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Aging and Cancer

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Synonyms

Evolutionary connections between aging and cancer

Overview

Is aging a cause of cancer or cancer a cause of aging? Here the evolutionary connections between aging and cancer are debated, and it is shown that cancer is an unlikely evolutionary cause of aging.

Nowadays aging is explained in two completely opposite ways. The first (non-programmed aging paradigm) explains aging as something not determined by adaptive necessities but due to the progressive accumulation of the effects of many degenerative phenomena. The second (programmed aging paradigm) explains aging as an adaptive phenomenon and therefore genetically determined and regulated.

One of the main differences between the two interpretations is that programmed aging paradigm predicts the existence of specific genetically programmed mechanisms that determine aging, and indeed these mechanisms are absolutely necessary to admit the possible validity of this thesis. On the contrary, the non-programmed aging paradigm does not admit the possibility of such mechanisms, and indeed their existence, if unexplained in other ways, would make this paradigm untenable (Libertini 2008).

However, it is well known the existence of sophisticated mechanisms that limit the ability of cell duplication and cause other alterations in proportion to the number of replications (Fossel 2004; Libertini and Ferrara 2016). These mechanisms are based on the progressive shortening of the telomere if not counteracted by telomerase enzyme, which is full active in germ line cells but more or less inhibited in other cells (Fossel 2004; Libertini 2015a). These limits in cell duplication together with the related phenomena of cell senescence and gradual cell senescence are interpreted by programmed aging paradigm as mechanisms that are essential to explain aging (Libertini 2015b).

For the opposite thesis, the aforementioned mechanisms constitute a big problem, such as to make the whole thesis untenable, if for their existence a valid justification different from that proposed by the programmed aging paradigm is not given.

For this question, which is certainly fundamental for the validity of non-programmed aging paradigm even if it is often overlooked by its

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supporters, there is only one interpretative proposal so far, namely, that the mechanisms limiting cell duplication and the correlated phenomena constitute a general defense against the pathological proliferation of cells, namely, the oncological diseases. For this explanation, aging would be only a harmful side effect of a necessary and indispensable defense (Campisi 1997; Wright and Shay 2005; Rodier and Campisi 2011). This has been effectively described as an evolutionary trade-off between cancer and aging (Campisi 2000; Stone et al. 2016; Young 2018), an idea that is well consistent with two popular explanations of aging as non-programmed phenomenon, antagonistic pleiotropy theory (Williams 1957) and disposable soma theory (Kirkwood 1977).

However, there are numerous objections to this explanation that make it completely unacceptable (Fossel 2004; Libertini 2008, 2013; Milewski 2010; Mitteldorf 2013). It is opportune to examine them carefully because if this explanation is untenable, there is no other proposed justification for such mechanisms in the context of non-programmed aging paradigm, and consequently, with the overcoming of this last trench of defense, this paradigm becomes no longer sustainable.

Here is a brief description of these objections:

