Available online at www.sciencedirect.com
SCIENCE DIRECT
Biochimica et Biophysica Acta 1765 (2006) 14 – 24
BIOCHIMICA ET BIOPHYSICA ACTA
BBA
http://www.elsevier.com/locate/bba

Review

β-catenin-mediated signaling: A novel molecular target for chemoprevention with anti-inflammatory substances

Joydeb Kumar Kundu [a], Kang-Yell Choi [b], Young-Joon Surh [a,*]

[a] *National Research Laboratory of Molecular Carcinogenesis and Chemoprevention, College of Pharmacy, Seoul National University, Shinlim-dong, Kwanak-ku, Seoul 151-742, South Korea*
[b] *Department of Biotechnology, Yonsei University, Seoul 120-752, South Korea*

Received 17 October 2004; received in revised form 16 August 2005; accepted 23 August 2005
Available online 7 September 2005

Abstract

Inflammation is thought to play a role in the pathophysiology of cancer. Accumulating evidence from clinical and laboratory-based studies suggests that substances with anti-inflammatory activities are potential candidates for chemoprevention. Recent advances in cellular and molecular biology of cancer shed light on components of intracellular signaling cascades that can be potential molecular targets of chemoprevention with various anti-inflammatory substances. Although cyclooxygenase-2, a primary enzyme that mediates inflammatory responses, has been well recognized as a molecular target for chemoprevention by both synthetic and natural anti-inflammatory agents, the cellular signaling mechanisms that associate inflammation and cancer are not still clearly illustrated. Recent studies suggest that β-catenin-mediated signaling, which regulates developmental processes, may act as a potential link between inflammation and cancer. This review aims to focus on β-catenin-mediated signaling pathways, particularly in relation to its contribution to carcinogenesis, and the modulation of inappropriately activated β-catenin-mediated signaling by nonsteroidal anti-inflammatory drugs and chemopreventive phytochemicals possessing anti-inflammatory properties.

Keywords: Chemoprevention; β-catenin-mediated signaling; Cyclooxygenase-2; NSAID; Chemopreventive phytochemical

Contents

* Corresponding author. Tel.: +82 2 880 7845; fax: +82 2 874 9775.
E-mail address: surh@plaza.snu.ac.kr (Y.-J. Surh).

0304-419X/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbcan.2005.08.006

1. Introduction

Chemoprevention is a non-invasive and cost-effective strategy in reducing cancer associated morbidity and mortality. The term 'chemoprevention' refers to the use of non-toxic substances to delay, reverse or suppress multistage carcinogenesis [1]. In spite of immense advances in the understanding of pathophysiology of cancer and development of new anticancer therapies, the mortality resulting from common forms of cancer is still unacceptably high. Chemoprevention offers a unique scope to intervene in each stage of carcinogenesis by a wide variety of substances of either natural or synthetic origin [1]. As inflammation is causally linked to cancer [2], substances with potent anti-inflammatory activities are anticipated to exert chemopreventive effects. Recent progress in unraveling intracellular signaling networks that contribute to multistage carcinogenesis has made it possible to identify signal transducing molecules or events as potential targets for chemoprevention [1].

Although enzymes mediating inflammatory response such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) have been identified as molecular targets for the prevention of cancer by anti-inflammatory substances [3], cellular signaling network linking inflammation and carcinogenesis has not been fully elucidated. Recently, activation of a eukaryotic transcription factor nuclear factor-κB (NF-κB) has been recognized as a bridge between inflammation and cancer [2]. Besides NF-κB, the activation of an evolutionarily conserved signaling pathways amplified by soluble Wnt ligands, which are secreted by activated macrophages [4], has been implicated in creating such a link. An inappropriate activation of Wnt-signaling contributes to cellular proliferation through up-regulation of T Cell Factor (TCF)/β-catenin-regulated transcription of various proliferative genes [5].

Chronic inflammation-associated accumulation of β-catenin in prostate cancer suggests that β-catenin may act as a potential link between inflammation and cancer [6]. β-catenin has been shown to function as a signaling molecule involved in the process of development, proliferation and differentiation [7]. Multiple lines of evidences suggest that stabilization and subsequent nuclear accumulation of β-catenin are positively linked to various human malignancies [5,8–11]. Several recent studies have also demonstrated β-catenin as a putative regulator of COX-2 [12–14], suggesting β-catenin as a potential target for chemoprevention by anti-inflammatory substances. The present review focuses on the modulation of β-catenin-mediated signaling as a plausible mechanism of chemoprevention by various anti-inflammatory substances.

2. An overview of the β-catenin-mediated signaling pathway

2.1. Migration of membrane-bound β-catenin to cytosol

The multifunctional protein β-catenin exists in different subcellular locations depending upon physiological conditions or cellular environment including cell density [15], types of cells [16,17], interaction with other signaling molecules [18–20], disease status [21–23], etc. While the membrane bound β-catenin interacts with the cytosolic tail of E-cadherin and connects actin filaments through α-catenin to form cytoskeleton, the free cytosolic form predominantly participates in cellular signaling [24,25] (Fig. 1). The interaction between β-catenin and E-cadherin is vulnerable to dissociation either by a point mutation of the phosphorylation site on the cytosolic domain of E-cadherin or tyrosine phosphorylation of β-catenin [26–28]. The tyrosine phosphorylation of β-catenin appears to be mediated via the activation of receptor tyrosine kinases like the extracellular growth factor (EGF) receptor [29] or cytoplasmic tyrosine kinases including Src [30]. The inhibition of constitutive- and Wnt1-induced activation of β-catenin signaling in human colon cancer and embryonic kidney (HEK293) cells, respectively, by a tyrosine kinase inhibitor

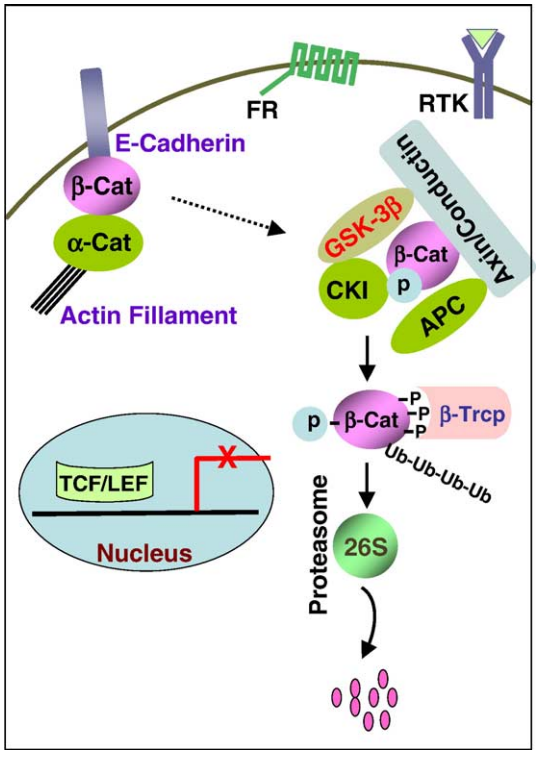

Fig. 1. A β-catenin degradation pathway. β-catenin exists in cells in two distinct pools, one being a major membrane-bound form that links E-cadherin and actin filaments to form cytoskeleton and the other being a free cytosolic form. Membrane-bound β-catenin may be released into cytosol by tyrosine phosphorylation of β-catenin [26–28], or by nitric oxide releasing drugs or MMPs through dissociation of cadherin–catenin complex [32]. In unstimulated cells, the free cytosolic β-catenin undergoes proteasomal degradation via phosphorylation and subsequent ubiquitination [144]. Because of such cytosolic degradation, β-catenin does not translocate to nucleus where β-catenin interacting partner TCF remains repressed by binding with transcriptional repressors. Cytoplasmic β-catenin is first phosphorylated at serine 45 residue by casein kinase I (CKI) [35–38] and subsequently at serine-33/-37 and threonine 41 residues by GSK-3β, a member of a multiprotein complex consisting of APC, GSK-3β and scaffold protein Axin/Conductin. Phosphorylated β-catenin is recognized by the ubiquitin ligase βTrcp followed by degradation via the 26S proteasomal system [44,45]. Both APC and Axin play crucial role in this process by binding with different arm repeats of β-catenin, facilitating GSK-3β-mediated phosphorylation of β-catenin [33,34,39]. β-Cat, β-Catenin; α-Cat, α-Catenin.

STI-571 further indicates that tyrosine phosphorylation of β-catenin may facilitate β-catenin-mediated signaling [31]. In addition, the dissociation of E-cadherin-β-catenin complex may be facilitated by nitric oxide-releasing drugs, through the activation of matrix metalloproteinases (MMPs) thereby enriching the cytosolic pool of β-catenin [32].

2.2. Cytosolic degradation of β-catenin

It has been reported that free cytoplasmic β-catenin undergoes the rapid turnover by a large multiprotein complex consisting of glycogen synthase kinase-3β (GSK-3β), adenomatous polyposis coli (APC) and Axin/Conductin [33,34]. The β-catenin is phosphorylated at serine 45 residue by casein kinase (CK)-I [35–38] and subsequently at serine-33/-37 and threonine 41 residues by GSK-3β [33,39,40]. The phosphorylation of β-catenin at serine-45 residue by CK-I makes β-catenin a better substrate for GSK-3β [35–38] (Fig. 1).

The tumor suppressor protein APC can also bind to β-catenin and promotes its degradation [34,41,42]. The association of β-catenin with APC appears to be dependent on the phosphorylation of APC by GSK3β [33,43]. Phosphorylated β-catenin is ubiquitinated by cellular β-transducin repeat-containing proteins (β-Trcp) and subsequently degraded by 26S proteasomes [44,45].

