Cyclooxygenase-2 Gene Expression

Transcriptional and Posttranscriptional Controls in Intestinal Tumorigenesis

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Summary

Cyclooxygenases (COX) also known as prostaglandin (PG) synthases, are present in two forms, COX-1 and COX-2. Whereas COX-1 is responsible for cytoprotective functions in a number of organs, COX-2, which is normally absent at basal levels, is induced under certain conditions including pathophysiological states like acute inflammation, arthritis, as well as in cancer and cancer-related angiogenesis. Overexpression of COX-2 enhances PGE₂ synthesis, thereby resulting in increased cellular proliferation, which is an important role for the molecule in cancer progression. In addition, increased PGE₂ levels protect the cancer cells from the deleterious effects of ionization radiation (IR). COX-2 expression is tightly controlled under normal conditions. At the transcriptional level, COX-2 gene expression is controlled by multiple elements in a 800-bp region proximal to the transcription start site. Many cellular transcription factors bind these elements to regulate the COX-2 gene transcription. Among them, the key factors are NF-κB and β-catenin. Of these, β-catenin is especially interesting because it can egulate COX-2 both directly by binding to the promoter elements as a complex with either TCF-4/LEF or p300, or indirectly by inducing expression of PEA-3, which subsequently binds to its cognate element in the COX-2 promoter to induce transcription. COX-2 mRNA is also tightly regulated at the post-transcriptional levels of mRNA stability and translation. This is mediated by AU-rich sequence elements located in the 3′UTR of the COX-2 mRNA. Multiple RNA binding proteins have been identified that bind to the AU-rich sequences in the COX-2 3′-UTR to mediate this process. HuR, a ubiquitously expressed protein, is overexpressed in colon and other cancer cells, and it increases the stability and translation of COX-2 mRNA. In contrast, CUGBP2 is induced in cells undergoing apoptosis and it inhibits translation of COX-2 mRNA. Another protein that have been identified induce the translation is hnRNPA1, whereas those that inhibit the translation are TIA1, TTP, TIAR, and AUF1.

Key Words: Posttranscriptional; gene regulation; cyclooxygenase-2; AU-rich sequences; prostaglandins; transcription; mRNA translation; RNA binding protein; 3′-untranslated region; HuR; CUGBP2; tristetraprolin.

1. Introduction

Cancer is a hyperproliferative disorder in which invasion and angiogenesis lead to tumor metastasis. The World Health Organization (WHO) has estimated that 1,300,000 new cases of cancer occur each year and 55,000 people will die in the United States alone. Colorectal cancer is the second leading cause of cancer-related deaths in the western world. The estimated number of new cases of colorectal cancer in the United States for 2002 was 107,000, and approx 48,000 people dies from the cancer or its complications (1). To prevent the onset of cancer, the National Institute of Health (NIH) in
the United States has recommended a high-fiber, low-fat diet, consisting of more fruits and vegetables. The incidence in many countries, such as India, had been very low in the past, but more recently a rapid increase was projected resulting from adaptation of more Western-style diets (2). This is because the diet from these regions was comprised primarily of fruit and vegetables, as well as spices such as turmeric that contain the active anticancer ingredient, curcumin (3–5). However, Western diets are high in fats and red meat and low in fiber, a major risk factor for colon carcinogenesis (2).

Additional risk factors for colon carcinogenesis include age (>50 yr), gender (women > men) and lifestyle factors such as alcohol abuse, smoking, and sedentary habits (6–12).

Colon cancer, if identified early, can be treated. Screening of colon cancer can be done by colonoscopy to find polyps; removing these polyps at an early stage can prevent cancer progression. Long-term polyps may develop into cancer but screening tests can find these lesions early and they can be treated. Hence, regular colonoscopy is recommended in the United States for those over 50 yr of age (13,14). The reoccurrences of colon cancer is common and it is estimated in about 40% of the cases; cancer will return after 3 to 5 yr of treatment (15). Cancer may recur in the colon or rectum, or in another part of the body.

Colorectal cancers result from the progression of a normal colonic mucosa to an adenomatous polyp, and eventually to a malignant cancer (see Fig. 1). There are at least five to seven major events that occur in the cancer progression. Two major pathways may lead to cancer—chromosomal instability and microsatellite instability (16–18). Because of the acquired or inherited mutations in DNA repair-related proteins, a defect in the DNA repair is observed, resulting in the microsatellite instability-related cancers (19–21). About 85% of colorectal cancers are due to chromosomal instability. Many genes are involved in the pathway to tumorigenesis, including the adenomatous polyposis coli (APC, chromosome 5q), deleted in colon cancer (DCC, 18q) and p53 (17p) (22,23).

The loss of the APC gene is a primary event in cancer progression. APC, located in chromosome 5q21, is considered a gatekeeper and mutations in the gene result in loss of signal transduction and cell adhesion (24–28). A major function of APC is to control β-Catenin levels in the cell. β-Catenin is an important transcription factor that controls the expression of many genes involved in cancer progression. It is also a member of the Wnt signaling pathways and plays a role in development (29–32). β-Catenin is also a component of the cell–cell adhesion machinery. It binds to cytosolic tail of E-cadherin and connects actin filaments through β-catenin to form the cytoskeleton (33,34). APC binds to β-catenin and targets itself for ubiquitination-mediated degradation in the cytoplasm of the epithelial cell. Loss of APC results in loss of this degradation event thereby increasing the accumulation of β-catenin, which in turn translocates to the nucleus and transcriptionally activates expression of genes essential for tumor progression. A key target of β-catenin is the cyclooxygenase (COX)-2 gene, which is discussed below (35–38). Other genes that are consistently observed to have mutations are p53 and K-Ras, and both also regulate COX-2 expression (38–40). These mutations are not the only cause of cancer, but overexpression and loss of other gene expression by other mechanisms can also lead to the cancer phenotype. An example of decreased expression in colon carcinogenesis is that of transforming growth factor (TGF)-β, which occurs late in the cancer progression, whereas induction of COX-2 occurs early and is sustained throughout the cancer progression (41–44). In addition, COX-2 levels may