

Commentary

Modeling collective cell behavior in cancer: Perspectives from an interdisciplinary conversation

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Collective cell behavior contributes to all stages of cancer progression. Understanding how collective behavior emerges through cell-cell interactions and decision-making will advance our understanding of cancer biology and provide new therapeutic approaches. Here, we summarize an interdisciplinary discussion on multicellular behavior in cancer, draw lessons from other scientific disciplines, and identify future directions.

Introduction

Efforts to understand cancer have traditionally examined how a single cell acquires, through a series of stepwise muta-

tions, the ability to survive, grow, and move when it otherwise should not. The focus on individual cells has led to important discoveries about the functions of on-

cogenes and tumor suppressors, cell-cycle checkpoints, control of cell growth, repair of DNA damage, and mechanisms of cell death; however, it has fallen far



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short of illuminating a more integrated and systemic understanding of cancer development. More recently, there has been a shift away from the “one rogue cell” view of cancer, with more and more cancer biologists and engineers beginning to view this disease as a complex system, in which the acquired abilities of cancer cells are critically tied to their interactions with other cell types, both mutated and not, and firmly rooted in cellular behaviors beyond cell survival, growth, division, and movement (e.g., invasion, quiescence, spatial patterning, and remodeling the environment).

Collective cell behavior, which is strongly influenced by context, contributes to distinct stages of tumor progression, including initiation, metastasis, recurrence, and response to treatment. For example, when teratocarcinoma cells

are taken from a mouse tumor and injected into a developing embryo, the pup develops normally. If these cells are then isolated and injected into an environment that supports tumors, teratomas are again obtained, demonstrating the importance of the surrounding environment in suppressing tumor formation.¹ Cells frequently act collectively to escape the primary tumor and invade the surrounding stroma, and metastasis can be more efficient when cells traverse the vasculature together rather than alone.² Similarly, treatment response may depend on intercellular interactions. For example, tumor cells evade BRAF mutant therapies by modulating growth factor signaling through hepatocyte growth factor from stromal fibroblasts.³ Finally, a dynamic interplay between tumor cells and the immune system contributes critically to the

acquisition of malignancy and response to treatment.⁴ Despite this, we currently lack quantitative and conceptual models that consider the diversity of cell-cell interactions that occur across multiple spatial and temporal scales. Such models are required to explain the spectrum of collective behavior that is associated with cancer.

A group of researchers from diverse biological and quantitative fields recently gathered for a 5-day innovation lab facilitated by the National Cancer Institute titled “Modeling Emergent Cellular Behavior in Cancer” (February 25–26 and March 1–2, 5, 2021) to consider the processes by which the behavior of individual cells and their interactions generate the collective behavior of cancerous tissues, and to draw lessons from other scientific disciplines that have met similar

challenges. Here, we summarize the major themes of this conversation.

Collective behavior emerges from interactions among different cells. It is increasingly clear that distinct types of collective behavior in cancer are rooted in the relationship among cells. Cancer cells can interact with each other or with non-malignant cells. Non-malignant cells, such as macrophages and fibroblasts, can also interact with each other. Interactions can be short lived (e.g., diffusible, electrical signals, or active stresses) or long lived (e.g., secreted components such as the extracellular matrix [ECM] that can alter tissue stiffness, ligand availability, etc.). In turn, these interactions are embedded within the context of the surrounding tissue, the immune system, and the chemical and physical microenvironment. By learning how cells interact to give rise to tumor behavior, we can then manipulate these interactions to prevent tumor progression and improve the design of future drugs targeting these interactions. At a minimum, this understanding requires identifying the cellular partners involved, the direction of interaction(s), the nature of the intercellular signal (e.g., mechanical, electrical, or chemical), and how these properties are interpreted by the cell. Spatial molecular atlases of tumor microenvironments provide informative measurements on these key components of collective behavior; however, further development of experimental and computational approaches is needed to understand how these dynamic systems generate collective outcomes.

