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The tumor suppression theory of aging

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ABSTRACT

Despite continued increases in human life expectancy, the factors determining the rate of human biological aging remain unknown. Without understanding the molecular mechanisms underlying aging, efforts to prevent aging are unlikely to succeed. The tumor suppression theory of aging introduced here proposes somatic mutation as the proximal cause of aging, but postulates that oncogenic transformation and clonal expansion, not functional impairment, are the relevant consequences of somatic mutation. Obesity and caloric restriction accelerate and decelerate aging due to their effect on cell proliferation, during which most mutations arise. Most phenotypes of aging are merely tumor-suppressive mechanisms that evolved to limit malignant growth, the dominant age-related cause of death in early and middle life. Cancer limits life span for most long-lived mammals, a phenomenon known as Peto's paradox. Its conservation across species demonstrates that mutation is a fundamental but hard limit on mammalian longevity. Cell senescence and apoptosis and differentiation induced by oncogenes, telomere shortening or DNA damage evolved as a second line of defense to limit the tumorigenic potential of clonally expanding cells, but accumulating senescent cells, senescence-associated secretory phenotypes and stem cell exhaustion eventually cause tissue dysfunction and the majority, if not most, phenotypes of aging.

1. Introduction

Prevention of premature deaths from violence, poor hygiene and curable diseases has increased human life expectancy well past 80 years (Oeppen and Vaupel, 2002). However, the underlying cause(s) of human aging remain largely unknown, and the rate of biological aging essentially unchanged. Years of life gained from further progress in the treatment of diseases is therefore spent in a state of ever increasing frailty and dependence, making the further extension of human life expectancy less and less desirable. Modern medicine has undoubtedly improved quality of life for most elderly humans (Vaupel, 2010), but the prevention of death without the prevention of aging promises little more than additional years spent in dehumanizing geriatric care, which is by many understandably seen as a nightmare rather than a medical goal worth pursuing.

Evolutionary theories of aging developed in the 20th century explain very well why we age (the reason) (Kirkwood and Austad, 2000), but unfortunately not how. Despite centuries of efforts to understand how we age, aging has essentially remained a disjointed collection of phenotypes (Finkel, 2015; López-Otín et al., 2013). Biogerontology can describe what is happening, but is unable to explain why or how the many molecular mechanisms presumably involved ultimately determine the rate of human aging. At least when looking at the practical application of aging research, the last century has produced little more than an illustrious queue of self-aggrandizing quacks and lunatics (Sengoopta, 2003). There are few sound reasons why encouraging observations in rodents, without any understanding of etiology (Campisi et al., 2019), should suddenly lead to anything useful.

Single cause theories of aging remain important in aging research. One obvious reason for this is the need for simplification. Another reason is the necessity to at least break up the aging process into potentially treatable parts, even if no single treatment can be expected to do much (Kirkwood, 2005). Efforts in the last 70 years to elucidate the molecular mechanism of aging have been one big disappointment, partially because during the same time, caloric restriction (CR) has become widely accepted as a universal mechanism to delay aging across the phylogenetic tree, and CR "mimetics", pharmacological agents that increase life span by inducing CR-like effects, are seen as the most promising and realistic avenue to prevent or slow aging. In the preceding article, I argued that CR does little more than prevent the excessive obesity present in most laboratory animals. Agents like metformin, NAD+, resveratrol and rapamycin, but many other genetic and pharmacologic interventions as well, induce weight loss, and there is little reason to assume that they prevent aging in any way other than

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causing a beneficial reduction in body weight. This fallacy of caloric restriction has survived so long because, against an obese control, CR really does delay aging. In this article, I will argue that obesity accelerates and CR decelerates aging against an obese control mostly through its effect on cell proliferation rate. Proliferation drives aging because most mutations arise during cell division when DNA damage is converted into irreparable mutations.

2. The tumor suppression theory of aging

2.1. Overview

Somatic mutations have long been proposed as a cause of aging (Failla, 1958; Szilard, 1959) and genomic instability is one of the four primary hallmarks of aging (López-Otín et al., 2013). The tumor suppression theory of aging outlined here differs from previous theories in that clonal expansion and malignancy is proposed as the relevant consequence of somatic mutation and that impairment, loss of cellular function, or cell death as a consequence of somatic mutation is largely irrelevant. To counter the tumorigenic potential of clonally expanding cells, we have evolved tumor suppression mechanisms that remove or limit proliferation of stem cells. Accumulating senescent cells and loss of capacity for self-renewal and repair eventually cause the phenotypes we experience in very old age. This theory of aging, briefly mentioned in (Wolf, 2021b) and illustrated in Fig. 1, evolved out of an analysis of the effects of obesity and CR on cell proliferation and aging, and was originally part of the preceding article about the fallacy of caloric restriction (Wolf, 2021a).

The idea of DNA as the store of a human age is obvious: our biological age has to be stored somewhere. Most of our tissues renew themselves at a considerable rate (Milo and Phillips, 2015; Post and Clevers, 2019), and, besides long-lived proteins (Toyama and Hetzer, 2013), little to store age remains besides the accumulated, irreversible mutations in DNA. Aging is irreversible: in billions of humans, there has been no case of spontaneous rejuvenation ever. Nor are there any people who, by some genetic, metabolic, nutritional or other wonder, have slowed down their rate of aging by any significant amount. Many interventions that increase somatic mutations strikingly resemble aging. Exposure to mutagenic UV-containing sunlight causes premature skin aging (Yaar and Gilchrest, 2007). Genotoxic stress causes premature hair greying (Inomata et al., 2009). Smoking causes not only cancer (Hecht, 2003) but also premature aging in exposed organs (Choukrallah et al., 2020; Morita et al., 2009; Okada et al., 2013). Radiation and mutagenic chemotherapy leads not only to therapy-related secondary cancer (Allan

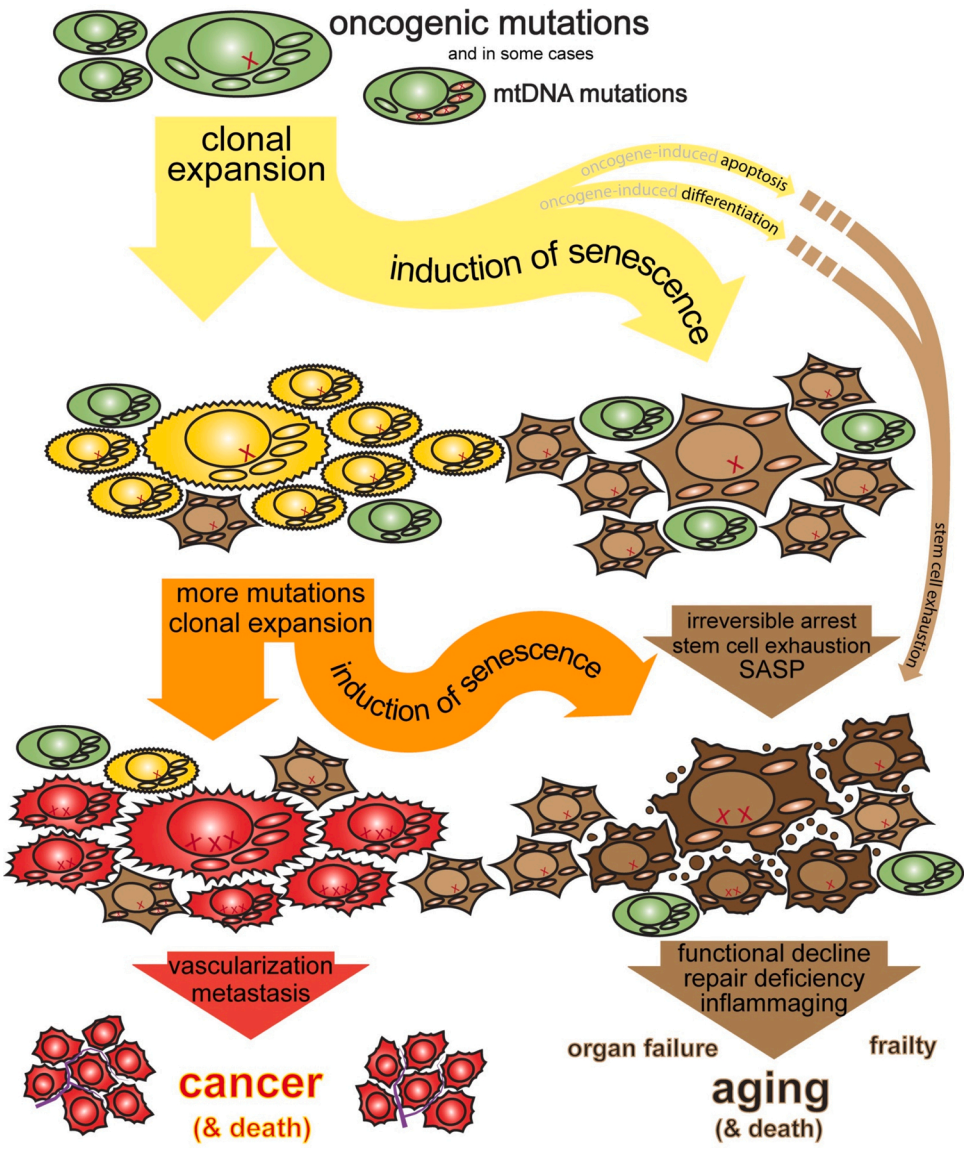

Fig. 1. The dual fate of cells acquiring oncogenic mutations. As mutations (x) inevitably accumulate with age, malignancy or its suppression is the ultimate fate awaiting both individual cells and the organisms as a whole. The tumor suppressor theory of aging proposes that (what we experience as) aging is the consequence of tumor suppressive mechanisms that have evolved to counter the threat of malignancy in expanding clones of cells by inducing cell senescence, differentiation and apoptosis.

