Role of Epigenetic Factors in Cancer Formation: A Review

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***Abstract*— *Epigeneticsrefers to the mechanisms that alter gene expression without altering the primary DNA sequence. Epigenetic modifications are commonly described as important players in cancer progression. They comprise DNA methylation, histone modifications, nucleosome positioning, and small, noncoding microRNAs. The information carried by epigenetic modifications plays a critical part in the regulation of all DNA-based events, such as transcription, DNA repair, and replication.* Ab*normal expression patterns or genomic modifications in chromatin regulators can have intense results and can lead to the induction and maintenance of various cancers. Epigenetics also represents an attractive opportunity of reverting cancer-specific alterations, which may leadto a possibility of stopping this disease. Epigenetic changes have been identified as putative cancer biomarkers for early detection, disease monitoring, prognosis, and risk assessment. Emerging findings in this area are contributing to cancer management and monitoring, and* further *progress* is *expected.*

Keywords*— *Cancer; epigenetics; DNA methylation; histones modifications; microRNA; epigenetic therapy.

I. INTRODUCTION

The term ‘‘epigenetics’’ was initially coined by Conrad Waddington to define heritable variations in a cellular phenotype that were independent of alterations in the DNA sequence. When Conrad Waddington coined the word ‘epigenetics’ in the early 1940s, the term was used to explain why genetic variations sometimes did not lead to phenotypic variations and how genes might interact with their environment to yield a phenotype (Waddington, 2012).But the word currently refers specifically to the study of mitotically and/or meiotically heritable changes in gene expression that occur without changes in the DNA sequence (Berger, Kouzarides, Shiekhattar, &Shilatifard, 2009).The disruption of such changes underlies a wide variety of pathologies, including cancer(Esteller, 2008).Cancer is a stepwise process where cellsexperience metabolic and behavioural changes, leading them to proliferate in an excessive and untimely way. Variations arise through alterations in mechanisms that control cell proliferation and lifespan, relationships with neighbouring cells, and capacity to escape the immune system. Epigenetic alterations are common in cancer and probably cooperate with genetic alterations to drive cancer development ,therefore Much of the focus of disease-related research has been on cancer (Conerly& Grady, 2010).

The epigenetic regulation of DNA-templatedprocedures has been deeply studied over the last 15 years. DNA methylation, histone modification, nucleosome remodeling, and RNA-mediated targeting control many biological progressions that are central to the beginning of cancer. Most of these heritable changes are established during differentiation and are stably maintained through multiple cycles of cell division, enabling cells to have distinct identities while comprising the identical genetic information. Here, we present the basic principles behind these epigenetic pathways and highlight the evidence suggesting that their misregulation can culminate in cancer (Dawson &Kouzarides, 2012). We also discuss the prospect of epigenetic therapy in designing efficient strategies for cancer treatment.

II. MATERIALS AND METHODS

This review involved assessing the Role of Epigenetic Factors in Cancer Formation. We reviewed the literature published from2008 to 2016 searching for the relevant publications through multiple databases. These were PubMed, EMBASE, and MEDLINE. We used key phrases: Cancer; epigenetics; DNA methylation; histones modifications; microRNA. These databases were accessed through Hinari and Open Athens.

III. DISCUSSION

The findings in terms of DNA methylation, Histone modification, Chromatin remodeling, and microRNAs have been discussed separately as epigenetic factors in cancer formation.

3.1 DNA methylation in cancer

In terms of DNA methylation, cancer cells show genome-wide hypomethylation and site-specific CpG island

promoter hypermethylation (Esteller, 2008).DNA methylations in normal tissues arepartly dependent on therelative levels and activities of DNA methylation-related enzymes such as DNAmethyltransferases (DNMT) and DNA demethylases. DNA methylation is primarily notedwithin centromeres, telomeres, inactive X-chromosomes, and repeat sequences.CpG island methylation is associated with the suppression of gene expression. Three variants of DNA methylation, that is, hypomethylation, loss of imprinting (LOI), and hypermethylation, have been evidently linked to cancer (Feinberg &Tycko, 2004).

3.1.1 DNA hypomethylation

DNA hypomethylation refers to the loss of DNA methylation in a region where it usuallyoccurs and it is generally assumed to be a genome-wide phenomenon; thus it is globallyassessed. DNA hypomethylation has been described in several tumor types(Wolff et al., 2010). DNA hypomethylation occurs at many genomic sequences, such as repetitive elements, retrotransposons, introns and the like, resulting in genomic instability(Esteller, 2008).This mechanism described as by which genes that show oncogenic properties, such as CancerTestis Antigens, that exhibit a methylated promoter region in normal cells, can becomereactivated in cancer cells by the loss of this methylation, resulting in hypomethylation(Straussman et al., 2009).

