Aging as a consequence of the adaptation-maladaptation dilemma

Thomas Lissek[1]

[1] Corresponding Author

Address: Interdisciplinary Center for Neurosciences, Heidelberg University, Im Neuenheimer Feld 366, 69120 Heidelberg, Germany, Lissek@nbio.uni-heidelberg.de

Abstract

In aging, the organism is unable to counteract certain harmful influences over its lifetime which leads to progressive dysfunction and eventually death, thus delineating aging as one failed process of adaptation to a set of aging stimuli. A central problem in understanding aging is hence to explain why the organism cannot adapt to these aging stimuli. The adaptation-maladaptation theory of aging proposes that in aging adaptation processes such as adaptive transcription, epigenetic remodeling and metabolic plasticity drive dysfunction themselves over time (maladaptation) and thereby cause aging-related disorders such as cancer and metabolic dysregulation. Molecular mediators of this adaptation-maladaptation dilemma include CREB, Myc and IL-6. The central conundrum of aging is thus that the set of adaptation mechanisms that the body uses to deal with internal and external stressors overlaps with the set of aging stimuli. The only available option for the organism to counteract this maladaptation might be a genetic program to progressively reduce the output of adaptive cascades (e.g. via genomic methylation) which then leads to reduced physiological adaptation capacity and syndromes like frailty, immunosenescence and cognitive decline. The adaptation-maladaptation framework of aging entails that certain biological mechanisms can simultaneously protect against aging as well as drive aging and that aging might have components that are programmed and others that are not programmed. Several known longevity interventions such as exercise and dietary restriction seem to shift the adaptation-maladaptation balance in favor of adaptation and the key to longevity might lie in uncoupling adaptation from maladaptation.

Introduction

Biological organisms are self-regulating systems that constantly adapt to their environments. This ability for adaptation is tightly linked to the organism's survival. In aging, the organism is unable to counteract the negative effects of certain aging stimuli which can be both endogenous (e.g. oxidative stress, DNA repair errors, transcriptional variability, molecular hyperfunction) or exogenous (e.g. radiation damage, infections, environmental conditions that induce stress). This leads to progressive organismal dysfunction and eventually death. Aging can thus be conceptualized as one overarching failed adaptation process in response to a set of aging stimuli. As the body possesses many highly effective adaptation mechanisms to deal with stressors, one of the central problems in understanding aging is to explain why this adaptation failure occurs.

The adaptation-maladaptation dilemma in aging

Is there something unique about the aging stimuli compared to those stimuli that can be successfully adapted to? The adaptation-maladaptation framework of aging posits that aging is the result of maladaptation and a "recursion barrier" in which the adaptation mechanisms that normally protect the organism from dysfunction through beneficial adaptation drive maladaptation themselves [1] (Fig. 1) and have side-effects that cannot be countered by adaptive mechanisms. The body cannot protect itself from its own adaptation mechanisms or, phrased differently, the set of adaptive mechanisms cannot adapt to itself. One fundamental component of aging is thus a continuous increase of maladaptation and its consequences over the life-time (Fig. 2A). Consequently, one way to counter chronic maladaptation might be to reduce the output of these adaptive cascades over time via an aging-program (Fig 2B), thereby however creating the side-effect of decreased beneficial adaptation capacity and an increased susceptibility to stressors. Thus, aging might broadly have two components, one non-programmed (i.e. maladaptation) and one programmed (i.e. genetic programs to progressively reduce the activity of adaptive cascades to avoid maladaptation). In the end, the organism has to balance the negative side effects from adaptive mechanisms with their essential physiological functions and calibrate their activity over the life-time. The central problem

for the organism is hence that the set of its adaptation mechanisms overlaps with or is contained within the set of aging stimuli and that in aging the ratio of adaptation to maladaptation always decreases, one way or the other [1]. Aging might thus at least partly be driven by an inability to solve the adaptation-maladaptation dilemma and the framework describing this hypothesis is termed the adaptation-maladaptation theory of aging (AM-theory).

This could explain the central observation that in aging many adaptive functions are decreased (e.g. neural plasticity [2], muscle anabolism [3] and immunity [4]) while maladaptation tends to increase (e.g. diabetes [5], autoimmunity [6], atherosclerosis [7] and cancer [8]). The reduction of adaptive functions would be a side-effect of the organism's effort to counteract progressive maladaptation.

Parts of this framework are reminiscent of hyperfunction theory [9] in that it posits that the elevated function of certain molecular cascades is an important driver in age-related diseases. In AM-theory, the important cascades are those that drive adaptation, especially those that can implement long-term remodeling processes and can thus cause long-term damage. Elevated activity of adaptation mechanisms and subsequent dysfunctional remodeling can also be caused by external stimuli (e.g. stress) and would thus explain modulation of the aging process by environmental factors. In order to counteract increasing maladaptation, the body might have evolved dedicated programs to progressively reduce the effects of maladaptation which is in line with the "aging as a program"-framework [10]. Perhaps the progressive changes in methylation patterns that characterize aging and build the basis for several epigenetic aging clocks [11], implement a reduction in adaptive functionality to protect the organism from maladaptation. Thus, in aging, the organism would have to balance the two negative processes of maladaptive function with decreases in beneficial adaptation capacity and resulting increased negative effects from other aging stimuli. It is possible that in different individuals, this choice is made differently (e.g. some people die of cancer (hyperadaptation) while others die of neurodegeneration (hypoadaptation)). It is interesting to note that neurodegenerative diseases and cancer have an inverse correlation to each other [12], thus implying that in some organisms, the choice might be made for higher adaptive capacity but higher cancer risk, while in others it might be made for lower adaptive capacity and lower cancer risk.

Molecular pathways mediating the adaptation-maladaptation dilemma of aging

At the molecular level, several adaptation regulators have been implicated in maladaptation. CREB and its co-regulators such as CRTC and CBP are central regulators of stimulus-dependent cellular plasticity (Fig. 3A) and important for memory formation [13,14], metabolic regulation [15,16], immune function [17,18], muscle regeneration [19] and plasticity [20], skin physiology [21], bone physiology [22], cardiovascular function [23,24] and developmental processes [25]. Yet, they are also involved in cancer progression [26], autoimmunity [27], depression [28] and metabolic dysfunction [29,30]. Increasing CREB levels in the brain leads to enhancements in memory performance [31,32] but also maladaptive circuit remodeling, hyperexcitability and neuronal cell death [33]. In the aged rodent brain, a decrease in the levels and activation of CREB and CBP have been reported when compared to young animals [34-39] (one study showed increased CREB phosphorylation levels with age but a decreased induction after stimulation [40]), suggesting a possible compensatory downregulation. Exogenously increasing CREB levels in the aged brain rescues age-related memory performance [41]. Overexpressing the CREB coregulator CRTC2 in muscle cells leads to an anabolic state and enhanced exercise capacity [20].

In C. elegans, CREB inactivation was shown to decrease memory [42-44] but to increase lifespan [45] (one study did not observe lifespan effects [42]) (Fig. 3B). Similarly, reduction of the CREB co-activator increases lifespan [45]. However, in increased temperatures, deletion of CREB in sensory neurons has a deleterious effect on lifespan in C. elegans [46]. The complex role of CREB signaling hence illustrates the conundrum of decreasing adaptive fitness and increasing lifespan as a consequence of the adaptation-maladaptation dilemma. In mice with a diverse genetic background, caloric restriction enhances lifespan but at the cost of memory performance [47]. Interventions that impair memory formation, a major hallmark of aging in animals, thus also increase lifespan, thereby seeming to counteract aging. Reductions in the levels of the adaptive transcription factor Myc (Fig. 3A), which in humans is induced in skeletal muscles after exercise [48] and whose overexpression in rodent muscles leads to enhanced protein synthesis [49], lead to similar observations, namely a reduction in many physiological homeostatic

functions but also a reduced cancer incidence (i.e. reduced maladaptation) and an increased lifespan [50] (Fig. 3B). Interestingly, in humans, Myc gene methylation increases with age [51], hinting at the possibility that methylation-based silencing of Myc is part of an aging program to reduce maladaptation. In fruit flies, the acetyltransferase chameau increases adaptability under starvation at the cost of reduced longevity, thus confirming an inverse correlation between acute adaptation capacity and lifespan [52].

Also interesting in this regard are observations of an induction of cancer-like metabolic programs in neurons after synaptic stimulation [53] and in muscle fibers during hypertrophy [54], but rather than neurons and muscle cells using a cancer program, it is probably the case that cancer cells use a universal adaptive metabolic program for their progression.