and Travis, 2005), but also to premature frailty, multi-morbidity and increased mortality (Armstrong et al., 2014; Cupit-Link et al., 2017; Robison and Hudson, 2014), which has been attributed to the system-wide persistent accumulation of senescent cells (Short et al., 2019). Premature aging syndromes invariably destroy genomic integrity: almost all of them are disorders of DNA repair or maintenance of genomic integrity (Hoeijmakers, 2009). DNA repair is a longevity assurance system (MacRae et al., 2015). Somatic mutations can also explain why men die earlier than women: men lack a second X chromosome. When males are the heterogametic sex (like in mammals), they die earlier than females, but when females are the heterogametic sex (like in birds), males live 7.6 % longer than females (Xirocostas et al., 2020), and male birds seem to have similar or longer lifespans than female birds (Austad and Fischer, 2016; Clutton-Brock and Isvaran, 2007). Biallelic expression of tumor suppressors escaping X-inactivation (Dunford et al., 2017) can explain why the heterogametic sex (XY in mammals, ZW in birds) dies, on average, earlier than its homogametic counterpart across a range of taxa (Xirocostas et al., 2020).

2.2. The somatic mutation theory of aging

Somatic mutations as the cause of aging were proposed (among others) by Szilard(Szilard, 1959) because the phenotype of animals exposed to non-lethal amounts of mutation-inducing radiation resembled aging so much(Curtis, 1964). Why does the somatic mutation theory of aging, despite all the above evidence, receive so little support? First, for a long time, it was difficult to quantify mutations in somatic cells, so estimating the functional consequences of somatic mutations was difficult. Second, radiation-induced aging did not resemble normal aging very well: radiation mostly affects dividing cells, whereas aging seemed to happen mostly in non-dividing cells (Strehler, 1959). Furthermore, the amount of mutations necessary to shorten life span was much more than that acquired during normal aging. To match the observed age-dependent exponential increase in mortality, mutations had to be assumed to cause aging mainly by damaging recessive elements, but the rate of aging did not depend on ploidy (Strehler, 1986). Rose states that “by the end of the 1960s, somatic mutation was dead as a general theory of aging” (Rose, 2005), which appears to be more or less true up to the present, at least for its original form. Recently, Ferucci et al. conclude that “solid evidence that the accumulation of somatic mutations during normal aging is associated with the phenotypes of aging is lacking” (Ferrucci et al., 2020).

In my opinion, the most important and crucial flaw of the somatic mutation theory of aging, and in current thinking about the role of somatic mutations in aging in general, is that it is mistaken about the consequence of somatic mutations. Mutations were and, up to this day, are universally thought of as damaging and pathogenic (Freitas and De Magalhães, 2011; Kennedy et al., 2012; López-Otín et al., 2013; Vijg and Dong, 2020; Vijg et al., 2017; Vijg and Montagna, 2017), leading to “cell functional loss and human disease”(Vijg and Dong, 2020), like in the Hallmarks of Aging, where genomic instability is viewed as “resulting in dysfunctional cells that… may jeopardize tissue and organismal homeostasis” (López-Otín et al., 2013). Aging itself is characterized by a loss of function, and so it is common thinking that the mechanistic cause of aging must also result in a loss of function (see for example the introduction in (Kinzina et al., 2019)). Looking at individual somatic mutations, I think this is mistaken. Elimination and replacement of damaged cells is ubiquitous (Milo and Phillips, 2015) and preserves function rather than impairing it (Clevers et al., 2014; Post and Clevers, 2019). Despite our vastly improved knowledge of somatic mutations in adult tissues, there is little evidence for any significant deterioration of function due to somatic mutations (Vijg and Dong, 2020).

Cancer is caused by mutations in oncogenes and tumor suppressor genes (Fearon and Vogelstein, 1990; Hoeijmakers, 2001; Michor et al., 2004; Stratton et al., 2009). Cancer genome sequencing has unequivocally revealed the “mountains” (frequently altered genes) and “hills” (less frequently altered genes) of positive selection in the cancer genome (Vogelstein et al., 2013). The opposite however, the relative absence of mutations in essential genes, is not observed (Bakhoum and Landau, 2017; Martincorena et al., 2017; Yadav et al., 2016). And while this might not be surprising given that humans have two copies of most genes, that most mutations are recessive (Wilkie, 1994), and a pervasive robustness of biological systems (De Visser et al., 2003; Félix and Barkoulas, 2015; Kim and Fernandes, 2009; Wagner, 2013), this absence of negative selection is strong evidence that somatic mutations do not cause significant negative selection or elimination of cells, further contradicting the currently prevailing dogma of functional impairment as the consequence of somatic mutation.

2.3. The fundamental problem of malignant growth

RNA and DNA as the storage medium for the blueprint of life originated approximately 4 billion years ago in short-lived prokaryote life forms (Betts et al., 2018; Brasier et al., 2015) who depended little on the ability to store information reliably for decades. Only very recently (some 500 million years ago), possibly prompted by an abundance of high-energy oxygen (Marshall, 2006), did single-celled organisms rapidly evolve into multicellular life forms and then into even larger bony fish. These grew lungs and started to walk on land all within the few dozen million years of the Cambrian explosion (Erwin et al., 2011; Marshall, 2006). At that time, however, all life had firmly settled on DNA as a now inconveniently fragile storage medium. The sudden rapid increase in organism size and life span was and had to be accompanied by concurrent improvements in genome maintenance and protection against newly appearing mutagenic oxygen radicals (Fridovich, 1975; Halliwell, 1978).

Together with increasing size and life spans, uncontrollable cell growth became a fundamental problem for large, long-lived multicellular organisms. Cell sizes are roughly the same in big and small animals (Savage et al., 2007), so, from cell number alone, cancer risk can be assumed to scale with body size. Cancer risk increases with age as mutations accumulate, so long lived animals face a further increase in cancer risk. As a consequence, long-lived animals, including humans, evolved mechanisms to limit malignant growth together with life span and body size, a phenomenon called Peto’s paradox (Caulin and Maley, 2011; Hiatt et al., 1977; Peto et al., 1975), which states that cells of large, longer-lived animals have a much lower risk of turning cancerous over a certain time than those of smaller animals (Abegglen et al., 2015). And even though a decline of metabolic rate (and most probably cell division and mutation accumulation rate as well) with body size (Glazier, 2005; Savage et al., 2004) makes a calculated 3 trillion-fold difference in the per gram of tissue cancer risk between mice and humans (Peto, 2015) unlikely, species-specific per-cell cancer risk differences are undoubtedly enormous. The presence of cancer and the evolution of cancer resistance by themselves demonstrate that malignant growth is an important factor limiting lifespan in apparently most long-lived vertebrates.

2.4. Life-history characteristics in large animals

Cancer is a significant cause of death not only in mice and humans, but in most animals where cause of death has been investigated (Leroi et al., 2003; Madsen et al., 2017). Apocryphal stories about supposedly cancer-resistant species such as sharks (Lane, 1992; Mathews, 1992) or naked mole rats (Tian et al., 2013) exist, but are not true (Braude et al., 2021; Delaney et al., 2016; Finkelstein, 2005; McCutcheon, 1997; Ostrander et al., 2004; Taylor et al., 2017). Among the few other species largely protected from extrinsic mortality, cancer accounted for 39 % of deaths in long-lived dog breeds and almost half of deaths in old dogs (Bronson, 1982). Breed-specific cancer mortality ranged from 15 to 56 %, and tended to increase with body size (Dobson, 2013). Cancer accounts for the vast majority of deaths in laboratory mice (Blackwell

et al., 1995; Lipman et al., 2004; Miller and Chrisp, 2002; Pettan-Brewer and M. Treuting, 2011; Storer, 1966; Ward, 2006).

2.5. Human cancer epidemiology

Peto's paradox underlies one of the strongest arguments for the tumor suppression theory of aging, so cancer needs to be a valid and important driver in the evolution of human life span, not only in modern humans, but also in the prehistoric environment that shaped the genetically determined current human maximum life span.