2.3. Mechanisms of β-catenin stabilization

β-catenin needs to be stabilized in the cytoplasm to act as a component of the cellular signaling network (Fig. 2). The genetic mechanism of β-catenin stabilization involves the mutation of β-catenin gene (*ctnnb1*) and/or the mutational change of its regulatory partners such as APC or Axin [46–50]. While mutation of *ctnnb1* has been reported to cause β-catenin stabilization [51–55], an extensive body of data suggests that elevated expression of β-catenin and its nuclear localization may occur without any significant mutational changes in *ctnnb1* [56–60]. According to a study by Li et al. [61], mutations of *ctnnb1* is highly prevalent in rat colon tumors but less common in rat hepatomas, suggesting that the *ctnnb1* mutations occur in a tissue- or organ-specific manner. Besides stabilization of β-catenin as a consequence of mutational alterations involving a gain of function of *ctnnb1* or a loss of function of *APC*, the protein may be stabilized by epigenetic mechanisms through the inactivation of the upstream regulator GSK-3β which results from phosphorylation of its serine-9 residue.

2.4. Regulation of gene transcription by β-catenin-mediated signaling

Once stabilized in cytoplasm, β-catenin translocates into the nucleus and interacts with TCF/Lymphoid Enhancer Factor (LEF), a family of high mobility group (HMG) Box proteins capable of binding to DNA in a sequence-specific manner but lacking intrinsic transactivation potential [62]. In unstimulated cells, TCFs remain under repression through interaction with

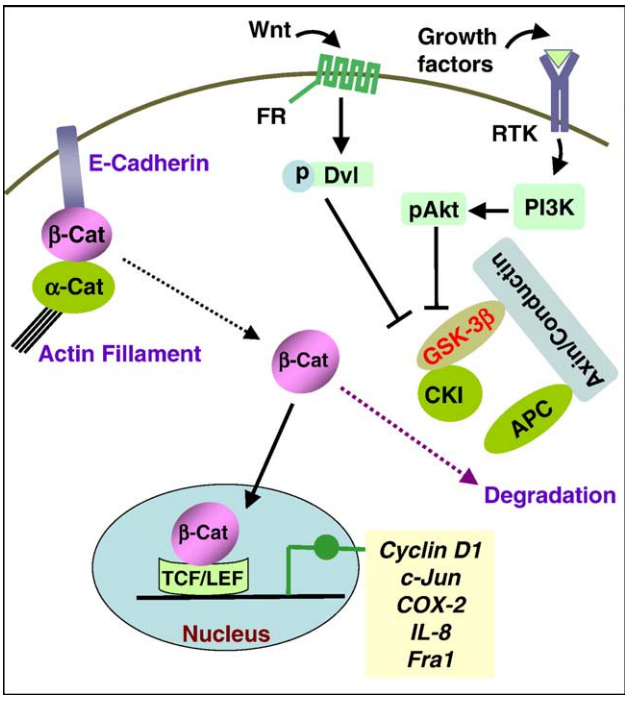

Fig. 2. Mechanisms of β-catenin stabilization. β-Catenin is stabilized by several mechanisms including inactivation of GSK-3β, mutation of APC or Axin [46–48,50], etc. Upon exposure of cells to soluble Wnt ligands, which interact with frizzled receptor (FR), recruits a small phosphoprotein deshevelled (Dvl) that inactivates GSK-3β [78]. Stabilized β-catenin translocates to the nucleus, where it binds to TCF/LEF thereby regulating transcription of target genes [5]. On the other hand, stimulation of cells with growth factors leads to receptor tyrosine kinase (RTK)-mediated activation of the PI3K-Akt pathway. PI3K-mediated phosphorylation of Akt induces to inactivation of GSK-3β through serine-9 phosphorylation, thereby causing stabilization of β-catenin [145]. Solid line: signaling upon stimulation; Dotted line: signaling during unstimulated condition.

transcriptional co-repressors such as groucho and histone deacetylase (HDAC) [63,64]. It has been proposed by Billin and collaborators [63] that the activation of LEF1-dependent genes by β-catenin in HEK293 cells involves a two step mechanism, the first being attenuation of the enzymatic activity of HDAC1 by β-catenin resulting in the derepression of LEF1 followed by the binding of β-catenin to free LEF1 (Fig. 2).

Nuclear localization of β-catenin and subsequent formation of the β-catenin-TCF/LEF transcription complex cause enhanced transcription of a variety of genes (Fig. 2) encoding proteins involved in such processes as cell cycle regulation, cell adhesion and cellular development [5,65]. Genes that undergo β-catenin/TCF-mediated transactivation include *c-myc*, *cyclin D1* [66], *gastrin* [67], *MMP-7* [68], *keratin1* [69], urokinase plasminogen activated receptor (*uPAR*) [70], *CD44* [71], immunoglobulin transcription factor-2 (*ITF-2*) [72], *PPARδ* [73] and *Fra-1* [70]. Recently, the activation of β-catenin/TCF signaling has been shown to regulate transcriptional activation of some other genes including an orphan G-protein coupled receptor Gpr49 [74] and membrane-type *MMP* [75]. By analyzing β-catenin-induced alterations of gene expression after transduction of either dominant stable β-catenin or its transactivation-deficient counterpart in primary human hepato-

cytes, Levy et al. [69] have demonstrated that *IL-8* promoter contains a unique consensus for the TCF binding site that is critical for IL-8 activation by β-catenin. Moreover, the existence of a TCF binding element (TBE) in the *COX-2* promoter region raises the possibility of β-catenin to regulate COX-2 expression [12,13], which is down-regulated by a variety of anti-inflammatory substances.

3. Role of β-catenin-mediated signaling in carcinogenesis

Accumulating data from both in vitro and in vivo studies suggest the implication of β-catenin-mediated signaling in tumorigenesis [76–80]. Cytosolic stabilization and subsequent nuclear translocation of β-catenin resulting in transcriptional activation of a variety of TCF-regulated proliferative genes and oncogenes appear to be a potential cause of various human cancers [5,9,10,78,81–85]. The contributory role of aberrant β-catenin signaling, as a consequence of *ctnnb1* gene mutation, has been documented in various cancers including colon carcinoma [86–88], hepatocellular carcinoma [89–91], rat hepatic carcinoma [92], human uterine endometrial carcinoma [51,53,93,94], pituitary adenoma [95], and cancers of prostate [54], ovary [96,97] and urinary bladder [52]. The involvement of β-catenin signaling, without any appreciable alterations in *ctnnb1* gene, has also been observed in urothelial carcinomas [60], pilomatricomas [56] and rectal carcinomas [57]. While several studies have revealed that mutations in *ctnnb1* frequently occurs in melanoma [98] and lungs carcinoma [99], other studies report *ctnnb1* mutation as a rare event in these cancers [58,59].

As a regulator of intracellular signaling network involved in oncogenic process, activated β-catenin signaling favors cellular proliferation as well as exerts anti-apoptotic effects in various cancers [100]. In a recent study, β-catenin positive hepatocellular carcinoma derived from phenobarbital-treated *c-myc*/transforming growth factor-α transgenic mice displayed increased proliferation and the tumor size [101]. Similarly, a correlation between nuclear expression of β-catenin and an increased incidence and the size of tumors in patients with hepatocellular carcinoma suggests that altered expression of β-catenin in hepatocellular carcinoma may promote malignant progression by stimulating tumor cell proliferation [102]. According to Shang et al. [103], mutant β-catenin may promote proliferation and survival ability of the immortalized murine hepatocyte cell line AML12, but stabilized β-catenin that mediates enhanced expression of c-myc and cyclin D1 is not sufficient to cause complete oncogenic transformation. Several studies have documented a positive correlation between β-catenin accumulation and cancer cell proliferation [91,104–107]. Stimulation of Wnt signaling by the Wnt3a, LiCl or constitutively active S33Y mutant β-catenin resulted in an increased proliferation of multiple myeloma cells [104]. The overexpression of E2F1 activity and a loss of p53- and p27-dependent cell cycle checkpoints were attributed to the enhanced proliferation of non-small cell lung cancer by activated β-catenin signaling [105].

A significant correlation between nuclear accumulation of β-catenin and high proliferation rates of soft tissue sarcomas [106], hepatocellular carcinoma [91] and basal cell carcinoma [107] was also reported. Although the accumulation of β-catenin was observed in 62 % of rat oral epithelial dysplasia induced by 4-nitroquinoline-1-oxide, there was no significant difference in β-catenin protein expression [50]. While analyzing the β-catenin abundance and its target gene expression in transmissible murine colonic hyperplasia, Sellin et al. [108] observed a significant alterations in subcellular distribution of β-catenin and increased cellular levels of β-catenin target genes, such as *c-myc* and *cyclin D1*. A wide variety of anti-inflammatory substances have been shown to inhibit nuclear accumulation of β-catenin and expression of its target genes (e.g., *c-myc*, *cyclin D1*, *c-Jun*, etc.) thereby eliciting anti-proliferative effects [109–112].

4. Down-regulation of inappropriately activated β-catenin-mediated signaling by anti-inflammatory substances

Since inflammation is causally linked to carcinogenesis, substances with potent anti-inflammatory activities are anticipated to exert chemopreventive effects [1,113]. Accumulating evidence from epidemiologic, clinical and laboratory studies suggests that nonsteroidal anti-inflammatory agents (NSAIDs) as well as naturally occurring anti-inflammatory substances are able to prevent certain forms of cancers [114,115]. Progress in the understanding of molecular mechanisms of chemoprevention by anti-inflammatory substances led to the identification of several molecular targets including COX-2 [3,116]. Various molecules of intracellular signaling cascades regulating COX-2 are targeted by a wide variety of anti-inflammatory substances. These include a distinct set of transcription factors such as NF-κB, activator protein 1 (AP-1), cyclic AMP response element binding protein (CREB), CCAAT/enhancer binding protein (CEBP), Ets transcription factors, etc. and their upstream kinases [1,117]. Depending on the types of stimuli or cells, anti-inflammatory substances exert chemopreventive activity by down-regulating COX-2 induction through blockade of the activation of either a single or a combination of transcription factors and related upstream kinases.

