Introduction

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LEARNING OBJECTIVES

1. Explain, "molecularly targeted anti-cancer agents".
2. List the characteristics or "hallmarks" of cancer cells.
3. Relate the function of "enabling characteristics" of cancer cells to the "hallmarks" of cancer cells.

INDEX TERMS: molecular targets, cancer cell characteristics, cancer cell transformation, cancer cell growth and proliferation

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INTRODUCTION

Cancer is a global health concern without geographical, racial, or ethnic borders. In the United States, in 2011, it is predicted that 1.6 million people will receive a new cancer diagnosis and 570,000 deaths will occur due to cancer.[1] Although cancer mortality has decreased in recent years, it is still more deadly than heart disease for individuals under 85 years of age.[1]

Chemotherapy is often the most effective cancer treatment, yet patient toxicity and drug resistant tumors are common obstacles in achieving and maintaining a cancer-free status.[2] While new chemotherapeutic strategies are developed, the status quo of chemotherapy is less than acceptable, especially in advanced disease.[3,4] For this reason, anti-cancer agents have evolved from chemotherapy that kills proliferating cells indiscriminately to molecular-targeted agents that inhibit or alter individual molecules to be effective. However, knowledge of the tumor cell molecular profile is necessary to provide predictive outcomes for the clinical efficacy of molecularly targeted agents. To further reduce cancer mortality, the analysis of empirical evidence that denotes the origins of cancer, both cellular and molecular, and the study and design of novel therapeutic agents that possess focused biomolecular actions, are at the forefront of clinical cancer research.

What Defines a Cancer Cell?

The utility of molecularly targeted anti-cancer agents and the advances of clinical cancer research, can best be understood upon description of the molecules and events that define cancer cell transformation. In 2000, Hanahan and Weinberg authored a seminal paper that was published in *Cell* and entitled "The Hallmarks of Cancer". Their work described that a cell must possess six characteristics in order to be transformed into a cancer cell. Those six "hallmarks" were depicted as 1) sustained proliferative signaling, 2) evasion of growth suppression, 3) resistance to cell death, 4) enabling replicative immortality, 5) induction of angiogenesis, and 6) activation of invasion and metastasis.[5] After ten years of empirical data collection and analysis and extensive evaluation of the literature, Hanahan and Weinberg reinforced the ideas proposed in their original article and detailed "emerging hallmarks" of cancer cells. Notably, cancer cells employ mechanisms that 1) deregulate cellular energetics and 2) avoid immune destruction. Furthermore, cancer cells possess "enabling characteristics" that involve 1) genome instability and mutation and 2) tumor-promoting inflammation.[6] The aforementioned "hallmarks" and enabling characteristics are described herein.

Cancer Cell Characteristics

Sustained proliferative signaling

In normal tissues the concentration of molecules (cytokines and growth factors) that positively regulate cell growth (size) and numbers is restricted to ensure tissue homeostasis. As medical laboratory scientists we are well aware of the detrimental effects that accompany an over-proliferation of cells within the bone marrow and we refer to this phenomenon as hematological malignancy. Cancer cells evolve mechanisms (e.g.

chromosomal translocations in leukemias) such that the tissue microenvironment no longer controls whether or not a cell divides; that control is taken over by the cancer cell. The stimulus for cell division is often in the form of a growth factor that produces proliferative effects by autocrine signaling (the cell makes its own growth factor) or by over-production of surface receptors (ensures that contact is made with growth factors even in low concentration). In any case, this aberrant proliferative signaling results in cells that progress through the cell cycle inappropriately.[6]

Evasion of growth suppression

The microenvironment of nearly every tissue and cell possesses molecules that negatively regulate cell proliferation. Notably, the tumor suppressor protein p53, is a molecule that senses cellular stress and DNA damage and also functions to activate programmed cell death, or apoptosis. A normally functioning p53 molecule halts cell cycle progression. However, more than 50% of human cancers harbor a mutant or absent p53 gene product. Therefore, p53 is unable to function as a growth-suppressing molecule and as described below, as an inducer of apoptosis and in both cases, contributes to the transformation of normal to tumor tissue.[6]

Resistance to cell death

The decision for a normal cell to live or die is determined in large part by equilibrated pro-apoptotic (pro-death) and anti-apoptotic (pro-survival) proteins. Cancer cells often over-express genes encoding anti-apoptotic proteins, thereby disrupting the normal death/survival equilibrium. The increased presence of anti-apoptotic proteins permits cell survival under conditions that would normally be deleterious to a cell and leads to tumor formation.[6]

