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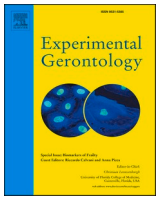

Review

Programmed versus non-programmed evolution of aging. What is the evidence?

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ABSTRACT

The evolutionary meaning and basic molecular mechanisms involved in the determination of longevity remain an unresolved problem. Currently, different theories are on offer in response to these biological traits and to explain the enormous range of longevities observed in the animal kingdom. These theories may be grouped into those that defend non-programmed aging (non-PA) and those that propose the existence of programmed aging (PA). In the present article we examine many observational and experimental data from both the field and from the laboratory and sound reasoning accumulated in recent decades both compatible and not with PA and non-PA evolutionary theories of aging. These analyses are briefly summarized and discussed. Our conclusion is that most of the data favour programmed aging with a possible contribution of non-PA antagonist pleiotropy in various cases.

1. Introduction

The programmed (PA) or non-programmed (non-PA) nature of aging is currently the subject of debate (Longo et al., 2005; Goldsmith, 2014, 2019; Jones et al., 2014; Lohr et al., 2019; Mitteldorf, 2019; Podlutsky, 2019; Cohen et al., 2020). Non-PA theories, mainly represented by the 'mutation accumulation theory' (Medawar, 1952), the 'antagonist pleiotropy theory' (Williams, 1957), and the 'disposable soma (DS) theory' (Kirkwood, 1977), consider aging as a random side effect without a specific biological function. In contrast, PA theories are supported by the observation that diverse species can have hugely different species-specific longevities—up to one million-fold difference—and the discovery of >40 different mouse longevity-modifying genes, usually organized in signalling pathways (Folgueras et al., 2018). These facts mean that longevity is necessarily written in the genome of each species and likely constitutes an adaptation. Giacinto Libertini (1988) and Vladimir Skulachev (1997) were the first to propose PA, focusing on telomere shortening as the aging physiological mechanism in the former case, and on mitochondria and reactive oxygen species (ROS) in the latter. Other PA-proponents focused on group selection (Longo et al., 2005; Barja, 2010, Mitteldorf, 2016a; Trubitsyn, 2020). Many biogerontology-related facts discovered during the past few decades, coming from both the laboratory and from field studies, increasingly support the notion that aging is controlled by a genetic program that unfolds after reaching adult maturity and is an adaptive feature at the group or higher level (Barja et al., 1994; Barja, 2010; Skulachev, 1997; Bowles, 1998; Guarente and Kenyon, 2000; Kenyon, 2001; Bredesen, 2004; Longo et al., 2005; Goldsmith, 2014; Jones et al., 2014; Mitteldorf, 2016a). Intermediate positions between proponents of PA and non-PA aging have also appeared (de Magalhães, 2012; Blagosklonny, 2013; Lenart and Bienertová-Vašků, 2017; Flatt and Partridge, 2018).

In the present work, we support the PA theory for many reasons (see later), the most important being the more than five orders of magnitude difference in longevity among animal species (200-fold among mammals). An internal genetic aging program determining the mean aging rate of each animal species should exist, because longevity is a species-specific trait. However, that aging program is not isolated from the outside since it also reacts to environmental clues like dietary restriction (DR), lowering the aging rate of the affected individual (Barja, 2019). Together with the afferent sensing signals arriving from the cytoplasm,

Abbreviations: BER, base excision repair; DBI, double-bond index of membrane fatty acids; DR, dietary restriction; DRs, dietary restrictions in general (dietary, protein, and methionine restriction); DS, disposable soma evolutionary theory of aging; ETC, electron transport chain; MFRTA, mitochondrial free radical theory of aging; mitROSp, rate of mitochondrial ROS production; PA, programmed aging; ROS, reactive oxygen species.

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the extracellular medium, and the environment, the aging program and its efferent effectors (the executors of aging) constitute the cell aging regulation system (CARS; Barja, 2019). This system is consistent with the determination of longevity by transcription factors in multiple tissues of different species (Dobson et al., 2019; Fischer et al., 2022). The aging effectors, corresponding to the previous mechanistic "theories" of aging, do not work separately from each other. They work together to produce a particular aging rate as the CARS (aging program) output. Detailed discussion of intracellular aging program functioning and the proposal that those mechanistic "theories of aging" (telomere shortening, mitochondrial free radical production, autophagy, apoptosis, inflammaging, etc.) could be fused into a "unified theory of aging" has been published (Barja, 2019) and will not be detailed here again.

In the present article, many observational and experimental data and reasons accumulated in recent decades supporting, or not, PA and non-PA evolutionary theories of aging are briefly summarized and discussed.

2. Mutation accumulation and antagonist pleiotropy theories. Can they explain aging?

Many relevant facts are inconsistent with non-PA wear-and-tear evolutionary theories of aging. A major one concerns the oft-quoted prediction of a strong decline in the force of natural selection with age, hypothetically assuming that old animals would hardly ever be observed in the wild (Medawar, 1952; Williams, 1957). In defiance of that prediction, it is currently known that in many species old animals do exist in the wild in very substantial numbers (Promislow, 1991; Ricklefs, 1998; Bonduriansky and Brassil, 2002; Moorad and Promislow, 2010, Nussey et al., 2013). This diminishes the plausibility of the mutation accumulation as well as the antagonist pleiotropy hypothesis, because these postulate that aging is due to the decline in the force of natural selection with age in the wild. The field data indicate that aging can indeed contribute to death in the wild and this can have evolutionary implications. Senescence is commonly detected in nature (Nussey et al., 2013) and in many species a significant number of animals reach old age in the wild (Mitteldorf, 2016a). Medawar's assumption also predicts that genes expressed early in life should be under increased selective constraint compared to genes expressed late in life. However, a recent study in different tissues of 948 human individuals found that while the force of purifying selection is stronger on genes expressed early versus late in life (Medawar's hypothesis), several highly proliferative tissues exhibit the opposite pattern (Yamamoto et al., 2022). It is unknown what is the situation concerning this in species with different longevities, and it has been described that DR, that increases longevity, does not decrease the number of point mutations in *D. melanogaster* flies and mice (Edman et al., 2009; Newell and Heddle, 2002).

