Review of: "Somatic evolution of Cancer: A new synthesis"

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Potential competing interests: No potential competing interests to declare.

Peer review comments

on the article "Somatic evolution of cancer:

A new synthesis (V1)"

1. Confusing title and aimless introduction.

This article lacks a clear structure, meaningful subtitles, and readability. The purpose and meaning of the article are not immediately evident, and the term "synthesis" needs clarification. The lengthy introduction and the following chapter, which could be considered part of the introduction, do not provide sufficient clarity to the reader. There is excessive discussion of common topics such as various interpretations of cancer, somatic mutations, chromothripsis, tissue microenvironment, cell-to-cell cooperation, cross-talk between different cells, and blood vessel co-option, without in-depth exploration. Key phrases like "remarkable similarity in cancer and wound healing pathways," "competition between normal and mutant cells," "cancer-causing mutants gaining a selective advantage," or "mutants outcompeting normal ASCs" are introduced but not adequately discussed. Therefore, both chapters require significant revision to streamline the introduction and align it with the article's objectives.

It is only in Chapter 3, titled "The New Synthesis," that the authors clarify the meaning of this term. They state, „*The mechanisms for surpassing the normal regulation on cell division* ***are already present in the body.*** *They are highly complex but very well coordinated with stage specific mechanisms of regulation. All mechanisms of shifting between the two levels of coordination* (that means non-cancerous and cancerous cells) ***have evolved and preexist in the cell*** *and* ***can be activated by a set of triggers****. By the new synthesis, cancer is not about escaping the regulation mechanisms by some novel mechanisms acquired by mutations.* Accordingly, "New Synthesis" refers to non-mutational malignant transformation through intrinsic cell mechanisms. However, this concept is not novel and has been supported by various authors over the last 10-15 years, notably in the field of Evolutionary Cancer Cell Biology.

2. Insufficient research

The primary shortcoming of this work is the failure to reference the extensive body of literature in the Evolutionary Cancer Cell Biology (ECCB) field. Since 2000, ECCB research, particularly focused on polyploidy, hyperpolyploidy, and polyploid giant cancer cells (PGCCs), has expanded significantly. Notable researchers like Sundaram, M., Rajaraman, M.M. et al. (2004) and Domazet-Loso and Tautz have contributed seminal work in this area.

In the recommended V2 revision, I strongly suggest consulting the bibliography ofhttps://doi.org/10.3390/ijms241914567 (Int. J. Mol. Sci. 2023, 24, 14567) and doi:10.20944/preprits202306.0833, both published by Jekaterina Erenpreisa's research group. These references include authors such as Lineweaver et al., Trigos et al., Vinogradov, Kasperski, Vinnitski, Anatskaya, Mirzayans, and many others. Additionally, my recent articles (doi: 10.20944/preprints202308. 1688 and https://doi.org/10.20944/preprints202309.2156.v1) and several of my previous papers are recommended for review.

In addition to the hypothesis of non-mutational carcinogenesis, this paper presents statements that closely align with ECCB theories, such as: "Cancer cells escape the regulation of normal cell proliferation" or "Cancer is a phenomenon of uncontrolled growth of certain cells that escape the regulatory mechanisms of the body" or "Mechanisms and pathways to escape the normal regulation of cell proliferation need not evolve de novo" and "Cancer evolves through pre-evolved functions. To avoid accusations of plagiarism, a comprehensive V2 revision should incorporate and expand upon the aforementioned literature.

As the authors appear unaware of ECCB data and hypotheses, they propose a unique hypothesis suggesting that carcinogenesis may be linked to wound healing mechanisms (EGF theory). They argue,“Consequently when healing is near completion a different set of signals coming from the healed tissue downregulates cell proliferation and wound healing mechanisms. In cancers since there is no real wound, the signals that control the process after healing are not generated at all. Therefore the process of making new cells to replace the perceived damaged tissue continues without a full stop“.

3. Non-mutational or partially mutational carcinogenesis?

To justify their hypothesis, the authors explore the possibility of atypical signals from wound healing triggering carcinogenesis. They suggest that “the wound healing process needs not a single signal but a variety of signals to get going. Therefore, a misguided trigger could be in question. One possibility is that ***a series of mutations*** could make some of the inducible pathways constitutive of wound healing“.

They point to mutations related to the EGF signaling pathway, which is crucial in regulating wound healing dynamics. Elevated EGF levels observed in damaged tissue lead the authors to hypothesize that this could be a clue to their theory. *Three types of mutations* related to EGF signaling are known to occur in various cancer types, resulting in EGF receptor over-expression, internal EGF synthesis by cancer tissue, and constitutive downstream EGF signaling pathways. In all three cases, cells become independent or hypersensitive to external EGF signaling, potentially misinterpreting it as a signal of injury. According to the authors, the critical question is not whether one of these mutations occurs but whether a cell with such a mutation can survive and outcompete normal cells.“.

4. The „New synthesis theory“ vs. the evolutionary cancer genome theory

The paragraphs above highlight the inconsistency of the non-mutational "New Synthesis" theory, as it appears to rely on mutagenic elements like the EGF hypothesis. In contrast, the Evolutionary Cancer Genome Theory argues for a reductive evolution of multicellularity to a lower level of cell organization, driven by DNA-damaged cells lacking stemness and

differentiation potential, which require repair. According to this evolutionary perspective, repaired cells come under the control of an ancient gene regulatory network (aGRN), leading to cancer via polyploidy and hyperpolyploidy within the PGCC cancer group.

In conclusion, a substantial revision (V2) is necessary to address the issues raised in this peer review. Acknowledging and citing ECCB literature, clarifying the "New Synthesis" concept, and addressing inconsistencies in the hypothesis are essential steps to strengthen the article.

Sincerely,

Vladimir F. Niculescu

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