HHS Public Access

Author manuscript

Nat Rev Clin Oncol. Author manuscript; available in PMC 2022 April 04.

Published in final edited form as:

Nat Rev Clin Oncol. 2021 May ; 18(5): 261–279. doi:10.1038/s41571-020-00459-9.

Targeting cancer-promoting inflammation — have anti-inflammatory therapies come of age?

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Abstract

The immune system has crucial roles in cancer development and treatment. Whereas adaptive immunity can prevent or constrain cancer through immunosurveillance, innate immunity and inflammation often promote tumorigenesis and malignant progression of nascent cancer. The past decade has witnessed the translation of knowledge derived from preclinical studies of antitumour immunity into clinically effective, approved immunotherapies for cancer. By contrast, the successful implementation of treatments that target cancer-associated inflammation is still awaited. Anti-inflammatory agents have the potential to not only prevent or delay cancer onset but also to improve the efficacy of conventional therapeutics and next-generation immunotherapies. Herein, we review the current clinical advances and experimental findings supporting the utility of an anti-inflammatory approach to the treatment of solid malignancies. Gaining a better mechanistic understanding of the mode of action of anti-inflammatory agents and designing more effective treatment combinations would advance the clinical application of this therapeutic approach.

Inflammation is part of the innate immune response to danger signals, tissue disruption and/or infection. Transient and properly terminated inflammation is beneficial yet chronic inflammation increases cancer risk[1]. Numerous environmental factors, including carcinogenic microbes, pollutants, tissue-damaging radiation, tobacco smoke, diesel exhaust fumes, particulate matter and dietary factors, can evoke chronic inflammation in multiple organ systems, especially those that are exposed to the external environment[1]. Left

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Author contributions

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Competing interests

M.K. has received research support from Merck and Aduro Pharmaceuticals. J.H. and B.S. declare no competing interests.

Supplementary information

Supplementary information is available for this paper at https://doi.org/10.1038/s41571-020-00459-9.

unresolved, chronic inflammatory responses can result in tumour promotion[1]. Tumour-associated inflammation, which entails intricate interactions between epithelial and stromal cells, can in some cases lead to epigenetic alterations that drive malignant progression and even initiate tumorigenesis. More generally, however, chronic inflammation results in the production of growth factors that support the development of newly emergent tumours and cause them to behave as “wounds that do not heal”[2]. Inflammation-reducing chemopreventive strategies that inhibit either the initiation or propagation of persistent inflammation might therefore prevent or delay cancer onset[3]. Anti-infective agents, nonsteroidal anti-inflammatory drugs (NSAIDs) and other commonly used drugs capable of reducing inflammation, such as statins and metformin, have been reported to decrease cancer risk and incidence[4-8].

Cancer cell-intrinsic or therapy-elicited mechanisms, including metabolic changes, cell stress and cell death, also constitute important sources of tumour-associated inflammation[1]. The continuous production of various cytokines, chemokines and growth factors within the tumour microenvironment (TME) supports cancer cell proliferation, evolution and survival as well as tumour vascularization and immune dysregulation, all of which contribute to tumour progression, invasion, metastasis and therapy resistance. Thus, the use of anti-inflammatory agents, either alone or in combination with cytotoxic agents and targeted therapies, is an appealing strategy for the treatment of inflammation-driven cancers. This approach is effective in various animal models[9-11], although the complexity and plasticity of human cancers and their ecosystem present major hurdles that need to be overcome for anti-inflammatory therapy to become truly successful. For example, the inhibition of inflammation mostly slows down tumour growth rather than killing cancer cells and therefore needs to be combined with cancer-specific cytotoxic drugs to fully eradicate the tumours. In addition, owing to the depletion of general survival factors, anti-inflammatory drugs can inflict bystander effects on non-cancerous tissues, which can in turn result not only in TME remodelling and therapy resistance but also in the increased susceptibility of non-malignant cells to non-specific cytotoxicity that can lead to toxicities[12,13].

