Review of: "Mutational selection: fragile sites, replicative stress, and genome evolution"

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Potential competing interests: No potential competing interests to declare.

David Haig is Professor of Organismic and Evolutionary Biology, at Harvard University. He has written an excellent paper on fragile genome sites, replicative stress, and genome evolution that reads like a lecture on his particular research and teaching area.. He analyzes the evolution of genes in the *gametogenic germline* of multicellular organisms.

The paper reports on the competition in the gametogenic germline between new mutations and unmutated progenitors, showing that successful genes accumulate functions that are easily broken by small mutational changes, putting their mutants at a selective disadvantage and assuming that their germline phenotypes evolve to be fragile rather than robust. The author shows that genes involved in DNA replication and repair are predicted to evolve traits that challenge their abilities, and concludes that such loss-of-competence mutations are a selective disadvantage that can test the competence of the replication and repair machinery.

The paper is based on Weismann's 1892 germline definition since mutations occurring in any of the germline cells can potentially be transmitted to progeny, whereas mutations in somatic cells cannot. It excludes a recent common definition with totipotent and pluripotent germline cells because these have somatic as well as germ-cell descendants. Germline mosaicism, loss-of-function mutation, and somatic loss-of-function mutations, as well as easily breached germline phenotypes, mutation rejection, and mutation robustness are reviewed. It is shown that mutations can be eliminated by the death of a single cell or a small clone of cells.

I think the evolutionary value of the present work would benefit from comparative insights into the *non-gametogenic (NG) germline* of pre-metazoans, protists, and cancers. The NG germline of protists and cancer derives from the Urgermline of the common AMF ancestor from which amoebozoans, metazoans, and fungi have branched. Homologous to the Urgermline, it is an oxygen-sensitive cell line with easily fragile asymmetric ACD phenotypes that undergo loss of function under stressful hyperoxia. Hyperoxia causes severe unrepairable DNA DSB defects or loss-of-function mutations in the NG germline because it lacks the appropriate cell cycle-bound repair capabilities to repair severe DNA defects. Such cells do not die but switch to a defective symmetric SCD phenotype that can restore the genomic integrity of the germline through cell and nuclear fusion and hyperpolyploid giant nuclei.

However, in the genomes of premetazoans and cancer, it is not as straightforward to distinguish between the germline genome and the somatic genome as suggested by the Weismann assumption. When the ACD phenotype is compromised, a new germline clone can be derived from the somatic cells by soma-to-germ transition (SGT). Somatic cells are oxygen-resistant and the unexpressed germline genome resists hyperoxia in somatic cells without damage.

Somatic cell lines contain both genomes, germline and somatic. Germline mosaicism occurs both in parasitic protists such as Entamoeba in the form of more or less pathogenic or virulent strains and cancers through multiple SGT processes.

References

1. doi: 10.20944/preprints202308.1688.v1

2. doi: https://doi.org/10.1016/j.gimo.2023.100809