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Rejuvenating aged stem cells: therapeutic strategies to extend health and lifespan

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Aging is associated with a global decline in stem cell function. To date, several strategies have been proposed to rejuvenate aged stem cells: most of these result in functional improvement of the tissue where the stem cells reside, but the impact on the lifespan of the whole organism has been less clearly established. Here, we review some of the most recent work dealing with interventions that improve the regenerative capacity of aged somatic stem cells in mammals and that might have important translational possibilities. Overall, we underscore that somatic stem cell rejuvenation represents a strategy to improve tissue homeostasis upon aging and present some recent approaches with the potential to affect health span and lifespan of the whole organism.

Keywords: autophagy; calorie restriction; Cdc42; health span; lifespan; parabiosis; partial reprogramming; senolytic; stem cell aging; stem cell rejuvenation

Physiological aging is associated with a general impairment in stem cell function [1]. Recent evidence shows that this process does not occur at the same speed in every organ, and this is strongly associated with increased mortality and age-related diseases [2]. Interestingly, many of the current therapeutical approaches to limit or delay aging target the effects arising from decreased aged stem cell function. For this reason, targeting directly aged somatic stem cells might represent a more effective strategy to improve tissue homeostasis over time, and in some circumstances, may also improve health and lifespan in the elderly (Fig. 1).

The strategies proposed to rejuvenate tissue-resident aged stem cells to date mainly involve physical exercise, diet manipulation and fasting, or target senescence, autophagy, epigenetic reprogramming, circulating blood factors or stem cell polarity (Fig. 2). Here, we briefly review some of the most recent strategies identified to improve function of aged tissue-resident somatic stem cells in mammals and discuss their possible translational applications.

Exercise and diet interventions

The beneficial effect of exercise on health has been known for a long time [3]. Many studies on this topic have focused on the changes induced by exercise on the skeletal muscle, as this is the most directly affected tissue. It has been shown that moderate intensity running for 30 min per day for 8 weeks increases the

Abbreviations
BM, bone marrow; CASIN, Cdc42 activity-specific inhibitor; CMA, chaperone-mediated autophagy; CR, calorie restriction; FMD, fasting-mimicking diet; HFSC, hair follicle stem cells; HSC, hematopoietic stem cells; HSPC, hematopoietic stem and progenitor cells; ISC, intestinal stem cells; MSC, mesenchymal stem cells; MuSC, muscle stem cells; Ndufs6, NADH dehydrogenase iron–sulfur protein 6; NMR, naked mole rats; NSC, neural stem cells; OSKM, Oct4, Sox2, Klf4, c-Myc; SASP, senescence-associated secretory phenotype.

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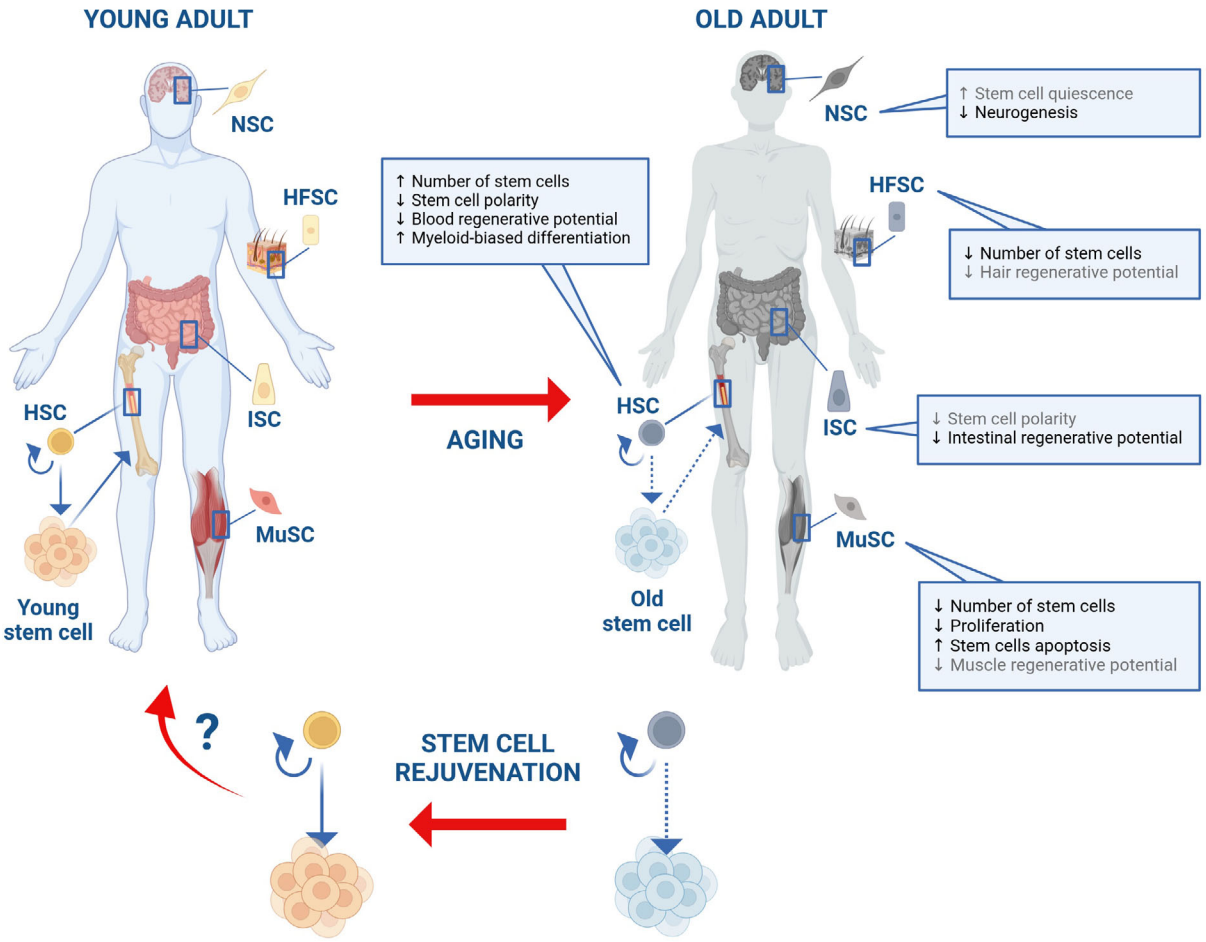

Fig. 1. Cartoon summarizing the effects of aging on several human somatic stem cells [5,7,17,76,80–100]. The strategy proposed in the cartoon suggests the use of rejuvenated stem cells as a therapeutic tool to improve the homeostasis of the entire tissue/organ by restoring the stem cell regenerative potential. For this reason, stem cell rejuvenation can represent a promising approach to simultaneously rejuvenate several organs and to globally improve organism health and lifespan in the elderly. Aging effects on stem cells are written in gray when they have been proven in mice, but not in human. Graphics created with Biorender.

number of skeletal muscle stem cells (MuSC, also known as satellite cells) in old mice, which are lost with aging [4]. A similar increase was detected in aged humans after a 12-week resistance exercise training [5]. Free access to a running wheel during 3 weeks did not increase the number of MuSCs in aged mice, but improved their regenerative capacity, giving rise to new muscle fibers in the presence of an injury [6]. In mice, it has also been reported that there is a recovery of intercellular interactions in the MuSC niche and a downregulation of genes involved in inflammation after 5 weeks of voluntary running [7]. However, the rejuvenating effects on MuSCs seem to disappear once the mice stop exercising [6].