The past decade has witnessed a burgeoning of effective treatments based on the activation of anti-tumour immune responses, for example, using immune-checkpoint inhibitors (ICIs) or genetically engineered T cells[14]. Such immunotherapies induce durable responses in a subset of patients; however, primary or acquired therapy resistance occurs in the vast majority of patients. In many cases, immunotherapy resistance is attributable to the presence of a pro-inflammatory and immunosuppressive TME[15] (BOX 1). In this context, anti-inflammatory drugs that target immunosuppressive cells or cytokines might render the cancer more susceptible to immune-mediated rejection. Moreover, akin to the treatment of autoimmune diseases, selective targeting of the key drivers of immunotherapy-induced inflammation might increase the response-to-toxicity ratio and thereby improve therapeutic outcomes. Consequently, the combination of anti-inflammatory therapy with immunotherapy might evolve into a successful approach for circumventing the obstacles associated with current treatment modalities.

As a canonical cancer hallmark[16], inflammation influences all stages of cancer development and treatment. The central inflammatory mediators governing cancer-autonomous

intracellular modulation and intercellular communication within the TME have been covered in several reviews[1,17-21]. Herein, we draw on advances highlighting the use of anti-inflammatory agents for the prevention and/or treatment of solid malignancies, either in isolation or in combination with other therapeutic modalities. Rather than surveying all cancer-related inflammatory traits and mediators, we discuss what we believe are special opportunities and perils for anti-inflammatory approaches. Antiangiogenic agents and multi-kinase inhibitors, some of which exert anti-inflammatory effects, already occupy well-established places in the anticancer armamentarium and will not be included in this Review.

Anti-inflammatory treatments for cancer

Anti-infective agents

Several infectious diseases that result in chronic inflammation have been credibly linked to cancer initiation[2]. Accordingly, anti-infective agents have an important role in reducing the burden of inflammation-related cancers (FIG. 1).

Antiviral therapies.—Currently, hepatitis B virus (HBV) or hepatitis C virus (HCV) infections remain the leading causes of hepatocellular carcinoma (HCC)[5]. In addition to the direct oncogenic effects[22], HBV or HCV infections can cause cancer-promoting inflammation. HBV vaccination has substantially reduced the global HCC burden and is continuing to do so; data from a population-based study indicate that the incidence of HCC in vaccinated birth cohorts is 75% lower than that in unvaccinated cohorts[23]. For infected individuals, interferon-based therapies, nucleoside or nucleotide analogues, and direct-acting antiviral agents, which inhibit the replication of HBV or HCV and/or promote their immune-mediated clearance, are estimated to decrease HCC risk by 50–80%[5]. Antiviral treatment is also effective in decreasing disease recurrence and improving postoperative survival outcomes in patients with HCC[24-26]. However, curative antiviral treatment of HBV or HCV infection alone is insufficient to entirely prevent HCC occurrence or recurrence, possibly owing to the presence of cirrhosis, diabetes, excess alcohol consumption, impaired liver function or other patient characteristics (such as age, sex, lifestyle and others)[27-30].

Similarly, >90% of cervical cancers can be attributed to infection with human papillomavirus (HPV) types 16, 18, 31, 33, 45, 52 or 58 (REF.[31]). The results of international randomized controlled trials (RCTs) have demonstrated the substantial efficacy of HPV vaccines against cervical precancerous lesions (cervical intraepithelial neoplasia grade 2+). According to a large-scale meta-analysis reported in 2019 (REF.[32]), 5–9 years of population-based vaccination not only reduced the prevalence of HPV infection but also decreased the prevalence of cervical intraepithelial neoplasia grade 2+ by 51% in screened girls aged 15–19 years and by 31% in women aged 20–24 years. More recently, the results of a nationwide study in Sweden demonstrated that the cumulative incidence of cervical cancer was reduced from 94 cases per 100,000 in women who were unvaccinated to 47 cases per 100,000 in women vaccinated with the quadrivalent HPV vaccine (targeting HPV types 6, 11, 16 and 18) at 10–30 years of age[33]. Therefore, HPV vaccination has been implemented for cervical cancer prophylaxis in multiple age groups across different

countries. High-level vaccination coverage in the population would likely result in cervical cancer elimination[6], although specific antiviral drugs for treating established HPV infections are still lacking.

Epstein–Barr virus (EBV), the first tumour virus identified in humans, is associated with gastric cancer, nasopharyngeal cancer and lymphoma[34]. Currently, however, no approved therapies are available to prevent or treat EBV infection, despite intense research efforts.

