REVIEW

Chemoprevention of colorectal cancer -experimental and clinical aspects-

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Abstract : Colorectal cancer is a leading cause of cancer-related mortality worldwide. Therefore, an appropriate prevention strategy should be urgently established. Chemoprevention involves the use of oral agents to suppress the development of cancer. Recent progress in the molecular analysis of colorectal cancer has revealed many candidate molecules for chemoprevention. Many new agents targeting these molecules have also been developed. These agents are largely classified into three categories : 1) Signal transduction modulators including epidermal growth factor (EGF) receptor inhibitors, anti-vascular endothelial growth factor (VEGF) antibodies, and inhibitors of oncogene products. 2) Epigenetic modulators including peroxisome proliferative activated receptor (PPAR)-γ agonists, estrogen receptor (ER)-β, and histone deacetylase inhibitors. 3) Anti-inflammatory modulators including cyclooxygenase (COX)-2, EP 1-4, and NF-kB. Of these agents, some actually proceeded to human clinical trials, and have been shown to be active chemopreventive agents. J. Med. Invest. 56 : 1-5, February, 2009

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INTRODUCTION

Colorectal cancer is a disease with a high incidence and mortality rate, and has been increasing in prevalence worldwide (1). Therefore, various prevention strategies have been investigated. Primary prevention attempts to prevent the occurrence of colorectal cancer by lifestyle modification, and secondary prevention aims to arrest the progression of colorectal cancer through early diagnosis and treatment. In addition to these, recently, chemoprevention, the use of oral drugs to prevent cancer, has attracted much attention. Many compounds have been tested to assess their inhibition of colorectal carcinogenesis in animal models, and some of them have been proceeded to clinical trials for chemoprevention.

Recent progress in the molecular analysis of colorectal carcinogenesis has revealed many candidate molecules for chemopreventive agents. In this review, we summarize new findings regarding experimental data and clinical trials for the chemoprevention of colorectal cancer.

ANIMAL MODEL OF COLORECTAL CANCER

It is very important to use an animal model for the evaluation of chemopreventive agents against colorectal carcinogenesis. There are two kinds of rodent model for colorectal cancer. One is the model of chemical carcinogenesis employing carcinogens such as azoxymethane, 1, 2-dimethylhydrazine (DMH), N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG), etc. Of these, the azoxymethane model is

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the most widely used as a model of sporadic colorectal carcinogenesis, and is reportedly very similar to human colorectal cancer in terms of the clinical symptoms, clinical course, and pathological findings (2). The other one is the genetic model harboring gene mutations such as APC, p53, etc. The Min mouse and Apc delta716 knockout mouse, both of which have APC mutations, are also used worldwide (3, 4).

In 1987, Bird reported a tiny lesion consisting of large, thick crypts in a methylene blue-stained specimen of the colon from mice treated with azoxymethane, and suggested to be a precursor lesion of colorectal cancer in the animal model (5). Then, abundant evidence was reported to support that aberrant crypt foci (ACF) are a precursor lesion of colorectal cancer. Thus, ACF are often used as a target lesion to test chemopreventive effects in animal models of colorectal carcinogenesis.

CHEMOPREVENTIVE AGENTS AND TARGET MOLECULES

Recent progress in the molecular analysis of colorectal cancer has made it possible to target a specific molecule for chemoprevention (6). Many promising target molecules have been reported so far (Table 1). These can be mainly classified into 3 categories based on the mechanism : 1) signal transduction modulation, 2) epigenetic modulation, and 3) anti-inflammatory modulation.

1) Signal transduction modulator

The signal transduction pathway has been searched for a long time as a target of chemotherapy and chemoprevention. EGF receptor inhibitors (Erlotinib, etc.), anti-EGF receptor antibody (Cetuximab), and anti-VEGF antibody (Bevacizumab) are well-known as therapeutic agents for cancer and commonly used worldwide (7). Although these agents have not yet been applied to chemoprevention, they themselves or their analogues may be put to practical use as chemopreventive agents of colorectal cancer in the future. Since mutations of K-ras and p53 are frequently observed in colorectal cancer, their oncogenic pathway is a possible target. Anti-ras agents such as Tipifarnib and perilyl alcohol, and anti-p53 agents such as CP31398 have been reported to inhibit colorectal carcinogenesis in animal models (8). Other signal transduction modulators targeting Bcl-2, ODC, GST-pi, etc., have also been examined for their chemopreventive effect on colorectal cancer.

