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## EDITED AND REVIEWED BY

Samuel A. Cushman,  
United States Department of Agriculture  
(USDA), United States

## \*CORRESPONDENCE

Luca Ermini,  
✉ luca.ermi@yahoo.co.uk  
Diego Mallo,  
✉ dmallo@asu.edu  
Dimitrios Kleftogiannis,  
✉ dimitrios.kleftogiannis@uib.no  
Ahmet Acar,  
✉ acara@metu.edu.tr

<sup>†</sup>These authors have contributed equally to this work and share first and senior authorship

RECEIVED 16 March 2023

ACCEPTED 05 April 2023

PUBLISHED 14 April 2023

## CITATION

Ermini L, Mallo D, Kleftogiannis D and Acar A (2023), Editorial: Cancer evolution. *Front. Genet.* 14:1187687. doi: 10.3389/fgene.2023.1187687

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# Editorial: Cancer evolution

Luca Ermini<sup>1\*†</sup>, Diego Mallo<sup>2\*†</sup>, Dimitrios Kleftogiannis<sup>3\*†</sup> and Ahmet Acar<sup>4\*†</sup>

<sup>1</sup>NORLUX NeuroOncology Laboratory, Department of Cancer Research, Luxembourg Institute of Health, Luxembourg, Luxembourg, <sup>2</sup>Arizona Cancer Evolution Center, Biodesign Institute and School of Life Sciences, Arizona State University, Tempe, AZ, United States, <sup>3</sup>Department of Informatics, Computational Biology Unit and Centre for Cancer Biomarkers, University of Bergen, Bergen, Norway, <sup>4</sup>Department of Biological Sciences, Middle East Technical University, Universiteler Mah, Ankara, Turkiye

## KEYWORDS

cancer evolution, evolutionary biology, somatic cell, cancer phylogenetics, tumor heterogeneity

Editorial on the Research Topic  
Cancer evolution

## Introduction

Cancer is a complex disease (Donaldson et al., 2015; Yalcin et al., 2020) characterised by the breakdown of multicellular cooperation between somatic cells (Aktipis et al., 2015) that results in a set of convergent (Fortunato et al., 2017) traits known as *the hallmarks of cancer* (Hanahan, 2022). Cancer cells can proliferate extensively within a tissue, spread beyond the normal regulatory boundaries, and even colonise distant sites (Hanahan, 2022). Cancer progression is understood to be a complex Darwinian adaptive system (Greaves and Maley, 2012), with cancer cells acting as the equivalent of an asexually reproducing, unicellular quasi-species. Tumours are defined as large populations of genetically-diverse cell subpopulations competing for a limited number of nutrients while being selectively influenced by endogenous and exogenous factors. Because evolution and Darwinian selection are contingent and blind to the future, the outcome of this competition is the survival of clones well suited to flourish under specific conditions. Many clones dominant at one point in time may reach evolutionary dead ends and die out, while others may be able to persist. The level of genetic diversity found in cancer cannot be fully explained by Darwinian evolution, so non-Darwinian mechanisms have been proposed to account for cancer evolution (Vendramin et al., 2021). Neutral evolution, macroevolutionary changes, and the role of non-genetic determinants all appear to impact cancer progression significantly (Williams et al., 2016). The architecture of cancer seems sophisticated and intricate, and a thorough understanding of evolution is required for developing novel, evolutionary-informed therapeutic approaches (Gatenby and Brown, 2020). For this Research Topic, we gathered five studies covering three key aspects of cancer evolution.

## Somatic population genetics

Understanding the dynamics and possibly predicting cancer progression requires knowing how evolutionary forces alter the allele frequencies in somatic cells. Population genetic studies have generated critical insights in cancer evolution (Williams et al., 2019), including two of the articles in this Research Topic.