Antibacterial therapies.—*Helicobacter pylori*, a bacteria that is carried by ~50% of the world population, is the strongest risk factor for gastric cancer and has therefore been designated by the WHO as a class I carcinogen[35]. Data from RCTs indicate that *H. pylori* eradication with broad-spectrum antibiotics not only prevents gastric cancer in individuals with asymptomatic infection or in those without precancerous lesions but also lowers the rates of metachronous gastric cancer development in patients with early stage gastric cancer or high-grade adenoma[35-37]. Among >2,250 residents of a high-risk region for gastric cancer in China, 2 weeks of *H. pylori* treatment resulted in early reductions in gastric cancer incidence and mortality that persisted beyond >22 years[38].

Commensal bacteria, such as *Fusobacterium nucleatum*, have been found to increase the risk of colorectal cancer (CRC) development and to promote the progression of this disease[39-42]. Moreover, computational bioinformatics studies have identified microbial genetic signatures in blood or tumour tissues that distinguished patients with different cancer types from cancer-free individuals; these signatures provide a high-resolution landscape of cancer-associated microbes[43]. However, further studies are required to determine whether these bacteria induce cancer-promoting inflammation.

The antitumour effects of broad-spectrum antibiotics have been demonstrated in animal models, particularly in models of gastrointestinal cancers[41,44,45]; however, the current lack of species-specific antibiotics and the deleterious consequences of commensal dysbiosis have limited the therapeutic potential of microbial modulation in patients with cancer[46]. A future approach could entail the use of species-specific bacteriophages to selectively eliminate carcinogenic or tumour-promoting bacteria[47]. Vaccination against specific cancer-promoting microbes could also be considered, but antibacterial vaccines are rare and have mostly been ineffective.

Anti-fungal treatment.—Fungal infections have been found to be associated with oesophageal squamous cell carcinoma (ESCC) both in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, who have increased susceptibility to chronic fungal infections, and in individuals without autoimmune disease[48]. These findings suggest that anti-fungal treatments could be used to reduce the incidence of ESCC; indeed, such therapy had anticancer effects in a mouse model of auto-immune polyendocrinopathy-candidiasis-ectodermal dystrophy-related ESCC[48].

Nonsteroidal anti-inflammatory drugs

NSAIDs are widely used as antipyretics, analgesics or anti-platelet agents (platelet aggregation inhibitors) for cardiovascular disease (CVD) prophylaxis, operating through

the inhibition of cyclooxygenase (COX) activity. One such NSAID, aspirin, has been identified as a broad-spectrum cancer-preventive agent based on data from clinical and epidemiological studies[24] (FIG. 1). Since 2015, the US Preventive Services Task Force has recommended the routine use of aspirin for the prevention of CRC among individuals aged 50–59 years who have a high risk of CVD and a low risk of bleeding[49]. A systematic review and meta-analysis of observational studies on aspirin use and digestive-tract cancers published up to March 2019 revealed that regular users had a 27% lower CRC risk (across 45 studies), a 33% lower ESCC risk (13 studies), a 39% lower risk of adenocarcinoma of the oesophagus and gastric cardia (10 studies), a 36% lower risk of stomach cancer (14 studies), a 38% lower risk of hepatobiliary cancer (5 studies) and a 22% lower risk of pancreatic cancer (15 studies) than non-users[7]. However, in other large-cohort prospective studies, regular aspirin use was not associated with a statistically significant reduction in pancreatic cancer risk, except in individuals with diabetes or higher baseline levels of systemic inflammation[50]. Nevertheless, the anti-inflammatory properties of aspirin make it a viable chemopreventive for those with an elevated risk of inflammation-related cancer. In two nationwide observational cohort studies of patients with chronic viral hepatitis in Sweden or Taiwan[51,52], the long-term use of low-dose aspirin (≤160 or ≤100 mg daily, respectively, for ≥90 days) reduced the risk of HCC by 31% and 29%, respectively, without increasing the risk of gastrointestinal bleeding. Aspirin also seems to benefit patients with a hereditary cancer risk: in a double-blind RCT, patients with Lynch syndrome who were assigned to aspirin treatment had a 37% lower risk of developing CRC compared with those who received placebo[53]. An analysis of data from two large-cohort prospective observational studies performed in the USA revealed that regular aspirin use for at least 6 years decreased the overall incidence of gastrointestinal-tract cancers by 15% and of CRC by 19% but had no effect on breast, prostate or lung cancer incidence[54]. Furthermore, pooled results from RCTs in the setting of CVD prophylaxis (8 eligible trials encompassing 25,570 patients and 674 cancer deaths) demonstrated that daily aspirin use mitigated distant metastasis and deaths from certain cancers, specifically adenocarcinomas (particularly those that were non-metastatic at diagnosis)[55].

