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Review

Colorectal cancer: epigenetic alterations and their clinical implications

Alberto Puccini[a], Martin D. Berger[a], Madiha Naseem[a], Ryuma Tokunaga[a], Francesca Battaglin[a], Shu Cao[b], Diana L. Hanna[a], Michelle McSkane[a], Shivani Soni[a], Wu Zhang[a], Heinz-Josef Lenz[a,b,*]

[a] Division of Medical Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
[b] Department of Preventive Medicine, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, USA

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ABSTRACT

Colorectal cancer (CRC) is a heterogeneous disease with distinct molecular and clinical features, which reflects the wide range of prognostic outcomes and treatment responses observed among CRC patients worldwide. Our understanding of the CRC epigenome has been largely developed over the last decade and it is now believed that among thousands of epigenetic alterations present in each tumor, a small subgroup of these may be considered as a CRC driver event. DNA methylation profiles have been the most widely studied in CRC, which includes a subset of patients with distinct molecular and clinical features now categorized as CpG island methylator phenotype (CIMP). Major advances have been made in our capacity to detect epigenetic alterations, providing us with new potential biomarkers for diagnostic, prognostic and therapeutic purposes. This review aims to summarize our current knowledge about epigenetic alterations occurring in CRC, underlying their potential future clinical implications in terms of diagnosis, prognosis and therapeutic strategies for CRC patients.

1. Introduction

Colorectal cancer (CRC) is a considerable health issue worldwide. Globally, it is the third most common cancer, with an incidence of 1.4 million cases and about 700.000 deaths in 2012 [1]. Unfortunately, it is predicted that the number of cases will rise by > 60% by 2030 with an incidence of 2,2 million new cases and 1,1 million deaths [2].

Over the last decades, improved screening strategies and more effective therapies have led to a decrease in mortality rates in different countries. It has also led to an increase in the median overall survival (OS) for metastatic colorectal cancer (mCRC) patients, which has now reached > 30 months. Nevertheless, more powerful diagnostic tools and more effective and personalized treatment are urgently needed in daily clinical practice.

In 1990, Fearon and Vogelstein proposed a model for the genetic basis of CRC [3], and since then the development and progression of CRC have been widely studied, leading to a profound knowledge about genetic and epigenetic mechanisms that play specific roles in this process. Indeed, the original multistep model considered tubular and tubulovillous adenomas as the premalignant lesions of CRC, arising mainly via APC mutations or deletions and leading to chromosomal instability. It is now recognized that approximately 30% of CRCs develop from the serrated pathway, that includes hyperplastic polyps (HPs), sessile serrated adenoma (SSA), traditional serrated adenoma (TSA). This pathway is associated with microsatellite instability, aberrant DNA hypermethylation, and BRAF mutation.

Approximately 90% of CRCs develop sporadically, and only a few cases (< 10%) are hereditary. Familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC), MUTYH-associated polyposis (MAP), Peutz-Jeghers syndrome (PJS) and Serrated polyposis syndrome (SPS) are the main hereditary causes of CRC.

Nowadays, three major pathways for CRC development have been characterized, the most common of which is the chromosomal instability (CIN), that represents 70–80% of tumors. The second most common is the microsatellite instability (MSI) pathway, accounting for 5–20% of tumors, according to the stage of disease. The last group is the CpG island methylation phenotype (CIMP), identified by Toyota and colleagues in 1999 [4], which represents about 15% of CRCs. Recent approaches which enable comprehensive genome-wide analysis of the methylome have provided extensive knowledge about aberrant methylation in different types of tumors. By focusing on the state-of-the-art of epigenetic alterations in CRC, our review will contribute to this considerably growing research field, leading to potential changes in crucial clinical aspects, such as early diagnosis, prognosis and treatment.

* Corresponding author at: Division of Medical Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, 1441 Eastlake Avenue, Suite 3456, Los Angeles, CA 90033, USA.
E-mail address: lenz@med.usc.edu (H.-J. Lenz).

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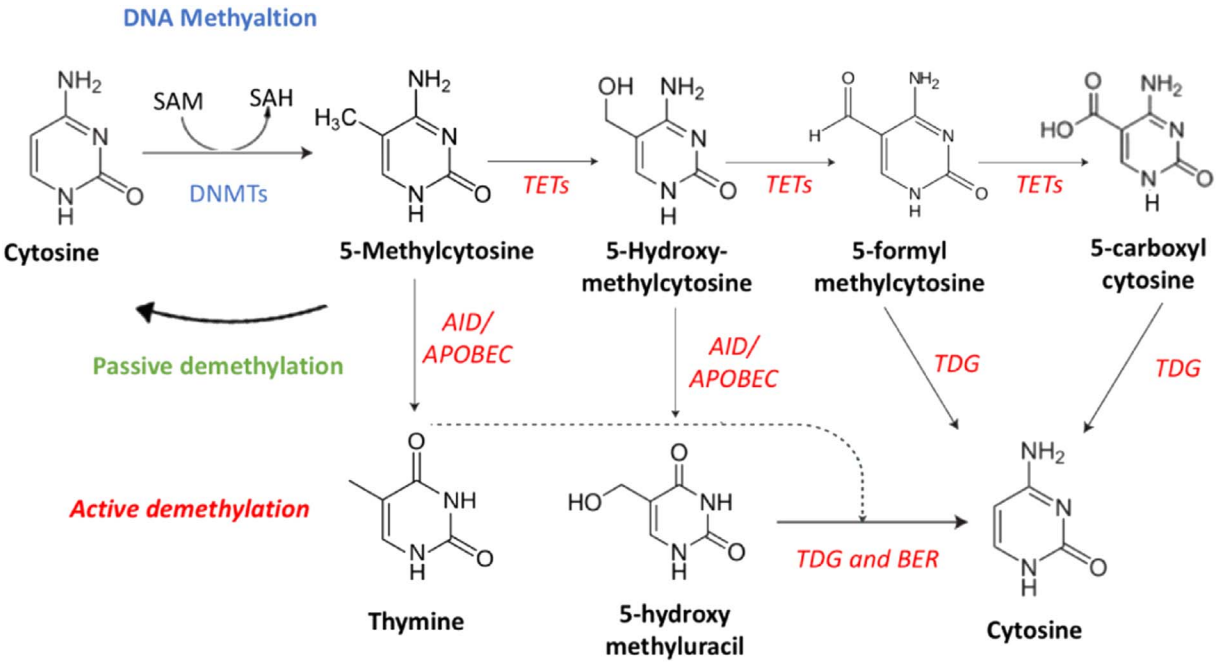

