Review

Targeting Inflammation in Cancer Prevention and Therapy

Jelena Todoric[1,2], Laura Antonucci[1], and Michael Karin[1,3]

Abstract

Inflammation is associated with the development and malignant progression of most cancers. As most of the cell types involved in cancer-associated inflammation are genetically stable and thus are not subjected to rapid emergence of drug resistance, the targeting of inflammation represents an attractive strategy both for cancer prevention and for cancer therapy. Tumor-extrinsic inflammation is caused by many factors, including bacterial and viral infections, autoimmune diseases, obesity, tobacco smoking, asbestos exposure, and excessive alcohol consumption, all of which increase cancer risk and stimulate malignant progression. In contrast, cancer-intrinsic or cancer-elicited inflammation can be triggered by cancer-initiating mutations and can contribute to malignant progression through the recruitment and activation of inflammatory cells. Both extrinsic and intrinsic inflammation can result in immu-

nosuppression, thereby providing a preferred background for tumor development. In clinical trials, lifestyle modifications including healthy diet, exercise, alcohol, and smoking cessation have proven effective in ameliorating inflammation and reducing the risk of cancer-related deaths. In addition, consumption of certain anti-inflammatory drugs, including aspirin, can significantly reduce cancer risk, suggesting that common nonsteroidal anti-inflammatory drugs (NSAID) and more specific COX2 inhibitors can be used in cancer prevention. In addition to being examined for their preventative potential, both NSAIDs and more potent anti-inflammatory antibody-based drugs need to be tested for their ability to augment the efficacy of more conventional therapeutic approaches on the basis of tumor resection, radiation, and cytotoxic chemicals. *Cancer Prev Res; 9(12); 895–905. ©2016 AACR.*

Chronic Inflammation and Invasive Tumour Growth: Wounds that Do Not Heal

A correlation between inflammation and cancer was identified in 1863, by Rudolf Ludwig Carl Virchow (1), who recognized the inflammatory process as one of the predisposing conditions for tumor development, described as an "Out of the 'normal' inflammatory hyperplasia" (2), frequently associated with alteration of the physiological healing process. In response to tissue injury, a multifactorial network of chemical signals, initiated and amplified upon recruitment and infiltration of leukocytes (neutrophils, monocytes, and eosinophils) from the venous system to the sites of damage, initiates and maintains a host response designed to "heal" the afflicted tissue. In addition to cell proliferation and tissue repair, inflammation is also responsible for clearing dead cells and other debris. This kind of physiological inflammatory response is self-limiting and is terminated after the assaulting agent is removed or the repair is completed (3, 4). However, if inflammation is unregulated, it can become chronic, inducing malignant growth and tumor initiation in the surrounding tissue,

due to the persistent production of growth factors as well as reactive oxygen and nitrogen species that interact with the DNA of the proliferating epithelium and result in permanent genomic alterations (5, 6). In addition to tumor initiation, inflammation plays a decisive role in tumor promotion, malignant conversion, and metastatic dissemination. Many different inflammatory mediators can stimulate tumor development, including cytokines, chemokines, growth factors, free radicals, prostaglandins, and proteolytic enzymes. These factors are produced by a variety of cells that populate the tumor microenvironment such as macrophages, neutrophils, lymphocytes, dendritic cells, natural killer cells, fibroblasts, adipocytes, and endothelial cells and sometimes also by the cancer cells themselves. Some of these factors act directly on cancer cells, stimulating their proliferation and inhibiting their death while promoting the accumulation of oncogenic mutations, whereas other factors manifest their protumorigenic activity by acting on other components of the tumor microenvironment. While epidemiologic studies indicate that at least 20% of all cancers begin as a direct consequence of chronic inflammatory disease (Table 1; refs. 7, 8), inflammatory processes elicited by the tumor itself are likely to be involved in the majority of solid malignancies, as recently demonstrated for colorectal cancer (9, 10). Inflammation is the common mechanism of action for numerous cancer risk factors, including infection, obesity, tobacco smoking, alcohol consumption, exposure to microparticles, dysbiosis, and chronic inflammatory diseases such as pancreatitis and colitis. Considering the extreme commonality of inflammatory changes in different cancer types, preventing or reversing inflammation is an important approach to cancer control.

The major goal of cancer prevention that can be divided into primary, secondary, and tertiary prevention is to reduce the risk of cancer occurrence or recurrence and disease complications after

[1]Laboratory of Gene Regulation and Signal Transduction, Department of Pharmacology, School of Medicine, University of California San Diego, La Jolla, California. [2]Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria. [3]Department of Pathology, School of Medicine, University of California San Diego, La Jolla, California.

J. Todoric and L. Antonucci made equal contributions to this study.

Corresponding Author: Michael Karin, Department of Pharmacology, University of California, San Diego, 9500 Gilman Drive, M/C: 0723, La Jolla, CA 92093. Phone: 858-534-0872; Fax: 858-534-8158; E-mail: karinoffice@ucsd.edu

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Table 1. Risk factor and inflammatory conditions correlated with cancer development and estimated new case from Cancer Statistics, 2016

Cancer type	Estimated new cases in 2016	Risk factors correlated with inflammation
Pancreas	53,070	Cigarette smoking, chronic pancreatitis diabetes, obesity, Lynch syndrome
Lung and bronchus	224,390	Cigarette, cigar and pipe smoking, bronchitis
Stomach	26,370	*H. pylori*
Colon and rectum	134,490	Obesity, physical inactivity, long-term smoking, alcohol consumption, chronic inflammatory bowel disease (e.g., ulcerative colitis or Crohn disease)
Esophagus	16,910	Reflux esophagitis, Barrett esophagus
Lymphoma	81,080	Epstein-Barr virus, HIV
Liver and intrahepatic bile duct	39,230	HBV and/or HCV, heavy alcohol consumption, obesity, diabetes, tobacco smoking, cholangitis
Melanoma of the skin	76,380	Skin inflammation
Uterine cervix	12,990	HPV
Uterine corpus (endometrium)	60,050	Obesity and abdominal fatness Lynch syndrome and diabetes
Brest cancer	246,660	Obesity, long-term, heavy smoking, physical inactivity, and alcohol consumption
Urinary bladder	76,960	Smoking, cystitis/bladder syndrome
Oral cavity and pharynx	48,330	Excessive alcohol consumption. HPV infection, tobacco use
Kidney and renal pelvis	62,700	Obesity and tobacco smoking, chronic renal failure
Leukemia	60,140	Obesity, cigarette smoking, T-cell leukemia virus type I (HTLV-I)

diagnosis (11). Avoiding exposure to known risk factors is an important means in primary prevention, as it has the potential to reduce the number of cancer deaths by 30%. In addition to screening procedures that detect preclinical pathologic changes, other components of secondary prevention are chemoprevention and immunoprevention. The aim of immunoprevention is to control initiation or development of cancer by modulating the immune system, whereas chemoprevention entails the use of natural, synthetic, or biologic chemical agents to reverse, suppress, or prevent malignant progression to invasive cancer. Only a relatively small number of agents have been specifically approved for cancer chemoprevention, including the 2 anti-inflammatory drugs celecoxib and diclofenac, whereas for other medications, including aspirin and statins, commonly used to treat a variety of common, non–cancer-related medical situations, even if data are accumulating to support a significant negative association with cancer occurrence, at the current level of evidence, their potential chemopreventive properties should be considered in high-risk situations or by using a personalized approach of maximizing individual benefits and minimizing the potential for adverse effects (12).

## Preventable Cancer Risk Factors

Obesity and cancer

According to the World Health Organization's 2014 report, 39% adults worldwide are overweight and 13% are obese (13). Obese individuals are at a substantial elevated risk to develop cancer and at least 3.6% of all new cancer cases in adults older than 30 years are obesity-related (14). There is a close relationship between obesity and inflammation, which led to the development of a new concept of "metaflammation" (15). Furthermore, the major mechanism through which obesity promotes cancer is inflammation-related (16). A hallmark of obesity, adipocyte hypertrophy is characterized by changes in the abundance and type of mediators secreted by adipocytes. While lean adipocytes produce anti-inflammatory factors such as adiponectin, IL4, and IL10, adipocytes from obese individuals are a source of proinflammatory mediators including leptin, IL1, IL6, and TNF. These proinflammatory adipokines initiate a cascade of changes that result in broader adipose tissue inflammation, characterized by proinflammatory macrophage infiltration, increased T-cell proliferation, T-helper (T_H)1 cell polarization and inhibition of Treg

