Adaptive Medicine 15: 6-9, 2023
DOI: 10.4247/AM.2023.ACD272

Review Article

Some Essential Issues in Cancer Biology

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The search for a definitive cure for cancer is one of the most exciting challenges in the fields of genetics, cell biology, and tissue research. Cancer is a group of many different diseases with the ability to invade peripheral tissues and to metastasize to other parts of the body (with rare exceptions, such as glioma, which does not metastasize). In precision medicine, next-generation genomics, proteomics, and metabolomics are now using to better elucidate the unique characteristics of a patient's cancer for developing tailored and personalized treatment plans. Here, we describe some of the biological and molecular aspects of cancer that warrant special attention and support this new approach to care.

Key words: Cancer, metastasis, tumor heterogeneity, cancer dynamics, cancer ecology, cancer evolution, precision medicine

Some history

Malignant bone tumors have been found in species as far back as dinosaurs. Despite being an ancient disease, the biological characteristics of cancer have remained relatively unchanged over time. Hippocrates was probably the first person to describe the disease. Since cancer was first discovered, several advances have been made in its management. Surgery and radiotherapy were the first treatment modalities, and these were followed by systemic approaches. Chemotherapy, which was developed in the 1960s, was a major breakthrough in the treatment of cancer [1].

Later, small-molecule targeted therapies and large-molecule approaches involving monoclonal antibodies were developed. Monoclonal antibodies were initially designed to target specific tumor cell receptors, and they are now also used as checkpoint inhibitors to activate the immune system. Several gene therapies, such as CAR-T cell therapy and adenovirus-mediated gene delivery, have been developed. The goal of gene therapy is to enhance the antitumor cellular and humoral immune response to selectively kill tumor cells. Cancer vaccines may be the next breakthrough in tumor immunotherapy [2].

Despite the substantial medical advances in cancer treatment, the word cancer remains taboo in several societies and is often replaced with the term "malignant tumor." For patients with a poor prognosis, palliative care may be the best option. Palliative care may involve alternative, complementary, and integrative medicine.

Carcinogens

Carcinogenesis is the formation of cancer. Tumorigenesis is the formation of tumors. Cancer is caused by physical, chemical, and biological agents. These agents include natural or artificial radiation, air and water pollution, smoke from cigarettes, natural radon emissions, alcohol, food additives, food processing derivatives, agrotoxic products, and viruses such as human papillomavirus, Epstein–Barr virus, and human immunodeficiency virus. These agents cause cancer by causing damage to DNA.

DNA Targets

Carcinogens affect two types of DNA. Proto-oncogenes are a group of genes that can be mutated by carcinogens to become active oncogenes. The overexpression of oncogenes can lead to the formation of tumors. Carcinogens also affect tumor suppressor genes, which are associated with the inhibition of proto-oncogenes or the repair of DNA damage. An example of a tumor suppressor gene is P53, which is

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Received: October, 24, 2022; Revised: December, 31, 2022; Accepted: March, 17, 2023
 ISSN (L) 2076-944X. https://am1.mkc.edu.tw

involved in DNA repair and is sometimes referred to as the "genome guardian" [4].

Mutated proto-oncogenes and tumor suppressor genes can cause normal cells to become cancerous. Mutated genes that modify important cellular and molecular pathways to promote cancer growth are called driver genes and include *KRAS*, *NRAS*, *MEK*, and *BRAF* [5]. Other genes are only bystanders and are called passengers. Targeted therapy is used to block the action of driver genes rather than treating the cancer as a whole.

Hallmarks

Genetic mutations can lead to the following main characteristics of cancer: sustained proliferative signaling, evasion of growth suppressors, inhibition of apoptosis, replicative immortality, enhancement of genome instability, deregulation of cellular metabolism, tumor-promoting inflammation, angiogenesis induction, immune destruction avoidance, and invasion and metastasis [6].