Importantly, the post-diagnosis administration of aspirin has been shown to be sufficient to reduce overall gastrointestinal or oesophageal cancer mortality[56]. The survival benefit from post-diagnosis aspirin use specifically in patients with CRC was greater among those with *PIK3CA*-mutant and COX2-positive tumours[57] or among those with low tumoural levels of PD-L1 (REF.[58]). The ongoing Add-Aspirin trial (ISRCTN74358648) is evaluating the effect of aspirin use after primary radical therapy for gastroesophageal, colorectal, breast or prostate cancer on disease recurrence and survival outcomes, with a predefined feasibility analysis revealing that this adjuvant therapy approach is well tolerated with a low incidence of toxicities (0.5% grade 3 and no upper gastrointestinal bleeding of any grade)[59]. However, a cautionary note comes from the ASPREE study; in this placebo-controlled RCT, low-dose aspirin (100 mg daily) was associated with increases in bleeding risk, in the incidence of cancers diagnosed with metastasis and, correspondingly, in cancer mortality in older adults (>65 years of age) without CVD, dementia or physical disability[60-62].

Celecoxib and rofecoxib, two selective COX2 inhibitors, have demonstrated efficacy in the prophylaxis of colorectal adenomas (or adenomatous polyps) but are not routinely

recommended for such indications because of their serious CVD risks[63-65]. A randomized phase II trial revealed that the addition of celecoxib to chemoradiotherapy did not provide an overall survival (OS) or progression-free survival (PFS) benefit in patients with unresectable stage III non-small-cell lung cancer[66]. In a trial involving patients with CRC, preoperative treatment with celecoxib did not improve responses to neoadjuvant immunotherapy with anti-PD-1 plus anti-CTLA4 antibodies[67], although results of a preclinical study indicate that the inhibition of prostaglandin E_2 (PGE_2) synthesis (for example, through genetic ablation of COX expression) can overcome immune evasion in some mouse models of cancer[68].

Of therapeutic significance, the intraoperative administration of ketorolac, an inhibitor of both COX1 and COX2, reduced the frequency of distant disease recurrence in patients with breast cancer, particularly in those with an elevated BMI (≥25 kg/m^2)[69]. The use of other non-aspirin NSAIDs, such as ibuprofen, has also been associated with a decreased CRC risk, but further investigation of their overall therapeutic value in the prevention and/or treatment of cancer is warranted[70].

Lipid-lowering drugs

High serum levels of LDL, a protein complex that is loaded with cholesterol, can lead to harmful inflammation. Statins are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors that block cholesterol biosynthesis and are prophylactically used to treat CVD. Statins also have poorly understood anti-inflammatory properties, which are in fact important for their protective activity against CVD and have not been reported for other cholesterol-lowering treatments[71]. Early observations of the association between statin use and CRC risk came from RCTs in the setting of CVD[71]. In the population-based case–control Molecular Epidemiology of CRC study[72], self-reported statin use for at least 5 years was significantly associated with a lower CRC risk (OR 0.50, 95% CI 0.40–0.63), even after adjustment for the presence or absence of hypercholesterolaemia as well as NSAID use, among other factors (OR 0.53,95% CI 0.38–0.74). A retrospective cohort study has revealed that prior statin use might reduce post-colonoscopy CRC incidence[73]. However, the results of meta-analyses of RCTs and other cohort studies indicate only modest protective effects of statins on CRC[74-76].

In a cohort of 7,657 patients with newly diagnosed CRC, post-diagnosis statin use was associated with decreased cancer-specific mortality (fully adjusted HR 0.71, 95% CI 0.61–0.84)[77]. Nonetheless, when additional confounding variables were considered, neither population-based cohort studies nor the Surveillance, Epidemiology, and End Results (SEER)–Medicare database provided evidence supporting improved cancer-specific survival among statin users[78,79].

