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Editorial

Twelve unanswered questions in cancer inspired by the life and work of Leland Chung: "if this is true, what does it imply"?

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Introduction

Perhaps one can describe best Leland Chung as a humble visionary. Starting with his post-doctoral training at the Brady Urological Institute, he established himself not only as a leader in the fields of cancer biology and prostate cancer but as a true thinker. He was a gentle giant in Urologic research, guiding his students with a quiet manner and prodigious intellect.

Dr. Chung was an early driver of how the tumor microenvironment affected tumor growth and metastasis and made many valuable contributions that opened these fields for the world. In addition to his basic science discovery work, Dr. Chung was a pioneer in the field of translational science. He showed the field how to translate lab discoveries to diagnostics and therapies to help patients. He was driven to make a difference.

When his mentor Dr. Coffey passed away, this group published an homage to him by publishing an editorial in this journal "Ten unanswered questions in cancer: 'If this is true, what does it imply?'" In addition to being his close friend, Leland was certainly one of Don's greatest students. Dr. Chung lived this mantra, passing this insight to his own students. It is only fitting that we publish a similar editorial in honor of Dr. Chung. We continue to seek truth, we are guided by these unanswered questions and the implications for our research, for our understanding of cancer biology, and for our patients.

Question 1: who does and does not get cancer?

Beyond the small percentage of cancer patients whose disease is attributable to heritable (i.e., BRCA mutations, FAP) or environmental (i.e., smoking) drivers, it remains unclear what determines who gets cancer and who does not [1]. While cancer risk increases dramatically with age, approximately 60% of men and women die in old age without a hint of clinically detectable cancer. Autopsy studies have shown that among these people, many do have traces of subclinical malignant disease, but it is unclear if these cancers would have become clinically important if the person had lived long enough or if undefined factors have protected them from disease progression. Approximately 25% of newly diagnosed cancer patients over 65 have a history of prior cancer [2]. It is now known, however, if this is due to genetic, epigenetic, or environmental factors. Insights into the question of "who gets cancer, who does not, and why?" will contribute to our understanding of the complexity of disease progression and may lead us down new avenues toward cancer prevention and cure.

Question 2: is there a universal set of microenvironmental conditions that promotes the development of a single pre-malignant cell to begin its cycle of uncontrolled cell division?

Tumors initiate and develop within a physical environment that contains nutrients, molecular signals in the form of soluble factors and components of the extracellular matrix, stressors, and other cell types, such as immune cell infiltration. Differential regulation of the tumor microenvironment can have both pro-tumorigenic and anti-tumorigenic effects [3-5]. In prostate cancer specifically, tumor microenvironmental factors have been shown to play a key role in cancer progression, including connective tissue growth factors and stromal-derived mediators of inflammation and angiogenesis regulators [6]. Is it also likely that microenvironmental factors influence the ability and likelihood of a single pre-malignant cell to begin its cycle of uncontrolled cell division? Is it possible that there is a universal set of conditions that can initiate a single cell to survive and propagate into a large, complex tumor? If this base set of microenvironmental features could be defined, it would enhance our understanding of the first step in cancer initiation.

Question 3: when does cancer become incurable?

A one cm^3 tumor consists of approximately 1 billion cancer cells. In general, this localized tumor mass can be cured by surgery or radiation, but is not curable by systemic therapies such as combination chemotherapy. Resistance to therapeutic interventions has classically been explained as a result of genetic tumor cell heterogeneity in which at least one cancer cell has stochastically developed a mutation that actuates resistance to a given therapy [7, 8]. In the classic view, resistance to each different therapy requires that the appropriate mutations that confer the different types of resistance are acquired by at least one cell. If this is true, how many cells does this require?

Alternative models suggest that different cancer clones can cooperate to adapt to therapeutic stress [9, 10]. Therapy resistance has also been attributed to a therapy-resistant population of cancer stem cells give rise to a recurrent population [11]. We have recently suggested a model of therapeutic resistance based on the ability of a cancer cell to undergo a polyaneuploid transition (PAT) in which a stressed cancer cell exits the cell cycle after whole genome duplication to protect itself from therapeutic insult. Cells in this polyaneuploid cancer cell (PACC) state can then reenter the cell cycle after the therapeutic stress is gone and repopulate a tumor population [12].

