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Review

Importance of epigenetic changes in cancer etiology, pathogenesis, clinical profiling, and treatment: What can be learned from hematologic malignancies?

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ABSTRACT

Epigenetic alterations represent a key cancer hallmark, even in hematologic malignancies (HMs) or blood cancers, whose clinical features display a high inter-individual variability. Evidence accumulated in recent years indicates that inactivating DNA hypermethylation preferentially targets the subset of polycomb group (PcG) genes that are regulators of developmental processes. Conversely, activating DNA hypomethylation targets oncogenic signaling pathway genes, but outcomes of both events lead in the overexpression of oncogenic signaling pathways that contribute to the stem-like state of cancer cells. On the basis of recent evidence from population-based, clinical and experimental studies, we hypothesize that factors associated with risk for developing a HM, such as metabolic syndrome and chronic inflammation, trigger epigenetic mechanisms to increase the transcriptional expression of oncogenes and activate oncogenic signaling pathways. Among others, signaling pathways associated with such risk factors include pro-inflammatory nuclear factor κB (NF-κB), and mitogenic, growth, and survival Janus kinase (JAK) intracellular non-receptor tyrosine kinase-triggered pathways, which include signaling pathways such as transducer and activator of transcription (STAT), Ras GTPases/mitogen-activated protein kinases (MAPKs)/extracellular signal-related kinases (ERKs), phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR), and β-catenin pathways. Recent findings on epigenetic mechanisms at work in HMs and their importance in the etiology and pathogenesis of these diseases are herein summarized and discussed. Furthermore, the role of epigenetic processes in the determination of biological identity, the consequences for interindividual variability in disease clinical profile, and the potential of epigenetic drugs in HMs are also considered.

Contents

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1. Introduction

During an individual lifetime, epigenetic regulators integrate external factors, such as toxics, diet [1] or drugs [2,3], and internal factors present in the cellular microenvironment like cytokines [4] or growth factors [5], for gene expression regulation. These regulators selectively switch on or off specific part of the genome thus determining basic cell functions, including cell fate, by controlling the specific genes to be selectively expressed or suppressed in the presence of determined signaling molecules through heritable changes in gene expression occurring without DNA sequence modification. Considering such role, it can be anticipated that epigenetic regulators are major players in the biological processes resulting in the establishment of personal molecular identity. Not surprisingly, in hematologic malignancies (HMs), whose clinical features display a high inter-individual variability even in diseases originating from the same cell types [6,7], a large body of recent data suggests a pivotal pathogenic role for disease-associated epigenetic changes. HMs or blood cancers include cancers originating from adult primary hematopoietic organs (e.g. bone marrow, blood) such as myelomas and leukemias, and those originating from secondary lymphoid organs (e.g. lymph nodes) such as lymphomas. Unfortunately, these diseases are often chronic, require repeated treatment cycles, and are associated with poor prognosis and post-treatment morbidity in many cases [8–11]. The occurrence of chemoresistance to classical anticancer drugs has raised the need for new therapeutic approaches [12,13]. Furthermore, the incidence of HMs has been increasing [6,14], at least in part due to the growing incidence of chronic diseases and conditions associated with major risk factors like metabolic syndrome and chronic inflammation [15–17]. Epigenetic changes are reversible [5,18], thus, constitute a group of potential pharmacological targets for HMs.

The present review critically summarizes recent evidence on changes affecting the epigenetic regulation in HMs. Emerging data strongly indicating that epigenetic changes bridge the gap between risk factors, such as metabolic syndrome or chronic inflammation, and HMs will also be discussed. The role of epigenetic processes in personal molecular identity determination, the consequences for inter-individual variability in disease clinical profile, and the potential of epigenetic drugs in HMs will also be considered.

2. Normal epigenetic regulation and cancer epigenome

2.1. DNA methylation: transcriptional control of gene expression

DNA is packaged and structured into nucleosomes, the basic units of the chromatin, by highly alkaline proteins named histones. Packaged genes are in nucleosomes in a transcriptionally repressed configuration, and are maintained inactive by DNA methylation [19,20]. Epigenetic changes affecting genes mainly include DNA methylation and factors controlling it, such as histone modifications and non-coding RNA expression.

DNA methylation is essential for normal development, where it is associated with other pivotal epigenetic processes such as X-chromosome inactivation, genomic imprinting, and suppression of repetitive elements; in mammalian cells, DNA unmethylation results in a rapid inactivation of genes [21]. DNA methylation mainly includes de novo methylation that sets up DNA methylation patterns in early development (mediated by DNA methyltransferase (DNMT) 3A/B), and maintenance methylation that copies methylation patterns to the daughter strands during DNA replication (mediated by DNMT1) [21]. DNA methylation occurring at gene promoter, i.e. at the nucleotide 5-methylcytosine of promoter region, has been thoroughly investigated, and thus, is understood better than methylation occurring in gene bodies and intergenic regions. DNA methylation occurring at gene promoter alters the ability of a gene to interact with transcription factors through DNA conformational changes. Normal inactive genes are silenced by this mechanism (Fig. 1A). Instead, gene suppression occurs through DNA hypermethylation (Fig. 1B), which can be induced or reinforced by histone methylation, histone deacetylation, and histone dephosphorylation mediated, respectively, by histone lysine methyltransferases (KTMs), histone deacetylases (HDACs), and histone serine/threonine/tyrosine phosphatases [19,22]. Conversely, transcriptionally active genes are demethylated (Fig. 1C). DNA demethylation can be mediated by DNA demethylases [23] and DNA glycosylases [24], or induced by histone demethylation, histone acetylation, and phosphorylation mediated respectively, by histone lysine demethylases (KDMs) histone acetyltransferases (HATs), and histone serine/threonine/tyrosine kinases [22,25,26]. Upregulation or downregulation of small non-coding RNA molecules like microRNAs (miRNAs) can modify gene response to DNA methylation, post-transcriptionally; miRNAs modulate gene expression by targeting protein-coding RNAs [27,28].

Cell type-specific DNA methylation is present in a small percentage of promoter regions, in mammals, with a far greater proportion occurring across gene bodies with highly conserved sequences. Although not well understood, experimental evidence indicates that intragenic methylation might reduce or enhance transcription elongation efficiency in a tissue-specific basis [29–31]. A recently suggested model stipulates that “the repression of intragenic transcription by gene-body methylation is largely epiphenomenal”, implying that gene-body methylation levels would be predominantly shaped by the accessibility of the DNA to methylating enzyme complexes [32]. However, further studies are needed to validate such hypothesis, particularly considering previously reported data suggesting that DNA methylation downstream of the transcription start site (mainly