AIMS Biophysics, 4(1): 152-177.
DOI: 10.3934/biophy.2017.1.152
Received: 19 December 2016
Accepted: 08 February 2017
Published: 23 February 2017

http://www.aimspress.com/journal/biophysics

Review

Molecular mechanisms of intestinal inflammation leading to colorectal cancer

Sonia Shastri [1], Ravichandra Vemuri [1], Nuri Gueven [2], Madhur D. Shastri [1,2,*] and Rajaraman Eri [1,*]

[1] School of Health Sciences, Faculty of Health, University of Tasmania, Launceston, Tasmania, Australia
[2] Division of Pharmacy, School of Medicine, Faculty of Health, University of Tasmania, Hobart, Tasmania, Australia

* **Correspondence:** Email: Rajaraman.Eri@utas.edu.au; Madhur.Shastri@utas.edu.au; Tel: +61-3-6226-5017; Fax: +61-3-6226-5555.

Abstract: Inflammatory bowel disease (IBD) is recognized as a leading cause in the development of colorectal cancer (CRC). Inflammatory bowel disease associated colorectal cancer (IBD-CRC) is a growing healthcare burden, causing significant morbidity and mortality world-wide. In the present review, relevant preclinical models of IBD-CRC, a concise overview of potential molecular mechanisms that are involved and responsible for IBD associated colonic tumorigenesis along with the current and the future therapeutic approaches including the role of novel natural and synthetic compounds for the prevention and treatment of IBD-CRC are outlined. This review will benefit various clinicians and translational researchers working in the area of IBD-CRC to have a quick snap-shot of the ongoing trends in IBD-CRC research and discoveries.

Keywords: inflammatory bowel disease; colorectal cancer; inflammatory bowel disease associated colorectal cancer

1. Introduction

1.1. Inflammatory bowel disease associated colorectal cancer

Inflammatory bowel disease (IBD) is a chronic relapsing inflammation of the intestine that affects either all or some parts of the gastrointestinal tract (GIT). Prolonged activation of the intestinal mucosal immune system promotes the release of biological markers associated with IBD, causing persistent inflammation [1]. The incidence and prevalence of IBD are known to be the highest in western industrialized nations. Europe and the United States of America being the countries with highest prevalence of IBD, with an estimated 2.2 and 1.4 million people affected respectively [2,3]. IBD is differentiated into two broad categories; ulcerative colitis (UC) and Crohn's disease (CD). UC is limited to the colon or rectum, while inflammation during CD can affect any part of the GIT from the oesophagus to the anus [4]. UC is mainly characterized by the formation of continuous superficial lesions along the proximal or distal colon. On the other hand, CD results in the formation of deep-fissured ulcers, fistulae, and perforations in the bowel [1,4].

The aetiology of IBD has not been fully explored and still on its way to have a clear picture; however, dysregulation of the immune response via luminal, genetic and environmental factors are considered to increase the risk of IBD [5]. The onset of IBD can occur at any stages of life. Although, it is more frequently seen in the elderly population, 20% of IBD cases are diagnosed during childhood or adolescence [6]. Atypical symptoms and extraintestinal manifestations of IBD cause major difficulties for the identification and diagnosis of the disease in paediatric patients. Comparatively, the incidence rate of CD in children is nearly double (0.2 to 8.5 per 100,000) than UC [7]. Overall, the impact of UC predominates as 7 to 12 per 100,000 cases diagnosed annually compared to 5 to 7 cases of CD [8]. Currently, there is no cure for IBD. Moreover, there are no specific biomarkers for the identification of IBD disorders, and therefore, endoscopic, clinical, radiologic and other therapeutic measures remain the core source for their diagnosis.

The connection between IBD and colorectal cancer (CRC) is well established. IBD is known to play a substantial role in sustaining and promoting CRC development [9]. Long-term chronic inflammation of the colon, as observed in IBD patients, is correlated with an enhanced risk of developing colorectal cancer. An association between IBD and CRC was first reported by Crohn and Rosenberg in 1925 [9]. The accumulating preclinical and clinical data suggest an increased risk of developing intestinal carcinogenesis in patients suffering from IBD [10,11]. In a meta-analysis by Eaden et al., patients with UC were reported to have a 9-fold increase in the cumulative incidence of CRC development 20 years after initial UC diagnosis [12]. Among IBD patients, UC-driven CRC has been a focal point of interest in the majority of preclinical and clinical studies. However, a 2.5 to 4.5-fold increased risk of developing CRC has also been reported in patients with CD [13]. The chances of developing CRC in patients with CD are up to 33 times higher than in the general population. The majority of risk factors associated with IBD-CRC are yet to be fully elucidated. Nevertheless, the major contributory factors, which are known to enhance the likelihood of IBD-CRC progression, include the duration and extent of colonic inflammation or other existing IBD-related inflammatory conditions like sclerosing cholangitis etc. [14,15].

Chemoprevention with anti-inflammatory agents and immunomodulators have been shown to reduce the risk of developing IBD-CRC. However, their effects remain conflicting [16,17]. Newer technologies such as chromo-endoscopy for the early detection of dysplasia needs to be established [18]. An animal model of a particular disease state is critical to unravelling the pathological mechanisms behind a disease. However, we currently lack a suitable animal model to recapitulate the

pathogenesis of IBD-CRC as in humans. Nevertheless, there are animal models to study IBD and CRC and combining such models could help us in improving the understanding on IBD-CRC. The various models of IBD-CRC, the molecular pathways associated with this disease and various potential novel therapies that can be used for the management of IBD-CRC are discussed below.

2. Experimental Models to Study IBD Associated Colorectal Cancer

2.1. In-vitro models

In-vitro models represent the first critical step towards elucidating the mechanism(s) responsible in the complex pathophysiology of IBD-CRC. Moreover, these models remain a primary and fundamental tool for the identification of novel therapeutic interventions. Several studies documented the use of cell lines representing colon-associated CRC. These cell lines include HCT116, SW620, HCT15, DLD1, HT29, LOVO, SW408, Caco2, Isreco1, SNU1033 or SNU407 [19–22]. Such studies have provided an essential information towards the recognition and involvement of various inflammatory biomarker(s) involved in IBD-CRC, with a view towards understanding the specific aspects of tumor biology, assessment of endogenous inflammatory mediators and expression of relevant genes. The identified biomarkers in IBD-CRC include various cytokines and chemokines, like interleukin (IL)-6 and IL-8, transcription factors, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and runt-related transcription factor (RUNX).

In-vitro organoid culture is a breakthrough that facilitates an accurate study of characteristic pathophysiological features of many biological disorders including IBD and CRC [23]. For instance, the establishment of intestinal and CRC organoids provides an opportunity to study the underlying mechanisms involved in IBD and CRC, and thereby contribute to improved treatments for these disorders [24,25,26]. Organoid culture has emerging trends which can help in overcoming the current shortcomings that hinder us from studying the development and pathobiology of IBD-CRC. Although, in-vitro analysis is critical and permits faster and simpler assessment of biological phenomena, these models are restricted to investigate specific stages of tumor development. Importantly, the loss of tissue context is one of the major limitations of these models. Comparatively, in-vivo models provide comprehensive insight of the factors that affect tumor development, as well as attributing processes, such as proliferation, invasion, angiogenesis and metastasis. A number of strategies have been employed to develop murine models of IBD, to evaluate the pathogenesis behind IBD, as well as IBD-CRC. Some of the most widely used murine models that represent human IBD, include dextran sodium sulphate (DSS) and *Winnie* [27,28]. These models are briefly discussed below.

2.2. In-vivo mouse models: Pivotal tools in understanding IBD-CRC

2.2.1. Genetically engineered mice models

The germline mutation in the adenomatous polyposis coli gene (APC) gives rise to familial adenomatous polyposis (FAP) syndrome and is associated with the development of polyps in the colon and rectal regions during CRC [29]. Various attempts have been made to generate mouse models that recapitulate the human FAP syndrome. The *Min* mouse model has been utilized to investigate the risk factors and clinical application of chemoprotective drugs such as piroxicam and acarbose during CRC [30,31]. This *Min* mouse model carries a heterozygous germline mutation in APC gene that resembles the progressive and developmental phase of polyps formation as observed in patients with FAP syndrome. However, the formation of polyps in small intestine remains one of the major limitations of this model since polyps are usually confined to colon and rectum in patients suffering from FAP [32].

Nevertheless, certain modifications in the APC gene resulted in a double mutant mouse model where the formation of polyps is confined to colon region [33]. Moreover, homozygous deletion of mismatch repair gene such as MSH1, MSH2, and MSH6 in this model produced a robust mouse model that mimics the features related to hereditary nonpolyposis colorectal cancer (HNPCC) [34]. These genetically modified models have their own limitations and continued advancements might make these models more efficient for CRC research.

Other genetically engineered mice model utilized to study IBD-CRC focused on homozygous deletion of Mucin2 (*MUC2*$^{-/-}$) gene [35]. Depletion of this gene was not only associated with morphological alterations in the intestinal epithelium leading to inflammation of the colon but also gave rise to invasive colon adenocarcinoma [36]. Such models help us better understand the protective role of MUC2 in IBD and IBD-CRC. Mice deficient in mothers against decapentaplegic homolog 3 (*Smad3*$^{-/-}$) gene are known to develop colonic lesions, mucosal hyperplasia, polyploid tumors, metastatic carcinoma and increases infiltration of inflammatory cells [37]. However, this model lacks the information regarding the role of microflora in pathogenesis of tumor generation [38].

2.2.2. Chemically induced mice models

Several chemically induced murine models of intestinal inflammation have been established. Among them, DSS model of IBD remains one of the most extensively used models in the study of IBD. DSS is a polysulphated polysaccharide having molecular weights ranging from 5 KDa to 500 KDa [39]. The molecular weight of DSS and the degree of induced colonic inflammation are known to be directly proportional to each other. This model has proved highly valuable, due to its ease of development, reliability, reproducibility and wide availability of the agent.