These characteristics are mediated by the altered expression or regulation of numerous proteins, growth factors (EGF, FGF, alpha TGF, PDGF), growth factor receptors (EGFR, TGFR), protein kinases (TK, PI3K, MAPK), transcription factors (Jun, Fos, Myc, Myr, E2F), DNA-repairing enzymes, telomerases, cyclins, caspases, cytokines, immune blockers, integrins, and metalloproteinases. Recent discoveries regarding the associations between epigenetic and microenvironmental factors and cancer have been made. Senescent cells and polymorphic microbiomes may play a role in the microenvironment of tumors [7].

Staging

During tumorigenesis, the primary tumor increases in volume and becomes more heterogenous both genetically and phenotypically. This increases the likelihood of the tumor becoming malignant and the likelihood that tumor cells are shed into the bloodstream. Tumors are classified according to their size. If a tumor is too large to be surgically removed, a patient may be administered preoperative chemotherapy or immunotherapy to reduce the size of the tumor, making it possible for the tumor to be surgically removed.

Microenvironment

The role of the tumor microenvironment has been highlighted in recent decades. The tumor microenvironment has been found to be critical to the establishment of a primary tumor and to the malignant progression and metastasis of the tumor. The extracellular matrix and local host cells, such as fibroblasts, adipocytes, pericytes, macrophages, lymphocytes, and neutrophiles, are all influenced by the tumor and contribute to its growth. Therapies targeting the tumor microenvironment are currently being tested in ovarian cancer [8].

Metastasis

Tumor behavior and progression varies according to the organ or tissue of the primary tumor. Different types of cancer are associated with different genetic markers and cellular events, causing different tumor behavior and outcomes.

During metastasis, new tumors form in organs according to the type of cancer [9]. Metastasis is a complex process with several stages. Metastasis involves the intravasation (to the capillaries) and extravasation (to the host tissue) of cancer cells. Cancer cells may remain dormant for some time for developing into metastatic lesions.

Moreover, several primary tumors release soluble factors into the blood, which lead to the formation of pre-metastatic niches in distant sites. These niches accumulate bone marrow–derived hematopoietic cells, extracellular matrix proteins, and exosomes derived from the primary tumor, among other factors. Research has identified different types of cancer metastasis that exhibit distinct patterns of gene expression; these patterns are constantly changing [10].

Tumor Heterogeneity

Tumor heterogeneity means that tumor cells are genetically, molecularly, and phenotypically nonhomogeneous. Tumors may have a high degree of clonality and subclonality, which can lead to increased resistance to treatment.

Clones may have positive or negative interactions [11]. The strongest negative interaction observed among neoplastic populations is competition, which usually arises due to limitations of nutrients or oxygen and can be manifested phenotypically by molecules secreted by one cell clone that are able to kill or damage cells from another clone.

Positive interactions result in cooperation among clones in the forms of commensalism, in which one clone benefits from another without affecting it; synergism, where both clones work together reach to achieve better results; and mutualism, where both clones benefit from each other. A full understanding of the cooperation among tumor cells can be gained using methods and concepts from evolutionary game theory, and this knowledge

of tumor ecology can aid in the design of potentially evolution-proof therapies that disrupt this cooperation [12].

Personalized medicine can address the complexity of tumors by creating maps of the genetic makeup of cancer clones, which can be used to determine the most appropriate treatment for a given patient [13].

Cellular Dynamics

Tumors have two cell types that may be spatial or functional. The proliferative compartment is characterized by actively dividing cells. By contrast, the nonproliferative compartment contains cells that are not dividing but that can still contribute to tumor growth due to genetic instability. Together, these two compartments lead to the development of a tumor.

In the nonproliferative compartment, cells are quiescent in the G0 phase of the cycle and are not dividing. Many of these cells are cancer stem or progenitor cells and have the ability to self-renew, and they may remain in this state for many years. This compartment also contains quiescent cells that can contribute to metastases, in some cases surviving in "sanctuary" microenvironments, such as the bone marrow. In some cases, both the proliferative and nonproliferative compartments exist in the same tumor site.

These cellular dynamics depends on the tumor type. In leukemia and lymphoma, cells in the proliferative compartment are the most active. In other tumors, cells may be both quiescent and active. In many cases, cells in each compartment can interact. The passage of cells from one compartment to the other may depend on the presence of paracrine or microenvironmental stimulus. A quiescent cell may begin dividing and enter the proliferative compartment depending on the presence of certain signals in the environment.