Similar to other approaches to HCC chemoprevention, a profound beneficial effect of statin use has been observed in patients with viral hepatitis, diabetes or liver cirrhosis yet lower or no statistically significant effects have been observed in the general population[80-87]. Of note, the statin-related benefits were greater in Asian populations than in Western populations. Observational studies and clinical trials have also revealed that statins might be protective against *H. pylori*-related gastric cancer in both Asian and Western populations[88]. Well-

designed, prospective, multicentre studies are needed to further validate the chemopreventive activity of statins.

Metformin

Type 2 diabetes mellitus (T2DM) has been linked to an increased incidence of and mortality from many types of cancers, including colorectal, pancreatic, hepatobiliary, breast and endometrial cancers[89]. Metformin is an oral biguanide used for the first-line treatment of T2DM. Data from epidemiological studies and meta-analyses have demonstrated an association between metformin use and a reduced incidence of pancreatic, hepatocellular, lung, colorectal and breast cancers in patients with T2DM[89]. Of note, a systematic review encompassing 10 studies involving a total of 334,307 patients with T2DM revealed that metformin use was associated with a 50% lower risk of HCC[90-92]. Specifically, this association was seen in a meta-analysis of observational studies ($n = 8$) after adjusting for potential confounding factors, such as the use of other antidiabetic agents; however, the evidence is still insufficiently strong to recommend chemoprevention using metformin in patients at high risk of HCC[90-92]. Therefore, additional prospective trials or observational studies evaluating the ability of metformin to reduce HCC risk are needed.

The results of a multicentre, double-blind, placebo-controlled phase III trial involving 151 patients without diabetes who had previously had single or multiple colorectal adenomas or polyps resected by endoscopy support a potential role for metformin in CRC prevention[93]. In this group, treatment with low-dose metformin (250 mg per day) resulted in a significantly lower incidence of metachronous polyps (RR 0.67, 95% CI 0.47–0.97) or adenomas (RR 0.60, 95% CI 0.40–0.92)[93].

Given its low cost and good safety profile (the most serious complication is lactic acidosis, with an incidence of about 3–10 cases per 100,000 person-years)[94], metformin has been extensively investigated as a possible therapeutic and chemopreventive agent in different cancer settings[95] (FIG. 1). The anticancer activity of metformin is being evaluated in numerous ongoing phase II and III trials (Supplementary Table 1). For example, the combinational use of metformin and low-dose aspirin is being investigated for tertiary prevention (to avoid disease recurrence) after the resection of stage I–III CRC (NCT03047837)[96]. Encouragingly, in an open-label, phase II study involving patients with advanced-stage *EGFR*-mutant non-small-cell lung cancer[97], the addition of metformin to EGFR tyrosine-kinase inhibitor therapy significantly prolonged PFS (median 13.1 months versus 9.9 months with EGFR tyrosine-kinase inhibitors alone; $P = 0.03$) and OS (median 31.7 months versus 17.5 months, respectively; $P=0.02$).

Targeted anti-inflammatory agents

IL-1 antagonists.—In the double-blind, placebo-controlled phase III CANTOS trial that had the primary aim of investigating the efficacy of the anti-IL-1β antibody canakinumab in preventing recurrent CVD, this anti-inflammatory therapy was found to have unanticipated activity in preventing lung cancer[98]. The CANTOS study included 10,061 patients who had atherosclerosis, a previous myocardial infarction and high serum levels of high-sensitivity C-reactive protein (CRP; ≥2 mg/l) but were free of previously diagnosed cancer. Of note,

canakinumab therapy led to a dose-dependent reduction in circulating CRP and IL-6 levels. At a median follow-up duration of 3.7 years, canakinumab (300 mg subcutaneously every 3 months) was associated with a 67% reduction in lung cancer incidence ($P < 0.0001$), with a 39% reduction also seen with 150 mg dosing ($P=0.034$), as well as with a 77% reduction in lung cancer mortality ($P = 0.0002$), compared with placebo. However, fatal infections or sepsis occurred more frequently with canakinumab than with placebo, warranting caution. Further trials specifically designed to evaluate the efficacy of canakinumab in cancer prevention and treatment are ongoing (Supplementary Table 1).