1. There are species that at ages existing in the wild show no age-related increasing mortality (e.g., bivalve mollusks, sturgeon, rockfish, turtles, certain perennial trees (Finch 1990)). The animals with this characteristic have been defined as animals with "negligible senescence" (Finch 1990, p. 206). Disregarding the fact that their existence is not explained by non-programmed aging paradigm and is hardly compatible with it (Libertini 2015a), moreover these species show no age-related increasing oncogenic risk, as proven by their constant mortality at any age. For non-programmed aging thesis, this would mean that a constant oncogenic risk is compatible with the absence of detectable senescence, while this would be not true for species with age-related increasing mortality. This inconsistency is not explained by non-programmed paradigm (Libertini 2008).
2. The same level of telomerase activity of young individuals has been shown in old individuals of "animals with negligible senescence" as rainbow trout and lobster (Klapper et al. 1998a, b), and rockfish species (Black 2002). Therefore, for these species, as proven by their constant mortality rate, the absence of inhibition of telomerase activity is not a cause of increasing oncogenic risk. The hypothesis of an oncogenic effect of telomerase is implausible in these species, and the hypothesis that telomerase is an oncogenic factor in other species should be demonstrated (Libertini 2008).
3. If telomerase is inhibited, telomeres shorten at each duplication, and when they reach a critical length, there is dysfunctional telomere-induced instability of the chromosome and so an increased vulnerability to cancer (DePinho 2000; Artandi 2002; Artandi and DePinho 2010; Ma et al. 2011; Wu et al. 2003). In patients suffering from dyskeratosis congenita, where telomerase activity is altered, there is a high incidence of cancer (Dokal 2000). Therefore, telomerase activity is not an oncogenic factor, and an unrestrained telomerase activity, a common feature in the successive stages of malignancy, has been described as subsequent to and not preceding cancer onset (Fossel 2004): "The role of the telomere in chromosomal stability (Blagosklonny 2001; Campisi et al. 2001; Hackett et al. 2001) argues that telomerase protects against carcinogenesis (Chang et al. 2001; Gisselsson et al. 2001), especially early in carcinogenesis when genetic stability is critical (Elmore and Holt 2000; Kim and Hruszkewycz 2001; Rudolph et al. 2001), as well as protecting against aneuploidy and secondary speciation (Pathak et al. 2002). The role of telomerase depends on the stage of malignancy as well as cofactors (Oshmura et al. 2000); expression is late and permissive, not causal (Seger et al. 2002)" (Fossel 2004, p. 78).
4. In normal mice, increased telomerase activity – artificially induced – determines an increased life span without an increased

incidence of cancer (Bernardes de Jesus et al. 2012).

5. The replicative senescence and the alterations of cell functions determined by cell senescence and by gradual cell senescence (see the entries) weaken the capacities of immune system (Fossel 2004). For a long time, it is known that the efficiency of this system is inversely related to cancer incidence (Rosen 1985). It appears illogical that mechanisms hypothesized as a defense against cancer would weaken an important defense against it (Libertini and Ferrara 2016).
6. Gradual cell senescence, i.e., the progressive repression of critical regulatory sequences in subtelomeric DNA as a consequence of telomere shortening (Fossel 2004; Libertini and Ferrara 2016), contributes to progressively weaken the functional capacities of the tissues and the fitness of the whole organism but cannot help against the cell proliferation of a neoplasia.
7. Cell senescence, a fundamental cellular program (Ben-Porath and Weinberg 2005) triggered with increasing probability in relation to telomere shortening (Blackburn 2000), is characterized by replicative senescence and by the alterations of gradual cell senescence at the highest level (Fossel 2004). While replicative senescence, i.e., the block of further duplications, could be in support of the thesis that cell senescence is a defense against cancer, senescent cells manifest also the secretion of substances that increase both mutation rates and oncogenic risk (Parrinello et al. 2005; Coppé et al. 2008). Moreover, in mice, experiments that eliminate selectively senescent cells (defined as $p16^{Ink4a+}$ cells), apart from contrasting several age-dependent changes and increasing life span, show a delay in the progression of malignant diseases (Baker et al. 2016). In short, cell senescence increases oncogenic risk and is hardly justifiable as a defense against cancer, as well said by Mitteldorf: "If cellular senescence is designed to cut off cancerous cell lines, why would senescent cells remain alive and toxic? They could, instead, be programmed to be good citizens and dismantle themselves via apoptosis to facilitate recycling of proteins and nutrients. The fact that senescent cells emit poisons is completely consonant with the theory that cellular senescence is a form of programmed organismal death. But from the perspective of the cancer theory, the poisoning of the body must be regarded as an unexplained evolutionary error" (Mitteldorf 2013, p. 1058).
8. "Senescent cells are present in premalignant lesions and sites of tissue damage and accumulate in tissues with age" (Biran et al. 2017, p. 661). Here, to maintain the hypothesis that cell senescence is a defense against cancer, it is necessary to explain why, before the onset of cancer, senescent cells accumulate in premalignant lesions and in the tissues of elderly persons, causing inflammation and so increasing the risk of cancer.
9. A work shows that, in cancer therapies, "several chemotherapeutic drug induce [cell] senescence" (Demaria et al. 2017, p. 165) and that the elimination of these therapy-induced senescent cells "reduced several short- and long-term effects of the drugs, including ... cancer recurrence ..." (Demaria et al. 2017, p. 165). However this does not prevent the author to proclaim that "Cellular senescence suppresses cancer by irreversibly arresting cell proliferation" (Demaria et al. 2017, p. 165).
10. In a human population studied in the wild (Ache of Paraguay), the survivors at ages 60 and 70 were approximately 30% and 20%, respectively, but there was no detectable incidence of cancer (Hill and Hurtado 1996). Only for few older individuals (> 70 years, when the survivors were only 1 in 5), the cancer could have been a possible cause of death. The rarity of cancer in wild populations is confirmed by same anecdotal but authoritative testimonies by Price (Price 1939):