Luddy et al. investigated the principle of *evolutionary triage* (Gatenby et al., 2014), which connects the frequency of a gene mutation in a population with its contribution to cancer cell fitness. A mutation that improves fitness will spur cell proliferation, increasing the likelihood of its being found in a Research Topic of tumours. Instead, a mutation that does not affect fitness will only be detected at a frequency consistent with the underlying mutation rate. Luddy et al. used this framework to investigate genes associated with tumour-immune interactions in two lung adenocarcinoma cohorts with different molecular subtypes and found distinct convergent signatures of purifying selection. Targeting genes or molecular pathways under purifying selection may have therapeutic efficacy similar to targeting driver genes and may open up new therapeutic pathways (Gatenby and Brown, 2020).

Kurpas and Kimmel developed two alternative evolution models and applied them to cancer data to test if cancer cells follow Darwinian evolution. Both models describe the combined fitness effect of driver and passenger mutations in cancer cells; the only difference is how cellular fitness affects the likelihood of occupying the space of a dying cell. In one model, population fitness is constant in the absence of mutations, consistent with Darwinian selection, whereas fitness is not constant in the alternative. The two models were fitted to breast cancer samples, and it was found that the model consistent with Darwinian selection fits the data better.

## Molecular signatures

Molecular signatures can elucidate mechanisms of cancer progression and inform the clinical practice of many cancer types, perhaps most notably breast cancer (Lal et al., 2017).

Yan et al. developed a novel prognostic signature grounded on a set of necroptosis-related genes to predict breast cancer patient outcomes based on median risk scores. Patients above and below the median are classified as high-risk and low-risk, respectively. High-risk patients encounter low overall survival and worse predicted tumour, node, and metastasis stages.

Cisneros et al. studied the role of stress-induced mutagenesis (SIM) in cancer and introduced new statistical methods to identify its signature. Using somatic mutations found in tumour and normal tissue and SIM cell lines, they identified clusters of mutations consistent with stress-induced mutagenesis. These genetic clusters were less conserved in cancer, indicating a loss of regulatory control of SIM, and stress-induced mutagenesis was related to patient survival. This study shows that an evolutionary conserved adaptive mutation response, already present in bacteria, is a source of genomic instability that fuels cancer initiation, progression, and therapeutic resistance (Fitzgerald et al., 2017). This process may explain tumours' ability to evolve under selective pressures, supporting evolutionary-based treatment strategies (Natterson-Horowitz et al., 2023).

## Integrative multi-omics

Multi-omic studies explore the interaction between multiple biological factors to provide a more holistic view of biological processes and their relative effect on an outcome (Song et al., 2020). The development of a new multi-omics tool completes this Research Topic on cancer evolution.

Huzar et al. describe MOCA, a multi-omics toolkit for comparing gene expression and genetic evolution patterns in single cells and testing their consistency. MOCA was applied to published datasets and revealed links between genetic and phenotypic changes that can aid in understanding tumorigenesis, therapy resistance, and cancer progression. A significant shift toward single-cell technologies is expected in the coming years (Rozenblatt-Rosen et al., 2020), and MOCA will enable better exploitation of these upcoming datasets.

## Conclusion

Cancer is an evolutionary process of somatic cells, and therefore the somatic evolutionary theory is critical to understanding and treating this major cause of death. The articles in this Research Topic emphasise and exemplify this fact. Evolutionary therapies are promising treatment strategies that use the most recent advances in somatic evolutionary theory to manipulate the evolution of cancer cells, controlling their growth or driving them to extinction. These advancements have the potential to improve the quality of life of cancer patients by transforming cancer into a chronic disease or, in some cases, eradicating it.

## Author contributions

All listed authors contributed significantly, directly, and intellectually to the work and approved its publication.

## Funding

This work was partly supported by US National Cancer Institute grants NIH R01 CA140657, NIH U54 CA217376, NIH U2C CA233254, and R21 CA257980 (DM). AA is supported by the International Fellowship for Outstanding Researchers Program administered by TUBITAK (grant number 118C197).

## Acknowledgments

We thank the authors who contributed to this Research Topic and the expert reviewers for their timely work and efforts.

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