Short Review

Patho-Epigenetics

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Key Words

Patho-epigenetics · Epigenetic regulation · DNA methylation · Polycomb and Trithorax complexes · Histone modification · Tumorigenesis

Abstract

Patho-epigenetics is a new discipline dealing with the description of pathologic changes elicited by epigenetic dysregulation. Patho-epigenetic processes contribute to the development of both rare syndromes and diseases of high prevalence in human populations. In this short review, we summarize the basic epigenetic regulatory mechanisms in a nutshell and briefly outline how epigenetic reprogramming contributes to all forms of tumorigenesis and plays a role both in the initiation and progression of neoplasms.

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Epigenetic Regulatory Mechanisms

Epigenetic mechanisms maintain the coregulation and cell type-specific usage of promoters from cell generation to cell generation. Both DNA and certain histone molecules, the principal components of chromatin, may carry 'epigenetic marks' deposited by 'writer' molecules such as DNA methyltransferases methylating the C-5 position of cytosines within CpG dinucleotides, histone acetylases, histone methyltransferases, or Polycomb and Trithorax group protein complexes (reviewed by Jin et al. [1]). It is important to note that certain Polycomb and Trithorax proteins not only covalently modify histones but also remain associated with mitotic chromatin, contributing thereby to the inheritance of cell type-specific transcription patterns [2, 3]. The deposited marks determine the chromatin structure: an open chromatin or euchromatin structure is usually associated with active promoters

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whereas a closed, more condensed chromatin structure (heterochromatin) silences nearby promoters. Various epigenetic marks such as 5-methylcytosine or modified histone tails are bound and interpreted by ‘reader’ factors including 5-methylcytosine-binding proteins, transcription factors, and chromatin-remodeling complexes that affect and regulate transcription.

Epigenetic changes are reversible, so epigenetic marks can be removed by ‘eraser’ mechanisms. The Tet (ten-eleven translocation) family of dioxygenases converts 5-methylcytosine to 5-hydroxymethylcytosine, 5-formylcytosine and 5-carboxylcytosine followed by base excision repair (active demethylation; reviewed by Wu and Zhang [4]). Alternatively, the DNA methylation signal can also be depleted passively, provided that the recruitment of maintenance DNA methyltransferase DNMT1 is inefficient during DNA replication (reviewed by Smith and Meissner [5]). Histone modifications are removed by histone deacetylases and histone lysine demethylases [6, 7].

In addition to the epigenetic marks generated by enzymes that modify DNA or histones, direct binding of distinct nonhistone proteins to regulatory regions of the genome may also constitute epigenetic marks that can be inherited to daughter cells. So called ‘pioneer’ transcription factors or ‘bookmarking’ proteins remain bound to chromatin even in mitotic chromosomes, and accelerate transcriptional reactivation following mitosis. They are capable of binding to highly methylated DNA sequences, opening up chromatin through the replacement of linker histone H1, and inducing cytosine demethylation. Pioneer transcription factor binding to tissue-specific enhancers precedes the transcriptional activation of genes associated by such premarked enhancers [8].

It was observed that the transcriptional start sites of active genes were marked by H2A.Z, a histone variant bound to mitotic chromosomes. H2A.Z may alter nucleosome occupancy and permit promoter activation after chromosome decondensation. Kelly et al. [9] and Kelly and Jones [10] speculated that altered nucleosome occupancy may form a novel epigenetic mechanism.

Epigenetic marks may spread from a site of initiation to neighboring chromatin areas and may result in the establishment of extended heterochromatic or euchromatic regions, i.e. nuclear subcompartments repressing or facilitating transcription, respectively (reviewed by Doerfler [11] and Gyory and Minarovits [12]). Long-distance chromatin interactions may insulate chromatin domains and allow coregulation of promoters within loops by preventing the spread of chromatin modifications from adjacent areas. Certain chromatin loops may be preserved in mitotic chromosomes and could possibly contribute to epigenetic memory [13].