Question 4: how does diet affect an individual cancer cell's development, metabolism, and responses to therapy?

Diet is a controllable aspect of our lifestyles that can be a risk factor in many diseases. Current data has established correlations and associations between different dietary choices and cancer incidences, suggesting that diet can be modulated to lower a person's risk of developing cancer [13]. Diet has also been associated with cancer progression. One study showed that mice that are subjected to a high-fat diet have increased breast cancer progression when compared to mice that fed a low-fat diet [14]. There also have been correlations between obesity and worse prognosis in patients with colorectal, kidney, and pancreatic cancers [15]. Poorer outcomes are associated with obesity in men diagnosed with prostate cancer [16, 17]. These poor outcomes are generally attributed to a pro-inflammatory body environment and/or unclear metabolic changes in the body as a whole. While much of the focus of diet in cancer is related to the ingestion of carcinogens, one unanswered question is how diet, at the organismal level, can influence cancer metabolism at the cellular level.

Cancer cells access nutrients obtained from food like any other cell in the body [18]. Although the mechanism of action is unclear, a combination treatment of metformin and statin drugs that alter glucose and lipid metabolism resulted in a 54% reduction in mortality when administered to men with high-risk prostate cancer [19]. If we could identify a cancer cell's metabolic needs to proliferate, metastasize, and evade therapy, it may be possible to exploit those needs and adjust dietary intake to alter nutrient availability. Understanding the vast network that links diet and cancer at the individual cellular level may aid in developing new prevention and treatment strategies.

Question 5: which cancer cells are metastasis competent?

Metastasis is responsible for more than 90% of all cancer-related deaths. Curative measures such as surgical tumor resection and external beam radiation cannot be used to kill metastatic cancer cells that have spread beyond the primary tumor site. The metastatic cascade is comprised of five key steps: invasion at the primary tumor site, intravasation into the circulation, survival in the circulation, extravasation into the secondary site, and colonization into a clinically detectable lesion [20-22]. A successful, *ergo* lethal, metastatic lesion can only be created by a cancer cell that can complete all five steps, i.e., metastasis competent. Invasion occurs when a cancer cell acquires motile characteristics that enable movement through the extracellular matrix (ECM), often accompanied by a decrease in proliferative capacity. To spread to distant organs, the motile cancer cell must encounter and enter (intravasate) the circulatory system by squeezing through the vascular lining. Once in the circulation, the cancer cell must survive the shear stress of blood flow, immune cell detection, and anoikis (cell death occurs when cells lose adhesion). The cancer cell must then exit (extravasate) the circulation by squeezing back through the vascular lining. Lastly, the cancer cell must survive to colonize its new tissue microenvironment, returning to its proliferative, non-motile phenotype. There are compounding barriers to successful metastasis at each of the five steps. Many cells in the primary tumor will never express genes required for motility and invasion. Of the cells that do, only a subset will encounter, enter, and survive in the circulatory system long enough to reach a secondary organ site. Of the cells that do reach secondary sites, an even fewer number will regain the proliferative capacity required for metastatic outgrowth. In fact, mathematical modeling shows only 1 in every ~1 billion cells that enter the circulatory system successfully creates a metastatic lesion [23]. But what do those one in a billion cancer cells have in common? Is there a rare subset of cancer cells that *a priori* possesses the ability to perform all five steps of the metastatic cascade? If so, the identification of such metastasis-competent cancer cells remains an urgent goal of cancer research.

Question 6: why are certain secondary sites more conducive to the survival of metastases from certain cancers?