How can the observations of compromised adaptability but increased lifespan be explained? The animals in these studies are lab animals in which the decrease in memory and other adaptive functions is most likely not survival-limiting because environmental stress is heavily reduced (e.g. lower exposure to infectious agents, no predation risk, ample food supply). Consequently, the reduced maladaptation rate (e.g. lower cancer and lower metabolic dysregulation) might translate to an increased lifespan. It would be predicted that in the wild, with increased stressor exposure, these animals would perform worse and not survive as long. In the context of evolution and the individual, the AM-dilemma entails that curbing adaptive responses would be beneficial for some animals (i.e. those that have a hyperadaptive balance) but, importantly, detrimental to others (e.g. those that have a hypoadaptive state). Perhaps then, organisms, also from an evolutionary perspective, can choose to perish from either a hyperadaptive or a hypoadaptive phenotype.

A subcategory of maladaptation, next to dysfunctional remodeling, is damage induced by adaptation mechanisms which also has been previously outlined [1]. One example is the induction of adaptive genes such as Npas4 and Fos via DNA double strand breaks (DSBs) [55] (Fig. 3C). Environmental enrichment, which induces immediate early genes [56], is neuroprotective [57] but also leads to induction of DSBs which is exacerbated by A-beta amyloid [58]. Interestingly, neural activity seems to simultaneously upregulate DNA repair mechanisms in some cases via the very molecules whose induction depends on DSB formation, such as Npas4 [59] (i.e. Npas4 induction depends on DSB formation while

Npas4 itself regulates DSB repair (Fig. 3C)). Npas4 is neuroprotective [60] and Npas4-mediated DNA repair has been linked to organismal lifespan in mice [59]. Relatedly, calcineurin has been implicated as a positive regulator of activity-dependent DSB formation [61] and Npas4 induction in neurons [62] and calcineurin inhibition in C. elegans leads to lifespan extension [63]. The transcriptional repressor DREAM has recently been shown to negatively regulate DNA repair mechanisms [64]. In neurons, DREAM negatively regulates immediate early gene induction and memory [65] and its deletion slows brain aging [66]. Thus, it seems that neurons simultaneously upregulate immediate early genes, DSB induction and DNA repair machinery when activated. A recent study has also demonstrated that many base excision repair genes are bound by CREB in neurons and that treatment with BDNF upregulates transcription of these genes [67]. Perhaps then a dysbalancing of these processes could partly explain age-related increases in genomic changes in neurons in humans [68,69]. If the repair cascades do not work properly, this would lead to an relative overtaking of damaging mechanisms during adaptation and could drive dysfunction. Maybe dysregulated gene expression patterns in aging and subsequent maladaptation are partly caused by genomic changes to regulatory regions as a result of DNA damage from adaptive gene inductions. As another example of potentially negative side-effects from physiological adaptation mechanisms, the activity-dependent gene Arc, which is required for learning and memory [70], also increases A-beta-amyloid formation in the brain [71].

Determinants of the adaptation-maladaptation balance

An important problem then is how adaptation and maladaptation are differentially induced by the same molecules. In which context does activation of a molecule such as CREB lead to adaptation and in which case to maladaptation? One important factor might be signaling dynamics. The same molecules can have drastically different downstream effects, depending on their activation patterns such as transient vs. sustained time courses [72]. For instance, interleukin 6 (IL-6) is involved in processes both potentially beneficial (e.g. promoting insulin sensitivity [73], downregulating inflammation [74]) and harmful (e.g. cancer progression [75]). It is induced in skeletal muscle by acute exercise [76] and upregulated in blood plasma after exercise [77]. In older individuals, blood baseline

IL-6 levels are higher [78] while exercise-mediated IL-6 induction in muscle has been reported to be blunted [79] (although similar inductions between young and aged have been reported [78]). Interestingly, with chronic exercise, IL-6 baseline levels in the blood decrease [80,81]. Arc, a memory regulator in the brain which is induced by learning tasks [70], is elevated at baseline in the rodent hippocampus of cognitively impaired aged animals and its behavioral induction is blunted [82]. Certain adaptation mediators are hence increased at baseline during aging and their induction by physiological stimulation can be reduced. Beneficial interventions such as exercise can lead to an acute induction but a chronic downregulation of these molecules. This phenotype might be in part explained by a desensitization of adaptive cascades after acute stimulation such as in adaptive transcription in neurons [83]. Dynamics might hence be crucial when it comes to a biological mechanism's role in exerting anti- or pro-aging effects. Many adaptive transcription mechanisms whose activation is associated with pro-longevity effects [84] are simultaneously associated with aging-related disorders such as cancer and metabolic dysregulation [85]. If we consider that different molecular activation patterns can lead to very different outcomes (e.g. sustained ERK activation drives differentiation while transient activation drives proliferation in certain cells [86]), we see that signaling dynamics might be an important regulating factor in the adaptation-maladaptation dilemma of aging.

Implications and predictions of the adaptation-maladaptation theory of aging

The adaptation-maladaptation hypothesis thus posits that adaptation and maladaptation are intricately linked to each other and that aging is at least partially a consequence of the adaptation-maladaptation dilemma. The only option for the organism to deal with this dilemma might be to balance progressive dysfunctions from non-programmed maladaptation with those from programmed adaptation reductions, with progressive decline in the ratio of adaptation to maladaptation and hence aging being inevitable. What are some implications and predictions of this theory?

First, it explains why certain processes and molecules are implicated in both protection against aging-related decline as well as in driving aging, such as activity of CREB, Fos and other adaptation genes (see above and previous work [1,85]). After all, why would the

deletion of genes that mediate resilience to stress and increase adaptability (e.g. positive memory regulators) cause an extended lifespan? In AM-theory, this is because these processes drive both beneficial adaptation (e.g. learning and memory, adaptive immune function, activity-dependent muscle remodeling) and maladaptation (e.g. cancer, metabolic and cardiovascular remodeling) and in conditions where maladaptation is life-limiting (i.e. many laboratory environments) downregulating these pathways leads to lifespan extension. Thus, there is under most conditions a fundamental trade-off between fitness and lifespan. Adaptation is one of the central determinants of fitness and its reduction leads to many physiological impairments but also to decreased maladaptation and, in the absence of overwhelming stressors, to longer lifespans. In laboratory animals, curbing adaptive processes hence usually leads to enhancements in lifespan because these animals are isolated from stressors. In the wild, many “anti-adaptive” longevity interventions might not translate to longer survival. AM theory is hence in line with antagonistic pleiotropy [87] which states that certain gene variants that increase fitness (i.e. adaptation) early on can have detrimental effects in later life (i.e. maladaptation).

Second, AM-theory posits that aging has both components that are not programmed (e.g. adaptative hyperfunction, molecular damage from adaptive mechanisms) and programmed (e.g. continuous reduction of plasticity mediators over time). Organisms can die from hypoadaptation (e.g. infectious diseases) or hyperadaptation (e.g. cancer, cardiovascular remodeling).

Third, AM-theory links adaptive mechanisms to maladaptation regardless of organizational level (e.g. cellular, tissue, organism) and is thus scale-independent. It can be applied to cells, tissues, organ systems and the whole body. It can for instance accommodate the notion that single-celled organisms age, as has been proposed [88,89], if they face the AM-dilemma. Perhaps aging is then the result of an underlying error in the functional organization of all biological systems. Consequently, AM-theory would for instance lessen the importance of a ”developmental” perspective on aging. Rather, it implies that adaptation is fundamental and since development is an adaptation-intensive processes, the curbing of adaptive cascades can lead to delayed and altered development and delayed aging, in some cases independent of each other.

Fourth, because of different trade-off choices in the AM-dilemma, some proposed longevity-interventions might have different effects in different individuals. In individuals with a hypoadaptive phenotype, anti-adaptive interventions could perhaps lead to an increased susceptibility to infection, sarcopenia and dementia among other things.

Fifth, it is able to incorporate different theories of aging such as hyperfunction, aging as a program and damage-related theories of aging. AM theory posits for instance that damage can cause aging in those cases in which beneficial adaptation is insufficient which usually happens later in life and usually due to programmed downregulation of adaptation cascades. It explains that as long as organisms or cells could adapt to and compensate for the damage it does not drive aging-related pathology.

Sixth, it answers the question of why animal bodies across different species would enable or implement the downregulation of beneficial molecules such as CREB that protect it from so many aging effects. It is because these drive maladaptation. This could even extend to the behavioral level. Many elderly organisms develop behavioral patterns that isolate them from stressors. Thus in order to deal with a reduced stress adaptability, organisms retreat and isolate themselves.

Implications for translational efforts

The key to longevity might be to raise beneficial adaptation and decrease maladaptation, to thus uncouple the processes of adaptation and maladaptation from each other (i.e. shifting the adaptation-maladaptation balance). This would entail the induction of metaplasticity (i.e. changing the adaptability of the system). Interestingly, well-studied environmental interventions including exercise and environmental enrichment which work via adaptive transcriptional cascades [84] seem to be able to achieve this (Fig. 4). Environmental enrichment for instance induces neuronal metaplasticity in neurons in the brain [90] and exercise induces enhanced neuronal plasticity [91] and metaplasticity in skeletal muscles [92], as well as a reduced cancer incidence [93]. These interventions hence lead to increases in adaptation and simultaneous decreases in maladaptation (also see previous work [1]).