Supplementary Fig. 1a shows the age-dependent cause of death for the US population from 1999−2019. Accidents and other extrinsic mortality like infections dominate in early adulthood up to middle age, when absolute mortality is lowest. When non-age-related sources are removed, cancer and cardiovascular disease are the two dominant causes of mortality, and cancer is the dominant cause of death in children (Supplementary Fig. 1b). Despite most cancers of childhood now being successfully treated in medically advanced societies like the US, cancer makes up 40 %, 34 % and 28 % of deaths in the 5–9, 10–14 and 15−19 year old groups.

Approximately 80 % of childhood cancers are cured in high income countries, whereas mortality in low income countries is above 90 %, so prehistoric childhood cancers were probably about five times more lethal than with access to modern treatment (Lam et al., 2019). For adults, cancer incidence is about threefold cancer mortality (Siegel et al., 2020). On the other hand, cardiovascular disease (CVD) is significantly associated with risk factors rare in prehistoric societies: diabetes, smoking, high blood pressure and elevated cholesterol levels (Berry et al., 2012; Lloyd-Jones et al., 2006). In turn, diabetes is associated with obesity and sedentary lifestyle (Lascar et al., 2018), high blood pressure is associated with obesity (again, accounting for 65%–75% of the risk) (Hall et al., 2015) and high intake of alcohol and salt. High blood cholesterol is associated with a diet high in saturated fats. Since primitive humans consumed mostly low fat, plant-based food, above CVD risk factors were probably more or less inexistent during prehistoric evolution. Whereas most North Americans falls into the highest two of five CVD risk categories (Berry et al., 2012), prehistoric CVD mortality was probably close to that observed in groups having none of the above risk factors, which results in a profoundly lower risk for all kinds of CVD (Berry et al., 2012; Lloyd-Jones et al., 2006). Mortality with all CVD risk factors optimal is about one fourth of that in the most populous risk category, those with one major risk factor (Berry et al., 2012).

If, to mimic prehistoric conditions, cancer mortality is increased 5-fold for ages 1–19 and 3-fold for ages above 20, and death from cardiovascular disease reduced by 75 %, cancer becomes the most common age-related cause of death by far, accounting for the majority of age-related deaths up until age 80–84 (Supplementary Fig. 1c). In contrast, deaths from other ICD-10 chapters, including deaths from CVD, stay around or below 10 %.

Despite cancer being the dominant age-related cause of death in early and middle life, absolute risk of death in high income societies like the US is very low up until late middle age. Age-related mortality from non-infectious disease is negligible in those under 40 years old(Supplementary Fig. 2). Cumulative survival from all causes except accidents, infections and congenital malformations does not drop markedly before the 50's and 60's, and remains above 50 % up into the 70's (Supplementary Fig. 2). Nevertheless, cancer on average precedes other age-related causes of death such as cardiovascular disease and typical end-of-life ailment such as dementia, pneumonia and age-related organ failure, irrespective of whether or not adjusted for prehistoric mortality. Adjusting for prehistoric increased cancer mortality and lower CVD incidence shifts peak mortality to younger ages by about 3–4 years, as expected if cancer precedes other causes of age-related mortality (Supplementary Fig. 2).

2.6. The (evolutionary) value of longevity

It is still a common fallacy that aging (or cancer) is rarely observed in the wild, due to opinions resembling Peter Medawars careless assumption that wild animals "simply do not live that long" (Medawar, 1952). This is not true (Nussey et al., 2013). Humans, many flying animals and other species have evolved remarkable longevity after managing to escape high extrinsic mortality. Intelligent, long-lived birds show increased reproductive success as they get older, bigger, gain more experience and learn more tricks (Lecomte et al., 2010). Ravens, albatrosses and other birds learn skills like food source patterns or appropriate nest site selection over years(Dunk et al., 1997; Nevoux et al., 2007; Reed et al., 1999). Reproductive success is often best in experienced, veteran breeding pairs that have mastered a set of key skills crucial for survival and raising offspring (Angelier et al., 2007), and aging is often a primary natural limit on reproduction in these successful individuals (Bouwhuis et al., 2012; Nussey et al., 2013; Reed et al., 2008; Weimerskirch, 1992). Reproductive success in larger and/or long-lived species appears to be skewed towards a few highly productive individuals not only in birds, but also terrestrial animals such as seals (Le Boeuf et al., 2019) and humans (Favre and Sornette, 2012), and these few highly successful individuals disproportionally profit from longer lifespans.

Humans have evolved a rate of aging that assures their performance into late middle age. This is not only reflected in the retirement age of most industrialized societies, but also in the hunting performance of traditional societies (Walker et al., 2002), and the age of menopause, which results in the presence of dependent children well in the 50's of their parents. Furthermore, once humans survived childhood, their mortality was remarkably low, and significantly lower than that of closely related primates (Finch, 2010; Gurven and Kaplan, 2007). After reaching puberty, prehistoric humans entered a phase of low mortality, whose overall reproductive payoff probably depended significantly on the length of this period of adulthood marked by health, high performance and low mortality, especially in males (Favre and Sornette, 2012). A quantitative understanding of the prehistoric relative evolutionary value of preventing death at different ages is lacking, but it is not unreasonable to conclude that malignancy was an important age-related source of mortality at the upper end of human reproductive activity, the edge at which the reproductive value of additional health span drops below the cost associated with achieving it, and age-related mortality (Supplementary Fig. 2) starts to become significant.

2.7. The wonderful consequences of Peto's paradox

In my opinion, the annoying fragility of DNA (Duncan and Miller, 1980), and the necessity to copy it with ever lower error rates (Caulin and Maley, 2011) has become the most important choke point in achieving even longer live spans. Peto's paradox wonderfully affirms and substantiates the tumor suppression theory of aging. Not because it shows that cancer limits mammalian lifespan, and the irrelevance of body size and life span to cancer risk (Peto, 2015), but because it proves the centrality and difficulty of maintaining genomic integrity as the cause of aging. Cancer is caused by mutations (Fearon and Vogelstein, 1990; Stratton et al., 2009). If preventing them would be easy, we would not have evolved cell senescence and other costly mechanisms of premalignant cell elimination that exhaust our stem cell pools. We would simply have evolved (much) better genomic maintenance to prevent mutations and cancer altogether. Of course this is just possible if evolving better genome maintenance would be easy. Or cheap (in terms of evolutionary investment). But we didn't. And we didn't, because all the DNA repair, maintenance and damage prevention mechanisms we evolved to counter the annoying fragility of DNA is already costly, complex or difficult to improve, and must make up a large, if not the largest, fraction of the lifespan-limiting maintenance and repair functions (Kirkwood, 2005).

This validation might be speculative, but more or less has to be true because single cause mechanistic theories of aging are inherently stupid: evolutionary life-history theories of aging (chiefly the disposable soma theory of aging) tell us that evolution should quickly "fix" dominant causes of aging. The only way to save the tumor suppression theory of aging from this crushing argument is to conclude that the many components of the sophisticated machinery to protect, repair and maintain DNA integrity constitute the majority of the lifespan-limiting maintenance and repair functions (Kirkwood, 2005). If somatic mutation would be fixable, it should have been fixed, to eliminate cancer. But not only in humans, but probably in thousands of other long-lived species as well, cancer has not been fixed.

Simple models predict evolutionary pressure to eliminate age-related diseases only up to the peak reproductive and child-caring years, but not much beyond (Hamilton, 1966; Williams, 1957). For humans, this might be more or less true, but for other species, it seems wrong. Mice have a generation time of less than 3 months, yet a maximum life span of more than 3 years (Weindruch et al., 1986). Mouse mothers can meet their great-great grandchildren within a year while still being quite fertile (Harman and Talbert, 1970; Talbert, 1971). Female mouse fertility starts to decline significantly after one year, yet birth remains possible up until 2 years (Talbert and Krohn, 1966). Even though this is vanishingly unlikely in the wild, old mice can easily survive more than ten generations of offspring. Mouse maximum lifespans are therefore somewhat in discrepancy with the evolutionary theory that longevity is mostly a trade-off with fertility (Kirkwood and Holliday, 1979; Williams, 1957) and that higher fertility will lead to high rates of senescence (Hamilton, 1966). Why have mice evolved such a long maximum life span? The tumor suppression theory offers an answer: because in small animals, tumor suppression must be relatively cheap. Aging and death are obstacles to reproduction, after all. Despite their small body size and short life span, the mouse germline and somatic mutation rate is less than an order of magnitude higher than in humans (Milholland et al., 2017). Longevity is a function of optimal resource allocation (Kirkwood, 2017a), and species maximum longevity should be determined by the actual cost of longevity as well, not only age of maturity and external mortality (Jones and Vaupel, 2017). Maturation might not always mark the onset of significant senescence as predicted (Williams, 1957) if, due to a small size, even a low allocation of resources towards protecting genomic integrity and tumor suppression might assure maximum lifespans many multiples the age of maturity, and without marked tradeoffs in fertility (Bouwhuis and Vedder, 2017; Jones et al., 2014; Wensink et al., 2017).

