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Prospects for Chemoprevention of Colorectal Neoplasia

Emerging Role of Anti-Inflammatory Drugs

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An Emerging Role for Anti-inflammatory Agents for Chemoprevention

Andrew T. Chan and Elmar Detering

Abstract

There have been a number of promising recent developments in the prevention of colorectal cancer. This book examines in detail important aspects of the current status of and future prospects for chemoprevention of colorectal tumors, particularly using anti-inflammatory drugs. Research into the mechanisms that lead from early colorectal adenoma to colorectal cancer is discussed. The role and modes of action of available anti-inflammatory drugs, such as aspirin, celecoxib, and sulindac are described and recent data from trials of aspirin are reviewed. In addition, the possible impact of nutritional agents with anti-inflammatory properties is considered, and strategies applicable in those with a high level of genetic risk are evaluated. An important feature of the book is its interdisciplinary perspective, offering highly relevant information for gastroenterologists, internists, general practitioners, oncologists, colorectal and gastroenterological surgeons, and public health practitioners.

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Colorectal cancer (CRC) is a compelling example of a chronic disease for which there is a critical need for novel preventive strategies. CRC is the second most common cancer in developed countries, with about 1 million new cases and 600,000 deaths worldwide each year. The incidence rates (IR) of CRC vary markedly worldwide, being highest in Europe, North America, and Oceania. The lifetime risk of CRC in Western populations such as the United States (US) is 5%. In Europe, there were 412,900 new cases and 217,400 deaths due to CRC during 2006. While the incidence of CRC has been declining in the US since the 1980s, several countries, especially those that are economically transitioning to a more urbanized/westernized lifestyle, have been seeing important increases (GLOBOCAN 2008).

Given the poor outcomes of advanced CRC, considerable emphasis has been focused on prevention through population screening for the early detection of CRCs and adenomatous polyps, the precursor for the vast majority of cancers. Although screening modalities such as fecal occult blood testing and endoscopy are efficacious, patient uptake is often suboptimal, limiting its real-world effectiveness. Thus, there is a clear imperative to consider alternative preventative strategies, including chemoprevention.

'Chemoprevention' describes the use of drugs or other (including natural) agents to inhibit or prevent the development or progression of malignant changes in cells. An important milestone in the evolution of agents for chemoprevention was the discovery of the "inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs" by Sir John Vane in 1971, who received the Nobel Prize in 1982 (together with Bergstrom and Samuelsson) (Vane 1971). Their work was seminal in establishing cyclooxygenase (COX), also known as prostaglandin synthase (PTGS), as the principle target enzyme for aspirin and aspirin-like drugs now commonly known as non-steroidal anti-inflammatory drugs (NSAIDs) (Vane 1982). The COX-1 and COX-2 isoenzymes are responsible for formation of prostaglandins and related biologically active substances, important mediators of inflammation.

Historically, in vitro and animal studies with aspirin and NSAIDs as potential chemopreventive agents began early in the 1980s. In humans, sulindac was among the first drugs with demonstrated chemopreventive efficacy in studies of patients with familial adenomatous polyposis (FAP), an autosomal dominant hereditary CRC syndrome that has provided tremendous insight into the pathogenesis of sporadic colorectal cancer. The key distinguishing feature of classic FAP is the development of hundreds to thousands of adenomatous polyps throughout the colon, often beginning as early as the second decade of life. Colorectal adenocarcinomas inevitably develop in FAP patients, typically by age 40. In early studies, sulindac treatment caused marked regression of polyps in patients with FAP (Giardiello et al. 1993).

The FAP model also paved the way for further analysis of the NSAIDs celecoxib and rofecoxib, selective COX-2 inhibitors, as potential chemopreventatives in colorectal adenoma and cancer (Steinbach et al. 2000; Hallak et al. 2003; Arber et al. 2006; Bertagnolli et al. 2006). Despite their demonstrated efficacy in well-designed clinical trials of both FAP and sporadic adenoma, the occurrence of

cardiovascular events associated with these agents has dampened enthusiasm for their routine use for chemoprevention.

