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Review

Epigenetic modifications in colorectal cancer: Molecular insights and therapeutic challenges

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ABSTRACT

Colorectal cancer, a leading cause of mortality worldwide, is a multistep disorder that results from the alteration of genetic and epigenetic mechanisms under contextual influence. Epigenetic aberrations, including DNA methylation, histone modifications, chromatin remodeling and non-coding RNAs, affect every aspect of tumor development from initiation to metastasis. Cancer stem cell promotion is also included in the wide spectrum of epigenetic dysregulations. Elucidation of this complex crosstalk network may offer new insights in the molecular interactions involved in the pathogenesis of colorectal carcinogenesis. In the era of translational medicine new horizons are opened for the pursuit of personalized therapeutic approaches and the development of novel and accurate diagnostic, prognostic and therapy-assessment markers. This review discusses the implications of epigenetic mechanisms in tumor biology and their applications "from bench to bedside".

1. Introduction

Colorectal cancer (CRC) is a leading cause of morbidity and mortality worldwide, with more than 600,000 deaths annually [1]. It is a multistep disorder that results from the accumulation of genetic and epigenetic aberrations under microenvironmental influence. Abnormalities in key regulatory genes and pathways, including p53, Wnt, DNA mismatch repair genes and Ras drive the progression of the disease from benign adenoma, to carcinoma and eventually to metastatic disease [2]. Genomic instability is pivotal for CRC development and is attributed to chromosomal instability (CIN) and microsatellite instability (MSI). Such dysregulations may cause sporadic or hereditary syndromes of CRC. CIN is a major defect found in cases of CRC (about 80%), which leads to gain or loss of whole chromosomes or chromosomal parts and the dysfunction of crucial genes such as Ras, adenomatous polyposis coli (APC) and p53. In MSI tumors a defect in mismatch repair genes is observed [3–5].

Epigenetic regulation refers to heritable and possibly reversible changes in the phenotypic expression of the genome, which alter gene expression without affecting DNA sequence [6,7]. In the wide gamut of epigenetic mechanisms are included, DNA methylation, histone modifications, chromatin remodelers and non-coding RNAs, which are implicated in the activation of oncogenes, the loss of function of tumor suppressors and the loss of imprinting [4,7,8]. By fine-tuning the accessibility of DNA, epigenetics orchestrate various physiological procedures (transcription, replication, repair) from developmental to differentiated stages and possess a pivotal role in the process of tumorigenesis. Genetic and epigenetic aberrations are involved in a complex network and can both predispose to or cause the development of each other (Fig. 1) [5,7,9]. The understanding of these mechanisms may contribute to the optimization of diagnostic and prognostic systems as well as the generation of novel and targeted therapeutic approaches.

Abbreviations: 5-FU, fluorouracil; A, acetyl-groups; ALDH1, aldehyde dehydrogenase-1; AP-1, activator protein 1; APC, adenomatous polyposis coli; ASO, anti-sense oligonucleotides; Bmi1, B lymphoma Mo-MLV insertion region 1 homolog; BMP, bone morphogenetic protein; CSC, cancer stem cell; CBP, CREB-binding protein; CDH1, cadherin-1; CDKN2A, cyclin-dependent kinase inhibitor 2A; CDX1, caudal type homeobox-1; CGI, CpG islands; CIMP, CpG island methylator phenotype; CIN, chromosomal instability; CpG, cytosine guanine; CRC, colorectal cancer; DNMT, DNA methyltransferase; DNMTi, DNMT inhibitor; EGCG, epigallocatechin 3-gallate; ERK, extracellular signal-regulated kinase; EZH2, histone methyltransferase enhancer of Zeste 2; FDA, Food and Drug Administration; H, histone; HAT, histone acetyltransferases; HDAC, histone deacetylase; HDACi, HDAC inhibitor; HDMT, histone demethylases; HIF, hypoxia inducible factor; HMT, histone methyltransferase; HOTAIR, hox transcript antisense intergenic RNA; IGF2, insulin-like growth factor-2; K, lysine residue; KLF4, kruppel-like factor 4; linc, long intergenic non-coding; LINE, long interspersed nuclear element; LOI, loss of imprinting; me, methylation; LRES, long range epigenetic silencing; LSD1, lysine specific demethylase 1; me, methylation; MGMT, O-6-methylguanine-DNA methyltransferase; MLL4, mixed lineage leukemia-4; miRNA/miR, microRNA; MSI, microsatellite instability; MTD, maximum tolerated dose; NRF1, nuclear respiratory factor 1; NuRD, nucleosome remodeling and histone deacetylase; PCAF, (CBP)/p300 associated factor; PFS, progression-free survival; PI3K, phosphatidylinositide 3-kinase; PPARδ, peroxisome proliferator activated receptor δ; PRC, polycomb repressive complex; PTEN, phosphatase and tensin homolog; RUNX3, runt-related transcription factor 3; SAM, S-adenosyl-methionide; SEPT9, septin 9; VEGF, vascular endothelial growth factor; YY1, yin yang 1; ZEB, zinc finger E-box-binding homeobox