2.8. Mechanisms and drivers of somatic mutation accumulation

In a profound and fundamental study, Tomasetti and Vogelstein demonstrate that the number of stem cell divisions explains two thirds of the variation in cancer risk(Tomasetti and Vogelstein, 2015) of a tissue. This is an old idea (Albanes and Winick, 1988; Preston-Martin et al., 1990) based on the finding that the majority of oncogenic mutations arise during normal cell division(Ames et al., 1993), when repairable DNA damage is fixed into irreparable mutations during DNA replication. The number of stem cell divisions is the number of stem cells times the rate of stem cell division in a certain tissue, and this finding firmly establishes cell division as the key quantitative driver of mutagenesis. Tomasetti and Vogelstein's conclusion that most cancer risk is due to random mutations arising during DNA replication in normal, noncancerous stem cells leads to the obvious conclusion that any factors that can modulate stem cell division rates would obviously have a large impact on cancer risk.

Decreased proliferation under CR is almost universal (Hursting et al., 2003). Moderate (20 %) CR caused a more than six fold decrease in mouse bladder cell proliferation, while IGF-1 treatment caused an ~7-fold increase in proliferation (relative to 20 % CR) (Dunn et al., 1997; Hursting et al., 2003). Organ-dependent differences are obviously large, but marked (up to 10-fold) drops in proliferation rate are common and generally quite significant with even low or moderate levels of CR (Hsieh et al., 2005; James and Muskhelishvili, 1994; Lok et al., 1988, 1990). Treating cultured cells with CR sera reduced cell proliferation, and IGF-1 and insulin supplementation reversed it (de Cabo et al., 2003). High fat diet-induced obesity promotes colonic stem cell expansion during cancer initiation (DeClercq et al., 2015). Cancer, in particular hematopoietic neoplasia (lymphoma), is extremely common and the dominant cause of death in mice (Blackwell et al., 1995; Lipman et al., 2004; Miller and Chrisp, 2002; Pettan-Brewer and M. Treuting, 2011; Storer, 1966; Ward, 2006). The powerful effect of nutrient and growth signaling on proliferation not only explains the large gains in rodent longevity with CR. It is probably not unreasonable to suspect that the, from an evolutionary viewpoint, unnaturally high prevalence of malignancy in many strains of laboratory mice is a consequence of the unnaturally high food intake and the resulting obesity. Tumor incidence is decreased three- to six-fold in mice eating 40 % less (Harbison et al., 2016). Cancer mortality is also associated with increased body mass in 82 breeds of dogs (Fleming et al., 2011), where breed differences in body size are determined significantly by a single IGF-1 allele (Sutter et al., 2007). IGF-1 is a powerful stimulator of cell growth and replication and elevated IGF-1 is a risk factor for several human cancers (Sonntag et al., 1999). Plasma IGF1 levels at 6 months age inversely correlate with median mouse lifespan across strains (Yuan et al., 2009) and human height is associated with longevity and risk of death from cancers unrelated to smoking (He et al., 2014; Samaras and Storms, 1992; Smith et al., 2000).

Caloric restriction is so well accepted as an age-retarding intervention because it delays almost all phenotypes of aging in such a coordinated fashion (Masoro, 1985, 1988, 2005; van den Boogaard et al., 2020; Yu et al., 1985). The ability of CR to delay aging might derive largely from its ability to reduce cell proliferation rate via evolutionary conserved nutrient signaling pathways. CR produces not only dramatic reductions in murine cancers (Speakman and Mitchell, 2011) but also reduced pathologies and increased life span(Sonntag et al., 1999). Severe stunting, low IGF-1, but increased longevity with protein restriction despite compensatory overeating (Miller et al., 2005; Solon-Biet et al., 2014) suggest anabolic growth through mTOR-controlled proliferation (Dowling et al., 2010), but not metabolism or calorie intake as the key determinant of organismal aging rate (Levine et al., 2014). Cell proliferation rates are exquisitely sensitive to nutritional status (Hsieh et al., 2005), especially proteins that regulate mTOR (Richardson et al., 2021). The acceleration of cell division by obesity and somatotrophic growth signaling (Bartke, 2019; Bartke et al., 2013) and it deceleration by CR (Dunn et al., 1997) and disruption of IGF-1 signaling (Berryman et al., 2008) powerfully implicate proliferation and accompanying mutation accumulation as the fundamental driver of aging.

2.9. The inner moat of carcinogenesis

Besides maintaining DNA integrity, long-lived life forms evolved a second line of defense against tumorigenesis: the neutralization of cells showing signs of malignant transformation. At least three of these tumor-suppressive mechanisms exist: cell senescence, differentiation and apoptosis (Fig. 1). Cell senescence artificially limits a cell's capacity for self-renewal (Campisi, 2013) and the robust association of senescent cells with cancer illustrates that cellular senescence primarily works as a barrier to malignant tumorigenesis *in vivo* (Burd et al., 2013). For the organism, stable cell-cycle arrest is not a bug, it's the feature of senescent cells and probably a cheap (in terms of necessary extra energy expenditure) and therefore effective way of limiting cancer growth. Telomere shortening, another hallmark of aging (López-Otín et al., 2013), is sometimes seen as a cause of aging by itself (Chakravarti et al., 2021; Whittemore et al., 2019). It is not. Telomerase is a powerful oncogene (Nault et al., 2013), as it provides unlimited replicative potential (Cong et al., 2002). Telomere shortening is insignificant in the

stem cell compartment, where telomerase maintains telomere length (Flores et al., 2008), like in the germline. Unfortunately, most publications about "telomere length" investigate just circulating leucocyte telomere length (Epel et al., 2004), a convenient yet (in my opinion) largely meaningless parameter reflecting the amount of telomere shortening during hematopoietic stem cell differentiation, which might reflect inflammatory status but not aging (Carulli et al., 2016; Jongbloed et al., 2019; Laimer et al., 2016). Telomeres shorten rapidly during differentiation (Flores et al., 2008), and this is a highly effective mechanism to limit the tumorigenic potential of differentiating and expanding clones of cells.

Senescent cells can be seen as frozen cancer cells, arrested in their development before they could potentially kill the organism by turning into a cancer. Clonally expanded cells can make up significant portions of various organs and, despite none of them being cancerous, they form what seems like perfectly normal tissue (Martincorena et al., 2018, 2015; Tomasetti, 2019; Yokoyama et al., 2019). Growth arrest alone does not explain the functional decline seen in aging, as senescent cell burden probably remains low in many organs at an age when many phenotypes of aging are already apparent. But even few senescent cells can cause physical dysfunction (Xu et al., 2018) via the senescence-associated secretory phenotype (SASP)(Coppé et al., 2008) and bystander effects (Nelson et al., 2012). This is not unreasonable. The SASP is beneficial in wound healing (Demaria et al., 2014), and the pleiotropic role of senescence (Campisi, 2005) and the associated SASP explain why apparently excessive chronic inflammation appears even when relatively few senescent cells are present (Xu et al., 2018): the inflammatory response protects the body against infection and injury, which was an extremely valuable function in prehistoric times (Finch, 2010). Widespread senescence only appears in the evolutionary shadow of old age. The possibly vicious circle of ubiquitous senescence, widespread SASP and chronic inflammation might be an evolutionary accident brought about by the unforeseen, unprecedented surge in human longevity.

For effective tumor suppression, cell senescence has to kick in well prior to tumor formation. Mutations are stepping stones to the, on average, four or five driver mutations present in a full-blown cancer (Cieslik and Chinnaiyan, 2020). Proliferation vastly increases the probability that any of its progeny will acquire additional mutations, not only by increasing the number of cells already harboring a critical mutation, but also by having increased rates of mutation-prone cell replication (Jaiswal et al., 2014). Cell senescence resembles a prison for attempted murder: any perceived attempt is (and has to be) treated as guilty. The number of genes able to drive clonal expansion and cancer is probably a few hundred (Bailey et al., 2018; Futreal et al., 2004; Tamborero et al., 2013) and more than 1% of all human genes are by mutation implicated in carcinogenesis (Sondka et al., 2018). Due to this diversity of oncogenes, senescence has to be triggered by the phenotype of (excess) proliferation and is broadly activated by both oncogene-driven as well as anabolic growth-driven replication. The term "oncogene-induced senescence" is somewhat of a misnomer. A cell cannot identify mutated genes, let alone classify them as oncogenic. Oncogene-induced senescence is established by phenotype, after the hyper-replicative phase following oncogene expression, and the hyper-replication causes DNA damage, which induces DNA damage response (DDR)-mediated senescence (Di Micco et al., 2006). The multiple stimuli that trigger senescence (Campisi and Di Fagagna, 2007; Hernandez-Segura et al., 2018) are those that were effective in preventing malignant growth. Evolving a mechanism that can reliably distinguish between dangerous, malignant and benign, physiological replication is probably impossible.

