Commentary

“Logos” of Cancer Evolution

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Despite significant advancements in medicine, progress in combating cancer remains limited. Cancer is widely understood as a product of evolutionary processes, primarily through the lens of the Somatic Mutation Theory (SMT), which posits that random genetic mutations drive carcinogenesis via Darwinian selection. However, emerging evidence challenges this reductionist view. While childhood cancers align with Darwinian evolution, sporadic adult cancers exhibit patterns more consistent with Lamarckian or quasi-Lamarckian mechanisms. Clonal evolution studies of various cancers reveal complex, non-linear architectures, questioning the adequacy of traditional models. These findings suggest that a unifying evolutionary framework—akin to Heraclitus’ *logos*—may be necessary to fully comprehend carcinogenesis.

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Introduction

Medicine has witnessed remarkable scientific and technological advancements, yet progress in the fight against cancer remains limited, with notable exceptions for certain cancer types[1]. As Theodosius Dobzhansky famously stated in 1973, "Nothing makes sense in biology except in the light of evolution," and cancer is no exception. Recognizing cancer as a byproduct of evolutionary processes has significantly deepened our understanding of carcinogenesis.

Somatic Mutation Theory and Its Limitations

The theory of cancer evolution is generally attributed to Peter Nowell. In the 1970s, Dr. Nowell proposed a gene-centric Darwinian model of somatic evolution in carcinogenesis, now widely known as the Somatic Mutation Theory (SMT). Despite limited genetic data at the time, his model highlighted mutational heterogeneity in cancer and suggested that random genetic alterations accumulate

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through "somatic evolution." More recent models of evolutionary carcinogenesis have emerged, offering profound insights, yet they often fail to fully account for microenvironmental selection factors that drive cancers toward more malignant phenotypes[2]. In essence, the neo-Darwinian SMT posits that random genetic mutations generate new phenotypes, with the fittest selected through a cumulative process. This perspective, however, is reductionist and may not adequately explain complex biological phenomena.

Darwinian Evolution in Childhood Cancers

Childhood cancers and certain leukemias may require only a single mutation to initiate, whereas most adult cancers necessitate the disabling of multiple checkpoint mechanisms, typically through several driver mutations[3]. Childhood tumors, characterized by small mutational burdens, often follow multiple evolutionary trajectories within a single tumor. For instance, the natural history of childhood acute lymphoblastic leukemia (ALL) is largely clinically silent and well advanced by the time of diagnosis. In ALL patients, a prenatal or initial "hit" is common—occurring at a rate approximately 100 times higher than the clinical incidence of ALL—indicating low evolutionary penetration. Secondary gene copy number changes, which confer a Darwinian selective advantage, are critical to increasing the population of at-risk cells, with the cytokine TGF-beta potentially playing a supportive role. Single-cell analysis using multicolor probes for mutant genes reveals a complex, tree-like structure of genetically distinct subclones in ALL, reminiscent of Darwin's 1837 diagram of evolutionary divergence[4].

Lamarckian and Quasi-Lamarckian Evolution in Sporadic Cancers

In contrast, the Darwinian SMT struggles to explain sporadic adult carcinomas. With aging, somatic mutations accumulate in healthy human cells. For example, approximately 25% of cells in sun-exposed skin carry cancer driver mutations without developing into cancer. Martincorena et al. conducted targeted gene sequencing of normal esophageal epithelium from nine donors of varying ages, uncovering strong positive selection for clones with mutations in 14 cancer-related genes. By middle age, over half of the esophageal epithelium is colonized by mutant clones. Strikingly, mutations in the cancer driver gene *NOTCH1* were more prevalent in normal epithelium than in esophageal cancer[5]. This suggests a quasi-Lamarckian, non-Darwinian evolutionary process[1]. Similarly, a hepatocellular carcinoma study supported a Lamarckian model, showing no evidence of

positive Darwinian selection[6]. These observations imply that cancer is not merely a phenotype or genotype but a behavioral manifestation.

The Need for a New Evolutionary Framework

Whether tumor evolution is predominantly Darwinian or non-Darwinian remains unresolved. Childhood cancers align with Darwinian evolution, while sporadic cancers suggest Lamarckian or quasi-Lamarckian mechanisms. This duality highlights the limitations of existing models and the potential need for a broader evolutionary perspective.

Conclusion

Heidegger regarded Heraclitus, alongside Anaximander and Parmenides, as a primordial philosopher who contemplated the essence of being (*Das Sein*)[7]. Heraclitus proposed that a universal law—*logos*—governs all change, ensuring proportionality, regularity, and order. While everything in the universe transforms, this *logos* remains constant[8]. In pre-Socratic thought, *logos* is the organizing principle of the micro- and macrocosms, a force that nature conceals yet demands exploration. The absence of a single evolutionary theory to explain carcinogenesis suggests that, rather than new cancer-specific evolutionary theories, a fundamentally new theory of evolution—rooted in a *logos*-like framework—may be required.

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