expansion (Fig. 1). Furthermore, natural killer (NK) cells that produce IFNγ, mast cells, and B cells accumulate in obese adipose tissue and impact subsequent systemic metabolic changes (17). In addition to systemic metabolic dysregulation, proinflammatory adipokines alter the tumor microenvironment and promote angiogenesis and cancer cell proliferation. For example, leptin and IL6 secreted by obese adipocytes activate Janus kinases (JAK) and STAT3 resulting in inhibition of apoptosis and increased VGEF secretion, which promotes tumor vascularization. STAT3 also stimulates cancer cell proliferation (18, 19). Metabolic dysfunction in obesity is also characterized by increased systemic concentrations of insulin and IGF1, both of which stimulate cancer cell proliferation and enhance cancer growth (20). Furthermore, free fatty acids released from adipose tissue in obesity accumulate in the liver and lead to development of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatits (NASH), which increases the risk of hepatocellular carcinoma (HCC; ref. 21). Weight loss in obese subjects reduces serum concentrations of inflammatory markers including C-reactive protein, IL6, and TNF and decreases macrophage numbers in adipose tissue, liver, and colon. Weight loss is also associated with reduced activity of tumor-promoting transcription factors, including AP-1, STAT3, and NF-κB (16, 18, 22, 23). Bariatric surgery is commonly used for weight reduction in extremely obese individuals and was found to reduce cancer incidence and mortality (24). Therefore, weight loss represents an effective anti-inflammatory strategy proven to be effective for cancer prevention and control. Additional modulation of obesity-related inflammation is possible through the use of anti-inflammatory nutritional supplements such as omega-3 fatty acids, whose consumption ameliorates adipose tissue inflammation (25). By reducing the concentration of proinflammatory arachidonic acid (AA) metabolites, omega-3 fatty acids reduce the production of eicosanoids that can activate AP-1 and NF-κB signaling and promote angiogenesis (26). Recommendations made by the Joslin Diabetes Research Center at Harvard Medical School for the treatment of obesity stated that omega-3 fatty acids should be taken twice a week using food sources such as fatty fish (27). Moreover, cholesterol-lowering and antidiabetic drugs, such as statins and metformin, respectively, that are often used in obese patients have also shown beneficial effects in preventing some types of cancer (28).

Figure 1.
Mechanisms linking obesity, inflammation, and cancer. In obesity, enlarged adipocytes secrete proinflammatory adipokines such as leptin, TNFα, CCL-2, and IL6 and localy induce an M1 macrophage phenotype. In addition to macrophages, mast and T cells infiltrate adipose tissue in obesity and aggravate an inflammatory state. The adipose tissue–derived inflammatory mediators also exert their effects systemically and may activate inflammatory pathways such as NF-κB and STAT3 pathway in premalignant and malignant cells and promote a microenvironment favorable for tumorigenesis.
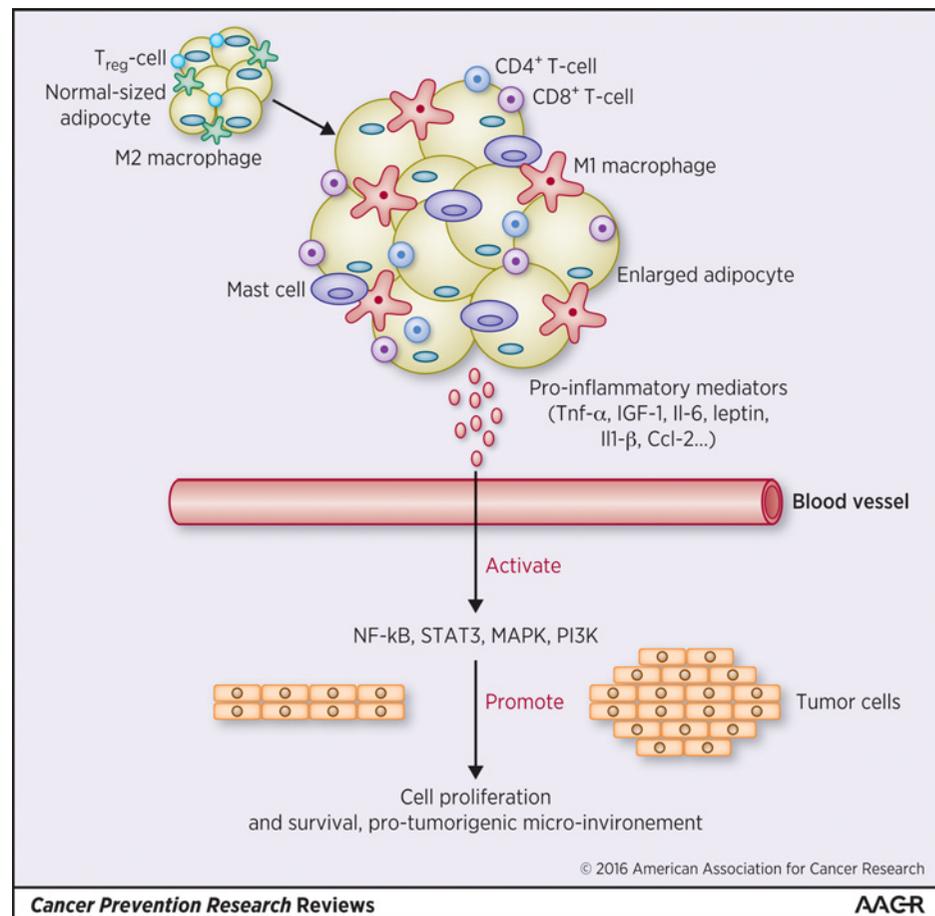
In particular, metformin, commonly used as oral antihyperglycaemic drug and statins [3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors], was proposed to decrease the risk of hepatocellular carcinoma up to 50% and 60%, respectively, modifying several steps of RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, and Wnt/β-catenin signaling (28).

Alcohol and cancer

There is a strong association between alcohol consumption and increased risk of cancer especially head and neck, esophageal, breast, liver, and pancreatic cancers (29–31). Much of the effort to date has focused on alcoholic liver disease (ALD), which accounts for 70% of alcohol-related mortality (32). Alcohol intake leads to alcoholic steatohepatitis (ASH; Fig. 2), fibrosis, and cirrhosis, eventually culminating in HCC (33). The mechanisms involved in the pathogenesis of ALD include endotoxin-induced liver damage, oxidative stress, and inflammation (34). Several inflammatory cytokines including TNF, IL1 and IL6, all of which are tumor-promoting (8), are elevated in ALD (35). All of these cytokines were found to promote HCC development and also contribute to the pathogenesis of pancreatic cancer (36). As shown in NASH-driven HCC (37), TNF antagonists may also inhibit the development of ASH-driven HCC (38), but in this case, they can increase the risk of infection. A key mediator of ALD is lipopolysaccharide (LPS) released by Gram-negative bacilli in the gut and transported to the liver through the portal vein (39). LPS activates liver macrophages via TLR4 to produce tumor promoting cytokines, including TNF and IL6 and activate hepatic stellate cells (HSC), which produce TGFβ, a potent immunosuppressive cytokine (40). By causing dysbiosis and destroying the gut permeability barrier, excessive alcohol consumption can also increase the risk of colorectal cancer (41, 42). Meta-analysis indicates that cessation of alcohol consumption decreases HCC risk by 6% to 7% a year (43). Excessive alcohol consumption is also a major etiologic factor in chronic pancreatitis and pancreatic ductal adenocarcinoma (PDAC; refs. 44, 45). Similar to its effects on liver cancer, alcohol-induced deterioration of the gut permeability barrier and LPS entry into the pancreas promote pancreatic inflammation and fibrosis (46), resulting in acinar-to-ductal metaplasia, an initiating event in PDAC development. Therefore, reducing alcohol consumption should significantly decrease the risk of some of the most aggressive cancers.