3.1.2 LOI (Loss of Imprinting)

Imprintingrefers to parental allele-specific expression of genes and LOI is the loss of parental allele-specific monoallelic expression of genes. Hypermethylation, one of the two parental alleles frontrunners to monoallelic expression of the gene.LOI accounts for the loss of this differential expression of parental alleles, and hasbeen often observed in tumors with embryonic origin(Kacem&Feil, 2009).

3.1.3 DNA hypermethylation

DNA hypermethylationdenotes the addition of methylation in a locus originally unmethylated. It tends to occur at specific regulatory sites in the promoter region and may show a tumor-specific pattern.The most recognized epigenetic disruption in human tumors is the CpG island promoter hypermethylation–associated silencing of tumor suppressor genes such as CDKN2A (cyclin-dependent kinase inhibitor 2A), MLH1 (mutL homolog-1), BRCA1 (breast cancer associated-1) and VHL (von Hippel-Lindau tumor suppressor)(Jones &Baylin, 2007).Promoter methylation of tumor suppressor genes is recognized as a strong and important method of the inactivation of tumor suppressor genes (Sharma, Kelly, & Jones, 2010).There are a number of proposed mechanisms by which methylation can inhibit gene expression, such asdirect blockage of transcription factors, by evading them from binding to their target sites, and by recruitment of methyl-binding domain (MBDs) proteins (Hoque et al., 2008).

3.2 Histone modification in cancer

Histones are regulators of chromatin dynamics either by changing chromatic structure by altering electrostatic charge or providing protein recognition sites by specific modifications(Mills, 2010). Histones can go through multiple post-translational modifications which may consist of acetylation, methylation, phosphorylation, ubiquitination, sumoylation, and ADP ribosylation. These happen in a very targeted and amino acid-specific mode, the most studied of which are acetylation and methylation of specific lysine residues on histones H3 and H4. These histone modification arrangements are controlled by enzymes including histone acetyltransferases (HATs) and deacetylases (HDACs). Histone methyltransferases (HMTs) and demethylases (HDMs) introduce and remove methyl groups(Strahl&Alis, 2000).

3.2.1 Histone acetylation

The acetylation of lysine residues on histones is usuallylinked with active gene transcription.Histone acetyltransferases (HATs) can be grouped into three categories based on their sequence similarities: Gcn5/ PCAF, p300/CBP, and the MYST families(Yang, 2004).Mutations or translocations of these genes are observed in colon, uterine, and lung tumors and in leukemia's(Esteller, 2007).Histone deacetylases (HDACs) remove acetyl groups from histone tails, and at least 18 HDAC genes have been identified in the human genome. HDACs have been implicated in cancer due to their aberrant binding and consequent silencing of tumor suppressor genes(Marks et al., 2001).Germ line mutations of HDACs increase the risk of breast and lung cancers, and abnormal HDAC overexpression has also been observed in various cancers(Miremadi, Oestergaard, Pharoah, & Caldas, 2007).

3.2.2 Histone methylation

Methylation of arginine and lysine residues on histones or nonhistone proteins such as TFs regulate chromatin structure and therefore gene expression(Greer & Shi, 2012). Two groups of proteins those areconnected with either transcriptional maintenance or repression that are termed Trithorax or Polycomb group proteins, respectively. Modifications in HMTs in the course oftumorigenesis may be in the mixed lineage leukemia (MLL) protein, which are frequently connected with tumorigenesis and poor prognosis by generating abnormal patterns of H3K4me3(Balgobind, Zwaan, Pieters, & Van den Heuvel-Eibrink, 2011). In addition, alternative splicing and mutations in MLL1, MLL2, and MLL3 genes have been recognized in bladder, breast, and pancreatic cancers and in glioblastoma(Gui et al., 2011).

Polycomb group proteins such as EZH2 have histone H3 lysine 27 methyltransferaseaction. Overexpression of EZH2 has been stated in some cancers such as prostate, breast, lung, and bladder and appears to result in an increase in H3K27me3(Chase & Cross, 2011).Lysine-specific histone demethylase 1 (LSD1), lysine-specific demethylase 6A (KDM6A/UTX), and jumonji C-domain containing proteins (JARID1A-D) have all been associated in tumorigensis including bladder, breast, kidney, and colon cancer(Rotili& Mai, 2011).