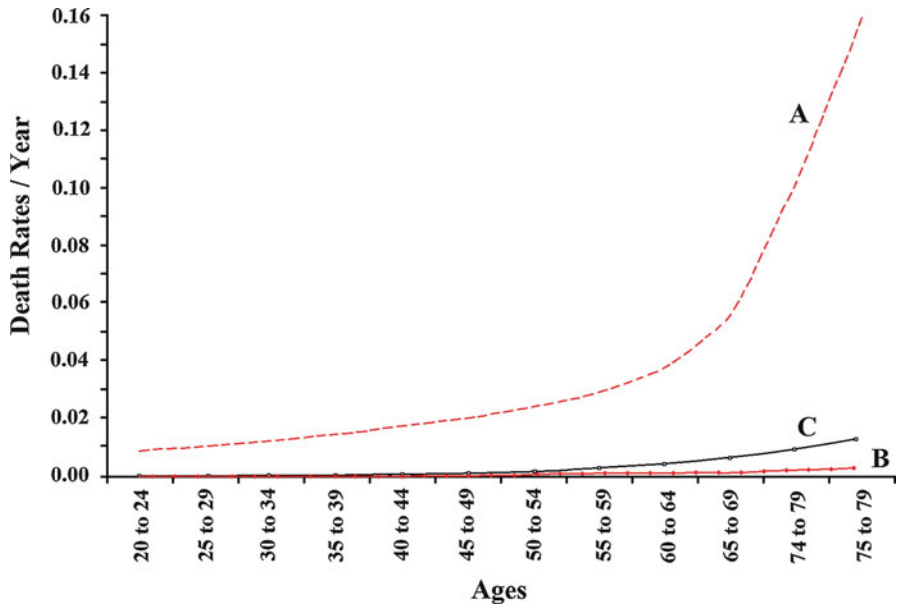
    Dr. J. Romig, "a surgeon [of Anchorage] of great skill and with an experience among the Eskimos and the Indians, both the primitives and the modernized . . . stated

that in his thirty-six years of contact with these people he had never seen a case of malignant disease among the truly primitive Eskimos and Indians, although it frequently occurs when they become modernized" (Price 1939, p. 83).

Dr. J. R. Nimmo, the government physician in charge for Torres Strait Islands people, told Dr. Price that: "in his thirteen years with them he had not seen a single case of malignancy, and seen only one that he had suspected might be malignancy among the entire four thousand native populations. He stated that during this same period he had operated on several dozen malignancies for the white populations, which numbers about three hundred" (Price 1939, p. 179).

Therefore, for human populations, cancer is a rare disease in the wild, while it is well known that its frequency in modern population is high. If we compare the death rates of Ache in the wild with the possible death rates by cancer in the same population and the observed death rate by cancer in a modern population (Fig. 1), it possible to note that death rates caused by aging are always much greater than death rates caused by cancer. It appears illogical that a hypothetic defense against cancer determines the death of the greater part of the population, unaffected by cancer, and, using only data from observations in the wild, before cancer becomes a detectable cause of death (Libertini 2013).