Enabling replicative immortality

Normal cells are programmed to pass through cell growth and division only a finite number of times. Beyond that number, we understand the cell to be terminally differentiated (e.g. the normal maturation of a red blood cell) and to senesce. Senescence is a result of shortened telomeres. Telomeric DNA resides at the ends of chromosomes and protects chromosomal content. With every cell division, the telomeres shorten. Cancer cells have devised a mechanism to evade telomere shortening and in fact are able to lengthen this DNA sequence via increased activity of the enzyme telomerase. Telomerase adds nucleotides to telomeric sequences and its over-expression promotes cell survival and immortality.[6]

Induction of angiogenesis

All normal tissues and organ systems require an adequate supply of oxygen and nutrients for proper function. Tumor cells also require a nutrient supply for survival and activate what is commonly referred to as an "angiogenic switch" in which the formation of new vasculature is perpetually promoted. The normally quiescent vasculature is stimulated to grow and branch toward a growing tumor mass in order to provide sustenance and a mechanism of tumor cell metabolic waste evacuation. Angiogenesis therefore ensures a quality of life for the cancer cells that would not normally be present.[6]

Activation of invasion and metastasis

Within a normal tissue, cells express adhesive receptors involved in attachment to other cells of that tissue and to the extracellular matrix. For a tumor cell to escape its tissue of origin, to "invade" local tissues, and to eventually metastasize to distant tissues, it must lose or greatly reduce expression of adhesion molecules. Without a mechanism for normal or tumor tissue to hold on to a cancer cell, invasion commences followed by a step-wise process that promotes colonization of distant sites, called metastasis and the possibility of prolonged cancer cell survival.[6]

Emerging Hallmark: Deregulation of cellular energetics

Under normal, aerobic conditions, a cell metabolizes glucose into pyruvate via glycolysis in the cytosol for a small energy pay off and further breaks down pyruvate in the mitochondria for a large energy payoff. For energy production to occur in the mitochondria by oxidative phosphorylation, adequate oxygen levels are required and therefore, energy production by glycolysis is only favored under anaerobic conditions. In a mechanism similar to that of angiogenesis, cancer cells possess the ability to switch their metabolism to favor what is termed "aerobic glycolysis" in which glucose is metabolized almost exclusively by the "low energy pay off" glycolytic pathway. For this metabolic switch to occur, cancer cells increase glucose uptake by increasing the expression of the glucose transporter, GLUT1. The function of this metabolic switch remains to be fully elucidated, but may be attributed to the increased requirement for organelle synthesis in rapidly dividing

cell populations.[6]

Emerging Hallmark: Avoiding immune destruction

The immune system is adept at surveillance for and destruction of abnormal cells including cancer cells. However, cancer cells may function to inhibit the destructive capabilities of immune cells by secreting immunosuppressive molecules such as TGF-ß or by recruiting immunosuppressive cells such as regulatory T cells. Critical evaluation of this emerging hallmark will better define the role of immune function with regard to cancer cells in the coming years.[6]

Enabling Characteristics: Genome instability and mutation and tumor-promoting inflammation

The human genome is remarkably well protected from spontaneous mutation because of systems that detect and repair damaged DNA. For a normal cell to transform into a cancer cell, the machinery involved in DNA maintenance and repair is often defective, allowing for mutations to accumulate and for any of the cancer hallmarks to be expressed. While an unstable genome contributes to cancer cell transformation and proliferation, inflammation has a similar effect. In fact, inflammatory cells appear to contribute to several of the aforementioned "hallmark" processes by secreting growth factors, molecules that promote angiogenesis, invasion, metastasis, etc.[6] Both genomic instability and inflammation are therefore aberrations to normal tissue homeostasis.

In this focus section, the article "Proteasome Inhibitors In Cancer Therapy: A Novel Approach to a Ubiquitous Problem" and "Anti-hormones: Mechanism and use in Treatment of Breast Cancer" describes therapies that can circumvent several of the cancer cell hallmarks in hematological malignancies such as multiple myeloma and in breast cancer. Additionally, "Cancer Stem Cells" entails the recent findings that most cancers contain a subpopulation of cancer stem cells that display self-renewal activities, yet another hallmark of cancer. These three articles represent an evolving dogma with regard to cancer therapeutics and evaluation of patient response to treatment.

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