What is a state? In developing an understanding of collective behavior, it is important to define the concept of a cell state. Different fields use the term in unique ways. In cellular and molecular biology, an individual cell's state is defined as the configuration of its molecular components. At the coarse-grained level, we can define cell state $S(t)$ at a given time by the amount x_i of each molecule i in the cell. $S(t)$ is a *state vector*; $S(t) = [x_1(t), x_2(t) \dots x_M(t)]$ for a cell of N components. Single-cell RNA sequencing measurements yield a state vector that includes thousands of transcript types. A more complete description might also incorporate the intracellular location and movement of molecules over time and properties that emerge from the molecules such as a cell's mechanical, morpho-

metric, and electrical descriptors. Cells and groups of cells are dynamical systems with state variables that change over time autonomously (e.g., through mutation and biological noise) or due to microenvironmental factors and cell-cell interactions. Therefore, we need to look beyond a catalog of cell states to understand how interactions shape this system to generate population-level outcomes in cancer.

Interactions and the study of collective behavior in cancer

Interactions are required for collective behavior. The collective behavior of communities of cells arises from their cellular interactions. Quantitatively, "interaction" means that the state of one cell depends on the state of another, without regard to mechanism. Interactions can be as simple as attraction or repulsion. The outcome of even the simplest interactions on communities of cells can be non-intuitive. For example, simple systems involving motile "cells" that only repel and lacking feedback are capable of collectively organizing into domains of high and low density.⁵ Adding feedback to these simple interactions can result in far more surprising collective behaviors. Such systems are described as "self-organizing" because their collective behavior emerges from the interactions among the cells and the feedback these interactions have on cell state. The properties of a self-organizing system depend on interactions: cells communicate information and alter their state in a manner that depends on their location (which determines the strength of the interaction) and current state (which determines the outcome of the feedback). These systems therefore exhibit the ability to perform information processing or regulated response to changing conditions. Because regulation keeps the system within some bounds, it requires that information about deviations from those bounds feeds back into the system. Cancers can be challenging to treat because cells block, short circuit, or modulate the layers of interactions and feedback controls that regulate healthy tissues.³

Interactions are also impacted by stochastic processes acting at both the molecular and tissue scale. For example, during the development of tumors, not all carcinoma cells will contribute to tumor growth, invasion, or metastasis. The

growth of clinically detectable carcinomas can be an all-or-none process, with a fraction of nascent lesions switching to a proliferative state while many others remain indolent. Moreover, evolutionary processes like neutral drift can allow small numbers of clones to become dominant within a population without having a measurable selective advantage. Tumor growth, therefore, is driven by the "forces" of cell-cell interactions, but it is also influenced by rare events and tipping points that may themselves be a consequence of interactions within the tumor microenvironment. Unfortunately, studies of tumor growth often do not capture this phenomenon. Preclinical tumor models are frequently designed to be deterministic and fully penetrant. When using these models, researchers typically measure tumor growth; however, models that capture the intrinsic stochasticity of cancers could measure the probability of events associated with tumor progression, thereby better revealing the mechanisms that allow tumors to move through key bottlenecks in their evolution and spread.

New study designs are attempting to address this issue by studying bifurcations in outcome that occur in natural systems as the number and composition of tumors are altered systematically. For example, in a Lewis lung carcinoma model, implantation of 10^6 cells produces tumors in 100% of the animals, while implantation of 10^3 cells produces dormant, non-proliferative lesions in 100% of animals. However, when 10^4 cells are implanted, ~50% of the lesions remain dormant while ~50% proliferate to yield invasive tumors, with growth rates that match the tumors generated from 10^6 cells.⁶ This is an example of a tipping point in the system, where a small change in an input signal or underlying parameter can cause the system to evolve toward a completely new state. Here, the surrounding tissue presumably loses its ability to maintain homeostasis because of interactions with tumor cells. Such feedback generated through cell-cell interactions can lead to many different and non-intuitive outcomes in these complex systems.

What are the important interactions to observe and manipulate? To learn how feedback is operating, the first step is to identify which cells are involved. The next step is to learn how interactions among cells generate feedback. Finally, it is

important to identify the range of parameters for which feedback can maintain the system within a particular state. Feedback can take many different forms (Figure 1).

