Review of: "Introduction to Evolutionary Cancer Cell Biology (ECCB) and Ancestral Cancer Genomics"

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Potential competing interests: No potential competing interests to declare.

The article is concise and clear in elucidating the knowledge related to the Evolutionary Cancer Cell Biology (ECCB) theory, introducing the general content of the cancer hypothesis branch. As a supplement to the article "Somatic Evolution of Cancer: A New Synthesis," it responds to the doubts raised in the review.

Currently, there is no consensus on the origin of cancer, and there are both supportive and opposing views in the academic community for various hypotheses. This short essay by the author explores the evolutionary origin of cancer, providing new perspectives for the prevention and study of such unconventional diseases. For aspects not thoroughly discussed in the essay, the author provides several comprehensive reviews in the "Final Consideration and Perspectives" section for readers who wish to delve deeper, earning praise for author’s meticulous effort.

If possible, it is hoped that the author can clarify the following points in further revisions:
1. Confirm the representative studies in the development and deepening of the ECCB theory, summarizing major research results in chronological order with publication dates, along with the academic community's opinions and the author's own evaluation.
2. Starting from the first point, confirm the main content and conclusions of ECCB research and elaborate on the shortcomings of this theory and future directions for development. From this point onwards, the article's narrative rhythm needs reorganization as the current structure is confusing.
3. Clearly explain how ECCB aims to unify all evolutionary insights, hypotheses, and theories into a cohesive framework. Specifically, detail how the research is conducted, which evolutionary insights, hypotheses, and theories are incorporated into the ECCB theory, as these aspects are currently lacking in the narrative.
4. The impact of cancer-driving genes and their mutations on cancer development is widely studied, with thousands of research papers discussing the effects of mutations on cancer. ECCB suggests that somatic cell mutations are only secondary, and downstream events in tumor development are crucial. Can the author provide research evidence supporting this non-traditional theory? Relevant wet lab experimental literature should be cited for verification.
5. Confirm the similarities and differences between ECCB theory and the cancer atavism theory. The article seems to present ECCB as a broader concept encompassing research on atavism theory. For example, ECCB states that the decisive moment in its research is when Domazet-Lošo and Tautz introduced phylostratigraphic research to determine the age of cancer genes. This point appears to lack consensus in the academic community, as evidenced by the in-depth discussion in the article "Evolutionary, Non-Mutational Cancers Cannot Be Considered Atavistic." The author's two articles

have different definitions and discussions about this, which one should readers adopt. The author should reconsider and elaborate on this point.

6. Regarding Davies and Lineweaver's research, the article starts the "ECCB Beginnings" section by introducing the earliest beginnings of ECCB thinking and concludes the "Evolutionary Cancer Genomics" section by stating that the views of this research are inconsistent with ECCB's views. This leaves readers confused as to whether the citation of this article supports or opposes the ECCB theory. The author should clarify the stance.

7. Elaborate on the connection between the concepts presented in this article and "Somatic Evolution of Cancer: A New Synthesis."

8. The idea of using phylostratigraphic research to determine the age of cancer genes introduced by Domazet-Lošo and Tautz has further developed cancer origin hypotheses. However, the systematics stratigraphy model has been criticized for being imprecise and unreliable due to assumptions such as constant protein evolution rates at all sites and variations in evolutionary rates caused by gene duplication and new functional changes leading to increased BLAST error rates and gene loss in more distant taxonomic groups. If the foundation of phylostratigraphic evolution is not robust, how can the results of the research be trusted? The author should address reflections on this aspect.

As a brief overview, the author provides a comprehensive explanation of the ECCB theory from different perspectives, but the abundance of points and their diverse nature may confuse readers. It is hoped that the author can better clarify the structure of the article. Overall, this article presents a new definition for cancer research from different perspectives.