Alternative models employing carcinogenic agents like azoxymethane (AOM) have been established to imitate IBD-CRC. One such widely accepted murine models representing IBD-CRC is AOM/DSS. AOM, a chemical carcinogen and a metabolite of 1,2-dimethylhydrazine, is known to induce CRC in rodents. Metabolic activation of AOM via hydroxylation results in the formation of methylazoxymethanol (MAM), a reactive metabolite that causes pro-mutagenic lesions [40]. Numerous enzymes are associated with the metabolic activation of AOM. However, CYP2E1, an isoform of cytochrome P450 enzymes, is known to play a vital role in the conversion of AOM to MAM [41]. Corresponding to DSS, some of the top benefits of applying AOM to study IBD-CRC include stability, reproducibility, potency, simple mode of application and cost effectiveness [42].

A single hit of AOM in combination with repeated cycles of DSS has proven to shorten the duration required for the induction of IBD-CRC [43]. Different AOM/DSS administration protocols, for the induction of colorectal tumors, have been tested and are summarized in a review by Robertis et al. [44]. Till date, AOM/DSS model remain one the best prototypes in the study of human IBD-CRC. For instance, AOM/DSS induced tumors are formed in the distal colon, together with the formation of pre-cancerous lesions and foci of aberrant crypts (ACF). Consistent to human CRC, other abnormalities induced by AOM/DSS, include deregulation of APC/beta-catenin-signaling pathway and regulation of correlated genes, such as myelocytomatosis oncogene (c-Myc), cyclin D1 and cyclin-dependent kinase 4 (cdk4). Mutation of Kristen rat sarcoma (K-RAS) viral oncogene, increased expression of inducible nitrogen synthase (iNOS) and cyclooxygenase-2 (COX-2) has also been reported [44].

Another widely accepted class of chemical carcinogen include the use of heterocyclic aromatic amines and alkylnitrosamide to induce colonic lesions in rodents [45,46]. Repeated bouts of heterocyclic amine (PhIP) for 104 weeks develops tumor in rodents [46]. Additionally, a combination of high doses of PhIP together with AOM was shown to enhance the tumorigenic and mutagenic effect [47]. Contrariwise, no such effect was observed with low doses of PhIP [47]. Compared to AOM/DSS model, this model is not correlated with P53 and KRAS mutations, which is known to play a key role during early stage transition from IBD to CRC. However, induction of APC mutation and microsatellite instability make this model more relevant to study sporadic CRC [48].

Administration of 3, 2'-dimethyl-4-aminobiphenyl (DMBA) or intra-rectal injection of methylnitrosourea (MNU) are also used to induce lesions (colonic or rectal) and epithelial neoplasms in rodents respectively [45,49]. However, repeated injections and infiltration of the neoplasm to adjacent tissues make DMBA, a less potent carcinogen [45]. Although, no biochemical activation is required for MNU however, intra-rectal administration limits its use in comprehensive studies [49].

2.2.3. Combination models

The intestinal mucus is well known to play a pivotal role in limiting the extent of inflammation and infection. Gel-forming mucins, especially Mucin2 (MUC2), is one of the major components of the mucus system [50]. Defective colonic mucus formation, mainly MUC2, is implicated in the pathogenesis of IBD and related disorders [36]. *Winnie* model of IBD is derived from *N*-ethyl-*N*-Nitrosourea (ENU) mutagenesis. This model possesses missense mutation in D3 and D4 domains of MUC2. Disruption of MUC2 secretory function leads to the activation of unfolded protein response (UPR), and endoplasmic reticulum (ER) stress, resulting in a spontaneous and severe model of IBD [28].

Recently, *Winnie* and DSS model of IBD were merged together and trailed for the characterization of molecular and cellular pathways linking IBD and CRC [51]. After the completion of DSS protocol in *Winnie* model, glandular morphological abnormalities, resembling pre-cancerous evolution was observed. Other pre-cancerous changes include architectural derangement consistent to high-grade dysplasia, and penetration of crypts beyond muscularis mucosae. A pattern of altered expression of pro-inflammatory cytokines and other inflammatory markers was also noticed [51]. Nevertheless, there is still a need for further research attempts to strengthen the effectiveness of this

model in exploring the progression of IBD-CRC. Identical to AOM/DSS, development of AOM/*Winnie* model to correlate IBD and CRC will help us to obtain meaningful and comprehensive etiological data on IBD-CRC and hence, the opportunities for the treatment of such malignancies.

3. Insight into the Molecular Mechanisms of IBD-CRC

The mechanisms responsible for the transformation of chronically inflamed tissue to early pre-cancerous lesion remain largely unknown. The various proposed molecular mechanisms that may account for IBD-CRC include-

3.1. Oxidative stress, genetic and epigenetic alterations

Oxidative stress is a key component responsible for the progression of various inflammatory disorders, including IBD and CRC [52,53]. An imbalance in the production and elimination of reactive oxygen species (ROS), and reactive nitrogen species (RNS), are hallmark features of oxidative stress. Various types of ROS and RNS released into the tissue microenvironment include nitrogen, hydrogen peroxide, superoxide, hydroxyl radicals, and singlet oxygen [52,53] which brings the tissue damage. Numerous studies have documented the increased expression and detrimental effects of ROS/RNS in human IBD [54,55,56]. ROS has been implicated in human IBD and CRC. Nanoparticle(s)-mediated suppression of ROS has shown to reduce the symptoms of IBD [57]. DNA damage-dependent interaction between the ROS/RNS is one the major contributory factors influencing the growth of the tumor. Oxidative stress induced disruption of DNA methylation patterns leads to genomic instability and mutations. For instance, oxidative stress induced DNA damage of tumor suppressor (p53) and proto-oncogenes (Ras) during tumorigenesis by inactivating p53 and by activating the Ras, drives UC to CRC [58,59].

Recent reports have shown the pathogenic role of oxidative stress in mice model of IBD-CRC [60–64]. However, the role of ROS/RNS in IBD-CRC is still unclear. Using preclinical murine models of IBD-CRC, the direct and indirect function of ROS/RNS, and resulting epigenetic changes during the early transition from IBD to dysplasia should be clearly defined.

The epigenetic abnormalities involved in IBD-CRC are not yet fully understood. However, inflammation-driven heritable changes in the expression of genes and associated regulatory pathways have been recognized to play a substantial part in IBD and CRC. Various genetic and epigenetic deformities that may influence the transition from IBD to CRC include changes in DNA methylation through chromosomal and microsatellite instability, mutations in tumor suppressor genes, such as TP53, APC, and INK4, as well as alterations in genes like MLH that control DNA stability [65–70]. Activation and up-regulation of DNA methyltransferase (Dnmt1 and Dnmt3) genes have also been reported [71,72]. Importantly, the expression of these genes has a broad impact on DNA methylation profile and hence, been positively correlated with IBD-CRC.

Post-translational histone modifications are also one of the epigenetic irregularities which are known to be associated with CRC [73]. Histones are the proteins that regulate normal functioning of genes in healthy cells. During cancer, the lysine and arginine residues of unstructured N-terminal tail of histones get modified by various chemical reactions including phosphorylation, acetylation,

ubiquitination and methylation [73]. However, histone modification due acetylation and methylation are predominantly characterized in CRC pathogenesis [73–76]. The functioning of histone acetylation modification is regulated by histone deacetylases (HDACs)/histone acetyltransferases (HATs) whereas, histone methylation is controlled by histone methyltransferases (HTMs)/histone demethylases (HDMs), in a reversible manner [76,77]. During CRC, lysine-9 residues gets modified by deacetylation and methylation in histone H3, lysine- 16 gets monoacetylated while lysine-20 residues in histone H4 undergoes trimethylation [78,79]. Several studies have been conducted to identify the possible link between histone deacetylation and IBD-CRC using HDAC inhibitors in DSS and AOM/DSS models of IBD and IBD-CRC [80,81]. For instance, HDAC inhibitors like valproic acid suppress the release of pro-inflammatory cytokines (IL-6, TNF-α and INF-γ), increases the apoptosis and histone H3 acetylation in DSS model of IBD [80]. Another HDAC inhibitor (ITF2357) attenuated the inflammation, growth and number of tumors by increasing histone H3 acetylation, inhibiting HDAC enzyme as well as NF-κB signaling, enhancing apoptosis in lamina propria and IL-10 release [81].

Other most prominent epigenetic modifications involve the action of microRNAs (miRNAs), which holds potential for the study of IBD-CRC. miRNAs belong to multiple gene families and are a class of small, endogenous non-coding RNA molecules having 18–24 nucleotide. These molecules are known to directly bind the messenger RNAs (mRNAs), causing their degradation or translation repression and thereby, regulate the process of gene expression [82]. Expression of several miRNAs have been reported to be elevated in patients with IBD or progressive IBD-CRC such as miR-26b, miR-17, miR-21, miR-126, miR-155, miR-143, miR-192 etc. [83–89]. miRNAs are known to regulate the expression of multiple genes and inflammatory mediators that are imperative in the development of IBD and IBD-CRC [90,91]. For instance, miR-126 was observed to increase the inflammatory response via the activation of NF- κB signaling [92]. Likewise, miR-155 was shown to be involved in the activation of JAK/STAT signaling during IBD [93]. As a proof of concept, inhibition of miRNAs was found to reduce the severity of IBD and IBD-CRC [85,87]. Additional research is still required to fully understand the regulatory relationship between miRNAs and their targeted genes during IBD-CRC, to progress towards miRNA therapeutics.

3.2. Innate/Adaptive immune related mechanism

Like several other chronic inflammatory conditions, dysregulation of the immune response in patients with IBD or IBD-CRC, triggers infiltration and accumulation of immune cells; that provokes the release of several pro-inflammatory cytokines and chemokines. These cells comprise, neutrophils, tumor-associated macrophages, cluster of differentiation (CD)4 and CD8 cells, endothelial cells, natural killer (NK) cells, dendritic cells, as well as mesenchymal cells [94,95]. The release of pro-inflammatory cytokines/chemokines plays an essential role as a predictive marker for the early identification of inflammation. However, spontaneous hyper-production of pro-inflammatory mediators counteracts their effector functions, contributing to aberrant immune responses, as seen in IBD-CRC [95]. The release of various other inflammatory cytokines/chemokines, such as IL-1β, IL-6, IL-8, IL-17, IL-18, IL-21, IL-23, interferon-gamma (INF-γ), CCL22, CCL12 and tumor necrosis factor-alpha (TNF-α), have been reported during IBD [94, 96–100]. Each of these mediators, notably IL-6, TNF-α, IL-17 and IL-23,

is implicated in IBD associated tumor development [101,102,103]. Suppression of these cytokines was found to ameliorate the symptoms of IBD-CRC progression [102,104,105].

