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Review

Histone modifications as a pathogenic mechanism of colorectal tumorigenesis

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ABSTRACT

Epigenetic regulation of gene expression has provided colorectal cancer (CRC) pathogenesis with an additional trait during the past decade. In particular, histone post-translational modifications set up a major component of this process dictating chromatin status and recruiting non-histone proteins in complexes formed to "handle DNA". In CRC, histone marks of aberrant acetylation and methylation levels on specific residues have been revealed, along with a plethora of deregulated enzymes that catalyze these reactions. Mutations, deletions or altered expression patterns transform the function of several histone-modifying proteins, further supporting the crucial role of epigenetic effectors in CRC oncogenesis, being closely associated to inactivation of tumor suppressor genes. Elucidation of the biochemical basis of these new tumorigenic mechanisms allows novel potential prognostic factors to come into play. Moreover, the detection of these changes even in early stages of the multistep CRC process, along with the reversible nature of these mechanisms and the technical capability to detect such alterations in cancer cells, places this group of covalent modifications as a further potential asset for clinical diagnosis or treatment of CRC. This review underlines the biochemistry of histone modifications and the potential regulatory role of histone-modifying proteins in CRC pathogenesis, to date. Furthermore, the underlying mechanisms of the emerging epigenetic interplay along with the chemical compounds that are candidates for clinical use are discussed, offering new insights for further investigation of key histone enzymes and new therapeutic targets.

Contents

Abbreviations: AP2A1, adaptor related protein complex 2, subunit alpha 1; APAF1, apoptotic protease activating factor 1; APC, adenomatous polyposis coli; BRCA1, 2, breast cancer 1, 2; CARM1, co-activator-associated arginine methyltransferase 1; CBP, cAMP-responsive element binding (CREB)-binding protein; CDO1, cysteine dioxygenase, type I gene; CDC2, cell division cycle-2; C/EBP, CCAAT enhancer-binding protein; ceRNAs, competitive endogenous RNAs; DMAP1, DNA methyltransferase 1-associated protein 1; DNMTs, DNA methyltransferases; DNMT1, 3B, DNA methyltransferase 1, 3B; ECEL1, endothelin-converting enzyme-like 1; EED, embryonic ectoderm development protein; EMT, epithelial to mesenchymal transition; EZH2, enhancer of zeste homolog 2; 5FU, 5-fluorouracil; G9a, lysine 9 (K9) of histone H3-specific methyltransferase; HATs, histone acetyltransferases; HDACs, histone deacetylases; HDMs, histone demethylases; HMTs, histone methyltransferases; HOTAIR, Hox transcript antisense intergenic RNA; HSPC105, short-chain dehydrogenase/reductase family 42E mem; JHDMs, Jumonji C-domain containing histone demethylases; JMJD1A, Jumonji-domain containing 1A; K, lysine; KLF4, Krüppel-like factor 4; 15-LOX-1, 15-lipoxygenase-1; LSD1, lysine-specific demethylase 1; MAGEA3, melanoma-associated antigen 3; MBD1, 2, 3, methyl-CpG-binding domain protein 1, 2, 3; MeCP2, methyl-CpG-binding protein 2; miRNAs, microRNAs; MLH1, MutL homolog 1; MLL1, 3, myeloid/lymphoid leukemia 1, 3; MREs, miRNA response elements; MSI, microsatellite instability; ncRNAs, non-coding RNAs; NDRG1, N-myc downstream-regulated gene 1; NEURL, neuralized-like protein 1; NF-κB, nuclear factor kappa B; PCAF, p300/CBP-associated factor; PIK3CB, phosphoinositide-3-kinase, catalytic, beta polypeptide; PPARγ, peroxisome proliferator-activated receptor gamma; PRC1, 2, Polycomb repressive complex 1, 2; PRDM, PR domain zinc finger proteins; PRMT1, 5, protein arginine methyltransferase 1, 5; PSMD9, 26S proteasome non-ATPase regulatory subunit 9; PTEN, phosphatase and tensin homolog; R, arginine; RGC32, response gene to complement 32; RIZ1, retinoblastoma protein-interacting zinc finger; RUNX3, runt-related transcription factor 3; SAHA, suberoylanilide hydroxamic acid; siRNA, small interfering RNA; SIRT1, sirtuin 1; SMYD3, SET and MYND domain-containing protein 3; STAT1, 3, signal transducer and activator of transcription 1, 3; SUV39H1, histone-lysine N-methyltransferase; SUZ12, suppressor of zeste 12 homolog; TCF12, transcription factor 12; TIMP3, tissue inhibitor of metalloproteinase 3; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TSA, trichostatin A; VEGFR1, vascular endothelial growth factor receptor 1; Wnt10B, wingless-type MMTV integration site family, member 10B; XAF1, X-linked inhibitor of apoptosis-associated factor 1; ZEB1, zinc finger E-box-binding homeobox 1.