4.1. β-catenin as a putative upstream regulator of COX-2

As mentioned earlier, molecular mechanisms of chemopreventive activities of many anti-inflammatory agents have been ascribed to their inhibitory effects on COX-2 expression through down-regulation of the transcription factors such as NF-κB, AP-1, and their up-stream kinases, known as mitogen-activated protein kinases (MAPKs) or other kinases involved in the PI3K/Akt signaling pathway [1]. However, recent studies suggest that the expression of COX-2 may be regulated by the β-catenin/TCF-mediated signaling. The first indication of an interaction between COX-2 and β-catenin pathways came from studies utilizing *APC*-mutant mice, which showed an elevated

level of COX-2 in intestinal polyps, whereas a null mutation of the COX-2 gene reduced the number and the size of intestinal tumors [118]. Since *APC* mutation leads to the stabilization and nuclear translocation of β-catenin, the reduction of COX-2 protein expression upon addition of wild-type *APC* to the *APC*-mutated HT-29 human colorectal cancer cells [14] and an increase in basal COX-2 protein and mRNA levels upon overexpression of β-catenin in murine mammary cell lines [119] indicate the functional relationship between the β-catenin signaling pathway and COX-2 expression. Howe et al. [119] have also suggested that overexpression of Wnt-1 in mouse mammary epithelial cells may result in significant up-regulation of COX-2 through the activation of polyoma enhancer activator-3 (PEA3), an Ets transcription factor regulating *COX-2*.

Correlating the up-regulation of COX-2 and nuclear accumulation of β-catenin in human colorectal cancer cells characterized by the mutation of *APC* gene, Dimberg et al. [120] have suggested that COX-2 is a down-stream target of the APC/β-catenin/TCF pathway. Further evidence for the regulation of the expression of COX-2 by β-catenin has been reported by Kim and colleagues [121], who demonstrated that the treatment of rabbit articular chondrocytes with interleukin-1β (IL-1β) increased expression of COX-2. The IL-1β treatment also induced nuclear accumulation of β-catenin, which has been further aggravated by the treatment of cells with the GSK-3β inhibitor or the proteasome inhibitor. These results indicate that transcriptionally active β-catenin is sufficient to induce COX-2 expression. The transcriptional regulation of COX-2 by β-catenin has also been supported by the study of Araki and colleagues [12], who demonstrated that the COX-2 promoter contains TCF binding element (TBE) and that COX-2 was down-regulated after induction of full length APC in the human colorectal HT29-APC cell line. The same study also revealed that COX-2 promoter luciferase activity has been down-regulated by APC in a promoter reporter construct containing wild type TBE but not with mutant TBE, suggesting that COX-2 is down-regulated by APC and up-regulated by nuclear accumulation of β-catenin.

4.2. β-catenin is a target of NSAIDs retaining anticarcinogenic potential

Emerging evidence supporting the transcriptional regulation of COX-2 by β-catenin-mediated signaling has led to the exploration of β-catenin as a molecular target for chemoprevention by anti-inflammatory agents (Fig. 3). Various NSAIDs have been shown to decrease the β-catenin/TCF-mediated signaling (Table 1) [122]. Dihlmann et al. [109] demonstrated that the treatment of human colon carcinoma cells either with indomethacin or aspirin resulted in a decrease in β-catenin/TCF transcriptional activity and cyclin D1 expression without disrupting the β-catenin/TCF complex [109]. Dihlmann and colleagues [123] also demonstrated that treatment of human colon cancer (SW480 and SW948) cells with aspirin resulted in the phosphorylation-dependent degradation of β-catenin, but aspirin-induced degradation of β-catenin in HEK293 cells was

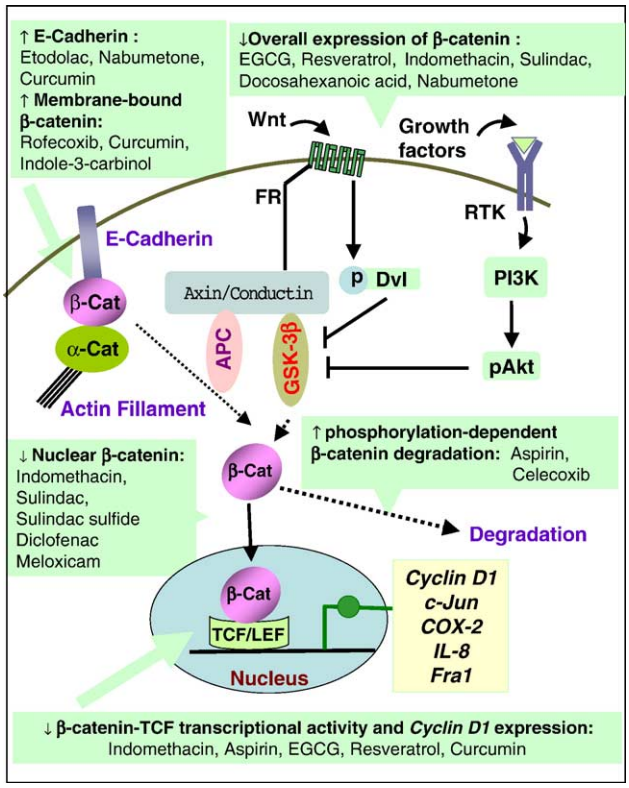

Fig. 3. Modulation of aberrant β-catenin mediated signaling by anti-inflammatory substances. Anti-inflammatory substances may exert chemopreventive effects by blocking β-catenin-mediated signaling through several possible mechanisms, such as increase in E-cadherin expression resulting in an elevated pool of membrane-bound β-catenin, restoration of GSK-3β activity by blocking PI3K/Akt- or Wnt/Dvl-mediated inactivation of GSK-3β, promoting proteasomal degradation of β-catenin, preventing nuclear translocation of β-catenin, and blocking formation of β-catenin-TCF/LEF complex and/or its DNA binding.

independent of β-catenin phosphorylation. Similarly, an increased turn over of β-catenin during apoptosis of human colorectal cancer HCT-116 cells has been reported by Lee et al. [124]. A decrease in the expression of β-catenin and cyclin D1 in various colorectal cancer cells [110,125] and down-regulation of DNA binding of β-catenin/TCF in SW480 and HCT116 cells [125] by indomethacin have been demonstrated. Recently, Boon et al. [126] demonstrated that treatment with sulindac for 6 months significantly lowered nuclear accumulation of β-catenin in adenomas from patients with familial adenomatous polyposis (FAP) in comparison to their pretreatment states. Similarly, a decrease in nuclear accumulation of β-catenin was evident during sulindac-induced regression of intestinal tumors, but not colon tumors, in Min^{+} mice [127].

The chemoprevention of rat colorectal cancer by indomethacin, meloxicam or sulindac has been attributed to the diminished nuclear β-catenin immunoreactivity induced by these agents [128]. Indomethacin inhibited proliferation, induced G1 arrest and promoted apoptosis in both COX-2 expressing (HT29, HCA-7, SW480 and HCT116) and COX-2-negative (SW480 and HCT116) human colorectal cancer cells [129]. The drug also diminished β-catenin protein expression suggesting that the down-regulation of β-catenin-mediated

Table 1
Modulation of β-catenin-mediated signaling by NSAIDs

NSAIDs	Effect on β-catenin-mediated signaling	Cell/Tissue	References
Indomethacin	↓ Nuclear β-catenin immunoreactivity	Rat colorectal tumors	[128]
	↓ Nuclear β-catenin content, ↓ cyclin D1 protein expression	SW480 cells	[110]
	↓ β-catenin protein expression	HT-29, HCA-7, SW480, HCT116 cells	[129]
	↓ Expression of β-catenin and cyclin D1, ↓ β-catenin/TCF DNA binding, ↑ c-Myc expression	SW480 and HCT116 cells	[125]
	No alterations in subcellular distribution of β-catenin, No change in β-catenin/TCF DNA binding, ↓ β-catenin/TCF activity	SW948 cells	[109]
	↓ Cyclin D1 protein expression	SW480, HCT116, LoVo cells	[109]
Sulindac	↓ Nuclear β-catenin immunoreactivity	Rat colorectal tumors	[128]
	APC-independent increase in β-catenin/TCF activity	SW620 colon cancer cells	[135]
	↓ Nuclear β-catenin	Adenoma from FAP patients	[126]
	↑ Membrane bound β-catenin in intestinal polyp	$APC^{\Delta 716}$ mice	[118]
	↓ Immunoreactivity of β-catenin	Min^{+} mice	[127]
Sulindac sulfide	↓ Nuclear β-catenin content, ↓ cyclin D1 protein expression	SW480 cells	[110]
	↓ Phosphorylated β-catenin level, ↓ Met and cyclin D1 protein expression, ↓ β-catenin/TCF activity	DLD1 and SW480 cells	[126]
Aspirin	No alterations in subcellular distribution of β-catenin, No change in β-catenin/TCF DNA binding,	SW948 cells	[109]
	↓ Cyclin D1 protein expression	SW480, HCT116, LoVo cells	[109]
	↓ β-catenin/TCF dependent transcription, ↑ Phosphorylation and degradation of β-catenin, ↑ Phosphorylation-independent degradation of β-catenin	SW480 cells	[123]
	↑ Degradation of β-catenin	HCT116 cells	[124]
Rofecoxib	↑ Membrane bound β-catenin in intestinal polyp	$APC^{\Delta 716}$ mice	[118]
	No alterations of β-catenin content and cyclin D1 Expression	SW480 cells	[110]
Diclofenac	↓ Nuclear β-catenin content, ↓ cyclin D1 protein expression, No correlation between inhibition of cyclin D1 and TCF activity	SW480 cells	[110]
Celecoxib	No alterations in β-catenin immunoreactivity	Rat colorectal tumors	[128]
	↓ Frequency and multiplicity of β-catenin accumulated crypts, ↓ nuclear β-catenin staining	AOM-induced aberrant Crypt foci in F344 rats	[132]
	↑ Caspase- and proteasome-dependent degradation of β-catenin	Caco-2 cells	[133]
Meloxicam	↓ Nuclear β-catenin immunoreactivity	Rat colorectal tumors	[128]
Etodolac	↑ Expression of E-cadherin protein and its mRNA transcript, No change in β-catenin expression	Caco-2 cells	[146]
Nabumetone	↓ β-catenin protein expression, ↑ Expression of E-cadherin and GSK-3β in uninvolved intestinal mucosa	MIN Mouse	[147]
	↓ Expression of cyclin D1 and nuclear β-catenin, ↑ Expression of E-cadherin and GSK-3β in uninvolved intestinal mucosa	AOM-treated rat	[147]