Dysregulation of novel innate immune mechanism nucleotide oligomerization domain (NOD)-like receptor proteins (NLRPs) has been linked to IBD and IBD-CRC. Various anti-tumorigenic activities of NOD in the gut, include inhibition of Toll-like receptor (TLR) signaling, balancing T cell-mediated immune responses, alleviates production of anti-inflammatory cytokines, like IL-10, and inhibition of potent inducers of inflammation (inflammasomes) [106,107]. It is still contraversial whether IBD-CRC is fully dependent on NOD or NLRPs. However, dampened production of NOD/NLRPs in mouse model of IBD-CRC has shown to increase IBD severity and rapid progression towards tumor development [108,109,110].

3.3. Immune signaling pathways

Several immune signaling pathways are known to be involved in IBD and CRC. Nonetheless, the activation of two major oncogenic transcription factors/pathways, NF-κB and signal transducer and activator of transcription 3 (STAT3) drives the process of chronic inflammation and carcinogenesis. These pathways are mostly activated via pro-inflammatory stimuli. Several lines of evidence indicate, that activation of NF-κB and STAT3 pathways, lead to the production of a myriad of inflammatory mediators contributing to inflammation-induced CRC [111,112,113]. Inhibition of these transcription factors/pathways thought to play a significant role in limiting the extent of tumorigenic processes, like cell proliferation, apoptosis, metastasis and angiogenesis, occurring during IBD-CRC [111,113,114]. The process of activation of NF-κB via canonical pathway consist of dimers of RelA, p50 and RelC subunits. During unstimulated state, these dimers remain bound to specific inhibitors, IκB proteins, in the cytoplasm. However, stimulus from microbial infections, IL-1, TNF-α and lipopolysaccharide (LPS) activates the IκB kinase complex (IKKα and IKKβ) and triggers the proteosomal degradation of IκB. Consequently, unbound subunits RelA/p50 translocate to the nucleus and begins the transcription of target genes. An alternative pathway for NF-κB stimulation requires the IκB-Kinase-alpha (IKKα) subunit-mediated proteosomal degradation. The unbound p52/RelB dimers translocate and start the transcription of target genes in the nucleus. During inflammation, persistent activation of NF-κB leads to cancer [115,116]. A preclinical study by Greten et al., has also shown the role of IKKβ in activation NF-κB signaling and linking inflammation and tumorigenesis in AOM/DSS model of IBD-CRC [117].

Activation of NF-κB liberates IL-6 from myeloid, macrophages, lymphocytes, monocytes and other cancerous cells. IL-6 forms a complex by binding to its soluble IL-6R receptors, that further engages with glycoprotein gp130 subunit and results in the activation of various downstream signaling pathways involving STAT3, Janus Kinase (JAK) and phosphatidylinositol 3 kinase (PI3K-Akt) [118]. STAT3 is a transcription factor which assist cell proliferation and survival by inhibiting apoptosis, metastases, cell adhesion, angiogenesis and inflammation [119]. Not only IL-6, but other inflammatory mediators such as IL-11, hepatocyte growth factor (HGF), IL-22 and vascular endothelial growth factor (VEGF) activates STAT3 during IBD and IBD-CRC [119,120,121]. IL-6 promotes tumor development via activation of STAT3 mediated intestinal epithelial cell proliferation and survival in mouse model of IBD-CRC [113]. In addition,

persistent activation of NF-κB in tumor cells is mediated by STAT3 which prompts the retention of RelA into nucleus and hence, amplify the effect of NF-κB during malignant transformation [114].

3.4. Role of host microbiota in IBD-CRC

The intestinal tract is a home to diverse species of microorganisms, including microbes, viruses, and fungi, that contribute towards maintaining the homeostasis. Recently, however, there have been reports on the role of intestinal microbiota in IBD and CRC development [122–125]. Multiple mechanisms have been postulated regarding the action of intestinal microbiota in the pathogenesis of IBD and CRC. An imbalance of the normal microbiota (dysbiosis) is thought to be one of the key mechanisms linked to the development of IBD-CRC [126]. Dysbiosis is associated with the production of carcinogenetic genotoxins, the release of pro-inflammatory mediators and activation of critical cellular inflammatory signaling pathways, and hence, implicated in the causation of IBD-CRC [107,127,128]. For instance, toxins released from bacteria such as *Escherichia coli, Bacteroides fragilis, Citrobacter rodentium* and *Clostridium defficile* are shown to directly influence the growth of tumor in the colon [128]. Moreover, the role of bacteria like *H. hepaticus* was found to be critical during inflammation and initiation of carcinogenesis in murine models of IBD [14].

Dysbiosis leads to the activation of pattern recognition receptors (PRRs) including TLRs. During inflammation, entry of pathogens into lamina propria triggers the activation of TLRs resulting in the release of pro-inflammatory cytokines and subsequent stimulation of the innate immune system cells that binds to microbe-associated molecular patterns (MAMP), ending in uncontrolled NF-κB signaling [127]. Among 13 TLRs, TLR2 and TLR4 are gaining wide attention for their role in the progression of IBD-CRC. TLR2 is reported to have a protective role in AOM/DSS model of IBD-CRC [129]. Contrastingly, mice deficient in TLR4 was found to have reduced number of tumors and COX-2 expression [130]. Differences in the microbiota in different mice models of IBD-CRC might contribute to these conflicting findings. Further studies are warranted to strengthen such observations.

4. Current and Future Management Strategies

The most common types treatments of CRC or IBD-CRC include surgery, chemo- and radiation therapy. Surgical resection is usually recommended when patients are unresponsive to pharmacological interventions or radiation therapies [131]. Cytocidal drugs and biological agents are administered to the patients in conjunction with surgery, chemo- or radiation therapy [132]. However, these approaches are reported to have a number of drawbacks and may cause severe and potentially life-threatening complications. Most importantly, these approaches are also associated with higher rates of tumor recurrence.

The generation of in-vitro attempts and various animal models of IBD, CRC, as well as IBD-CRC, have been pivotal in testing many biological molecules, as an anti-tumor agent. For instance, the anti-inflammatory and anti-tumorigenic potential of monoclonal antibodies and anti-cytokine agents, such as TNF-α inhibitors, has been tested in patients with IBD and IBD-CRC [105]. However, as seen with other chemotherapeutic agents, their prolonged use is associated with

significant side effects. Moreover, these agents are quite expensive, and importantly, many patients do not respond to these therapies leading to remission of chronic inflammation and tumor formation that require surgical intervention. Nevertheless, there are studies suggesting the potential role of several natural and synthetic compounds in the management of IBD, CRC, and potentially IBD-CRC, by targeting the release of inflammatory markers associated with such disorders. These compounds are summarized in Table 1. together with their role and potential mode of action (Figure 1). Herein, we have briefly described below the novel therapeutic agents that might play a key role in discontinuing the inflammatory/tumorigenic response during IBD-CRC.

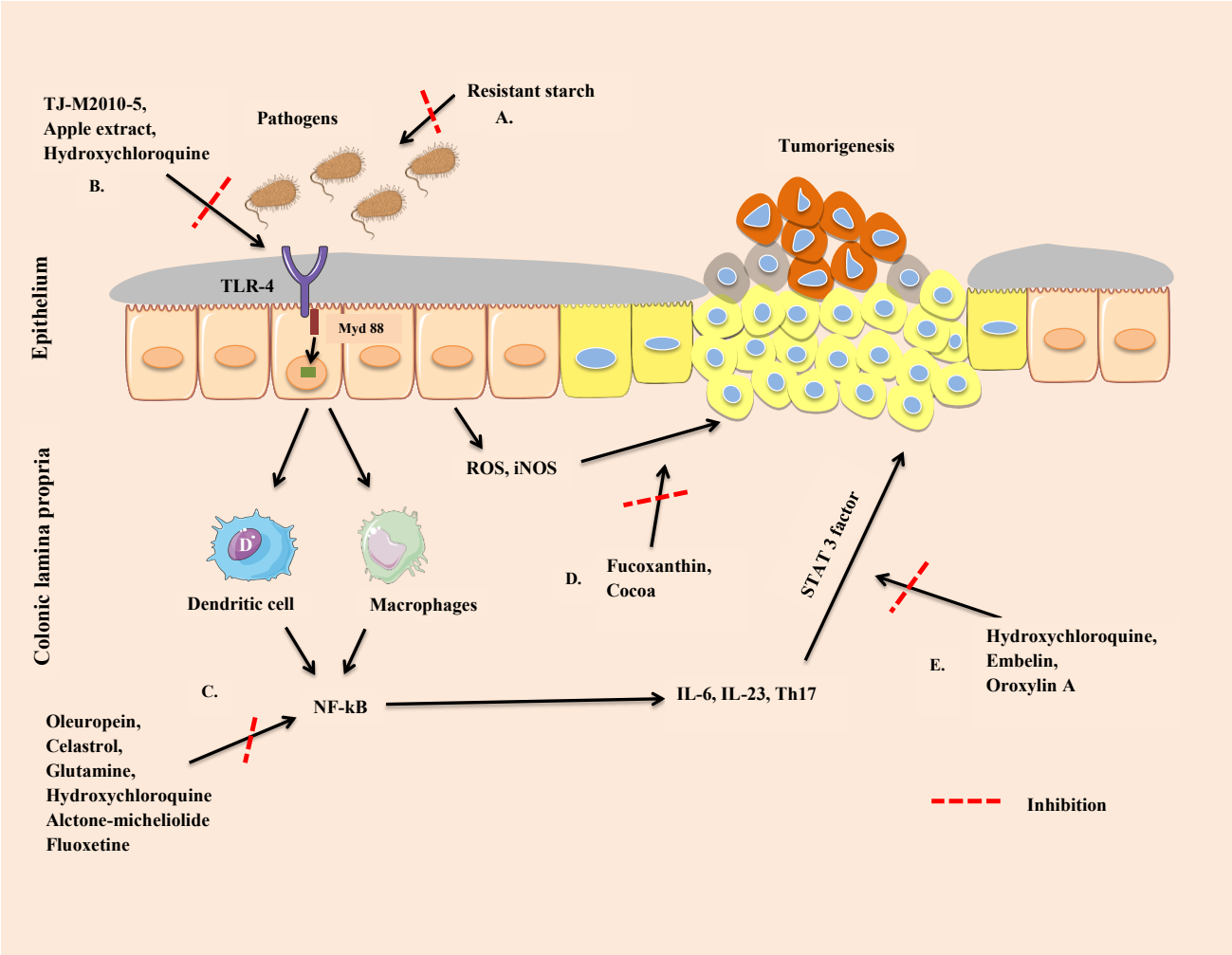

Figure 1. Targeting IBD-CRC using natural or synthetic drugs inhibit. (A) the entry of gut pathogens into lamina propria by releasing short chain fatty acids, (B) dysbiosis mediated activation of innate immune TLR/Myd88 (myeloid differentiation 88) signaling, (C) activation of NF-κB mediated release of pro-inflammatory cytokines such as TNF-α, IL-6, IL-23, IL-22, IL-17 from dendritic cells and macrophages, (D) overproduction of oxidative and nitrosative stress and DNA damage, (E) IL-6/STAT3 pathway induced cell proliferation.

