 1). Moreover, taurine metabolism plays a role in the functioning of

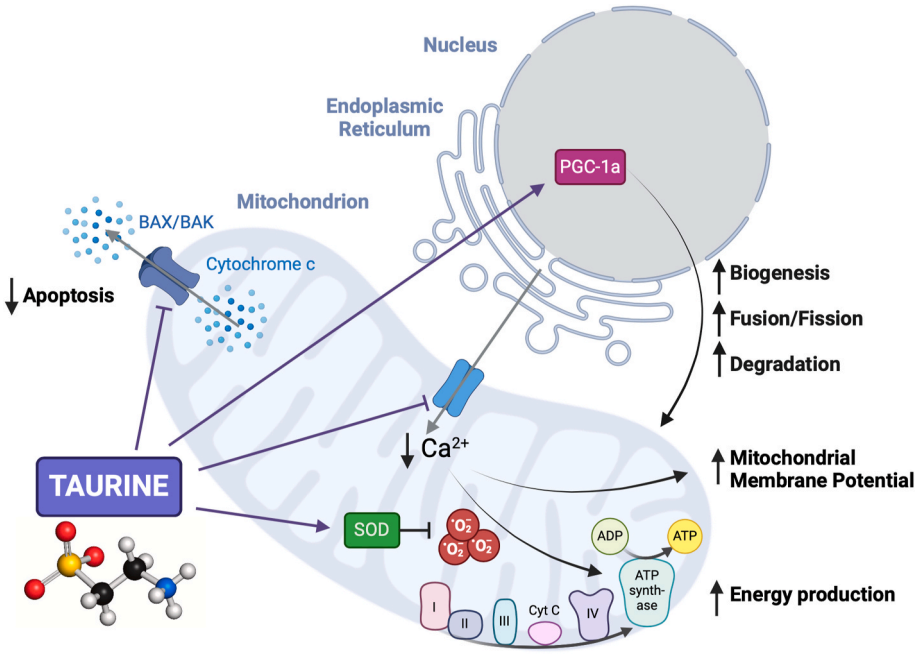

Fig. 1. Taurine anti-aging mitotherapeutic mechanisms.

complex I within the mitochondria. When taurine levels are depleted, complex I activity can be reduced, which subsequently influences energy metabolism. This is primarily attributable to an increase in the $NADH/NAD^+$ ratio, which governs energy metabolism and can lead to diminished energy metabolism and malfunction [18]. Furthermore, blocking the function of complex I results in the onset of cellular senescence [1].

The traditional linear dose-response relationship linking increasing ROS levels to biological damage is evolving by introducing the concept of "mitohormesis." Mitohormesis refers to a natural response in which reduced mitochondrial stress leads to improved health and viability in cells, tissues, or organisms, leading to healthy aging [22]. This stress response involves mitonuclear communication, which is a coordinated dialogue between the mitochondria and the cellular nucleus. Signals crucial to this interaction include ROS, mitochondrial metabolites, proteotoxic signals, the mitochondria-cytosol stress response, and the release of mitokines (molecules that enable the communication of mitochondrial stress). Activation of the mitohormetic response has been shown to extend lifespan and enhance healthspan, particularly by improving metabolism and the immune system, in various animal models, from worms to mammals [23,24]. Mitohormesis is mainly mediated by peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α), which acts as the chief activator of mitochondrial function. PGC-1α is inactivated in the cell cytoplasm; however, some stimuli (cold exposure, exercise, and starvation/caloric restriction) can translocate it to the cell nucleus, increasing mitochondrial biogenesis. Importantly, taurine is another supplement that can activate PGC-1α, thus improving energy metabolism [21,25] (Fig. 1).

Overall, Mas-Bargues' review sheds light on the crucial interplay between mitochondrial function, stem cell senescence, and organismal aging, providing insights into strategies for mitigating age-related decline and promoting healthy longevity [1]. However, the review only offers *in vitro* data about the different mitotherapies, and does not provide prospective insights regarding the translational potential of the mitotherapies to the clinic. This commentary adds a new anti-aging mitotherapy, consisting of taurine supplementation, which has proved to be able to modulate ROS production, energetic metabolism and mitochondrial biogenesis, thereby boosting mitochondrial health and increasing lifespan in worms and mice. Moreover, taurine supplementation is currently being tested in aging-focused clinical trials [26].

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CRediT authorship contribution statement

Matilde Alique: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Investigation, Funding acquisition, Data curation, Conceptualization. **Cristina Mas-Bargues:** Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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