signaling may be attributed to the antiproliferative/chemopreventive activity of COX-2 inhibitors [129]. More recently, indomethacin was reported to inhibit growth of human colon cancer cells HT29, which was accompanied by an enhanced expression of APC and E-cadherin, and a marked increase in the relocation of nuclear and cytoplasmic β-catenin to the cell membrane [130]. A potent selective COX-2 inhibitor celecoxib has been found to suppress β-catenin-accumulated crypts in premalignant lesions of rat colonic epithelium [131]. While celecoxib decreased 1,2-dimethylhydrazine-induced adenoma and colon carcinoma formation in rats without any appreciable change in β-catenin immunoreactivity [128], it prevented the multiplicity of β-catenin-accumulated crypts with decreased immunostaining for nuclear β-catenin in azoxymethane-induced aberrant crypt foci in F344 rats [132] A COX-2-independent mechanism of chemoprevention of colorectal cancer by celecoxib has recently been reported [133]. According to this study, treatment of Caco-2 human colon cancer cells with celecoxib resulted in a caspase- and proteasome-dependent degradation of β-catenin [133]. Another COX-2 selective NSAID rofecoxib enriched the membrane-bound β-catenin level in polyps from $APC^{\Delta 716}$ mice [118], but the compound did not cause any change in the levels of β-catenin or cyclin D1 in SW480 cells [110]. The modulation of β-catenin-mediated signaling by other NSAIDs such as meloxicam, diclofenac, etodolac, and nabumetone is summarized in Table 1.

4.3. Suppression of β-catenin-mediated signaling by chemopreventive phytochemicals

Anti-inflammatory phytochemicals present in our daily diet have been known to possess chemopreventive potential. Examples are curcumin from turmeric, epigallocatechin gallate (EGCG) from green tea, resveratrol from grapes, docosahexanoic acid from fish oil, sulforaphane from broccoli, indole-3-carbinol from cabbage, genistein from soybean, etc. [1]. Besides NSAIDs, many of these dietary anti-inflammatory substances target β-catenin-mediated signaling in exerting chemopreventive effects [1,134] (Table 2, Fig. 3). Although an early study reported that curcumin had no inhibitory effect on β-catenin/TCF activity in SW480 colon cancer cells [135], the compound

Table 2
Modulation of β-catenin-mediated signaling by chemopreventive phytochemicals

Phytochemicals	Effect on β-catenin-mediated signaling	Cell/Tissue	References
EGCG	↓ β-catenin/TCF transcriptional activity, ↓ Expression of β-catenin and cyclin D1, No change in TCF-4 expression	HEK293 cells	[148]
White tea/Green tea	↓ Expression of β-catenin, cyclin D1 and c-Jun	C57BL/6J-APC (*Min*$^{+}$) mice intestinal tumor	[112]
Sulforaphane	↑ β-catenin responsive reporter activity ↓ HDAC activity, No change in expression of β-catenin and HDAC protein expression	HEK293 and HCT116 cells	[149]
Resveratrol	↓ β-catenin and cyclin D1 expression, ↓ cyclin D1 promoter activity, ↓ cyclin D1 mRNA	SW480 cells	[111]
Curcumin	↓ β-catenin/TCF DNA binding and transcriptional activity, ↓ c-Myc protein expression, ↑ caspase-mediated cleavage of β-catenin,	HCT116 cells	[136]
	No alterations in β-catenin/TCF activity	SW620 cells	[135]
	Restoration of E-cadherin and β-catenin	Transgenic adenocarcinoma of mouse prostate model	[150]
Indole-3-carbinol	↑ E-cadherin and β-catenin level	MCF-7 and MDA-MB 468 cells	[138]
Ursolic acid	↑ β-catenin cleavage, ↑ caspase activation	Human prostate epithelial cells	[139]
Docosahexanoic acid	↓ β-catenin protein expression, ↓ β-catenin positive cells	Caco-2 cells	[151]
Genistein	↓ H_2O_2-induced tyrosine phosphorylation of β-catenin	Bovine pulmonary artery endothelial cells	[152]
β-Lapachone	↑ β-catenin cleavage, ↑ caspase activation	HCT116 cells	[140]

induced apoptosis of p53$^{+/+}$, p53$^{-/-}$ and p21$^{+/+}$ HCT116 colon cancer cells by down-regulating β-catenin/TCF DNA binding and transactivation, resulting in diminished c-Myc expression by caspase-3-mediated degradation of β-catenin [136,137]. The green tea polyphenol EGCG, at a physiologic concentration, suppressed proliferation of human embryonic kidney (HEK293) cells by blocking transcriptional activation of β-catenin/TCF and attenuating the expression of β-catenin and cyclin D1 [112]. A similar effect of white tea and green tea has been observed in intestinal tumors from C57BL/6J-MIN^{+} mice. The combination of sulindac with white or green tea further potentiated the down-regulation of β-catenin/TCF signal cascade in these tumors [112]. The growth arrest and the induction of apoptosis in SW480 cells by resveratrol resulted from down-regulation of β-catenin protein and its target gene *cyclin D1* [111]. Indole-3-carbinol attenuated migration and invasion of human breast epithelial cells by restoring the membrane-bound β-catenin pool through up-regulation of E-cadherin and β-catenin expression [138]. Some other dietary anti-inflammatory substances have been shown to induce apoptosis of various colorectal carcinoma and hepatocarcinoma cells in association with enhanced caspase-mediated cleavage of β-catenin protein [139,140].

5. Future perspectives

Although inappropriate β-catenin-mediated signaling has been largely implicated in colorectal carcinogenesis, recent studies suggest that β-catenin acts as a key player in other forms of cancer. A prototype tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) has been reported to mediate tyrosine phosphorylation of β-catenin of E-cadherin–β-catenin complex in the human rectal adenocarcinoma cell line RCM-1 [141]. Furthermore, the treatment of mouse skin with 7,12-dimethylbenz[a]anthracene and TPA resulted in the inactivation of GSK-3β [142] and elevated expression of β-catenin [143] in both papillomas and squamous cell carcinomas, implicating β-catenin in mouse skin tumor promotion. The complex mechanism involving the distribution of β-catenin in different cellular compartments ranging from membrane to nucleus and strict regulation of this oncoprotein at multiple intracellular segments by upstream kinases and tumor suppressor proteins indicate the significance of β-catenin as a critical signaling molecule.

Multiple lines of evidence suggest that an inappropriate activation of β-catenin-mediated signaling contributes to carcinogenesis through up-regulation of β-catenin/TCF-regulated proliferative genes. Because of a causal relationship between inflammation and cancer, attention has been focused on compounds with anti-inflammatory properties as potential chemopreventive agents. Recent studies suggest that β-catenin may act as a putative regulator of COX-2 that has been recognized as a molecular target for a wide variety of anti-inflammatory agents. Therefore, β-catenin-mediated signaling, which acts as a hub in intracellular signaling network, may be considered as a novel molecular target for chemoprevention by anti-inflammatory substances. However, considering the indispensable role of β-catenin in the developmental process, indiscriminate down-regulation of this critical signaling pathway may confer deleterious effect.

Acknowledgements

This work was supported by the National Research Laboratory (NRL) Grant from the Ministry of Science and Technology, Republic of Korea.

References

[1] Y.-J. Surh, Cancer chemoprevention with dietary phytochemicals, Nat. Rev., Cancer 3 (2003) 768–780.
[2] F.R. Greten, M. Karin, The IKK/NF-κB activation pathway—A target for prevention and treatment of cancer, Cancer Lett. 206 (2004) 193–199.