Table 1. Classification of novel therapeutic compounds and their role and mechanism of action in ameliorating IBD-CRC.

Compound	Class	Inhibitory Effect	Potential Mode of Action	References
Oleuropein	Natural Product	INF-γ, TNF-α, IL-6, COX-2 and IL-17A	Blockade of immune signaling pathways, such as STAT3 and NF-κB	[137]
GNDPs2	Natural Product	TNF-α, IL-6 and IL-1β	Inhibition of pro-inflammatory cytokine release	[138]
Celastrol	Natural Product	TNF-α, IL-6 and IL-1β, COX-2 and iNOS	Downregulation of NF-κB pathway	[139]
Resistant Starch	Natural Product	COX-2, IL-1β and TNF-α	Decreased NF-κB expression and altered gut microbiota	[142]
Fucoxanthin	Natural Product	TNF-α, IL-6 and iNOS	Suppression of oxidative stress	[143]
Cocaine	Natural Product	COX-2 and iNOS	Suppression of oxidative stress	[144]
Apple extract (AP)	Natural Product	IL-6, TNF-α and INF-β	Suppression of NF-κB signaling	[173]
Digitoflavone	Natural Product	IL-6, TNF-α and IL-1β	Suppression of oxidative stress	[174]
Oroxylin A	Natural Product	IL-6 and IL-1β	Attenuation of IL-6/STAT3 signaling	[150]
TJ-M2010-5	Synthetic analogue	TNF-α, IL-6, IL-11, IL-17A, IL-22, COX-2 and IL-23	Downregulation TLR signaling	[155]
Glutamine supplements	Synthetic/pre-existing drugs	TNF-α, IL-6, COX-2 and iNOS	Downregulation of NF-κB signaling	[175,176]
Tropisetron	Synthetic/pre-existing drugs	TNF-α, IL-6 and IL-1β, TLR4, COX-2 and β-catenin	Inhibition of pro-inflammatory cytokine release	[156]
Fluoxetine	Synthetic/pre-existing drug	TNF-α	Inhibition of TNF-α-mediated NF-κB signaling	[158]
Cimetidine and clobenpropit	Synthetic/pre-existing drug	IL-6, TNF-α, IL-1β, COX-2 and iNOS	Modulation of oxidation and antioxidant ratio	[159]
Hydroxychloroquine	Synthetic/pre-existing drug	IL-6, TNF-α, COX-2 and IL-1β	Attenuation of TLR4 activation, STAT3 and NF-κB pathway	[162]
Embelin	Synthetic analogue	IL-6, IL-17A, IL-23A and IL-1β,	Attenuation of IL-6/STAT3 signaling	[163]
ITF2357	Synthetic analogue	INF-γ	Inhibition of NF-κB activation	[81]

5. Naturally-occurring Compounds

5.1. Oleuropein

Oleuropein is a natural phenolic secoiridoid obtained from olive leaves and is known to have anti-inflammatory, anti-tumorigenic and anti-proliferative properties. It has been tested in several inflammatory models such as DSS-colitis and also in prostate and breast cancer cells [133–136]. In a recent study by Giner et. al., the anti-cancer potential of oleuropein was investigated in AOM/DSS model of IBD-CRC [137]. Oleuropein treatment reduced the colonic neoplasms by 64% as compared to control (100%) by downregulating the level of cytokines, enhancing the expression of apoptosis genes and limiting the activation of signaling pathway associated with IBD-CRC [137].

5.2. GDNPs2

GDNPs2 is a naturally occurring nanoparticle, extracted from edible ginger, identified as one of the most effective novel nanoparticles for the management of IBD-CRC. Oral administration of GDNPs2 attenuated the symptoms associated with IBD-CRC, raised the production of anti-inflammatory cytokines such as IL-10 and IL-22, and enhanced the proliferation of intestinal epithelial cells in mice model of IBD-CRC [138]. They have also shown merits like overcoming potential toxicity and limiting the production scale which is essential to prepare synthetic nanoparticles.

5.3. Celastrol

Celastrol (tripterine) is a compound isolated from a Chinese herb and is known to possess anti-tumorigenic and anti-inflammatory properties. Recent, in-vitro and in-vivo experiments explored the anti-tumorigenic and anti-inflammatory potential of celastrol in IBD-CRC. The compound was observed to downregulate the production of inflammatory markers, oncogenes, p53 mutated genes that are involved in the process of IBD associated carcinogenesis [139,140].

5.4. Resistant starch

Resistant Starch (RS) is among the dietary components which were tested against IBD-CRC. RS fermentation is known to produce short-chain fatty acids (SCFAs). These fatty acids are a contributing factor towards the maintenance of the intestinal homeostasis, as well as, attenuation of carcinogenesis [141]. Recently, Hu et al. evaluated the potential of RS in AOM/DSS model of IBD-CRC. Interestingly, RS was found to prevent the further progression of IBD-CRC mostly via encouraging the production of SCFAs and altering the gut microbiota [142].

5.5. Fucoxanthin and cocoa

Fucoxanthin is isolated from edible brown algae and is considered as one of the ROS/RNS scavengers. The anti-cancer potential of fucoxanthin was tested using mice model of IBD-CRC. It was reported that fucoxanthin ameliorated the progression of IBD-CRC development by reducing the occurrence of neoplasms. Fucoxanthin-induced upregulation of superoxide dismutase (endogenous anti-oxidative enzyme), as well as, downregulation of malondialdehyde (endogenous oxidant)

prevents the cells from DNA damage and therefore, capable of impeding the process of carcinogenesis [143]. Similarly, cocoa, a naturally occurring polyphenolic compound suppressed the progression of IBD-CRC in AOM/DSS model. The anti-oxidative nature of this compound was found to downregulate the concentrations of malondialdehyde, COX-2, and iNOS and create an upsurge in the levels of antioxidant enzymes like superoxide dismutase [144].

5.6. Konjac glucomannan and inulin

One of the fibrous substances "inulin and Konjac Glucomannan", diminished the progression of IBD-CRC via recovering the leukocyte phagocytic capacity, reducing the extent of tumor invasion and attenuating the production of pro-inflammatory mediators like TNF-α and IL-1β [145]. Further reduction in hyperplasia–dysplasia transition in IBD-CRC mice model was initiated after dietary consumption of fruit "*Ziziphus jujuba*", enriched with polysaccharides, flavonoids, oleamide, and triterpenoids [146].

5.7. Sesquiterpene and fisetin

Sesquiterpene is one of the promising molecules which is considered to be a potent inhibitor of NF-κB signaling pathway and therefore, attenuated IBD-CRC progression in AOM/DSS model [147]. Likewise, another dietary flavonoid, fisetin, was shown to ameliorate IBD-CRC development via a reduction in enzymatic and non-enzymatic antioxidant levels including superoxide dismutase [148].

5.8. Astaxanthin and oroxylin A

Astaxanthin, a natural carotenoid, inhibited IBD-CRC in AOM/DSS model by downregulating the expression of inflammatory mediators such as NF-κB, IL-1β, COX-2, and IL-6 [149]. Similarly, oroxylin A, a flavone obtained from medicinal plants, was reported to be effective in in-vitro and in-vivo models of IBD-CRC by inactivating the IL-6/STAT3 pathway [150].

5.9. Bio-active peptides

Recently, a melanocortin-derived tripeptide, KVP has been depicted as an anti-inflammatory and anti-carcinogenic agent in murine models of IBD-CRC [151]. KVP was found to obstruct the development of CRC by reducing the tumor burden in AOM/DSS model. However, studies are warranted to decipher the exact mechanism via which KVP reduces the tumor load to act against the advancement of IBD-CRC [152].

6. Synthetic/Pre-Existing Drugs

There is an increasingly expanding array of synthetic/pre-existing molecules aimed at reducing the extent of inflammatory responses during IBD-CRC. These agents are briefly discussed below.

6.1. Ursodeoxycholic acid

Ursodeoxycholic acid drops the release of excessive bile acids and hence, reduces the risk of developing CRC [153,154]. Excessive release of secondary bile acids in the lumen of colon is considered as one of the risk factors causing IBD-CRC. Correspondingly, "TJ-M2010-5", a novel synthetic inhibitor of TLR/MyD88 signaling restricts the development of IBD-CRC in AOM/DSS model. Apart from reducing the levels of pro-inflammatory cytokines, TJ-M2010-5, also promotes the dimerization of MyD88 and alters its configuration, hence negatively regulates the tumorigenesis process [155].

6.2. Tropisetron

Serotonin, a neurotransmitter, and its associated receptors are found to be overexpressed in IBD and promoted CRC. Inhibition of serotonin receptors by antagonist tropisetron proved to be protective in AOM/DSS model. Tropisetron is used as an antiemetic in chemotherapy, inhibited the IBD-CRC and significantly reduced the inflammatory mechanisms in colitis [156,157]. Another drug "fluoxetine" is an antidepressant from the class of serotonin reuptake inhibitors also attenuated DSS-induced inflammation and IBD-CRC in DSS and AOM/DSS mice models, respectively. The major mechanism involved was the inhibition of TNF-α mediated NF-κB signaling in COLO-205 cells, as well as in mouse models of IBD-CRC. It also inhibited the production of myeloperoxidase (MPO) and macrophage inflammatory protein 2 (MIP2) secretion [158].

