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IDEA TO WATCH

Thoughts & Opinion

Cancer progression: A journey through the past (with the same stops)?

> Nothing in cancer makes sense except in the light of evolution.
>
> Mel Graves (2018) BMC Biology 16 (22)

The origin and fate of cancer cells touch every aspect of biology, from the genetic scale to the organism's multicellular organisation and its relationship with the environment. From cells and their microenvironment to their harbouring organism and its environment, tumour progression is, by all means, an evolutionary phenomenon. Nordling[1] was one of the first taking a step towards evolution in cancer, originating the notion of cancer onset as a multi-stage accumulation of mutations. That process entails transforming a cell from a healthy phenotype towards a cancer one resulting from a collection of mutations, which sooner or later co-emerge with the local microenvironment, reproducing the well-known cancer hallmarks.[2] How that complex process is triggered and evolves remains a puzzle. However, any approach should consider the mechanistic integration between evolutionary history and the myriad hallmarks of cancer plus the interaction between genes and the immediate tumour microenvironment as essential ingredients for evolution.

In this issue, Lineweaver and colleagues[3] contribute to filling the gap. They propose a novel hypothesis that moves one step forward the atavistic model of cancer, that is, the idea that cancer in multicellular organisms resembles an atavistic cellular machinery characteristic of ancestral unicellular organisms. Their model, named the Serial Atavism Model, presents the idea that cancer progression is not a one-shot reversion towards a quasi-unicellular state of cells; instead, it emerges from a series of ordered steps that erode the multicellular organisation of metazoans. The authors invite us to embrace their disruptive and novel idea and to think of tumour progression as an ordered and regular phenomenon across species and cancer types. They hypothesise that the sequence of changes from a healthy phenotype to cancer and its further evolution may follow a similar trajectory but in a reverse direction relative to the transition from single-cell organisms to multicellularity. They also extend their model to reaching eukaryogenesis, oxidative phosphorylation and the transition to adaptive immunity.

The new proposal made by Lineweaver et al. is thought-provoking, and it is worthy of attention and evaluation. However, a serial steps consideration such as theirs constrains the possible evolutionary trajectories towards hallmarks deeply encrypted in the evolutionary history. But, their perspective fires up new questions. For example, do cancer cells find short-cuts in their evolution towards hallmarks that, despite an ancient origin, present adaptive advantages in the local context, or are they prisoners of their evolutionary history? How does this hypothesis explain the emergence of tumour heterogeneity? And how is that linked to the dynamic local environment or local ecology?[4] Further efforts need to consider that the order of events (intra or extracellular) matters in cancer evolution.[5] Although the authors did not intend to answer these fundamental questions, their hypothesis and suggested evaluation could point to that direction deserving further testing; above all, because, through the understanding of the fundamental process of tumour progression, we move the frontier of the unknown to gain clarity to improve patients' survival.

This article comments on the hypothesis paper by Charles H. Lineweaver et al., https://doi.org/10.1002/bies.202000305

CONFLICT OF INTERESTS

The author declares no conflict of interest.

Simon P. Castillo

Computational Pathology and Integrative Genomics Team, Division of Molecular Pathology & Centre for Evolution and Cancer, Centre for Cancer and Drug Discovery, The Institute of Cancer Research, London, UK

Correspondence

Simon P. Castillo, Computational Pathology and Integrative Genomics Team, Division of Molecular Pathology & Centre for Evolution and Cancer, Centre for Cancer and Drug Discovery, The Institute of Cancer Research, London, UK.

Email: simon.castillo@icr.ac.uk

ORCID

Simon P. Castillo https://orcid.org/0000-0002-0606-2160

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