The surgery of the primary tumor "wakes up" the growth of a distant metastasis through the intercompartmental movement of cells. In this context, chemotherapy and radiotherapy are double-edged swords. As these treatments kill preferentially cycling cells from the proliferative compartment, cell depletion in these compartments may trigger the passage of quiescent cells to the proliferative state.

Furthermore, chemotherapy and radiotherapy kill only responsive cells; therefore, they may be selecting unresponsive cell clones in the proliferative compartment that are more aggressive than their counterparts. This evolutionary phenomenon is termed competitive release and is mediated by multimolecular mechanisms [14]. Initially, resistant clones are microscopic and therefore undetectable by standard imaging modalities, such as X-ray, computed tomography, and magnetic resonance imaging. Eventually, the tumor relapse will occur.

Chemotherapy can act as a carcinogen for the unresponsive clones that remain alive, enhancing their mutation rate and consequently their malignancy. Thus, these observations indicate a paradox in which the treatment may be stimulating the replenishment or recurrence of the tumor and causing it to become more aggressive and treatment-resistant.

Novel therapeutic strategies that involve the targeting of quiescent cancer cells and the simultaneous targeting of quiescent and proliferating cancer cells have been proposed [15]. Other approaches, such as adaptive therapy, which shifts the focus from just eliminating tumor cells to preventing the growth of resistant populations to maintain long-term control of the disease, have been proposed [16].

Body-wide Tumor Ecology

New research has suggested that tumors are a part of a larger, interconnected system. This system facilitates communication between the tumor and the host through vascular, lymphatic, neuroendocrine, and immune systems [17]. Furthermore, aging, comorbidities, and medications play a major role in cancer progression and the therapeutic response.

Final Considerations

Many different types of cancer exist. Creating a cure for cancer, if it is possible, will take a long time. Although advancements have been made in cancer treatment, several challenges remain. Some types of cancer, such as some types of lymphoma, leukemia, and testicular cancer, can be treated quickly and effectively, suggesting that creating a cure for cancer is possible.

We can now produce drugs specially designed by biotechnology to block specific driver genes or key protein targets. Drugs are being developed that have greater specificity and selectivity and lower toxicity than existing drugs. In vitro cell culture models are being applied for developing functional precision medicines and for improving drug sensitivity screening [18]. Immunotherapies are also being developed, with favorable results.

Nevertheless, microenvironmental and evolutionary factors markedly reduce the effectiveness of monotherapies. At present, cocktails of drugs are used to target multiple tumor genes or proteins, and multiagent therapies are used in which the first drug achieves tumor cell toxicity and renders the cell more vulnerable to a second drug. These therapies are highly successful in maintaining durable tumor

control [19].

Despite the medical advances achieved in the last decades, the lifetime risk of cancer is approximately 50% in Western populations, prognoses for patients with metastatic cancer remain poor, and drug resistance is the norm [20]. Some of the challenges related to tumor therapies are briefly mentioned below.

First, the high spatial heterogeneity and rapid evolution of malignant tumors necessitate the thorough and frequent sampling of tumors to assess progression and metastasis; however, this is not feasible. Second, the aforementioned treatment paradox, whereby treatment promotes the spread of tumor cells to distant sites, indicates the need for better therapies. Third, the lack of effective preclinical models for some tumor types is problematic. Currently, animal models, which can mimic certain key features but do not completely reflect the human disease, are used to understand cancer evolution [21].

Tumor ecology and Darwinian evolution are fascinating concepts and popular areas of research [22]. A better understanding of tumor biology is required. We must find effective cancer treatments and eventually create a cure.

Several incurable cancers, such as prostate cancer, can be controlled and managed as a chronic disease, with favorable survival expectancy and life quality [23]. When developing new treatments for cancer, we must consider the type of cancer, the tumor environment, and how the cancer responds to treatment.

Conflicts of Interest

Authors set that there are no conflicts of interest with this publication.

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