[3] Y.-J. Surh, K.-S. Chun, H.-H. Cha, S.-S. Han, Y.-S. Keum, K.K. Park, S.S. Lee, Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: down-regulation of COX-2 and iNOS through suppression of NF-κB activation, Mutat. Res. 480–481 (2001) 243–268.
[4] K. Smith, T.D. Bui, R. Poulsom, L. Kaklamanis, G. Williams, A.L. Harris, Up-regulation of macrophage wnt gene expression in adenoma–carcinoma progression of human colorectal cancer, Br. J. Cancer 81 (1999) 496–502.
[5] P.J. Morin, β-catenin signaling and cancer, BioEssays 21 (1999) 1021–1030.
[6] E. Ho, T.W. Boileau, T.M. Bray, Dietary influences on endocrine-inflammatory interactions in prostate cancer development, Arch. Biochem. Biophys. 428 (2004) 109–117.
[7] A. Wodarz, R. Nusse, Mechanisms of Wnt signaling in development, Annu. Rev. Cell Dev. Biol. 14 (1998) 59–88.
[8] U. Gat, R. DasGupta, L. Degenstein, E. Fuchs, De Novo hair follicle morphogenesis and hair tumors in mice expressing a truncated β-catenin in skin, Cell 95 (1998) 605–614.
[9] D. Hartmann, From Alzheimer's disease to skin tumors: the catenin connection, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 10522–10523.
[10] D.R. Chesire, C.M. Ewing, W.R. Gage, W.B. Isaacs, In vitro evidence for complex modes of nuclear β-catenin signaling during prostate growth and tumorigenesis, Oncogene 21 (2002) 2679–2694.
[11] M. Takahashi, M. Mutoh, T. Kawamori, T. Sugimura, K. Wakabayashi, Altered expression of β-catenin, inducible nitric oxide synthase and cyclooxygenase-2 in azoxymethane-induced rat colon carcinogenesis, Carcinogenesis 21 (2000) 1319–1327.
[12] Y. Araki, S. Okamura, S.P. Hussain, M. Nagashima, P. He, M. Shiseki, K. Miura, C.C. Harris, Regulation of cyclooxygenase-2 expression by the Wnt and ras pathways, Cancer Res. 63 (2003) 728–734.
[13] L.R. Howe, K. Subbaramaiah, W.J. Chung, A.J. Dannenberg, A.M. Brown, Transcriptional activation of cyclooxygenase-2 in Wnt-1-transformed mouse mammary epithelial cells, Cancer Res. 59 (1999) 1572–1577.
[14] L.C. Hsi, J. Angerman-Stewart, T.E. Eling, Introduction of full-length APC modulates cyclooxygenase-2 expression in HT-29 human colorectal carcinoma cells at the translational level, Carcinogenesis 20 (1999) 2045–2049.
[15] C. Dietrich, J. Scherwat, D. Faust, F. Oesch, Subcellular localization of beta-catenin is regulated by cell density, Biochem. Biophys. Res. Commun. 292 (2002) 195–199.
[16] D.E. Aust, J.P. Terdiman, R.F. Willenbucher, K. Chew, L. Ferrell, C. Florendo, A. Molinaro-Clark, G.B. Baretton, U. Lohrs, F.M. Waldman, Altered distribution of β-catenin, and its binding proteins E-cadherin and APC, in ulcerative colitis-related colorectal cancers, Mod. Pathol. 14 (2001) 29–39.
[17] A. Reinacher-Schick, B.M. Gumbiner, Apical membrane localization of the adenomatous polyposis coli tumor suppressor protein and subcellular distribution of the β-catenin destruction complex in polarized epithelial cells, J. Cell Biol. 152 (2001) 491–502.
[18] F. Cong, H. Varmus, Nuclear-cytoplasmic shuttling of Axin regulates subcellular localization of β-catenin, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 2882–2887.
[19] B.R. Henderson, Nuclear-cytoplasmic shuttling of APC regulates β-catenin subcellular localization and turnover, Nat. Cell Biol. 2 (2000) 653–660.
[20] E.K. Suh, B.M. Gumbiner, Translocation of beta-catenin into the nucleus independent of interactions with FG-rich nucleoporins, Exp. Cell Res. 290 (2003) 447–456.
[21] C.B. Anderson, K.L. Neufeld, R.L. White, Subcellular distribution of Wnt pathway proteins in normal and neoplastic colon, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 8683–8688.
[22] B.R. Henderson, F. Fagotto, The ins and outs of APC and β-catenin nuclear transport, EMBO Rep. 3 (2002) 834–839.
[23] R. Koesters, F. Niggli, M. von Knebel Doeberitz, T. Stallmach, Nuclear accumulation of β-catenin protein in Wilms' tumours, J. Pathol. 199 (2003) 68–76.
[24] R. Kemler, From cadherins to catenins: cytoplasmic protein interactions and regulation of cell adhesion, Trends Genet. 9 (1993) 317–321.
[25] H. Aberle, S. Butz, J. Stappert, H. Weissig, R. Kemler, H. Hoschuetzky, Assembly of the cadherin–catenin complex in vitro with recombinant proteins, J. Cell. Sci. 107 (Pt 12) (1994) 3655–3663.
[26] S. Shibamoto, K. Higano, R. Takada, F. Ito, M. Takeichi, S. Takada, Cytoskeletal reorganization by soluble Wnt-3a protein signalling, Genes Cells 3 (1998) 659–670.
[27] J. Behrens, L. Vakaet, R. Friis, E. Winterhager, F. Van Roy, M.M. Mareel, W. Birchmeier, Loss of epithelial differentiation and gain of invasiveness correlates with tyrosine phosphorylation of the E-cadherin/β-catenin complex in cells transformed with a temperature-sensitive v-SRC gene, J. Cell Biol. 120 (1993) 757–766.
[28] T. Muller, A. Choidas, E. Reichmann, A. Ullrich, Phosphorylation and free pool of β-catenin are regulated by tyrosine kinases and tyrosine phosphatases during epithelial cell migration, J. Biol. Chem. 274 (1999) 10173–10183.
[29] H. Hoschuetzky, H. Aberle, R. Kemler, Beta-catenin mediates the interaction of the cadherin–catenin complex with epidermal growth factor receptor, J. Cell Biol. 127 (1994) 1375–1380.
[30] M. Hamaguchi, N. Matsuyoshi, Y. Ohnishi, B. Gotoh, M. Takeichi, Y. Nagai, p60v-src causes tyrosine phosphorylation and inactivation of the N-cadherin–catenin cell adhesion system, EMBO J. 12 (1993) 307–314.
[31] L. Zhou, N. An, R.C. Haydon, Q. Zhou, H. Cheng, Y. Peng, W. Jiang, H.H. Luu, P. Vanichakarn, J.P. Szatkowski, J.Y. Park, B. Breyer, T.C. He, Tyrosine kinase inhibitor STI-571/Gleevec down-regulates the β-catenin signaling activity, Cancer Lett. 193 (2003) 161–170.
[32] J.M. Mei, G.L. Borchert, S.P. Donald, J.M. Phang, Matrix metalloproteinase(s) mediate(s) NO-induced dissociation of β-catenin from membrane bound E-cadherin and formation of nuclear beta-catenin/LEF-1 complex, Carcinogenesis 23 (2002) 2119–2122.
[33] B. Rubinfeld, I. Albert, E. Porfiri, C. Fiol, S. Munemitsu, P. Polakis, Binding of GSK3β to the APC-β-catenin complex and regulation of complex assembly, Science 272 (1996) 1023–1026.
[34] S. Munemitsu, I. Albert, B. Souza, B. Rubinfeld, P. Polakis, Regulation of intracellular β-catenin levels by the adenomatous polyposis coli (APC) tumor-suppressor protein, Proc. Natl. Acad. Sci. U. S. A. 92 (1995) 3046–3050.
[35] S. Amit, A. Hatzubai, Y. Birman, J.S. Andersen, E. Ben-Shushan, M. Mann, Y. Ben-Neriah, I. Alkalay, Axin-mediated CKI phosphorylation of β-catenin at Ser 45: a molecular switch for the Wnt pathway, Genes Dev. 16 (2002) 1066–1076.
[36] T. Hagen, A. Vidal-Puig, Characterisation of the phosphorylation of β-catenin at the GSK-3 priming site Ser45, Biochem. Biophys. Res. Commun. 294 (2002) 324–328.
[37] C. Liu, Y. Li, M. Semenov, C. Han, G.H. Baeg, Y. Tan, Z. Zhang, X. Lin, X. He, Control of β-catenin phosphorylation/degradation by a dual-kinase mechanism, Cell 108 (2002) 837–847.
[38] C. Sakanaka, Phosphorylation and regulation of β-catenin by casein kinase I epsilon, J. Biochem. (Tokyo) 132 (2002) 697–703.
[39] H. Aberle, A. Bauer, J. Stappert, A. Kispert, R. Kemler, β-catenin is a target for the ubiquitin–proteasome pathway, EMBO J. 16 (1997) 3797–3804.
[40] K. Orford, C. Crockett, J.P. Jensen, A.M. Weissman, S.W. Byers, Serine phosphorylation-regulated ubiquitination and degradation of β-catenin, J. Biol. Chem. 272 (1997) 24735–24738.
[41] L.K. Su, B. Vogelstein, K.W. Kinzler, Association of the APC tumor suppressor protein with catenins, Science 262 (1993) 1734–1737.
[42] B. Rubinfeld, B. Souza, I. Albert, O. Muller, S.H. Chamberlain, F.R. Masiarz, S. Munemitsu, P. Polakis, Association of the APC gene product with β-catenin, Science 262 (1993) 1731–1734.
[43] K. Willert, R. Nusse, Beta-catenin: a key mediator of Wnt signaling, Curr. Opin. Genet. Dev. 8 (1998) 95–102.
[44] M. Hart, J.P. Concordet, I. Lassot, I. Albert, R. del los Santos, H. Durand, C. Perret, B. Rubinfeld, F. Margottin, R. Benarous, P. Polakis, The F-box protein β-TrCP associates with phosphorylated β-catenin and regulates its activity in the cell, Curr. Biol. 9 (1999) 207–210.
[45] E. Latres, D.S. Chiaur, M. Pagano, The human F box protein beta-Trcp