3.3 Chromatin remodeling in cancer

Chromatin Remodeling Complexes Nucleosome occupancy is a key mechanism for gene expression, and it has been known for some time that chromatin remodelers are responsible for regulating this process(Sadeh& Allis, 2011).ATP dependent chromatin remodelers are generally divided into four main families: the switching defective/sucrose non-fermenting (SWI/ SNF) family, imitation SWI (ISWI) family, inositol requiring 80 (INO80) family, and nucleosome remodeling and deacetylation chromatin helicase DNA binding (NuRD/Mi2/CHD) family(Ho & Crabtree, 2010).These ATPase dependent remodelers act in the context of multi subunit complexes and have dual roles as activators and repressors of gene expression. The importance of chromatin remodeling machines is becoming apparent with the realization that many of them are mutated in several types of cancer(Hargreaves & Crabtree, 2011). SNF5 of the SWI/SNF core subunit is at the nexus of the link between chromatin remodeling and tumorigenesis including renal carcinomas and melanomas (Lin, Wong, Martinka, & Li, 2009).

3.4 microRNAs in Cancer

microRNAs can play important roles in carcinogenesis by a plethora of mechanisms, such as by modulating angiogenesis, apoptosis, as well as the expression of genes involved in cell migration/invasion, and so on. For example, miR-221 and miR-222 are highly expressed in various cancerous conditions, such as human thyroid papillary carcinomas, glioblastoma and they target and down-regulate the p27 (Kip1)(Visone et al., 2007; le Sage et al., 2007).The miR-17–92 cluster was the first oncogenic miRNAs (oncomirs) identified in human and it contains a number of oncogenic miRNAs, such as miR-17, miR-18, miR-19a, miR-19b-1, miR-20a, and miR-92-1. The major known function of the miR-17–92 cluster is related to transcriptional factors c-Myc(Hayashita et al., 2005). The let-7 family of miRNAs has also been well-studied. Modifications in its members have been interrelated to several types of cancer. For example, the let-7 family of miRNAs is aberrantly down-regulated in breast and lung tumors, leading to RAS pathway oncogenic activation(Peter, 2009).

IV. EPIGENETIC THERAPY

The reversible nature of the profound epigenetic changes that occur incancer has led to the possibility of ‘epigenetic therapy’ as a treatment option. This is why so much attention has been focused in recent years on the quest for epigenetic drugs, which could reverse the causal epigenetic aberrations that occur in cancer, leading to the restoration of a‘normal epigenome’. Many epigenetic drugs have been discovered in the recent past that can efficiently reverse DNA methylation and histone modification abnormalities that occur in cancer (Yoo& Jones, 2006). Two main classes of epigenetic drugs, namely DNA methyltransferase (DNMT) inhibitors and histone deacetylase (HDAC) inhibitors, are presently used in clinical trials fordealing cancers (McCabe, Brandes, &Vertino, 2009). DNMT inhibitors 5-azacytidine and 5-aza-2′-deoxycytidine, which are both analogs of cytosine, have demonstrated clinical activity at low doses against hematological neoplasms. HDAC inhibitors, which offer more promising targets for epigenetic anticancer therapy (Bots &Johnstone, 2009; Cang, Ma, & Liu, 2009). HDAC inhibitors will act on the genes known to be regulated by histone deacetylation. They have shown antitumor, growth inhibitory, pro-apoptotic, and pro-differentiation properties (Minucci&Pelicci, 2006).Suberoylanilidehydroxamic acid (SAHA), which is an HDAC inhibitor, has now been approved for use in clinic for treatment of T cell cutaneous lymphoma.

V. CONCLUSIONS AND PERSPECTIVES

Epigenetic mechanisms can be viewed as an interface between the environment and the genome, the deregulation of which may disrupt key cellular processes, ultimately resulting in oncogenic transformation and tumor development. Deeper understandings of the global patterns of these epigenetic modifications and their correspondingchanges in cancer have enabled the design of better treatment strategies. The inherent reversibility of epigenetic modifications represents an exhilarating opportunity for the development of novelstrategies for cancer prevention. A combinatorial approach utilizing different epigenetic therapeutic approaches along with typical chemotherapy holds substantialpromise for effective treatment of cancer in future. Such approaches might also help in sensitizing cancer cells, particularly cancer stem cells, which are obstinate to standard chemotherapy. Further understanding of cancer stem cells along with progress of more specific epigenetic drugs may hold the key to our capacity to effectively reset the abnormal cancer epigenome.

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