Tobacco smoking and cancer

Cigarette smoke induces the production and release of several inflammatory mediators (47–49) and activates signaling pathways involved in the regulation of inflammation, cell survival, and cell proliferation (50). Importantly, tobacco smoke enhances RAS activity through activation of receptors for advanced glycation end-products (RAGE; ref. 51). Elevated RAS activity is a characteristic of several epithelial-derived cancers including lung and pancreatic cancers (52) and it induces downstream NF-κB activation and elevated expression of inflammatory cytokines and chemokines (51). In addition to NF-κB, reactive oxygen species
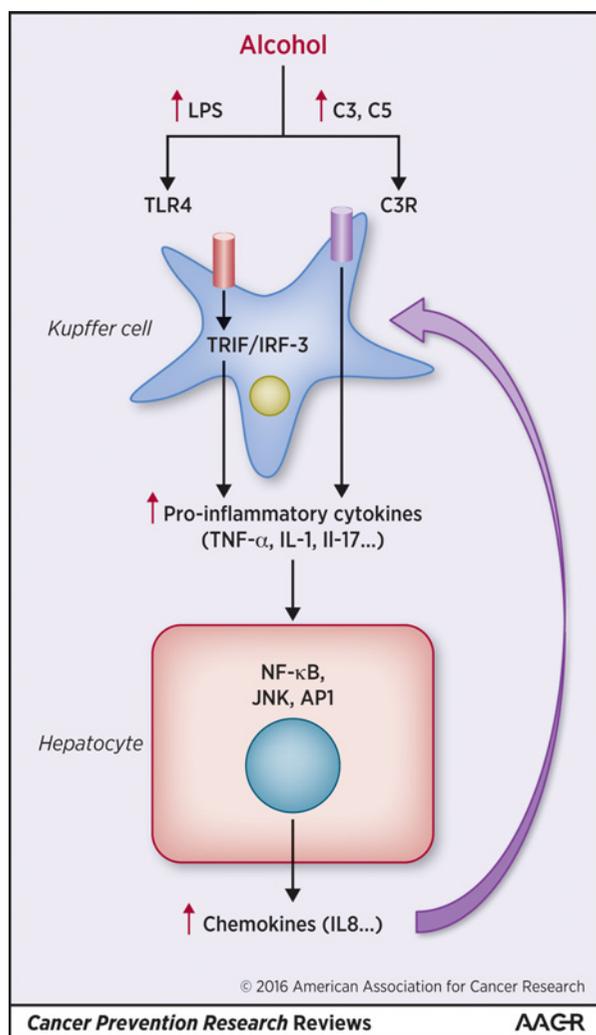
Figure 2.
Inflammation in ALD. Alcohol consumption increases gut permeability and facilitates translocation of bacteria-derived LPS from the gut to the liver. LPS activates TLR4-TRIF/IRF-3 pathway in Kupffer cells, which results in increased proinflammatory cytokine production subsequently leading to hepatocyte damage. Alcohol consumption also activates complement C3 and C5, which bind to the receptors on Kupffer cells and increase their TNFα production, which leads to activation of NF-κB and other inflammatory pathways in hepatocytes and hepatocyte injury. In response to proinflammatory stimuli, hepatocytes secrete chemokines to attract more inflammatory cells.

(ROS) in tobacco smoke activate AP-1, which mediates IL8 production, monocyte and macrophage activation, and development of corticosteroid-resistant inflammation (53). Short-term tobacco smoke exposure in mice resulted in activation of IKKβ and JNK signaling and induction of inflammatory cytokines in myeloid cells and had a promoting effect on lung cancer development in mice (54). Importantly, IKKβ and JNK ablation reduced tobacco smoke–induced malignant cell proliferation and lung cancer promotion. Therefore, it is likely that anti-inflammatory intervention may slow down the development and progression of lung cancer. Anti-inflammatory therapy and smoking cessation could be useful in secondary prevention that attempts to address a disease at its earliest stage, such that prompt inter-

vention may slow down disease progression or in a best case, stop it completely!

Microbiome, inflammation, and cancer

Helicobacter pylori and hepatitis C virus are among the most-well described pathogens that promote cancer development (Table 1), both of which induce tumorigenesis through epithelial injury and inflammation (55). In addition to specific bacterial pathogens, global microbiota changes and imbalance can also promote tumor development (56). Activation of Toll-like receptors (TLR) by microbial products represents one of the strongest proinflammatory signals (57). Mice lacking TLR4, whose activation by LPS results in production of proinflammatory mediators, are protected against HCC, PDAC, and inflammation-induced colorectal cancer development (56, 58, 59). *Tlr4*, whose basal expression in the intestinal mucosa is low, is upregulated in patients with inflammatory bowel disease (IBD) who are at high risk of developing colitis-associated cancer (CAC; refs. 59, 60). Therefore, TLR4 signaling blockade may be of value in prevention or treatment of several different inflammation-associated cancer types.

Localized loss of the intestinal epithelial barrier, resulting in increased translocation of commensal microbiota, was found to activate an inflammatory IL23/IL17 cytokine cascade leading to accelerated colorectal tumorigenesis (9). Ablation of the NLRP6 inflammasome component resulted in dysbiosis and increased abundance of colitogenic bacteria that promote colorectal cancer development through a mechanism dependent on microbe-induced increase in CCL-5 secretion by epithelial cells, leading to subsequent infiltration of IL6-producing immune cells and increased epithelial proliferation (61). However, the relationship between inflammation and the microbiota during tumorigenesis is not one-sided. For instance, IL10-deficient mice that develop spontaneous colitis exhibit dysbiosis, which promotes development of colorectal cancer (62). Colitis may also exacerbate tumorigenesis by inducing the expansion of microorganisms with genotoxic capabilities (63). Such microorganisms are enriched in patients with IBD as well as in patients with colorectal cancer (63). Consumption of probiotics and prebiotics may exert some beneficial effects that can be used in cancer prevention (64). The World Health Organization (WHO) defines probiotics as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (65). Prebiotics are "selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health" (66). Importantly, attenuated inflammation may be the major mechanism by which some pre- and probiotic organisms inhibit cancer development (67).

Exercise, inflammation, and cancer prevention

Inflammatory disorders and cancer progression are characteristically associated with accumulation of distinctive genetic mutations, preceded by exposure to several risk factors, classified as non-modifiable (sex, age, presence of genetic mutations, ethnicity) and modifiable (specific behaviors, bad habits, and lifestyle). For instance, exercise is beneficial both for cancer prevention and as supportive therapy for patients with cancer that in addition to improving patients' quality of life is capable of slowing down disease progression (68). The recruitment of lymphocytes to the blood stream after physical exertion was observed in 1893, by Schulte (68), and may account for reduction of risk of breast,

colon, and prostate cancers (68, 69). During an acute bout of exercise, both epinephrine and norepinephrine drive NK cell mobilization, thereby enhancing antitumor immunity (70). In addition, muscle-derived factors, known as myokines, including IL15, IL7, and IL6, can regulate NK cell proliferation, maturation, and activation (71).

Drugs, inflammation, and cancer prevention

Nonsteroidal anti-inflammatory drugs. Nonsteroidal anti-inflammatory drug (NSAID; including aspirin, ibuprofen, naproxen) use has been linked to reduced cancer risk (72). Acetylsalicylic acid (ASA), also known as aspirin, is one of the most widely used drugs in the world, particularly for prevention of cardiovascular diseases (73). Multiple clinical trials had demonstrated a link between long-term aspirin use and a reduction in the incidence and mortality for several cancer types with an overall effect of 20% to 25% (72). The strongest beneficial effect has been found in esophageal adenocarcinoma, colorectal and stomach cancers and a smaller effect was observed in breast, lung, and prostate cancers (72). No benefit was found for hematopoietic malignancies, pancreatic and endometrial cancer (72). Several possible mechanisms were suggested to explain the association between NSAID and aspirin use and cancer prevention including COX1/2 inhibition, immune response modulation, effect on the PI3K signaling, inhibition of certain proinflammatory and protumorigenic transcription factors, maintenance of cancer stem cell homeostasis, and decreased glycolytic rate in cancer cells (74). The mechanism of action of COX1/2 inhibition seems to be reduced production of inflammatory mediators such as prostaglandins and leukotrienes (75). Increased expression of *Cox2* and its major metabolite prostaglandin E2 (PGE2) has been observed in many different types of cancer in which they enhance angiogenesis, apoptosis resistance, tumor growth, and metastasis (76). PGE2 activates MAPK, PI3K/AKT and NF-κB signaling and induces expression of several factors implied in tumorigenesis including VEGF, proto-oncogene Bcl-2, EGFR, and different matrix metalloproteinases (MMP-2 and MMP-9; ref. 76). But NSAIDs may also act through different mechanisms including induction of apoptosis through cytochrome *c* release from mitochondria and subsequent activation of caspase-9 and -3, and/or interference with cell-cycle progression and inhibition of carcinogen activation and stimulation of immunosurveillance (77). Recent studies show that epigenetic modifications may also be involved in the chemopreventive actions of ASA, leading to suppressed histone deacetylase (HDAC) activity and increased H3K27 acetylation which results in reduced expression of *iNos*, *Tnf*, and *Il6* (73).

Nevertheless, long-term NSAID administration can result in side effects including renal failure and gastrointestinal (GI) symptoms including mucosal lesions, bleeding, peptic ulcer, and intestinal inflammation which causes perforation and strictures in small and large intestines (78). Such adverse effects may actually increase cancer risk. Furthermore, NSAID intake increases the risk of deep vein thrombosis and its potentially life-threatening complications of pulmonary embolism, myocardial infarction, and stroke (79). Several selective COX2 inhibitors that impair tumor growth and metastasis (celecoxib, rofecoxib, valdecoxib, apricoxib, etoricoxib, and lumiracoxib) were approved for marketing, but later withdrawn mostly due to increased risk of thromboembolic events. Celecoxib is the only selective COX2 inhibitor that is still available in the United States and Europe (80). Combining COX2 inhibitors with 5-LOX inhibitors can block synthesis of both prostaglandins and leukotrienes, resulting in reduced gastrointestinal toxicity (78). In this context, the herbal medicines including the natural hydro-alcoholic extract of *Cordia myxa* fruit is considerably effective in treatment of acute inflammation in rats, and the active ingredients of its seeds, such as alpha-amyrins, have anticancer and anti-inflammatory activities by inhibiting COX2 and 5-LOX (78).

