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COMMENTARY

A comment on the article of Zoran Ivanovic and Marija Vlaski-Lafarge (2022): On cancer, stemness and deep evolutionary homologies

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The comment of Ivanovic and Vlaski-Lafarge on my article "Cancer genes and cancer stem cells in tumorigenesis: Evolutionary deep homology and controversies" opens up a welcome discussion on the evolutionary history of cancer. The authors have appreciative words about my work, for which I am very grateful. At this point, I would like to contribute a few words on polyploidy, cancer genes, age, and colonial organization.

First, one must distinguish between *somatic polyploidy*, *genetic polyploidy*, and *germline polyploidy*. Somatic polyploidy is polyploidy that occurs in tissues such as heart muscle, bone marrow, liver, placenta, and tissue regeneration. It differs from ploidy, which is inherited and occurs in all cell types of the organism. This genetic polyploidy is common in plants and a few animals, such as amphibians, but not in humans. Germline polyploidy, on the other hand, is an ancient, premetazoan form of polyploidy that occurs in the G + S cell systems of amoebozoans, early metazoans, and cancer and to some extent in invertebrates and their sexual reproduction. It manifests either as *developmental polyploidy* capable of generating stem cells or, as in the case of stress and harmful living conditions, as *non-developmental polyploidy* resulting in no stem cells.[1]

In humans and mammals, somatic polyploidy is part of the normal postnatal morphogenetic program (organogenesis) but can also occur in response to stress and pathological stimuli. In adult organs such as the heart and liver, polyploidization of cardiomyocytes and hepatocytes occurs by limiting cytokinesis and karyokinesis and slowing proliferation.[2] In adult mammalian organs with low mitotic activity, polyploidization occurs as a result of hyperfunction and stress. Stress promotes polyploidization in both quiescent and proliferating cells. In quiescent cardiomyocytes and hepatocytes, stress leads to DNA re-replication, whereas in proliferating cardiomyocytes, polyploidization can be promoted by premature cell cycling or an arrest in cell differentiation.

Germline polyploidy can be observed in the life cycles of cancer and pathogenic amoebae (*Entamoeba*). It is an evolutionary process that evolved in the Amorpha common ancestors and was adopted by the branching clades Amoebozoa, Metazoa, and Fungi (AMF) to generate germline stem cells (GSCs). GSCs are generated by the germline via polyploid reproductive RG/GSC cycles evolved by the ancestors. Germline polyploidy,[3] germline stem cells, and some transitional stages of the PR/GSC cycle also occur in metazoans, mostly in a covert manner and linked to reproductive cell structures. CSCs belong to the GSCs. Normal somatic polyploidy and tissue regeneration occurring in healthy humans cannot be equated with the germline polyploidy reactivated in cancer. Normal human stem cells (ESC, ASC) are also not the origin of CSCs.

Stem cell-producing polyploidy is initiated and executed by the germline and has the purpose of producing new germlines and somatic cell lines. The archetype of this germline polyploidy evolved many Mya (million years ago) in

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the innercyst cells and metacyst cells of the common ancestor. The protective wall structure of the ancestral cyst was retained by the amoebae but also by certain invertebrates in association with reproductive germline processes and stem cell production. In the native PGCCs (aCLS-like) structures of cancer, which also produce CSCs, the ancestral wall was replaced by a thinner cell envelope but the RP/GSC cycle remained, regardless of the form it took.

The G + S life cycle of cancer and amoebae is a self-contained developmental program executed by an evolutionary gene network of unicellular origin founded between 1000 and 600 Mya in the genome of the ancestors. This premetazoan gene module, which controls and regulates the G + S cycle, is silently conserved in the genome of all metazoans and is reactivated in cancer. Parts of it, such as intermediate germ cell stages, were also observed in metazoan organogenesis and sexual reproduction.

The G + S cell system of cancer and amoebae are "sister cell systems", both descended from the common Amorpha ancestor. This close homologous relationship is reflected in several common features. These include (i) stem cell-producing germlines, (ii) germlines damaged by excess oxygen, (iii) loss of stemness potential due to DNA injury, (iv) genome repair through MGRSs/PGCCs, (v) transitions from soma to germ (SGT) and from germ to soma cells (GST) also known as MET and EMT, (vi) high phenotype plasticity from ACD to SCD and back again, and (vii) intrinsic systemic pressure to produce new "healthy" germlines and germline stem cells (GSCs/CSCs). All these common features argue against a simple reverse *approximate recapitulation* of evolution, as noted by Ivanovic and Vlaski-Lafarge. The common features show a stable, self-contained gene module common to cancer and amoebae.

Recent work on the age of cancer genes and their archetypes shows that the genes of the G + S life cycle of cancer are unicellular UC genes.[4,5] All these data support the hypothesis about the premetazoan origin of the cancer cell system. During the transition period to multicellularity, suppressor and anti-suppressor genes were added; they are the archetypes of tumor suppressor genes (TSGs) and oncogenes. Suppressor and anti-suppressor had the task of enabling new evolutionary pathways by hindering the life cycle of the pre-metazoans, but leaving the door open to reactivate the old G + S system in cases of evolutionary dead ends. Further evolution of cancer and host genomes proceeded separately. However, the G + S genome of cancer was constantly extended by specific anti-host genes.

Finally, some remarks on the "colonial organization", including CFU, the "ancient tool kit" and the appearance of the first colonial prometazoans. The colonial organization may evolve even earlier than thought (approximately 900 Mya). The potential of the colonial organization was transferred to the amoebozoans (see Dictyostelium) but also to the metazoans, which can express colonial forms but do not necessarily have to originate from colonial prometazoans. It is evident that early metazoans originate from the monosomatic germline of the G + S cell system. It is possible that at the beginning of the early metazoan era, the monosomatic germline that differentiates a single somatic cell type learned to increase its differentiation potential and become multisomatic, as seen today in sponges.

Conflict of interests

The author has no competeing interests to declare.

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