In 1889, Stephen Paget published his paper describing the affinity of breast cancer metastases for the bones [23, 24]. Since then, the "seed and soil" effect of cancer metastasis has been well established, with metastases from a particular site more likely to occur at sites specific to that cancer [25]. Cancer cells are shed by the primary tumor into the bloodstream, both passively and as a result of tumor cells' migration towards high-nutrient sites adjacent to the circulation [26]. These circulating tumor cells (CTCs) then travel through the bloodstream and disseminate to various organs as directed by blood flow [27]. Those that land in characteristic secondary sites are more likely to survive, proliferate, and become a metastatic tumor. Thus, though it is known that cancer cells travel to secondary sites indiscriminately, it remains unknown why these disseminated tumor cells are more likely to survive in certain organs depending on the cancer of the primary site, and why each cancer type has different favored secondary sites.

Question 7: why has most basic science cancer treatment research failed to translate effectively to the clinic?

85% of early clinical trials for novel drugs fail despite successful pre-clinical testing, and the greatest proportion of those failures are cancer drug trials [28]. Our use of *in vitro* and *in vivo* models cannot perfectly mimic the complexities of a human body and the impact of disease on the complex system. Mouse models, the typical model for pre-clinical trials, are poor models for human diseases, with higher utility for snapshots of a certain process or mechanism within a disease state [29]. An example of promising basic science research not directly leading to successful translation is matrix metalloproteinase (MMP) inhibitor trials. Researchers aimed to inhibit the degradation of the ECM, a process utilized by cancer cells to invade and metastasize. These trials, despite promise in early stages of testing, ultimately failed in later stages due to serious side effects that were not present in murine pre-clinical trials [28]. The limitations of our current models have become increasingly ap-

parent. How can we improve our current models or create new, better ones? How do we balance ethical concerns with the pressing need for improved cancer treatments?

Question 8: how can we cure a disease that is continuously evolving?

Cancer had been recognized and named decades before the first cancer treatment (radiation) became available in the late 19th century [30]. The first cancer chemotherapy was used in the 1940's and novel therapies have been introduced year after year [31]. While tremendous progress has been made to increase survival, once patients progress to metastatic disease, a cure is largely elusive. Combinations of systemic hormonal and chemotherapies are rarely curative for carcinomas. One explanation for the incurability of cancer is the accumulation of new genetic and epigenetic alterations that allow cancer cells to survive and continue to proliferate, even under new microenvironments or when faced with external stressors. There is no identified common set of mutations shared by all cancers. Furthermore, it has been shown that cancer cells evolve in response to therapy. In addition to the cancer cells' adaptions to survive anti-cancer therapies, they also adapt to continually evade the body's anti-tumor mechanisms [32, 33]. The ability of a cancer cell to evade the immune system is the topic of intense research but remains largely unresolved. Understanding how and when tumors create immune deserts, evade immune detection, and modify checkpoints remains unclear [34-37].

Question 9: can we force cancer to remain within the inhospitable environment it creates, causing its own destruction?

The ability to survive defines a cancer cell's success. Uncontrollable growth allows cancer cells to create their own habitat within the host and consume available resources in the area [38]. As a tumor consumes resources, however, it inherently creates a hypoxic, nutrient poor, inhabitable space. The trade-off of advantageous growth, therefore, is death if no solution is achieved to solve the problem of nutrient poverty (i.e., the hallmark of cancer neoangiogenesis) [39]. This hostile habitat has also been described to drive the adaptation of metastasis competent cancer cells. Cancer that metastasizes can, again, succeed, but not without cost. The risk to a primary cancer cell for intravasation into the circulation is high: a high likelihood of death. However, the risk of death in circulation may be less than a cancer cell's certain death in the highly competitive, highly crowded, nutrient poor, hypoxic tumor microenvironment. A single cancer cell's success in metastasizing leads to generations of successful cancer cells surviving now at a secondary location. Outrunning the self-inflicted paucity of resources can be thought of as a balancing force to the risks of cancer's uncontrollable growth. Will cancer that does not metastasize die from its own uncontrollable growth? In the cancer research field, we should consider known limitations as targetable vulnerabilities. If we force cancer to remain within the inhospitable environment of the primary tumor, we could then cure virtually all cancer through surgery or radiation. Could a natural death due to starvation, sans chemotherapy or treatment, be cancer's downfall?