Corticosteroids. Corticosteroids, most commonly used as antiemetic drugs that prevent chemotherapy-induced nausea and vomiting, are the most effective anti-inflammatory drugs for many chronic inflammatory diseases and were shown to have anticancer activity (81). For example, pretreatment with dexamethasone increased effectiveness of chemotherapy in xenograft or syngeneic experimental tumor models of glioma, breast, lung, and colon cancers (82). Dietary consumption of DEX has a chemopreventive effect in mice exposed to tobacco smoke, leading to decreased lung tumor incidence (83). Recent studies had shown that DEX in combination with carfilzomib and lenalidomide, significantly improved progression-free survival of patients with relapsed multiple myeloma (ref. 84; ClinicalTrials.gov number, NCT01080391). In contrast high-dose inhaled (ICS) and oral corticosteroid (OCS) treatment, used to reduce local and systemic inflammation in patients with asthma and chronic obstructive pulmonary disease (COPD), was found to increase the risk of squamous lung cell carcinoma in men (85).

Statins and metformin. Statins are a family of drugs that lower blood cholesterol concentration by blocking the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which results in impaired cholesterol synthesis and by enhancing cholesterol clearance from the circulation (86). In addition to its cholesterol-lowering effects statins also have anti-inflammatory properties (87), which makes them powerful agents in prevention of atherosclerosis and resulting in life-threatening conditions, heart attack, and stroke. Statins are able of reducing systemic proinflammatory cytokine and C-reactive protein (CRP) levels and macrophage infiltration (88, 89). By exerting anti-inflammatory and other effects, statins also reduce the risk of development of several cancer types including colorectal cancer, HCC, and breast cancer (90–92). The proposed antitumoral mechanisms of statins are increased apoptosis due to downregulation of the RAF/MEK/ERK pathway, inhibition of degradation of cell-cycle regulators p21 and p27, inhibition of c-Myc activation, and inhibition of several key proinflammatory pathways including NF-κB and COX2 (93). Metformin, a drug used for treatment of type 2 diabetes mellitus, was found to be associated with decreased incidence of a variety of cancer types including colon, breast, lung, prostate, ovarian, and pancreatic cancers (94). Its antineoplastic effect is mediated through activation of the AMPK pathway, which counteracts the protumorigenic effect of hyperinsulinemia, the reduction of systemic glucose concentration, which counteracts Warburg effect and through its anti-inflammatory properties (95).

Targeting Recruitment and Polarization of Tumor-Associated Macrophages

Macrophages, an essential component of the innate immune system in humans, can represent up to 50% of the tumor mass, which makes them an important part of the tumor stroma, where they are commonly referred to as tumor-associated macrophages

(TAM). TAMs can generally promote cancer cell proliferation, stimulate tumor angiogenesis and extracellular matrix break-down, suppress antitumor immune responses, and enhance tumor invasion and metastasis (96). Their recruitment into the tumor microenvironment from the blood stream is primarily regulated by cytokines, chemokines, and growth factors that are derived from tumor and stromal cells. The tumor-derived C-C chemokine ligand 2 (CCL2), acting via its receptor C-C chemo-kine receptor 2 (CCR2), is a direct mediator of monocyte recruit-ment into primary tumors (97). TAMs are classified as either classically activated M1 or alternatively activated M2 macro-phages (98). The T_H1 cytokine IFNγ and LPS are the major inducers of the M1 phenotype, whereas T_H2 cytokines, such as IL4, IL10, and IL-13, stimulate M2 polarization (99). During the course of tumor development, the TAM phenotype is modulated by different factors in the tumor microenvironment and it changes from the M1 to the M2 phenotype, which is claimed to have stronger tumor-promoting properties (100). M2 macrophages are associated with poor prognosis in many different cancer types and can promote cell-cycle progression and angiogenesis while inhi-biting apoptosis (101). However, the M1/M2 model is an over-simplified representation of the functional diversity of macro-phages. In fact, M1 and M2 characteristics often coexist within the same cell, and there is a broad variety of macrophage subtypes between the M1 and M2 poles (102). Furthermore, the most potent tumor-promoting cytokines, such as IL6, TNF, IL1, and IL23 are considered as M1 cytokines (103).

Because of their important role in linking inflammation and cancer, the targeting of TAM recruitment and differentiation provides an opportunity for cancer prevention and treatment. Depletion of CCL2 with a neutralizing antibody prevents monocyte recruitment to the primary tumor site and reduces pulmonary metastasis of human breast cancer cells (104). A human anti-CCL2 antibody, CNTO 888, showed preliminary antitumor activity in patients while being well tolerated (105). Blockade of CCR2 with small-molecule antagonist showed antitumor activity in pancreatic cancer in animal studies (106) and this strategy is now being tested in clinical trials (ClinicalTrials.gov Identifier: NCT02732938). Trabectedin, a DNA-binding drug approved in Europe for the treatment of soft tissue sarcoma, has been shown to selectively deplete mononuclear phagocytes *in vivo*, including TAMs (105). Rap-idly growing tumors often outgrow their blood supply, which results in formation of hypoxic areas with TAM accumulation (107). Binding of semaphorin 3A to its receptor neuropilin-1 (Nrp1) recruits TAMs toward the hypoxic area where they adopt the M2 phenotype and release proangiogenic factors (105). Inhibition of Nrp1 reduced TAM migration and prevented their phenotypic switch to M2-like immunosuppressive cells with angiogenic activity making it an interesting target for anticancer therapy. Several therapies convert macrophages from an M2 to an M1 phenotype (108). Tasquinimod is a small-molecule compound that reduces the immunosuppressive potential of the tumor microenvironment (109). A recent study demon-strated its ability to induce a shift of imunosuppresive M2 to proinflammatory M1 macrophages in colon and breast cancer models (110). Colony-stimulating factor 1 (CSF-1) and its receptor, CSF-1R, mediate migration, differentiation, and sur-vival of macrophages (105). Treatment with anti-CSF-1R anti-body resulted in TAM depletion in several tumor types *in vitro* and *in vivo* and a clinical benefit for patients with diffuse-type

giant cell tumors (105). Importantly, CSF-1 triggers M2 phe-notype in macrophages, and treatment with anti-CSF-1R/GM-CSF antibodies resulted in their cell death (105). TAMs express significant amounts of COX2 and the selective COX2 inhibitor celecoxib was shown to switch their phenotypic characteristics from M2- to M1-like, which was followed by a reduction in number of colon polyps in an animal study on colon cancer (111). Recent studies had shown that decreasing TAM survival, by the targeting folate receptor-β (FR-β), a marker for the M2-polarized phenotype, is another promising strategy against cancer, in an experimental glioma model (112).

Targeting Proinflammatory Pathways

NF-κB and STAT3 are 2 critical transcription factors that are activated in many types of cancers (8, 113, 114). The STAT proteins family, which includes 7 members, regulates multiple processes related to cellular proliferation, survival, and angio-genesis (115). Among the different STATs, the one most impor-tant for cancer is STAT3, whose activity is stimulated by IL6, IL11 and other members of their cytokine family, as well as different growth factors (116). In HCC and liver adenomas, STAT3 activity is stimulated by various oncogenic mutations (117), but more often than not, STAT3 is maintained in an activated state due to elevated production of IL6 and other cytokines (116). STAT3 signaling also has important roles in tumor microenvironment where it promotes IL23-mediated protumorigenic immune responses while inhibiting expression of antitumorigenic IL12 (118). Inhibition or ablation of STAT3 can mediate tumor regression (119). Therefore, inhibition of STAT3 provides a rational strategy to block carcinogenesis at an early stage and induce regression of established tumors.