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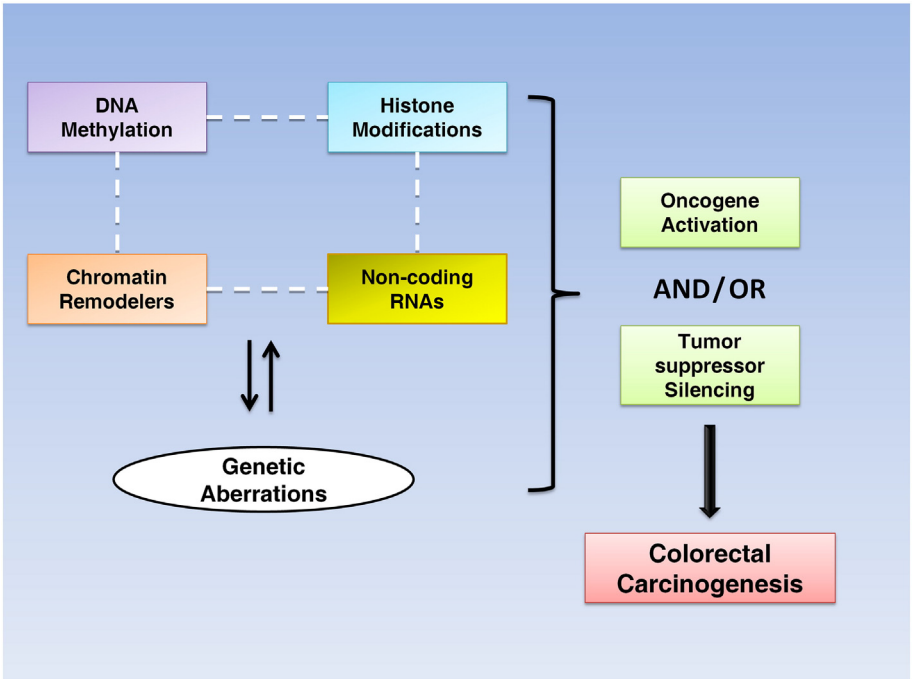

Fig. 1. Schematic representation of the mechanisms that lead to colorectal cancer. Genetic and epigenetic aberrations are involved in a complex network, responsible for modulations in gene expression patterns. Activation of oncogenes and/or silencing of tumor suppressors promote colorectal carcinogenesis.

2. DNA methylation

2.1. DNA hypomethylation

In normal cells DNA methylation plays a significant role in securing DNA stability through transcriptional silencing of genetic elements such as repetitive nucleotide sequences and endogenous transponsons. Furthermore DNA methylation reassures gene imprinting, transcriptional blockage of the genes on the inactive X-chromosome and normal growth, development and differentiation, while it also contributes in homeostasis maintenance and genomic adaption in response to environmental stimuli [10]. Global genomic hypomethylation, characterized by the gradual and genome wide depletion of methylated cytosine bases (5-methyl-cytosine) in cancer cells, is observed even in early stages across CRC development and progression [3]. DNA hypomethylation represents an epigenetic alteration that gathers in an age-dependent manner, possibly due to gradual acquisition of errors during DNA methylation mediated by constitutive methyltransferases and correlates to genomic damage. Demethylation of pericentromeric regions seems to induce DNA recombination errors and inaccurate chromosome duplication [11]. More precisely global DNA hypomethylation mainly takes place on cytosine guanine (CpG) dinucleotides within mobile and repetitive genetic elements such as satellite DNA sequences (including the aforementioned centromeres), long interspersed nuclear element (LINE) repeats and retrotransponsons [5]. This pattern of hypomethylation could be involved in tumorigenesis through the increased accumulation of chromosome breakage and the induction of expression of formerly silenced genetic elements (e.g. retrotransponsons) resulting in the disorganization of the normal nucleotide sequence and the impairment of chromosomal stability. The above could explain why DNA hypomethylation is mostly seen in CIN CRCs [3]. LINE-1 is frequently hypomethylated in CRC, exhibits a relatively stable demethylation state across CRC progression, even at early stages. Its enhanced activation through hypomethylation is associated with increased genomic instability and enhanced cancer ability to penetrate surrounding tissues and metastasize. [12,13]. Apart from genomic instability, another mechanism of colorectal carcinogenesis development and promotion, attributed to hypomethylation, is oncogene positive transcriptional regulation [8,10]. The events that propel global demethylation are not yet fully elucidated. APC mutation, which is a driving event in colorectal tumorigenesis, seems however to be able to control DNA methyltransferase (DNMT) expression and activity, which concomitantly results in demethylation of a number of genes and forces intestinal cells to remain in a more undifferentiated and progenitor-like state. Accordingly, genetic and epigenetic interactions constitute a possible mechanism involved in tumor initiation and progression [14].

Loss of imprinting (LOI) is defined as the impairment of the epigenetically regulated in a parent-of-origin manner, monoallelic, selective expression of certain genes, which could lead to developmental abnormalities. Imprinted genes also frequently (about 40% of CRC cases) undergo genome-wide hypomethylation early in the process of colorectal tumorigenesis [8,15]. In CRC tissues and cell lines, LOI of the insulin-like growth factor-2 gene (IGF2), leads to aberrant expression of the normally epigenetically-repressed maternally-inherited copy. Upregulation of the encoded protein levels, enhances the activation of IGF1 receptor (IGF1R) and its downstream signaling pathways, including phosphatidylinositide 3-kinase (PI3K)/Akt and GRB2/Ras/extracellular signal-regulated kinase (ERK) [5,15].

2.2. DNA hypermethylation

DNA methylation in humans takes place on the fifth position carbon of the pyrimidine ring of cytosines located in CpG dinucleotides. This process is mediated by three DNA methyltransferases (DNMT1, DNMT3A and DNMT3B), which require the methyl donor-cofactor S-adenosylmethionide (SAM) in order to add a methyl-group to cytosine residues [13]. CpG dinucleotides are unequally spread throughout the genome, gathered in small DNA stretches called CpG islands (CGIs). These CpG-rich regions are mostly present close to the promoter region of almost 50% of all human genes [3]. While the vast majority of CpG dinucleotides found in DNA sequences between genes are methylated, CpG islands are generally unmethylated in normal colonic epithelial cells [4,13]. There is an established association between aberrant DNA methylation of CGIs located close to gene promoter region and abnormal inhibition of gene