Whereas mechanisms to maintain genome integrity are classic MRFs which cost only energy, cell senescence is clearly pleiotropic. High ability for self-renewal allows for a youthful organism but favors cancer. Too little ability for self-renewal protects against cancer but leads the many hallmarks of aging. In groups with marginal rates of obesity like Japanese women (where average BMI is 21.7)(WHO, 2015), malignant growth is (despite low rates of smoking) the most common cause of death by far (~30 %), outnumbering obesity-driven cardiovascular disease (Twig et al., 2016) approximately twofold (Ministry of Health, 2018). Life expectancy in Japanese women is 87.5 years (Ministry of Health, 2019). In contrast, in the US, heart disease slightly outnumbers cancer (Murphy et al., 2021), with obesity lowering life expectancy (to 76.2 and 81.2 years for males & females in 2018) (Murphy et al., 2021) and shifting the leading cause of death away from cancer. 50 % deaths from cancer would be the "ideal balance" between too much and too little cell senescence that would be expected in a population aging according to the tumor suppressor theory of aging. However, cancer deaths stay below 50 % due to effective cancer treatment, of which radiotherapy and chemotherapy, like endogenous cancer suppression, work primarily by inducing DDR-mediated apoptosis and cell senescence (Jackson and Bartek, 2009; Ou and Schumacher, 2018).

2.10. The tumor suppression theory of aging – appraisal of a hypothesis

The tumor suppression theory of aging postulates that most of the seemingly complex phenotype of aging emerges from mechanisms of tumor suppression, chiefly cellular senescence, but also apoptosis and differentiation (Fig. 1). These have evolved to limit the further proliferation of clonally expanding cells, or remove such cells from the regenerating stem cell pool.

An important conundrum in aging research is the apparent incompatibility of the metabolic malleability of aging with the concept of damage accumulation as the cause of aging. Aging represents, or is at least seen as, a collection of phenomena (Finkel, 2015) reflecting damage accumulation, as predicted from evolutionary arguments (Kirkwood, 2005, 2017b). Molecular mechanisms of damage, however, should diverge between organisms whose life span differs by several orders of magnitude, so pathways affecting aging should diverge as well. This is not easily reconciled with the observed malleability of aging via conserved pathways from yeast to mammals. This has led to controversial, programmed or quasi-programmed theories of aging that require regular debunking (Blagosklonny, 2006, 2013; de Magalhães, 2012; Gems and de la Guardia, 2013; Goldsmith, 2014; Kowald and Kirkwood, 2016; Libertini, 2014; Longo et al., 2005; Zimniak, 2012) or the postulated existence of "longevity programs" (Longo, 2019). Cell proliferation rates in mice are extremely sensitive to changes in caloric intake (Hsieh et al., 2005),and via the modulation of cell proliferation, the tumor suppressor theory of aging can explain the apparent metabolic regulation of aging with a mechanistic explanation, somatic mutations being a form of damage supported by convincing evolutionary as well as experimental evidence. The tumor suppression theory of aging also resolves another conundrum, the apparent mismatch of the disposable soma theory, which suggests life span to be limited by energy available for maintenance, with the effects of caloric restriction, which increases longevity despite less energy being available (Shanley and Kirkwood, 2000). Put more simply, why would the body not repair when energy is available, but instead do so when energy is scarce (Mitteldorf, 2001)? The solution, of course, is that when energy is available, the body invests heavily in growth and fitness to maximize reproduction, and this is achieved through accelerated replication. Accelerated aging is at this point only a minor, evolutionary irrelevant, side effect. On the other hand, CR forces a reduction of energy-intensive cell proliferation and, as a consequence, in the rate of aging.

2.11. Aging - really just tumor suppression?

Of the highly influential Hallmarks of Aging (López-Otín et al., 2013), only four (genomic instability, telomere attrition, epigenetic alterations and loss of proteostasis) are upstream, primary hallmarks that would qualify as underlying, proximal causes of aging. As explained above, telomere attrition is an elegant tumor suppression mechanism,

but not a serious candidate for a proximal cause of aging. Epigenetic alterations accumulate with age(Rando and Chang, 2012) and can be used to derive impressive biomarkers of aging (Horvath and Raj, 2018), but depend on other causative factors such a DNA damage to explain their accumulation over time (Kane and Sinclair, 2019). Epigenetic alterations are involved in many of the changes observed with aging (Pal and Tyler, 2016), but the plasticity and reprogrammability of epigenetic markers, while encouraging as a target of interventions (Lardenoije et al., 2015; Ren et al., 2017), is poorly compatible with the observed irreversibility of aging. Steady state DNA damage or genotoxic stress can result in cellular functional decline (Vermeij et al., 2014) and impinges on many secondary hallmarks of aging, most notably by its ability to drive cells into a DNA damage response, apoptosis and senescence (Yousefzadeh et al., 2021a). Lumped together with somatic mutations, DNA damage can explain many aspects of aging and cancer (van den Boogaard et al., 2020). However, like epigenetic alterations, DNA damage is reversible (Hoeijmakers, 2009). Mechanisms of DNA damage are mostly chemical and species-independent and steady state nuclear DNA damage is not correlated with species life span (Barja and Herrero, 2000), so explaining the heterogeneity of life spans with DNA damage is difficult.

The ability of enhanced tumor suppression to induce premature aging (Beausejour and Campisi, 2006; Campisi, 2005; Donehower, 2002; Ferbeyre and Lowe, 2002; Keyes et al., 2005; Sharpless and DePinho, 2007; Tyner et al., 2002) powerfully supports the tumor suppression theory of aging. The ability to induce premature aging (Kujoth et al., 2005; Trifunovic et al., 2004), however, doesn't necessarily prove a significant involvement in normal aging (Vermulst et al., 2007). At least with the current, unreliable markers of senescence, senescent cell do not seem to accumulate to high proportions (Wang et al., 2009; Yousefzadeh et al., 2020), and some cell types, notably epithelia, do not seem to senesce (at least when applying standard markers of senescence) (Giangreco et al., 2008; Stern and Bickenbach, 2007), but instead die or differentiate (Gandarillas, 2012; Gandarillas and Watt, 1997; Ying et al., 2018) to remove them from the stem cell pool (Fig. 1). Methods to detect and quantify mutations and evaluate their spread in tissues due to clonal expansion are still rapidly developing (Laurenti et al., 2021). A definitive consensus on the extent of clonality and its organ-specific development with age is still some time ahead. Insufficient quantitative evidence as how and where mutations cause disease-relevant stem cell exhaustion is for the moment certainly an important weakness in the tumor suppression theory of aging, but downright stem cell depletion is in many cases not necessary to explain impaired stem cell function. Senescence represents many diverse cellular states united only by stable proliferative arrest (Van Deursen, 2014). Consistent markers are lacking (Sharpless and Sherr, 2015), but this is not surprising when keeping in mind that senescence is triggered by diverse signs of impending tumor formation. There are large gaps in tracking senescent cells *in vivo*, let alone quantifying which kind of cells die, and why, during natural turnover or senolytic treatment. Several attempts to mark senescent cells with a specific promoter driving expression of red fluorescent protein markers for in vivo imaging did not seem to result in any presentable fluorescence images (Jeon et al., 2017; Liu et al., 2019). Due to differences in cell division history and frequency, organ- and cell-specific variations in the load of somatic mutations are large. Skin, an organ exposed to mutagenic UV radiation, accumulates such huge numbers of mutations that in aged, sun-exposed yet anatomically normal epidermis, expanded clones make up large patches of tissue (Martincorena et al., 2015). Notch inactivating mutations not only trigger immortalization, but also promote differentiation of adjacent wild type cells, effectively replacing entire sections of epithelium (Alcolea et al., 2014). Patches of seemingly normal but essentially premalignant epithelium are continuously eliminated by the immune system, as revealed by the more than 100-fold increase in skin cancer rates after long-term immunosuppression (Euvrard et al., 2003). Such patches can be recognized by the immune system because the number of mutations they carry (Martincorena et al., 2015) is higher than most human cancers (Alexandrov et al., 2013) and enough to allow distinction from self. Driver mutations seem to promote growth only during the initial expansion of mutant clones (Martincorena et al., 2016), hinting at the induction of a growth-limiting form of cell senescence in the absence of classical senescence markers. How fast powerful mutagens like UV radiation drive cell senescence and aging is apparent in the perfection of skin in small children (despite injury and regeneration alternating at astonishing speeds), which is lost even before reaching adulthood. In esophageal epithelium, expanded clones make up 40–80% of tissue in patients over 60. Like in skin, Notch-mutated clones can colonize large patches of normal epithelium, and driver mutations can be acquired in infancy as an inevitable consequence of normal aging (Martincorena et al., 2018; Yokoyama et al., 2019). Notch-mutations were more common in normal tissue than in esophageal cancer, suggesting that vigorous growth in notch-mutated clones might trigger tumor-suppressive mechanisms that effectively inhibit later carcinogenesis(Martincorena et al., 2018). In older liver, mean and median expanded clone volumes were quite large (1.14 mm^3 and 0.59 mm^3) and increased with fibrosis and tissue injury (Zhu et al., 2019). The nodular architecture of cirrhotic liver restrained clonal growth (Zhu et al., 2019). Like in esophagus, some recurrent mutations were more frequent in normal tissue than in liver cancer, suggesting a potentially tumor-suppressive effect of certain kinds of mutation-driven rapid proliferation, some of which might even increase hepatic fitness (Zhu et al., 2019). In colonic epithelium, only 1 % of crypts harbored driver mutations. Crypt fission was rare and not associated with driver mutations, indicating that the peculiar architecture of the colon is a barrier to the spatial expansion of clones (Lee-Six et al., 2019). On the other hand, clones of respiration-deficient cells harboring near homoplasmic mtDNA mutations constitute above 10 and 15 % of crypts in those over 70 and 80, respectively (Taylor et al., 2003), induce crypt fission (Greaves et al., 2006) and a metabolic rewiring that favors malignant transformation (Nikkanen et al., 2016; Smith et al., 2020). So at least in colon, not only nuclear, but mtDNA mutations as well might contribute to organismal aging by driving clonal expansion and senescence (Wolf, 2021b).