There are 3 major approaches to inhibit STAT3 signaling: inhibition of tyrosine kinases, such as JAK1 and 2, that are responsible for STAT3 activation (AG-490, ruxolitinib, etc.); STAT3 dimerization inhibitors that target its SH2 domain (Static, S3I-M2001, STAT3 inhibitory peptide, etc.); and nonspecific compounds that indirectly inhibit STAT3, such as resveratrol and curcumin, which inhibit many other targets (ref. 115; Fig. 3). Among tyrosine kinase inhibitors some are rather specific for JAK2 family members, whereas others inhibit several different kinases that lead to STAT3 activation (115). JAK inhibitors have already been tested in several clinical trials mostly for hematological/oncological and inflammatory diseases and some of them such as ruxolitinib and tofacitinib have been approved for use in psori-asis, myelofibrosis and rheumatoid arthritis (120, 121). Current-ly, these drugs are being evaluated as neoadjuvants in several types of cancer, including pediatric refractory or recurrent solid tumors, hematologic malignancies (122), pancreatic adenocarcinoma, triple-negative breast cancer, urothelial cancer, multiple myelo-ma, acute myeloid leukemia, myelodysplastic syndrome lympho-ma (ClinicalTrials.gov number, NCT02265510), endometrial cancer, gastric cancer, head and neck squamous cell carcinoma, melanoma, microsatellite-unstable colorectal cancer, non–small cell lung cancer (ClinicalTrials.gov number, NCT02559492, NCT02646748), and estrogen receptor–positive invasive meta-static breast cancer (ClinicalTrials.gov number, NCT01594216). Despite their clinical approval and marketing in myelofibrosis and rheumatoid arthritis, JAK inhibitors exert rather serious side effects including anemia, thrombocytopenia, headaches, nausea, and neurotoxicity (123). However, more selective

Figure 3.
Targeting STAT3 proinflammatory pathway. Schematic representation of the major targetable events during STAT3 activation, and the corresponding compounds with cancer-preventive properties.
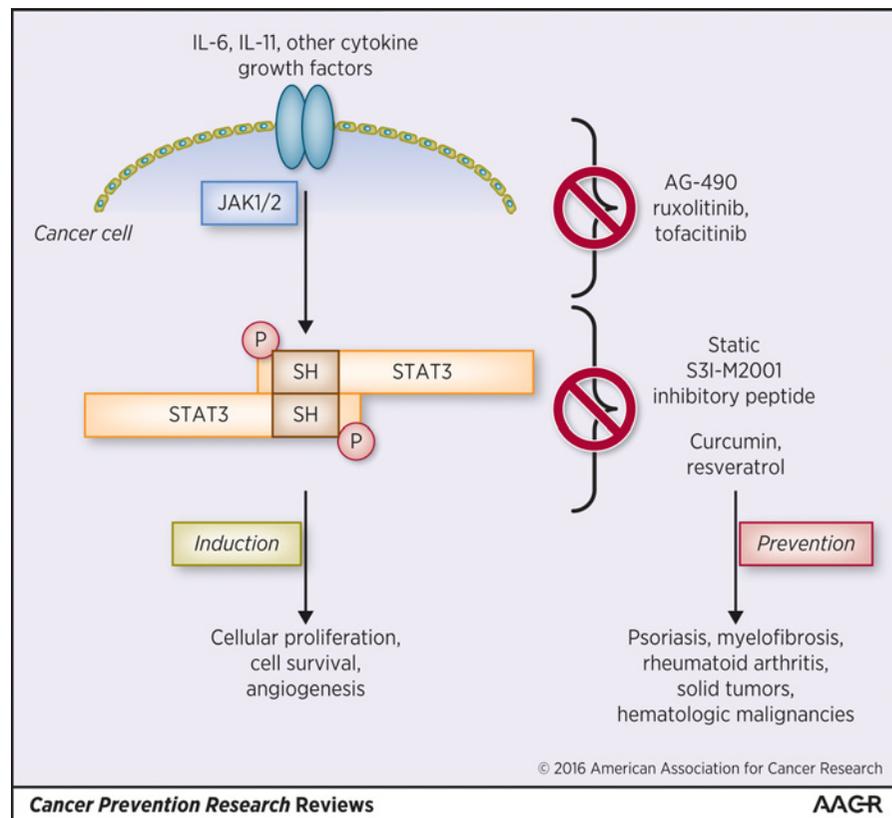
inhibitors with fewer side effects are currently being developed. Yet, it is doubtful whether such agents will ever find use in cancer prevention.

The NF-κB pathway is constitutively activated in many cancers, both in malignant cells and in components of the tumor microenvironment (114). NF-κB activation in malignant cells increases the expression of genes, whose products promote cell survival and proliferation, whereas NF-κB activation in components of the tumor stroma increases expression of inflammatory cytokines and growth factors (8, 114). NF-κB activation also promotes epithelial-to-mesenchymal transition (EMT) and tumor angiogenesis (124). Although NF-κB activation plays a major role in the induction of inflammation, long-term and extensive inhibition of NF-κB can result in profound inflammation due to enhanced production of IL1β upon activation of the NLRP3 inflammasome (125). This can result in severe neutrophilia (126), a serious condition that led to termination of any further clinical development. Nonetheless, the cancer prevention literature is full of reports using natural anti-inflammatory agents, including curcumin, resveratrol, ursolic acid, capsaicin, silibinin, silymarin, guggulsterone, and plumbagin, all of which are claimed to act as NF-κB inhibitors (127–131). Most likely, however, these are rather mild and nonspecific NF-κB inhibitors, most of which affect multiple targets, including STAT3. Because of their rather mild effects, such agents, many of which are used as nutritional supplements, can be used in cancer prevention (132), but it is doubtful whether they will ever find use as anticancer drugs.

The major problem associated with NF-κB inhibition is enhanced activation of the NLRP3 inflammasome (125). The inflammasome is a multimeric complex consisting of the intracellular Nod-like receptors (NLR) and the adaptor protein ASC that serves as a platform for activation of caspase-1 (133). Inflammasomes have a crucial role in host defense against infection as well as various autoinflammatory conditions (134). Upon NLR oligomerization and subsequent interaction between the adaptor protein ASC and the CARD domain, caspase-1–mediated processing results in production of the proinflammatory cytokines IL1β and IL18 or a rapid inflammatory form of cell death called pyroptosis (125). NF-κB is the first signal that primes NLR and pro-IL1β expression (135), but persistent NF-κB activation is also responsible for dysregulated NLRP3 inflammasome activation by inducing the mitophagic clearance of damaged mitochondria (125).

The role of NLR-containing inflammasomes in mediating cancer initiation and progression by creating a proinflammatory microenvironment for inducing malignant transformation and suppression of local immunity caused by NK or T cells open the way for novel strategy in cancer prevention. Between the 22 NLRs in the human and the 34 NLRs in the mouse genome, NLRP3 (NLR family, pyrin domain containing 3) is the best characterized. The NLRP3 inflammasome plays an important role in several inflammatory disorders including IBD (136), and its activation is negatively regulated by selective mitochondrial autophagy (mitophagy; ref. 125), whose dysregulation promotes inflammatory diseases, including pancreatitis (137, 138) and may increase cancer risk (139). The natural diterpenoid Andrographolide (Andro), which was approved in China for the treatment of various inflammatory conditions, inhibit tumor growth in mice at a high dose (about 200 mg/kg), and attenuates colitis progression and prevents carcinogenesis by inhibiting NLRP3 activity and stimulating autophagy (134).

Cytokines as Targets for Cancer Prevention and Therapy

The complex of IL6 and its nonsignaling receptor (IL6R) binds glycoprotein 130 (gp130) that forms a dimer, which results in activation of the JAK/STAT pathway and induces expression of other inflammatory cytokines and suppresses apoptosis (140). During tumorigenesis, IL6 has served detrimental effects including stimulation of cell survival and proliferation, regulation of stem cell renewal, and induction of angiogenesis. A humanized anti-IL6 receptor monoclonal antibody toclizumab is an FDA-approved immunosuppressive drug that blocks IL6 signaling. It is used in the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis (141). Chimeric monoclonal antibody siltuximab that binds IL6 showed good tolerance in patients with cancer in a phase I clinical trial and is currently investigated for the treatment of several tumor types including prostate cancer and metastatic renal cell cancer (141). Long-term treatment with anti–IL6-blocking antibody was associated with very few side effects in a mouse model of pancreatic cancer prevention (141). Thus, IL6 emerges as a promising potential target for cancer prevention. The proinflammatory chemokine IL8 and its receptors CXCR1 and CXCR2 were also linked to cancer and inflammation (141). Treatment with monoclonal antibodies, siRNA, or small-molecule inhibitors of IL8 or CXCR1/2 reduced tumor growth in preclinical studies, which makes them attractive targets for cancer prevention and therapy. A combination therapy with a small-molecule inhibitor of CXCR1/2 activation (reparixin) and paclitaxel in patients with HER-2–negative breast cancer is a major clinical study currently conducted (141). Another proinflammatory cytokine with reported role in promoting tumorigenesis is IL17A (142). TGFβ and IL6 are needed for the differentiation and IL23 for the maintenance of T_H17 cells that produce IL17A. Antibodies against IL17A (ixekizumab and secukinumab) and its receptor IL17AR (brodalumab) are in clinical trials for chronic inflammatory conditions and autoimmune diseases and an anti-IL23 antibody ustekinumab was FDA-approved for the treatment of psoriatic arthritis (143). However, preventive application of such drugs should take in account reported antitumor effects of IL17 in established tumors (143) as well as its role in autoimmunity.