In the case of the antagonist pleiotropy theory, there is a further difficulty because the theory is based on the assumption of a theoretical decrease in the force of natural selection with age in the wild as well as on the hypothesis that some genes could have antagonist pleiotropic effects. These genes would increase fitness in the young but would decrease it in old age (Williams, 1957). This theory is more attractive than the earlier mutation accumulation one (Medawar, 1952) because pleiotropic effects in general of various genes are known, although it is not known whether this is related to the aging process. It is currently known that many genes influence two or more phenotypic traits. Genome-wide association studies at the turn of the century surprisingly showed that for typical traits, even the most important genomic loci have small effects explaining a modest fraction of the genetic variance. This has been labelled the mystery of the "missing heritability" (Manolio et al., 2009). Most of that "missing heritability" has been explained mainly by single nucleotide polymorphisms with effects well below genome-wide statistical significance (Yang et al., 2010). Many genes work cooperatively in dozens or hundreds of tangled networks among gene products including epistatic and pleiotropic effects and feed-back loops from protein products to their codifying or related genes. The increase in longevity in response to DR is a good example of this. Therefore, pleiotropy is not unusual. It is rather the rule. One reason for this is the strongly limited gene number—around 20,000 to 25,000 in humans—compared to the much larger number of needed proteins including the hugely variable ones like immunoglobulins and olfactory receptor molecules. Varying the gene expression of hundreds of genes is required just to produce a single phenotype, the increased longevity in response to DR. Producing all the highly varied phenotypic traits of one organism with such luxury in gene numbers per trait would demand millions of genes, which would be impossible to reach with the limited number of structural genes, a small percentage of genome size. Instead, organizing the genes to work together strongly interrelatedly, which involves their pleiotropic action in many different functions, liberates most of cellular DNA for functions other than codifying the body proteins. For instance, transposable elements account for 25–40 % of genomic mammalian DNA (Griffiths et al., 1999; Hayward and Gilbert, 2022), whereas only about 1 % of human genomic DNA is made up of protein-coding genes. It is increasingly thought that most genomic DNA does not represent selfish garbage DNA (ENCODE, www.encodeproject.org). Rather, at least part of the non-coding DNA is present in the nucleus, likely to control gene expression and development, as well as to help promote biological evolution and increase the evolvability of the species (Zrimec et al., 2020; Colonna Romano and Fanti, 2022).

The widespread presence of pleiotropy does mean, however, that aging is necessarily due to antagonist pleiotropic effects of single genes. Aging, like many other traits, can result from the coordinated action of hundreds of genes working in complex networks although likely showing a hierarchy from "master" to "target" genes (Barja, 2008), rather than the product of many single genes with pleiotropic action (Williams, 1957). Furthermore, among the approximately one hundred already known single-gene mutations that increase animal longevity (Folgueras et al., 2018), half of them do not have other known functions apart from modifying longevity (Mitteldorf, 2016a). Among those having this function, the best-described ones are the genes involved in the insulin/IGF-1-like signalling pathway. This pathway is used in vertebrates for important functions like the regulation of blood glucose by insulin, and to stimulate growth of the organism through cell division promoted by hormones like IGF-1 and GH. But the insulin/IGF-1-like signalling pathway is also used to modify longevity. In mice, mutations at any point in this pathway, from the hypothalamic-pituitary system to the blood, and then to the cytoplasm of the targeted cells, modify organism longevity. They include the mouse longevity mutants Ames dwarf (Prop 1df/df), Snell dwarf (Pou1f1dw/dw), Ghrh−/−, Ghrhrli/li, Ghr−/−, Pappa−/−, Insrflox/flox, Irs1−/−, Irs2flox/flox, Pik3caD933A/−, Tg-pten, Akt1+/−, Mtorδ/δ, Mtor+/−/Mist8+/−, and Rps6kb1−/− (Brown-Borg et al., 1996; Folgueras et al., 2018). But such longevity-modifying genes are not exclusive to mammals. They are present in animals with different levels in the evolution of complexity, including yeast, worms like *C. elegans*, insects like *Drosophila*, and mammals like mice. Therefore, such aging affecting genes are highly conserved and very old in biological evolution, and they were already present even before the evolution of metazoans (Clark, 2004; Mirisola and Longo, 2022). This suggests their adaptive character as products of natural selection. Importantly, the presence in unicellular protists of insulin/IGF-1-like signalling genes shows that their aging function is much older than the other ones, because obviously yeast does not have pancreas (nor blood or hormones). Nor can these genes use mitosis in protists to grow multicellular and larger either. Therefore, even in cases like this in which an antagonist pleiotropic effect is known, aging on one side, and glucose regulation or multicellular body growth on the other, the ancestral biological function of the genes seems to be regulation of aging. Only when multicellular animals appeared were those genes with aging effects co-opted by natural selection to regulate blood glucose and body growth as additional functions–exactly the reverse of the prediction of antagonist pleiotropy of aging. Thus, even in some cases of pleiotropy including aging effects, these can represent a biological

function related to aging regulation rather than a side-effect. All these arguments, plus many others succinctly offered in Tables 1 and 2 (see later), indicate that antagonist pleiotropy and the other non-PA theories cannot explain aging. Some of them at best perhaps explain a modest part of it. Instead, most aging may be explained by the existence of an aging program that runs at widely different speeds in different animal species (PA evolutionary theory).

Finally, although non-PA evolutionary theories of aging predict that evolution should inevitably lead to increased mortality and declining fertility with age after maturity, a study in 46 different species found that there is great variation in the wild, including increasing, constant, decreasing, humped, and bowed trajectories for both long- and short-lived species (Jones et al., 2014; Jones and Vaupel, 2017). This is very difficult to explain by non-PA wear-and-tear evolutionary theory but fits well with the concept that aging is differently programmed in different species.