The brain is another organ that is affected by exercise. Neurogenesis increases in mice transplanted with plasma from exercised aged mice, that had access to a running wheel for 6 weeks, compared to sedentary counterparts, improving spatial learning and memory [8]. However, although some studies reported an increase in the number of neural stem cells (NSC) [7,9], a rejuvenating effect in their transcriptome [10], and a recovery of the intercellular interactions with the NSC niche [7] after voluntary running for several weeks, the mechanistic link between these changes and the increase in neurogenesis has yet to be clearly proved.

Some other aged stem cells also benefit from exercise, such as tendon stem cells [11]. On the contrary, hematopoietic stem cells (HSC) do not change in number or improve their regenerative capacity in the aged bone marrow (BM) after mice are given free access to a running wheel for 4–7 weeks, although osteogenic and lymphoid progenitors are increased [7,12,13]. It is

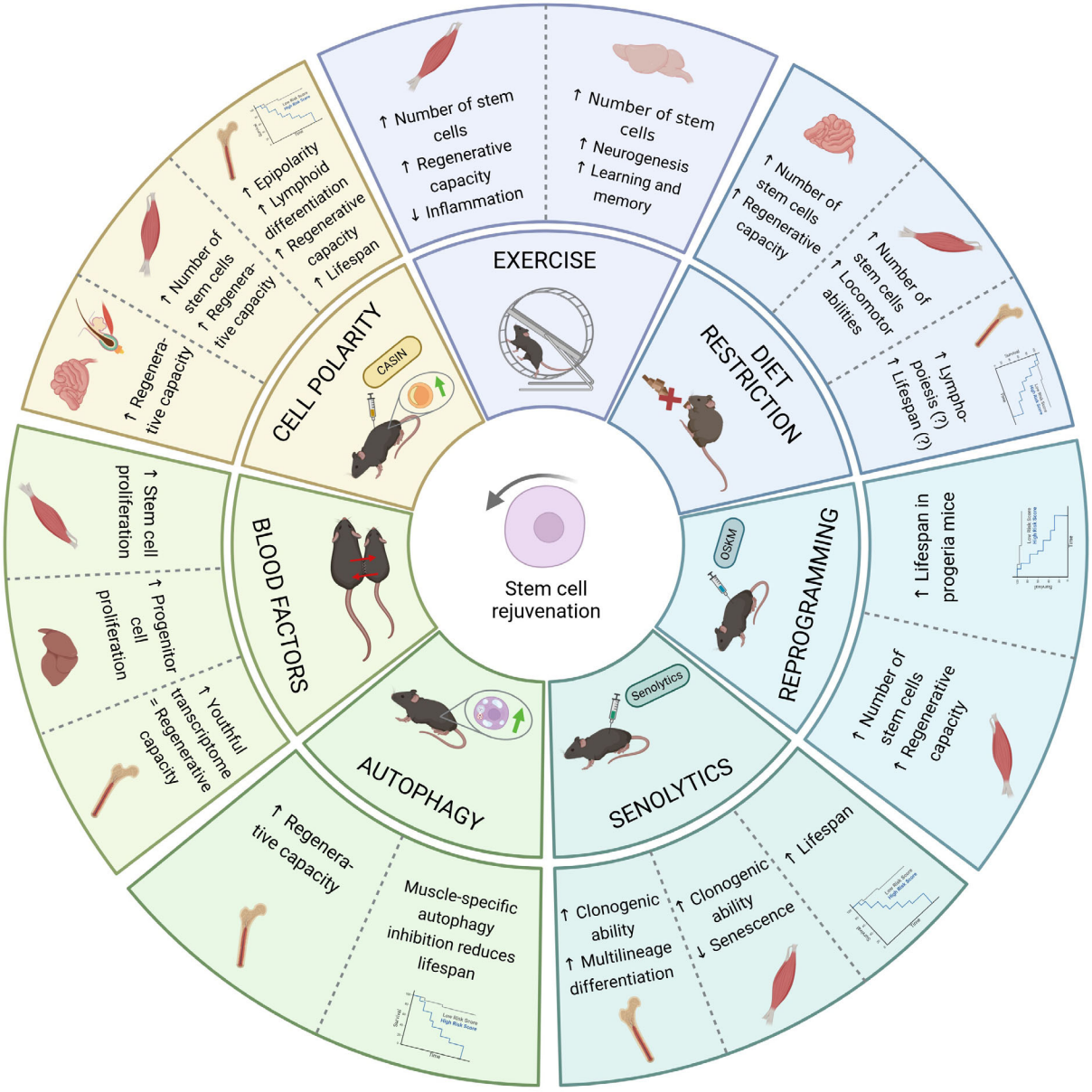

Fig. 2. Cartoon depicting interventions to rejuvenate aged somatic stem cells. Several strategies to increase stem cell function and lifespan have been described so far. This cartoon summarizes the interventions proposed to rejuvenate aged somatic stem cells and their effect, specifying the stem cell type where the intervention has been experimentally applied, and highlighting when the described intervention had an effect in extending the organism lifespan. A question mark indicates cases with contradictory results. Graphics were created with Biorender.

worth noting that many variables need to be taken into account when studying the effects of exercise, such as sex, age, and initial weight of the individuals included in the study and in the control groups [7]. The use of inbred strains is recommended to minimize the genotypic differences [14]. Moreover, the type of exercise performed, its duration and, in the case of skeletal muscle, the muscle analyzed, can affect the rejuvenating effects [5]. Overall, exercise ameliorates the regenerative capacity of some tissues and is a clear strategy to improve health in the elderly. Nevertheless, it remains unclear if exercise alone is able to increase lifespan [14].

Calorie restriction (CR) and fasting are two other strategies that have been largely studied for their rejuvenating capacities. Intestinal stem cells (ISC) increase

in number and replicate more after CR [15] and fasting-mimicking diet (FMD) [16], and their capacity to form organoids is improved after fasting [17]. In the skeletal muscle, MuSCs seem to enter a deep quiescent state after fasting, which is not recovered by re-feeding [18]. This slows muscle regeneration but improves the survival of these stem cells [18], effects which are also observed using CR [19]. FMD followed by re-feeding showed an increase in MuSC number to more youthful levels, with an improvement in the locomotor abilities of the aged mice [20].

Other types of somatic stem cells, like mesenchymal stem cells (MSC) or hair follicle stem cells (HFSC), showed rejuvenating effects after FMD and CR, respectively [20,21]. On the other hand, the effect of fasting and CR on the hematopoietic system is more controversial. A 30% dietary restriction decreased the number of HSCs, which accumulate with aging, increasing their repopulating capacity after transplantation [22], and prolonged fasting reverted the lymphoid-myeloid bias that characterizes aged HSCs [23]. However, the number of HSCs was not changed after life-long CR, with no improvement in their regenerative capacity nor recovery of the myeloid bias [12,24]. Moreover, 30% dietary restriction decreased differentiation towards the lymphoid lineage [12,22,24] and CR impaired T-cell function, increasing mice mortality after infection [25]. Contradictory results have also been found regarding the effects on lifespan, with an increase in median but not maximum lifespan detected with FMD [20], and increased lifespan dependent on sex, strain, and percentage of caloric restriction observed with CR [26]. In addition, the pharmacological compound rapamycin, which mimics dietary restriction, has the ability to extend lifespan in mice, but with some side effects that need to be controlled by adjusting the treatment strategy or using analog compounds [27,28]. Altogether, although some stem cell rejuvenating effects have been described, the lack of consistent results across the different fasting and CR strategies in the different organs, together with the variability described in some studies as for sex, strain, and age of onset of the diet [19,29], make it difficult at present to define a clear diet to achieve holistic stem cell rejuvenation and lifespan extension.