Immunoprevention Meets Inflammation

Vaccines that protect against certain viral infection play important role in cancer prevention. For instance, hepatitis B virus (HBV) is a major cause of HCC whose impact has been dramatically reduced in all countries due to massive vaccination efforts (144). The most effective way to prevent HBV infection and reduce HCC development is vaccination (145). The prophylactic vaccine that is currently in use is generated by recombinant DNA technology and contains HBsAg protein and adjuvants. For patients who have already been infected by HBV and developed chronic hepatitis, secondary prevention becomes more important. Currently, antiviral drugs used in patients with chronic hepatitis B include the immunomodulator PEGylated IFNα and oral nucleos(t)ide analogues (146). IFNs activate various IRF family members that regulate transcription of numerous targets, including genes involved in control of viral mRNA translation or degradation (146). However, the mechanism of IFNα-mediated cell protection against viral infection is not fully understood. In addition to HBV, hepatitis C virus (HCV) is another important cause of HCC, against which there is no preventive vaccine (147). However, the recent development of highly effective anti-HCV drugs will lead to major decrease in HCV-induced HCC (147). Human papilloma virus (HPV) is a major cause of cervical intraepithelial neoplasia that can progress to invasive cervical cancer (148). Recently, we have witnessed the development of an effective HPV vaccine that if properly distributed amongst young adults will lead to a major decrease in the impact of cervical and other urogenital cancers. In summary, vaccination against cancer-causing viruses is one of the most effective and economical ways to reduce the toll of several inflammation-related cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539–45.
2. Schmidt A, Weber OF. In memoriam of Rudolf Virchow: a historical retrospective including aspects of inflammation, infection and neoplasia. Contrib Microbiol 2006;13:1–15.
3. Norling LV, Serhan CN. Profiling in resolving inflammatory exudates identifies novel anti-inflammatory and pro-resolving mediators and signals for termination. J Intern Med 2010;268:15–24.
4. Karin M, Clevers H. Reparative inflammation takes charge of tissue regeneration. Nature 2016;529:307–15.
5. Maeda H, Akaike T. Nitric oxide and oxygen radicals in infection, inflammation, and cancer. Biochemistry (Mosc) 1998;63:854–65.
6. Shaked H, Hofseth LJ, Chumanevich A, Chumanevich AA, Wang J, Wang Y, et al. Chronic epithelial NF-kappaB activation accelerates APC loss and intestinal tumor initiation through iNOS up-regulation. Proc Natl Acad Sci U S A 2012;109:14007–12.
7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
8. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883–99.
9. Grivennikov SI, Wang K, Mucida D, Stewart CA, Schnabl B, Jauch D, et al. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. Nature 2012;491:254–8.
10. Wang K, Kim MK, Di Caro G, Wong J, Shalapour S, Wan J, et al. Interleukin-17 receptor a signaling in transformed enterocytes promotes early colorectal tumorigenesis. Immunity 2014;41:1052–63.
11. Spratt JS. The primary and secondary prevention of cancer. J Surg Oncol 1981;18:219–30.

12. Gronich N, Rennert G. Beyond aspirin-cancer prevention with statins, metformin and bisphosphonates. Nat Rev Clin Oncol 2013;10:625–42.
13. World Health Organization. Obesity and overweight. Geneva, Swirzerland: WHO Media Centre; 2015. Available from: http://who.int/mediacentre/factsheets/fs311/en/.
14. Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol 2015;16:36–46.
15. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006; 444:860–7.
16. Font-Burgada J, Sun B, Karin M. Obesity and cancer: the oil that feeds the flame. Cell Metab 2016;23:48–62.
17. McNelis JC, Olefsky JM. Macrophages, immunity, and metabolic disease. Immunity 2014;41:36–48.
18. Park EJ, Lee JH, Yu GY, He G, Ali SR, Holzer RG, et al. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell 2010;140:197–208.
19. He G, Yu GY, Temkin V, Ogata H, Kuntzen C, Sakurai T, et al. Hepatocyte IKKbeta/NF-kappaB inhibits tumor promotion and progression by preventing oxidative stress-driven STAT3 activation. Cancer Cell 2010;17: 286–97.
20. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev Cancer 2008;8:915–28.
21. Kew MC. Obesity as a cause of hepatocellular carcinoma. Ann Hepatol 2015;14:299–303.
22. Pendyala S, Neff LM, Suarez-Farinas M, Holt PR. Diet-induced weight loss reduces colorectal inflammation: implications for colorectal carcinogenesis. Am J Clin Nutr 2011;93:234–42.
23. Bai Y, Sun Q. Macrophage recruitment in obese adipose tissue. Obes Rev 2015;16:127–36.
24. Sjostrom L, Gummesson A, Sjostrom CD, Narbro K, Peltonen M, Wedel H, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. Lancet Oncol 2009;10:653–62.
25. Todoric J, Loffler M, Huber J, Bilban M, Reimers M, Kadl A, et al. Adipose tissue inflammation induced by high-fat diet in obese diabetic mice is prevented by n-3 polyunsaturated fatty acids. Diabetologia 2006;49: 2109–19.
26. Sears DD, Miles PD, Chapman J, Ofrecio JM, Almazan F, Thapar D, et al. 12/15-lipoxygenase is required for the early onset of high fat diet-induced adipose tissue inflammation and insulin resistance in mice. PLoS One 2009;4:e7250.
27. Guidelines JDRCD March 29, 2007. Available from: https://www.joslin.org/docs/Nutrition_Guideline_Graded.pdf.
28. Ampuero J, Romero-Gomez M. Prevention of hepatocellular carcinoma by correction of metabolic abnormalities: role of statins and metformin. World J Hepatol 2015;7:1105–11.
29. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev 2009;18: 541–50.
30. Grewal P, Viswanathen VA. Liver cancer and alcohol. Clin Liver Dis 2012;16:839–50.
31. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW Jr, et al. Alcohol, tobacco and breast cancer–collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer 2002;87:1234–45.
32. Sheron N, Hawkey C, Gilmore I. Projections of alcohol deaths–a wake-up call. Lancet 2011;377:1297–9.
33. Crawford JM. Histologic findings in alcoholic liver disease. Clin Liver Dis 2012;16:699–716.
34. Bataller R, Gao B. Liver fibrosis in alcoholic liver disease. Semin Liver Dis 2015;35:146–56.
35. Khoruts A, Stahnke L, McClain CJ, Logan G, Allen JI. Circulating tumor necrosis factor, interleukin-1 and interleukin-6 concentrations in chronic alcoholic patients. Hepatology 1991;13:267–76.
36. Li N, Grivennikov SI, Karin M. The unholy trinity: inflammation, cytokines, and STAT3 shape the cancer microenvironment. Cancer Cell 2011;19:429–31.
37. Nakagawa H, Umemura A, Taniguchi K, Font-Burgada J, Dhar D, Ogata H, et al. ER stress cooperates with hypernutrition to trigger TNF-dependent spontaneous HCC development. Cancer Cell 2014;26:331–43.
38. European Association for the Study of L. EASL clinical practical guidelines: management of alcoholic liver disease. J Hepatol 2012;57:399–420.
39. Schnabl B, Brenner DA. Interactions between the intestinal microbiome and liver diseases. Gastroenterology 2014;146:1513–24.
40. Watanabe A, Sohail MA, Gomes DA, Hashmi A, Nagata J, Sutterwala FS, et al. Inflammasome-mediated regulation of hepatic stellate cells. Am J Physiol Gastrointest Liver Physiol 2009;296:G1248–57.
41. Purohit V, Bode JC, Bode C, Brenner DA, Choudhry MA, Hamilton F, et al. Alcohol, intestinal bacterial growth, intestinal permeability to endotoxin, and medical consequences: summary of a symposium. Alcohol 2008; 42:349–61.
42. Tsuruya A, Kuwahara A, Saito Y, Yamaguchi H, Tsubo T, Suga S, et al. Ecophysiological consequences of alcoholism on human gut microbiota: implications for ethanol-related pathogenesis of colon cancer. Sci Rep 2016;6:27923.
43. Heckley GA, Jarl J, Asamoah BO, U GG. How the risk of liver cancer changes after alcohol cessation: a review and meta-analysis of the current literature. BMC Cancer 2011;11:446.
44. Lang MB, Segersvard R, Grundsten M, Segerdahl M, Arnelo U, Permert J, et al. Management of alcohol use disorders in patients with chronic pancreatitis. JOP 2012;13:654–9.
45. Duell EJ. Epidemiology and potential mechanisms of tobacco smoking and heavy alcohol consumption in pancreatic cancer. Mol Carcinog 2012;51:40–52.
46. Gu H, Fortunato F, Bergmann F, Buchler MW, Whitcomb DC, Werner J. Alcohol exacerbates LPS-induced fibrosis in subclinical acute pancreatitis. Am J Pathol 2013;183:1508–17.
47. Mio T, Romberger DJ, Thompson AB, Robbins RA, Heires A, Rennard SI. Cigarette smoke induces interleukin-8 release from human bronchial epithelial cells. Am J Respir Crit Care Med 1997;155:1770–6.
48. Kode A, Yang SR, Rahman I. Differential effects of cigarette smoke on oxidative stress and proinflammatory cytokine release in primary human airway epithelial cells and in a variety of transformed alveolar epithelial cells. Respir Res 2006;7:132.
49. Pace E, Ferraro M, Siena L, Melis M, Montalbano AM, Johnson M, et al. Cigarette smoke increases Toll-like receptor 4 and modifies lipopolysaccharide-mediated responses in airway epithelial cells. Immunology 2008;124:401–11.
50. Lee J, Taneja V, Vassallo R. Cigarette smoking and inflammation: cellular and molecular mechanisms. J Dent Res 2012;91:142–9.
51. Reynolds PR, Kasteler SD, Schmitt RE, Hoidal JR. Receptor for advanced glycation end-products signals through Ras during tobacco smoke-induced pulmonary inflammation. Am J Respir Cell Mol Biol 2011;45: 411–8.
52. Bos JL. ras oncogenes in human cancer: a review. Cancer Res 1989;49: 4682–9.
53. Walters MJ, Paul-Clark MJ, McMaster SK, Ito K, Adcock IM, Mitchell JA. Cigarette smoke activates human monocytes by an oxidant-AP-1 signaling pathway: implications for steroid resistance. Mol Pharmacol 2005;68: 1343–53.
54. Takahashi H, Ogata H, Nishigaki R, Broide DH, Karin M. Tobacco smoke promotes lung tumorigenesis by triggering IKKbeta- and JNK1-dependent inflammation. Cancer Cell 2010;17:89–97.
55. Peek RM Jr, Blaser MJ. Helicobacter pylori and gastrointestinal tract adenocarcinomas. Nat Rev Cancer 2002;2:28–37.
56. Dapito DH, Mencin A, Gwak GY, Pradere JP, Jang MK, Mederacke I, et al. Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. Cancer Cell 2012;21:504–16.
57. Moresco EM, LaVine D, Beutler B. Toll-like receptors. Curr Biol 2011;21: R488–93.
58. Ochi A, Nguyen AH, Bedrosian AS, Mushlin HM, Zarbakhsh S, Barilla R, et al. MyD88 inhibition amplifies dendritic cell capacity to promote pancreatic carcinogenesis via Th2 cells. J Exp Med 2012;209:1671–87.
59. Fukata M, Chen A, Vamadevan AS, Cohen J, Breglio K, Krishnareddy S, et al. Toll-like receptor-4 promotes the development of colitis-associated colorectal tumors. Gastroenterology 2007;133:1869–81.
60. Di Caro G, Marchesi F, Laghi L, Grizzi F. Immune cells: plastic players along colorectal cancer progression. J Cell Mol Med 2013;17:1088–95.