3. Is the disposable soma hypothesis consistent with the available evidence?

The third non-PA theory, the DS theory (Kirkwood, 1977), is based on dividing total body energy into just two parts, that used for maintenance (defense plus repair) and that other used for reproduction. But there is a most important difficulty with this idea. The strong increase in weight-specific metabolic rate as both body size and, usually, longevity decrease across species within each animal group (e.g., mammals) is exactly the opposite of what the theory predicts. Animals of small body size process very large amounts of energy per gram, but despite this have very short lives, instead of very long ones (as predicted by the theory). Therefore, aging cannot be the result of a shortage of energy available for defense plus repair as the theory postulates. In addition, many mammalian females expend huge amounts of energy during reproduction compared to males (e.g., men spend around 0.2 % of their 24-hour metabolic rate during sexual intercourse) mostly due to the long periods of pregnancy, lactation, and offspring care performed exclusively by the female, especially in those first two periods. However, mammalian females do not live less than their sexual companions due to such high involvement of energy in reproduction as predicted by the theory (Barja, 2008). On the contrary, women outlive men by around 7 % in almost every country worldwide, and this is also true for rodents and other species (Lemaître et al., 2020). Moreover, DR increases longevity (Pamplona and Barja, 2006) while DS theory predicts the contrary due to the strong decrease in energy intake during DR that would leave less energy available for defense plus repair according to the DS theory. These problems make it unlikely that aging could be due to a lack of energy for maintenance (defense plus repair) as predicted by DS theory. Other additional questions concerning DS are discussed at length in (Mitteldorf, 2016a).

The higher behavioral activity and immune function of DR animals compared to ad libitum (AL) fed ones, despite their lower energy intake, is the opposite of what DS predicts: that a larger part of the energy corresponding to those functions should be saved during DR to be invested in reproduction, leading to decreased longevity. AL feeding, compared to DR, decreases animal longevity although in AL energy availability is greater than in DR. Furthermore, why isn't the high lifespan phenotype (expressed in DR but not in AL) expressed in the AL-fed animal? The animal has the ability to increase its longevity but does not use it when in AL. Many authors believe that the DR response is an

Table 1
Facts supporting or compatible or not with PA and non-PA evolutionary theory.

Fact[Refs.]	PA	Non-PA
Around 10^5 fold variation in species longevity[1]	S	I
Old animals are present in the wild at significant levels[2–4]	S	Non-S
Strongly varied trajectory of fertility and mortality in the wild[5,6]	S	I
>100 highly conserved single gene mutations modify longevity (aging is very old)[4,7–8]	S	Non-S
Pro-aging effects of longevity mutations are frequent[4,9]	C	Non-S
IGF-1/insulin-like path already present in yeast[4,10]	S	I with APL
Epigenetic modulation of longevity[a,11–13]	S	I
Low rate of telomere shortening in long-lived species[b,14]	S	I
Higher weight-specific metabolic rate in short-lived species of small body size	C	I with DS
Low mitROS production, % FRL, DBI, oxidative molecular damage and nuclear mtDNA fragments in long-lived species[c,15–18]	S	I
Similar or lower *total tissue* antioxidants or nDNA and protein repair in long-lived species[19–21]	S	I
Higher chaperone levels in long-lived species[22]	C	C

S, supportive; non-S, non-supportive; C, Compatible; I, Incompatible; MA, Mutation Accumulation theory; APL, Antagonist Pleiotropy theory; DS, Disposable Soma theory; % FRL (% free radical leak at mitochondrial ETC). References in the Table: 1-AnAge; 2-Ricklefs, 1998; 3-Nussey et al., 2013; 4-Mitteldorf, 2016a; 5-Jones et al., 2014; 6-Jones and Vaupel, 2017; 7- Brown-Borg et al., 1996; 8-Clark, 2004; 9-Folgueras et al., 2018; 10-Mirisola and Longo, 2022; 11-Mitteldorf, 2016b; 12-Horvath and Raj, 2018; 13-Horvath, 2021; 14-Whittemore et al., 2019; 15-Pamplona and Barja, 2007; 16-Hulbert et al., 2007; 17-Naudí et al., 2013; 18-Barja, 2019; 19-Pérez-Campo et al., 1998; 20-Page and Stuart, 2012; 21-Salway et al., 2011b; 22-Salway et al., 2011a.

[a] Increasing evidence although still not generally considered a demonstrated fact.

[b] A single study is available comparing both birds and mammals.

[c] Low mitROSp, %FRL and DBI also in species with exceptional longevity for their body size and metabolic rate like birds and bats.

Table 2
DR results supporting and compatible, or not, with PA and non-PA.

Fact	PA	Non-PA
DRs increase longevity in a coordinated and conserved manner, changing the expression of hundreds of genes[1,2]	S	Non-S
Lower energy intake and higher longevity in DR[3,4]	C	I with DS
Higher energy expenditure in reproduction and similar or greater longevity in females vs males	C	I with DS
Similar or greater longevity of multiparous women[5–7]	C	I with DS
Lack of published proposal of a plausible physiological mechanism by which high reproduction could decrease defense + repair	–	I with DS
DR induced changes in fertility and increases in longevity are separately regulated[8–14]	S	I with DS
DR also increases longevity in housing without mates[15–17]	S	I with DS
DR animals are more active, show higher immunity, and live longer[1–4; 18–21]	S	I with DS
Ad libitum feeding decreases animal longevity although energy availability is more abundant than in DR	S	I
DR increases longevity smoothly in proportion to the degree of food restriction.[4,21]	S	I with DS and APL
Lack of decrease in somatic mutations in DR have been described[22,23]	C	Non-S with MA and APL
Increases in autophagy occur and are needed for the expression of the life-extension effect of DR[24,25]	C	S
Similar or lower nDNA repair and lack of consistent changes in total tissue endogenous antioxidants in DR animals[1, 26–27]	C	I
Decreases in mitROS production, % FRL, and DBI in DR animals[28,29]	S	I

S, supportive; non-S, non-supportive; C, compatible; I, incompatible; MA, mutation accumulation theory; APL, antagonist pleiotropy theory; DS, disposable soma theory; DR, dietary restrictions (calorie, protein and methionine restriction); nDNA, nuclear genomic DNA. For references concerning specific facts see main text. References in the Table 1-Weindruch et al., 2001; 2-Park and Prolla, 2005; 3-Weindruch and Sohal, 1997; 4-Sohal and Weindruch, 1996; 5- Kuningas et al., 2011; 6-Blümel et al., 2022; 7-Grandi et al., 2023; 8-Roth and Polotsky, 2012; 9-Adler et al., 2013; 10-Mitteldorf, 2016a; 11-Schwartz et al., 2016; 12-Krittika and Yadav, 2019; 13-Zajitschek et al., 2019; 14-Isola et al., 2022; 15-Salmon et al., 1990; 16-Carey et al., 2005; 17-Burger et al., 2007; 18- McCarter et al., 1997; 19-Weed et al., 1997; 20-Ghimire and Kim, 2015; 21-Weindruch et al., 1986; 22-Edman et al., 2009; 23-Newell and Heddle, 2002; 24-Lapierre et al., 2015; 25-Lim et al., 2023; 26-Sohal et al., 1994; 27-Stuart et al., 2004; 28-Gredilla and Barja, 2005; 29-Pamplona and Barja, 2007.