Partial reprogramming

An exciting strategy that has been proposed for cell rejuvenation is reprogramming cells to a more undifferentiated state by inducing expression of the Yamanaka factors Oct4, Sox2, Klf4 and c-Myc (OSKM). Although *in vivo* reprogramming by the OSKM factors has resulted in the induction of teratomas [30,31], partial reprogramming without achieving complete cellular dedifferentiation does not appear to be associated with tumorigenesis [32–34]. A cyclic induction of OSKM was able to increase the numbers of MuSCs and HFSCs in adult mice with progeria and to improve regeneration of the skeletal muscle [32]. This improvement in muscle regeneration was also observed upon transient expression of the reprogramming factors in aged mice [34] and was shown to be driven by the effects of the reprogramming on the muscle niche cells, which activated MuSCs through downregulation of Wnt4 [35]. Partial reprogramming also rejuvenated MSCs at the transcriptome level [36]. Other cells and tissues showed rejuvenating effects after OSKM induction, such as the brain, showing improved memory [37]; the retinal ganglion cells, showing increased axon regeneration and a reversion of vision loss in mice with glaucoma [34]; and some cell types of the pancreas, liver, spleen, and blood, with signs of rejuvenation at the transcriptome, epigenome and metabolome level [38]. However, in these latter examples, it was not determined if the functional improvements were due to a rejuvenation of the tissue-resident stem cells. Moreover, lifespan extension after *in vivo* partial reprogramming in mammals has only been described in progeria mice [32]. Hence, further studies will be needed to better understand the effect of reprogramming on stem cells and lifespan, and to define an optimal treatment strategy to achieve rejuvenation without the risk of cancer induction.

Senescence

Cellular senescence is characterized by a stable cell-cycle arrest of dysfunctional cells which also present with a senescence-associated secretory phenotype (SASP) [39]. The accumulation of senescent cells upon aging has been shown to limit lifespan and health span in mice [40]. Clearance of senescent cells with senolytics was shown to exert promising results on HSCs and MuSCs [41,42] in mice and also on human MSCs *in vitro* [43]. Clearance of senescent cells by ABT263 administration restores HSC function in mice. HSCs from ABT263-treated aged mice showed a significant increase in their clonogenic activity *in vitro* and improved long-term and multilineage engraftment upon BM transplantation. Similarly, ABT263 treatment of MuSCs isolated from aged mice improved their clonogenicity in culture, in association with a significant reduction in the number of MuSCs expressing p16, phosphorylated p38 and the DNA damage marker γ-H2AX, typical markers that accumulates upon MuSC senescence [42].

Recently, the rescue of the senescence-driven alteration in mitochondrial dynamics and ROS production [44,45] and in NADH dehydrogenase iron–sulfur protein 6 (Ndufs6) [46] has been proposed as a solution to rejuvenate aged MSCs. Following up on this, transplantation of rejuvenated MSCs has been suggested as an anti-aging strategy counteracting senescence in different tissues [44,47–49]. Moreover, it has been reported that NAD^+ metabolism controls SASP production [50]. The supplementation of NAD^+ and of its precursor rejuvenates MuSCs, melanocyte stem cells and NSCs, and enhances lifespan in mice [51]. Further, it has been shown that senescent human MSCs are rejuvenated *in vitro* by rescuing the NAD^+/NADH redox alterations in their metabolism [52]. Interestingly, CAR-T cells have been engineered to target senescent cells, becoming novel senolytic drugs in aged mice [53].

Senescent cells form an inflamed niche that mirrors the inflammation associated with aging by arresting stem cell proliferation and regenerative potential. In young and aged mice, the reduction of senescent cells or of the inflammation associated with senescent cells accelerates tissue regeneration. On the contrary, transplantation of senescent cells delays regeneration [41]. Mice treated with a bi-weekly administration of a combination of the senolytics dasatinib and quercetin starting at 24–27 months of age (equivalent to age 75–90 years in humans) showed a significantly higher median post-treatment lifespan and lower mortality hazard. However, it remains unknown whether this extension of murine median lifespan involves the rejuvenation of resident somatic stem cells upon clearance of senescent cells [54]. Senolytic treatment of aged human pluripotent stem cell-derived brain organoids has been shown to alleviate physiological aging and COVID-19 neuropathology [55], and currently, several senolytics are used in clinical trials [56].

Autophagy

Autophagy is a highly conserved pathway that degrades defective cellular organelles and aggregates of misfolded protein through lysosomes. Compromised autophagy is a hallmark of aging [57]. *In vitro*, interventions targeting autophagy have shown to improve the function and to directly rejuvenate different somatic stem cells [58–60]. Chaperone-mediated autophagy (CMA) decreases in murine HSCs during aging, impairing HSC activation. CMA blockage in young HSCs partially phenocopies the proteome alterations observed in aged HSCs, while both genetic and pharmacological activation of CMA improve aged HSC function by reducing oxidized protein levels, by restoring GAPDH activity and by increasing the glycolytic flux. Here we note that the administration of a CMA pharmacological activator to $CD34^+$ human hematopoietic stem and progenitor cells (HSPC) derived from donors older than 59 years markedly increases the multi-lineage potential and sustains the overall cell output upon long-term culture of these cells [60]. A direct effect of autophagy on lifespan has been extensively studied in yeast, *Caenorhabditis elegans* and in *Drosophila melanogaster*. However, it still remains unclear whether direct modulation of autophagy, systemically or in specific organs, has a causal role in lifespan extension in mammals, as in mammals the effect of autophagy on lifespan extension is mostly evaluated in association with or dependence to caloric restriction [61]. Reduced survival compared to aged-matched controls has been shown exclusively in a muscle-specific autophagy-deficient mouse model ($Atg7^{-/-}$ mice), and this is directly associated with autophagy impairment in the tissue. Nevertheless, it remains unknown if this effect depends on the direct alteration of autophagy in MuSCs [60]. Despite these promising observations and the ability to extend the lifespan of several mouse models, many autophagy-targeting drugs have failed to reproduce in humans the achievements obtained in mice [61].

Circulating blood factors

Another rejuvenation strategy that systemically targets the organism is parabiosis, which consists of the exchange of blood circulation between heterochronic animals, as systemic factors present in young blood or plasma have been shown to have a protective effect against age-related diseases in various tissues [62,63], while blood or plasma from old mice induces senescence and ages young tissues [64,65]. Administration of young-derived blood products in humans is currently under evaluation as a possible anti-aging strategy [66]. Parabiosis directly affects different somatic stem cells in mice. The exposure of aged murine satellite cells to young serum enhances the expression of the Delta family of Notch ligands, increasing Notch activation and enhancing proliferation *in vitro*. Similarly, heterochronic parabiosis enhances proliferation of aged liver progenitor cells and restores molecular determinants of young liver regeneration [65]. Interestingly, one single exchange of heterochronic blood reduces the number of proliferating NSCs, severely decreasing hippocampal neurogenesis in young mice, while the analysis of hippocampal neurogenesis in aged mice shows the absence of a significant positive effect after exchange to young

blood [65]. Single-cell transcriptomic atlas across aged tissues and organs and their rejuvenation in heterochronic parabiosis demonstrated the improvement of aging-associated phenotypes in multiple tissues, with a reduced accumulation of senescent cells in the spleen, skin, liver, and brain, in association with a decrease in the number of apoptotic cells in the spleen, skin, liver, and skeletal muscle. Single-cell transcriptomic analysis indicates that HSPCs are the most responsive cell type to young blood exposure, showing of a restored youthful transcriptional regulatory program and cytokine and cell–cell communications. Moreover, the age-associated decline of lymphopoiesis improves upon reintroduction of the identified rejuvenating factors [62].