Patho-Epigenetics

Disturbances in the epigenetic regulation may play an important role in tumorigenesis and contribute to the development of a variety of diseases. A couple of years ago, we attested the birth of a new discipline, ‘Patho-Epigenetics’, dealing with the description of pathologic changes elicited by epigenetic dysregulation [14]. The application of epigenetic concepts to the understanding and treatment of human diseases was summarized last year in two books [15, 16]. The chapters in these books clearly demonstrate that disturbances in various epigenetic processes may alter the epigenotype of cells, and such an ‘epigenetic reprogramming’ may manifest in pathological changes, disease initiation and progression. As a matter of fact, the pathogenetic importance of epigenetic dysregulation – first revealed by cancer researchers [17] – has been realized by now in all major domains of medicine. Epigenetic research significantly contributed not only to the understanding of key pathogenic events occurring in rare diseases like ICF syndrome (immunodeficiency, centromere instability, facial abnormalities; a chromatin disorder of gene silencing), Rett syndrome

(associated with the dysfunction of a methyl-CpG-binding protein), and imprinting disorders, but also facilitated the molecular characterization of high-prevalence diseases such as autoimmune syndromes, major psychiatric syndromes, atherosclerosis and malignant tumors including glioblastoma multiforme, lung carcinoma, breast cancer, and prostate cancer [18–28].

Recently, it has been recognized that microbial pathogens could also dysregulate epigenetic mechanisms in their host cells (reviewed in Minarovits [14] and Niller et al. [29, 30]). The first human pathogen associated with the induction of patho-epigenetic alterations in host cells was, as far as we know, the human immunodeficiency virus (HIV), the causative agent of AIDS [31].

In the next part of the review, we briefly summarize the role of epigenetic pathways in various tumorigenic processes including bacterial infection-associated, chemical, hormone-induced, metal and radiation-induced carcinogenesis and describe how epigenetic ideas changed the basic concepts in the field of virus-induced neoplasms.

The Importance of Epigenetic Dysregulation in Carcinogenesis

In addition to genetic changes including mutations, deletions, gene amplifications and chromosomal alterations, epigenetic reprogramming also plays an important role in tumorigenic processes [32]. All major classes of cancer-causing agents including bacteria, chemical carcinogens, hormones, metals, radiation and viruses elicit epigenetic alterations, and epigenetic changes occur in all stages of tumorigenesis. Here we wish to give an overview of recent data associated mainly with the early stages of tumorigenesis.

Tumorigenesis Triggered by Bacterial Infection

Epigenetic alterations, the so-called epigenetic field of cancerization, could be detected at the earliest stages of tumorigenesis in apparently healthy tissues of individuals who were at increased risk of *Helicobacter pylori*-associated gastric carcinoma, and similar observations were made as to esophageal, lung, breast or renal cancer (reviewed by Ushijima [33]). In case of gastric mucosa, *H. pylori*-triggered inflammation was implicated in the establishment of the epigenetic field defect, manifesting as aberrant DNA methylation [34]. Because epigenetic alterations are reversible, Ushijima and Hattori [34] argued that epigenetic drugs and anti-inflammatory drugs may be useful for the epigenetic prevention of gastric cancer.

In a *Citrobacter rodentium*-induced transmissible murine colonic hyperplasia and carcinogenesis model, epigenetic modulation of certain signaling pathways preceded epithelial mesenchymal transition, an important event in tumorigenesis [35].

Chemical Carcinogenesis

Research in chemical carcinogenesis focused traditionally on genotoxic carcinogens and their mutagenic effects. There are, however, nongenotoxic carcinogens as well, e.g. phenobarbital, that do not damage DNA. Both classes of chemical carcinogens may cause epigenetic dysregulation (reviewed by Pogribny and Beland [36]). In fact, the alteration of the epigenome in chemical carcinogen-induced neoplasms was similar to the patterns observed in tumors of ‘spontaneous’ origin, or in leukemias, carcinomas and sarcomas elicited by tumor viruses: genome-wide hypomethylation accompanied by regional hypermethylation.