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1. Introduction

Being one of the most common types of malignancy, along with one of the most frequent etiologies of cancer mortality in both genders worldwide, colorectal cancer (CRC) still presents a major public health problem to confront and a rapidly evolving research field to keep up with (Jemal et al., 2011; Siegel et al., 2012). Nevertheless, it is well established that sporadic and hereditary CRC constitute the histological and clinical outcome of a multistage, though hierarchically structured, genetic process characterized by the sequential accumulation of genetic and epigenetic alterations (Fearon and Vogelstein, 1990).

CRC genetic alterations present a well studied field over the past three decades providing an overall paradigm of the multistep carcinogenesis process. Driver mutations affect major intracellular signaling pathways implicated in proliferation, differentiation, cell adhesion and migration, apoptosis, DNA stability and repair (Saif and Chu, 2010).

Focusing on epigenetic alterations, a recently evolving research area, accumulating data indicate an additional trait of CRC pathogenesis. The term epigenetics refers to heritable changes that although not affecting DNA sequence, they play a critical regulatory role in gene expression. Epigenetic changes include DNA methylation, loss of imprinting, post-translational histone modifications, nucleosome positioning, chromatin looping and small non-coding RNAs interference (van Engeland et al., 2011). Among these alterations, the most extensively characterized is aberrant DNA methylation including both global DNA hypomethylation, an age-dependent process with poor prognosis occurring at early stages in CRC (Suzuki et al., 2006), and CpG island hypermethylation, presenting an additional hit in the classic Knudson genetic model (Knudson, 2001) for inactivation of tumor suppressor genes (Herman and Baylin, 2003), with main example the mismatch repair gene *MutL homolog 1* (*MLH1*) implicated in CRC pathogenesis (Herman et al., 1998). Although individually studied, a complex interplay has emerged between DNA methylation and histone modifications that is mediated by biochemical interactions of histone and DNA methyltransferases (HMTs and DNMTs, respectively) with the recruitment of histone deacetylases (HDACs) (Cedar and Bergman, 2009; Tachibana et al., 2008; Zhao et al., 2009). Taking all these into account, an additional epigenetic phenotype has been attributed to CRC that is critically regulated by the post-translational modifications of histone residues, allowing the generation of a corresponding multistep epigenetic CRC model, with potential novel therapeutic targets.

The present review explores the biochemistry behind histone modifications and the respective regulatory role of histone-modifying proteins in CRC pathobiology. In addition, the underpinning mechanisms of the emerging epigenetic interplay along with targeted therapy in research are discussed, providing new insights for further investigation of pivotal histone enzymes and new mechanisms in favor of pharmaceutical treatment. Although the types of histone modifications will be described in separate sections for comprehensive purposes, one should bear in mind that these changes and the underlying mechanisms take place simultaneously or in parallel and are exposed to a constant and mutual regulation.

2. Biochemical basis of post-translational histone modifications in CRC

The basic nucleosome unit is composed of four core histone proteins, H2A, H2B, H3 and H4, that form an octamer around which a segment of DNA winds with 147 base pairs in 1.67 left-handed superhelical turns. Highly basic histone N-terminal domains are able to protrude from the nucleosome establishing contact with adjacent ones (Fig. 1). At least eight different types of modifications have been characterized on multiple sites of specific residues of the "free" N-terminal domains, notably lysine (K) and arginine (R). These include acetylation, methylation, phosphorylation, ubiquitylation, sumoylation, ADP ribosylation, deimination and proline isomerization. Acetylation and methylation constitute the vast majority of known modifications, being mediated by a number of specialized enzymes. Their functional role relies on the disruption of chromatin contacts and recruitment of non-histone proteins, thus defining chromatin's proper structure and allowing protein complex formation for DNA "handling" (Cosgrove et al., 2004; Kouzarides, 2007). The emerging variability on the type of modified residue, the type and number of modifications, or the different modifying proteins as well as the immediate interplay of these changes, gives us a hint of the underlying complexity that this mechanism involves.

In CRC, aberrant histone modification patterns have been detected, being generated by a plethora of deregulated enzymes. Mutations, deletions or altered expression profiles alter the function of several histone-modifying proteins, thus supporting the major role of epigenetic effectors in CRC tumorigenesis (Ellis et al., 2009). These events contribute to cancer initiation and progression by altering the physiological levels of gene expression–mostly by inactivating tumor suppressor genes (Konishi and Issa, 2007)–and by inducing genome instability due to direct effects in the higher order of chromatin, chromosome condensation and mitotic disjunction (Bannister and Kouzarides, 2011). Consequently, a new terminology, "histo-oncomodifications", has evolved describing the histone covalent alterations that have been linked to cancer (Fullgrabe et al., 2011). The participation of these changes even in early stages of oncogenesis, their reversible nature and the technical ability to detect such alterations in neoplasmatic cells places this