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Cancer epigenetics: Now harvesting fruit and seeding for common diseases

Epigenetics is now known to almost all researchers because it is a fundamental mechanism for life and disease. This is evidenced by the fact that as much as 0.83% of all the literature published in 2014 (from January to October) in PubMed contained the keyword of epigenetics. When publication trends are looked back on (Fig. 1), we can recognize three upsurges in epigenetics. The first was in the mid-1980s, the second in the mid-1990s, and the third in the early 2000s. The first upsurge came after the discovery of global hypomethylation in cancer, and the second came after the discovery of inactivation of tumor-suppressor genes by aberrant DNA methylation.

The third upsurge was after the proposal of the histone code [1]. This proposal not only opened up a new field of biology but also had a large impact on cancer epigenetics. Subsequently, cancer genome analyses revealed that many epigenetic regulators, such as genes involved in DNA methylation and demethylation, histone methylation and demethylation, and chromatin remodeling, are mutated in various types of cancers, as reviewed in this issue by Aumann and Abdel-Wahab [2] and in another publication [3]. Especially, mutations of the *TET* and *IDH* genes are now known to affect DNA demethylation and function as significant drivers of diverse tumor types as reviewed by Waterfall et al. [4]. The fact that epigenetic regulators are mutated in cancers and driving them vividly showed the importance of epigenetic alterations in cancers. Importantly, epigenetic alterations can also be induced by factors in our environment, especially chronic inflammation [5]. Surprisingly, epigenetic alterations only was recently shown to induce at least some pediatric tumors as reviewed by Ohnishi et al. [6].

During and after the second upsurge in publication, massive efforts have been made to identify genes with aberrant DNA methylation that have diagnostic and therapeutic values as reviewed by Hattori and Ushijima [7]. One of the early findings was identification of simultaneous methylation of multiple CpG islands, namely the CpG island methylator phenotype (CIMP). The CIMP enchanted a large number of researchers from various aspects, such as, first of all, its reality, cause, association with clinicopathological characteristics, and therapeutic value, as reviewed by Suzuki et al. [8]. Key characteristics of aberrant DNA methylation, namely its induction in specific genes and relatively high frequency in non-cancerous tissues, were also revealed while the efforts were being undertaken [9].

Owing to the fundamental discoveries and identification of diagnostic and therapeutic targets, cancer epigenetics is now bearing fruit. In diagnostics, cancer-specific DNA methylation is used for non-invasive detection of cancers, as reviewed by Toiyama et al. [10]. Epigenetic predictive and prognostic markers can be superior to clinically used ones [11,12]. Accumulation of aberrant DNA methylation can provide information that can never be obtained by other methods [12,13]. In therapeutics, DNA demethylating agents and histone deacetylase inhibitors are now clinically used, and agents for novel targets are being developed preclinically and clinically, as reviewed by Dhanak and Jackson [14]. In public health, epigenetics is applied to identify lifestyle and exposure to environmental factors, as reviewed by Barrow and Michels [15].

At the same time, cancer epigenetics has seeded concepts and tools for disease research other than cancer, such as immunological, neurological, cardiovascular, and metabolic disorders. In general, cancer research has advantages over other disease research in its excellent access to disease tissues and the clonal nature of the disease cells. Taking these advantages, cancer epigenetics strongly indicated that epigenetic alterations are also involved in other disorders. Different from somatic mutations, epigenetic alterations can be present in a large number of cells in non-cancer tissues that are polyclonal, suggesting that epigenetic alterations can change the function of an organ [9]. Also, specific genes can be affected by epigenetic alterations in multiple cells because of their target gene specificity. Further, chronic inflammation, a potent inducer of epigenetic alterations, is involved in various human disorders [16]. The trend that epigenetics is expanding to disorders other than cancer is again recognizable in the publication trends (Fig. 1).

This special issue of BBRC is devoted to serving these trends of cancer epigenetics, harvesting its fruits and seeding for other research areas. Key fundamental findings and translational research are reviewed by experts who contributed to the advancement of the field. I believe that the information is useful not only for cancer researchers but also for biologists and disease researchers from different disciplines.

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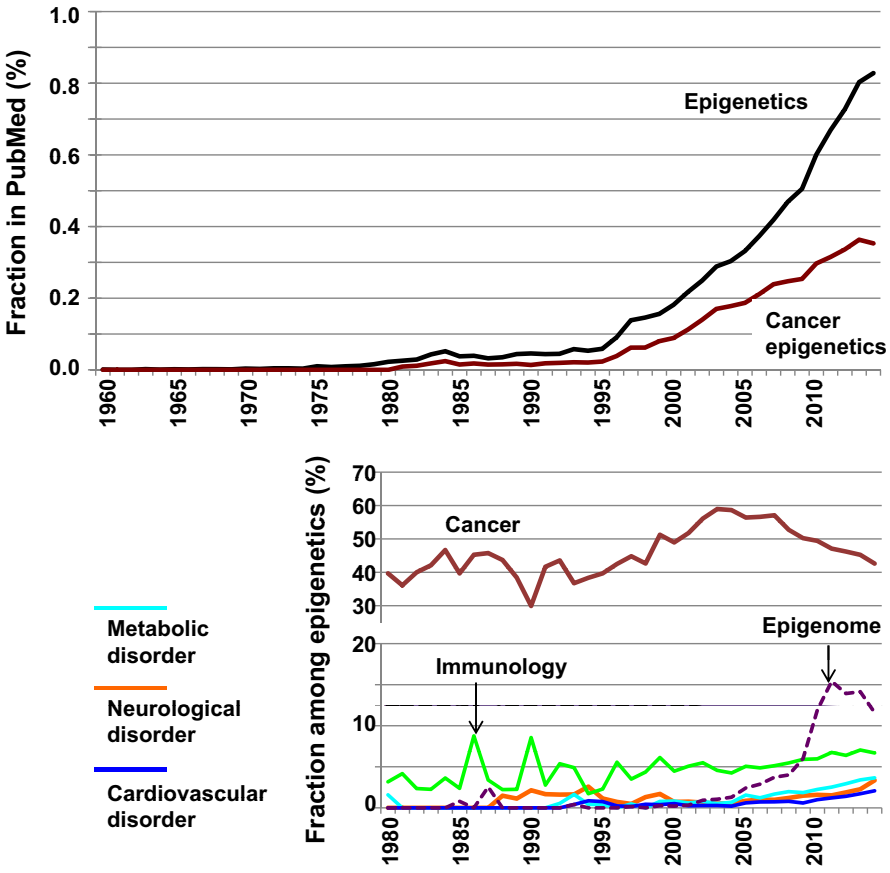

Fig. 1. Trends of publication related to epigenetics. PubMed was searched using the following terms for a specific keyword. Epigenetics, epigenetics OR epigenetic OR "DNA methylation" OR epigenome; Cancer, cancer OR neoplasm OR tumor; Epigenome, epigenomics OR epigenomic OR epigenome; Immunology, immunology OR "immunological disorder" OR "allergy"; Metabolic disorder, "metabolic disorder" OR "diabetes mellitus" OR "obesity"; Neurological disorder, neurology OR "neurological disorders" OR "Alzheimer's disease" OR "Parkinson's disease"; and Cardiovascular disorder, cardiology OR "heart failure" OR "hypertension" OR "cardiomyopathy" OR "vascular endothelial cell".

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