adaptive overcompensation reaction in times of scarcity, leading to higher or maintained biological fitness. A longer life would increase the total chances of reproduction and biological fitness, also in the AL animal that is experiencing plenty of surplus energy available for both maintenance (defense plus repair) and fecundity. Why doesn't the AL animal take advantage of the surplus energy which the DS predicts? According to the selfish gene theory, animals should maximize individual fitness. But they do not do so when in AL. This paradoxical behavior can be explained by PA, which can generate benefits for the community at the expense of the individual. Shortening the duration of life through PA importantly contributes to avoiding overpopulation. In the absence of aging, strong increases in population size would increase the risk of local extinction in the ecosystem through epidemics or famines (Mitteldorf, 2016a). The programmed increase in longevity in DR (Barja, 2019) helps to compensate for the decrease in fertility during the restriction period due to energy limitations, by enhancing the chances of reproduction through a reprogrammed longer life-span while waiting for more optimum periods of food availability.

DS theory is rooted in a hypothetical lack of energy for defense plus repair that is also contradicted by basic animal physiology. A single reproductive effort in a human male representing around 0.2 % of his 24-hour metabolic rate does not lead to any significant decrease in blood glucose or tissue ATP, and repeated reproductive efforts do not cause them either, not only because such energy investment is so infimum, but also because these energy-related substances are quickly replenished as they are subjected to strong physiological and biochemical homeostatic regulation. Proponents of DS theory, however, have never detailed what physiological mechanism or change in blood metabolites could plausibly link their postulated investment of extra energy in reproduction with a hypothetical decrease in tissue defences and repair. The decrease in energy availability is simply postulated in abstract terms without detailing the possible physiological mechanisms and substrates involved in decreased tissue maintenance. Thus, DS is a "physiological" theory lacking any proposed physiological mechanism that could be responsible for it. It is difficult to imagine how an expenditure of 0.2 % of energy during sexual intercourse could limit tissue defense and repair, decrease blood glucose in the presence of the many hormones continuously and powerfully regulating it, or lead to decreases in ATP availability in the main organs other than testes and some skeletal muscles.

Over-focusing on "reproduction" as if it were the only criterion for evolution (selfish gene theory) can contribute to flawed views like DS. Fecundity and longevity frequently show an inverse relationship when comparing different species like mice and men. But this is not due to any physiological constraint. Indeed, multiparity in humans seems to be related to increases rather than decreases in the longevity of the mother. The reason for the inverse correlation between fecundity and longevity across species is genetic rather than physiologic. Longevity and fecundity are specific traits of each animal species, just like body size and shape, and are thus genetically determined. Most likely, the genes controlling fecundity as well as those controlling longevity are genetically linked together to ensure their inverse quantitative relationship observed in most animal groups. This is likely possible because fecundity- and longevity-determining genes are target genes of the same complex hierarchical network of genes making up the nuclear aging program (Barja, 2008, 2019).

4. Physiological mechanisms of aging. Their relation to evolutionary PA and non-PA theories

Non-PA theories postulate "defense plus repair" as the physiological mechanism of aging responsible for the widely varied longevities of the different animal species. Indeed, defense and repair are also genetically-determined species-specific traits. Therefore, strictly speaking, even if longevity were solely caused by levels of defense plus repair, aging would continue to be genetically (and epigenetically?) determined (programmed). Consequently, the only difference with PA would be that in non-PA only genetically determined anti-aging mechanisms would exist, whereas in PA both pro-aging and anti-aging genetically determined mechanisms would contribute to determining the aging rate.

Contrary to what was expected from non-PA theories, long-lived animals do not present higher levels of *total cell* defense and repair against endogenous damage. Only in the case of repair of damage of extrinsic origin, as in the case of unscheduled DNA synthesis following UV radiation of skin–mitotic-fibroblasts (reviewed in Cortopassi and Wang, 1996), is higher repair in long-lived animals observed. The reason for this is that an animal intrinsically aging slowly could not phenotypically express its higher longevity if the high UV external radiation killed it much earlier because it was not properly protected from such aggression. This is why long-lived species have higher skin repair of damage from extrinsic radiation. But that higher skin repair does not contribute to a decrease in the rate of intrinsic aging in its internal organs. The situation is the opposite concerning endogenous total cell defences plus repair.

Endogenous *total tissue* antioxidant systems and nuclear DNA base excision repair (BER) correlate negatively (or not), with longevity across species, meaning that there is less or similar defense and repair in most cell compartments of long-lived species, likely because decreasing the rate of generation of endogenous damage (less mitROSp), reducing cell membrane sensitivity to oxidation (e.g. less membrane fatty acid double bond index, DBI), and various other endogenous aging mechanisms are a strategy to increase longevity (review at Barja, 2002; Pamplona et al., 2002; Pamplona and Barja, 2007; Barja, 2013; Naudí et al., 2013; Barja, 2019). Since the aging-related damage endogenously produced is low in long-lived species, they do not need to expend huge amounts of energy in maintaining elevated levels of defense and repair enzymes in internal organs.

However, it seems that specific adaptations at the mitochondrial level to this general strategy of defense have been added in endogenous organs. Thus, the mitochondrial form of the superoxide dismutase antioxidant enzyme (MnSOD) activity and protein amount, while not the cytosolic form CuZnSOD, shows a positive correlation with longevity in mammalian tissues and fibroblasts (Brown and Stuart, 2007; Page et al., 2010). Furthermore, recent results show that the mitochondrial form of DNA base excision repair (mitBER), which repairs oxidative damage to mtDNA bases, also correlates positively with longevity (Gredilla et al., 2020), differing from nuclear BER which does not correlate or correlates negatively with it (Page and Stuart, 2012) and does not change or decreases in DR (Stuart et al., 2004). In line with this, the only antioxidant overexpressor mouse that has shown significantly increased maximum longevity was precisely the one in which the antioxidant enzyme overexpressed (catalase in this case) was located inside the mitochondrial compartment, while in the same investigation catalase overexpression inside the nucleus or the peroxisome did not change mouse longevity (Schriner et al., 2005). This observation, however, contrasts with other studies showing that the overexpression of MnSOD does not increase lifespan in mice (Jang et al., 2009). Therefore, more studies are needed to validate or refute this concept.