Clonal expansion by itself (without necessarily depleting a pool of stem cells) seems to cause many phenotypes of aging as well. Selection of preleukemic clones with mutations imparting growth or survival advantages is assumed to underlie aging (Rossi et al., 2008) and, of course, carcinogenesis (Xie et al., 2014) in the hematopoietic stem cells (HSC) compartment. The diminished reconstituting ability of HSCs from elderly donors shows the decay in HSC function (Sharpless and DePinho, 2007), even though the HSC compartment compensates for a decreased regenerative capacity and skewed differentiation (Geiger et al., 2013; Rossi et al., 2005) with increased self-renewal (Signer and Morrison, 2013; Sun et al., 2014) and elevated absolute HSC numbers (de Haan and Lazare, 2018; de Haan et al., 1997). Impaired hydroxylation of 5-methylcytosine caused by TET2 mutation (Ko et al., 2010) leads to increased HSC self-renewal, splenomegaly (Moran-Crusio et al., 2011), clonal expansion, myeloid transformation and malignancy (Quivoron et al., 2011), and increased risk for coronary heart disease (in humans) (Jaiswal et al., 2017), all very much resembling the changes seen in aging (de Haan and Lazare, 2018; Geiger et al., 2013). Clonal expansion of a plasma cell manifesting in monoclonal gammopathy is present in 3.2 percent of patients over 50, increases with age (Kyle et al., 2006), and is an important risk factor for and precursor to multiple myeloma (Weiss et al., 2009). Clonal hematopoiesis without other hematologic abnormalities (CHIP), almost doubles risk for coronary heart disease (Jaiswal et al., 2017). Even though only ≈20 % of leukocytes are of clonal origin on average, CHIP carriers have a markedly increased risk of myocardial infarction, stroke, perhaps venous thrombosis and pulmonary embolism (Libby and Ebert, 2018) and higher all-cause mortality (Zink et al., 2017). Detection technology determines sensitivity and therefore estimated prevalence and extent of clonal hematopoiesis, which has been estimated from more than 10 % of persons older than 70 years (Jaiswal

et al., 2017), to about 25 % in 65−75 year olds and more than half in those over 85, when using whole genome data (Zink et al., 2017). The senescence marker p16INK4a exacerbates age-associated HSC dysfunction (Janzen et al., 2006) and a single nucleotide polymorphism (SNP) adjacent to p16INK4a increases risk of myocardial infarction 1.64 times (Helgadottir et al., 2007). p16INK4a inhibition has been proposed to improve aged tissue injury repair (Janzen et al., 2006) and senescent HSC removal could reportedly rejuvenate aged HSCs in mice (Chang et al., 2016). Systemic aging induced by a senescent HSC compartment suggest wide-ranging cell non-autonomous effects promoting aging in non-lymphoid organs (Yousefzadeh et al., 2021b).

Human mesenchymal stem cell numbers in bone marrow decline with age (Stolzing et al., 2008). Supporting senescence as a cause of stem cell depletion, muscle stem cell numbers decline with age (Sousa-Victor et al., 2015), and p16INK4a switches them from quiescence to senescence (Sousa-Victor et al., 2014), leading to a shrinking stem cell pool. A SNP near p16INK4a is associated with severely limited physical function in older people (Melzer et al., 2007). Extensive proliferation of a low proportion of highly plastic vascular smooth muscle cells (VSMCs) results in VSMC accumulation after injury and in atherosclerotic plaque formation (Chappell et al., 2016; Wirka et al., 2019). Atherosclerotic plaques derive from clonal expansion of a single (Misra et al., 2018) or few (Jacobsen et al., 2017) VSMCs that give rise to all the smooth muscle-derived cells comprising the majority of cells in an advanced plaque (Jacobsen et al., 2017; Misra et al., 2018). Whether clonal expansion is causally involved in human atherosclerosis as well is certainly a key question in understanding this extremely important human pathology.

DNA damage is a, if not the, major determinant of mutation accumulation, so DNA damage obviously play a central role in driving the aging process. Associations of DNA repair with life span have been observed long ago (Hart and Setlow, 1974). The DDR plays a central role in determining cell fate as one of several triggers that eliminate cells from the stem cell pool through senescence (Hernandez-Segura et al., 2018), apoptosis (Roos and Kaina, 2013) and differentiation (Harris, 1990; Inomata et al., 2009). These mechanisms evolved to limit tumorigenesis, but might also eliminate damaged cells and exhaust the stem cell pool without clonal expansion. It is somewhat premature to speculate about the relative contribution of replication-dependent mutation accumulation versus replication-independent DNA damage-mediated effects to organismal aging. Naturally, accumulating DNA damage is better at explaining aging in post-mitotic tissues and infrequently dividing cells.

Induction of replication in normally quiescent stem cells increases ROS, which trigger cell senescence (Sharpless and Sherr, 2015). ROS activating p38 MAPK limit the lifespan of hematopoietic stem cells (Ito et al., 2006). ROS cause telomere shortening and limit the carcinogenic potential of expanding cells by inducing telomere-dependent senescence (Passos et al., 2007). Activation of quiescent HSCs leads to ROS-mediated DNA damage and stem cell attrition (Walter et al., 2015). mTOR-mediated expansion of T cells also induced ROS (Mak et al., 2017; Sena et al., 2013), and loss of APC in intestinal stem cells triggers RAC1-driven ROS production during colorectal cancer initiation (Myant et al., 2013). ROS production therefore seems to be a shared physiological response occurring during stem cell exit from dormancy and proliferation, resulting in DNA damage and cell senescence that is maintained by a feedback loop (Passos et al., 2010; Takahashi et al., 2006) designed to trap cells in a senescent state and limit the proliferation of cells once outside a carefully maintained stem cell niche. This tightly connected interplay of ROS, DNA damage and telomere shortening triggered by cell division and expansion illustrates the obsessive-compulsive preoccupation of long-lived mammalian cells with tumor suppression. Much of the DNA damage deciding cell fate might be elicited as a consequence of proliferation and replication stress (Di Micco et al., 2006; Gaillard et al., 2015; Zeman and Cimprich, 2014), so that while DNA damage certainly plays a central roles in the aging process (Schumacher et al., 2021), DNA damage is a signaling intermediate (Flach et al., 2014).

DNA damage is used as a primary driver of tumor suppression mechanisms like senescence and apoptosis because of a fundamental problem in cell fate decision: mutations are invisible. Once a mutation is established during cell division, it is indistinguishable from its genuine, non-mutated counterpart. To limit malignant transformation, cells have evolved DNA damage as a proxy for potentially oncogenic DNA lesions mostly out of necessity (telomere shortening is another proxy). This is the reason why DNA damage is integrated into so many elaborate mechanisms of tumor suppression. Because DNA damage is a useful sign of dangerous damage and excess proliferation, it contributes to aging as a mediator of cell elimination despite not being the true cause of aging.

Further arguments against DNA damage (opposed to mutation-driven clonal expansion or excess proliferation in general) as a proximal cause of aging include that short- and long-lived species differ in mutation rates (Milholland et al., 2017) but not in nuclear DNA damage rates (Barja and Herrero, 2000). CR does not reduce DNA damage significantly in humans (Heilbronn et al., 2006). In mammals, long-lived and/or larger species tend to induce DDR-mediated apoptosis or senescence to prevent malignancy, whereas short-lived species tolerate genomic instability (Croco et al., 2017). Peto's paradox (Peto, 2015) and the centrality of mutation and proliferation in cancer (Tomasetti et al., 2017) and tumor suppression (Campisi et al., 2001; Franceschi, 1989) also argue against a simple age-related increase in DNA damage as the proximal cause of aging. Rapamycin is probably the most powerful age-retarding pharmacological intervention because mTOR sits at the end of several proliferative signaling chains (Sudarsanam and Johnson, 2010), including that from IGF-1 to PI3K, PTEN, Akt and finally mTOR (Chappell et al., 2011; Singh et al., 2019). Rapamycin is something like an anti-proliferative kill switch(Murakami et al., 2004), since mTOR integrates diverse environmental cues to control growth and proliferation, processes that use large amounts of energy and nutrients (Laplante and Sabatini, 2012). Rapamycin would therefore, despite scary side effects (Johnson and Kaeberlein, 2016; Laplante and Sabatini, 2012; Salmon, 2015), be efficient in retarding aging mediated by mutation and clonal expansion (Johnson et al., 2013; Martinet et al., 2014). Protein restriction reduces mTORC1 signaling only in male mice (Richardson et al., 2021), and it's male-only sex-specific effects resemble that of rapamycin (Strong et al., 2020), suggesting that proliferative mTOR signaling is the key component of nutritional life span extension, at least against an obese control. If DNA damage would cause aging, increased cell proliferation would, at least in proliferating tissues, be expected to slow aging, since replication is accompanied by DNA repair and stringent cell cycle checkpoints.