6.3. Cimetidine and clobenpropit

The antagonist of histamine receptors such as cimetidine (histamine receptor 2 inhibitor) and clobenpropit (histamine receptor 3 inhibitor) exhibited the chemopreventive efficacy in IBD-CRC. Clobenpropit is also known to inhibit histamine receptor 4. These inhibitors modulate the oxidative and anti-oxidative status and enhance apoptosis of cells due to an increase in the levels of histamine as reported in UC, CD, and CRC patients [159,160]. These studies also reported a potential role of histamine receptors in causing IBD-CRC.

6.4. GAP, hydroxychloroquine and embelin

"GAP [3-(4-geranyloxy-3-methoxyphenyl)-2-trans-propenoic acid] or (4-geranyloxy-ferulic acid)", a synthetic prodrug ameliorates the IBD-CRC via a reduction in oxidative stress by lowering the 8-OHdG levels (oxidative stress biomarker) in mice and proliferation of cells in-vivo [161]. Anti-inflammatory potential of antimalarial drugs such as hydroxychloroquine (HCQ) might make this medication useful for the treatment of IBD-CRC. HCQ ameliorates IBD-CRC by reducing the release of ROS in lamina propria and inactivation of TLR4 in macrophages [162]. "Embelin" is a small molecule inhibitor, enriched with various properties such as antioxidant, anti-cancer and anti-inflammatory. It exerts its action by reducing the infiltration of macrophages, $CD4^+$ T cells, proliferation of the tumor epithelial cells and inactivation of STAT3 pathway [163].

6.5. FTY720

S1P (metabolite) produced from sphingokinases (SphK1) are the proteins involved in various cellular processes (cell growth, invasion, cytokine and chemokine production). This metabolite is implicated in UC and CRC and is known to be a vital player for the persistent activation of the STAT3 signaling pathway. Inhibition of S1P by prodrug "FTY720" reduces the expression of S1P receptor S1PR and SphK1 and hence ameliorates the activation of NF-κB and IL-6/STAT3 pathways in IBD-CRC model [164,165,166].

6.6. Nimesulide, troglitazone and celecoxib

The role of COX-2 inhibitors in the treatment of CRC and intestinal inflammation has already been identified [167]. A study reported the chemopreventive effectiveness of nimesulide (selective COX-2 inhibitor) in AOM/DSS model. It suppressed the proliferation of cells, induce apoptosis and downregulate the levels of β-catenin, COX-2, and iNOS, and therefore, was found to be effective in sporadic as well as IBD associated carcinomas [168]. In the same study, PPAR ligands such as troglitazone exerted similar anti-cancer effects [168]. Another selective COX-2 inhibitor "celecoxib" act as a chemopreventive agent in IBD-CRC mice model by inhibiting the PI3K/Akt pathway [169].

6.7. Statin hydroxamate and ITF2357

Inhibition of histone deacetylase by statin hydroxamate and ITF2357 is another therapeutic approach which is currently tested in clinical trials. These compounds modulate the acetylation of NF-κB and inhibit the apoptosis of cells. Statin hydroxamate and ITF2357 also inhibit the release of bacterial endotoxins, suppress the production of pro-inflammatory cytokines, decrease the infiltration of macrophages and neutrophils in cancerous regions and elevate the apoptosis of mononuclear cells in lamina propria [81,170,171].

Considering, the present scenario and trends, there is an urgent need to identify and develop novel chemotherapeutic agents, which are cost effective, safe, patient compliant and free from adverse effects. Several novel classes of compounds, such as naturally occurring agents, pre-existing drugs, synthetic analogues, and dietary composites, have shown considerable promise in the management of inflammation associated CRC. A new technique named "photodynamic therapy" was developed for the treatment of IBD-CRC. It involves the treatment with liposomal formulation (metatetra hydroxyphenyl chlorine also called foslip), which in low doses lowers the influx of neutrophils and prevents the dysbiosis of gut microbiota and hence was found to be effective in IBD-CRC [172]. Furthermore, Vong et al. developed a novel oral nanotherapy by designing redox nanoparticles, which can be considered as a promising treatment for IBD-CRC [57].

Discovery of an active, multi-target mono-therapeutic agent, for patients with CRC, would change the course of cancer research. However, the complexity of such disorders makes it hard to implement such therapies. Nevertheless, in conjunction with currently used surgical and pharmacological interventions, prospective randomized controlled trials should focus on evaluating

the long-term efficacy, and side-effect profiles of the promising anti-cancer agents to pave the way towards eradicating inflammation-related carcinogenesis.

7. Conclusion

Various scientific findings evidence a functional link between IBD and CRC. The molecular mechanisms behind IBD-CRC progression are still not fully revealed and need attention. However, recent findings from animal studies implicate the potential role of various immune cells, signaling pathways, pro-inflammatory cytokines and other inflammatory markers in IBD-CRC development. Continued research in this field especially the discovery of various new natural and synthetic therapeutic moieties would help us decode the underlying mechanisms involved with IBD-CRC and would eventually lead to new therapeutic interventions which can significantly contribute in IBD-CRC clinics.

Acknowledgements

This work was supported by Early-Career Fellowship awarded to Dr Madhur D. Shastri by the Faculty of Health, University of Tasmania and Tasmanian Post-Graduate Research Scholarship (TGRS) awarded to Sonia Shastri.

Conflict of Interest

All authors declare no conflicts of interest in this paper.

References

1. Cosnes J, Gower-Rousseau C, Seksik P, et al. (2011) Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterol* 140: 1785–1794.
2. Shanahan F, Bernstein CN (2009) The evolving epidemiology of inflammatory bowel disease. *Curr Opin Gastroenterol* 25: 301–305.
3. Economou M, Pappas G (2008) New global map of Crohn's disease: Genetic, environmental, and socioeconomic correlations. *Inflamm Bowel Dis* 4: 709–720.
4. Mulder DJ, Noble AJ, Justinich CJ, et al. (2014) A tale of two diseases: the history of inflammatory bowel disease. *J Crohns Colitis* 8: 341–348.
5. Hanauer SB (2006) Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities. *Inflamm Bowel Dis* 12: S3–S9.
6. Dubinsky M (2008) Special issues in pediatric inflammatory bowel disease. *World J Gastroenterol* 14: 413–420.
7. Diefenbach KA, Breuer CK (2006) Pediatric inflammatory bowel disease. *World J Gastroenterol* 12: 3204–3212.
8. Ekbom A, Helmick C, Zack M, et al. (1991) The epidemiology of inflammatory bowel disease: a large, population-based study in Sweden. *Gastroenterol* 100: 350–358.

9. CROHN BB, Rosenberg H (1925) The sigmoidoscopic picture of chronic ulcerative colitis (non-specific). *Am J Med Sci* 170: 220–227.
10. Rutter MD, Saunders BP, Wilkinson KH, et al. (2006) Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterol* 130: 1030–1038.
11. Beaugerie L, Svrcek M, Seksik P, et al. (2013) Risk of colorectal high-grade dysplasia and cancer in a prospective observational cohort of patients with inflammatory bowel disease. *Gastroenterol* 145: 166–175.
12. Eaden J, Abrams K, Mayberry J (2001) The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 48: 526–535.
13. Canavan C, Abrams K, Mayberry J (2006) Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment Pharmacol Ther* 23: 1097–1104.
14. Itzkowitz SH, Yio X (2004) Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol* 287: G7–G17.
15. Kornfeld D, Ekbom A, Ihre T, et al. (1997) Is there an excess risk for colorectal cancer in patients with ulcerative colitis and concomitant primary sclerosing cholangitis? A population based study. *Gut* 41: 522–525.
16. Matula S, Croog V, Itzkowitz S, et al. (2005) Chemoprevention of colorectal neoplasia in ulcerative colitis: the effect of 6-mercaptopurine. *Clin Gastroenterol Hepatol* 3: 1015–1021.
17. Terdiman JP, Steinbuch M, Blumentals WA, et al. (2007) 5-Aminosalicylic acid therapy and the risk of colorectal cancer among patients with inflammatory bowel disease. *Inflamm Bowel Dis* 13: 367–371.
18. Kiesslich R, Goetz M, Lammersdorf K, et al. (2007) Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. *Gastroenterol* 132: 874–882.
19. Schneider MR, Hoeflich A, Fischer JR, et al. (2000) Interleukin-6 stimulates clonogenic growth of primary and metastatic human colon carcinoma cells. *Cancer Lett* 151: 31–38.
20. Sakamoto K, Maeda S, Hikiba Y, et al. (2009) Constitutive NF-κB activation in colorectal carcinoma plays a key role in angiogenesis, promoting tumor growth. *Clin Cancer Res* 15: 2248–2258.
21. Kang KA, Zhang R, Kim GY, et al. (2012) Epigenetic changes induced by oxidative stress in colorectal cancer cells: methylation of tumor suppressor RUNX3. *Tumor Biol* 33: 403–412.
22. Ning Y, Manegold PC, Hong YK, et al. (2011) Interleukin-8 is associated with proliferation, migration, angiogenesis and chemosensitivity in vitro and in vivo in colon cancer cell line models. *Int J Cancer* 128: 2038–2049.
23. Huch M, Koo BK (2015) Modeling mouse and human development using organoid cultures. *Development* 142: 3113–3125.
24. Van Limbergen J, Geddes K, Henderson P, et al. (2013) Paneth cell marker CD24 in NOD2 knockout organoids and in inflammatory bowel disease (IBD). *Gut*: gutjnl-2013-305077.
25. van de Wetering M, Francies HE, Francis JM, et al. (2015) Prospective derivation of a living organoid biobank of colorectal cancer patients. *Cell* 161: 933–945.
26. Fatehullah A, Tan SH, Barker N (2016) Organoids as an in vitro model of human development and disease. *Nat Cell Biol* 18: 246–254.