Raising adaptation could also be achieved by transgenic or pharmacological means. Viral overexpression of CREB in the brain has been shown to improve memory in aged rats [41]. Similarly, overexpression of other adaptive signaling molecules in aged animals improves memory performance to young levels, including Dnmt3a2 [94] and CaMKIV [95]. On the pharmacological side, HDAC inhibitors acting via CREB have been demonstrated to increase memory performance [96] and PDE4 inhibition via rolipram, which increases CREB activity, leads to memory enhancement in aged animals [97]. A caveat with these strategies is that they also might increase maladaptation if the dynamics are not chosen correctly (e.g. prolonged CREB overexpression leads to neural circuit maladaptation and neuronal death [33]).

Caveats and considerations

What are potential caveats and considerations in AM-theory?

Adaptation is a process involving many feedback loops and regulation mechanisms. It could be that decreasing adaptive capacities in one pathway increases adaptive capacities in another. Biological systems display counterefforts to external disturbance and thus usually also to interventions. Due to degeneracy, it could be that interventions that decrease the activity of one adaptation pathway lead to compensatory changes in another one (e.g. downregulation of CREB leads to upregulation of CREM [98]). The blocking of some adaptive cascades could potentially lead to upregulation of others and hence correct adaptive dysbalances. Thus, care must be taken when an “adaptation blocker” is applied as this could very well translate to an increase in adaptive capacity in another pathway. For instance, treatment with rapamycin which inhibits mTOR (adaptation mechanism 1 decrease) increases CREB phosphorylation (adaptation mechanism 2 increase) [99]. A related point concerns the causality of age-dependent downregulation of adaptation cascades. Are these pre-configured genetic programs and potentially connected to the methylation changes which build the basis for aging clocks? Or are the downregulations merely an automatic result of negative feedback loops? For instance, heightened CREB activity secondary to damage might lead to a subsequent compensatory downregulation of CREB levels.

Also, the role of adaptive cascades in physiological and pathophysiological processes is complex and conceptually straightforward descriptions of hyperadaptive vs. hypoadaptive phenotypes might not readily apply. For instance, CREB is important in both cancer progression [26] and immune function [17] which counters cancer. It would thus not be immediately clear what result inhibiting CREB would lead to. Decreased cancer progression due to lower malignancy or increased cancer progression due to immune dysfunction? This illustrates the need for more detailed stratification. CREB and other pathways oftentimes have context-specific co-regulators that are activated differentially according to tissue and stimulus-type (see a previous discussion for details [85]). Furthermore, the effect of many molecules within the organism depends on the underlying signaling dynamics such as maximum amplitude and time-course of activation. Different activation patterns of the same molecules can have drastically different downstream effects [72].

The above points highlight the problem with overly simplistic causality models as previously explored [100]. The organism is subjected to a set of interconnected aging stimuli simultaneously right after inception. Thus, asking “what comes first, damage or maladaptation?” might not make much sense. Similarly, the complex regulation patterns within adaptive pathways expressing degeneracy, feedback loops and context-dependent interactions render extraction of repeatable patterns difficult. In order to understand adaptation-maladaptation connections and how these could be uncoupled, probing the underlying dynamics of adaptation cascades will be important.

Conclusions

In conclusion, aging can be conceptualized as one failed adaptation process to a set of aging stimuli. The present work has proposed the adaptation-maladaptation dilemma as an explanation for this failure which states that aging results from the fact that set of the body’s adaptation mechanisms overlaps with the set of aging stimuli and drives progressive maladaptation. This creates a type of programming error in which the body cannot escape from the detrimental influences of its own operations, essentially leading to inescapable progressive dysfunction over time. Adaptation-maladaptation theory posits

that in order to counter maladaptation, the organism might need to reduce the output of adaptation cascades progressively. Failure to do so leads to cancer, diabetes and autoimmunity among other disorders. Success in doing so however results in frailty, immunosenescence and cognitive decline among other things. The organism is thus trapped in a dilemma which it cannot solve, resulting in the progressive dysfunction we call aging. Counteracting aging might be achieved by uncoupling beneficial adaptation from maladaptation, therefore allowing the organism continued absorption of stressors without introducing dysfunction.

Contributions

TL conceived and wrote the manuscript.

Acknowledgements

The figures were produced with BioRender.

Conflicts of interest

The author declares that no conflict of interest is present.

References

1. Lissek, T. Aging, adaptation and maladaptation. *Frontiers in Aging* **2023**, *4*, doi:10.3389/fragi.2023.1256844.
2. Burke, S.N.; Barnes, C.A. Neural plasticity in the ageing brain. *Nat Rev Neurosci* **2006**, *7*, 30-40, doi:10.1038/nrn1809.
3. Breen, L.; Phillips, S.M. Skeletal muscle protein metabolism in the elderly: Interventions to counteract the 'anabolic resistance' of ageing. *Nutr Metab (Lond)* **2011**, *8*, 68, doi:10.1186/1743-7075-8-68.
4. Weng, N.P. Aging of the immune system: how much can the adaptive immune system adapt? *Immunity* **2006**, *24*, 495-499, doi:10.1016/j.immuni.2006.05.001.
5. Sinclair, A.; Dunning, T.; Rodriguez-Manas, L. Diabetes in older people: new insights and remaining challenges. *Lancet Diabetes Endocrinol* **2015**, *3*, 275-285, doi:10.1016/S2213-8587(14)70176-7.

6. Goronzy, J.J.; Weyand, C.M. Immune aging and autoimmunity. *Cell Mol Life Sci* **2012**, *69*, 1615-1623, doi:10.1007/s00018-012-0970-0.
7. Head, T.; Daunert, S.; Goldschmidt-Clermont, P.J. The Aging Risk and Atherosclerosis: A Fresh Look at Arterial Homeostasis. *Front Genet* **2017**, *8*, 216, doi:10.3389/fgene.2017.00216.
8. White, M.C.; Holman, D.M.; Boehm, J.E.; Peipins, L.A.; Grossman, M.; Henley, S.J. Age and cancer risk: a potentially modifiable relationship. *Am J Prev Med* **2014**, *46*, S7-15, doi:10.1016/j.amepre.2013.10.029.
9. Blagosklonny, M.V. Answering the ultimate question "what is the proximal cause of aging?". *Aging (Albany NY)* **2012**, *4*, 861-877, doi:10.18632/aging.100525.
10. de Magalhaes, J.P. Programmatic features of aging originating in development: aging mechanisms beyond molecular damage? *FASEB J* **2012**, *26*, 4821-4826, doi:10.1096/fj.12-210872.
11. Horvath, S.; Raj, K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nat Rev Genet* **2018**, *19*, 371-384, doi:10.1038/s41576-018-0004-3.
12. Driver, J.A. Inverse association between cancer and neurodegenerative disease: review of the epidemiologic and biological evidence. *Biogerontology* **2014**, *15*, 547-557, doi:10.1007/s10522-014-9523-2.
13. Mamiya, N.; Fukushima, H.; Suzuki, A.; Matsuyama, Z.; Homma, S.; Frankland, P.W.; Kida, S. Brain region-specific gene expression activation required for reconsolidation and extinction of contextual fear memory. *J Neurosci* **2009**, *29*, 402-413, doi:10.1523/JNEUROSCI.4639-08.2009.
14. Guzowski, J.F.; McGaugh, J.L. Antisense oligodeoxynucleotide-mediated disruption of hippocampal cAMP response element binding protein levels impairs consolidation of memory for water maze training. *Proc Natl Acad Sci U S A* **1997**, *94*, 2693-2698, doi:10.1073/pnas.94.6.2693.
15. Herzig, S.; Long, F.; Jhala, U.S.; Hedrick, S.; Quinn, R.; Bauer, A.; Rudolph, D.; Schutz, G.; Yoon, C.; Puigserver, P.; et al. CREB regulates hepatic gluconeogenesis through the coactivator PGC-1. *Nature* **2001**, *413*, 179-183, doi:10.1038/35093131.
16. Song, Y.; Altarejos, J.; Goodarzi, M.O.; Inoue, H.; Guo, X.; Berdeaux, R.; Kim, J.H.; Goode, J.; Igata, M.; Paz, J.C.; et al. CRTC3 links catecholamine signalling to energy balance. *Nature* **2010**, *468*, 933-939, doi:10.1038/nature09564.
17. Barton, K.; Muthusamy, N.; Chanyangam, M.; Fischer, C.; Clendenin, C.; Leiden, J.M. Defective thymocyte proliferation and IL-2 production in transgenic mice expressing a dominant-negative form of CREB. *Nature* **1996**, *379*, 81-85, doi:10.1038/379081a0.
18. Chen, H.C.; Byrd, J.C.; Muthusamy, N. Differential role for cyclic AMP response element binding protein-1 in multiple stages of B cell development, differentiation, and survival. *J Immunol* **2006**, *176*, 2208-2218, doi:10.4049/jimmunol.176.4.2208.
19. Stewart, R.; Flechner, L.; Montminy, M.; Berdeaux, R. CREB is activated by muscle injury and promotes muscle regeneration. *PLoS One* **2011**, *6*, e24714, doi:10.1371/journal.pone.0024714.
20. Bruno, N.E.; Kelly, K.A.; Hawkins, R.; Bramah-Lawani, M.; Amelio, A.L.; Nwachukwu, J.C.; Nettles, K.W.; Conkright, M.D. Creb coactivators direct anabolic responses and enhance performance of skeletal muscle. *EMBO J* **2014**, *33*, 1027-1043, doi:10.1002/embj.201386145.
21. Horike, N.; Kumagai, A.; Shimono, Y.; Onishi, T.; Itoh, Y.; Sasaki, T.; Kitagawa, K.; Hatano, O.; Takagi, H.; Susumu, T.; et al. Downregulation of SIK2 expression promotes the melanogenic program in mice. *Pigment Cell Melanoma Res* **2010**, *23*, 809-819, doi:10.1111/j.1755-148X.2010.00760.x.
22. Long, F.; Schipani, E.; Asahara, H.; Kronenberg, H.; Montminy, M. The CREB family of activators is required for endochondral bone development. *Development* **2001**, *128*, 541-550, doi:10.1242/dev.128.4.541.