2) Epigenetic modulation

It is well known that peroxisome proliferator-activated receptor (PPAR)-γ and -δ play a role in the

Table 1 Candidate of chemopreventive agents and target molecules for colorectal cancer

Mechanism	Target	Agents
Signal transduction modulation	EGF receptor	Cetuximab, Erlotinib
	Bcl-2	ABT-737
	Ras	Tipifarnib, Perillyl alcohol
	p53	CP31398
	Matrixmetalloproteinases	Marimistat, Prinomastat
	ODC	DFMO, NSAIDs, Retinoids
	VEGF/VEGF receptor	Bevacizumab
	GST-pi	HGBP, TLK119
Epigenetic modulation	Peroxisome proliferator activated receptor(PPAR)	Rosiglitazone, Pioglitazone
	Vitamin D	Vitamin D3 analogue
	ER-β	Resveratorol, TAS-108
	Histone deacetylase	SAHA
	Retinoic acid receptor	Retinoids
Anti-inflammation	COX-2	NSAIDs, Celecoxib, Etodorac
	EP1-4	ONO-8711
	NF-κB	Bortezomib, Curcumin, Tea polyphenols, Statins, NSAIDs

process of colorectal carcinogensis. Of these, PPAR-γ agonists such as rosiglitazone and pioglitazone reportedly inhibit the formation of colorectal cancer in animal models (9). Currently, they are being tested in human trials. There are some studies in which vitamin D inhibited the development of colorectal adenoma and cancer. Other epigenetic modulators including ER-β, histone deacetylase, and retinoic acid receptor have been reported to be potential chemopreventive agents in animal models.

3) Anti-inflammatory modulation

Cyclooxygenase-2 (COX-2) is reportedly overexpressed in colorectal adenoma and cancer of rodents and humans. It is also reported that COX-2 promotes the cell growth and inhibits apoptosis of colorectal epithelia. When an Apc delta716 knockout mouse, a model of human familial adenomatous polyposis, was crossed with a COX-2 knockout mouse, the number and size of intestinal polyps were markedly reduced (10). Moreover, there are many studies showing that selective COX-2 inhibitors suppressed colorectal adenoma and cancer. Thus, the efficacy of targeting the COX-2 molecule for chemoprevention was theoretically confirmed in animal models. There are also many other anti-inflammatory agents including EP1-4 and NF-κB currently under investigation.

CLINICAL TRIAL FOR CHEMOPREVENTION

Representative human chemopreventive trials are shown in Table 2. They are mainly classified into 3 categories according to the target lesion. The first one is a trial that targets a pre-existing polyp. Giardiello, *et al.* reported that sulindac significantly suppressed the number and size of polyps in familial adenomatous polyposis patients in 1993 (11). This study prompted investigators to conduct a trial to examine whether or not sulindac suppresses sporadic polyps. However, it did not significantly suppress the number or size of the polyps (12). This trial revealed that a pre-existing polyp is not necessarily an appropriate target for chemoprevention; a large polyp close to a cancer may not be able to respond to chemopreventive agents. Thus, chemoprevention targeting the development of a new polyp in polypectomized patients was conducted thereafter. Several randomized trials showed that aspirin inhibited the development of polyps. Since COX-2 was shown to be a good target molecule for chemoprevention in animal experiments, as noted above, two large-scale randomized clinical trials using a selective COX-2 selective inhibitor (celecoxib) were performed. Arber, *et al.* reported that celecoxib (400 and 800 mg/day) significantly reduced the new development of

