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Peer Review

Review of: "Somatic Evolution of Cancer: A New Synthesis"

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This manuscript proposes an ambitious and intellectually stimulating synthesis that integrates the “somatic evolution/cheater cell” paradigm with the “cancer as a non-healing wound” framework, arguing that malignant transformation represents the exaptation and mis-triggering of pre-evolved wound-healing programs under context-dependent selection. The article’s major strength lies in its conceptual breadth: it engages evolutionary theory, stem cell biology, tumor microenvironment research, and epidemiology to construct a unifying framework. The emphasis on selection-limited rather than mutation-limited somatic evolution is thought-provoking and aligns with growing evidence on context-dependent clonal dynamics. The extensive parallels drawn between wound healing and the hallmarks of cancer are compelling and well-supported by literature, and the manuscript generates multiple explicit, testable predictions—an important strength for a theoretical synthesis.

However, several issues limit its scientific rigor and clarity. First, the manuscript is highly expansive and at times speculative, with some claims (e.g., lifestyle-driven chronic growth factor deficiency as a central selective force; broad skepticism about immunotherapy efficacy; reinterpretation of Peto’s paradox as nonexistent) presented more assertively than current empirical evidence justifies. These sections would benefit from clearer separation between hypothesis, indirect support, and established data. Second, while the wound–cancer overlap is well documented in the literature, the manuscript would be strengthened by a more systematic comparison—perhaps via summary tables distinguishing shared pathways, temporally restricted wound-specific mechanisms, and truly cancer-specific alterations. Third, the evolutionary arguments (e.g., pleiotropy with gametogenesis, cliff-edge fitness functions) are conceptually interesting but require either modeling support or clearer empirical anchoring. Fourth, some sections are repetitive and could be condensed substantially without loss of substance, improving readability and impact.

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Importantly, the predictions regarding immunotherapy limitations should be nuanced; while checkpoint blockade has variable response rates, durable responses in subsets of patients are well documented, and this should be acknowledged more explicitly to maintain balance. Likewise, the behavioral and enriched-environment hypotheses are intriguing but need clearer mechanistic linkage to the proposed selection landscape framework.

Declarations

Potential competing interests: No potential competing interests to declare.