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Aging is an adaptation that selects in animals against disruption of homeostasis☆

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ABSTRACT

During evolution, Muller's ratchet permanently generates deleterious germline mutations that eventually must be defused by selection. It seems widely held that cancer and aging-related diseases (ARDs) cannot contribute to this germline gene selection because they tail reproduction and thus occur too late, at the end of the life cycle. Here we posit however that by lessening the offspring's survival by proxy through diminishing parental care, they can still contribute to the selection.

The hypothesis in detail: The widespread occurrence of aging in animals suggests that it is an adaptation. But to what benefit? Aging seems to have only drawbacks. In humans, ARDs cause today almost all mortality; they include heart disease, cerebrovascular disease, Alzheimer's disease, kidney disease and cancer. Compensation seems unthinkable.

For cancer, the author proposed in a previous study a benefit to the species: purifying selection against deleterious germline genes that when expressed enhance *intracellular energy dissipation*. This multicausal energy dissipation, posited as the universal origin of *cancer initiation*, relates to cellular heat generation, disrupted metabolism, and inflammation. The organism reproduces during cancer's dormancy, and when approaching its end of life, the onset of cancer is accelerated in proportion to the cancer-initiating signal. Through cancer, the organism, now a parent, implements the self-actuated programmed death of Skulachev's phenoptosis. This "first death" enhances by proxy the offspring's chance of "second death" (or "double death") through diminished parental care. Repetition over generations realizes a purifying selection against genes causing energy dissipation.

The removal of the deleterious germline gene mutations permanently generated by Muller's ratchet gives a benefit. We generalize, motivated by the parallels between cancer and aging, the purifying selection posited for cancer to aging. An ARD would be initiated in the organ by multicausal *disruption of homeostasis*, and be followed by dormancy and senescence until its onset near the end of the life cycle. Just as for cancer, the ARD eventually enhances double death, and the realized permanent selection gives a benefit to the species through the selection against germ line genes that disrupt homeostasis.

Given their similarities, cancer and aging are combined in the posited Unified Cancer-Aging Adaptation (UCAA) model, which may be confirmed by next-generation sequencing data. Also because of the emerging important role of cellular senescence, the hypothesis may guide the development of therapies against both cancer and aging.

Introduction: The problem of aging

Aging [1–8] is essentially unexplained. Here we posit, in a nutshell, as explanation that aging is an adaptation that gives a benefit to the species—but not to the individual. In the lineage, it would select against germline genes that disrupt homeostasis. The selection functions in a circuitous way: during the life span, disruption of homeostasis of an organ, say the heart, initiates aging of the organ. At old age, after reproduction, dormancy ends and the initiating signal is activated and amplified. Failure of the organ (heart) is accelerated, causing death. This death in turn decreases the parental care given to the offspring, lessening its chance of survival; this decreases the frequency of the

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adverse germline genes in the population. Both parents and offspring are therefore affected. The combined overall result is selection against the pertinent germline genes.

According to the hypothesis, death by disease sometimes gives a benefit. Moreover, the hypothesis implies an unexpected evolutionary link between parental care and aging (including cancer). The novel ideas relate to primitive processes observable in our own lives and which are considered to be well understood. The ideas are unfamiliar and not easily taken in—they constitute a new, fundamentally novel point of view on life, a truly new paradigm.

Hereafter, we substantiate the hypothesis. For cancer we have in the previous study [9] posited the Cancer Adaption (CA) model[1], which selects against deleterious genes that upon expression enhance energy dissipation. Detrimental to the individual, cancer would, in a clear case of individual-species conflict, over many generations give a benefit to the species. Deleterious genes are permanently added by H.J. Muller's ratchet to the mutational load [10], not only in asexual but in sexual organisms as well [11].

According to Lopez-Otin et al. "At a deeper level, … cancer and aging share common origins." [12]. Many similarities and links between cancer and aging exist, for instance in cellular senescence [13]. The etiology of cancer involves inflammation [14], and Age Related Diseases (ARDs) [15,16] show a similar role for "inflammaging" [17]. Other similarities are polygenicity as shown by GWAS studies [18], involvement of mitochondria [19] and impediment by physical activity [20].

Here we posit for aging also a selection mechanism, but instead of selection against multicausal energy dissipation, selection against multicausal disruption of homeostasis [15,16]. One can therefore similar to the CA speak of the Aging Adaption (AA) model. Parallel partial processes permit the combination of the CA and AA to the Unified Cancer-Aging Adaptation (UCAA) model.