27. Dharmani P, Leung P, Chadee K (2011) Tumor necrosis factor-α and Muc2 mucin play major roles in disease onset and progression in dextran sodium sulphate-induced colitis. *PLoS One* 6: e25058.
28. Heazlewood CK, Cook MC, Eri R, et al. (2008) Aberrant mucin assembly in mice causes endoplasmic reticulum stress and spontaneous inflammation resembling ulcerative colitis. *PLoS Med* 5: e54.
29. Half E, Bercovich D, Rozen P (2009) Familial adenomatous polyposis. *Orphanet J Rare Dis* 4: 22.
30. Fodde R, Smits R (2001) Disease model: familial adenomatous polyposis. *Trends Mol Med* 7: 369–373.
31. Quesada CF, Kimata H, Mori M, et al. (1998) Piroxicam and acarbose as chemopreventive agents for spontaneous intestinal adenomas in APC gene 1309 knockout mice. *JPN J Cancer Res* 89: 392–396.
32. Corpet DE, Pierre F (2003) Point: From animal models to prevention of colon cancer. Systematic review of chemoprevention in min mice and choice of the model system. *Cancer Epidemiol Biomarkers Prev* 12: 391–400.
33. Aoki K, Tamai Y, Horiike S, et al. (2003) Colonic polyposis caused by mTOR-mediated chromosomal instability in Apc+/Δ716 Cdx2+/− compound mutant mice. *Nat Genet* 35: 323–330.
34. Heyer J, Yang K, Lipkin M, et al. (1999) Mouse models for colorectal cancer. *Oncogene* 18: 5325–5333.
35. Velcich A, Yang W, Heyer J, et al. (2002) Colorectal cancer in mice genetically deficient in the mucin Muc2. *Science* 295: 1726–1729.
36. Van der Sluis M, De Koning BA, De Bruijn AC, et al. (2006) Muc2-deficient mice spontaneously develop colitis, indicating that MUC2 is critical for colonic protection. *Gastroenterol* 131: 117–129.
37. Zhu Y, Richardson JA, Parada LF, et al. (1998) Smad3 mutant mice develop metastatic colorectal cancer. *Cell* 94: 703–714.
38. Yang X, Letterio JJ, Lechleider RJ, et al. (1999) Targeted disruption of SMAD3 results in impaired mucosal immunity and diminished T cell responsiveness to TGF-β. *EMBO J* 18: 1280–1291.
39. Perše M, Cerar A (2012) Dextran sodium sulphate colitis mouse model: traps and tricks. *Biomed Res Int* 2012.
40. Delker DA, McKnight SJ, Rosenberg DW (1998) The role of alcohol dehydrogenase in the metabolism of the colon carcinogen methylazoxymethanol. *Toxicol Sci* 45: 66–71.
41. Haase P, Cowen D, Knowles J (1973) Histogenesis of colonic tumours in mice induced by dimethyl hydrazine. *J Pathol* 109: Px.
42. Neufert C, Becker C, Neurath MF (2007) An inducible mouse model of colon carcinogenesis for the analysis of sporadic and inflammation-driven tumor progression. *Nat Protoc* 2: 1998–2004.
43. Tanaka T, Kohno H, Suzuki R, et al. (2003) A novel inflammation-related mouse colon carcinogenesis model induced by azoxymethane and dextran sodium sulfate. *Cancer Sci* 94: 965–973.

44. De Robertis M, Massi E, Poeta ML, et al. (2011) The AOM/DSS murine model for the study of colon carcinogenesis: From pathways to diagnosis and therapy studies. *J Carcinog* 10: 9.
45. Reddy BS, Ohmori T (1981) Effect of intestinal microflora and dietary fat on 3, 2'-dimethyl-4-aminobiphenyl-induced colon carcinogenesis in F344 rats. *Cancer Res* 41: 1363–1367.
46. Hasegawa R, Sano M, Tamano S, et al. (1993) Dose-dependence of 2-amino-1-methy1-6-phenylimidazo [4, 5-b]-pyridine (PhIP) carcinogenicity in rats. *Carcinogenesis* 14: 2553–2557.
47. Wanibuchi H, Salim EI, Morimura K, et al. (2005) Lack of large intestinal carcinogenicity of 2-amino-1-methyl-6-phenylimidazo [4, 5-b] pyridine at low doses in rats initiated with azoxymethane. *Int J Cancer* 115: 870–878.
48. Kobaek-Larsen M, Thorup I, Diederichsen A, et al. (2000) Review of colorectal cancer and its metastases in rodent models: comparative aspects with those in humans. *Comp Med* 50: 16–26.
49. Narisawa T, Magadia NE, Weisburger JH, et al. (1974) Promoting effect of bile acids on colon carcinogenesis after intrarectal instillation of N-Methyl-N' nitro-N-nitrosoguanidine in Rats. *J Natl Cancer Inst* 53: 1093–1097.
50. Einerhand AW, Renes IB, Makkink MK, et al. (2002) Role of mucins in inflammatory bowel disease: important lessons from experimental models. *Eur J Gastroenterol Hepatol* 14: 757–765.
51. Randall-Demllo S, Fernando R, Brain T, et al. (2016) Characterisation of colonic dysplasia-like epithelial atypia in murine colitis. *World J Gastroenterol* 22: 8334–8348.
52. Gorrini C, Harris IS, Mak TW (2013) Modulation of oxidative stress as an anticancer strategy. *Nat Rev Drug Discov* 12: 931–947.
53. Jackson AL, Loeb LA (2001) The contribution of endogenous sources of DNA damage to the multiple mutations in cancer. *Mut Res Fund Mol Mech Mutagen* 477: 7–21.
54. Kawanishi S, Hiraku Y, Pinlaor S, et al. (2006) Oxidative and nitrative DNA damage in animals and patients with inflammatory diseases in relation to inflammation-related carcinogenesis. *Biol Chem* 387: 365–372.
55. Tüzün A, Erdil A, İnal V, et al. (2002) Oxidative stress and antioxidant capacity in patients with inflammatory bowel disease. *Clin Biochem* 35: 569–572.
56. Nair J, Gansauge F, Beger H, et al. (2006) Increased etheno-DNA adducts in affected tissues of patients suffering from Crohn's disease, ulcerative colitis, and chronic pancreatitis. *Antioxid Redox Signal* 8: 1003–1010.
57. Vong LB, Yoshitomi T, Matsui H, et al. (2015) Development of an oral nanotherapeutics using redox nanoparticles for treatment of colitis-associated colon cancer. *Biomaterials* 55: 54–63.
58. Solomon H, Brosh R, Buganim Y, et al. (2010) Inactivation of the p53 tumor suppressor gene and activation of the Ras oncogene: cooperative events in tumorigenesis. *Discov Med* 9: 448–454.
59. Huang H, Wang H, Lloyd RS, et al. (2008) Conformational interconversion of the trans-4-hydroxynonenal-derived (6S, 8R, 11S) 1, N 2-deoxyguanosine adduct when mismatched with deoxyadenosine in DNA. *Chem Res Toxicol* 22: 187–200.
60. Barrett CW, Ning W, Chen X, et al. (2013) Tumor suppressor function of the plasma glutathione peroxidase gpx3 in colitis-associated carcinoma. *Cancer Res* 73: 1245–1255.

61. Curtin NJ (2012) DNA repair dysregulation from cancer driver to therapeutic target. *Nat Rev Cancer* 12: 801–817.
62. Khor TO, Huang MT, Prawan A, et al. (2008) Increased susceptibility of Nrf2 knockout mice to colitis-associated colorectal cancer. *Cancer Prev Res* 1: 187–191.
63. Meira LB, Bugni JM, Green SL, et al. (2008) DNA damage induced by chronic inflammation contributes to colon carcinogenesis in mice. *J Clin Invest* 118: 2516–2525.
64. Sohn JJ, Schetter AJ, Yfantis HG, et al. (2012) Macrophages, nitric oxide and microRNAs are associated with DNA damage response pathway and senescence in inflammatory bowel disease. *PLoS One* 7: e44156.
65. Kohonen-Corish MR, Daniel JJ, te Riele H, et al. (2002) Susceptibility of Msh2-deficient mice to inflammation-associated colorectal tumors. *Cancer Res* 62: 2092–2097.
66. Fleisher AS, Esteller M, Harpaz N, et al. (2000) Microsatellite instability in inflammatory bowel disease-associated neoplastic lesions is associated with hypermethylation and diminished expression of the DNA mismatch repair gene, hMLH1. *Cancer Res* 60: 4864–4868.
67. Redston MS, Papadopoulos N, Caldas C, et al. (1995) Common occurrence of APC and K-ras gene mutations in the spectrum of colitis-associated neoplasias. *Gastroenterol* 108: 383–392.
68. Burmer GC, Rabinovitch PS, Haggitt RC, et al. (1992) Neoplastic progression in ulcerative colitis: histology, DNA content, and loss of a p53 allele. *Gastroenterol* 103: 1602–1610.
69. Yashiro M (2015) Molecular alterations of colorectal cancer with inflammatory bowel disease. *Dig Dis Sci* 60: 2251–2263.
70. Mikami T, Yoshida T, Numata Y, et al. (2007) Low frequency of promoter methylation of O6-Methylguanine DNA methyltransferase and hMLH1 in ulcerative colitis-associated tumors. *Am J Clin Pathol* 127: 366–373.
71. Foran E, Garrity-Park MM, Mureau C, et al. (2010) Upregulation of DNA methyltransferase-mediated gene silencing, anchorage-independent growth, and migration of colon cancer cells by interleukin-6. *Mol Cancer Res* 8: 471–481.
72. Hartnett L, Egan LJ (2012) Inflammation, DNA methylation and colitis-associated cancer. *Carcinogenesis* bgs006.
73. Nakazawa T, Kondo T, Ma D, et al. (2012) Global histone modification of histone H3 in colorectal cancer and its precursor lesions. *Hum Pathol* 43: 834–842.
74. Li Q, Chen H (2012) Silencing of Wnt5a during colon cancer metastasis involves histone modifications. *Epigenetics* 7: 551–558.
75. Binder H, Steiner L, Przybilla J, et al. (2013) Transcriptional regulation by histone modifications: towards a theory of chromatin re-organization during stem cell differentiation. *Phys Biol* 10: 026006.
76. Bardhan K, Liu K (2013) Epigenetics and colorectal cancer pathogenesis. *Cancers* 5: 676–713.
77. Klose RJ, Zhang Y (2007) Regulation of histone methylation by demethylimination and demethylation. *Nat Rev Mol Cell Biol* 8: 307–318.
78. Wong JJL, Hawkins NJ, Ward RL (2007) Colorectal cancer: a model for epigenetic tumorigenesis. *Gut* 56: 140–148.
79. Portela A, Esteller M (2010) Epigenetic modifications and human disease. *Nat Biotechnol* 28: 1057–1068.