Table 2 Representative chemopreventive studies for colorectal cancer

	Sporadic/FAP	Agents	Period	Results	Author
Pre-existing polyp					
	FAP	Sulindac	4 yr	No change	Giardiello, *et al.* (2002)
	FAP	Celecoxib	6 mo	30% reduction	Steinbach, *et al.* (2000)
	Sporadic	Sulindac	4 mo	No change	Ladenheim, *et al.* (1995)
	FAP	Sulindac	9 mo	65% reduction	Giardiello, *et al.* (1993)
Development of new polyp					
	Sporadic	Celecoxib	3 yr	38% reduction	Bertagnolli, *et al.* (2006)
	Sporadic	Celecoxib	3 yr	35% reduction	Arber, *et al.* (2006)
	Sporadic	Aspirin	1 yr	37% reduction	Sandler, *et al.* (2003)
	Sporadic	Aspirin	1~3 yr	17% reduction	Baron, *et al.* (2003)
	Sporadic	Calcium	4 yr	15% reduction	Baron, *et al.* (1999)
Development of cancer					
	Sporadic	Vitamin D Calcium	6 yr	32% reduction No change	Martinez, *et al.* (1996)
	Sporadic	Vitamin D Calcium	4 yr	26% reduction No change	Bostick, *et al.* (1993)
	Sporadic	Folic acid	6 yr	31% reduction	Giovannucci, *et al.* (1993)

adenoma compared to a placebo group (13). Bertagnolli, *et al.* also reported that celecoxib (400 and 800 mg/day) significantly reduced the development of adenoma in a different large-scale trial (14). However, in these trials, severe cardiovascular events including myocardial infarction and stroke occurred in about 20% of cases. Therefore, it is considered that the COX-2 inhibitor is an effective agent for the prevention of colorectal cancer, but it cannot be recommended for chemoprevention because of potential cardiovascular events.

The third one is a trial that targets the development of cancer. This kind of trial is theoretically ideal because it examines if each agent indeed suppresses the development of cancer itself. However, it takes more than 4 years, and prolongation of the trial sometimes causes severe side effects and poor compliance.

CHEMOPREVENTION TARGETING ACF

Since ACF are the earliest precursor lesions of colorectal cancer (15, 16), they would be an appropriate target for chemoprevention (Fig. 1). The advantages of using ACF as targets over a polyp and cancer are as follows : (1) short-term treatment for evaluation, (2) fewer complications caused by drugs, and (3) good compliance. Thus, we performed an open trial in which sulindac was administered for various periods to subjects positive for ACF. The results showed that the majority of ACF were eradicated after only a few months. Based on this, we next performed a randomized double-blind trial targeting ACF consisting of groups receiving sulindac, etodolac (a selective COX-2 inhibitor), or a placebo. The detailed results of this study will be clarified in the near future.

EPILOGUE

Many candidate agents for chemoprevention are currently being tested, and some of them have actually shown potential chemopreventive activity in human trials. Although the COX-2 inhibitor failed to be a major chemopreventive agent, other effective new agents will be identified in the near future.

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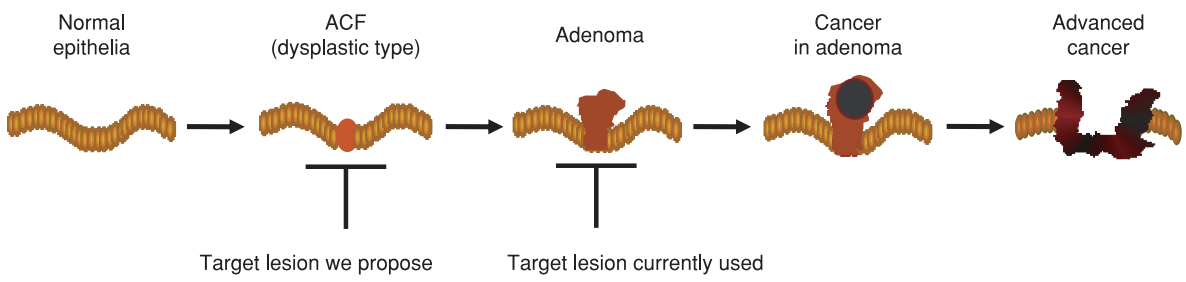

Figure 1 Colorectal carcinogenesis and target lesions for chemoprevention. In the majority of chemopreventive studies performed so far, adenoma has been used as a target lesion for evaluation. We propose the use of aberrant crypt foci (ACF), an earlier lesion, as a target. This makes it possible to evaluate the effect of a chemoprevenitve agent within a shorter period.

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