Globally, the evidence indicates that defense plus repair of the cell in endogenous organs is not the key to species longevity. At most cellular sites, including cytosol and the nucleus, contribution to longevity is achieved by alternative mechanisms including lowering the rate of generation of endogenous damage, or decreasing the sensitivity of cellular components to it (Pamplona and Barja, 2007). This eliminates the energetically costly and less efficient need to increase defense plus repair of endogenous damage in cells in general (Barja, 2013). In contrast, in the case of mitochondria, a decrease in damage generation (low mitROSp) seems to be used to contribute to the greater longevity of long-lived animals. This highlights again the particular relevance of mitochondrial ROS in aging (Pamplona and Barja, 2007; Barja, 2019), despite claims made to try to rule out the mitochondrial free radical theory of aging (Andziak and Buffenstein, 2006; Andziak et al., 2006; Buffenstein et al., 2008; Pérez et al., 2009).

5. Programmed aging

Animal species can differ by up to six orders of magnitude in longevity, indicating that aging is genetically programmed because it is a species-specific trait, just like body size or shape, and many other species-specific phenotypes. This fact constitutes the strongest evidence in favour of PA. Animals are energetically open systems that can locally decrease their entropy level at the expense of ingesting energy from their surrounding environment in the form of food. If it is advantageous to animals to avoid entropy-driven aging, they can do it by auto-organizing themselves, like when young or developing, using that source of external energy. The random damage remaining during aging can be repaired. It is currently known that such "perfect" repair is possible because some lower invertebrate species do not age at all, like the hydra, or do so at a very slow pace reaching at least 13,000 years in longevity. The large majority of animals, however, show aging at a species-specific very distinct and thus tightly-controlled rate. They show aging despite having the capacity to avoid it. This likely occurs because aging generates some biological benefit, if not to the individual, then to the group, the species, whole ecosystems, or life in general. Aging, like most physiological functions, is a regulated phenomenon. This genetic and physiological control of species longevity also explains why it is so difficult to modify it experimentally to a large extent. After one century scientists have succeeded in increasing the intra-species longevity of mammals by a maximum of 1.4-fold (with DR, or with single-gene mutants), which is very little compared to the up to 200-fold variation in longevity among different mammalian species. It is unreasonable to assume that random damage can lead to lifespans so different as 200-fold within mammals, and up to 10^5-one million-fold between different animal species, taking into account that the different animals are essentially constituted in most cases by very similar biological components (macromolecules).

The genetically-programmed character of aging fits well with one of the four Bernard Strehler rules of aging, the endogenous origin of aging (Strehler, 1962), which we might call the 'big effect' (Barja, 2019): the huge inter-species differences in longevity. Additionally, as previously noted, the longevity of individual animals of a given species has been successfully increased up to 1.4-fold in mammals, either in DR animals or in single-gene longevity mutants. This constitutes the 'small effect'. To defeat aging, manipulating the 'small effect' is not enough; the cause underlying the 'big effect' must be also unveiled. The 'small effect' is likely controlled by the same kind of program controlling the 'big effect', although in the case of the 'small effect' the output of the aging program must be less intense and/or should include a smaller number of aging effectors (Barja, 2019). Driven by this program, aging continues development and adult maturity, leading finally to old age and death.

In PA theory both endogenous ("biologically purposeful") production of damage (e.g., by controlling mitROSp) and opposing the damage through defences and repair contribute to the rate of aging typical of each species (Barja, 2002; Barja, 2013). Modulation of macromolecular composition-dependent sensitivity to damage, like the low DBI of membrane fatty acids (Pamplona et al., 2002; Hulbert et al., 2007; Naudí et al., 2013), the low methionine content in tissue proteins (Ruiz et al., 2005), and the high G-C content of mtDNA (Samuels, 2005) which protects lipids and proteins from oxidative modification or increases mtDNA structural stability in long-lived species, also contributes to this. Recently, it has also been found that it is the rate of telomere shortening, and not the telomere length, that correlates with mammalian longevity (Whittemore et al., 2019). That rate is lower, as in the case of mitROSp, in long-lived mammals and birds than in short-lived ones. All these mechanisms of aging correspond to endogenous factors produced and regulated by the organism. Consistent with this idea, the support mediated by metabolic and signalling pathways, as well as the adaptations at the genomic and transcriptomic levels in a longevity-specific way, must be also highlighted (López-Otín et al., 2016; Berry and Kaeberlein, 2021; Pamplona et al., 2021; Lu et al., 2022; Mota-Martorell et al., 2020a; Mota-Martorell et al., 2020b).

The adaptive character of aging (while not with non-PA theory) also fits well with the strong evolutionary conservation of the genes controlling longevity (e.g., insulin/IGF-1 signalling genes) across animal phyla from the simplest (unicellular) to the most complex multicellular animals. Aging is a very old adaptation (Clark, 2004), present already in unicellular protists like yeast (Mirisola and Longo, 2022), that has been selected for and maintained during hundreds of million years, at least from the time of the emergence of the eukaryotic cell through symbiogenesis, an essential evolutionary step for the subsequent emergence of multicellular animals. Cellular aging thus evolved into multicellular aging by coordinating the aging rates of the different cells systemically, a most relevant but poorly understood process.

Other mechanisms like autophagy, apoptosis, and inflammaging are also heavily involved in aging (Barja, 2019; Berry and Kaeberlein, 2021), although evidence for the appropriate correlation of these mechanisms with species longevity is still lacking and needs to be investigated. Globally, however, we do not know the specific weight of all these factors at the individual level or in an interactive way in determining the rate of aging, nor their potential to fully explain the up-to one-million-fold interspecies difference in longevity, or the up-to 200-fold difference observed in mammals.

Living things are biological systems that naturally developed and selected aging features at a species-specific rate as an evolutionarily adaptive trait at a level higher than the individual, overcompensating for its damaging detrimental effects at the individual level. Aging likely benefits ecological adaptation in the ecosystem (Barja, 2010; Mitteldorf, 2016a), shortens generation time, and, like sex, increases diversity, likely increasing evolvability (Mitteldorf and Martins, 2014). Group selection, strongly criticized from the 1960s to the 1980s mainly targeting Vero Copner Wynne-Edwards (Wynne-Edwards, 1962), has re-emerged as an important component of multilevel selection at the start of the 21st century (Werfel and Bar-Yam, 2004; Borrello, 2005; Eldakar and Wilson, 2008; Hermsen, 2022). Is the time ripe for considering the capacity of natural selection to act also at a level higher than the individual—as in the case of sex—as an evolutionary explanation for the widespread adoption of aging in most animals?

