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Perspective

Molecular Cancer Research

Cancer as a Social Dysfunction—Why Cancer Research Needs New Thinking

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Abstract

The incidence and mortality for many cancers continue to rise. As such, critical action is needed on many fronts to reshape how a society thinks, discusses, and fights cancer especially as the population grows and ages. Cancer can be described as a broken social contract that requires different conceptual frameworks such as game theory. To this end, it is our hope that this perspective will catalyze a discussion to rethink the way we approach, communicate, and fund cancer research; thinking of cancer as a broken social contract is only one example. Importantly, this endeavor will require infusion of ideas from other fields such as physics, computational medicine, complexity science, agent-based modeling, sociology, and ecology, all of which have the capacity to drive new insights into cancer biology and clinical medicine. *Mol Cancer Res; 16(9); 1346–7. ©2018 AACR.*

Despite the existence of nearly 800,000 published articles on cancer since 2013, deaths from cancer continue to rise at a rapid rate (1). Although per capita death rates have declined somewhat since 1990, there is a long way to go. Moreover, the cost of cancer treatments is skyrocketing and may reach $156 billion by 2020 in the United States alone (1–3). Globally, cancer death rates are projected to rise by 60% by 2030 (1–3). In the United States, there has been a 13% decrease in per capita cancer death rates over the past decade, but a large fraction of this decline has been due to prevention rather than improved treatment (4, 5). For example, the decrease in lung cancer mortality has been proportional to the decline in smoking, implying that improved treatment has played only a small role in lung cancer outcomes (5). Without real breakthroughs, cancer will bankrupt an aging population, under any health plan.

Viewing cancer with concepts from the social sciences, ecology, and game theory, cancer can be seen as a rebellion among a subset of cells that do not obey the social contract in the cell community to forego constant reproduction in order to contribute to a greater goal of organismal fitness. In that sense, a tumor is like a criminal gang that ceases to cooperate with the society as a whole for its own selfish interests. Although this may seem like an anthropomorphism of cancer, it is not as these descriptions are valid for any community of species with members interacting with each other as well as other species nearby. Thus, game theory is applicable even at the cellular level (e.g., bacteria; ref. 6). The irony is that this selfishness can destroy the whole society, criminal gang and all.

Thus, cancer is not a disease in the traditional sense of the word, but rather a social dysfunction within the community of the cells. The fact that it is a social dysfunction makes it fiendishly difficult to deal with because the other parts of the organism may not recognize the cancer for the damaging invader it is, and continue to respect their part of the contract, that of peaceful coexistence, until it is too late.

Cancer therapy has always been driven by the paradigm of the eradication of the proliferating cancer cells through surgical removal or inducing programmed cell death of the dividing tumor cells through chemotherapeutic, targeted molecule, or radiation treatment. Although localized tumors can be cured, systemic therapy virtually always fails to cure metastatic disease. Cancer cells appear to develop resistance to all systemic agents, including recent immunotherapies, either through intrinsic or adaptive resistance strategies that are represented by the broad concept of "tumor cell heterogeneity."

Because cancer is a social phenomenon, focusing on what goes on within a single cell is insufficient for attacking many of the underlying mechanisms that support cancer's spread. Although it is useful to sequence as many mutations of cancer as possible, what is also needed is an understanding of how members of the "gang" empower each other, and how they exploit the functions of the normal cells in their neighborhood.

To understand cancer as a broken social contract requires different conceptual frameworks. One such framework is game theory, an approach that has made valuable contributions to a wide variety of disciplines, including political science, economics, and evolutionary biology and does not require "sentience" (6). Game theory can be used to mathematically model and understand how heterogeneous cancer cells interact, cooperate, and interfere with each other and normal host cells to inform biology experiments. Unfortunately, a new approach, such as game theory applied to the microenvironment of a tumor, can be a hard sell for most cancer researchers. When we submitted an article showing how different tumor cells might well be cooperating with each other to overcome the defenses of the host that none could overcome on its own, a reviewer said that what we were proposing was impossible (7). Fortunately, we were able to publish it elsewhere, and it has since been cited

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as one of the foundational articles in the study of how the cooperative behavior of subclones can influence disease progression (8).

The recent Cancer Moonshot initiative is adding much needed funding and organizing resources across the federal government to accelerate progress in cancer research, prevention, and treatment. Comparing cancer discovery to the goal of getting to the moon is aspirational and certainly is a good way to capture the imagination of the public. But we as a community need to be careful. Simply putting more funding into cancer research using current paradigms is equating the cancer problem to the engineering problem of getting to the moon. Cancer is not an engineering problem; it is much more. We should not fall into the trap that continued reductionist approaches, such as more and deeper sequencing (e.g., the Single Cell Analysis Program, Human BioMolecular Atlas Program; ref. 9), is going to provide quantum leaps in understanding and new discovery. In practice, the Moonshot initiative tends to fund incremental, mainly reductionist science.

As long ago as 1962, the radiologist David Smithers pointed out that "Cancer is no more of a disease of cells than a traffic jam is a disease of cars" (10). A lifetime of study of the internal combustion engine would not help anyone to understand our traffic problems. The causes of congestion can be many. A traffic jam is due to failure of the normal relationship between driven cars and their environment and can occur whether they themselves are running normally or not (8). Too much of cancer science is focused on trying to understand the fine structure of the internal combustion engine, of DNA, RNA, and proteins without understanding the context in which these molecules exist. Just as weathermen and social planners can lend insight into traffic jams that cannot be predicted by mechanical engineers, fields such as physics, computational medicine, complexity science, agent-based modeling, sociology, and ecology all have the capacity to drive new insights into cancer and tumor biology.

Unfortunately, the peer review process does not reward paradigm-shifting thinking. Indeed, in these times of constrained resources, only safe, incremental, reductionist research is likely to be rewarded with funding. We must rethink the way we approach and fund cancer research; thinking of cancer as a broken social contract is only one example. We must challenge ourselves to think of others and fund them.

Disclosure of Potential Conflicts of Interest

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