1. Is it activating or inhibiting? Cells can signal to promote or inhibit a neighbor's activity. For example, growth factors can promote proliferation, while cell-cell contact and adhesion can inhibit proliferation. Note that judging what is *activating* or *inhibiting* is not always easy, because the same feedback may function differently depending on context.
2. Is the interaction reciprocal? Cells can engage in bidirectional signaling, mutually altering each other's behavior. For example, mutual activation leads to a growth-promoting positive feedback, and mutual inhibition to the potential for a biological switch.
3. Is the degree of interaction modified by the presence or absence of another signal? For example, some cells only respond to mitogenic signals in the presence of other permissive signals.

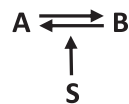
Except in special cases, the dynamical consequences of these interactions cannot be derived intuitively just by looking at the signs on these diagrams (e.g., positive or negative) because multiple signals can interact through feedback to generate nonlinear effects. For example, the 3-way interaction shown in Figure 1 illustrates one case of context dependence that leads to a nonlinear outcome, an interaction modification that could alter an existing interaction. The dynamics further complicate the outcome of interactions due to variability in the time required for information to pass through signal processing networks and manifest as transcriptional or translational changes, as well as the distance that molecules or cells need to diffuse. Computational modeling provides a powerful approach to resolve this complexity and predict the outcome of interactions.



Cell type **A** signals to cell type **B** often as part of a signaling cascade. This signal could activate or inhibit **B**.



A return signal from **B** alters the behavior of **A**. Appropriate combinations of activating and inhibiting effects create positive and negative feedbacks.



More complex networks emerge through higher order interactions, such as the **interaction modification**, where the presence of a signal **S** can alter the strength or sign of the interaction between **A** and **B**.

Figure 1. Modes of interaction and feedback

Further, experimental approaches to test these predictions are critical.

Questions of scale, or identifying the right size to understand cancer. We aim to study the cellular interactions that contribute to tumor progression in the most relevant context: the body of a human being. However, the complexity of the human body makes many such studies impractical, and the ethical and financial challenges associated with human trials are frequently insurmountable. We therefore need to examine the dynamic interactions that are important for disease progression in other contexts, such as animal and *in vitro* models. Defining a minimal model and the appropriate scale to probe and understand tumor biology presents several important conceptual and experimental questions. At the conceptual level, we must ask at what level of abstraction we should measure and analyze the progression of a tumor. For example, do we care about the state of actin in a tumor cell as it moves, or do we care about the active mechanics (which emerge from the dynamics of actin) among groups of cells as they push, pull, and guide themselves within and ultimately out of a tumor? Both are essential to tumor progression, but studying one often prevents the detailed analysis of the other because they operate at different time and length scales. At the experimental level, we must ask how many cell types are sufficient to model a tumor, and how many can be removed while retaining the relevant interactions and phenotypes? We must consider whether it is

even possible to know when an important cellular interaction is missing given how little we know about the impact of these interactions on tumor progression. Defining the right scale to study the collective behaviors of cancer cells, and the challenges of reductionism, is not trivial.

Lessons from other fields

What lessons can we learn about cancer biology from behavioral ecology? Investigation of collective behavior in animals provides a blueprint for how to study collective behavior in cells. The field asks how interactions among

individuals have collective outcomes that adjust to changing conditions. For example, simple olfactory interactions among ants allow colonies to respond to changes in food availability, although no leader directs them, and no ant makes any global assessments.

Ecological studies use perturbation experiments to provide clues to understanding the diverse outcomes of collective behavior in different environments. For example, ants are extremely diverse, with each of about 14,000 species having its own forms of collective behavior that are frequently regulated by olfactory interactions.⁷ By changing conditions in a perturbation experiment, it is possible to learn how interactions are used to respond to conditions. For example, to understand how changes in food availability or a rupture in a trail network alter interactions, we can offer food or remove it, or change the course of the trail network to understand the logic underlying the chemical interactions that produce recruitment trails. Perturbation experiments have also been used to show how ants use encounter rate to regulate foraging activity. Note that, because the environment and interactions are not independent of each other, experiments will be most informative if the perturbation occurs within the normal range of environmental conditions.