Inanimate objects (e.g., cars) slowly decay due to wear and tear. This cannot be the main cause of aging in animals since they can have hugely different rates of decay although they are essentially made up of similar macromolecules. Moreover, animal components are subjected to a continuous and fast turnover, not only replacing cells with new ones through cellular division, but also, importantly, constantly renewing small molecules, macromolecular components, and organelles inside cells, a critical fact overlooked by emphasis on cell replacement. This is perhaps due to the present emphasis on stem cells as a promising approach to future rejuvenation, and also to the erroneous belief that aging is solely due to a decrease in tissue cell division with age. On the contrary, the effects of aging are more marked in organs constituted by postmitotic tissue cells, as in the case of most neurons and skeletal and heart muscle cells. Many mouse proteins are replaced inside tissue cells within a few days, even if they are not damaged. The animal breaks them down to amino acids, to be used again to resynthesize proteins. If all the body parts, whole cells, and intracellular macromolecules of a mouse are constantly renewed, why doesn't it live for an indefinite amount of time in the absence of extrinsic mortality, rather than lasting a maximum of 4 years? This is a fundamental question. Considering the fast turnover of the mammalian components, "eternal youth" (absence of aging) should not be a rarity but rather a commonplace. However, the real situation is the opposite since most animal species show aging at a particular species-specific rate. In the face of fast turnover, the apparently strange thing that we must explain is why aging exists at all. The likely answer is that the animal endogenously generates its own aging rate because the group, the species, or the whole ecosystem derives a strong enough benefit from it, and that benefit out-weighs the decrease in individual fitness imposed by aging. If the absence of aging were evolutionarily advantageous, many animals could easily develop it thanks to the fast

and efficient turnover of animal components. Indeed, some examples of species showing no aging do seem to exist, although the majority of animals did not choose that strategy during their evolution. Animal decay is not unavoidable. That flawed view has been frequently based on concepts taken from physics like the universal tendency of systems to increase their entropy level (Toussaint et al., 1991). But this applies only to closed systems, not to open ones like living things that can locally decrease their own entropy at the expense of that in the environment, while the total entropy (that of the animal plus the environment) increases with time. Biological turnover, plus abundant energy coming from the environment in the form of food, can thus theoretically make "eternal" youth easy. Why are species without aging so uncommon? Because most multicellular animals internally generate their own aging rate at a species-specific speed for some biological adaptive purpose. Animal species with a short lifespan exist, mainly because they actively generate their own progressive degradative aging at a high rate through many different mechanisms including mitROS production (not simply by-products of respiration as is commonly and wrongly assumed; Barja, 2013), lipid peroxidation, shortening of telomeres, apoptosis, inflammaging, limited autophagy, and others yet to be uncovered. The reverse is the case in slowly aging animals.

In summary, it seems that most animals including humans are constantly committing slow progressive "suicide" (aging) for the benefit of the group or higher levels (species or ecosystems). Concerning evolutionary mechanisms of natural selection, aging could be advantageous because it can protect from epidemics and famines which could lead populations to extinction in local ecosystems (Mitteldorf, 2016a). Furthermore, the observed variability in lifespan can be beneficial to the group because: i) PA ensures that the aging rate is maintained within the range typical for the species but not with too tight a control, so that it is allowed to show smaller variations between organs or individuals, compared to those shown between different species. The result of this *loose control* would be the observed variability in individual life span within each animal species. This can be beneficial to the group because it ensures that not everyone dies at the same time, maintaining parental care; ii) it directly increases diversity and thus evolvability (Conrad, 1990; Wagner and Altenberg, 1996; Kirschner and Gerhart, 1998; Goldsmith, 2019; Mitteldorf, 2019); iii) it indirectly allows the generation-linked expression of increased diversity due to lowered sexual competition for females by the weaker or less sexually potent old, which helps to compensate for their greater behavioral experience compared to the young and strongly limits intergenerational breeding; this stimulates replacement of old genes by new ones, generates new gene combinations, and promotes evolutionary modification of the genotype, thereby increasing diversity and evolvability; iv) it can increase protection of the offspring due to greater parental care of the young, and decrease predation pressure on the young members linked to increased predation pressure on older, frail individuals (Mitteldorf, 2016a); and v) it allows the replacement of reproductive individuals that may accumulate mutations in the germ line over time.

Such mechanisms of group selection would be fast and strong enough to overcome individual anti-aging selection. Natural selection for aging also facilitates evolution by stimulating the replacement of individuals by others with different genetic makeup, thus increasing diversity (genetic variability), the raw material on which natural selection acts. Aging also shortens generation time, which speeds up evolutionary adaptation. PA can also help to clarify why aging occurs at different rates in different individuals, as well as in different organs, tissues, and cells of the same individual. That different organs age at different rates has been confirmed many times using many different techniques since the 1970s and recently in a multi-omics study in humans (Nie et al., 2022). This fact could be due to selection of organs mainly for the young age when they all work well, while later in life evolution would lead them alone to their fate, in agreement with the idea that the force of natural selection decreases with age (Medawar, 1952). The different rate of aging of different organs can also be compatible with PA theory because the aging program could control this by changing the tissue-specific gene expression of its target genes at different moments in the lifetime, analogously to what happens during development and maturation.

6. Evidence for and against programmed and non-programmed aging

Facts and reasons supporting and compatible, or not, with both PA and non-PA hypotheses are shown in Tables 1 and Table 2.

Table 1 mainly refers to different general evidence concerning longevity comparisons between species. A quick look at the table unavoidably leads us to infer that the present evidence overwhelmingly favours PA theories, since most current facts, results, and reasons listed in the tables are incompatible with or non-supporting of non-PA theories. This is especially true concerning mutation accumulation and DS theories. Antagonist pleiotropy could perhaps occur in some particular cases but it cannot be the main explanation for aging and longevity. For some facts and reasons, explanations are easily understood simply by looking at the table and will not be repeated here.