Hormone-Induced Tumors

Estrogens have been associated with the development of breast and uterine neoplasms in humans, and they are capable of inducing tumors in rodents. Although tumor induction by

estradiol and diethylstilbestrol was attributed to their genotoxic effects [37, 38], recent data suggest that they may cause epigenetic dysregulation as well. Prolonged exposure to elevated levels of estrogen resulted in the expansion of precancerous cells of the mammary gland in a rat model of breast carcinogenesis [39]. At week 12 of continuous 17 β -estradiol exposure, the global DNA methylation level decreased in the hyperplastic lesions. In parallel, the upregulation of DNA methyltransferases and hyperacetylation of histones was also observed [39]. In human mammary epithelial cells from healthy, disease-free women, the hypermethylation of the p16 (INK4a) promoter apparently preceded the clonal outgrowth of premalignant lesions. The inactivation of the p16 tumor suppressor gene may represent an early epigenetic change associated with increased breast cancer risk [40]. Estrogen may also suppress transcription by establishing repressive histone modifications and the induction of an antisense transcript at an imprinted gene [41]. The environmental xenoestrogen genistein, a soy phytoestrogen, also affects epigenetic regulation. Genistein induced phosphorylation and repression of the histone methyltransferase EZH2, a Polycomb protein, and reduced the level of a repressive histone mark in neonatal rat uterus [42]. One may speculate that such a xenoestrogen-elicited epigenetic change may facilitate the development of uterine leiomyoma in humans.

Metal Carcinogenesis

The pathogenetic events associated with metal carcinogenesis due to chronic exposure to nickel, chromium and inorganic arsenic compounds have remained poorly understood for a long time. Recent data support the idea that epigenetic mechanisms play an important role in their oncogenic potential [43–45].

In peripheral blood mononuclear cells of subjects with high occupational exposure to nickel, there was a change in the gene expression profile and an increase in the overall level of H3K4me3 (histone H3 trimethylated at lysine 4), a histone modification associated with open chromatin. In parallel, there was a decrease in H3K9me2 (histone H3 dimethylated at lysine 9), a repressive chromatin mark [43]. In contrast, in peripheral blood mononuclear cells of subjects exposed to arsenic in their drinking water, the global level of H3K9me2 increased and that of acetylated histone H3 (H3K9ac) decreased [43]. In cell culture and in vivo transgenic experiments, nickel also caused a loss in histone acetylation that worked together with nickel-induced DNA methylation in gene silencing (reviewed by Salnikow and Zhitkovitch [44]).

Arsenic, a carcinogenic metal of low mutagenic but high transforming activity, alters DNA methylation in its target cells: both global DNA hypomethylation and local hypermethylation of key tumor suppressor genes could be observed (reviewed by Salnikow and Zhitkovitch [44]). Arsenic may act as a cocarcinogen in estrogen-induced prostate carcinogenesis, and the coadministration of 17 β -estradiol with arsenic significantly altered the expression of epigenetic regulatory genes in human prostate epithelial cells cultivated in vitro [45]. A decreased expression of mRNAs coding for DNMT1 and MBD4, a methyl-CpG-binding protein, was especially noteworthy. In addition, the expression of certain genes coding for proteins involved in histone acetylation and methylation was also downregulated: the levels of mRNAs for HDAC3, a histone deacetylase, and HMT1, a histone methyltransferase, exhibited the most significant decrease [45]. It is interesting to note that in spite of DNMT1 downregulation, a DNA fingerprinting method detected de novo hypermethylation in certain genomic regions in cells treated with 17 β -estradiol and arsenic.