23. Fentzke, R.C.; Korcarz, C.E.; Lang, R.M.; Lin, H.; Leiden, J.M. Dilated cardiomyopathy in transgenic mice expressing a dominant-negative CREB transcription factor in the heart. *J Clin Invest* **1998**, *101*, 2415-2426, doi:10.1172/JCI2950.
24. Watson, P.A.; Reusch, J.E.; McCune, S.A.; Leinwand, L.A.; Luckey, S.W.; Konhilas, J.P.; Brown, D.A.; Chicco, A.J.; Sparagna, G.C.; Long, C.S.; et al. Restoration of CREB function is linked to completion and stabilization of adaptive cardiac hypertrophy in response to exercise. *Am J Physiol Heart Circ Physiol* **2007**, *293*, H246-259, doi:10.1152/ajpheart.00734.2006.
25. Bleckmann, S.C.; Blendy, J.A.; Rudolph, D.; Monaghan, A.P.; Schmid, W.; Schutz, G. Activating transcription factor 1 and CREB are important for cell survival during early mouse development. *Mol Cell Biol* **2002**, *22*, 1919-1925, doi:10.1128/MCB.22.6.1919-1925.2002.
26. Abramovitch, R.; Tavor, E.; Jacob-Hirsch, J.; Zeira, E.; Amariglio, N.; Pappo, O.; Rechavi, G.; Galun, E.; Honigman, A. A pivotal role of cyclic AMP-responsive element binding protein in tumor progression. *Cancer Res* **2004**, *64*, 1338-1346, doi:10.1158/0008-5472.can-03-2089.
27. Wang, X.; Ni, L.; Chang, D.; Lu, H.; Jiang, Y.; Kim, B.S.; Wang, A.; Liu, X.; Zhong, B.; Yang, X.; et al. Cyclic AMP-Responsive Element-Binding Protein (CREB) is Critical in Autoimmunity by Promoting Th17 but Inhibiting Treg Cell Differentiation. *EBioMedicine* **2017**, *25*, 165-174, doi:10.1016/j.ebiom.2017.10.010.
28. Newton, S.S.; Thome, J.; Wallace, T.L.; Shirayama, Y.; Schlesinger, L.; Sakai, N.; Chen, J.; Neve, R.; Nestler, E.J.; Duman, R.S. Inhibition of cAMP response element-binding protein or dynorphin in the nucleus accumbens produces an antidepressant-like effect. *J Neurosci* **2002**, *22*, 10883-10890.
29. Qi, L.; Saberi, M.; Zmuda, E.; Wang, Y.; Altarejos, J.; Zhang, X.; Dentin, R.; Hedrick, S.; Bandyopadhyay, G.; Hai, T.; et al. Adipocyte CREB promotes insulin resistance in obesity. *Cell Metab* **2009**, *9*, 277-286, doi:10.1016/j.cmet.2009.01.006.
30. Hogan, M.F.; Ravnskjaer, K.; Matsumura, S.; Huising, M.O.; Hull, R.L.; Kahn, S.E.; Montminy, M. Hepatic Insulin Resistance Following Chronic Activation of the CREB Coactivator CRTC2. *J Biol Chem* **2015**, *290*, 25997-26006, doi:10.1074/jbc.M115.679266.
31. Suzuki, A.; Fukushima, H.; Mukawa, T.; Toyoda, H.; Wu, L.J.; Zhao, M.G.; Xu, H.; Shang, Y.; Endoh, K.; Iwamoto, T.; et al. Upregulation of CREB-mediated transcription enhances both short- and long-term memory. *J Neurosci* **2011**, *31*, 8786-8802, doi:10.1523/JNEUROSCI.3257-10.2011.
32. Josselyn, S.A.; Shi, C.; Carlezon, W.A., Jr.; Neve, R.L.; Nestler, E.J.; Davis, M. Long-term memory is facilitated by cAMP response element-binding protein overexpression in the amygdala. *J Neurosci* **2001**, *21*, 2404-2412.
33. Lopez de Armentia, M.; Jancic, D.; Olivares, R.; Alarcon, J.M.; Kandel, E.R.; Barco, A. cAMP response element-binding protein-mediated gene expression increases the intrinsic excitability of CA1 pyramidal neurons. *J Neurosci* **2007**, *27*, 13909-13918, doi:10.1523/JNEUROSCI.3850-07.2007.
34. Asanuma, M.; Nishibayashi, S.; Iwata, E.; Kondo, Y.; Nakanishi, T.; Vargas, M.G.; Ogawa, N. Alterations of cAMP response element-binding activity in the aged rat brain in response to administration of rolipram, a cAMP-specific phosphodiesterase inhibitor. *Brain Res Mol Brain Res* **1996**, *41*, 210-215, doi:10.1016/0169-328x(96)00098-8.
35. Chung, Y.H.; Kim, E.J.; Shin, C.M.; Joo, K.M.; Kim, M.J.; Woo, H.W.; Cha, C.I. Age-related changes in CREB binding protein immunoreactivity in the cerebral cortex and hippocampus of rats. *Brain Res* **2002**, *956*, 312-318, doi:10.1016/s0006-8993(02)03562-x.
36. Morris, K.A.; Gold, P.E. Age-related impairments in memory and in CREB and pCREB expression in hippocampus and amygdala following inhibitory avoidance training. *Mech Ageing Dev* **2012**, *133*, 291-299, doi:10.1016/j.mad.2012.03.004.