Main novelties in the presented hypothesis for cancer and aging are the roles for (1) Muller's ratchet, (2) cellular senescence, and (3) protection of the young by (4) parental care, diminished by cancer and aging:

> Muller's ratchet → deleterious genes ↑→ mutational load ↑ →
> (Redistribution over chromosomes by crossing-over; in chromosomes with large load:) →
> Cellular senescence ↑→ cancer and aging ↑→ parental death (phenoptosis) ↑→
> Parental care ↓ → protection of offspring ↓→ death of offspring ↑→ mutational load ↓

The model presents a novel point of view on biology and medicine. During an organism's lifetime, conservation of the during evolution acquired genome [21] is considered to be just as important for the species as the creation of new functionality, which receives so much attention in Darwin's *Origin of species*.

We review aspects of aging pertinent for our hypothesis: its complexity, including its fuzziness, and the question whether aging is programmed. Aging is ill-defined [4]. Fremont-Smith wondered [22]: "What, indeed, *do* we mean by 'ageing'?" We consider aging's effects in the lineage, and we make it more definite by relating aging to the large set of linked non-communicable, often chronic, ARDs that plausibly affects all human organs. Thum [23]: "Age-related diseases [affect] all organs in our body."

ARDs are often preceded by senescence, a deterioration with age that lets organs remain functional and that gradually turns from beneficial to adverse [24]. Cellular senescence can be defined by the absence of cell division and the occurrence of β-galactosidase and $p16^{Ink4A}$ activity [13,25]. The long-held idea that senescence protects against cancer is being abandoned. Gonzalez-Meijem et al. [26]:

> Although senescence has historically been considered a protective mechanism against tumorigenesis, the activities of senescent cells are increasingly being associated with age-related diseases, including cancer.

Targeting cellular senescence by senolytics is being investigated as therapy against aging [27,28].

Many human diseases also occur in other animals [29] and, in contrast to earlier assumptions, aging occurs in most animals in the wild [30]. Aging may affect all animal species.

In old age, death is accelerated by organ (tissue) dysfunction through ARDs (Fig. 1). Almost all present human mortality (~90%) can be related to the so-defined aging [31].

After separation of cancer, the multifarious Set of ARDs (SARDs) comprises *cardiovascular disease, cerebrovascular disease, Alzheimer's disease, hypertension, obesity, diabetes (pancreas), osteoarthritis, osteoporosis, Parkinson's disease, kidney disease, liver disease, gallbladder disease, multiple sclerosis, macular degeneration, acute lateral sclerosis and several other diseases of organs* (15 items)—indeed, almost every organ seems affected [23].

Many of these diseases may eventually contribute to a co-morbidity linked to "geriatric syndromes" [34] which comprise at least 6 clinical conditions:

> . . . common conditions that geriatricians treat, including *delirium, falls, frailty, dizziness, syncope and urinary incontinence* are classified as geriatric syndromes. . . . *multiple organ systems*, tend to contribute . . . [emphases added]

In the distant past, old age and the geriatric syndromes may have been rare. Under primitive conditions even a small fitness decrease must lessen survival through its amplification by competition [3]. Today, humans live longer, and treatment of the SARDs and geriatric syndromes constitute a significant part of medical practice.

The complexity of aging is illustrated by the mentioned multifariousnesses: (1) many animal species, (2) many affected organs, (3) many diseases, (4) polygenicity, and (5) at least 6 geriatric syndromes. Additional multifariousnesses comprise: (6) many theories [7,35], (7) many physiological changes [35], (8) many non-coding RNAs [23,36–38], (9) 4 FOXO transcription factors [39,40] with numerous target genes, and (10) 7 sirtuin proteins [41–43] with numerous effects on physiology, (11) many exosomes [44,45], and (12) many investigated pharmaceutical therapies [46].

The search for the fundamental pattern underlying the observations is still on. Goldsmith (2014) states in his book *The evolution of aging* [5] that popular notions on aging are upon close inspection untenable—for instance, that aging involves an accumulation of damage similar to the wear-and-tear processes occurring in machines, or that it involves an accumulation of somatic mutations.

Is aging programmed? In the late 19th century, Weismann gave two arguments supporting this idea [1]. For the first argument, I give Kenyon's formulation (2002) in a personal communication to Mitteldorf [8]:

> The range of time scales for senescence across the biosphere extends from hours to thousands of years. No physical process of deterioration could act with such a variable rate, spanning six orders of magnitude; therefore the rate of aging must result from a biological program under evolutionary control.

In addition to the rate of aging [47], other attributes of aging such as fertility, mortality and survival vary strongly with the species [48]. The second argument has been formulated as "The old must die to make room for the young" [49]. One may therefore speak of the AA—and in

[1] We distinguish (1) the theoretical model, explanation or process, such as say the Cancer Adaptation (CA), and (2) the clinically observable phenomenon, say cancer; the posited AA is similarly distinguished from the clinically observed aging.