Question 10: can we reprogram the TME from "pro-tumor" to "anti-tumor" in all cancer patients?

The majority of tumor microenvironments (TMEs) have "pro-tumor" characteristics including regulatory T cells, M2-like macrophages, myeloid-derived suppressor cells (MDSCs), and increased angiogenesis [40, 41]. This "pro-tumor" TME supports cancer cell growth, metastasis, and immune evasion, heavily contributing to patient outcome and survival. In contrast, "anti-tumor" TMEs are characterized by cell types such as CD8 T cells and M1-like macrophages. Even though much work at the bench and in the clinic has explored different therapies, there is not a therapy against one cell type or target that reprograms the TME from "pro-tumor" to "anti-tumor" with success in all patients. Immune checkpoint inhibitors successfully do this in many patients with certain types of cancers and with characteristics such as mismatch repair-deficiency or microsatellite instability [42]. Other methods for reprograming the TME include dendritic cell vaccines, CAR T cell therapies, and targeting M2-like macrophages. Whether a single strategy, or multiple strategies, have the potential to create "anti-tumor" TME in all patients is yet to be determined.

Question 11: is there a magic bullet for cancer therapy that would effectively target all types of cancer?

The concept of a magic bullet was coined in the 1900s when the German Nobel laureate Paul Ehrlich formally articulated the notion of a targeted therapy that would be able to distinctly and differentially affect what an immune system recognizes pathologically as non-self (e.g., a microbe), while having no negative impact on self [43-45]. It is the imagery of a bullet reaching a very specific target. Since that time, in the field of cancer therapy, advances have been made in the delivery of chemotherapeutic agents with the aim to find effective cancer management agents that balance benefit with the pleiotropic cytotoxic risk of drug administration. The obvious challenge with cancer is that the set of components supporting the fundamental biological processes of the cancer cell overlap with those of the cells of healthy tissue. Therefore, debilitating a specific pathway, cellular component, or even organelle in a cancer cell would find an undesired target counterpart in the non-disease cells of the same patient. Furthermore, the various manifestations of disease progression, which are differential and unique to tissue type, reflect uncharacterized, tissue-specific differences supporting tumor persistence, suggesting that a single-target, all-encompassing chemotherapeutic agent for all cancer types is not feasible. Our recent work suggests that all treatment resistant cancer cells may pass through a common intermediate cell state. If this transitory cell state is required for lethality, a magic bullet which targets the abrogation of such a state may be used to render a previously drug-resistant cell type sensitive and opening the door for cancer cure [12].

Question 12: is understanding cancer enough to find a cure?

Historically, most cancer research is driven by the shared motivation to find a cure. While substantial progress has been made in understanding the intricate details of cancer biology, each discovery adds to the already complex nature of the disease. However, what if the "big question" is not "What is the cure?" but rather "Can a cure be administered?" This important distinction is emphasized in sickle cell disease [46]. Scientists know the exact genetic mutation and its corresponding location, as well as its effect on hemoglobin and oxygen circulation, yet a cure does not exist. Understanding the molecular and cellular biology of a disease defines potential therapeutic targets but does not equal a curative strategy. Without the proper tools available, solely understanding the biological components does not provide a cure. Before the advancements of modern science, some diseases could be cured without knowing the molecular causes. Scurvy, for example, common in sailors on long voyages with poor diet, was cured by the ingestion of citrus fruit. It wasn't until later that scientists identified that scurvy was caused by vitamin C deficiency, and cured by ingestion of ascorbic acid [47]. Will finding a cure for cancer, an increasingly complex disease that continues to evade treatment attempts, resemble that of scurvy or sickle cell disease? Even if we understand the complex biology of cancer, will we be able to engineer a cure? Maybe, we will get lucky through some good observational work, much as James Lind did.

Disclosure of conflict of interest

None.

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