Interestingly, the effect of heterochronic parabiosis is still very controversial as different groups are observing opposite outcomes [12,62]. It has been recently demonstrated that aged HSCs are extremely resistant to bloodborne systemic rejuvenation approaches. By transplanting murine aged HSCs into young recipients, it has been observed that the long-term exposure of old HSCs to a young BM niche microenvironment doesn't affect their cell-intrinsic aged state. Despite recapitulating the NSC rejuvenation, the exposure to young blood in heterochronic parabiosis is unable to functionally rejuvenate aged HSCs. In fact, regardless of exposure to young blood, aged HSCs upon transplantation show a reduced regenerative capacity and the persistence of a myeloid-biased output compared with young HSCs. Accordingly, the analysis of aged HSCs homed in the BM of young recipients upon heterochronic parabiosis showed that despite the relocation of these cells to young BM niches, they are not rejuvenated as they maintain an unchanged aged phenotype and an aged transcriptomic profile. Interestingly, aged HSCs appear to be refractory to other systemic rejuvenation strategies, such as exercise and life-long CR [12]. Surprisingly, in LmnaG609G/G609G and Bub1bH/H progeroid mouse models, HSCs are neither prematurely aged nor delayed in acquiring aging features in a long-lived mouse model in contrast to other tissues [12].

Studies performed in humans highlight that the rejuvenation effect of young blood administration is conserved [66]. Rounds of therapeutic plasma exchange promote a global shift to a younger systemic proteome in different cell types, also showing reduced cellular senescence and lower DNA damage accumulation thanks to a more youthfully balanced regulation of circulatory regulators of the JAK–STAT, MAPK, TGF-beta, NF-κB, and Toll-like receptor signaling pathways [66].

Cell polarity and Cdc42 activity

Cell polarization, defined as the uneven distribution of RNAs, proteins, organelles, and cytoplasm, occurs in many forms and the most widely known is the apical-basal polarity of epithelial cells. The capacity of establishing cell polarity, associated with the activity or the expression of specific polarity proteins, appears to be linked to aging of asymmetrically dividing cells and organisms [67]. Over the years it has been shown how polarity regulation is essential for homeostasis, especially in the epithelial tissue [68,69].

In the context of somatic stem cell rejuvenation, targeting cell polarity represents a potential strategy to improve tissue and organ regeneration. For example, the small RhoGTPase Cdc42 is involved in the establishment of cell polarity in many cell types and its activity level increases over time, driving loss of polarity and aging in stem cells [70–73]. Cdc42 activity can be efficiently targeted by using a specific small molecule inhibitor named CASIN (Cdc42 activity-specific inhibitor) [74]. CASIN treatment has been shown to rejuvenate different somatic stem cell types [71,75–77]. In detail, systemic treatment of aged mice with CASIN rejuvenates HFSCs by restoring canonical Wnt signaling [75] and ISCs by improving regeneration of aged crypts upon stress [76]. Recently, we reported that systemic inhibition of the activity of Cdc42 targets aged MuSCs and HSCs *in vivo*, and further, we proved that transplantation of CASIN-rejuvenated aged HSCs is sufficient to extend the lifespan and health span of aged recipient mice [73] (Fig. 3). CASIN treatment increases locomotor activity, endurance, and strength, in association with an improvement of skeletal MuSC function in aged mice. Moreover, Cdc42 inhibition increases myofiber cross-sectional area and MuSC proliferation and activation upon injury, resulting in improved tissue regeneration. Furthermore, CASIN treatment rejuvenates aged HSCs *in vivo* by restoring their epigenetic polarity and their localization within the BM, without affecting HSC number and proliferation. Rejuvenated HSCs in aged CASIN-treated mice are found closer to sinusoids, arteries, and endosteum compared to the stem cells in aged untreated mice and, similarly to young HSCs, CASIN-rejuvenated aged HSCs regenerate the hematopoietic system more efficiently upon both primary and secondary transplantation, and differentiate more readily into the B-lymphoid lineage compared to aged control HSCs. Surprisingly, scRNA-seq analysis reveals that CASIN treatment specifically alters the transcriptome of aged HSCs by increasing the

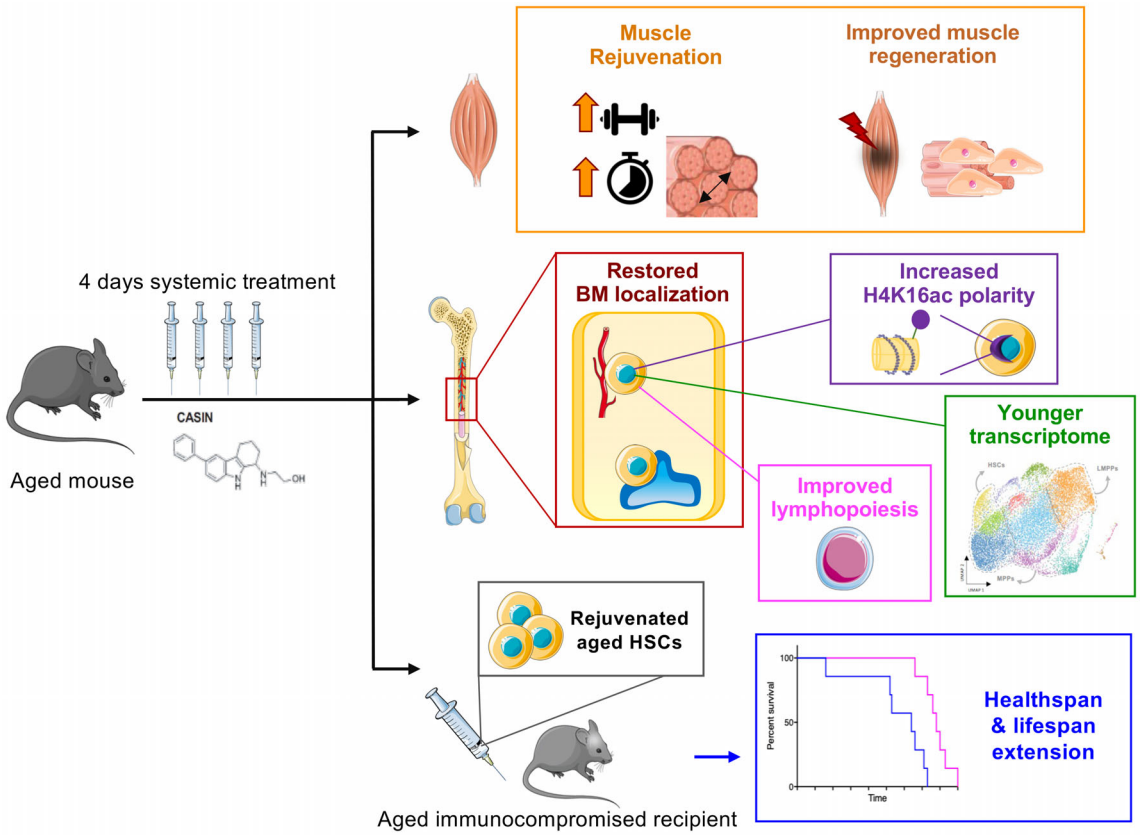

Fig. 3. Cartoon summarizing the major findings described in Montserrat *et al.* [73]. Rejuvenation of skeletal muscle stem cells (MuSCs) and hematopoietic stem cells (HSCs) with a short treatment with CASIN (Cdc42 activity-specific inhibitor) increases skeletal muscle function and restores the hematopoietic differentiation output. CASIN treatment restores HSC epipolarity, increases transcriptional network connectivity and restores HSC localization within the bone marrow to the same niches occupied by young HSCs. Importantly, the transplantation of CASIN-rejuvenated HSCs is sufficient to increase heath and lifespan in immunocompromised aged recipients, directly linking stem cell rejuvenation with lifespan extension. Graphics were modified from Servier Medical Art, licensed under a Creative Common Attribution 3.0 Generic License. http://smart.servier.com/.

transcriptional heterogeneity lost with aging and by restoring the connectivity across HSPC clusters, suggesting an improvement in their commitment and differentiation capacity. Despite the improvement in aged HFSCs, ISCs and MuSCs upon CASIN treatment, it was possible to demonstrate the direct link with the health and lifespan extension only for blood stem cells [73]. It would be intriguing to further investigate the uniqueness of the ability of HSCs to rejuvenate the entire body and the possible crosstalk with other somatic stem cells.