Chromium exists in several valence states and Cr(VI) exposure is associated with the development of lung cancer and nasal cancer (reviewed by Salnikow and Zhitkovitch [44]). The generation of Cr-DNA adducts, DNA protein and DNA interstrand cross-links as well as DNA breaks and oxidative base damage may contribute to Cr(VI) carcinogenesis. However,

epigenetic effects, including chromium-induced local DNA hypermethylation and inhibiting the generation of activating histone marks by chromium-induced cross-linking of HDAC1-DNMT1 complexes to chromatin, may also play a role in chromium-induced tumorigenesis (reviewed by Baccarelli and Bollati [46], Kondo et al. [47] and Schneckeburger et al. [48]).

Radiation-Induced Neoplasms

It is well documented that radiation may cause DNA double-strand breaks, and radiation-induced neoplasms frequently carry chromosomal aberrations and mutations [49]. However, in addition to genetic lesions, epigenetic mechanisms may also respond to radiation: histone modifications play a crucial role in DNA repair processes (reviewed by Hassa and Hottiger [50]). In addition, in a murine model, fractionated low-dose radiation exposure caused a significant decrease in global DNA methylation and a reduced expression of DNMT1 and methyl-binding proteins MeCP2 and MBD2 in the thymus [51]. The level of a modified histone, H4K20me3, decreased as well. One may speculate that such epigenetic changes may destabilize the genome and reprogram the epigenome of thymic lymphocytes resulting in lymphoma development.

Viral Carcinogenesis

It is well documented that oncoproteins and nontranslated RNA molecules of human tumor viruses interact with cellular signaling pathways resulting in an altered regulation of cell proliferation, phenotype and behavior. Using strict criteria for a causal relation, Pagano et al. [52] argued that human papillomavirus, Epstein-Barr virus, Kaposi's sarcoma-associated herpesvirus (KSHV), human T-lymphotropic virus type I, hepatitis C virus, and hepatitis B virus can be considered as causative agents of distinct neoplasms in humans. Early studies focused mainly on the interactions of the viral oncoproteins with cellular regulatory proteins controlling cell proliferation and apoptosis and demonstrated the ability of key viral oncogenes to cause 'malignant transformation' of cells either alone, or in combination with other oncogenes using in vitro and in vivo models [53]. Other efforts mapped the groups of cellular genes switched on or off by viral oncoproteins and studied the cell type-dependent expression of viral oncogenes in tumor biopsies, tumor-derived cell lines and transfected cells. It became obvious that cell type-specific epigenetic modifications of the viral genome (viral epigenotypes) affect the activity of viral promoters controlling the transcription of viral oncogenes [54]. It also became clear that viral oncoproteins, in addition to their interaction with various cellular signaling pathways, regularly interact with the cellular epigenetic machinery as well (epigenetic reprogramming). This topic has recently been reviewed [29, 55], and here we only wish to highlight some special aspects of oncoprotein-induced epigenetic dysregulation. It seems that most key human oncoproteins, including human papillomavirus E7, Epstein-Barr virus LMP1, KSHV LANA, hepatitis C virus core protein, and hepatitis B virus HBx, can upregulate or stimulate the activity of at least one DNA methyltransferase enzyme, resulting in hypermethylation and silencing of certain cellular promoters (table 1). It is a unique feature of hepatitis B virus HBx that it is capable of upregulating DNMT1, DNMT3A1 and DNMT3A2 resulting in hypermethylation of a set of target genes, and in parallel downregulating DNMT3B, preventing thereby methylation of certain repeated DNA sequences (tables 1, 2; reviewed by Niller et al. [29]). This yields the typical methylation pattern frequently observed in neoplasms of nonviral etiology: overall hypomethylation and focal hypermethylation of the tumor cell genome, compared to its normal counterpart. Human papillomavirus E7 is also unique, in a way, because in addition to stimulating the activity of DNMT1, a mediator of gene silencing, it also increases histone acetylation, a mechanism to switch on target promoters (reviewed by Niller et al. [29]). How gene-silencing and -activating mechanisms are targeted in virus-transformed cells remains to be established. It is

Table 1. Modulation of the host cell epigenotype by oncoproteins of human tumor viruses stimulating the activity, upregulating, or altering the location of cellular epigenetic regulators