2.12. Limitations of the tumor suppression theory of aging

The tumor suppression theory of aging certainly cannot explain all aspects of aging. The theory cannot explain aging of invertebrates such as yeast or postmitotic worms. Long-lived proteins such as the lens (protein) in the human eye age independent of cell replication. Turnover of human cardiomyocytes(Bergmann et al., 2009) and adipocytes (Spalding et al., 2008) is slow. Similarly, neurons are essentially postmitotic and might lose function with age independent of mutation and cell replication. However, recent, and therefore still potentially unreliable results in mice suggest that some loss of brain function with age might be caused by cell senescence in supporting cells other than neurons (Bussian et al., 2018; Zhang et al., 2019).

Mechanisms of aging mediated by steady state DNA damage probably complement replication- and clonal expansion-mediated aging, but are also sufficiently different conceptually to treat and think of them as separate mechanisms. DNA damage-mediated loss of function might certainly play an important role in the age-related functional decline of post-mitotic tissues (Lu et al., 2004). Old cells exist in a variety of organs (e Drigo et al., 2019), and even though their functional significance is

not yet clear, their influence would be independent of mutation and clonal expansion. Loss of genomic integrity (if this is meant to include both DNA damage and somatic mutations) is probably the most important causal mechanism of aging, if there is any remotely dominant single cause. And while a lot of DNA damage determining cell fate decisions might be a consequence of proliferation (Di Micco et al., 2006), and stem cell exhaustion the consequence of tumor suppression mechanisms (Janzen et al., 2006), DNA damage-mediated cell elimination might be antagonistically pleiotropic: it eliminates cancer during early and middle life, but in late life, it might in many cases be triggered "by mistake", i.e. due to DNA damage that has accumulated with age but in the absence of oncogenic mutations, and therefore contribute to the exhaustion of stem cells (Fig. 1).

Replication-independent aging might nevertheless be a relatively minor problem in the evolution of long lifespans. Despite lens proteins being much the same in humans and mice and experiencing similar wear and tear, temperatures, oxygen concentrations and exposure to external sources of damage, mice develop cataracts even though they age much faster than humans (Wolf et al., 2000). Why do human lenses last ~ 20 times longer? Good eyesight is valuable so natural selection has eliminated the earlier cataract formation we inherited from our short-lived ancestors, and selected those that make better lenses so that the decay of lens protein is slowed enough to make the lens last the human lifetime. Age-related hearing loss displays similar characteristics, appearing in old mice (Brown et al., 2008; Johnson et al., 1997) despite a mouse cochlea being built much the same as a human cochlea. Long-lived proteins such as lenses, dermal collagen or joints, and organs like the cochlea are relatively small parts of the human body, and the energy cost necessary to make them last longer is probably negligible compared to the benefit of slower aging.

The tumor suppression theory of aging postulates cancer and aging as the direct and indirect consequence of somatic mutations, with increased cancer and premature aging as the two principal outcomes of defective genome maintenance. Why one can dominate over the other seems to depend on the specific molecular nature of the defect. Elevated carcinogenesis seems to be the dominant phenotype of defective (error-prone) DNA replication, which probably produces somatic mutations in the relative absence of DNA damage (Heitzer and Tomlinson, 2014; Prolla et al., 1998). On the other hand, elevated DNA damage and the specific molecular nature of it might favor the induction of tumor suppression and cell elimination, leading to premature aging rather than cancer (Yousefzadeh et al., 2020), as is observed after artificially elevated tumor suppression (Ferbeyre and Lowe, 2002). Predicting whether cancer or aging is the penetrant phenotype of defective genome maintenance remains difficult (De Renty and Ellis, 2017) and whether cancer or aging is the dominant outcome probably also depends on organ-specific properties such as replication frequencies, the tissue microenvironment and other unknown factors.

2.13. Consequences for delaying aging

Removal of senescent cells would currently seem to be the only widely discussed intervention that offers reasonable promise to alleviate some aspects of aging. The large variation in the pace of tissue- and cell-specific mutation accumulation (Wang et al., 2009; Yousefzadeh et al., 2020) suggest that aggressive, global removal of senescent cells might have unpredictable side effects, but also that stem cells with no or few oncogenic mutations should remain in most organs, and these cells might regenerate the organ after senescent cells are removed. Removing senescent cells can apparently reverse some aspects of aging (Baar et al., 2017; Baker et al., 2016, 2011) and seems to have convinced many that senescent cells are responsible for many, if not most, of the aging phenotypes (Bhatia-Dey et al., 2016; Borghesan et al., 2020; McHugh and Gil, 2018). Even in the brain, an organ in which even partially preventing or reducing aging is seen as particularly difficult due to the central role of largely post-mitotic neurons, clearing senescent astrocytes and microglia could reportedly prevent pathology and preserve cognitive function (only in mice, of course) (Bussian et al., 2018). Removal of senescent oligodendrocyte progenitor cells was also reported to ameliorate cognitive deficits in a model of Alzheimer's disease (Zhang et al., 2019). Given that preserving brain function is so indispensable for successful aging, these findings are certainly cause for optimism. On the other hand, prominent clinical failures (Dolgin, 2020) show that, despite the same substance being very effective in pre-clinical research (Jeon et al., 2017; Villanueva, 2017), in the real world, senescent cells and their deleterious effects might not melt away like the catchy name "senolytic" suggests. This can have many reasons, but given the in some cases additional commercial incentive to represent results as encouraging as possible (De Magalhães et al., 2017), one can only assume that some longevity research is even less reproducible than life science in general (Drucker, 2016). Independent evaluation of small molecule senolytics in the NIA Interventions Testing Program (Nadon et al., 2017) might, if successful, add welcome reassurance and credibility to senescent cell removal as a viable anti-aging intervention. Furthermore, small molecule agents might be a blunt weapon of questionable specificity against senescent cells. If surface markers specific for even fractions of senescent cells do exist, eliminating key populations of senescent cells using CAR T cells might be a more targeted approach with less side effects (Amor et al., 2020).

Senescence is not the only way to deal with malignant and pre-malignant cells: eliminating them by apoptosis is an alternative option. Apoptosis seems to be favored by animals with very large body sizes (Abegglen et al., 2015; Sulak et al., 2016; Vazquez et al., 2018). Nudging pre-malignant cells towards apoptosis rather than senescence might be one way of reducing the burden of senescent cells and retard some phenotypes of aging. The increased cancer resistance that many large animals had to evolve independent of humans (Vazquez and Lynch, 2021) might very well give valuable hints at how to suppress cancer in humans as well (Keane et al., 2015; Seluanov et al., 2018).

Why did large, long-lived animals develop additional tumor suppression, but not better DNA repair and copying mechanisms? Gene duplications are a common genetic event (Reams and Roth, 2015), so enhanced tumor suppression via duplication of tumor suppressors (Vazquez and Lynch, 2021) might be genetically more pliable (Wagner, 2011). Better DNA repair might also be quite costly, since top level stem cells constitute only a small part of the body, whereas unnecessary maintenance and removal of DNA damage in already differentiated cells might constitute a considerable waste of energy.

If cancer and aging are both driven by somatic mutation, slowing it down is the only plausible way to prevent aging in healthy weight humans. Like for the primary prevention of cancer (Tomasetti et al., 2017), reducing the error rate of our DNA polymerase or more DNA repair prior to cell division would be expected to help. Also annoying is the unavoidable temperature-sensitive spontaneous deamination of cytosine residues to uracil or thymidine (Duncan and Miller, 1980; Nabel et al., 2012), which has to be constantly repaired (Krokan and Bjørås, 2013) and might contribute significantly to glioblastoma, prostrate, colorectal and other cancers (Martincorena and Campbell, 2015; Poulos et al., 2017). But even if primary prevention of most somatic mutations seems impossible for now, this does mean that all humans age at the same rate. Relatively little insight into the complex genetic determinants of human longevity and the large genetic diversity of humans also suggest that many factors determining human maximum lifespan remain undiscovered. The moderate yet significant heritability of longevity proves that genes produce variations in the individual rate of aging (Brooks-Wilson, 2013; Kaplanis et al., 2018; Robine and Allard, 1998; Vijg and Suh, 2005). Genome-wide association studies using the rate of mutation accumulation rather than achieved life span might be much more sensitive towards revealing genetic variations associated with better maintenance of genomic integrity in humans and should be feasible given the exploding amounts of genetic data available (Kaiser, 2015; Turnbull et al., 2018).

