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Mini-review

Epigenetic biomarkers of colorectal cancer: Focus on DNA methylation

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ABSTRACT

The original theory of the multi-step process of colorectal cancer (CRC), suggesting that the disease resulted from the accumulation of mutations in oncogenes and tumor suppressor genes in colonic mucosa cells, has been largely revised following the observation that epigenetic modifications of several genes occur in the average CRC genome. Therefore, the current opinion is that CRCs are the consequence of the accumulation of both mutations and epigenetic modifications of several genes. This mini-review article focuses on DNA methylation biomarkers in CRC. Recent large-scale DNA methylation studies suggest that CRCs can be divided into at least three-four subtypes according to the frequency of DNA methylation and those of mutations in key CRC genes. Despite hundreds of genes might be epigenetically modified in CRC cells, there is interest in the identification of DNA methylation biomarkers to be used for CRC diagnosis, progression, tendency to tissue invasion and metastasis, prognosis, and response to chemotherapeutic agents. Moreover, DNA methylation largely depends on one-carbon metabolism, the metabolic pathway required for the production of S-adenosylmethionine, the major intracellular methylating agent. Complex interactions are emerging among dietary one-carbon nutrients (folates, vitamin B6, vitamin B12, methionine, and others), their metabolic genes, CRC risk, and DNA methylation profiles in CRC. Moreover, active research is also focused on the possible contribution of folic acid dietary fortification during pregnancy and the possible methylation of CRC-related genes in the offspring.

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1. Introduction

Colorectal cancer (CRC) represents a serious health concern, with over one-million new cases diagnosed worldwide every year, and results from a multi-step process leading to the accumulation of genetic and epigenetic alterations in colon mucosa cells primarily affecting oncogenes, tumor suppressor genes and DNA repair genes, all involved in critical pathways of CRC initiation and progression [1]. The disease occurs sporadically in most of the cases and only 20–25% of the patients have a family history, suggesting a contribution for shared genes and environment. However, only 5–6% of CRC cases are due to inherited conditions predisposing an individual to the development of the disease, denoted as CRC genetic syndromes [2]. The term familial colorectal cancer (FCC) is used to categorize CRC families that do not meet the clinical criteria for a diagnosis of known hereditary CRC syndromes. In those families less penetrant genes and gene-environment interactions are likely to be at the basis of familial CRC aggregates. All the other CRC cases (75–80% of the total) occur sporadically as the result of complex interactions between susceptibility genes and environmental factors [2]. CRC genetic syndromes include major ones, such as familial adenomatous polyposis (FAP), attenuated FAP (AFAP), MUTYH-associated polyposis (MAP), and Lynch syndrome (hereditary nonpolyposis colorectal cancer: HNPCC), as well as rare syndromes such as hamartomatous polyposis conditions (Peutz-Jeghers syndrome: PJS), juvenile polyposis syndrome (JPS), and hyperplastic polyposis. The genetic screening in families with CRC syndromes has been successful and several genes have been so far discovered, including the tumor suppressor *Adenomatous Polyposis Coli* (*APC*) gene, the DNA repair *Mut Y homolog* (*MUTYH*) gene, the DNA mismatch repair (MMR) genes *MSH2, MLH1, MSH6*, and *PMS2*, the tumor suppressor *STK11* gene, the *SMAD4/DPC4* (deleted in pancreatic cancer locus 4) gene, the gene encoding the bone morphogenetic protein receptor 1A (*BMPR1A*), and the tumor suppressor phosphatase and tensin homolog (*PTEN*) gene [2]. In parallel, the genetic screening in FCC as well as in sporadic CRC cases has led to the identification of several loci likely contributing to disease risk (for an updated review see Ref. [2]). Other CRC risk factors include a family history of the disease, the presence of large serrated polyps, a diet rich in total fat and meat, cigarette

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smoking, alcohol intake, abdominal obesity, a sedentary lifestyle, male gender, and the use of nonsteroidal anti-inflammatory drugs [3–7]. By contrast, high intakes of folate, dietary fiber and other vitamins, colonoscopy with removal of adenomatous polyps, and postmenopausal hormone use have been associated with decreased CRC risk [8–11]. The term "epigenetics" is used to describe those mechanisms able to modify the expression levels of selected genes without necessarily altering their DNA sequence, including DNA methylation, histone tail modifications and chromatin remodeling, as well as mechanisms mediated by non-coding RNA molecules. Epigenetic modifications are often environmentally induced and tissue specific phenomena that can have similar effects to those of pathogenic mutations or functional polymorphisms, since they are able to silence, increase or reduce the expression of a selected gene in a given tissue. This is of particular relevance for cancer formation when cancer related genes, such as tumor suppressor genes or DNA repair genes, are involved [12]. This mini-review article focuses on DNA methylation in colorectal cancer, one of the most studied epigenetic events of the disease. It is now clear that epigenetic phenomena occur together with gene mutations and contribute to the progression of normal colonic mucosa to CRC [2]. Therefore, the aim of this manuscript is the description of one-carbon metabolism, the metabolic pathway responsible for the availability of one-carbon units for DNA methylation, and its role in CRC development. Then, the article will focus on DNA methylation in CRC and the current attempts to use epigenetic biomarkers for CRC diagnosis, classification, staging, prognosis and response to treatment. In addition, the possible contribution of the maternal diet during pregnancy to epigenetic modifications in the developing embryo possibly predisposing to cancer formation in adulthood is also discussed.