associates with the Cul1/Skp1 complex and regulates the stability of β-catenin, Oncogene 18 (1999) 849–854.
[46] J. Behrens, B. Lustig, The Wnt connection to tumorigenesis, Int. J. Dev. Biol. 48 (2004) 477–487.
[47] M.P. Ebert, G. Fei, S. Kahmann, O. Muller, J. Yu, J.J. Sung, P. Malfertheiner, Increased beta-catenin mRNA levels and mutational alterations of the APC and β-catenin gene are present in intestinal-type gastric cancer, Carcinogenesis 23 (2002) 87–91.
[48] R.C. Haydon, A. Deyrup, A. Ishikawa, R. Heck, W. Jiang, L. Zhou, T. Feng, D. King, H. Cheng, B. Breyer, T. Peabody, M.A. Simon, A.G. Montag, T.C. He, Cytoplasmic and/or nuclear accumulation of the β-catenin protein is a frequent event in human osteosarcoma, Int. J. Cancer 102 (2002) 338–342.
[49] B. Lustig, J. Behrens, The Wnt signaling pathway and its role in tumor development, J. Cancer Res. Clin. Oncol. 129 (2003) 199–221.
[50] K. Sato, Y. Okazaki, M. Tonogi, Y. Tanaka, G.Y. Yamane, Expression of β-catenin in rat oral epithelial dysplasia induced by 4-nitroquinoline 1-oxide, Oral Oncol. 38 (2002) 772–778.
[51] G. Moreno-Bueno, D. Hardisson, C. Sanchez, D. Sarrio, R. Cassia, G. Garcia-Rostan, J. Prat, M. Guo, J.G. Herman, X. Matias-Guiu, M. Esteller, J. Palacios, Abnormalities of the APC/β-catenin pathway in endometrial cancer, Oncogene 21 (2002) 7981–7990.
[52] H. Shiina, M. Igawa, K. Shigeno, M. Terashima, M. Deguchi, M. Yamanaka, L. Ribeiro-Filho, C.J. Kane, R. Dahiya, Beta-catenin mutations correlate with over expression of C-myc and cyclin D1 genes in bladder cancer, J. Urol. 168 (2002) 2220–2226.
[53] P.W. Schlosshauer, E.C. Pirog, R.L. Levine, L.H. Ellenson, Mutational analysis of the CTNNB1 and APC genes in uterine endometrioid carcinoma, Mod. Pathol. 13 (2000) 1066–1071.
[54] H.J. Voeller, C.I. Truica, E.P. Gelmann, Beta-catenin mutations in human prostate cancer, Cancer Res. 58 (1998) 2520–2523.
[55] Y. Yamada, T. Oyama, Y. Hirose, A. Hara, S. Sugie, K. Yoshida, N. Yoshimi, H. Mori, β-Catenin mutation is selected during malignant transformation in colon carcinogenesis, Carcinogenesis 24 (2003) 91–97.
[56] S.J. Ha, J.S. Kim, E.J. Seo, K.H. Lee, H.J. Lee, J.W. Kim, Low frequency of β-catenin gene mutations in pilomatricoma, Acta Derm.-Venereol. 82 (2002) 428–431.
[57] M. Nilbert, E. Rambech, Beta-catenin activation through mutation is rare in rectal cancer, Cancer Genet. Cytogenet. 128 (2001) 43–45.
[58] K. Omholt, A. Platz, U. Ringborg, J. Hansson, Cytoplasmic and nuclear accumulation of beta-catenin is rarely caused by CTNNB1 exon 3 mutations in cutaneous malignant melanoma, Int. J. Cancer 92 (2001) 839–842.
[59] P.M. Pollock, N. Hayward, Mutations in exon 3 of the β-catenin gene are rare in melanoma cell lines, Melanoma Res. 12 (2002) 183–186.
[60] R. Stoehr, R.C. Krieg, R. Knuechel, F. Hofstaedter, C. Pilarsky, D. Zaak, R. Schmitt, A. Hartmann, No evidence for involvement of β-catenin and APC in urothelial carcinomas, Int .J. Oncol. 20 (2002) 905–911.
[61] Q. Li, B.M. Dixon, M. Al-Fageeh, C.A. Blum, R.H. Dashwood, Sequencing of the rat β-catenin gene (Ctnnb1) and mutational analysis of liver tumors induced by 2-amino-3-methylimidazo[4,5-f]quinoline, Gene 283 (2002) 255–262.
[62] Q. Eastman, R. Grosschedl, Regulation of LEF-1/TCF transcription factors by Wnt and other signals, Curr. Opin. Cell Biol. 11 (1999) 233–240.
[63] A.N. Billin, H. Thirlwell, D.E. Ayer, Beta-catenin–histone deacetylase interactions regulate the transition of LEF1 from a transcriptional repressor to an activator, Mol. Cell. Biol. 20 (2000) 6882–6890.
[64] D. Levanon, R.E. Goldstein, Y. Bernstein, H. Tang, D. Goldenberg, S. Stifani, Z. Paroush, Y. Groner, Transcriptional repression by AML1 and LEF-1 is mediated by the TLE/Groucho corepressors, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 11590–11595.
[65] A. Novak, S. Dedhar, Signaling through β-catenin and Lef/Tcf, Cell. Mol. Life Sci. 56 (1999) 523–537.
[66] O. Tetsu, F. McCormick, Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells, Nature 398 (1999) 422–426.
[67] T.J. Koh, C.J. Bulitta, J.V. Fleming, G.J. Dockray, A. Varro, T.C. Wang, Gastrin is a target of the β-catenin/TCF-4 growth-signaling pathway in a model of intestinal polyposis, J. Clin. Invest. 106 (2000) 533–539.
[68] T. Brabletz, A. Jung, S. Dag, F. Hlubek, T. Kirchner, β-catenin regulates the expression of the matrix metalloproteinase-7 in human colorectal cancer, Am. J. Pathol. 155 (1999) 1033–1038.
[69] L. Levy, C. Neuveut, C.A. Renard, P. Charneau, S. Branchereau, F. Gauthier, J.T. Van Nhieu, D. Cherqui, A.F. Petit-Bertron, D. Mathieu, M.A. Buendia, Transcriptional activation of interleukin-8 by β-catenin-Tcf4, J. Biol. Chem. 277 (2002) 42386–42393.
[70] B. Mann, M. Gelos, A. Siedow, M.L. Hanski, A. Gratchev, M. Ilyas, W.F. Bodmer, M.P. Moyer, E.O. Riecken, H.J. Buhr, C. Hanski, Target genes of β-catenin-T cell-factor/lymphoid-enhancer-factor signaling in human colorectal carcinomas, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 1603–1608.
[71] N.A. Wong, M. Pignatelli, Beta-catenin—A linchpin in colorectal carcinogenesis? Am. J. Pathol. 160 (2002) 389–401.
[72] F.T. Kolligs, M.T. Nieman, I. Winer, G. Hu, D. Van Mater, Y. Feng, I.M. Smith, R. Wu, Y. Zhai, K.R. Cho, E.R. Fearon, ITF-2, a downstream target of the Wnt/TCF pathway, is activated in human cancers with β-catenin defects and promotes neoplastic transformation, Cancer Cells 1 (2002) 145–155.
[73] T.C. He, T.A. Chan, B. Vogelstein, K.W. Kinzler, PPARδ is an APC-regulated target of nonsteroidal anti-inflammatory drugs, Cell 99 (1999) 335–345.
[74] Y. Yamamoto, M. Sakamoto, G. Fujii, H. Tsuiji, K. Kenetaka, M. Asaka, S. Hirohashi, Overexpression of orphan G-protein-coupled receptor, Gpr49, in human hepatocellular carcinomas with β-catenin mutations, Hepatology 37 (2003) 528–533.
[75] M. Takahashi, T. Tsunoda, M. Seiki, Y. Nakamura, Y. Furukawa, Identification of membrane-type matrix metalloproteinase-1 as a target of the β-catenin/Tcf4 complex in human colorectal cancers, Oncogene 21 (2002) 5861–5867.
[76] F.T. Kolligs, G. Bommer, B. Goke, Wnt/β-catenin/tcf signaling: a critical pathway in gastrointestinal tumorigenesis, Digestion 66 (2002) 131–144.
[77] R.T. Moon, A.D. Kohn, G.V. De Ferrari, A. Kaykas, WNT and β-catenin signalling: diseases and therapies, Nat. Rev., Genet. 5 (2004) 691–701.
[78] P. Polakis, Wnt signaling and cancer, Genes Dev. 14 (2000) 1837–1851.
[79] T. Reya, H. Clevers, Wnt signalling in stem cells and cancer, Nature 434 (2005) 843–850.
[80] E. Sancho, E. Batlle, H. Clevers, Signaling pathways in intestinal development and cancer, Annu. Rev. Cell Dev. Biol. 20 (2004) 695–723.
[81] J. Cui, X. Zhou, Y. Liu, Z. Tang, M. Romeih, Wnt signaling in hepatocellular carcinoma: analysis of mutation and expression of β-catenin, T-cell factor-4 and glycogen synthase kinase 3-beta genes, J. Gastroenterol. Hepatol. 18 (2003) 280–287.
[82] T. Ikenoue, H. Ijichi, N. Kato, F. Kanai, T. Masaki, W. Rengifo, M. Okamoto, M. Matsumura, T. Kawabe, Y. Shiratori, M. Omata, Analysis of the β-catenin/T cell factor signaling pathway in 36 gastrointestinal and liver cancer cells, Jpn. J. Cancer Res. 93 (2002) 1213–1220.
[83] K. Rask, A. Nilsson, M. Brannstrom, P. Carlsson, P. Hellberg, P.O. Janson, L. Hedin, K. Sundfeldt, Wnt-signalling pathway in ovarian epithelial tumours: increased expression of β-catenin and GSK3β, Br. J. Cancer 89 (2003) 1298–1304.
[84] J. Roose, H. Clevers, TCF transcription factors: molecular switches in carcinogenesis, Biochim. Biophys. Acta 1424 (1999) M23–M37.
[85] E. Vincan, Frizzled/WNT signalling: the insidious promoter of tumour growth and progression, Front. Biosci. 9 (2004) 1023–1034.
[86] M.N. Kitaeva, L. Grogan, J.P. Williams, E. Dimond, K. Nakahara, P. Hausner, J.W. DeNobile, P.W. Soballe, I.R. Kirsch, Mutations in β-catenin are uncommon in colorectal cancer occurring in occasional replication error-positive tumors, Cancer Res. 57 (1997) 4478–4481.
[87] W.S. Samowitz, M.D. Powers, L.N. Spirio, F. Nollet, F. van Roy, M.L. Slattery, Beta-catenin mutations are more frequent in small colorectal adenomas than in larger adenomas and invasive carcinomas, Cancer Res. 59 (1999) 1442–1444.
[88] A.B. Sparks, P.J. Morin, B. Vogelstein, K.W. Kinzler, Mutational analysis of the APC/β-catenin/Tcf pathway in colorectal cancer, Cancer Res. 58 (1998) 1130–1134.
[89] A. de La Coste, B. Romagnolo, P. Billuart, C.A. Renard, M.A. Buendia, O. Soubrane, M. Fabre, J. Chelly, C. Beldjord, A. Kahn, C. Perret,

