Trends in Cancer

CellPress

Forum

Addressing the genetic/nongenetic duality in cancer with systems biology

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The dogma that cancer is a genetic disease is being questioned. Recent findings suggest that genetic/nongenetic duality is necessary for cancer progression. A think tank organized by the Shraman Foundation's Institute for Theoretical Biology compiled key challenges and opportunities that theoreticians, experimentalists, and clinicians can explore from a systems biology perspective to provide a better understanding of the disease as well as help discover new treatment options and therapeutic strategies.

Rethinking cancer

A pre-eminent view of cancer for over a century is that it is a genetic disease. However, several mutations in oncogenes that were presumed to be causative (driver mutations), are present in corresponding normal tissues. Similarly, overexpression of an oncogene, such as *MYC*, can by itself result in the transformation of a normal cell into a malignant phenotype. Although genetic alterations are observed in cells transformed by *MYC*, reducing *MYC* expression leads to normalcy of the malignant phenotype [1]. Thus, the role of nongenetic, epigenetic, environmental, and host factors has eclipsed a purely genetic perspective on cancer.

Other studies also suggest that both genetic and nongenetic mechanisms, including epigenetic mechanisms underlie various aspects of cancer [2–4]. Attempts to reconcile these two seemingly contrasting mechanisms have underscored the genetic/nongenetic duality of cancer [5,6]. They have also helped highlight the phenotypic plasticity of cancer cells. Furthermore, theoretical studies based on dynamical systems reveal how increased plasticity can result from the breakdown of regulatory links on the governing genetic networks [7]. Indeed, phenotypic plasticity and nongenetic mechanisms are now recognized as hallmarks of cancer [8].

Despite the laudable strides, however, we are still far from applying this new thinking to address cancer. With these challenges in mind, the Shraman Foundation's Institute for Theoretical Biology organized a think tank in July 2022, in Kona, Hawaii on cancer systems biology. The goal was to highlight how mathematicians, physicists, and engineers can work together with biologists and clinicians to understand cancer from a systems perspective and help discover new treatment options and strategies.

An important issue that reverberated in the group was, does the dogma that cancer is in essence a genetic disease suffice, or is the genetic/nongenetic duality necessary? The persuasive arguments and spirited discussions led to identifying the following challenges and opportunities that stem from the duality and can benefit from the combined efforts of an interdisciplinary approach across multiple scales (Figure 1).

Philosophy of cellular function and understanding cancer ecology

Is the principle of competition and survival of the fittest clones sufficient to explain cancer evolution, or does it involve more complex group dynamics and strategies (e.g., cooperation/defection and kin selection)?

Although game theory has been explored to address aspects of cancer, especially drug resistance, more complex group dynamics and strategies cancer cells leverage, and the application of Hamilton's rule and Price equation to understand their behavior remain unexplored. Such studies could result in improved treatment strategies to discourage the emergence of drug resistance or at least, delay it and thus, improve disease outcomes.

Can cancer cells 'learn'?

The Baldwin Effect refers to the phenomenon by which plasticity facilitates adaptive phenotypic and genetic evolution [9]. Thus, an important question that the think tank considered as worthy of exploration is, can learning guide evolution of cancer cells as they navigate the fitness landscape? There is emerging evidence that cells can 'learn', 'anticipate', and even exhibit a form of 'kin selection' and 'altruism' [10]. If so, how can this information be leveraged to devise better therapeutic strategies (e.g., adaptive or intermittent therapy)?

Why are some organs resilient to cancer?

Peto's paradox, namely the lack of correlation between body size and cancer risk, was addressed elegantly [11] when it was discovered that elephants have multiple copies of p53/haploid genome. However, humans have only one copy of p53/haploid genome. Some organs like breast and prostate are more prone to developing cancer, whereas others such as the seminal vesicles or the small intestine

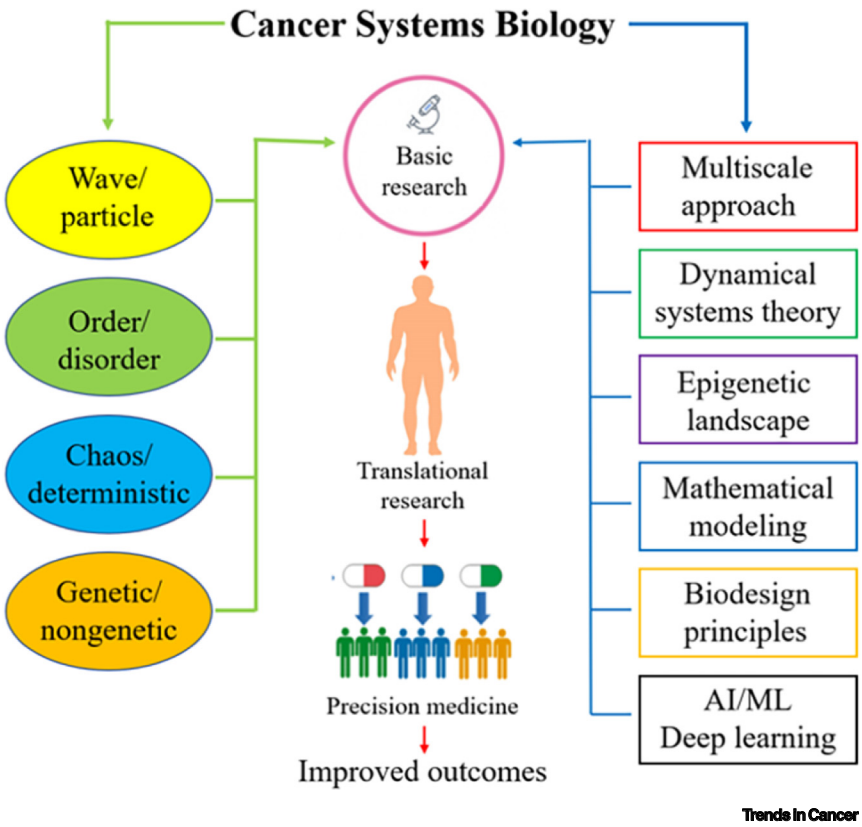

Figure 1. Schematic outlining the key frontier areas in cancer. Research on cancer systems biology done acknowledging the dualities in nature (oval circles) and using a multidisciplinary approach across scales will provide an unbiased, fundamental understanding of cancer with tremendous translational potential and improved patient outcomes. Abbreviations: AI, artificial intelligence; ML, machine learning.