61. Hu B, Elinav E, Huber S, Strowig T, Hao L, Hafemann A, et al. Microbiota-induced activation of epithelial IL-6 signaling links inflammasome-driven inflammation with transmissible cancer. Proc Natl Acad Sci U S A 2013;110:9862–7.

62. Arthur JC, Perez-Chanona E, Muhlbauer M, Tomkovich S, Uronis JM, Fan TJ, et al. Intestinal inflammation targets cancer-inducing activity of the microbiota. Science 2012;338:120–3.

63. Sears CL, Garrett WS. Microbes, microbiota, and colon cancer. Cell Host Microbe 2014;15:317–28.

64. Ambalam P, Raman M, Purama RK, Doble M. Probiotics, prebiotics and colorectal cancer prevention. Best Pract Res Clin Gastroenterol 2016;30:119–31.

65. FAO/WHO. Report of a Joint FAO/WHO expert consultation on evaluation of health, and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. Córdoba, Spain: Food and Agriculture Organization of the United Nations, World Health Organization; 2001.

66. Roberfroid M. Prebiotics: the concept revisited. J Nutr 2007;137:830S–7S.

67. Kuo SM. The interplay between fiber and the intestinal microbiome in the inflammatory response. Adv Nutr 2013;4:16–28.

68. Idorn M, Hojman P. Exercise-dependent regulation of NK cells in cancer protection. Trends Mol Med 2016;22:565–77.

69. Friedenreich CM, Neilson HK, Farris MS, Courneya KS. Physical activity and cancer outcomes: a precision medicine approach. Clin Cancer Res 2016;22:4766–75.

70. Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. J Clin Invest 2007;117:1175–83.

71. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al. Voluntary running suppresses tumor growth through epinephrine- and IL-6-dependent NK cell mobilization and redistribution. Cell Metab 2016;23:554–62.

72. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011; 377:31–41.

73. Guo Y, Liu Y, Zhang C, Su ZY, Li W, Huang MT, et al. The epigenetic effects of aspirin: the modification of histone H3 lysine 27 acetylation in the prevention of colon carcinogenesis in azoxymethane- and dextran sulfate sodium-treated CF-1 mice. Carcinogenesis 2016;37:616–24.

74. Schror K. Pharmacology and cellular/molecular mechanisms of action of aspirin and non-aspirin NSAIDs in colorectal cancer. Best Pract Res Clin Gastroenterol 2011;25:473–84.

75. Allaj V, Guo C, Nie D. Non-steroid anti-inflammatory drugs, prostaglandins, and cancer. Cell Biosci 2013;3:8.

76. Ghosh N, Chaki R, Mandal V, Mandal SC. COX-2 as a target for cancer chemotherapy. Pharmacol Rep 2010;62:233–44.

77. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–7.

78. Ranjbar MM, Assadolahi V, Yazdani M, Nikaein D, Rashidieh B. Virtual dual inhibition of COX-2/5-LOX enzymes based on binding properties of alpha-amyrins, the anti-inflammatory compound as a promising anticancer drug. EXCLI J 2016;15:238–45.

79. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. PLoS Med 2011;8:e1001098.

80. Grosch S, Maier TJ, Schiffmann S, Geisslinger G. Cyclooxygenase-2 (COX-2)-independent anticarcinogenic effects of selective COX-2 inhibitors. J Natl Cancer Inst 2006;98:736–47.

81. Rayburn ER, Ezell SJ, Zhang R. Anti-inflammatory agents for cancer therapy. Mol Cell Pharmacol 2009;1:29–43.

82. Wang H, Li M, Rinehart JJ, Zhang R. Pretreatment with dexamethasone increases antitumor activity of carboplatin and gemcitabine in mice bearing human cancer xenografts: in vivo activity, pharmacokinetics, and clinical implications for cancer chemotherapy. Clin Cancer Res 2004;10:1633–44.

83. Witschi H, Espiritu I, Ly M, Uyeminami D. The chemopreventive effects of orally administered dexamethasone in Strain A/J mice following cessation of smoke exposure. Inhal Toxicol 2005;17:119–22.

84. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372:142–52.

85. Jian ZH, Huang JY, Lin FC, Nfor ON, Jhang KM, Ku WY, et al. The use of corticosteroids in patients with COPD or asthma does not decrease lung squamous cell carcinoma. BMC Pulm Med 2015;15:154.

86. Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. Science 2001;292:1160–4.

87. Jain MK, Ridker PM. Anti-inflammatory effects of statins: clinical evidence and basic mechanisms. Nat Rev Drug Discov 2005;4:977–87.

88. Massey RU. Reflections from the Dean's office. Conn Med 1976;40:212.

89. Schonbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents? Circulation 2004;109: II18–26.

90. Tsan YT, Lee CH, Ho WC, Lin MH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis C virus infection. J Clin Oncol 2013;31:1514–21.

91. Poynter JN, Gruber SB, Higgins PD, Almog R, Bonner JD, Rennert HS, et al. Statins and the risk of colorectal cancer. N Engl J Med 2005;352:2184–92.

92. Bonovas S, Filioussi K, Tsavaris N, Sitaras NM. Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. J Clin Oncol 2005;23:8606–12.

93. Park JH, McMillan DC, Horgan PG, Roxburgh CS. The impact of anti-inflammatory agents on the outcome of patients with colorectal cancer. Cancer Treat Rev 2014;40:68–77.

94. Sehdev A, O'Neil BH. The role of aspirin, vitamin D, exercise, diet, statins, and metformin in the prevention and treatment of colorectal cancer. Curr Treat Options Oncol 2015;16:43.

95. Bost F, Sahra IB, Le Marchand-Brustel Y, Tanti JF. Metformin and cancer therapy. Curr Opin Oncol 2012;24:103–8.

96. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell 2010;141:39–51.

97. Shi C, Pamer EG. Monocyte recruitment during infection and inflammation. Nat Rev Immunol 2011;11:762–74.

98. Davies LC, Jenkins SJ, Allen JE, Taylor PR. Tissue-resident macrophages. Nat Immunol 2013;14:986–95.

99. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol 2004;25:677–86.

100. Chanmee T, Ontong P, Konno K, Itano N. Tumor-associated macrophages as major players in the tumor microenvironment. Cancers (Basel) 2014;6:1670–90.

101. Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. Nat Rev Cancer 2004;4:71–78.

102. Karnevi E, Andersson R, Rosendahl AH. Tumour-educated macrophages display a mixed polarisation and enhance pancreatic cancer cell invasion. Immunol Cell Biol 2014;92:543–52.

103. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436–44.

104. Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, Campion LR, et al. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. Nature 2011;475:222–5.

