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Review

Compendium of aberrant DNA methylation and histone modifications in cancer

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ABSTRACT

Epigenetics now refers to the study or research field related to DNA methylation and histone modifications. Historically, global DNA hypomethylation was first revealed in 1983, and, after a decade, silencing of a tumor suppressor gene by regional DNA hypermethylation was reported. After the proposal of the histone code in the 2000s, alterations of histone methylation were also identified in cancers. Now, it is established that aberrant epigenetic alterations are involved in cancer development and progression, along with mutations and chromosomal losses. Recent cancer genome analyses have revealed a large number of mutations of epigenetic modifiers, supporting their important roles in cancer pathogenesis. Taking advantage of the reversibility of epigenetic alterations, drugs targeting epigenetic regulators and readers have been developed for restoration of normal pattern of the epigenome, and some have already demonstrated clinical benefits. In addition, DNA methylation of specific marker genes can be used as a biomarker for cancer diagnosis, including risk diagnosis, detection of cancers, and pathophysiological diagnosis. In this paper, we will summarize the major concepts of cancer epigenetics, placing emphasis on history.

Contents

1. Introduction

Epigenetics referred to the study or research field for heritable modifications that regulated gene expression without changes in DNA sequences. The main mechanisms of epigenetic inheritance are recognized to be DNA methylation and histone modifications,

Abbreviations: K, lysine; ac, acetylation; me1, mono-methylation; me2, di-methylation; me3, tri-methylation; DNMT, DNA methyltransferase; FDA, U.S. Food and Drug Administration; POC, proof-of-concept.

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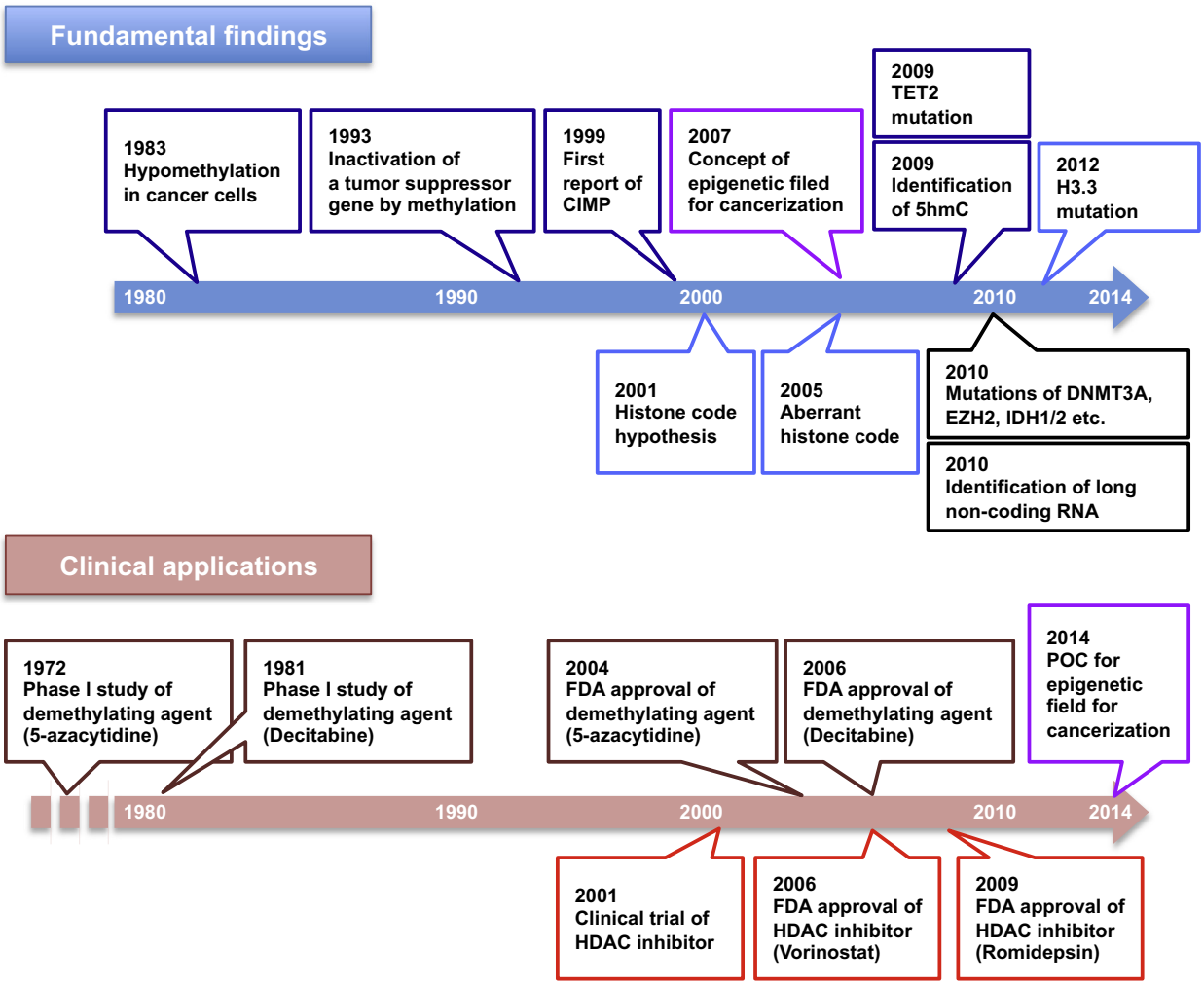