In addition, strategies to reduce DNA damage would certainly be an important tool to slow aging as they would reduce the rate of somatic mutation per cell division. Transcriptional regulation of maintenance functions such as DNA repair might be modulated favorably by hormesis. Efforts to increase the activity of protective transcription factors like NRF2 have been ongoing for years (Maher and Yamamoto, 2010; Martín-Montalvo et al., 2011; Strong et al., 2016), but the unwanted promotion of metastasis seems to be a reoccurring side effect of increased resistance to oxidative stress (Piskounova et al., 2015; Schafer et al., 2009; Sporn and Liby, 2012) and explains the cancer-promoting effect of increased NRF2 (de la Vega et al., 2018) and anti-oxidant supplementation (Albanes et al., 1996; Bjelakovic et al., 2007; The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group, 1994; Lignitto et al., 2019; Wiel et al., 2019).

There is certainly potential for human life extension. Many humans have access to an essentially unlimited supply of food, and would be able to invest heavily in genome maintenance without starvation. Spending more energy on maintaining DNA integrity might even allow some weight loss without having to exercise. The immune system (a critical factor for early survival) might be modulated and chronic sterile inflammation subdued to increase health span or even reverse some aspects of aging (Adler et al., 2007; Yousefzadeh et al., 2021b). Except during a viral pandemic, reducing activity of cytidine deaminase (Vieira and Soares, 2013), which converts cytosine to uracil in viral, but also in exposed single-stranded loops of normal DNA and leads to characteristic G->A mutations (Petljak et al., 2019), might be worthwhile, as such mutations can make significant contributions in cervical, bladder, head-neck and lung cancer (Martincorena and Campbell, 2015).

3. Conclusion

The current sorry state of aging research is attributable to two major problems. As laid out in detail in the preceding publication (originally part of this one (Wolf, 2021a)), caloric restriction has probably been misinterpreted as delayed aging. This might seem surprising given the lack of insight and consensus on what causes aging, but is understandable, since, against an obese control, caloric restriction really does delay most aspects of aging. And the vast majority of laboratory animals given unlimited access to food are very obese. But weight loss induced through pharmacologic or genetic means is also often ignored or mistaken for a reduction in the rate of aging. Quite a number of chemicals can, at an optimized, non-toxic dose, induce weight loss, and the accompanying increase in life span is often attributed to their effects on specific pathways rather than to generic weight loss (Wolf, 2021a). Over the past two or three decades, many academics working on retarding aging were apparently convinced that great strides have been made in tackling, or even solving the scientific problem of aging due to a mistaken exuberance about what appeared to be breakthroughs in the manipulation of mammalian aging (Campisi et al., 2019; Partridge et al., 2020). This has led to the impression that human longevity should be malleable using pharmacologic or even nutritional interventions (Fontana and Partridge, 2015; Madeo et al., 2019).

The second problem is the lack of progress on elucidating the molecular mechanisms of aging. This is, in my opinion, not due to a lack of effort, as some seem to think (Hayflick, 2021). I think it is more due to the pervasive acceptance of CR as delayed aging, and the resulting focus on elucidating its molecular mechanisms (Sciences, 2009). Medicine can be successful without understanding causality, and discover life-saving interventions by careful observation and trial and error. This convenient strategy, the ignorance of obesity and the convenience of mice and letting them eat how much they want, resulted in the acceptance of CR and other weight loss agents as interventions that prevent aging, not just obesity. To be worthy of public trust and funding, aging research really needs to open its eyes to what has been in plain sight for many years now, the failure of CR to delay aging in anything else than gluttonous obese laboratory animals(Mattison et al., 2012) and their human counterparts. But rather than those trying to defend CR with invertebrate distractions and linguistic trickery (Fontana et al., 2010), Planck's principle looks more likely to eliminate the sceptic (Hayflick, 2010).

On the other hand, thanks to the high prevalence of obesity in regions of middle and high incomes, many of the CR mimetics discovered in mice might turn out to be excellent weight loss drugs. Metformin, for example, can, through the induction of weight loss, prevent diabetes and many other ailments related to excess body weight in a high risk (i.e. obese) population (Knowler et al., 2002). Whether this is labelled prevention of aging, prevention of disease, or simply prevention of obesity might be important for politics, marketing or funding, but is irrelevant from a medical perspective. Of course, CR mimetics might have positive effects beside weight loss, but these should be convincingly demonstrated in a non-obese cohort before insinuating any beneficial impact on health or life span in normal weight individuals.

The disposable soma theory of aging, with its (correct) prediction of damage to macromolecules as the ultimate cause of aging (Kirkwood and Holliday, 1979) might have led many to think of (besides cancer, of course) damage and loss of function as the primary consequence of somatic mutation (Vijg and Dong, 2020; Vijg et al., 2017; Vijg and Montagna, 2017). The tumor suppressor theory of aging, if it were true, would put forward three new concepts in thinking about aging: First, mutations driving excess cell division are proposed as the main, proximal cause of aging and the relevant type of somatic mutation, not (like the prevailing view) those causing loss or impairment of function. Mutations arise mostly during proliferation, so second, the pace of stem cell division is concluded to determine the rate of aging, together with the mutation rate per mitosis. This makes the tumor suppression theory of aging compatible with findings linking longevity to growth, nutrition and obesity through their effects on the rate of cell division. And third, dedicated tumor suppression mechanisms like cell senescence are postulated to cause most of the phenotypes of functional decline that characterize aging. Cancer and aging would be seen as the side effects of too much and too little capacity for self-renewal, the latter having evolved to suppress the further. Because it is rests significantly on evolutionary arguments, the tumor suppression theory of aging, like the antagonistic pleiotropy and disposable soma theories of aging, explains primarily why we age: because the positive effect of tumor suppression through senescence and cell elimination was large enough to improve reproductive success. Since the etiology of cancer is well understood (Michor et al., 2004; Vogelstein et al., 2013), it is concluded that somatic mutations are, albeit indirectly, responsible for aging as well. Germline mutation accumulation rates, a reasonable proxy for the genetic accuracy of cell division in individual humans, predict longevity and reproductive life span (Cawthon et al., 2020). Human subjects in the top and bottom quartile seemed to have an approximately two-fold difference in their germline mutation rate, and a 4.7 year difference in life span (Cawthon et al., 2020).

3.1. An inconvenient truth

If the tumor suppression theory of aging would be correct, the only way to retard human aging would be a reduction of somatic mutation. Preventing aging would be the same as preventing cancer. Even before the Tomasetti and Vogelstein death knell (Tomasetti et al., 2017), primary prevention of cancer was an uphill struggle. For example, despite its notoriousness in nutrition research, there is limited evidence for the carcinogenicity of red meat in humans (Bouvard et al., 2015), and a complete overhaul of western dietary habits is only "likely" to result in a modest (~ 10 %) reduction in risk for certain cancers(Bouvard et al., 2015; Chan and Giovannucci, 2010). As suggested (Tomasetti et al., 2017), secondary prevention measures like, for example, colonoscopic polypectomy (Winawer et al., 1993; Zauber et al., 2012) are more realistic and offer better returns.

Unfortunately, reduction or prevention of somatic mutation is something that remains thoroughly out of reach of current medical

technology. The problem of aging will probably defy the assault of human ingenuity for some time to come.

In the meantime, removal of senescent cells seems to offer a reasonable chance of alleviating many phenotypes of very old age (Amor et al., 2020). Cell senescence is antagonistically pleiotropic, and accumulation of senescent cells probably an evolutionary accident brought about by the unforeseen increase in average human life expectancy. Together with a second antagonistically pleiotropic phenomenon, the age-related emergence of systemic and excessive chronic sterile inflammation (Furman et al., 2019; Ridker et al., 2017), these two phenomena might be mutually reinforcing evolutionary accidents responsible for many of the pathogenic processes promoting the irreversible functional decline of very old age. Evolution shaped human physiology, and survival of childhood was the biggest hurdle for individual reproductive success (Finch, 2010; Volk and Atkinson, 2008). A vigorous immune system helps enormously to survive childhood, but probably haunts modern humans now regularly surviving into the evolutionary shadow (Yousefzadeh et al., 2021b). Even though they do not prevent aging per se, in terms of looking at realistic strategies for increasing human health span, these two processes are, compared to the primary prevention of mutation, probably lower hanging fruit and offer plentiful possibilities in postponing the dreaded symptoms of old age.

Author contributions

A.M.W. wrote the paper.

Declaration of Competing Interest

The author declares no competing interests.

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Appendix A. Supplementary data

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