Cancer epigenomics: beyond genomics
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For many years cancer research has focused on genetic defects, but during the last decade epigenetic deregulation has been increasingly recognized as a hallmark of cancer. The advent of genome-scale analysis techniques, including the recently developed next-generation sequencing, has enabled an invaluable advance in the molecular mechanisms underlying tumor initiation, progression, and expansion. In this review we describe recent advances in the field of cancer epigenomics concerning DNA methylation, histone modifications, and miRNAs. In the near future, this information will be used to generate novel biomarkers of relevance to diagnosis, prognosis, and chemotherapeutic response.

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DNA methylation and cancer

Aberrant DNA methylation was the first epigenetic mark to be associated with cancer as a consequence of the alteration it causes in normal gene regulation [5]. These alterations are of three types: hypermethylation, hypomethylation, and loss of imprinting.

DNA hypermethylation refers principally to the gain of methylation at specific sites that are unmethylated under normal conditions. This aberrant methylation occurs mainly in promoter CpG islands (CGIs). Various restrictive criteria have been reported to define a CGI, an accepted definition considers a CGI to be a DNA sequence (>200-bp window) with a GC content greater than 50% and an observed/expected CpG ratio of more than 0.6 [6,7]. This phenomenon of aberrant promoter CGI hypermethylation has been associated with the stabilization of transcriptional repression and loss of gene function, and occurs fundamentally in tumor suppressor genes [8,9]. A recent study comparing colorectal cancer tissue with its normal counterpart also suggests that the majority of DNA methylation changes involved in gene regulation are located at the nonpromoter CGI shores, defined as regions next to CGIs, up to 2 kb long, with comparatively low GC density [10]. Intriguingly, most tissue-specific DNA methylation seems to occur not at CGIs but at CGI shores [11]. These studies support the hypothesis that epigenetic alterations affecting tissue-specific differentiation, such as DNA methylation, are a crucial mechanism by which epigenetic changes cause cancer.

Tumorigenesis is a multistep process, including initiation, promotion and progression, and a multifactorial pathology characterized by the accumulation of a multitude of alterations including genetic, cytogenetic, and epigenetic changes [1]. Feinberg and Vogelstein reported the first mutation known to result in a human transforming gene: the c-Ha-ras oncogene [2]. Since then, a large number of studies have focused on identifying new nonsense, silent DNA and point mutations, deletions, translocations and insertions, and polymorphisms associated with tumor cell growth [3]. High-throughput techniques have been essential for enabling the compilation of a catalogue of rare and common genetic variants.

However, a crucial and complementary player in gene regulation — epigenetics — has come to be associated with cancer initiation and development, especially since the recent advent of whole-genome approaches, known as epigenomics. Epigenetics may be defined as the mechanisms that initiate and maintain heritable patterns of gene function and regulation in a heritable manner without affecting the sequence of the genome. These mechanisms explain how two identical genotypes can give rise to different phenotypes in response to the same environmental stimulus. There are four types of mechanistic layers in the field of epigenetics: post-translational modifications of histone proteins, DNA methylation, chromatin remodeling, and noncoding RNAs. Evidence has been accumulating for more than 20 years of the role that DNA methylation plays in oncogenesis. However, the role of the other mechanisms is an emerging area of interest that is also turning out to be related to oncogenesis. Epigenetic abnormalities in cancer comprise a multitude of aberrations occurring in almost every component of chromatin involved in packaging the human genome [4]. High-throughput techniques have become common in the study of this disease, facilitating molecular targeting for cancer therapies. This review considers the recent advances and provides an overview of epigenomics and oncogenesis.