The main evidence favouring PA includes the following:

a) The most important evidence in favour of PA is the enormous variation in longevity across species which reaches up to a one-million-fold difference in longevity among animal species, and 200-fold in mammals.
b) Contrary to the long-held "belief" that aging is a laboratory artefact, when zoologists went to look at the prevalence of aging in the wild, they were surprised to find varied and relatively high percentages of old individuals in wild populations of many species (Mitteldorf, 2016a). This shows the strong value of objective direct observation compared to armchair theoretical speculation.
c) Among known longevity mutant genes in mammals pro-aging effects are much more common than anti-aging effects. Deletion of the aging-related gene results in increased longevity much more frequently than in a decrease, implying that the protein products of these genes actively promote aging instead of having anti-aging defense or repair functions. This is generally consistent with the idea that active pro-aging is adaptive and was naturally selected. Long-lived animals tend to have less or similar, instead of higher, *total tissue* antioxidant enzymes and endogenous forms of DNA repair than short-lived ones.
d) Many single gene mutations increase longevity in many different organisms, from yeast to mammals. Among these genes, many do not have any other known function apart from aging, while others, like insulin/IGF-1 signalling-related genes and pathways, have a dual role only in multicellular organisms. Since unicellular organisms precede multicellular ones during evolution, among the two known functions of the IGF-1/insulin-like pathway relevant to the present discussion, regulation of aging must be the original one (instead of a random "side effect"), and only millions of years afterwards could the pathway have been co-opted to also (pleiotropically) regulate blood glucose and multicellular organism growth. This would be the "antagonist pleiotropy theory" turned on its head.
e) There is increasing evidence that epigenetics is involved in longevity (Horvath and Raj, 2018; Horvath, 2021). Epigenetic clocks are the best aging clocks indicative of biological age reported to date and seem to be better markers of aging than chronological age (Mitteldorf, 2016b). There is increased evidence that at least part of the epigenetic changes with age in the nucleus, like CpG island methylations and histone modifications, are not random noise. Rather, they may be an important part of the aging program (Barja, 2019). Recently, strong evidence has started to emerge suggesting that they could also be involved in the interspecies differences in longevity (Horvath, 2021).

f) It is well known that telomere length does not correlate with longevity among mammalian species, with mouse telomers being much longer than those of humans. However, a single study has recently reported that what correctly correlates (negatively) with longevity is the rate of telomere shortening, not telomere length (Whittemore et al., 2019). For this comparison, both bird and mammalian species were included in the same correlative study. A previous study had found correlation of the rate of telomere shortening with species longevity in birds (Stuart et al., 2013). Further studies are sorely needed to ascertain whether mammalian telomere shortening is indeed faster in short-lived than in long-lived mammals.

g) Low rates of mitROS production, %FRL, DBI, and oxidative damage are observed in long-lived animals, including species with exceptional longevity but similar body size and metabolic rate to the short-lived ones, as in the case of birds and bats (Pamplona and Barja, 2007; Pamplona and Barja, 2011). The decreases in %FRL indicate that mitROS production at ETC is not an unavoidable product of respiration and that its value can be evolutionarily adjusted to contribute to modulating longevity. Accumulation of mtDNA fragments inserted in the nDNA increase chronological aging in yeast, and decrease by 100 % back to young levels in rapamycin-treated mice (Martínez-Cisuelo et al., 2016), which also increases longevity (Harrison et al., 2009).

h) Similar or lower *total tissue* antioxidants or repair systems in long-lived species. Early comprehensive reviews have shown that *total tissue* antioxidants (Barja, 2004) or BER in genomic DNA are lower or similar (rather than higher) in long-lived than in short-lived mammals and other vertebrates. However, recent studies have shown the opposite for mtDNA BER, which showed a positive correlation with mammalian longevity (Gredilla et al., 2020). Indirect studies of mitochondrial H_2O_2 release and scavenging suggest that the same may be true for mitochondrial antioxidants (Munro and Pamenter, 2019). Direct evidence of positive correlation of SOD with longevity is also available only for the MnSOD mitochondrial form (Brown and Stuart, 2007) but not for the cytosolic CuZnSOD (Pérez-Campo et al., 1998). Measurement of the many other enzymatic and non-enzymatic mitochondrial antioxidants in species with different longevities is sorely needed to clarify this most important issue. This could help to further confirm the validity of the mitochondrial free radical theory of aging (MFRTA), as one of the aging effector mechanisms within a recently proposed unified theory of aging (Barja, 2019).

i) Higher chaperone levels in long-lived species. This has been consistently found in various independent studies (Salway et al., 2011a). Better proteostasis could be an additional effector mechanism within the unified theory of aging (with a core central genetic, and perhaps epigenetic, aging program) contributing to superior longevity together with many other effector mechanisms, although a lack of correlation of protein repair with the longevity of 15 vertebrate endotherms has also been described (Salway et al., 2011b).

Table 2 refers to intra-species differences in longevity mainly concerning DR effects on longevity. DR increases mean and maximum longevity in mammals and many other animals, whereas other interventions like most pro-longevity drugs or exercise increase mean but not maximum longevity. Therefore, although not applicable to large human populations due to practical reasons, DR is a most appropriate approach to investigate aging mechanisms. DR is also useful to evaluate the validity of the different evolutionary theories of aging, particularly in the case of DS hypothesis (Table 2).

The main evidence favouring PA from DR includes the following:

a) The best-known experimental manipulations that increase mammalian longevity, DR, protein and methionine restriction, also modify the expression of hundreds of genes in a tissue and species-specific way, thus changing the amounts of the different aging program effector proteins in a precise way to increase longevity (Barja, 2019; Lu et al., 2022). The DR longevity increase effect is highly conserved in animals from yeast to mammals, indicating that it is the result of an adaptation to food availability, and not a secondary "by-product" of the decrease in energy intake as non-PA (DS) hypothesizes.

b) Animals fed Ad libitum (AL) do not show higher longevity than DR ones. Although the AL animal has an intrinsic capacity to increase its longevity, why that is higher lifespan not expressed? Other things being equal, a longer lifespan increases fitness through a greater total lifetime reproductive capacity, and according to the selfish gene theory, animals tend to increase their fitness. Moreover, in AL there is a greater energy intake than in DR, which should increase defences plus repair according to the DS hypothesis, and which should also lead to superior longevity. The existence of a program causing the increase in longevity in DR and its decrease in AL could explain those changes mechanistically. The evolutionary development of such a response to DR has been classically explained through the postponement of reproduction to times of plenty, avoiding the scarcity of food (or protein) at times of reproduction which would be limiting for offspring maintenance, growth, and maturation.

