Genes & Diseases (2023) 10, 1143–1144

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CORRESPONDENCE

On cancer, stemness, and deep evolutionary homologies

Recently, Niculescu published an interesting paper[1] concerning "deep homologies" between the formation of cancer stem cells by polyploidization and reproductive polyploidization of entamoeba. The life cycle of both systems shares the same genetic machinery inherited from the Last Eukaryote Common Ancestor (LECA). This theory claims that cancer is nothing more than the expression of a pre-existing life cycle that was reactivated in "sick and weakened metazoan cell that cannot continue its multicellular life and finds itself in the same dead-end situation".[1] Proposed amoeba/cancer homologies actually comply with the theories claiming that cancer represents inverse recapitulation of metazoan differentiated cell evolution to the pro-metazoan stage. However, the real polyploidy formation, based on endoduplication, is not specific to cancer. There is, for example, polyploidization of normal hepatocytes and fibroblasts, especially in tissue regeneration.[2] Endorduplication itself is a purely physiologic phenomenon during thrombopoiesis. In addition, this is not the only feature of the ancient single-cell eukaryote life cycle but is common to cancer and normal behavior of the primitive cell.

In our book titled "Anaerobiosis and stemness: an evolutionary paradigm",[3] we considered cancer stem cell case in view of an evolutionary paradigm (chapter 14 [3]). Therefore, we reviewed three hypotheses of cancer concerning the principle "back to the roots": (i) "prokaryotic homologue tool box"; (ii) cancer is atavism occurring when genetic or epigenetic malfunction unlocks an ancient gene controlling loose – knit of only partially differentiated cell; (iii) cancer cell represents a phenotypical reversion of the last eukaryote ancestor. The common point of these hypotheses is that a reverse approximate "recapitulation" of evolution leads to the stage of a single-cell eukaryote and that this recapitulation occurs during the genesis and evolution of cancer. We noticed however that the same mechanism could be applied to the commitment and differentiation of a normal stem cell.[3]

First, functional heterogeneity among cancer stem cells in a single tumor type cannot be considered abnormal, since such heterogeneity exists in normal stem and progenitor cell compartments.

Second, the normal stem cell self-renewal (division in a non-differentiated state) is reminiscent of the first simple cell division of a single-cell eukaryote, while the prototype for differentiation appeared during the diversification of single-celled eukaryotes after LECA, and the appearance of colonial pro-metazoan, as well as the complex life cycle of single-celled eukaryotes. Simple mitotic proliferation (non-sexual reproduction, prototype of self-renewal) of LECA is based on the minimal essential genome, which is the essential basis for the anaerobic/nanoaerobic life. Upgrade of this situation causes the asymmetric division comprising both self-renewal and differentiation, leading to the first colonial organization, the self-organized assemblage, exchanging information chemically. This upgraded minimal essential genome, which we named "ancient tool kit", was integrated during metazoan evolution in a way that is still present in somatic cells. It can be expressed every time when its suppression is genetically/epigenetically banned. It is activated during the self-renewal and commitment of somatic stem cells. Likewise, stem cell metabolism is tightly regulated by the set of various signaling pathways and genetic and epigenetic regulators that are evolutionary conserved. This is operationalized by the stemness "tool kit" that involves molecular and signaling pathways enabling their maintenance (table 11.1 [3]).

Third, the phenomenon of metastasis, might be considered as a deep homology of colonial-like organization single cell eukaryote evolutionary stage but is not specific either to the CS(P)C. In the normal stem cell context, there are

Peer review under responsibility of Chongqing Medical University.

https://doi.org/10.1016/j.gendis.2023.01.003

numerous examples of migration, and circulation of cells exhibiting the colony-forming ability (clonal expansion), appearing as a property of stem/progenitor cells in physiology and non-malignant pathophysiology. Indeed, they are perfectly mimicking the phenomenon of ancestral single-celled eukaryote colonial organization as, for example, the Colony Forming Unit-Spleen (CFU—S) phenomenon, which is the first historic proof for the existence of a multipotent stem/progenitor cell. It fairly resumes the single-cell eukaryote colonial model.[1] In addition, colonization of the bone marrow by HSC originating from the embryonic aorta is a well-known phenomenon. Thus, a typical colonial organization was initiated by a single cell/stem cell which after multiple symmetric and asymmetric divisions gives rise to the colonies consisting of stem cells and more differentiated progenitors/precursors. A colony is *de facto* a tumor, but not giving cancer. Along the colony formation, stem and progenitor cells can migrate through tissue in a steady state and in pathophysiological conditions. An illustrative example comes from neoblasts — a heterogeneous stem cell population capable of partial and total regeneration of the *Planaria* organism.

These properties are integral parts of the stem cell's functional nature. They are reminiscent of the properties traced all the way back to LECA and are under the control of the ancient gene tool kit. Thus, "invasive" cell growth and migration can be considered as one of the primary features of stemness and, although they unequivocally do take part in the phenomenon of cancer invasiveness, are not specific only for cancer.

Fourth, anaerobic energetic profile of stem cells is that a low O_2 environment is complementary to the ancient tool kit (enabling a simple mitotic division of an undifferentiated cell). Asymmetric division and differentiation are enabled by the environmental O_2 rise. As published by Niculescu himself,[4] the lifecycle of *E. invadens*, a single-celled anaerobic eukaryote, displays all basal mechanisms of stemness and cell differentiation observed in higher eukaryotes. In addition, our results[5] provide evidence that similar to mitochondria-containing anaerobic unicellular protists, somatic stem cells could survive in ischemia-like conditions using mitochondria in an anaerobic way. Therefore, energetic reliance on glycolysis even in the aerobic condition (Warburg effect) and anaerobic mitochondrial respiration that are associated primarily with tumors/cancers are not actually cancer-specific. In fact, these are metabolic signs reflecting the stem cell origin of cancer, and the metabolic signs are controlled by the ancient gene tool kit inhered from the LECA stage.

In conclusion, the main cancer hallmarks are nothing else than actual features of stemness. Reactivation of the ancient tool kit needed for the stemness expression is present in cancer but does not provoke cancer by itself. Cancer is induced when a genetic alteration results in dysregulation.

Conflict of interests

The authors declare no conflict of interests.

Acknowledgements

The authors thank Ivana Gadjanski, Ph.D., for the critical reading of the manuscript.

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17 October 2022
Available online 21 April 2023