Interestingly, cell polarity was also described in HSCs from naked mole rats (NMR), the longest-lived rodents. Remarkably, in NMRs the resilient phenotypes are characterized by an increased quiescent HSPC compartment and by absence of the age-related decline in HSC polarity (for Tubulin not Cdc42), which is not lost until 12 years of age [78].

Conclusions and perspectives

Collectively, these results provide the proof-of-concept that somatic stem cell rejuvenation is a possible strategy to improve the regenerative capacity of several tissues upon aging and that in some instances, stem cell rejuvenation globally improves the whole organism health span and lifespan. Mice are extensively used as model systems to recapitulate human physiology and most of the data that we have described above are based on murine studies. A few of these interventions have now also been translated into the human system; for example, senolytic treatments [54], blood transfer [66], and autophagy-targeting drugs have been used in patients [61]. Interestingly, it has been recently published that, in line with the alterations occurring in murine HSCs over time, Cdc42 activity also increases in association with loss of cell polarity in human HSCs

(hHSCs) upon aging [79,80]. Importantly, *ex vivo* CASIN treatment of aged hHSCs restores polarity and the engraftment profile to the levels of young hHSCs in xenotransplantation experiments [80].

In conclusion, several lines of evidence suggest that human somatic stem cell rejuvenation might represent in the next future a promising potential therapeutical strategy to comprehensively improve quality of life in the elderly, paving the way for a new era of stem cell anti-aging therapies.

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Conflict of interest

M. Carolina Florian discloses financial interest in Mogling Bio.

Author contributions

MCF conceived and designed the project. FM and SM-V wrote the paper. MCF revised the manuscript.

References

1 Brunet A, Goodell MA and Rando TA (2023) Ageing and rejuvenation of tissue stem cells and their niches. *Nat Rev Mol Cell Biol* **24**, 45–62.
2 Oh HSH, Rutledge J, Nachun D, Pálovics R, Abiose O, Moran-Losada P, Channappa D, Urey DY, Kim K, Sung YJ *et al.* (2023) Organ aging signatures in the plasma proteome track health and disease. *Nature* **624**, 164–172.
3 Goh J, Wong E, Soh J, Maier AB and Kennedy BK (2023) Targeting the molecular & cellular pillars of human aging with exercise. *FEBS J* **290**, 649–668.
4 Shefer G, Rauner G, Stuelsatz P, Benayahu D and Yablonka-Reuveni Z (2013) Moderate-intensity treadmill running promotes expansion of the satellite cell pool in young and old mice. *FEBS J* **280**, 4063–4073.
5 Verdijk LB, Snijders T, Drost M, Delhaas T, Kadi F and van Loon LJC (2014) Satellite cells in human skeletal muscle; from birth to old age. *Age* **36**, 545–557.
6 Brett JO, Arjona M, Ikeda M, Quarta M, de Morrée A, Egner IM, Perandini LA, Ishak HD, Goshayeshi A, Benjamin DI *et al.* (2020) Exercise rejuvenates quiescent skeletal muscle stem cells in old mice through restoration of cyclin D1. *Nat Metab* **2**, 307–317.
7 Liu L, Kim S, Buckley MT, Reyes JM, Kang J, Tian L, Wang M, Lieu A, Mao M, Rodriguez-Mateo C *et al.* (2023) Exercise reprograms the inflammatory landscape of multiple stem cell compartments during mammalian aging. *Cell Stem Cell* **30**, 689–705.e4.
8 Horowitz AM, Fan X, Bieri G, Smith LK, Sanchez-Diaz CI, Schroer AB, Gontier G, Casaletto KB, Kramer JH, Williams KE *et al.* (2020) Blood factors transfer beneficial effects of exercise on neurogenesis and cognition to the aged brain. *Science* **369**, 167–173.
9 Miguel ZD, Khoury N, Betley MJ, Lehallier B, Willoughby D, Olsson N, Yang AC, Hahn O, Lu N, Vest RT *et al.* (2021) Exercise plasma boosts memory and dampens brain inflammation via clusterin. *Nature* **600**, 494–499.
10 Buckley MT, Sun ED, George BM, Liu L, Schaum N, Xu L, Reyes JM, Goodell MA, Weissman IL, Wyss-Coray T *et al.* (2023) Cell-type-specific aging clocks to quantify aging and rejuvenation in neurogenic regions of the brain. *Nat Aging* **3**, 121–137.
11 Zhang J and Wang JHC (2015) Moderate exercise mitigates the detrimental effects of aging on tendon stem cells. *PLoS One* **10**, e0130454.
12 Ho TT, Dellorusso PV, Verovskaya EV, Bakker ST, Flach J, Smith LK, Ventura PB, Lansinger OM, Hérault A, Zhang SY *et al.* (2021) Aged hematopoietic stem cells are refractory to bloodborne systemic rejuvenation interventions. *J Exp Med* **218**, e20210223.
13 Shen B, Tasdogan A, Ubellacker JM, Zhang J, Nosyreva ED, Du L, Murphy MM, Hu S, Yi Y, Kara N *et al.* (2021) A mechanosensitive peri-arteriolar niche for osteogenesis and lymphopoiesis. *Nature* **591**, 438–444.
14 Garcia-Valles R, Gomez-Cabrera MC, Rodriguez-Mañas L, Garcia-Garcia FJ, Diaz A, Noguera I, Olaso-Gonzalez G and Viña J (2013) Life-long spontaneous exercise does not prolong lifespan but improves health span in mice. *Longev Healthspan* **2**, 14.
15 Igarashi M and Guarente L (2016) mTORC1 and SIRT1 cooperate to Foster expansion of gut adult stem cells during calorie restriction. *Cell* **166**, 436–450.
16 Rangan P, Choi I, Wei M, Navarrete G, Guen E, Brandhorst S, Enyati N, Pasia G, Maesincee D, Ocon V *et al.* (2019) Fasting-mimicking diet modulates microbiota and promotes intestinal regeneration to reduce inflammatory bowel disease pathology. *Cell Rep* **26**, 2704–2719.e6.
17 Mihaylova MM, Cheng CW, Cao AQ, Tripathi S, Mana MD, Bauer-Rowe KE, Abu-Remaileh M, Clavain L, Erdemir A, Lewis CA *et al.* (2018) Fasting activates fatty acid oxidation to enhance intestinal stem cell function during homeostasis and aging. *Cell Stem Cell* **22**, 769–778.e4.
18 Benjamin DI, Both P, Benjamin JS, Nutter CW, Tan JH, Kang J, Machado LA, Klein JDD, de Morree A,