37. Brightwell, J.J.; Gallagher, M.; Colombo, P.J. Hippocampal CREB1 but not CREB2 is decreased in aged rats with spatial memory impairments. *Neurobiol Learn Mem* **2004**, *81*, 19-26, doi:10.1016/j.nlm.2003.08.001.
38. Kudo, K.; Wati, H.; Qiao, C.; Arita, J.; Kanba, S. Age-related disturbance of memory and CREB phosphorylation in CA1 area of hippocampus of rats. *Brain Res* **2005**, *1054*, 30-37, doi:10.1016/j.brainres.2005.06.045.
39. Porte, Y.; Buhot, M.C.; Mons, N. Alteration of CREB phosphorylation and spatial memory deficits in aged 129T2/Sv mice. *Neurobiol Aging* **2008**, *29*, 1533-1546, doi:10.1016/j.neurobiolaging.2007.03.023.
40. Monti, B.; Berteotti, C.; Contestabile, A. Dysregulation of memory-related proteins in the hippocampus of aged rats and their relation with cognitive impairment. *Hippocampus* **2005**, *15*, 1041-1049, doi:10.1002/hipo.20099.
41. Yu, X.W.; Curlik, D.M.; Oh, M.M.; Yin, J.C.; Disterhoft, J.F. CREB overexpression in dorsal CA1 ameliorates long-term memory deficits in aged rats. *Elife* **2017**, *6*, doi:10.7554/eLife.19358.
42. Lakhina, V.; Arey, R.N.; Kaletsky, R.; Kauffman, A.; Stein, G.; Keyes, W.; Xu, D.; Murphy, C.T. Genome-wide functional analysis of CREB/long-term memory-dependent transcription reveals distinct basal and memory gene expression programs. *Neuron* **2015**, *85*, 330-345, doi:10.1016/j.neuron.2014.12.029.
43. Dahiya, Y.; Rose, S.; Thapliyal, S.; Bhardwaj, S.; Prasad, M.; Babu, K. Differential Regulation of Innate and Learned Behavior by Creb1/Crh-1 in Caenorhabditis elegans. *J Neurosci* **2019**, *39*, 7934-7946, doi:10.1523/JNEUROSCI.0006-19.2019.
44. Kauffman, A.L.; Ashraf, J.M.; Corces-Zimmerman, M.R.; Landis, J.N.; Murphy, C.T. Insulin signaling and dietary restriction differentially influence the decline of learning and memory with age. *PLoS Biol* **2010**, *8*, e1000372, doi:10.1371/journal.pbio.1000372.
45. Mair, W.; Morantte, I.; Rodrigues, A.P.; Manning, G.; Montminy, M.; Shaw, R.J.; Dillin, A. Lifespan extension induced by AMPK and calcineurin is mediated by CRTC-1 and CREB. *Nature* **2011**, *470*, 404-408, doi:10.1038/nature09706.
46. Chen, Y.C.; Chen, H.J.; Tseng, W.C.; Hsu, J.M.; Huang, T.T.; Chen, C.H.; Pan, C.L. A C. elegans Thermosensory Circuit Regulates Longevity through crh-1/CREB-Dependent flp-6 Neuropeptide Signaling. *Dev Cell* **2016**, *39*, 209-223, doi:10.1016/j.devcel.2016.08.021.
47. Ouellette, A.R.; Hadad, N.; Deighan, A.; Robinson, L.; O'Connell, K.; Freund, A.; Churchill, G.A.; Kaczorowski, C.C. Life-long dietary restrictions have negligible or damaging effects on late-life cognitive performance: A key role for genetics in outcomes. *Neurobiol Aging* **2022**, *118*, 108-116, doi:10.1016/j.neurobiolaging.2022.07.004.
48. Rundqvist, H.C.; Montelius, A.; Osterlund, T.; Norman, B.; Esbjornsson, M.; Jansson, E. Acute sprint exercise transcriptome in human skeletal muscle. *PLoS One* **2019**, *14*, e0223024, doi:10.1371/journal.pone.0223024.
49. Mori, T.; Ato, S.; Knudsen, J.R.; Henriquez-Olguin, C.; Li, Z.; Wakabayashi, K.; Suginohara, T.; Higashida, K.; Tamura, Y.; Nakazato, K.; et al. c-Myc overexpression increases ribosome biogenesis and protein synthesis independent of mTORC1 activation in mouse skeletal muscle. *Am J Physiol Endocrinol Metab* **2021**, *321*, E551-E559, doi:10.1152/ajpendo.00164.2021.
50. Wang, H.; Lu, J.; Stevens, T.; Roberts, A.; Mandel, J.; Avula, R.; Ma, B.; Wu, Y.; Wang, J.; Land, C.V.; et al. Premature aging and reduced cancer incidence associated with near-complete body-wide Myc inactivation. *Cell Rep* **2023**, *42*, 112830, doi:10.1016/j.celrep.2023.112830.
51. Ono, T.; Yamamoto, S.; Kurishita, A.; Yamamoto, K.; Yamamoto, Y.; Ujeno, Y.; Sagisaka, K.; Fukui, Y.; Miyamoto, M.; Tawa, R.; et al. Comparison of age-associated changes of c-myc gene methylation in liver between man and mouse. *Mutat Res* **1990**, *237*, 239-246, doi:10.1016/0921-8734(90)90005-c.

52. Venkatasubramani, A.V.; Ichinose, T.; Kanno, M.; Forne, I.; Tanimoto, H.; Peleg, S.; Imhof, A. The fruit fly acetyltransferase chameau promotes starvation resilience at the expense of longevity. *EMBO reports* **2023**, doi:10.15252/embr.202357023.
53. Bas-Orth, C.; Tan, Y.W.; Lau, D.; Bading, H. Synaptic Activity Drives a Genomic Program That Promotes a Neuronal Warburg Effect. *J Biol Chem* **2017**, *292*, 5183-5194, doi:10.1074/jbc.M116.761106.
54. Wackerhage, H.; Vechetti, I.J.; Baumert, P.; Gehlert, S.; Becker, L.; Jaspers, R.T.; de Angelis, M.H. Does a Hypertrophying Muscle Fibre Reprogramme its Metabolism Similar to a Cancer Cell? *Sports Med* **2022**, *52*, 2569-2578, doi:10.1007/s40279-022-01676-1.
55. Madabhushi, R.; Gao, F.; Pfenning, A.R.; Pan, L.; Yamakawa, S.; Seo, J.; Rueda, R.; Phan, T.X.; Yamakawa, H.; Pao, P.C.; et al. Activity-Induced DNA Breaks Govern the Expression of Neuronal Early-Response Genes. *Cell* **2015**, *161*, 1592-1605, doi:10.1016/j.cell.2015.05.032.
56. Jaeger, B.N.; Linker, S.B.; Parylak, S.L.; Barron, J.J.; Gallina, I.S.; Saavedra, C.D.; Fitzpatrick, C.; Lim, C.K.; Schafer, S.T.; Lacar, B.; et al. A novel environment-evoked transcriptional signature predicts reactivity in single dentate granule neurons. *Nat Commun* **2018**, *9*, 3084, doi:10.1038/s41467-018-05418-8.
57. Young, D.; Lawlor, P.A.; Leone, P.; Dragunow, M.; During, M.J. Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. *Nat Med* **1999**, *5*, 448-453, doi:10.1038/7449.
58. Suberbielle, E.; Sanchez, P.E.; Kravitz, A.V.; Wang, X.; Ho, K.; Eilertson, K.; Devidze, N.; Kreitzer, A.C.; Mucke, L. Physiologic brain activity causes DNA double-strand breaks in neurons, with exacerbation by amyloid-beta. *Nat Neurosci* **2013**, *16*, 613-621, doi:10.1038/nn.3356.
59. Pollina, E.A.; Gilliam, D.T.; Landau, A.T.; Lin, C.; Pajarillo, N.; Davis, C.P.; Harmin, D.A.; Yap, E.L.; Vogel, I.R.; Griffith, E.C.; et al. A NPAS4-NuA4 complex couples synaptic activity to DNA repair. *Nature* **2023**, *614*, 732-741, doi:10.1038/s41586-023-05711-7.
60. Zhang, S.J.; Zou, M.; Lu, L.; Lau, D.; Ditzel, D.A.; Delucinge-Vivier, C.; Aso, Y.; Descombes, P.; Bading, H. Nuclear calcium signaling controls expression of a large gene pool: identification of a gene program for acquired neuroprotection induced by synaptic activity. *PLoS Genet* **2009**, *5*, e1000604, doi:10.1371/journal.pgen.1000604.
61. Delint-Ramirez, I.; Konada, L.; Heady, L.; Rueda, R.; Jacome, A.S.V.; Marlin, E.; Marchioni, C.; Segev, A.; Kritskiy, O.; Yamakawa, S.; et al. Calcineurin dephosphorylates topoisomerase IIbeta and regulates the formation of neuronal-activity-induced DNA breaks. *Mol Cell* **2022**, *82*, 3794-3809 e3798, doi:10.1016/j.molcel.2022.09.012.
62. Lissek, T.; Andrianarivelo, A.; Saint-Jour, E.; Allichon, M.C.; Bauersachs, H.G.; Nassar, M.; Piette, C.; Pruunsild, P.; Tan, Y.W.; Forget, B.; et al. Npas4 regulates medium spiny neuron physiology and gates cocaine-induced hyperlocomotion. *EMBO Rep* **2021**, *22*, e51882, doi:10.15252/embr.202051882.
63. Tao, L.; Xie, Q.; Ding, Y.H.; Li, S.T.; Peng, S.; Zhang, Y.P.; Tan, D.; Yuan, Z.; Dong, M.Q. CAMKII and calcineurin regulate the lifespan of Caenorhabditis elegans through the FOXO transcription factor DAF-16. *Elife* **2013**, *2*, e00518, doi:10.7554/eLife.00518.
64. Bujarrabal-Dueso, A.; Sendtner, G.; Meyer, D.H.; Chatzinikolaou, G.; Stratigi, K.; Garinis, G.A.; Schumacher, B. The DREAM complex functions as conserved master regulator of somatic DNA-repair capacities. *Nat Struct Mol Biol* **2023**, *30*, 475-488, doi:10.1038/s41594-023-00942-8.
65. Mellstrom, B.; Sahun, I.; Ruiz-Nuno, A.; Murtra, P.; Gomez-Villafuertes, R.; Savignac, M.; Oliveros, J.C.; Gonzalez, P.; Kastanauskaite, A.; Knafo, S.; et al. DREAM controls the on/off switch of specific activity-dependent transcription pathways. *Mol Cell Biol* **2014**, *34*, 877-887, doi:10.1128/MCB.00360-13.
66. Fontan-Lozano, A.; Romero-Granados, R.; del-Pozo-Martin, Y.; Suarez-Pereira, I.; Delgado-Garcia, J.M.; Penninger, J.M.; Carrion, A.M. Lack of DREAM protein enhances