In a similar way, cancer researchers might use perturbation experiments to alter the diverse interactions in the tumor microenvironment that determine collective cellular behavior in order to learn

how tumor cells respond to local conditions. Such an approach reveals that the impact of these interactions can be profound. For example, Weaver and Bissell found that disruption of a single interaction between breast cancer cells and the ECM through blocking B1 integrin could correct tissue architecture in tumor organoids.⁸ In another example, disrupting a specific cell-cell interaction between tumor cells and macrophage through ablation of CSF-1 delayed the recruitment of macrophages to tumors and slowed metastasis, while overexpression of CSF-1 led to macrophage recruitment and accelerated metastasis.⁹ Beyond examining pre-existing interactions within tumors, introduction of novel interactions into the tumor microenvironment can provide similarly novel mechanisms for tumor growth and metastasis. For example, Polyak and colleagues overexpressed a library of secreted factors from individual tumor clones *in vivo* and found that CCL5 and IL11 could drive extensive tumor vascularization and growth.¹⁰

Emerging technologies will facilitate these types of experiments. Advanced systems for inducing mosaicism and tracking tumor clones *in vivo* allows researchers to monitor the effect of oncogenic mutations in single cells within the normal microenvironment.^{11,12} New engineered systems enable researchers to monitor and induce dynamic cell-cell interactions in complex environments in mouse.¹³ Microphysiological systems provide a reductionist approach for building mini cellular “ecosystems” that are more amenable to imaging, molecular analysis, and perturbation. Ongoing development and adoption of tools such as this is required to test and refine conceptual and computational models of multicellular processes in cancer.

Normal development and aging. Collective behavior in cancer emerges through the repurposing of the same basic biomolecular components used to build or maintain the normal tissue from which they are derived. For example, cell-cell interactions that are critical during normal pre- and post-natal development are typically suppressed in most adult tissues but can become reactivated in tumors. One set of interactions act to suppress the immune microenvironment around the placenta during fetal development and are critical to prevent rejection of the fetus

by the maternal immune system. Near parturition this process is reversed by proinflammatory factors, leading to physiologic rejection of the developed fetus. This natural immune suppression during pregnancy results in relief of the symptoms of autoimmune disorders in pregnant women.¹⁴ Conversely, tumors tolerated by pregnant mice are rejected after parturition. The reversible nature of maternal-fetal tolerance can help us understand how to harness the immune system to combat cancer.

On the other end of the developmental spectrum is aging, which is the best appreciated risk factor for cancer. Aging is associated with numerous genomic changes, but like cancer, these changes are not sufficient to explain aging without considering their impact on cell-cell interactions. One type of cell-cell interaction that is essential for developing and maintaining tissues is cell competition, where more fit cells actively remove or kill less fit cells.¹⁵ For example, normal tissues can respond to the altered behaviors or biophysical properties of neighboring neoplastic cells and extrude them, resulting in their apoptosis or invasion. This process depends on the existence of normal neighboring cells; as tissues age, increasing numbers of cells are damaged and the efficiency of cell purging decreases. Oncogenes such as *myc* can enable individual cells to induce the death of surrounding normal tissue, for example, *Myc* gain-of-function mutations allow mutant cells to outcompete and kill neighboring normal cells in *Drosophila*. Similarly, senescent cells secrete factors that can reprogram the behavior of nearby cells. It remains to be seen how these interactions contribute to the early and late stages of cancer progression.

Conclusion

Identifying cancer cell behaviors and enumerating their genetic and molecular underpinnings has explained much about cancer progression; however, key steps in the process have resisted explanation, limiting our understanding of initiation, metastasis, recurrence, and response to treatment. Studying cancer as a multicellular process, involving a diversity of interaction and feedback mechanisms at the tissue level will be critical for advancing the field. This will require the development of new model system and measurement

modalities, validated *in vivo*, that provide deep quantitative phenotypic and molecular data. Placing these measurements in the appropriate conceptual framework will require adapting concepts from adjacent fields and building new mathematical and computational models of multicellular phenomena. Testing these models will require new tools for perturbing tissues at the molecular, cellular, and tissue scales. Will developing these approaches finally facilitate understanding cancers as the complex systems that they are, and will this understanding have an impact in the clinic? We propose that because collective behaviors play important roles in cancer progression and resistance to treatment, untangling the network of cellular interaction that regulate collective behaviors will provide new strategies for slowing, halting, reversing, and even preventing cancer.

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