Somatic mutations of the β-catenin gene are frequent in mouse and human hepatocellular carcinomas, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 8847–8851.
[90] P. Legoix, O. Bluteau, J. Bayer, C. Perret, C. Balabaud, J. Belghiti, D. Franco, G. Thomas, P. Laurent-Puig, J. Zucman-Rossi, Beta-catenin mutations in hepatocellular carcinoma correlate with a low rate of loss of heterozygosity, Oncogene 18 (1999) 4044–4046.
[91] J.T. Nhieu, C.A. Renard, Y. Wei, D. Cherqui, E.S. Zafrani, M.A. Buendia, Nuclear accumulation of mutated β-catenin in hepatocellular carcinoma is associated with increased cell proliferation, Am. J. Pathol. 155 (1999) 703–710.
[92] Y. Yamada, N. Yoshimi, S. Sugie, M. Suzui, K. Matsunaga, K. Kawabata, A. Hara, H. Mori, Beta-catenin (Ctnnb1) gene mutations in diethylnitrosamine (DEN)-induced liver tumors in male F344 rats, Jpn. J. Cancer Res. 90 (1999) 824–828.
[93] T. Fukuchi, M. Sakamoto, H. Tsuda, K. Maruyama, S. Nozawa, S. Hirohashi, Beta-catenin mutation in carcinoma of the uterine endometrium, Cancer Res. 58 (1998) 3526–3528.
[94] T. Ikeda, K. Yoshinaga, S. Semba, E. Kondo, H. Ohmori, A. Horii, Mutational analysis of the CTNNB1 (β-catenin) gene in human endometrial cancer: frequent mutations at codon 34 that cause nuclear accumulation, Oncol. Rep. 7 (2000) 323–326.
[95] S. Semba, S.Y. Han, H. Ikeda, A. Horii, Frequent nuclear accumulation of β-catenin in pituitary adenoma, Cancer 91 (2001) 42–48.
[96] C. Gamallo, J. Palacios, G. Moreno, J. Calvo de Mora, A. Suarez, A. Armas, beta-catenin expression pattern in stage I and II ovarian carcinomas: relationship with β-catenin gene mutations, clinicopathological features, and clinical outcome, Am. J. Pathol. 155 (1999) 527–536.
[97] J. Palacios, C. Gamallo, Mutations in the β-catenin gene (CTNNB1) in endometrioid ovarian carcinomas, Cancer Res. 58 (1998) 1344–1347.
[98] B. Rubinfeld, P. Robbins, M. El-Gamil, I. Albert, E. Porfiri, P. Polakis, Stabilization of β-catenin by genetic defects in melanoma cell lines, Science 275 (1997) 1790–1792.
[99] N. Sunaga, T. Kohno, F.T. Kolligs, E.R. Fearon, R. Saito, J. Yokota, Constitutive activation of the Wnt signaling pathway by CTNNB1 (β-catenin) mutations in a subset of human lung adenocarcinoma, Genes Chromosomes Cancer 30 (2001) 316–321.
[100] A.C. Porter, R.R. Vaillancourt, Tyrosine kinase receptor-activated signal transduction pathways which lead to oncogenesis, Oncogene 17 (1998) 1343–1352.
[101] D.F. Calvisi, S. Ladu, V.M. Factor, S.S. Thorgeirsson, Activation of β-catenin provides proliferative and invasive advantages in c-myc/TGF-α hepatocarcinogenesis promoted by phenobarbital, Carcinogenesis 25 (2004) 901–908.
[102] M. Joo, H.K. Lee, Y.K. Kang, Expression of β-catenin in hepatocellular carcinoma in relation to tumor cell proliferation and cyclin D1 expression, J. Korean Med. Sci. 18 (2003) 211–217.
[103] X.Z. Shang, H. Zhu, K. Lin, Z. Tu, J. Chen, D.R. Nelson, C. Liu, Stabilized beta-catenin promotes hepatocyte proliferation and inhibits TNFα-induced apoptosis, Lab. Invest. 84 (2004) 332–341.
[104] P.W. Derksen, E. Tjin, H.P. Meijer, M.D. Klok, H.D. MacGillavry, M.H. van Oers, H.M. Lokhorst, A.C. Bloem, H. Clevers, R. Nusse, R. van der Neut, M. Spaargaren, S.T. Pals, Illegitimate WNT signaling promotes proliferation of multiple myeloma cells, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 6122–6127.
[105] A. Kotsinas, K. Evangelou, P. Zacharatos, C. Kittas, V.G. Gorgoulis, Proliferation, but not apoptosis, is associated with distinct β-catenin expression patterns in non-small-cell lung carcinomas: relationship with adenomatous polyposis coli and G(1)-to S-phase cell-cycle regulators, Am. J. Pathol. 161 (2002) 1619–1634.
[106] C. Kuhnen, P. Herter, O. Muller, T. Muehlberger, L. Krause, H. Homann, H.U. Steinau, K.M. Muller, Beta-catenin in soft tissue sarcomas: expression is related to proliferative activity in high-grade sarcomas, Mod. Pathol. 13 (2000) 1005–1013.
[107] G. Saldanha, V. Ghura, L. Potter, A. Fletcher, Nuclear β-catenin in basal cell carcinoma correlates with increased proliferation, Br. J. Dermatol. 151 (2004) 157–164.
[108] J.H. Sellin, S. Umar, J. Xiao, A.P. Morris, Increased β-catenin expression and nuclear translocation accompany cellular hyperproliferation in vivo, Cancer Res. 61 (2001) 2899–2906.
[109] S. Dihlmann, A. Siermann, M. von Knebel Doeberitz, The nonsteroidal anti-inflammatory drugs aspirin and indomethacin attenuate β-catenin/TCF-4 signaling, Oncogene 20 (2001) 645–653.
[110] S.H. Gardner, G. Hawcroft, M.A. Hull, Effect of nonsteroidal anti-inflammatory drugs on β-catenin protein levels and catenin-related transcription in human colorectal cancer cells, Br. J. Cancer 91 (2004) 153–163.
[111] A.K. Joe, H. Liu, M. Suzui, M.E. Vural, D. Xiao, I.B. Weinstein, Resveratrol induces growth inhibition, S-phase arrest, apoptosis, and changes in biomarker expression in several human cancer cell lines, Clin. Cancer Res. 8 (2002) 893–903.
[112] G.A. Orner, W.M. Dashwood, C.A. Blum, G.D. Diaz, Q. Li, R.H. Dashwood, Suppression of tumorigenesis in the Apc(min) mouse: down-regulation of β-catenin signaling by a combination of tea plus sulindac, Carcinogenesis 24 (2003) 263–267.
[113] F.R. Greten, L. Eckmann, T.F. Greten, J.M. Park, Z.W. Li, L.J. Egan, M.F. Kagnoff, M. Karin, IKKβ links inflammation and tumorigenesis in a mouse model of colitis-associated cancer, Cell 118 (2004) 285–296.
[114] Y.-J. Surh, Anti-tumor promoting potential of selected spice ingredients with antioxidative and anti-inflammatory activities: a short review, Food Chem. Toxicol. 40 (2002) 1091–1097.
[115] K.-S. Chun, Y.-J. Surh, Signal transduction pathways regulating cyclooxygenase-2 expression: potential molecular targets for chemoprevention, Biochem. Pharmacol. 68 (2004) 1089–1100.
[116] K. Subbaramaiah, A.J. Dannenberg, Cyclooxygenase 2: a molecular target for cancer prevention and treatment, Trends Pharmacol. Sci. 24 (2003) 96–102.
[117] A.N. Kong, R. Yu, V. Hebbar, C. Chen, E. Owuor, R. Hu, R. Ee, S. Mandlekar, Signal transduction events elicited by cancer prevention compounds, Mutat. Res. 480–481 (2001) 231–241.
[118] M. Oshima, N. Murai, S. Kargman, M. Arguello, P. Luk, E. Kwong, M.M. Taketo, J.F. Evans, Chemoprevention of intestinal polyposis in the $Apc^{delta716}$ mouse by rofecoxib, a specific cyclooxygenase-2 inhibitor, Cancer Res. 61 (2001) 1733–1740.
[119] L.R. Howe, H.C. Crawford, K. Subbaramaiah, J.A. Hassell, A.J. Dannenberg, A.M. Brown, PEA3 is up-regulated in response to Wnt1 and activates the expression of cyclooxygenase-2, J. Biol. Chem. 276 (2001) 20108–20115.
[120] J. Dimberg, A. Hugander, A. Sirsjo, P. Soderkvist, Enhanced expression of cyclooxygenase-2 and nuclear β-catenin are related to mutations in the APC gene in human colorectal cancer, Anticancer Res. 21 (2001) 911–915.
[121] S.J. Kim, D.S. Im, S.H. Kim, J.H. Ryu, S.G. Hwang, J.K. Seong, C.H. Chun, J.S. Chun, Beta-catenin regulates expression of cyclooxygenase-2 in articular chondrocytes, Biochem. Biophys. Res. Commun. 296 (2002) 221–226.
[122] S. Dihlmann, M. von Knebel Doeberitz, Wnt/β-catenin-pathway as a molecular target for future anti-cancer therapeutics, Int. J. Cancer 113 (2005) 515–524.
[123] S. Dihlmann, S. Klein, M.K. Doeberitz Mv, Reduction of β-catenin/T-cell transcription factor signaling by aspirin and indomethacin is caused by an increased stabilization of phosphorylated β-catenin, Mol. Cancer Ther. 2 (2003) 509–516.
[124] E.J. Lee, H.G. Park, H.S. Kang, Sodium salicylate induces apoptosis in HCT116 colorectal cancer cells through activation of p38 MAPK, Int. J. Oncol. 23 (2003) 503–508.
[125] G. Hawcroft, M. D'Amico, C. Albanese, A.F. Markham, R.G. Pestell, M.A. Hull, Indomethacin induces differential expression of β-catenin, gamma-catenin and T-cell factor target genes in human colorectal cancer cells, Carcinogenesis 23 (2002) 107–114.
[126] E.M. Boon, J.J. Keller, T.A. Wormhoudt, F.M. Giardiello, G.J. Offerhaus, R. van der Neut, S.T. Pals, Sulindac targets nuclear β-catenin accumulation and Wnt signalling in adenomas of patients with familial adenomatous polyposis and in human colorectal cancer cell lines, Br. J. Cancer 90 (2004) 224–229.