rarely, if at all, develop cancer despite their physical proximity to the cancer-prone organs. Why/how are these organs so resilient to cancer? The think tank felt that understanding how the protein interaction network (PIN) topography in the cells of these organs is different from those that are highly prone to cancer, may shed new light on the resilience/vulnerability to the disease – it may unshroud a weak Peto's paradox.

Can one develop an economic theory of cell function and tumor inventory management?

How does a cell decide to allocate resources (dubbed, an economic theory of cell function)? For a cell, are there equivalent inventory management concepts in biology such as, just in time production (in metabolism there appear to be), investment, return on investment, etc.? Perhaps, reverse engineering could help answer some of these questions. Although seemingly a daunting task at first glance, creating a large database of functional forms and leveraging artificial intelligence (AI) and machine learning (ML) to generate functional forms via evolutionary algorithms is a tractable possibility. Another approach is to describe the design patterns for common behavioral functions. Designing patterns provide general solutions which can be implemented in multiple ways. An implementation can be converted back to a design pattern to identify its functional role and hence can convert actual network patterns back to design patterns to identify their function.

Phenotypic plasticity

What role does phenotypic plasticity play in cancer evolution from initiation and progression to metastasis and treatment resistance?

Traditionally, cancer was assumed to be a genetic disease; therefore, plasticity was not considered a hallmark of cancer until recently. However, it is important to understand how cancer cells regain control of phenotypic plasticity that is typically a taboo to most terminally differentiated cells, and result in phenotypic heterogeneity. Elucidating the mechanisms of phenotypic plasticity can shed new light on the disease, especially metastasis and the emergence of drug resistance.

Can protein conformation influence cell fate decisions in cancer?

Phenotypic plasticity is thought to be majorly manifested through epigenetic programs and chromatin remodeling. However, emerging evidence suggests that protein conformational dynamics, especially intrinsically disordered protein (IDP) conformation also plays an important role in determining cellular phenotypes. IDPs are proteins that lack rigid 3D structure and occupy hub positions in scale-free cellular PINs. Remarkably, there is positive correlation between intrinsic protein disorder content and biological complexity, and ~80% of cancer-associated proteins are IDPs [12,13]. Conformational noise that emanates from IDP conformational dynamics that is distinct from the well-defined transcriptional noise, modulates phenotypic switching reversibly by rewiring the PIN and thereby, contributes to the phenotypic heterogeneity underscoring a key nongenetic mechanism [14]. Hence, it should be possible to predict the different steady states that a PIN can potentially occupy by modeling its dynamics. At steady state, the probability that the system will occupy an attractor is proportional to the stability of the PIN configuration of the attractor. Thus, a set of attractors and their probabilities of being occupied by the system represent a

high-dimensional landscape as envisioned by Waddington in the epigenetic landscape metaphor. Therefore, a dynamical systems approach to study IDPs appears a promising endeavor.

Computational approaches for predicting disease outcome

Is there a necessity for new mathematical approaches for addressing biological complexity and stochasticity?

This is an important question that the think tank felt needs serious consideration since current theories and approaches are mostly repurposed from other branches of physical sciences. However, biological systems are interconnected hierarchical infrastructures that have been optimized through evolution over prolonged periods of time. There is little parallel to such systems in the nonliving world. Hence, biology may benefit from new mathematics specially tailored towards addressing such systems. Furthermore, a fundamental question that one encounters while addressing cancer from a biological complexity perspective is that, is cancer evolution or devolution [15]? Thus, new ideas from applied math, ergodicity, and network/graph theory may prove useful in gaining a deeper understanding.

Do we need better approaches for modeling biological and cellular communication networks and their interactions with the environment?

This is a growing area, especially with the application of AI and deep learning through cloud-based computing. The behavior of cancer cells is highly coupled with the biological networks of individual cells, as well as the networks of communication among cellular communities of the tumor microenvironment. Such complex interactions often lead to nonlinear relationships that are not always amenable to analytical models. Therefore, network centric study of cancer aided by ML approaches can lead to more accurate prediction of its future progression and better therapies.

Concluding remarks

The Kona Meeting led to the positing of the above-mentioned ideas as important goals and priorities for cancer biologists that may lead to a better understanding of the disease and development of new treatments. However, because many of these ideas/hypotheses are radical and may lack preliminary data, they are unlikely to be funded by regular funding agencies such as the National Institutes of Health. Therefore, we implore philanthropists and private foundations to recognize their value and support these studies. We also urge reviewers and editors to encourage new thinking and creativity rather than stifle ideas and hypotheses because they are unproven or even worse, because they question prevailing wisdom. Perhaps, the quote by John Maynard Keynes, 'The difficulty lies, not in the new ideas, but in escaping the old ones, which ramify, for those brought up as most of us have been, into every corner of our minds', may serve as words of wisdom for the members of this burgeoning interdisciplinary community.

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Declaration of interests

No interests are declared.

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