105. Mantovani A, Allavena P. The interaction of anticancer therapies with tumor-associated macrophages. J Exp Med 2015;212:435–45.

106. Sanford DE, Belt BA, Panni RZ, Mayer A, Deshpande AD, Carpenter D, et al. Inflammatory monocyte mobilization decreases patient survival in pancreatic cancer: a role for targeting the CCL2/CCR2 axis. Clin Cancer Res 2013;19:3404–15.

107. Murdoch C, Giannoudis A, Lewis CE. Mechanisms regulating the recruitment of macrophages into hypoxic areas of tumors and other ischemic tissues. Blood 2004;104:2224–34.

108. Senovilla L, Aranda F, Galluzzi L, Kroemer G. Impact of myeloid cells on the efficacy of anticancer chemotherapy. Curr Opin Immunol 2014; 30:24–31.

109. Shen L, Sundstedt A, Ciesielski M, Miles KM, Celander M, Adelaiye R, et al. Tasquinimod modulates suppressive myeloid cells and enhances cancer immunotherapies in murine models. Cancer Immunol Res 2015;3:136–48.

110. Olsson A, Nakhle J, Sundstedt A, Plas P, Bauchet AL, Pierron V, et al. Tasquinimod triggers an early change in the polarization of tumor associated macrophages in the tumor microenvironment. J Immunother Cancer 2015;3:53.

111. Nakanishi Y, Nakatsuji M, Seno H, Ishizu S, Akitake-Kawano R, Kanda K, et al. COX-2 inhibition alters the phenotype of tumor-associated

macrophages from M2 to M1 in ApcMin/+ mouse polyps. Carcinogenesis 2011;32:1333–9.

112. Nagai T, Tanaka M, Tsuneyoshi Y, Xu B, Michie SA, Hasui K, et al. Targeting tumor-associated macrophages in an experimental glioma model with a recombinant immunotoxin to folate receptor beta. Cancer Immunol Immunother 2009;58:1577–86.

113. Aggarwal BB, Sethi G, Ahn KS, Sandur SK, Pandey MK, Kunnumakkara AB, et al. Targeting signal-transducer-and-activator-of-transcription-3 for prevention and therapy of cancer: modern target but ancient solution. Ann N Y Acad Sci 2006;1091:151–69.

114. Karin M. Nuclear factor-kappaB in cancer development and progression. Nature 2006;441:431–6.

115. Mankan AK, Greten FR. Inhibiting signal transducer and activator of transcription 3: rationality and rationale design of inhibitors. Expert Opin Investig Drugs 2011;20:1263–75.

116. Taniguchi K, Karin M. IL-6 and related cytokines as the critical lynchpins between inflammation and cancer. Semin Immunol 2014;26:54–74.

117. Pilati C, Amessou M, Bihl MP, Balabaud C, Nhieu JT, Paradis V, et al. Somatic mutations activating STAT3 in human inflammatory hepatocellular adenomas. J Exp Med 2011;208:1359–66.

118. Kortylewski M, Xin H, Kujawski M, Lee H, Liu Y, Harris T, et al. Regulation of the IL-23 and IL-12 balance by Stat3 signaling in the tumor microenvironment. Cancer Cell 2009;15:114–23.

119. Fagard R, Metelev V, Souissi I, Baran-Marszak F. STAT3 inhibitors for cancer therapy: Have all roads been explored? JAKSTAT 2013;2:e22882.

120. Mesa RA, Yasothan U, Kirkpatrick P. Ruxolitinib. Nat Rev Drug Discov 2012;11:103–4.

121. Zerbini CA, Lomonte AB. Tofacitinib for the treatment of rheumatoid arthritis. Expert Rev Clin Immunol 2012;8:319–31.

122. Loh ML, Tasian SK, Rabin KR, Brown P, Magoon D, Reid JM, et al. A phase 1 dosing study of ruxolitinib in children with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms: A Children's Oncology Group phase 1 consortium study (ADVL1011). Pediatr Blood Cancer 2015;62:1717–24.

123. Plimack ER, Lorusso PM, McCoon P, Tang W, Krebs AD, Curt G, et al. AZD1480: a phase I study of a novel JAK2 inhibitor in solid tumors. Oncologist 2013;18:819–20.

124. Min C, Eddy SF, Sherr DH, Sonenshein GE. NF-kappaB and epithelial to mesenchymal transition of cancer. J Cell Biochem 2008;104: 733–44.

125. Zhong Z, Umemura A, Sanchez-Lopez E, Liang S, Shalapour S, Wong J, et al. NF-kappaB restricts inflammasome activation via elimination of damaged mitochondria. Cell 2016;164:896–910.

126. Hsu LC, Enzler T, Seita J, Timmer AM, Lee CY, Lai TY, et al. IL-1beta-driven neutrophilia preserves antibacterial defense in the absence of the kinase IKKbeta. Nat Immunol 2011;12:144–50.

127. Bhardwaj A, Sethi G, Vadhan-Raj S, Bueso-Ramos C, Takada Y, Gaur U, et al. Resveratrol inhibits proliferation, induces apoptosis, and overcomes chemoresistance through down-regulation of STAT3 and nuclear factor-kappaB-regulated antiapoptotic and cell survival gene products in human multiple myeloma cells. Blood 2007;109:2293–302.

128. Shishodia S, Majumdar S, Banerjee S, Aggarwal BB. Ursolic acid inhibits nuclear factor-kappaB activation induced by carcinogenic agents through suppression of IkappaBalpha kinase and p65 phosphorylation: correlation with down-regulation of cyclooxygenase 2, matrix metalloproteinase 9, and cyclin D1. Cancer Res 2003;63:4375–83.

129. Singh S, Aggarwal BB. Activation of transcription factor NF-kappa B is suppressed by curcumin (diferuloylmethane) [corrected]. J Biol Chem 1995;270:24995–5000.

130. Salamone F, Galvano F, Cappello F, Mangiameli A, Barbagallo I, Li Volti G. Silibinin modulates lipid homeostasis and inhibits nuclear factor kappa B activation in experimental nonalcoholic steatohepatitis. Transl Res 2012;159:477–86.

131. Ahn DW, Seo JK, Lee SH, Hwang JH, Lee JK, Ryu JK, et al. Enhanced antitumor effect of combination therapy with gemcitabine and guggulsterone in pancreatic cancer. Pancreas 2012;41:1048–57.

132. Aggarwal BB, Vijayalekshmi RV, Sung B. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. Clin Cancer Res 2009;15:425–30.

133. Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. Nat Rev Immunol 2016;16:407–20.

134. Guo W, Sun Y, Liu W, Wu X, Guo L, Cai P, et al. Small molecule-driven mitophagy-mediated NLRP3 inflammasome inhibition is responsible for the prevention of colitis-associated cancer. Autophagy 2014;10:972–85.

135. Qiao Y, Wang P, Qi J, Zhang L, Gao C. TLR-induced NF-kappaB activation regulates NLRP3 expression in murine macrophages. FEBS Lett 2012; 586:1022–6.

136. Nunes T, de Souza HS. Inflammasome in intestinal inflammation and cancer. Mediators Inflamm 2013;2013:654963.

137. Antonucci L, Fagman JB, Kim JY, Todoric J, Gukovsky I, Mackey M, et al. Basal autophagy maintains pancreatic acinar cell homeostasis and protein synthesis and prevents ER stress. Proc Natl Acad Sci U S A 2015;112: E6166–74.

138. Li N, Wu X, Holzer RG, Lee JH, Todoric J, Park EJ, et al. Loss of acinar cell IKKalpha triggers spontaneous pancreatitis in mice. J Clin Invest 2013;123:2231–43.

139. Aghajan M, Li N, Karin M. Obesity, autophagy and the pathogenesis of liver and pancreatic cancers. J Gastroenterol Hepatol 27 Suppl 2012;2:10–4.

140. Heinrich PC, Behrmann I, Haan S, Hermanns HM, Muller-Newen G, Schaper F. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J 2003;374:1–20.

141. Crusz SM, Balkwill FR. Inflammation and cancer: advances and new agents. Nat Rev Clin Oncol 2015;12:584–96.

142. Wang K, Karin M. The IL-23 to IL-17 cascade inflammation-related cancers. Clin Exp Rheumatol 2015;33:S87–90.

143. Teng MW, Bowman EP, McElwee JJ, Smyth MJ, Casanova JL, Cooper AM, et al. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. Nat Med 2015;21:719–29.

144. Bertoletti A, Gehring AJ. Immune therapeutic strategies in chronic hepatitis B virus infection: virus or inflammation control? PLoS Pathog 2013;9:e1003784.

145. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med 1997;336:1855–59.

146. Koumbi L. Current and future antiviral drug therapies of hepatitis B chronic infection. World J Hepatol 2015;7:1030–40.

147. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol 2014;61:S58–68.

148. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. Vaccine 2006;24 Suppl 1:S1–15.

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