Fig. 1. DNA methylation and DNA demethylation pathways DNA methylation (high left corner – blue characters) and DNA demethylation (active – red italic characters; passive – green characters) pathways. See text for details. SAM: *S*-Adenosyl methionine; SAH: *S*-adenosylhomocysteine; DNMT: DNA methyltransferase; AID: activation-induced deaminase APOBEC: apolipoprotein B mRNA-editing enzyme complex; TDG: thymine-DNA glycosylase; BER: Base excision repair.

2. Molecular pathways leading to CRC

2.1. Chromosomal instability (CIN)

CIN is a hallmark characteristic of most CRC cases (80–85%), and it is characterized by extensive abnormality in chromosome number (aneuploidy) and loss of heterozygosity (LOH). CIN can be observed in several forms, including chromosomal numerical abnormalities, small sequence modifications such as base deletions or insertions; chromosomal rearrangements and gene amplification [5]. CRC-related tumor suppressor genes are thought to be altered in the early phase of cancer development, and adenomatous polyposis coli (APC) mutation is the first step in the translation of normal mucosa to neoplastic tissue, leading to the activation of WNT pathway. Subsequent mutations that occur in genes, such as KRAS, TP53, SMAD4 and type II TGF-β receptor (TGFBR2), lead to the progression from polyp to cancer.

Since Vogelstein proposed the adenoma-cancer model, our knowledge about molecular pathogenesis of CRC has markedly increased. Although conventional tubular and tubulo-villous adenomas are well-recognized as precursor lesions of the chromosomal instability pathway, recently a new premalignant form has been recognized: serrated polyps. The serrated neoplasia pathway develops by the accumulation of insertion or deletion mutations throughout the genome, leading to microsatellite instability-high (MSI-H) adenocarcinomas, BRAF or KRAS mutation, and CIMP that can be either low level (CIMP-L) or high level (CIMP-H) (reviewed in [6]).

2.2. Microsatellite instability (MSI)

MSI is a hypermutable phenotype caused by the loss of DNA mismatch repair (MMR) activity due to either mutations or epigenetic silencing of MLH1, MSH2, MSH6, and PMS2 genes. Most MSI CRCs have lost expression of MLH1, mainly due to acquired hypermethylation of the promoter of the MLH1 gene, which occurs in tumors with the CpG island methylator phenotype (CIMP) [7]. The familial form of MSI CRC is hereditary non-polyposis CRC (HNPCC, or Lynch syndrome), which is caused by germline mutations in the mismatch repair genes MLH1, PMS2, MSH6, or MSH2, and accounts for about 3–5% of all CRC cases.

About 15% of sporadic CRCs have MSI as a mechanism of development and progression. These patients show distinct characteristics which are important for clinical practice. Tumors with MMR deficiency exhibit a high frequency of microsatellite instability, because these regions are more susceptible to DNA mutations when MMR genes are compromised.

2.3. CpG island methylator phenotype (CIMP)

CIMP colon cancer is a unique molecular subgroup, characterized by a global genome hypermethylation in specific DNA regions, called CpG island. These are sequences > 200–500 bases in length with > 50% CpG content [8]. Usually, CpG islands overlap the promoter region of 60–70% of genes and tend to be protected from methylation; however, they can become aberrantly methylated in cancer. Methylation of CpG islands within the promoter region causes transcriptional silencing, although it seems that only few methylated genes show a decreased gene expression in CRC. Many studies have expanded the idea of CpG islands to “CpG island shores,” which are also abnormally methylated in cancer. CpG island shores are regions of DNA with a low density of CpG dinucleotides that are up to 2 kb upstream of a CpG island. The methylation of CpG island shores is correlated with transcriptional inactivation and expression of splice variants [9]. More details will be addressed below.

3. DNA methylation

Epigenetics is commonly defined as changes in gene functions that are heritable during cell division and that cannot be explained by alteration in DNA sequence. Different epigenetic mechanisms are considered to have a role in cancer development, such as DNA methylation, histone modifications, nucleosome positioning and non-coding RNAs, specifically microRNA expression [10]. In fact, the most widely studied epigenetic alteration in cancer is aberrant DNA methylation.

DNA methylation in mammals occurs primarily at CpG residues (Fig. 1): genome wide, 60–80% of the CpG residues are methylated. However, in CpG islands and active regulatory regions, only 10% of the CpGs are methylated [11].