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BOOK REVIEW

Book Review: Rethinking Cancer: A New Paradigm for the Postgenomics Era. Rethinking Our Path in the Fight Against Cancer

Ying-Yu Cui[1,2,3*]

[1] Department of Cell Biology, Tongji University School of Medicine, Shanghai 200331, China
[2] Institute of Medical Genetics, Tongji University School of Medicine, Shanghai 200331, China
[3] State Key Laboratory of Cardiology, Tongji University School of Medicine, Shanghai 200331, China

Correspondence to: Ying-Yu Cui, Department of Cell Biology, Tongji University School of Medicine, Shanghai 200331, China; Email: yycui@tongji.edu.cn

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Rethinking Cancer: A New Paradigm for the Postgenomics Era [1] is a groundbreaking book edited by leading scientists Bernhard Strauss, Marta Bertolaso, Ingemar Ernberg, and Mina J. Bissell, and published by MIT Press in April 27, 2021.

1 Introduction

Since National Cancer Act signed by former US President Richard Nixon in Dec 23, 1971, R. Dulbecco Blueprint for human genome published in *Science* in 1986, Human Genome Project (HGP) finished in April 2003, till recently former US President Biden is diagnosed with prostate cancer, what have been left behind in the trillion-dollar race for conquering cancer? The book "Rethinking Cancer: A New Paradigm for the Postgenomics Era" gives human a clear answer, despite the accumulation of massive data and significant advances in detection and therapy technology, human is still powerless against many cancers with conventional clinic treatment measures!

2 Core Themes

As we know, current consensus in cancer research classically defines cancer as a disease resulting from specific mutations in certain genes, the so-called the theory of somatic mutation on carcinogenesis or the philosophical reductionism. Here, these leading scientists argue for a new paradigm for cancer research in this book, proposing a complex systems view of cancer supported by empirical evidence, emphasizing the interplay between genetic, cellular, and environmental factors, and offering a more holistic framework for understanding and treating cancer, the so-called philosophical holism. They present the conceptual building blocks for the new paradigm as follows:

First, examine the theoretical foundations by adopting a systems approach, which encompasses key concepts such as nonlinear dynamics, post-treatment recurrence, cellular attractors (i.e., stable phenotypic states governed by dynamic systems) [2, 3], network theory, mutually reinforcing symptom systems [4, 5], and non-coding DNA – often termed the 'dark matter' of the human genome [6].

Then, address the timeline of cancer progression, drawing on evolutionary theory and clinical experience [7].

Finally, reveal the dominant role of the tissue microenvironment in cancer, analyzing topics including altered metabolic pathways [8], the disease-defining influence on metastasis [9], and the interconnectedness of different environmental niches across levels of organization [10]. Briefly, its contents are presented along different "DIMENSIONs" of cancer as THEORY, SYSTEMS, TIME and MICRO-/ENVIRONMENT, sequentially and respectively.

2.1 Genomic Critique

Beginning with critiquing the conventional genomic paradigm, which attributes cancer primarily to specific gene mutations, authors argued that while advances in genome sequencing have provided unprecedented insights into the molecular makeup of cancer cells, this knowledge has not been translated into proportional therapeutic breakthroughs, for example, consensus started to build that understanding cancer as a perturbation in a complex multimodal, molecular

interacting network will not lead to straightforward actionable treatments because of the lack of proven systems-biology-based treatment tests or difficulties in using multiscale modeling for diagnosis, despite impressive recent advancements in computational powers and single-cell sequencing analysis methods, and even artificial intelligent (AI) agents as well [6]. What these approaches have uncovered instead is enormous heterogeneity at the genomic level, often presented as "complexity": not only between different cancers but also of the same cancer type in different patients, and even between the individual cancer cells within a single tumor in one patient. Therefore, they highlight the complexity of cancer as a systemic disease, influenced by nonlinear interactions, cellular attractors, and the tissue micro-environments [11].

2.2 Systems Biology

Authors explored concepts such as network theory, non-coding DNA (the "dark matter" of the genome), and the role of metabolic pathways in cancer progression, trying to underscore the importance of understanding cancer as a dynamic, evolving system rather than a static collection of mutations [12]. Briefly, application of systems biology in cancer research is one central theme of the book.

2.3 Metabolism and Microenvironment

In continuation, the book explored how altered metabolic pathways and niches influence tumor behavior, emphasize the interconnectedness of cancer cells and their surroundings, offering new avenues for therapeutic intervention, dedicating significant attention to the tissue microenvironment, which plays a critical role in cancer development and metastasis [13–15].

2.4 Evolutionary Perspective

Drawing on evolutionary theory, the book examines the timeline of cancer progression. It highlights how cancer cells adapt and evolve over time, often leading to recurrence after treatment. This evolutionary perspective provides a framework for understanding treatment resistance and designing more effective therapies, e.g., adaptive therapy is a good case in point. Adaptive therapy is a new therapeutic strategy originally designed for cancer treatment, maintains the relative number of drug-sensitive cancer cells through interval administration, and then inhibits the number of drug-tolerant cancer cells through growth competition, ultimately delaying or even eliminating cancer cell drug resistance that occurs later in routine treatment, and finally achieve long-term low-load tumor-bearing survival of patients [16–18].

2.5 Philosophical Insights

In addition, readers will benefit from the book's interdisciplinary approach, integrating contributions from biology, philosophy of science, and clinical research. For instance, Marta Bertolaso's philosophical perspective on cancer as a processual rather than a mechanistic phenomenon enriches the discussion, bridging the gap between scientific research and theoretical frameworks (Table 1). Thus, it can stimulate readers' interdisciplinary insights.

Table 1 Comparison between Holism and Reductionism of Carcinogenesis and Therapy

Dimension	Processual Perspective (Holism)	Mutation-centric View (Reductionism)
Ontological Basis	Whitehead's process philosophy (relational being)	Newtonian mechanism (substantialism)
Explanatory Focus	Breakdown of systemic dynamic stability	Accumulation of genetic sequence variations
Intervention Strategy	Microenvironment modulation (niche reconstruction)	Targeting mutated genes (molecular repair)

3 Strengths and Limitations

Academically, the book's emphasis on a systems-based approach offers a fresh perspective on cancer research, challenging reductionist views and encouraging interdisciplinary collaboration.The arguments are backed by robust empirical evidence, making the case for a paradigm shift both compelling and scientifically rigorous. While the content is highly technical, the editors have done an excellent job of presenting complex ideas in a clear and accessible manner. While the book excels in theoretical innovation, it could have provided more concrete examples of how the proposed paradigm could be implemented in clinical practice, for example, more essential experimental models such as spatial transcriptomics, in silico models, and organoids etc. may be used as more powerful tools that support a systems perspective. In addition, the dense, academic style may limit its appeal to a broader audience, particularly those without a background in systems biology or philosophy of science.

4 Conclusion

Summarily, this book is a timely contribution to the field of cancer research and treatment in clinic, addressing the limitations of current genomic approaches and proposing innovative solutions for the postgenomics era. It is a must-read for researchers, clinicians, and policymakers in the field of oncology. By advocating for a systems-based approach, the book not only critiques the limitations of current genomic research but also paves the way for more effective and holistic cancer therapies. Its interdisciplinary insights and forward-thinking perspective make it a valuable addition to the literature on cancer biology and important data collection influencing future research, education, or policy. It is highly recommended for cancer researchers, systems biologists, philosophers of science, and advanced students in oncology or biomedical sciences.

Conflicts of Interest

The author declares no conflicts of interest.

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