Kim S *et al.* (2022) Fasting induces a highly resilient deep quiescent state in muscle stem cells via ketone body signaling. *Cell Metab* **34**, 902–918.e6.
19 Boldrin L, Ross JA, Whitmore C, Doreste B, Beaver C, Eddaoudi A, Pearce DJ and Morgan JE (2017) The effect of calorie restriction on mouse skeletal muscle is sex, strain and time-dependent. *Sci Rep* **7**, 5160.
20 Brandhorst S, Choi IY, Wei M, Cheng CW, Sedrakyan S, Navarrete G, Dubeau L, Yap LP, Park R, Vinciguerra M *et al.* (2015) A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. *Cell Metab* **22**, 86–99.
21 Forni MF, Peloggia J, Braga TT, Chinchilla JEO, Shinohara J, Navas CA, Camara NOS and Kowaltowski AJ (2017) Caloric restriction promotes structural and metabolic changes in the skin. *Cell Rep* **20**, 2678–2692.
22 Tang D, Tao S, Chen Z, Koliesnik IO, Calmes PG, Hoerr V, Han B, Gebert N, Zörnig M, Löffler B *et al.* (2016) Dietary restriction improves repopulation but impairs lymphoid differentiation capacity of hematopoietic stem cells in early aging. *J Exp Med* **213**, 535–553.
23 Cheng CW, Adams GB, Perin L, Wei M, Zhou X, Lam BS, da Sacco S, Mirisola M, Quinn DI, Dorff TB *et al.* (2014) Prolonged fasting reduces IGF-1/PKA to promote hematopoietic-stem-cell-based regeneration and reverse immunosuppression. *Cell Stem Cell* **14**, 810–823.
24 Lazare S, Ausema A, Reijne AC, van Dijk G, van Os R and de Haan G (2017) Lifelong dietary intervention does not affect hematopoietic stem cell function. *Exp Hematol* **53**, 26–30.
25 Goldberg EL, Romero-Aleshire MJ, Renkema KR, Ventevogel MS, Chew WM, Uhrlaub JL, Smithey MJ, Limesand KH, Sempowski GD, Brooks HL *et al.* (2015) Lifespan-extending caloric restriction or mTOR inhibition impair adaptive immunity of old mice by distinct mechanisms. *Aging Cell* **14**, 130–138.
26 Mitchell SJ, Madrigal-Matute J, Scheibye-Knudsen M, Fang E, Aon M, González-Reyes JA, Cortassa S, Kaushik S, Gonzalez-Freire M, Patel B *et al.* (2016) Effects of sex, strain, and energy intake on hallmarks of aging in mice. *Cell Metab* **23**, 1093–1112.
27 Schreiber KH, Arriola Apelo SI, Yu D, Brinkman JA, Velarde MC, Syed FA, Liao CY, Baar EL, Carbajal KA, Sherman DS *et al.* (2019) A novel rapamycin analog is highly selective for mTORC1 in vivo. *Nat Commun* **10**, 3194.
28 Arriola Apelo SI, Neuman JC, Baar EL, Syed FA, Cummings NE, Brar HK, Pumper CP, Kimple ME and Lamming DW (2016) Alternative rapamycin treatment regimens mitigate the impact of rapamycin on glucose homeostasis and the immune system. *Aging Cell* **15**, 28–38.
29 Hahn O, Drews LF, Nguyen A, Tatsuta T, Gkioni L, Hendrich O, Zhang Q, Langer T, Pletcher S, Wakelam MJO *et al.* (2019) A nutritional memory effect counteracts the benefits of dietary restriction in old mice. *Nat Metab* **1**, 1059–1073.
30 Ohnishi K, Semi K, Yamamoto T, Shimizu M, Tanaka A, Mitsunaga K, Okita K, Osafune K, Arioka Y, Maeda T *et al.* (2014) Premature termination of reprogramming in vivo leads to cancer development through altered epigenetic regulation. *Cell* **156**, 663–677.
31 Abad M, Mosteiro L, Pantoja C, Cañamero M, Rayon T, Ors I, Graña O, Megías D, Domínguez O, Martínez D *et al.* (2013) Reprogramming in vivo produces teratomas and iPS cells with totipotency features. *Nature* **502**, 340–345.
32 Ocampo A, Reddy P, Martinez-Redondo P, Platero-Luengo A, Hatanaka F, Hishida T, Li M, Lam D, Kurita M, Beyret E *et al.* (2016) In vivo amelioration of age-associated hallmarks by partial reprogramming. *Cell* **167**, 1719–1733.e12.
33 Lu Y, Brommer B, Tian X, Krishnan A, Meer M, Wang C, Vera DL, Zeng Q, Yu D, Bonkowski MS *et al.* (2020) Reprogramming to recover youthful epigenetic information and restore vision. *Nature* **588**, 124–129.
34 Sarkar TJ, Quarta M, Mukherjee S, Colville A, Paine P, Doan L, Tran CM, Chu CR, Horvath S, Qi LS *et al.* (2020) Transient non-integrative expression of nuclear reprogramming factors promotes multifaceted amelioration of aging in human cells. *Nat Commun* **11**, 1545.
35 Wang C, Rabadan Ros R, Martinez-Redondo P, Ma Z, Shi L, Xue Y, Guillen-Guillen I, Huang L, Hishida T, Liao HK *et al.* (2021) In vivo partial reprogramming of myofibers promotes muscle regeneration by remodeling the stem cell niche. *Nat Commun* **12**, 3094.
36 Roux AE, Zhang C, Paw J, Zavala-Solorio J, Malahias E, Vijay T, Kolumam G, Kenyon C and Kimmel JC (2022) Diverse partial reprogramming strategies restore youthful gene expression and transiently suppress cell identity. *Cell Syst* **13**, 574–587.e11.
37 Rodríguez-Matellán A, Alcazar N, Hernández F, Serrano M and Ávila J (2020) In vivo reprogramming ameliorates aging features in dentate gyrus cells and improves memory in mice. *Stem Cell Reports* **15**, 1056–1066.
38 Chondronasiou D, Gill D, Mosteiro L, Urdinguio RG, Berenguer-Llergo A, Aguilera M, Durand S, Aprahamian F, Nirmalathasan N, Abad M *et al.* (2022) Multi-omic rejuvenation of naturally aged