Fig. 1. History of cancer epigenetics. An overview of cancer epigenetics is shown focusing on fundamental findings and clinical applications.

and epigenetics now mainly refers to the study or research field related to DNA methylation and histone modifications. In mammals, epigenetic inheritance is important for pre-implantation development [1], fetal development [2], cell differentiation [3] and tissue differentiation [4]. It is also involved in gametogenesis and cellular reprogramming during the generation of cloned animals and iPS cells [5].

At the same time, aberrant epigenetic modifications (epigenetic alterations) are now considered to be involved in the pathogenesis of several diseases, including pediatric tumors [6]. Especially, aberrant DNA methylation is deeply involved in cancer development and progression because DNA methylation pattern is inherited with a high fidelity in somatic cells [7]. Once aberrant DNA methylation is induced, it is accurately transmitted to daughter cells after cell division. Aberrant DNA methylation is one of the major mechanisms of inactivation of tumor-suppressor genes, along with mutations and chromosomal losses [8].

Historically, the first discovery of epigenetic alterations in cancer goes back to 1983 when global DNA hypomethylation was reported [9]. After a decade, regional DNA hypermethylation was demonstrated to cause silencing of a tumor suppressor gene [10]. The CpG island methylator phenotype (CIMP) was reported first in colorectal tumors in 1999 [11], and thereafter, the presence of CIMP has become known in other types of cancers [12]. As for histone modifications, the impact of histone deacetylase (HDAC) inhibitors (HDACis) on cancer cell proliferation was known in the 1990s [13]. After the proposal of the "histone code" [14], its disturbances have been reported in various types of cancer. Most recently, cancer genome analyses revealed the presence of mutations of epigenetic regulators, including those of *TET* and *IDH* genes [15]. Epigenetic drugs, such as DNA demethylating agents and HDACis, have already become an option for cancer treatment [16].

In this review, we will summarize an overview and trends of cancer epigenetics according to its history (Fig. 1).

1.1. Global hypomethylation in cancer

Global hypomethylation in cancer denotes a decrease in overall content of 5-methylcytosine, and was revealed as the first epigenetic abnormality in cancer by Feinberg and Vogelstein in 1983 [9] (Fig. 1). They analyzed DNA methylation in cancerous and non-cancerous tissues by Southern blotting of DNA digested with methylation-sensitive restriction enzymes, and found a substantial reduction in DNA methylation in cancer tissues. Gama-Sosa and colleagues also investigated the difference in DNA methylation level between cancerous and non-cancerous tissues by a high-performance liquid chromatography, and showed a reduction of 5-methylcytosine content in cancer tissues [17]. Such hypomethylation was also found in pre-malignant adenomas [18,19].

Global hypomethylation involves repetitive sequences, which is observed not only in cancers but also in non-cancerous tissues [20], such as normal mucosae exposed to chronic inflammation