learning and memory and slows brain aging. *Curr Biol* **2009**, *19*, 54-60, doi:10.1016/j.cub.2008.11.056.
67. Lautrup, S.; Myrup Holst, C.; Yde, A.; Asmussen, S.; Thinggaard, V.; Larsen, K.; Laursen, L.S.; Richner, M.; Vaegter, C.B.; Prieto, G.A.; et al. The role of aging and brain-derived neurotrophic factor signaling in expression of base excision repair genes in the human brain. *Aging Cell* **2023**, e13905, doi:10.1111/acel.13905.
68. Lodato, M.A.; Rodin, R.E.; Bohrson, C.L.; Coulter, M.E.; Barton, A.R.; Kwon, M.; Sherman, M.A.; Vitzthum, C.M.; Luquette, L.J.; Yandava, C.N.; et al. Aging and neurodegeneration are associated with increased mutations in single human neurons. *Science* **2018**, *359*, 555-559, doi:10.1126/science.aao4426.
69. Lu, T.; Pan, Y.; Kao, S.Y.; Li, C.; Kohane, I.; Chan, J.; Yankner, B.A. Gene regulation and DNA damage in the ageing human brain. *Nature* **2004**, *429*, 883-891, doi:10.1038/nature02661.
70. Plath, N.; Ohana, O.; Dammermann, B.; Errington, M.L.; Schmitz, D.; Gross, C.; Mao, X.; Engelsberg, A.; Mahlke, C.; Welzl, H.; et al. Arc/Arg3.1 is essential for the consolidation of synaptic plasticity and memories. *Neuron* **2006**, *52*, 437-444, doi:10.1016/j.neuron.2006.08.024.
71. Wu, J.; Petralia, R.S.; Kurushima, H.; Patel, H.; Jung, M.Y.; Volk, L.; Chowdhury, S.; Shepherd, J.D.; Dehoff, M.; Li, Y.; et al. Arc/Arg3.1 regulates an endosomal pathway essential for activity-dependent beta-amyloid generation. *Cell* **2011**, *147*, 615-628, doi:10.1016/j.cell.2011.09.036.
72. Purvis, J.E.; Lahav, G. Encoding and decoding cellular information through signaling dynamics. *Cell* **2013**, *152*, 945-956, doi:10.1016/j.cell.2013.02.005.
73. Weigert, C.; Hennige, A.M.; Brodbeck, K.; Haring, H.U.; Schleicher, E.D. Interleukin-6 acts as insulin sensitizer on glycogen synthesis in human skeletal muscle cells by phosphorylation of Ser473 of Akt. *Am J Physiol Endocrinol Metab* **2005**, *289*, E251-257, doi:10.1152/ajpendo.00448.2004.
74. Xing, Z.; Gauldie, J.; Cox, G.; Baumann, H.; Jordana, M.; Lei, X.F.; Achong, M.K. IL-6 is an antiinflammatory cytokine required for controlling local or systemic acute inflammatory responses. *J Clin Invest* **1998**, *101*, 311-320, doi:10.1172/JCI1368.
75. Kumari, N.; Dwarakanath, B.S.; Das, A.; Bhatt, A.N. Role of interleukin-6 in cancer progression and therapeutic resistance. *Tumour Biol* **2016**, *37*, 11553-11572, doi:10.1007/s13277-016-5098-7.
76. Steensberg, A.; van Hall, G.; Osada, T.; Sacchetti, M.; Saltin, B.; Klarlund Pedersen, B. Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. *J Physiol* **2000**, *529 Pt 1*, 237-242, doi:10.1111/j.1469-7793.2000.00237.x.
77. Ostrowski, K.; Schjerling, P.; Pedersen, B.K. Physical activity and plasma interleukin-6 in humans--effect of intensity of exercise. *Eur J Appl Physiol* **2000**, *83*, 512-515, doi:10.1007/s004210000312.
78. Sacheck, J.M.; Cannon, J.G.; Hamada, K.; Vannier, E.; Blumberg, J.B.; Roubenoff, R. Age-related loss of associations between acute exercise-induced IL-6 and oxidative stress. *Am J Physiol Endocrinol Metab* **2006**, *291*, E340-349, doi:10.1152/ajpendo.00052.2005.
79. Hamada, K.; Vannier, E.; Sacheck, J.M.; Witsell, A.L.; Roubenoff, R. Senescence of human skeletal muscle impairs the local inflammatory cytokine response to acute eccentric exercise. *FASEB J* **2005**, *19*, 264-266, doi:10.1096/fj.03-1286fje.
80. Zheng, G.; Qiu, P.; Xia, R.; Lin, H.; Ye, B.; Tao, J.; Chen, L. Effect of Aerobic Exercise on Inflammatory Markers in Healthy Middle-Aged and Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Front Aging Neurosci* **2019**, *11*, 98, doi:10.3389/fnagi.2019.00098.
81. Hamer, M.; Sabia, S.; Batty, G.D.; Shipley, M.J.; Tabak, A.G.; Singh-Manoux, A.; Kivimaki, M. Physical activity and inflammatory markers over 10 years: follow-up in men and women

from the Whitehall II cohort study. *Circulation* **2012**, *126*, 928-933, doi:10.1161/CIRCULATIONAHA.112.103879.
82. Myrum, C.; Kittleson, J.; De, S.; Fletcher, B.R.; Castellano, J.; Kundu, G.; Becker, K.G.; Rapp, P.R. Survey of the Arc Epigenetic Landscape in Normal Cognitive Aging. *Mol Neurobiol* **2020**, *57*, 2727-2740, doi:10.1007/s12035-020-01915-4.
83. Rienecker, K.D.A.; Poston, R.G.; Segales, J.S.; Finholm, I.W.; Sono, M.H.; Munteanu, S.J.; Ghaninejad-Esfahani, M.; Rejepova, A.; Tejeda-Garibay, S.; Wickman, K.; et al. Mild membrane depolarization in neurons induces immediate early gene transcription and acutely subdues responses to a successive stimulus. *J Biol Chem* **2022**, *298*, 102278, doi:10.1016/j.jbc.2022.102278.
84. Lissek, T. Activity-Dependent Induction of Younger Biological Phenotypes. *Adv Biol (Weinh)* **2022**, *6*, e2200119, doi:10.1002/adbi.202200119.
85. Lissek, T. The Universal Role of Adaptive Transcription in Health and Disease. *OSF Preprints* **2022**, doi:10.31219/osf.io/yxqpe.
86. Marshall, C.J. Specificity of receptor tyrosine kinase signaling: transient versus sustained extracellular signal-regulated kinase activation. *Cell* **1995**, *80*, 179-185, doi:10.1016/0092-8674(95)90401-8.
87. Williams, G.C. Pleiotropy, Natural Selection, and the Evolution of Senescence. *Evolution* **1957**, *11*, 398-411, doi:10.1111/j.1558-5646.1957.tb02911.x.
88. Florea, M. Aging and immortality in unicellular species. *Mech Ageing Dev* **2017**, *167*, 5-15, doi:10.1016/j.mad.2017.08.006.
89. Steiner, U.K. Senescence in Bacteria and Its Underlying Mechanisms. *Front Cell Dev Biol* **2021**, *9*, 668915, doi:10.3389/fcell.2021.668915.
90. Buschler, A.; Manahan-Vaughan, D. Brief environmental enrichment elicits metaplasticity of hippocampal synaptic potentiation in vivo. *Front Behav Neurosci* **2012**, *6*, 85, doi:10.3389/fnbeh.2012.00085.
91. Chatzi, C.; Zhang, Y.; Hendricks, W.D.; Chen, Y.; Schnell, E.; Goodman, R.H.; Westbrook, G.L. Exercise-induced enhancement of synaptic function triggered by the inverse BAR protein, Mtss1L. *Elife* **2019**, *8*, doi:10.7554/eLife.45920.
92. Gundersen, K. Muscle memory and a new cellular model for muscle atrophy and hypertrophy. *J Exp Biol* **2016**, *219*, 235-242, doi:10.1242/jeb.124495.
93. McTiernan, A.; Friedenreich, C.M.; Katzmarzyk, P.T.; Powell, K.E.; Macko, R.; Buchner, D.; Pescatello, L.S.; Bloodgood, B.; Tennant, B.; Vaux-Bjerke, A.; et al. Physical Activity in Cancer Prevention and Survival: A Systematic Review. *Med Sci Sports Exerc* **2019**, *51*, 1252-1261, doi:10.1249/MSS.0000000000001937.
94. Oliveira, A.M.; Hemstedt, T.J.; Bading, H. Rescue of aging-associated decline in Dnmt3a2 expression restores cognitive abilities. *Nat Neurosci* **2012**, *15*, 1111-1113, doi:10.1038/nn.3151.
95. Fukushima, H.; Maeda, R.; Suzuki, R.; Suzuki, A.; Nomoto, M.; Toyoda, H.; Wu, L.J.; Xu, H.; Zhao, M.G.; Ueda, K.; et al. Upregulation of calcium/calmodulin-dependent protein kinase IV improves memory formation and rescues memory loss with aging. *J Neurosci* **2008**, *28*, 9910-9919, doi:10.1523/JNEUROSCI.2625-08.2008.
96. Vecsey, C.G.; Hawk, J.D.; Lattal, K.M.; Stein, J.M.; Fabian, S.A.; Attner, M.A.; Cabrera, S.M.; McDonough, C.B.; Brindle, P.K.; Abel, T.; et al. Histone deacetylase inhibitors enhance memory and synaptic plasticity via CREB:CBP-dependent transcriptional activation. *J Neurosci* **2007**, *27*, 6128-6140, doi:10.1523/JNEUROSCI.0296-07.2007.
97. Bach, M.E.; Barad, M.; Son, H.; Zhuo, M.; Lu, Y.F.; Shih, R.; Mansuy, I.; Hawkins, R.D.; Kandel, E.R. Age-related defects in spatial memory are correlated with defects in the late phase of hippocampal long-term potentiation in vitro and are attenuated by drugs that enhance the cAMP signaling pathway. *Proc Natl Acad Sci U S A* **1999**, *96*, 5280-5285, doi:10.1073/pnas.96.9.5280.