2. One-carbon metabolism and its relevance to CRC risk

2.1. One-carbon metabolism

Folate metabolism, better known as one-carbon metabolism, provides the one-carbon units required for several intracellular processes, including the synthesis of DNA and RNA precursors necessary for DNA replication and repair, the synthesis of amino-acids, and the synthesis of S-adenosylmethionine (SAM), required for methylation reactions (Fig. 1). Folates are essential nutrients entirely derived from dietary sources, mainly from the consumption of green leafy vegetables, fruits, cereals, and meat. They should be distinguished from folic acid which is the synthetic form of the vitamin added to foods and found in dietary supplements. After intestinal absorption, dietary folates are reduced and methylated into the liver to form 5-methyltetrahydrofolate (5-MTHF), which is released into the blood and taken up by the cells. Folic acid is converted to a natural biological form of the vitamin as it passes through the intestinal wall, with enzymatic reduction and methylation resulting in the circulating form of the vitamin, 5-MTHF [13]. Several sophisticated membrane transport systems are required for the cellular uptake of folates, including the reduced folate carrier (RFC1), folate receptors (hFR) and the proton-coupled folate transporter (PCFT). Methylenetetrahydrofolate reductase (MTHFR) plays a pivotal role in regulating DNA methylation reactions, through the reduction of 5,10-methylenetetrahydrofolate (5,10-MTHF) to 5-methylTHF, the one-carbon donor for the remethylation of homocysteine (Hcy) to methionine mediated by the activity of methionine synthase (MTR). Cobalamin (or vitamin B12) is a cofactor in this reaction, and methionine synthase reductase (MTRR) is required for the maintenance of MTR in its active state (Fig. 1). Methionine is then converted into SAM, the major intracel-

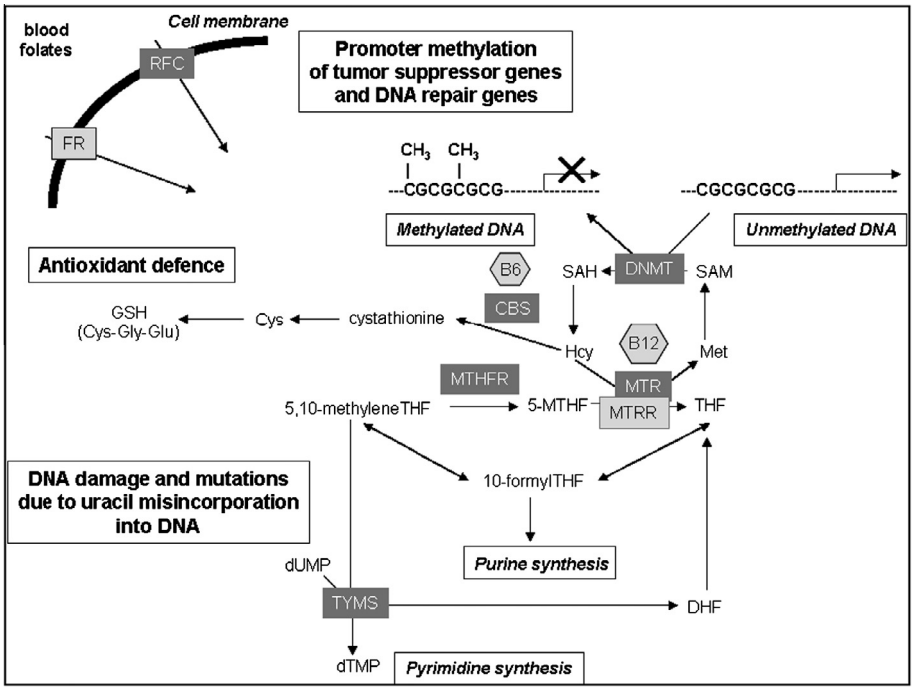

Fig. 1. Simplified overview of the one-carbon metabolic pathway. The diagram shows the complex reactions linking folate metabolism to DNA methylation and to the synthesis of pyrimidines and purines, and their possible contribution to the silencing of tumor suppressor and DNA repair genes (promoter methylation), or to point mutations resulting from impaired uracil misincorporation into the DNA (see the text for details). Metabolites: Cys: cysteine; dTMP: deoxythymidine monophosphate; dUMP: deoxyuridine monophosphate; DHF: dihydrofolate; 10-formyl-THF: 10-formyl-tetrahydrofolate; GSH: glutathione; Hcy: homocysteine; Met: methionine; 5-MTHF:5-methyltetrahydrofolate; 5,10-MTHF = 5,10-methylenetetrahydrofolate; SAH: S-adenosylhomocysteine; SAM: S-adenosylmethionine; THF: tetrahydrofolate. Enzymes: CBS: cystathionine β-synthase; DNMT: DNA methyltransferase; hFR: human folate receptor; MTHFR: methylenetetrahydrofolate reductase; MTR: methionine synthase; MTRR: methionine synthase reductase; RFC1 = reduced folate carrier; TYMS: thymidylate synthase. Cofactors: B6 = vitamin B6; B12 = vitamin B12.

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