Concerns about NSAID-associated cardiovascular toxicity have refocused attention on the chemopreventive properties of aspirin, the oldest of the "modern" anti-inflammatory drugs. Aspirin not only has a favorable cardiovascular profile but is already widely used for the prevention of cardiovascular events. Several epidemiological studies (Chan 2011), randomized controlled trials (RCTs) of colon polyp recurrence (Cole et al. 2009; Chan et al. 2007; Baron et al. 2003; Sandler et al. 2003; Benamouzig et al. 2003; Logan et al. 2008), and RCTs in patients with hereditary CRC syndromes (Burn et al. 2011a, 2011b; Chan et al. 2005, 2008, 2009), have shown that aspirin reduces incidence of colorectal neoplasia. In five cardiovascular-prevention RCTs, Rothwell and colleagues previously observed that daily aspirin at any dose reduced risk of CRC by 24 % and of CRC-associated mortality by 35 % after a delay of 8–10 years (Rothwell et al. 2010). Thus, aspirin may be currently the most promising agent considering it demonstrated effectiveness and its favorable cardiovascular safety profile. Because CRC and vascular disease have overlapping risk factors (e.g., diabetes, obesity, physical inactivity), use of aspirin for the dual purpose of cancer and vascular disease prevention has considerable appeal. Moreover, emerging data show that aspirin may be associated with a lower risk of death from cancer of sites other than the colorectum (Rothwell et al. 2011, 2012). Thus, despite aspirin's known association with gastrointestinal toxicity, the overwhelming benefits of aspirin for a wide range of the most common chronic diseases could overall tip the scales in favor of aspirin as the chemopreventive agent of choice for many individuals Chan et al. (2012) and Avivi et al. (2012)

Our knowledge about the mechanism underlying the anti-neoplastic benefit of these anti-inflammatory agents is growing, but yet incomplete. At present, the known effects of these agents in inhibiting COX-1 and COX-2 appear to play a significant role. COX-1 is considered a constitutive enzyme, found in most tissues, including gastrointestinal mucosa (Schror 2009). COX-2, on the other hand, is undetectable in most normal tissues, with expression induced in areas of inflammation. More importantly, COX-2 been shown to be upregulated in various carcinomas and to have a central role in tumorigenesis (Chan et al. 2007). Nonetheless, there have been many COX-independent mechanisms proposed for aspirin's anti-cancer benefit. Moreover, there remains a need to further elucidate downstream pathways of COX-2 that influence cancer.

In recent years, there has been a substantial new body of evidence demonstrating the potential of anti-inflammatory drugs as chemopreventive agents for colorectal cancer. This volume will review the current body of evidence for aspirin in sporadic neoplasia (Chap. 7, Rothwell) and hereditary cancers (Chap. 9, Burn) and NSAIDs (Chap. 5, Arber). We will also describe the many proposed anti-cancer mechanisms of NSAIDs and aspirin (Chap. 3, Patrigani; Chap. 2, Dixon; Chap. 4, Rodriguez; and Chap. 6, Piazza) and the evidence for the use of alternative agents with similar anti-inflammatory mechanisms of action (Chap. 8, Hull). Taken together, this volume will provide several different perspectives that

demonstrate the emerging role of anti-inflammatory agents for chemoprevention for CRC and other chronic diseases.

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Mechanistic Aspects of COX-2 Expression in Colorectal Neoplasia

Dan A. Dixon, Fernando F. Blanco, Annalisa Bruno and Paola Patrignani

Abstract

The cyclooxygenase-2 (COX-2) enzyme catalyzes the rate-limiting step of prostaglandin formation in pathogenic states and a large amount of evidence has demonstrated constitutive COX-2 expression to be a contributing factor promoting colorectal cancer (CRC). Various genetic, epigenetic, and inflammatory pathways have been identified to be involved in the etiology and development of CRC. Alteration in these pathways can influence COX-2 expression at multiple stages of colon carcinogenesis allowing for elevated prostanoid biosynthesis to occur in the tumor microenvironment. In normal cells, COX-2 expression levels are potently regulated at the post-transcriptional level through various RNA sequence elements present within the mRNA 3′ untranslated region (3′UTR). A conserved AU-rich element (ARE) functions to target COX-2 mRNA for rapid decay and translational inhibition through association with various RNA-binding proteins to influence the fate of COX-2 mRNA. Specific microRNAs (miRNAs) bind regions within the COX-2 3′UTR and control COX-2 expression. In this chapter, we discuss novel insights in the mechanisms of altered post-transcriptional regulation of COX-2 in CRC and

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how this knowledge may be used to develop novel strategies for cancer prevention and treatment.

Abbreviations

CRC	Colorectal cancer
CV	Cardiovascular
CIN	Chromosomal instability
APC	Adenomatous polyposis coli
FAP	Familial adenomatous polyposis
EGF	Epidermal growth factor
TGF	Transforming growth factor
COX	Cyclooxygenase
PG	Prostaglandin
$(TX)A_2$	Thromboxane
PGI_2	Prostacyclin
GI	Gastrointestinal
NSAIDs	Nonsteroidal anti-inflammatory drugs
mPGES	Microsomal Prostaglandin E Synthase
15-PGDH	15-hydroxyprostaglandin dehydrogenase
PPAR	Peroxisome proliferator-activated receptor
AU	Rich elements (AREs)
miRNAs	MicroRNAs
HuR	Hu antigen R
TIA-1	T cell intracellular antigen 1
RBM3	RNA-binding motif protein 3

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