98. Hummler, E.; Cole, T.J.; Blendy, J.A.; Ganss, R.; Aguzzi, A.; Schmid, W.; Beermann, F.; Schutz, G. Targeted mutation of the CREB gene: compensation within the CREB/ATF family of transcription factors. *Proc Natl Acad Sci U S A* **1994**, *91*, 5647-5651, doi:10.1073/pnas.91.12.5647.
99. Rastogi, R.; Jiang, Z.; Ahmad, N.; Rosati, R.; Liu, Y.; Beuret, L.; Monks, R.; Charron, J.; Birnbaum, M.J.; Samavati, L. Rapamycin induces mitogen-activated protein (MAP) kinase phosphatase-1 (MKP-1) expression through activation of protein kinase B and mitogen-activated protein kinase kinase pathways. *J Biol Chem* **2013**, *288*, 33966-33977, doi:10.1074/jbc.M113.492702.
100. Brash, D.E. Rethinking Causation for Data-intensive Biology: Constraints, Cancellations, and Quantized Organisms. *BioEssays* **2020**, *42*, doi:10.1002/bies.201900135.

Figures and figure legends

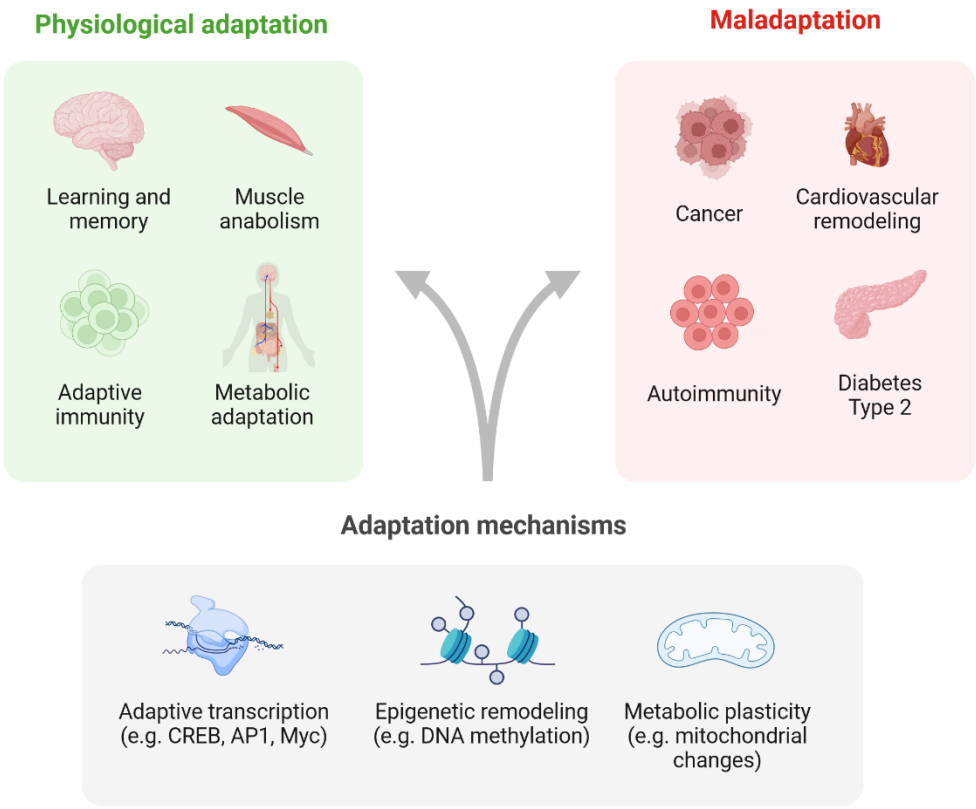

Figure 1. Biological adaptation mechanisms simultaneously implement physiological adaptation and pathological maladaptation ("the adaptation-maladaptation dilemma"). The body's adaptation mechanisms, such as adaptive transcription, stimulus-dependent epigenetic remodeling and metabolic plasticity, simultaneously implement beneficial adaptive functions (e.g. learning and memory, muscle anabolism, adaptive immunity) as well as maladaptive phenotypes (e.g. cancer, autoimmunity, type 2 diabetes). This duality delineates the adaptation-maladaptation dilemma and presents the organism with a fundamental problem: enable high activity of adaptation cascades and increase fitness but also shorten lifespan due to diseases such as cancer or decrease adaptive fitness but also decrease maladaptive disease risk and increase lifespan.

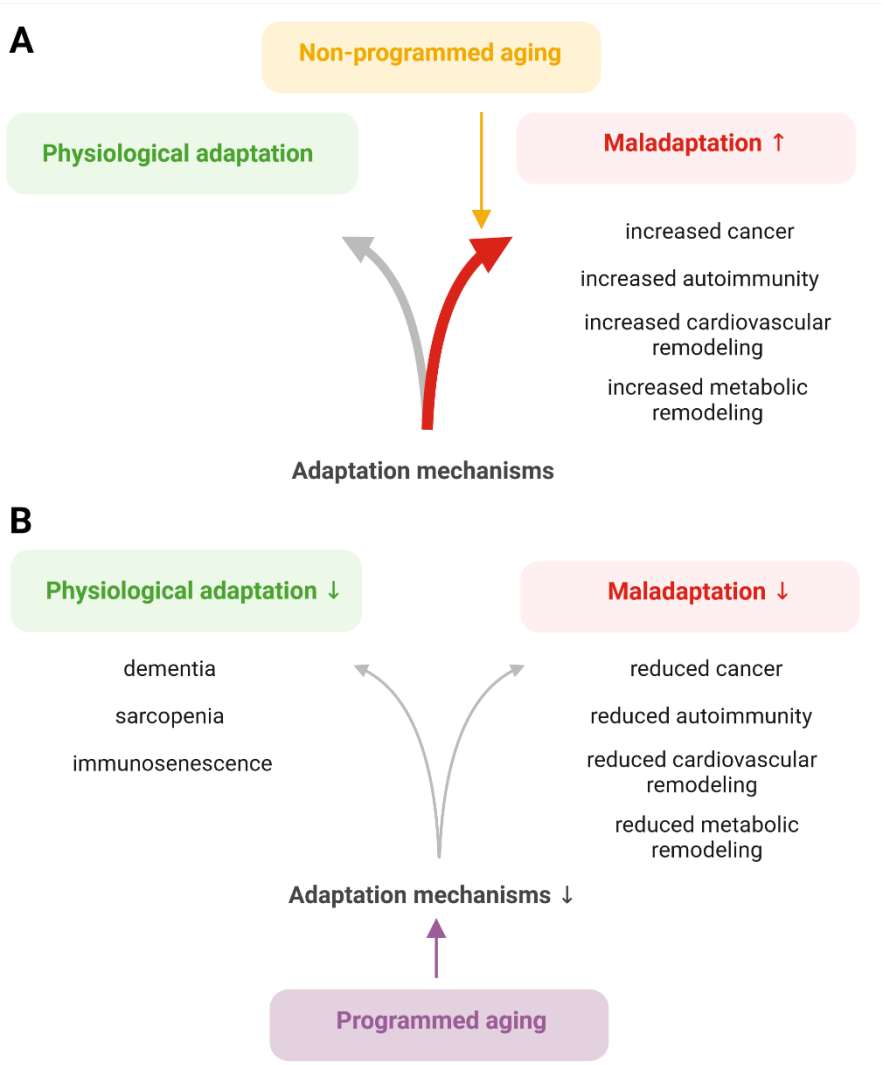

Figure 2. Aging as a two-component process with increasing maladaptation necessitating an aging program to decrease adaptative function. **A**, Increasing maladaptation over time leads to increased incidence of hyperadaptive age-related disorders (e.g. cancer, autoimmunity, atherosclerosis, type 2 diabetes) and constitutes the non-programmed component of aging. **B**, In order to counteract maladaptation the body might implement an aging program (e.g. through genomic methylation) which decreases adaptation mechanisms in a body-wide manner. This causes a reduction in maladaptation at the cost of also reducing many physiological adaptation phenotypes and leads to hypoadaptive symptom complexes such as dementia, sarcopenia and immunosenescence.