c) DR induces decreases in fertility and increases in longevity. These two changes are correlated in many species but not causally. Both are effects of DR but they are mechanistically independent traits. Analogously, in interspecies comparisons within the same phylogenetic class, it is frequently observed that species with high fertility are usually shorter-lived than those with lower fertility. Fertility inversely correlates with longevity across species. But again, this is not due to a direct physiological causal connection between these two traits. Rather, both are genetically linked within the same aging program (Barja, 2008) and that is why they phenotypically correlate. That correlation is also consistent with the existence of an aging program. The DS hypothesis of aging, instead, confuses an evolutionary genetic association with a (non-existent) physiological causal linkage between fertility and longevity.

d) DR increases longevity smoothly in proportion to the degree of food restriction. The greater the intensity of DR, the stronger is the afferent signal to the nuclear aging program, which reacts to it with greater changes in aging effectors which cause a higher increase in longevity (Barja, 2019). The CARS is organized so that a decrease in energy (or protein) intake induces the nuclear aging program to decrease its pro-aging and increase its anti-aging effector activities by selectively modifying the expression of its multiple target genes. In contrast, according to the DS hypothesis, the lower the energy availability, the less energy is invested in defences plus repair and the result is a decrease (instead of increase) in longevity.

e) DR does not decrease somatic mutation accumulation. This is not consistent with a decrease in somatic mutation as a mechanism of DR-induced longevity. Even in the case of mtDNA damage by mitROS, the increase in longevity across species or in DR is not due to lowering of mtDNA point mutations and deletions, because they do not reach the much higher threshold (around 70 %) needed to decrease ATP production in the presence of high mtDNA heteroplasmy. The mechanism linking low mitROSp with high longevity seems to be the decrease they cause in mtDNA fragment insertion into nuclear DNA (Caro et al., 2010; Cheng and Ivessa, 2010; Martínez-Cisuelo et al., 2016; Barja, 2019; Puertas and González-Sánchez, 2020), which can corrupt nuclear genetic information and is independent of such kinds of thresholds.

f) DR, protein restriction, and methionine restriction decrease mitROS production, %FRL, DBI, and oxidative molecular damage at the mitochondrial and tissue levels in all the experimental models where these pro-longevity interventions have been applied (Pamplona and Barja, 2007; Pamplona and Barja, 2011), supporting the existence of a PA.

g) High autophagy in DR. This change could be consistent with both PA and non-PA DS theory because high autophagy would be one of the changes in effector activity induced by the aging program in response to DR (Barja, 2019), and because an increase in autophagy would increase repair of macromolecular and organellar damage. However, an increase in autophagy, as in other defences or repair in general, would require increases in energy expenditure, whereas DR decreases energy intake and thus the general availability of energy for defense plus repair.

7. Conclusions

Most of the facts, evidence, and reasoning gathered in this article and listed in Tables 1 and 2 support or are compatible with PA theory. Conversely, the large majority of them are incompatible with non-PA theory or do not support it. This is especially true concerning DS, which is incompatible with most of them, and is not supported by current evidence. A strong divergence exists between the still mainstream non-PA theory—especially in the case of MA and DS—and real data coming from both the wild and laboratory experiments. Considerable evidence is also incompatible with APL non-PA theory which, however, could perhaps apply to a minority of cases. Ironically, since PA and non-PA are opposing theories, perhaps might both explain part of aging? PA would evolutionarily explain most of aging whereas APL could perhaps explain a minor but significant part of the aging process. This latter possibility would be consistent with the finding that, although old animals do exist in the wild, and reaching high proportions in many cases, in other species there can be low proportions of old individuals in wild populations. It would also be consistent with the possibility of some antagonist pleiotropic effects in which aging would be a secondary side effect that is not selected for.

All the foregoing, taken together, leads us to conclude that PA should be considered the most likely explanation of why aging exists. At a minimum, open debate on PA vs non-PA among specialists should be developed, instead of simply asserting, without solid support, that non-PA "is the evolutionary theory of aging", as if it were a demonstrated truth with no viable alternatives. Such a view should be replaced by healthy and open-minded debate among gerontologists and other specialists in the field. Since most evidence supports PA theory, a genetic and perhaps epigenetic program for aging must exist inside each of our cells. These cellular programs must be loosely coordinated systemically at the organism level. Such a view could explain most of the huge differences in aging rate and longevity seen among animal species.

Importantly, non-PA does not provide hope of decreasing the huge harm and toll on human life and society due to aging. Non-PA discourages this, leading only to passive acceptance of aging as due to entropy, randomness, wear and tear, and imperfect defences and repair, and therefore as something unavoidable. This view has generally been accepted in the population because no one ever saw a single non-aging human. But no one ever saw a single human flying until science and technology made this possible with the airplane. If non-PA continues to dominate gerontology, few scientists will look for something (the nuclear aging program) that the mainstream theory says does not and cannot exist.

In contrast, changing the accepted paradigm from non-PA to PA will strongly stimulate molecular biology researchers to search for the nuclear aging program. We want to stimulate molecular biologists interested in PA in gerontology, by stating "please look at the nucleus." This will likely open the door to a much faster pathway to solving the aging problem which will immensely benefit humankind in terms of the perspective on health and illness, social security, financial investment in the care of the old, and sociological position. Fast development of a scientific branch is strongly dependent on having a correct theory which can appropriately guide studies and experiments. Without this, progress will continue to be slow and too many experiments will lead to no true advancement of the discipline.

Attaining negligible human senescence in the future could perhaps also lead to a second big leap in evolutionary development of the human being resulting from the huge increase in personal experience obtained by individuals maintaining health and youth for much longer than they do now. This would exponentially increase the potency of the human brain and its creative innovation, as happened in the past when brain size strongly increased during evolution from our non-human primate ancestors, thereby enormously increasing the development of human society.

CRediT authorship contribution statement

G.B. conceptualized and wrote the outline of the manuscript; J.G., M. J., R.P., and G.B. did the investigation; R.P. and G.B. wrote, edited, and reviewed the manuscript. All the authors read and approved the final manuscript.

Declaration of competing interest

The authors declare no competing interests.

Data availability

No data were used for the research described in the article.

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