80. Glauben R, Batra A, Fedke I, et al. (2006) Histone hyperacetylation is associated with amelioration of experimental colitis in mice. *J Immunol* 176: 5015–5022.
81. Glauben R, Batra A, Stroh T, et al. (2008) Histone deacetylases: novel targets for prevention of colitis-associated cancer in mice. *Gut* 57: 613–622.
82. Griffiths-Jones S, Grocock RJ, Van Dongen S, et al. (2006) miRBase: microRNA sequences, targets and gene nomenclature. *Nucleic Acids Res* 34: D140–D144.
83. Wu F, Zikusoka M, Trindade A, et al. (2008) MicroRNAs are differentially expressed in ulcerative colitis and alter expression of macrophage inflammatory peptide-2α. *Gastroenterol* 135: 1624–1635.
84. Olaru AV, Selaru FM, Mori Y, et al. (2011) Dynamic changes in the expression of MicroRNA-31 during inflammatory bowel disease-associated neoplastic transformation. *Inflamm Bowel Dis* 17: 221–231.
85. Shi C, Yang Y, Xia Y, et al. (2015) Novel evidence for an oncogenic role of microRNA-21 in colitis-associated colorectal cancer. *Gut* 308–455.
86. Svrcek M, El-Murr N, Wanherdrick K, et al. (2013) Overexpression of microRNAs-155 and 21 targeting mismatch repair proteins in inflammatory bowel diseases. *Carcinogenesis* bgs408.
87. Polytarchou C, Hommes DW, Palumbo T, et al. (2015) MicroRNA214 is associated with progression of ulcerative colitis, and inhibition reduces development of colitis and colitis-associated cancer in mice. *Gastroenterol* 149: 981–992.
88. Cristóbal I, Manso R, González-Alonso P, et al. (2015) Clinical value of miR-26b discriminating ulcerative colitis-associated colorectal cancer in the subgroup of patients with metastatic disease. *Inflamm Bowel Dis* 21: E24–E25.
89. Ludwig K, Fassan M, Mescoli C, et al. (2013) PDCD4/miR-21 dysregulation in inflammatory bowel disease-associated carcinogenesis. *Virchows Arch* 462: 57–63.
90. Yang L, Belaguli N, Berger DH (2009) MicroRNA and colorectal cancer. *World J Surg* 33: 638–646.
91. Kanaan Z, Rai SN, Eichenberger MR, et al. (2012) Differential MicroRNA expression tracks neoplastic progression in inflammatory bowel disease-associated colorectal cancer. *Hum Mutat* 33: 551–560.
92. Feng R, Chen X, Yu Y, et al. (2010) miR-126 functions as a tumour suppressor in human gastric cancer. *Cancer Lett* 298: 50–63.
93. Fasseu M, Tréton X, Guichard C, et al. (2010) Identification of restricted subsets of mature microRNA abnormally expressed in inactive colonic mucosa of patients with inflammatory bowel disease. *PloS One* 5: e13160.
94. Wang W, Li X, Zheng D, et al. (2015) Dynamic changes and functions of macrophages and M1/M2 subpopulations during ulcerative colitis-associated carcinogenesis in an AOM/DSS mouse model. *Mol Med Rep* 11: 2397–2406.
95. Francescone R, Hou V, Grivennikov SI (2015) Cytokines, IBD, and colitis-associated cancer. *Inflamm Bowel Dis* 21: 409–418.
96. Sarra M, Pallone F, MacDonald TT, et al. (2010) IL-23/IL-17 axis in IBD. *Inflamm Bowel Dis* 16: 1808–1813.

97. Reinecker HC, Steffen M, Witthoeft T, et al. (1993) Enhand secretion of tumour necrosis factor-alpha, IL-6, and IL-1β by isolated lamina ropria monouclear cells from patients with ulcretive cilitis and Crohn's disease. *Clin Exp Immunol* 94: 174–181.
98. Banks C, Bateman A, Payne R, et al. (2003) Chemokine expression in IBD. Mucosal chemokine expression is unselectively increased in both ulcerative colitis and Crohn's disease. *J Pathol* 199: 28–35.
99. Wiercinska-Drapalo A, Flisiak R, Jaroszewicz J, et al. (2005) Plasma interleukin-18 reflects severity of ulcerative colitis. *World J Gastroenterol* 11: 605–608.
100. Bisping G, Lügering N, Lütke-Brintrup S, et al. (2001) Patients with inflammatory bowel disease (IBD) reveal increased induction capacity of intracellular interferon-gamma (IFN-γ) in peripheral CD8+ lymphocytes co-cultured with intestinal epithelial cells. *Clin Exp Immunol* 123: 15–22.
101. Hyun YS, Han DS, Lee AR, et al. (2012) Role of IL-17A in the development of colitis-associated cancer. *Carcinogenesis* bgs106.
102. Onizawa M, Nagaishi T, Kanai T, et al. (2009) Signaling pathway via TNF-α/NF-κB in intestinal epithelial cells may be directly involved in colitis-associated carcinogenesis. *Am J Physiol Gastrointest Liver Physiol* 296: G850–G859.
103. Matsumoto S, Hara T, Mitsuyama K, et al. (2010) Essential roles of IL-6 trans-signaling in colonic epithelial cells, induced by the IL-6/soluble–IL-6 receptor derived from lamina propria macrophages, on the development of colitis-associated premalignant cancer in a murine model. *J Immunol* 184: 1543–1551.
104. Atreya R, Mudter J, Finotto S, et al. (2000) Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: evidence in crohn disease and experimental colitis in vivo. *Nat Med* 6: 583–588.
105. Popivanova BK, Kitamura K, Wu Y, et al. (2008) Blocking TNF-α in mice reduces colorectal carcinogenesis associated with chronic colitis. *J Clin Invest* 118: 560–570.
106. Fukata M, Chen A, Vamadevan AS, et al. (2007) Toll-like receptor-4 promotes the development of colitis-associated colorectal tumors. *Gastroenterol* 133: 1869–1869.
107. Garrett WS, Punit S, Gallini CA, et al. (2009) Colitis-associated colorectal cancer driven by T-bet deficiency in dendritic cells. *Cancer Cell* 16: 208–219.
108. Allen IC, TeKippe EM, Woodford RMT, et al. (2010) The NLRP3 inflammasome functions as a negative regulator of tumorigenesis during colitis-associated cancer. *J Exp Med* 207: 1045–1056.
109. Allen IC, Wilson JE, Schneider M, et al. (2012) NLRP12 suppresses colon inflammation and tumorigenesis through the negative regulation of noncanonical NF-κB signaling. *Immunity* 36: 742–754.
110. Chen GY, Liu M, Wang F, et al. (2011) A functional role for Nlrp6 in intestinal inflammation and tumorigenesis. *J Immunol* 186: 7187–7194.
111. Eckmann L, Greten T (2004) IKKbeta links inflam. mation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell* 118: 285–296.

112. Cooks T, Pateras IS, Tarcic O, et al. (2013) Mutant p53 prolongs NF-κB activation and promotes chronic inflammation and inflammation-associated colorectal cancer. *Cancer Cell* 23: 634–646.
113. Grivennikov S, Karin E, Terzic J, et al. (2009) IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. *Cancer Cell* 15: 103–113.
114. Bollrath J, Phesse TJ, von Burstin VA, et al. (2009) gp130-mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. *Cancer Cell* 15: 91–102.
115. Ghosh S, Karin M (2002) Missing pieces in the NF-κB puzzle. *Cell* 109: S81–S96.
116. Karin M (2006) Nuclear factor-κB in cancer development and progression. *Nature* 441: 431–436.
117. Greten FR, Eckmann L, Greten TF, et al. (2004) IKKβ links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell* 118: 285–296.
118. Rose-John S (2012) IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. *Int J Biol Sci* 8: 1237–1247.
119. Yu H, Pardoll D, Jove R (2009) STATs in cancer inflammation and immunity: a leading role for STAT3. *Nat Rev Cancer* 9: 798–809.
120. Pickert G, Neufert C, Leppkes M, et al. (2009) STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. *J Exp Med* 206: 1465–1472.
121. Putoczki TL, Thiem S, Loving A, et al. (2013) Interleukin-11 is the dominant IL-6 family cytokine during gastrointestinal tumorigenesis and can be targeted therapeutically. *Cancer Cell* 24: 257–271.
122. Chichlowski M, Sharp JM, Vanderford DA, et al. (2008) Helicobacter typhlonius and Helicobacter rodentium differentially affect the severity of colon inflammation and inflammation-associated neoplasia in IL10-deficient mice. *Comp Med* 58: 534–541.
123. Uronis JM, Mühlbauer M, Herfarth HH, et al. (2009) Modulation of the intestinal microbiota alters colitis-associated colorectal cancer susceptibility. *PloS One* 4: e6026.
124. O'mahony L, Feeney M, O'halloran S, et al. (2001) Probiotic impact on microbial flora, inflammation and tumour development in IL-10 knockout mice. *Aliment Pharmacol Ther* 15: 1219–1225.
125. Tözün N, Vardareli E (2016) Gut microbiome and gastrointestinal cancer: les liaisons dangereuses. *J Clin Gastroenterol* 50: S191–S196.
126. Yamamoto M, Matsumoto S (2016) Gut microbiota and colorectal cancer. *Genes and Environ* 38: 1–7.
127. Abreu MT (2010) Toll-like receptor signalling in the intestinal epithelium: how bacterial recognition shapes intestinal function. *Nat Rev Immunol* 10: 131–144.
128. Grivennikov SI (2013) Inflammation and colorectal cancer: colitis-associated neoplasia, In: *Seminars in immunopathology*, Springer-Verlag, 229–244.
129. Lowe EL, Crother TR, Rabizadeh S, et al. (2010) Toll-like receptor 2 signaling protects mice from tumor development in a mouse model of colitis-induced cancer. *PloS One* 5: e13027.