Epigenetic regulator	Viral oncoprotein	Effect
DNMT1	EBV LMP1, EBV LMP2A, KSHV LANA, HBV HBx, HCV core protein, HPV E7	Promoter silencing
DNMT3A	EBV LMP1, EBV LMP2A, KSHV LANA, HBV HBx	Promoter silencing
DNMT3B	EBV LMP1, EBV LMP2A, KSHV LANA, HCV core protein	Promoter silencing
MeCP2	KSHV LANA	Promoter silencing Promoter activation
PRC1	EBV LMP1	Promoter silencing Promoter activation
PRC2	EBV EBNA3A (EBNA3), EBV EBNA3C (EBNA6)	Promoter silencing
Histone acetyltransferases	EBV EBNA2, HPV E7	Promoter activation
Histone deacetylases	KSHV LANA	Promoter silencing
Histone demethylase, KDM6B (targeting H3K27me3)	EBV LMP1, HPV E7	Promoter activation
Histone demethylase, KDM6A (targeting H3K27me3)	HPV E6 and/or E7	Promoter activation

Table 2. Modulation of the host cell epigenotype by oncoproteins of human tumor viruses inhibiting or downregulating cellular epigenetic regulators

Epigenetic regulator	Viral oncoprotein	Effect
DNMT3B	HBV HBx	Hypomethylation of repetitive sequences
Histone deacetylases	EBV LP (EBNA5)	Coactivation
Histone demethylases, KDM3A (targeting H3K9me2)	EBV LMP1, EBV LMP2A	Promoter silencing

interesting to note, however, that KSHV LANA is capable of recruiting a de novo DNA methyltransferase to cellular promoters [56]. In addition, KSHV LANA, by its interaction with MeCP2, may repress or activate genes in a context-dependent manner (reviewed by Niller et al. [29]). Epstein-Barr virus LMP1 (latent membrane protein 1) upregulates the Polycomb-repressive complex 1 protein Bmi-1 that silences certain cellular promoters but activates other target genes implicated in leukemogenesis [57]. The nuclear proteins EBNA3A and EBNA3C recruit Polycomb-repressive complex 2 that inactivates a target promoter by increased histone H3 lysine 27 trimethylation [58]. Thus, oncoviruses may elicit complex epigenetic changes and the same oncoprotein may affect more than one epigenetic regulatory mechanism in virus-infected cells.

The Role of Epigenetic Changes in Tumor Progression

In addition to tumor initiation, epigenetic events contribute to tumor progression as well (reviewed by Jones and Baylin [17] and Munoz et al. [32]). In case of colorectal cancer, the combination of sequential genetic and epigenetic changes yields 3 different pathways of progression [59]. Epithelial-mesenchymal transition, an event regulated by epigenetic mechanisms, is a key step in the formation of metastases. Invasion and metastasis formation by hepatocellular carcinoma depends on the inactivation of the *E-cadherin* gene. In the absence of E-cadherin protein, cell-to-cell adhesion is lost. It was found that C-terminal-binding protein 1 – a corepressor associated with histone deacetylation events [60] – suppressed E-cadherin expression [61]. Epithelial-mesenchymal transition can be induced by TGF- β in normal and cancerous breast epithelial cells. The master regulator Sox4 apparently controls the transition by regulating the Polycomb histone methyltransferase EZH2 [62]. EZH2, by trimethylating histone H3 lysine 27, marks key genes involved in the epithelial-mesenchymal transition. Epigenetic changes may promote the progression of endometrial, hepatocellular and lung carcinomas, regulate the expression of metastasis suppressor genes and certain metastasis-promoting microRNAs characteristic for pancreatic cancer, and may serve as prognostic biomarkers as well [63–68].

We concluded that epigenetic dysregulation is involved in the pathogenesis of a wide spectrum of diseases. Regarding neoplastic development, epigenetic reprogramming contributes to all forms of tumorigenesis and plays a role both in the initiation and progression of neoplasms.

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