tissues by a single cycle of transient reprogramming. *Aging Cell* **21**, e13578.
39 Basisty N, Kale A, Jeon OH, Kuehnemann C, Payne T, Rao C, Holtz A, Shah S, Sharma V, Ferrucci L *et al.* (2020) A proteomic atlas of senescence-associated secretomes for aging biomarker development. *PLoS Biol* **18**, e3000599.
40 Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, Saltness R, Jeganathan KB, Verzosa GC, Pezeshki A *et al.* (2016) Naturally occurring p16Ink4a-positive cells shorten healthy lifespan. *Nature* **530**, 184–189.
41 Moiseeva V, Cisneros A, Sica V, Deryagin O, Lai Y, Jung S, Andrés E, An J, Segalés J, Ortet L *et al.* (2023) Senescence atlas reveals an aged-like inflamed niche that blunts muscle regeneration. *Nature* **613**, 169–178.
42 Chang J, Wang Y, Shao L, Laberge RM, Demaria M, Campisi J, Janakiraman K, Sharpless NE, Ding S, Feng W *et al.* (2016) Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. *Nat Med* **22**, 78–83.
43 Grezella C, Fernandez-Rebollo E, Franzen J, Ventura Ferreira MS, Beier F and Wagner W (2018) Effects of senolytic drugs on human mesenchymal stromal cells. *Stem Cell Res Ther* **9**, 108.
44 Li X, Hong Y, He H, Jiang G, You W, Liang X, Fu Q, Han S, Lian Q and Zhang Y (2019) FGF21 mediates mesenchymal stem cell senescence via regulation of mitochondrial dynamics. *Oxid Med Cell Longev* **2019**, 4915149.
45 Khanh VC, Yamashita T, Ohneda K, Tokunaga C, Kato H, Osaka M, Hiramatsu Y and Ohneda O (2020) Rejuvenation of mesenchymal stem cells by extracellular vesicles inhibits the elevation of reactive oxygen species. *Sci Rep* **10**, 17315.
46 Zhang Y, Guo L, Han S, Chen L, Li C, Zhang Z, Hong Y, Zhang X, Zhou X, Jiang D *et al.* (2020) Adult mesenchymal stem cell ageing interplays with depressed mitochondrial Ndufs6. *Cell Death Dis* **11**, 1075.
47 Yeo GEC, Ng MH, Nordin FB and Law JX (2021) Potential of mesenchymal stem cells in the rejuvenation of the aging immune system. *Int J Mol Sci* **22**, 5749.
48 Cheng M, Yuan W, Moshaverinia A and Yu B (2023) Rejuvenation of mesenchymal stem cells to ameliorate skeletal aging. *Cells* **12**, 998.
49 Merimi M, El-Majzoub R, Lagneaux L, Moussa Agha D, Bouhtit F, Meuleman N, Fahmi H, Lewalle P, Fayyad-Kazan M and Najar M (2021) The therapeutic potential of mesenchymal stromal cells for regenerative medicine: current knowledge and future understandings. *Front Cell Dev Biol* **9**, 661532.
50 Nacarelli T, Lau L, Fukumoto T, Zundell J, Fatkhutdinov N, Wu S, Aird KM, Iwasaki O, Kossenkov AV, Schultz D *et al.* (2019) NAD+ metabolism governs the proinflammatory senescence-associated secretome. *Nat Cell Biol* **21**, 397–407.
51 Zhang H, Ryu D, Wu Y, Gariani K, Wang X, Luan P, D'Amico D, Ropelle ER, Lutolf MP, Aebersold R *et al.* (2016) NAD+ repletion improves mitochondrial and stem cell function and enhances life span in mice. *Science* **352**, 1436–1443.
52 Yuan X, Liu Y, Bijonowski BM, Tsai AC, Fu Q, Logan TM, Ma T and Li Y (2020) NAD+/NADH redox alterations reconfigure metabolism and rejuvenate senescent human mesenchymal stem cells in vitro. *Commun Biol* **3**, 1–15.
53 Amor C, Feucht J, Leibold J, Ho YJ, Zhu C, Alonso-Curbelo D, Mansilla-Soto J, Boyer JA, Li X, Giavridis T *et al.* (2020) Senolytic CAR T cells reverse senescence-associated pathologies. *Nature* **583**, 127–132.
54 Xu M, Pirtskhalava T, Farr JN, Weigand BM, Palmer AK, Weivoda MM, Inman CL, Ogrodnik MB, Hachfeld CM, Fraser DG *et al.* (2018) Senolytics improve physical function and increase lifespan in old age. *Nat Med* **24**, 1246–1256.
55 Aguado J, Amarilla AA, Taherian Fard A, Albornoz EA, Tyshkovskiy A, Schwabenland M, Chaggar HK, Modhiran N, Gómez-Inclán C, Javed I *et al.* (2023) Senolytic therapy alleviates physiological human brain aging and COVID-19 neuropathology. *Nat Aging* **3**, 1561–1575.
56 Chaib S, Tchkonia T and Kirkland JL (2022) Cellular senescence and senolytics: the path to the clinic. *Nat Med* **28**, 1556–1568.
57 Aman Y, Schmauck-Medina T, Hansen M, Morimoto RI, Simon AK, Bjedov I, Palikaras K, Simonsen A, Johansen T, Tavernarakis N *et al.* (2021) Autophagy in healthy aging and disease. *Nat Aging* **1**, 634–650.
58 Hansen M, Rubinsztein DC and Walker DW (2018) Autophagy as a promoter of longevity: insights from model organisms. *Nat Rev Mol Cell Biol* **19**, 579–593.
59 Dong S, Wang Q, Kao YR, Diaz A, Tasset I, Kaushik S, Thiruthuvanathan V, Zintiridou A, Nieves E, Dzieciatkowska M *et al.* (2021) Chaperone-mediated autophagy sustains haematopoietic stem-cell function. *Nature* **591**, 117–123.
60 Carnio S, LoVerso F, Baraibar MA, Longa E, Khan MM, Maffei M, Reischl M, Canepari M, Loefler S, Kern H *et al.* (2014) Autophagy impairment in muscle induces neuromuscular junction degeneration and precocious aging. *Cell Rep* **8**, 1509–1521.
61 Danics L, Abbas AA, Kis B and Pircs K (2023) Fountain of youth-targeting autophagy in aging. *Front Aging Neurosci* **15**, 1125739.
62 Ma S, Wang S, Ye Y, Ren J, Chen R, Li W, Li J, Zhao L, Zhao Q, Sun G *et al.* (2022) Heterochronic parabiosis induces stem cell revitalization and systemic