130. Fukata M, Chen A, Vamadevan AS, et al. (2007) Toll-like receptor-4 promotes the development of colitis-associated colorectal tumors. *Gastroenterol* 133: 1869–1869.
131. Araki T, Toiyama Y, Okita Y, et al. (2016) Surgical treatment for ulcerative colitis-associated cancer or dysplasia, In: *Colitis-associated cancer*, Springer-Verlag, 109–130.
132. Nio K, Higashi D, Kumagai H, et al. (2016) Efficacy and safety analysis of chemotherapy for advanced colitis-associated colorectal cancer in Japan. *Anticancer Drugs* 27: 457–463.
133. Impellizzeri D, Esposito E, Mazzon E, et al. (2011) Oleuropein aglycone, an olive oil compound, ameliorates development of arthritis caused by injection of collagen type II in mice. *J Pharmacol Exp Ther* 339: 859–869.
134. Giner E, Recio MC, Ríos JL, et al. (2013) Oleuropein protects against dextran sodium sulfate-induced chronic colitis in mice. *J Nat Prod* 76: 1113–1120.
135. Acquaviva R, Di Giacomo C, Sorrenti V, et al. (2012) Antiproliferative effect of oleuropein in prostate cell lines. *Int J Oncol* 41: 31.
136. Elamin MH, Daghestani MH, Omer SA, et al. (2013) Olive oil oleuropein has anti-breast cancer properties with higher efficiency on ER-negative cells. *Food Chem Toxicol* 53: 310–316.
137. Giner E, Recio MC, Ríos JL, et al. (2016) Chemopreventive effect of oleuropein in colitis-associated colorectal cancer in c57bl/6 mice. *Mol Nutr Food Res* 60: 242–255.
138. Zhang M, Viennois E, Prasad M, et al. (2016) Edible ginger-derived nanoparticles: a novel therapeutic approach for the prevention and treatment of inflammatory bowel disease and colitis-associated cancer. *Biomaterials* 101: 321–340.
139. Lin L, Sun Y, Wang D, et al. (2015) Celastrol ameliorates ulcerative colitis-related colorectal cancer in mice via suppressing inflammatory responses and epithelial-mesenchymal transition. *Front Pharmacol* 6.
140. Shaker ME, Ashamallah SA, Houssen ME (2014) Celastrol ameliorates murine colitis via modulating oxidative stress, inflammatory cytokines and intestinal homeostasis. *Chem Biol Interact* 210: 26–33.
141. Fung KY, Cosgrove L, Lockett T, et al. (2012) A review of the potential mechanisms for the lowering of colorectal oncogenesis by butyrate. *Br J Nutr* 108: 820–831.
142. Hu Y, Le Leu RK, Christophersen CT, et al. (2016) Manipulation of the gut microbiota using resistant starch is associated with protection against colitis-associated colorectal cancer in rats. *Carcinogenesis* 37: 366–375.
143. Kong ZL, Kao NJ, Hu JY, et al. (2016) Fucoxanthin-rich brown algae extract decreases inflammation and attenuates colitis-associated colon cancer in mice. *J Food Nutr Res* 4: 137–147.
144. Pandurangan AK, Saadatdoust Z, Hamzah H, et al. (2015) Dietary cocoa protects against colitis-associated cancer by activating the Nrf2/Keap1 pathway. *Biofactors* 41: 1–14.
145. Wu WT, Tsai YT, Chen HL (2016) Konjac glucomannan and inulin oligosaccharide attenuated the progression of colitic-associated colon carcinogenesis and modulated immune response in mice. *FASEB J* 30: 1174.
146. Periasamy S, Liu CT, Wu WH, et al. (2015) Dietary Ziziphus jujuba fruit influence on aberrant crypt formation and blood cells in colitis-associated colorectal cancer in mice. *Asian Pac J Cancer Prev:* 16: 7561–7566.

147. Viennois E, Xiao B, Ayyadurai S, et al. (2014) Micheliolide, a new sesquiterpene lactone that inhibits intestinal inflammation and colitis-associated cancer. *Lab Invest* 94: 950–965.
148. Kunchari Kalaimathi S, Sudhandiran G (2016) Fisetin ameolirates the azoxymethane and dextran sodium sulfate induced colitis associated colorectal cancer. *Int J Pharm Clin Res* 8: 551–560.
149. Yasui Y, Hosokawa M, Mikami N, et al. (2011) Dietary astaxanthin inhibits colitis and colitis-associated colon carcinogenesis in mice via modulation of the inflammatory cytokines. *Chem Biol Interact* 193: 79–87.
150. Yang X, Zhang F, Wang Y, et al. (2013) Oroxylin A inhibits colitis-associated carcinogenesis through modulating the IL-6/STAT3 signaling pathway. *Inflamm Bowel Dis* 19: 1990–2000.
151. Kannengiesser K, Maaser C, Heidemann J, et al. (2008) Melanocortin-derived tripeptide KPV has anti-inflammatory potential in murine models of inflammatory bowel disease. *Inflamm Bowel Dis* 14: 324–331.
152. Viennois E, Ingersoll SA, Ayyadurai S, et al. (2016) Critical role of PepT1 in promoting colitis-associated cancer and therapeutic benefits of the anti-inflammatory PepT1-mediated tripeptide KPV in a murine model. *CMGH Cell Mol Gastroenterol Hepatol* 2: 340–357.
153. Seraj MJ, Umemoto A, Kajikawa A, et al. (1997) Effects of dietary bile acids on formation of azoxymethane-induced aberrant crypt foci in F344 rats. *Cancer Lett* 115: 97–103.
154. Tung BY, Emond MJ, Haggitt RC, et al. (2001) Ursodiol use is associated with lower prevalence of colonic neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. *Ann Intern Med* 134: 89–95.
155. Xie L, Jiang FC, Zhang LM, et al. (2016) Targeting of MyD88 homodimerization by novel synthetic inhibitor TJ-M2010-5 in preventing colitis-associated colorectal cancer. *J Natl Cancer Inst* 108: djv364.
156. Amini-Khoei H, Momeny M, Abdollahi A, et al. (2016) Tropisetron suppresses colitis-associated cancer in a mouse model in the remission stage. *Int Immunopharmacol* 36: 9–16.
157. Drechsler S, Bruntsch U, Eggert J, et al. (1997) Comparison of three tropisetron-containing antiemetic regimens in the prophylaxis of acute and delayed chemotherapy-induced emesis and nausea. *Support Care Cancer* 5: 387–395.
158. Koh SJ, Kim JM, Kim I-K, et al. (2011) Fluoxetine inhibits NF-κB signaling in intestinal epithelial cells and ameliorates experimental colitis and colitis-associated colon cancer in mice. *Am J Physiol Gastrointest Liver Physiol* 301: G9–G19.
159. Tanaka T, Kochi T, Shirakami Y, et al. (2016) Cimetidine and clobenpropit attenuate inflammation-associated colorectal carcinogenesis in male ICR mice. *Cancers* 8: 25.
160. Masini E, Fabbroni V, Giannini L, et al. (2005) Histamine and histidine decarboxylase up-regulation in colorectal cancer: correlation with tumor stage. *Inflamm Res* 54: S80–S81.
161. Miyamoto S, Epifano F, Curini M, et al. (2008) A novel prodrug of 4'-geranyloxy-ferulic acid suppresses colitis-related colon carcinogenesis in mice. *Nutr Cancer* 60: 675–684.
162. Yao J, Xie J, Xie B, et al. (2016) Therapeutic effect of hydroxychloroquine on colorectal carcinogenesis in experimental murine colitis. *Biochem Pharmacol* 115: 51–63.

163. Dai Y, Jiao H, Teng G, et al. (2014) Embelin reduces colitis-associated tumorigenesis through limiting IL-6/STAT3 signaling. *Mol Cancer Ther* 13: 1206–1216.
164. Liang J, Nagahashi M, Kim EY, et al. (2013) Sphingosine-1-phosphate links persistent STAT3 activation, chronic intestinal inflammation, and development of colitis-associated cancer. *Cancer Cell* 23: 107–120.
165. Kawamori T, Kaneshiro T, Okumura M, et al. (2009) Role for sphingosine kinase 1 in colon carcinogenesis. *FASEB J* 23: 405–414.
166. Snider AJ, Kawamori T, Bradshaw SG, et al. (2009) A role for sphingosine kinase 1 in dextran sulfate sodium-induced colitis. *FASEB J* 23: 143–152.
167. Wang D, DuBois RN (2010) The role of COX-2 in intestinal inflammation and colorectal cancer. *Oncogene* 29: 781–788.
168. Kohno H, Suzuki R, Sugie S, et al. (2005) Suppression of colitis-related mouse colon carcinogenesis by a COX-2 inhibitor and PPAR ligands. *BMC Cancer* 5: 1.
169. Setia S, Nehru B, Sanyal SN (2014) The PI3K/Akt pathway in colitis associated colon cancer and its chemoprevention with celecoxib, a Cox-2 selective inhibitor. *Biomed Pharmacother* 68: 721–727.
170. Glauben R, Sonnenberg E, Zeitz M, et al. (2009) HDAC inhibitors in models of inflammation-related tumorigenesis. *Cancer Lett* 280: 154–159.
171. Wei TT, Lin YT, Tseng RY, et al. (2016) Prevention of colitis and colitis-associated colorectal cancer by a novel polypharmacological Histone deacetylase inhibitor. *Am Assoc Cancer Res* 22: 4158–4169.
172. Reinhard A, Bressenot A, Dassonneville R, et al. (2015) Photodynamic therapy relieves colitis and prevents colitis-associated carcinogenesis in mice. *Inflamm Bowel Dis* 21: 985–995.
173. Zhang D, Mi M, Jiang F, et al. (2015) Apple polysaccharide reduces NF-kb mediated colitis-associated colon carcinogenesis. *Nutr Cancer* 67: 177–190.
174. Yang Y, Cai X, Yang J, et al. (2014) Chemoprevention of dietary digitoflavone on colitis-associated colon tumorigenesis through inducing Nrf2 signaling pathway and inhibition of inflammation. *Mol Cancer* 13: 48.
175. Tian Y, Wang K, Wang Z, et al. (2013) Chemopreventive effect of dietary glutamine on colitis-associated colon tumorigenesis in mice. *Carcinogenesis* bgt088.
176. Tian Y, Wang K, Fan Y, et al. (2016) Chemopreventive effect of dietary glutamineon colitis-associated colorectal cancer is associated with modulation of the DEPTOR/mTOR signaling pathway. *Nutrients* 8: 261.