[127] M.F. McEntee, C.H. Chiu, J. Whelan, Relationship of β-catenin and Bcl-2 expression to sulindac-induced regression of intestinal tumors in Min mice, Carcinogenesis 20 (1999) 635–640.
[128] W.A. Brown, S.A. Skinner, D. Vogiagis, P.E. O'Brien, Inhibition of beta-catenin translocation in rodent colorectal tumors: a novel explanation for the protective effect of nonsteroidal antiinflammatory drugs in colorectal cancer, Dig. Dis. Sci. 46 (2001) 2314–2321.
[129] M.L. Smith, G. Hawcroft, M.A. Hull, The effect of non-steroidal anti-inflammatory drugs on human colorectal cancer cells: evidence of different mechanisms of action, Eur. J. Cancer 36 (2000) 664–674.
[130] S. Kapitanovic, T. Cacev, M. Antica, M. Kralj, G. Cavric, K. Pavelic, R. Spaventi, Effect of indomethacin on E-cadherin and β-catenin expression in HT-29 colon cancer cells, Exp. Mol. Pathol. (in press).
[131] H. Mori, Y. Yamada, Y. Hirose, T. Kuno, M. Katayama, K. Sakata, K. Yoshida, S. Sugie, A. Hara, N. Yoshimi, Chemoprevention of large bowel carcinogenesis; the role of control of cell proliferation and significance of β-catenin-accumulated crypts as a new biomarker, Eur. J. Cancer Prev. 11 (Suppl 2) (2002) S71–S75.
[132] Y. Yamada, N. Yoshimi, Y. Hirose, A. Hara, M. Shimizu, T. Kuno, M. Katayama, Z. Qiao, H. Mori, Suppression of occurrence and advancement of β-catenin-accumulated crypts, possible premalignant lesions of colon cancer, by selective cyclooxygenase-2 inhibitor, celecoxib, Jpn. J. Cancer Res. 92 (2001) 617–623.
[133] T.J. Maier, A. Janssen, R. Schmidt, G. Geisslinger, S. Grosch, Targeting the β-catenin/APC pathway: a novel mechanism to explain the cyclooxygenase-2-independent anticarcinogenic effects of celecoxib in human colon carcinoma cells, FASEB J. 19 (2005) 1353–1355.
[134] M.L. Clapper, J. Coudry, W.C. Chang, β-Catenin-mediated signaling: a molecular target for early chemopreventive intervention, Mutat. Res. 555 (2004) 97–105.
[135] M. Bordonaro, J.M. Mariadason, F. Aslam, B.G. Heerdt, L.H. Augenlicht, Butyrate-induced apoptotic cascade in colonic carcinoma cells: modulation of the β-catenin–Tcf pathway and concordance with effects of sulindac and trichostatin A but not curcumin, Cell Growth Differ. 10 (1999) 713–720.
[136] A.S. Jaiswal, B.P. Marlow, N. Gupta, S. Narayan, Beta-catenin-mediated transactivation and cell–cell adhesion pathways are important in curcumin (diferuylmethane)-induced growth arrest and apoptosis in colon cancer cells, Oncogene 21 (2002) 8414–8427.
[137] S. Narayan, Curcumin, a multi-functional chemopreventive agent, blocks growth of colon cancer cells by targeting β-catenin-mediated transactivation and cell–cell adhesion pathways, J. Mol. Histol. 35 (2004) 301–307.
[138] Q. Meng, M. Qi, D.Z. Chen, R. Yuan, I.D. Goldberg, E.M. Rosen, K. Auborn, S. Fan, Suppression of breast cancer invasion and migration by indole-3-carbinol: associated with up-regulation of BRCA1 and E-cadherin/catenin complexes, J. Mol. Med. 78 (2000) 155–165.
[139] Y.H. Choi, J.H. Baek, M.A. Yoo, H.Y. Chung, N.D. Kim, K.W. Kim, Induction of apoptosis by ursolic acid through activation of caspases and down-regulation of c-IAPs in human prostate epithelial cells, Int. J. Oncol. 17 (2000) 565–571.
[140] B.T. Choi, J. Cheong, Y.H. Choi, β-Lapachone-induced apoptosis is associated with activation of caspase-3 and inactivation of NF-κB in human colon cancer HCT-116 cells, Anti-cancer Drugs 14 (2003) 845–850.
[141] K. Nabeshima, T. Inoue, Y. Shimao, H. Kataoka, M. Koono, TPA-induced cohort migration of well-differentiated human rectal adenocarcinoma cells: cells move in a RGD-dependent manner on fibronectin produced by cells, and phosphorylation of E-cadherin/catenin complex is induced independently of cell–extracellular matrix interactions, Virchows Arch. 433 (1998) 243–253.
[142] H. Leis, C. Segrelles, S. Ruiz, M. Santos, J.M. Paramio, Expression, localization, and activity of glycogen synthase kinase 3β during mouse skin tumorigenesis, Mol. Carcinog. 35 (2002) 180–185.
[143] N. Bhatia, V.S. Spiegelman, Activation of Wnt/β-catenin/Tcf signaling in mouse skin carcinogenesis, Mol. Carcinog. 42 (2005) 213–221.
[144] A. Kikuchi, Regulation of β-catenin signaling in the Wnt pathway, Biochem. Biophys. Res. Commun. 268 (2000) 243–248.
[145] C.A. Grimes, R.S. Jope, The multifaceted roles of glycogen synthase kinase 3β in cellular signaling, Prog. Neurobiol. 65 (2001) 391–426.
[146] M. Noda, Y. Tatsumi, M. Tomizawa, T. Takama, S. Mitsufuji, H. Sugihara, K. Kashima, T. Hattori, Effects of etodolac, a selective cyclooxygenase-2 inhibitor, on the expression of E-cadherin–catenin complexes in gastrointestinal cell lines, J. Gastroenterol. Hepatol. 37 (2002) 896–904.
[147] H.K. Roy, W.J. Karoski, A. Ratashak, T.C. Smyrk, Chemoprevention of intestinal tumorigenesis by nabumetone: induction of apoptosis and Bcl-2 downregulation, Br. J. Cancer 84 (2001) 1412–1416.
[148] W.M. Dashwood, G.A. Orner, R.H. Dashwood, Inhibition of β-catenin/Tcf activity by white tea, green tea, and epigallocatechin-3-gallate (EGCG): minor contribution of H_2O_2 at physiologically relevant EGCG concentrations, Biochem. Biophys. Res. Commun. 296 (2002) 584–588.
[149] M.C. Myzak, P.A. Karplus, F.L. Chung, R.H. Dashwood, A novel mechanism of chemoprotection by sulforaphane: inhibition of histone deacetylase, Cancer Res. 64 (2004) 5767–5774.
[150] S. Gupta, N. Ahmad, S.R. Marengo, G.T. MacLennan, N.M. Greenberg, H. Mukhtar, Chemoprevention of prostate carcinogenesis by alpha-difluoromethylornithine in TRAMP mice, Cancer Res. 60 (2000) 5125–5133.
[151] B.A. Narayanan, N.K. Narayanan, D. Desai, B. Pittman, B.S. Reddy, Effects of a combination of docosahexaenoic acid and 1,4-phenylenebis (methylene) selenocyanate on cyclooxygenase-2, inducible nitric oxide synthase and β-catenin pathways in colon cancer cells, Carcinogenesis 25 (2004) 2443–2449.
[152] J.M. Carbajal, R.C. Schaeffer Jr., H_2O_2 and genistein differentially modulate protein tyrosine phosphorylation, endothelial morphology, and monolayer barrier function, Biochem. Biophys. Res. Commun. 249 (1998) 461–466.