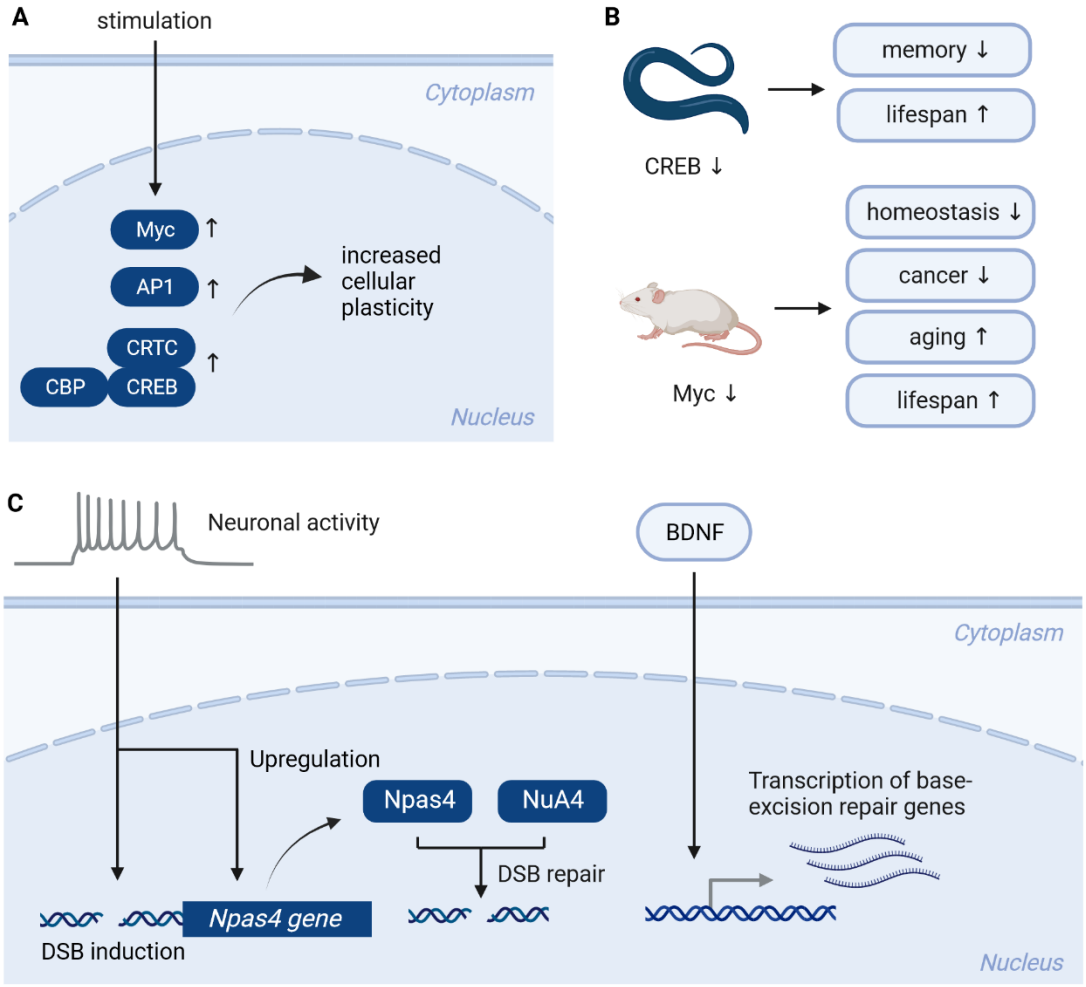

Figure 3. Molecular mechanisms in the adaptation-maladaptation dilemma of aging. **A**. At the cellular level, inducible transcription programs involving transcription factors such as CREB, AP1 and Myc couple stimulation to cellular plasticity in both adaptive processes (e.g. learning and memory) and maladaptive ones (e.g. cancer). **B,** Top: Reducing CREB in C. elegans leads to reduction of memory (a major hallmark of aging) but an increase in lifespan. Bottom: Reduction of the adaptive transcription factor Myc in mice leads to reduced homeostasis and accelerated aging but also to decreased cancer incidence and an increased lifespan. **C**, Inducible DNA damage and repair as an example of the adaptation-maladaptation dilemma. Neuronal activity induces Npas4, a neuroprotective gene important for neural plasticity, via DNA double strand breaks (DSBs). Npas4 in turn complexes with NuA4 to repair DSBs. Similarly, BDNF induces base-excision repair genes in neurons. The induction of beneficial adaptation mechanism

is hence coupled to directed DNA damage and its repair. Hypothetically, a dysbalancing in these adaptive damage-repair loops could lead to an overtaking of maladaptive genomic damage and aging-related dysfunction.

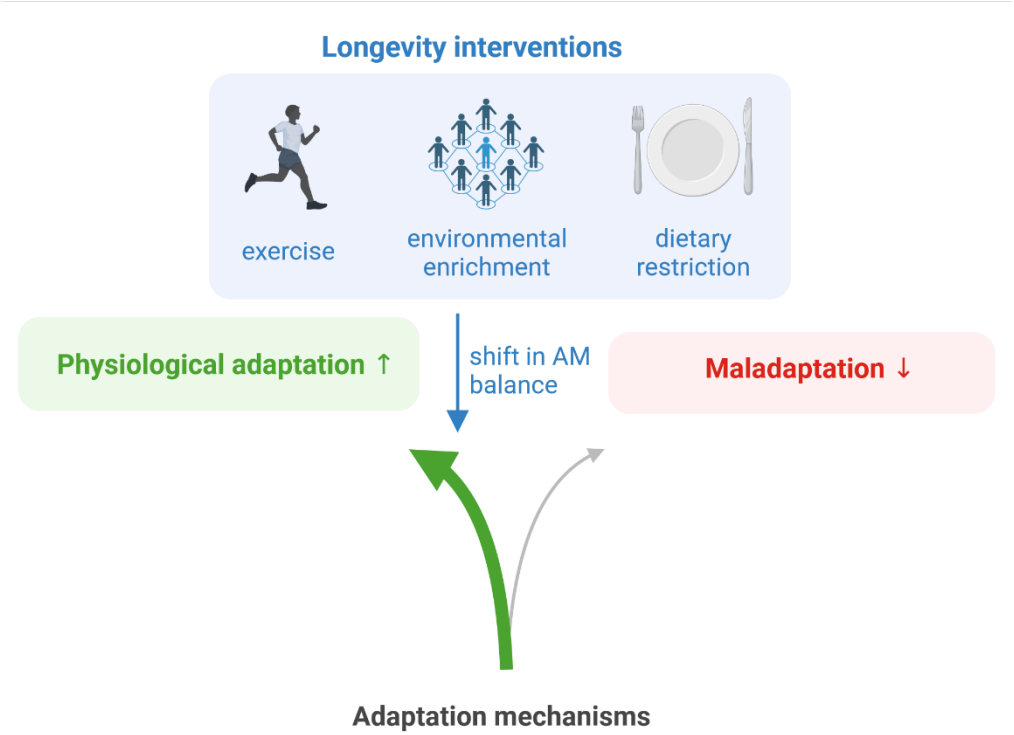

Figure 4. Longevity interventions induce a shift in the adaptation-maladaptation balance. Longevity interventions such as exercise, environmental enrichment and dietary restriction boost physiological adaptation capacities (e.g. learning and memory) while simultaneously decreasing maladaptation (e.g. reduced cancer incidence). Novel therapeutic approaches in pharmacology and gene therapy for aging could study and mimic this central phenotype.