11. Yeast (*S. cerevisiae*), a unicellular organism, reproduces by division into two cells, defined as "mother" and "daughter" cells. While the daughter cells are identical to the parent cells, mother cells are able to reproduce only for about 25–35 duplications (Jazwinski 1993), and, in proportion to the number of duplications, there are (i) increasing metabolic alterations (Laun et al. 2001; Lesur and Campbell 2004; Herker et al. 2004; Büttner et al. 2006; Fabrizio and Longo 2008) and (ii) growing



Aging and Cancer, Fig. 1 Image from (Libertini 2013), modified. A, overall death rates for Ache population in the wild (Hill and Hurtado 1996); B, plausible cancer death rates for the same population (Libertini 2013); C, cancer death rates in a modern population (Great Britain (General Register Office for Scotland 2010, etc.)). The causes of the strong increment of mortality shown in A cannot be a defense against the causes of the much lower mortality shown in B or even in C

vulnerability to replicative senescence and apoptosis (Jazwinski 1993; Fabrizio and Longo 2007; Laun et al. 2007). These phenomena are equivalent to aging in multicellular organisms, and a phylogenetic relation has been highlighted (Libertini 2015b). However, for this species their justification as defense against cancer is impossible because it is a unicellular species (Libertini 2015b).

Conclusion

The evolutionary paradox of a hypothetical defense against cancer, which in many ways causes a much higher mortality of the cancer itself, is avoided or perhaps underestimated by the supporters of non-programmed aging paradigm.

An exception is a work of Rodier and Campisi (2011) in which this paradox is explicitly stated and an explanation is sought. The authors recognize that the altered secretions of senescent cells have various actions that favor aging (e.g., inflammation, alterations of angiogenesis, and tissue integrity) and that the reduced number of stem cells jeopardizes healing and repair. They try the pleiotropic justification maintaining that there are early benefits avoiding cancer that are greater than the damage manifested by the deaths at later ages. In this explanation, they do not attempt a quantitative accounting, and the evidence before reported says that this explanation is untenable.

Moreover, they claim, without any theoretical argument or empirical proof, that a greater expression of telomerase at later ages, which would solve the hypothetical terrible trade-off between reduced cancer risk and aging, is unavailable as possible evolutionary pathway. In short, one of the few attempts to solve the paradox is not based on sound theoretical arguments and is contradicted by evidence.

The possible alternative, i.e., that telomerase restriction, cell senescence, gradual cell senescence, and limits in cell duplications capacities are all part of a complex mechanism aimed to determine aging and limit life span, is not considered by the authors: "The hypothesis that telomerase is restricted to achieve a net increase in lifespan via cancer prevention is certainly false. Were it not for the unthinkability of the alternative – programmed death – the theory would be dead in the water" (Mitteldorf 2013, p. 1058).

The obstinate affection by the advocates of nonadaptive aging theory to the hypothetical against-cancer role of telomerase restrictions is likely caused by the absence of any explanation compatible with the nonadaptive hypotheses and as a consequence of philosophical bias (Milewski 2010).

However, some doubts begin to appear even in long-term supporters of the old idea that some phenomena of aging are a defense against cancer: "The senescence response is widely recognized as a potent tumor suppressive mechanism. However, recent evidence strengthens the idea that it also drives both degenerative and hyperplastic pathologies [i.e., cancer], most likely by promoting chronic inflammation. Thus, the senescence response may be the result of antagonistically pleiotropic gene action" (Campisi 2013, p. 685).

Therefore, to counteract the evidence of the carcinogenic effects of cell senescence, the authoritative author postulated a pleiotropic antagonism between advantages and disadvantages of cell senescence.

Summary

There is a known correlation between increasing age and cancer risk. Indeed, even disregarding the cases where cancer is due to the effects of modern unhealthy substances or habits to which the organism is not evolutionarily adapted and whose actions accumulate in relation to age, the age-related telomere shortening increases the risk of telomere dysfunction and cancer. As for a possible paradoxical inverse relationship, namely, that the risk of cancer would be the main evolutionary factor that causes cancer, this hypothesis originates from the fact that the limits in the capacity of cell duplication would be a general defense against possible cancerous proliferations. Since these limits, certainly genetically determined and

modulated, could not be explained if aging as an adaptive and programmed phenomenon is excluded, the binding need to formulate an evolutionary justification for such limits induces to hypothesize that aging is an unfortunate side effect of mechanisms whose primary function is the defense against cancer. However, the evidence is clearly against this thesis.

Cross-References

- Aging Definition
- Aging Mechanisms
- Aging Pathology Cell senescence Gradual cell senescence
- Senolytic Drugs

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