rejuvenation across aged tissues. *Cell Stem Cell* **29**, 990–1005.e10.
63 Villeda SA, Plambeck KE, Middeldorp J, Castellano JM, Mosher KI, Luo J, Smith LK, Bieri G, Lin K, Berdnik D *et al.* (2014) Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. *Nat Med* **20**, 659–663.
64 Jeon OH, Mehdipour M, Gil TH, Kang M, Aguirre NW, Robinson ZR, Kato C, Etienne J, Lee HG, Alimirah F *et al.* (2022) Systemic induction of senescence in young mice after single heterochronic blood exchange. *Nat Metab* **4**, 995–1006.
65 Rebo J, Mehdipour M, Gathwala R, Causey K, Liu Y, Conboy MJ and Conboy IM (2016) A single heterochronic blood exchange reveals rapid inhibition of multiple tissues by old blood. *Nat Commun* **7**, 13363.
66 Hosseini L, Shahabi P, Fakhari A, Zangbar HS, Seyedaghamiri F, Sadeghzadeh J and Abolhasanpour N (2023) Aging and age-related diseases with a focus on therapeutic potentials of young blood/plasma. *Naunyn Schmiedebergs Arch Pharmacol* **397**, 1–13.
67 Budovsky A, Fraifeld VE and Aronov S (2011) Linking cell polarity, aging and rejuvenation. *Biogerontology* **12**, 167–175.
68 Ali NJA, Dias Gomes M, Bauer R, Brodesser S, Niemann C and Iden S (2016) Essential role of polarity protein Par3 for epidermal homeostasis through regulation of barrier function, keratinocyte differentiation, and stem cell maintenance. *J Invest Dermatol* **136**, 2406–2416.
69 Dias Gomes M, Letzian S, Saynisch M and Iden S (2019) Polarity signaling ensures epidermal homeostasis by coupling cellular mechanics and genomic integrity. *Nat Commun* **10**, 3362.
70 Kang PJ, Mullner R, Li H, Hansford D, Shen HW and Park HO (2022) Up-regulation of the Cdc42 GTPase limits the replicative life span of budding yeast. *Mol Biol Cell* **33**, br5.
71 Florian MC, Dörr K, Niebel A, Daria D, Schrezenmeier H, Rojewski M, Filippi MD, Hasenberg A, Gunzer M, Scharffetter-Kochanek K *et al.* (2012) Cdc42 activity regulates hematopoietic stem cell aging and rejuvenation. *Cell Stem Cell* **10**, 520–530.
72 Florian MC, Leins H, Gobs M, Han Y, Marka G, Soller K, Vollmer A, Sakk V, Nattamai KJ, Rayes A *et al.* (2020) Inhibition of Cdc42 activity extends lifespan and decreases circulating inflammatory cytokines in aged female C57BL/6 mice. *Aging Cell* **19**, e13208.
73 Montserrat-Vazquez S, Ali NJ, Matteini F, Lozano J, Zhaowei T, Mejia-Ramirez E, Marka G, Vollmer A, Soller K, Sacma M *et al.* (2022) Transplanting rejuvenated blood stem cells extends lifespan of aged immunocompromised mice. *NPJ Regen Med* **7**, 78.
74 Liu W, Du W, Shang X, Wang L, Evelyn C, Florian MC, Ryan MA, Rayes A, Zhao X, Setchell K *et al.* (2019) Rational identification of a Cdc42 inhibitor presents a new regimen for long-term hematopoietic stem cell mobilization. *Leukemia* **33**, 749–761.
75 Tiwari A, Tursky ML, Kirkland MA and Pande G (2014) Expansion of human hematopoietic stem/progenitor cells on decellularized matrix scaffolds. *Curr Protoc Stem Cell Biol* **28**, Unit 1C.15.
76 Nalapareddy K, Hassan A, Sampson LL, Zheng Y and Geiger H (2021) Suppression of elevated Cdc42 activity promotes the regenerative potential of aged intestinal stem cells. *iScience* **24**, 102362.
77 Umbayev B, Masoud AR, Tsoy A, Alimbetov D, Olzhayev F, Shramko A, Kaiyrlykyzy A, Safarova Y, Davis T and Askarova S (2018) Elevated levels of the small GTPase Cdc42 induces senescence in male rat mesenchymal stem cells. *Biogerontology* **19**, 287–301.
78 Emmrich S, Trapp A, Tolibzoda Zakusilo F, Straight ME, Ying AK, Tyshkovskiy A, Mariotti M, Gray S, Zhang Z, Drage MG *et al.* (2022) Characterization of naked mole-rat hematopoiesis reveals unique stem and progenitor cell patterns and neotenic traits. *EMBO J* **41**, e109694.
79 Florian MC, Klenk J, Marka G, Soller K, Kiryakos H, Peter R, Herbolsheimer F, Rothenbacher D, Denkinger M and Geiger H (2017) Expression and activity of the small RhoGTPase Cdc42 in blood cells of older adults are associated with age and cardiovascular disease. *J Gerontol A Biol Sci Med Sci* **72**, 1196–1200.
80 Amoah A, Keller A, Emini R, Hoenicka M, Liebold A, Vollmer A, Eiwen K, Soller K, Sakk V, Zheng Y *et al.* (2022) Aging of human hematopoietic stem cells is linked to changes in Cdc42 activity. *Haematologica* **107**, 393–402.
81 Matsumura H, Mohri Y, Binh NT, Morinaga H, Fukuda M, Ito M, Kurata S, Hoeijmakers J and Nishimura EK (2016) Hair follicle aging is driven by transepidermal elimination of stem cells via COL17A1 proteolysis. *Science* **351**, aad4395.
82 Liu B, Qu J, Zhang W, Belmonte JCI and Liu GH (2022) A stem cell aging framework, from mechanisms to interventions. *Cell Rep* **41**, 111451.
83 Hong X, Campanario S, Ramírez-Pardo I, Grima-Terrén M, Isern J and Muñoz-Cánoves P (2022) Stem cell aging in the skeletal muscle: the importance of communication. *Ageing Res Rev* **73**, 101528.
84 Muñoz-Cánoves P, Neves J and Sousa-Victor P (2020) Understanding muscle regenerative decline with aging: new approaches to bring back youthfulness to aged stem cells. *FEBS J* **287**, 406–416.
85 Kalamakis G, Brüne D, Ravichandran S, Bolz J, Fan W, Ziebell F, Stiehl T, Catalá-Martinez F, Kupke J, Zhao S *et al.* (2019) Quiescence modulates stem cell maintenance and regenerative capacity in the aging brain. *Cell* **176**, 1407–1419.e14.

86 Negredo PN, Yeo RW and Brunet A (2020) Aging and rejuvenation of neural stem cells and their niches. *Cell Stem Cell* **27**, 202–223.
87 Nalapareddy K, Nattamai KJ, Kumar RS, Karns R, Wikenheiser-Brokamp KA, Sampson LL, Mahe MM, Sundaram N, Yacyshyn MB, Yacyshyn B *et al.* (2017) Canonical Wnt signaling ameliorates aging of intestinal stem cells. *Cell Rep* **18**, 2608–2621.
88 Adelman ER, Huang HT, Roisman A, Olsson A, Colaprico A, Qin T, Lindsley RC, Bejar R, Salomonis N, Grimes HL *et al.* (2019) Aging human hematopoietic stem cells manifest profound epigenetic reprogramming of enhancers that may predispose to leukemia. *Cancer Discov* **9**, 1080–1101.
89 Florian MC, Klose M, Sacma M, Jablanovic J, Knudson L, Nattamai KJ, Marka G, Vollmer A, Soller K, Sakk V *et al.* (2018) Aging alters the epigenetic asymmetry of HSC division. *PLoS Biol* **16**, e2003389.
90 de Haan G and Lazare SS (2018) Aging of hematopoietic stem cells. *Blood* **131**, 479–487.
91 Xie Y, Chen D, Jiang K, Song L, Qian N, Du Y, Yang Y, Wang F and Chen T (2022) Hair shaft miniaturization causes stem cell depletion through mechanosensory signals mediated by a piezo1-calcium-TNF-α axis. *Cell Stem Cell* **29**, 70–85.e6.
92 Akunuru S and Geiger H (2016) Aging, clonality, and rejuvenation of hematopoietic stem cells. *Trends Mol Med* **22**, 701–712.
93 Pang WW, Schrier SL and Weissman IL (2017) Age-associated changes in human hematopoietic stem cells. *Semin Hematol* **54**, 39–42.
94 Pang WW, Price EA, Sahoo D, Beerman I, Maloney WJ, Rossi DJ, Schrier SL and Weissman IL (2011) Human bone marrow hematopoietic stem cells are increased in frequency and myeloid-biased with age. *Proc Natl Acad Sci USA* **108**, 20012–20017.
95 Kuranda K, Vargaftig J, de la Rochere P, Dosquet C, Charron D, Bardin F, Tonnelle C, Bonnet D and Goodhardt M (2011) Age-related changes in human hematopoietic stem/progenitor cells. *Aging Cell* **10**, 542–546.
96 Audesse AJ and Webb AE (2020) Mechanisms of enhanced quiescence in neural stem cell aging. *Mech Ageing Dev* **191**, 111323.
97 Mathews KJ, Allen KM, Boerrigter D, Ball H, Shannon Weickert C and Double KL (2017) Evidence for reduced neurogenesis in the aging human hippocampus despite stable stem cell markers. *Aging Cell* **16**, 1195–1199.
98 Miyachi K, Yamada T, Kawagishi-Hotta M, Hasebe Y, Date Y, Hasegawa S, Arima M, Iwata Y, Kobayashi T, Numata S *et al.* (2018) Extracellular proteoglycan decorin maintains human hair follicle stem cells. *J Dermatol* **45**, 1403–1410.
99 Fulle S, Sancilio S, Mancinelli R, Gatta V and Di Pietro R (2013) Dual role of the caspase enzymes in satellite cells from aged and young subjects. *Cell Death Dis* **4**, e955.
100 Franco I, Johansson A, Olsson K, Vrtačnik P, Lundin P, Helgadottir HT, Larsson M, Revêchon G, Bosia C, Pagnani A *et al.* (2018) Somatic mutagenesis in satellite cells associates with human skeletal muscle aging. *Nat Commun* **9**, 800.