Chapter 17
Cancer and Signaling Pathway Deregulation

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ABSTRACT

Cancer is a complex disease that is associated with a variety of genetic aberrations. The diagnosis and treatment of cancer have been difficult because of poor understanding of cancer and lack of effective cancer therapies. Many studies have investigated cancer from different perspectives. It remains unclear what molecular mechanisms have triggered and sustained the transition of normal cells to malignant tumor cells in cancer patients. This chapter gives an introduction to the genetic aberrations associated with cancer and a brief view of the topics key to decode cancer, from identifying clinically relevant cancer subtypes to uncovering the pathways deregulated in particular subtypes of cancer.

INTRODUCTION

With the development of high-throughput biotechnologies, various large-scale genomic data are available for screening genetic aberrations in cancer genome. Transforming such genome-wide data into meaningful biological interpretation of cancer is challenging. As much as information is provided by the data, confusion arises about which aberrations are the driver of cancer among the diverse genetic aberrations identified in cancer genome. Recent studies have found that cancer is a pathway disease. The genetic aberrations accumulated in all human cancers ultimately deregulate several biological pathways that control key cell functions. It is therefore important to look at cancer from pathway perspective rather than one gene at a time.

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BACKGROUND

Cancer is a genetic disease that involves various aberrant changes in the genome. These changes may be induced by external factors, such as radiation, chemicals, or viral infection. Other changes

may be inherited from previous generations or randomly occur in DNA replication. The genetic aberrations found in cancer exhibit high diversity: from gain or loss of entire chromosomes to a single mutation in a gene, structural changes, or epigenetic alterations. These aberrations consequently affect the activity of cancer-promoting oncogenes and tumor suppressor genes. Oncogenes are typically activated in cancer cells, promoting cell growth and evading programmed cell death, while tumor suppressors are inactivated in cancer cells, resulting in the loss of control over accurate DNA replication, normal cellular signaling, and immune protection. Through multiple processes, eventually, the normal cells are transformed into highly malignant derivatives.

RB, a tumor suppressor gene, is absent or mutated in at least one-third of all human tumors (Berman et al., 2009). Inactivation of RB happens when RB is mutated, which in turn activates the E2F proteins that control the activity of genes required for S-phase progression, rendering cells insensitive to antigrowth factors. Ras oncogene proteins are structurally altered in about 25% of human tumors due to mutations in the gene that encodes them (Tsatsanis & Spandidos, 2000), which enables RAS proteins to release proliferation signal into cells without stimulation by their normal upstream regulators (Medema & Bos, 1993). As a result, cells undergo uncontrolled self-sufficient proliferation. High proliferation and growth rates are necessary but not sufficient for the development of cancer. Tumor cell populations must expand so that the progressive errors can accumulate. Normal cells have programmed systems to correct mistakes or initialize cell death when sensing errors. Cancer cells must evade such processes for a tumor to grow. The P53 tumor suppressor protein, which can elicit apoptosis by activating proapoptotic Bax in response to DNA damage, is seen inactivated in greater than 50% of human tumors (Harris, 1996). Additionally, inappropriate activation of other oncogenes like EGFR, MYC, and PTEN is seen in many human tumors as well (Nicholson et al., 2001; Rodriguez-Pinilla et al, 2007; Freeman et al., 2003).

The observed genetic aberrations in cancer genome can either be the cause or be the consequence of cancer. Among them, few may be the drivers that trigger the transformation from normal cells to malignant cells. Identifying such drivers is critical for the diagnosis and treatment of cancer. Fortunately, a number of high-throughput technologies have been developed to screen genetic aberrations in human tumors. In particular, mutations in tumors can be detected by using SNP arrays (LaFramboise, 2009); DNA copy number of genes can be measured by CGH arrays (Vissers et al., 2005); DNA methylation can be studied by ChIP-chip experiments (Wu et al., 2006). In all these arrays, tumor genome is compared with normal or population genome. Recently, with the advances in the development of New Generation of Sequencing (NGS) technology, we expect that each of the array-based technologies will be replaced with its sequencing alternative (Korbel et al., 2007). The NGS technology can sequence the exact DNA sequences in cancer genome, so higher resolution can be achieved compared with arrays.

Regardless of the high diversity in the genetic aberrations observed in cancer, all human tumor cells share a common set of characteristics: self-sufficiency in growth signals, insensitivity to antigrowth signals, evasion of programmed cell death, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis (Hanahan & Weinberg, 2000). Each of these processes is governed by specific signaling pathways. A signaling pathway is a regulatory system that involves a cascade of biochemical reactions in response to extracellular stimulations. See Figure 1. Cell proliferation and death, alterations in metabolism, and activation of genes are cellular responses. In living cells, many genes work in concert to support cellular functions. Activation of genes in one pathway can, in turn, activate or inactivate genes in other pathways. Ultimately, an initial stimulus can lead to the activation or