Review of: "On the Origin of Aging by Means of Natural Selection"

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Richard Walker is an Honorary Professor of Ageing and International Health at Newcastle University with expertise in aging, particularly focusing on stroke and Parkinson's disease. His current work constitutes a comprehensive and intricate review of the current knowledge regarding aging, but it is too extensive for a single publication. This work has the potential to yield at least two distinct articles: one addressing the implications of Darwinian theory for aging and another delving into the molecular findings in this field. Given my greater expertise in molecular mechanisms, I will confine my review to this aspect of the work. I propose a title such as "Recent Advances in the Molecular Biology of Aging."

As reported by Richard Walker, aging is not caused by the random accumulation of DNA damage, but rather by the loss of redundancy within a finite number of irreplaceable elements, or redundant units, due to DNA double-strand breaks (DSBs) that diminish the population through apoptosis and cellular senescence. The author states:*"It is unclear whether DSBs and their accumulating adverse effects ever rise to high enough levels to explain the observed functional loss and increased disease risk that are hallmarks of aging. This is important because DSB effects decrease redundancy exclusive of ancillary effects of general DNA damage to the soma and thus, would explain how relatively small numbers DSB damage is effective in causing aging throughout the body. I presume that DNA damage doesn't have to accumulate in great amounts since aging can be initiated by relatively fewer and more specific DSB damages to redundant regulatory components of the soma".*

He argues that DNA DSBs involved in aging are non-mutagenic replicative aberrations capable of inducing a DNA damage response (DDR). However, the quality of DSB repair responses tends to decline with age. It is hypothesized that the ability of DSB repair, especially after prolonged exposure to inductive agents, may diminish with age.

The extended molecular biology paper needs to introduce and discuss several new points, such as which cells are susceptible to DSB damage. More recent findings on DSB repair, with a particular focus on protists, cancer, and evolutionary origins, must also be discussed. I propose to answer following questions:

1. Do DSBs occur in stem cells or in non-stem cells as well?

I miss a detailed listing of the cells from somatic tissue that suffer DNA DSB damage. Since the damage has a replicative background, I believe it primarily occurs in stem cells as a result of stress and metabolic changes. Subsequently, the stem cells either undergo apoptosis or become senescent, meaning they are eliminated by apoptosis or not. However, if they are not eliminated, they can no longer proliferate and differentiate (cell senescence). With advancing age, there is a

deficiency of functional stem cells and newly differentiated cells. The remaining non-stem cells accumulate mutations and gradually lose their function and fitness. Senescent stem cells have an altered genome that prevents replication, and altered genomic structures can no longer be repaired as age advances. But why not?

2. Can DNA DSBs really be repaired by HR and NHEJ as previously thought?

The earlier work by Ross and Kaina (2006), as cited by the author, asserts that DSB repair serves as a protective mechanism against apoptosis. In simpler terms, if unrepaired DSBs serve as the primary trigger for apoptosis, then DSB repair becomes an exceedingly crucial anti-apoptotic mechanism. According to Ross and Kaina, DSBs can be repaired through error-free homologous recombination (HR), which predominantly occurs during the late S phase and G2 phase of the cell cycle, or through error-prone non-homologous end-joining (NHEJ), which is more prevalent in the G1 phase. Depending on the phase of the cell cycle in which the DSB forms, defects in DSB repair can lead to varying outcomes. Genomic alterations resulting from the error-prone NHEJ processing of DSBs can trigger apoptosis. However, the text does not provide an explanation for why senescence persists after *error-free* HR repair and what ultimately becomes of senescent cells within the tissue.

The recent work by Xiao Tian et al. (2019), also cited in the present paper, shows that more efficient DNA DSB repair can occur through the SIRT6 protein. The researchers hypothesized that DSB repair plays an important role in determining lifespan, as mutations in DNA repair genes lead to phenotypes that resemble an accelerated aging process. The protein SIRT6 has the ability to promote DSB repair and is responsible for the variation in DSB repair capacity. In the course of the evolution of longevity, SIRT6 has optimized its effect and thus provided new targets for anti-aging measures.

However, experience shows that none of the multicellular mechanisms can definitively repair or prevent all DNA DSBs, resulting in aging and ultimately death. What prevents higher metazoans such as humans from completely repairing defective stem cells and abnormal parts of the genome in old age and enabling stem cells to multiply indefinitely?And how do unicellular organisms cope with their theoretically infinite life and cell division?

3. How are DNA DSBs in protists that damage stem cells and their genomes actually repaired?

Severe, irreversible DNA DSBs, which cannot be repaired through classical mechanisms like HR and NHEJ, are known to occur in protists, such as the parasitic Entamoebae. Entamoeba has an ancestral life cycle comprising an oxygen-sensitive, non-gametogenic germline capable of undergoing an asymmetric cell cycle to differentiate into germline stem cells (GSCs) and an oxygen-resistant somatic cell line that proliferates without differentiation. Excess oxygen, exceeding 6.0% O2, imposes stress on germ cells and germline stem cells, resulting in severe, irreversible DNA-DSBs and the loss of their function including stemness, asymmetric cell division, and differentiation potential. Nevertheless, these defective cells are not completely senescent; they survive and can continue to proliferate as DSCD cells through aberrant symmetric cell cycles.

Neither HR nor NHEJ can prevent the formation of DSCD cells or repair the damaged DSCD cells and their genome, which can, however, be reconstructed by a highly complex repair and reconstruction process of pre-metazoan, unicellular

origin. This mechanism was developed by the common ancestor of Amoebozoa, Metazoa, and fungi (AMF ancestor) and is not part of the repair toolkit of multicellular organisms and humans. When protist DSCDs reaches a significant density, individual cells fuse under the influence of appropriate signals to form multinucleate genome repair syncytia MGRS (homologous PGCC-like structures), where defective nuclei or their progeny fuse to create a giant hyperpolyploid nucleus. This giant nucleus is capable of reconstituting the genome in its original structure and restoring genomic integrity. MGRS generates a multitude of vital daughter cells (spores, buds) through amitosis, which can initiate a new germ and somatic life cycle. If the cell system lacks functional germ cells for differentiation, soma-to-germ transition (SGT) can also produce new differentiating germlines (clones).

References:

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4. Can unrepaired DSBs and DSCD cells lead to cancer and if so, how?

Cancer is a derepression of multicellularity features and a reactivation of the ancient pre-metazoan (unicellular) germ and soma cell cycle. In carcinogenesis, tumorigenesis, and recurrence, non-gametogenic germ cells and stem cells exhibit homologous DSB damage that cannot be repaired by either HR or NHEJ. Therefore, cells utilize homologous MGRS-like structures known as polyploid giant cancer cells (PGCCs). Hyperpolyploid giant repair nuclei can form through cell and nuclear fusion as well as from single DNA DSB-damaged cells. During carcinogenesis, MGRS processes reprogram precancerous DSCD cells for malignant transformation.

References:

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Concluding remarks

Consequently, severe DNA DSB defects leading to the loss of stem cell and differentiation capacity cannot be repaired by classical HR and NHEJ mechanisms. Unfortunately, multicellularity has ceased or lost ist pathways for DSB repair, and this deficiency results in stem cell depletion both in aging and in the pre-cancerous phase. In aging, only SGT/EMT processes can help generate some secondary stem cells and this is precisely one of the challenges of aging SGT/EMT processes lose their efficacy with age, producing fewer and fewer stem cells. As a result, aging somatic cells degenerate due to mutations, fail to fulfill their functions, and do not regenerate.