The first-in-class anti-IL-1α monoclonal antibody MABp1 was developed to target systemic inflammation in cancer. Data from phase I–III trials demonstrate that MABp1 is well tolerated, with no dose-limiting toxicities observed, and can result in the stabilization of disease and symptoms (lean body mass and/or pain, fatigue or anorexia) in patients with various treatment-refractory advanced-stage solid tumours[99,100]. The investigators of the phase III trial of this agent[99,100], which specifically involved patients with CRC refractory to oxaliplatin and irinotecan, concluded that MABp1 constitutes a new standard in the management of advanced-stage CRC.

Blockade of the TNF pathway.—Monoclonal antibody-based agents targeting TNF (infliximab) or its receptor (etanercept) have also been tested for tolerability and biological activity in patients with advanced-stage cancers; the observed therapeutic effects were modest, although the blockade of TNF signalling might contribute to disease stabilization[101-105]. ICIs are commonly associated with immune-related adverse events (irAEs) such as moderate-to-severe colitis[106]. Infliximab has been recommended for the management of irAEs that are refractory to glucocorticoids[107]. Furthermore, the treatment of advance-stage melanoma with either infliximab or certolizumab (another monoclonal antibody-based anti-TNF drug), each administered concomitantly with the anti-CTLA4 antibody ipilimumab and the anti-PD-1 antibody nivolumab, is currently being evaluated in a phase Ib trial (NCT03293784). Notably, anti-TNF therapy might not be feasible in patients with hepatitis given the indispensable role of TNF–TNFR1 signalling in liver regeneration[108].

Anti-IL-6 agents.—IL-6 is one of the most crucial cytokines bridging cancer-promoting inflammation and immunosuppression[109]. Anti-IL-6 drugs, which are routinely used in the treatment of autoimmune conditions, have been tested in anticancer applications. In several phase I–II clinical trials, however, the clinical response to the anti-IL-6R antibody tocilizumab or the anti-IL-6 antibodies clazakizumab and siltuximab has been poor in patients with prostate, lung or breast cancers, multiple myeloma, or cancer-related cachexia (reviewed previously[109,110]). Thus, monotherapy with agents targeting IL-6 might have limited activity against solid tumours in non-stratified patients, although anti-IL-6 therapy is effective in reversing irAEs caused by immunotherapy[111]. In particular, tocilizumab has been approved for the treatment of cytokine-release syndrome (CRS) associated with chimeric antigen receptor (CAR) T cell therapy[112].

Inhibition of TGFβ signalling.—Transforming growth factor-β (TGFβ)-targeted therapies have also been considered for the management of cancer. Galunisertib, a small-

molecule inhibitor of the TGFβR1 kinase, has been demonstrated to be safe in patients with various cancers[113]. When administered in combination with gemcitabine to patients with unresectable pancreatic ductal adenocarcinoma (PDAC) or with sorafenib to patients with advanced-stage HCC, galunisertib had modest therapeutic activity[114,115]. Pending the outcome of trials using galunisertib, more-potent and more-specific small-molecule inhibitors of TGFβR1 have been developed and are being tested in combination with chemotherapy or emerging immunotherapy modalities (Supplementary Table 1). In addition, isoform-specific anti-TGFβ, pan-TGFβ or bi-functional anti-PD-L1-TGFβR2 antibodies are all being tested in phase I trials of different anticancer indications[116].

Targeting cytokines mediating TAMs and MDSCs.—Antibodies or other antagonists targeting the colony-stimulating factor 1 receptor (CSF1R), the CC-chemokine receptor 2 (CCR2) or CCR5, which can deplete tumour-associated macrophages (TAMs) or otherwise abrogate their immunosuppressive inflammatory activities, have been found to be safe and tolerable in phase I trials[117-120]. Although anti-CSF1R antibodies did not have robust anticancer activity either alone or in combination with chemotherapy[117,118], CCR2 (REF.[119]) and CCR5 (REF.[120]) antagonism led to objective clinical responses in patients with advanced-stage PDAC or CRC, respectively. Owing to their immunomodulatory potential, these TAM-targeted agents are also being explored for potential synergy with ICIs[121].

The CXC-chemokine receptor 1 (CXCR1) and CXCR2 antagonist SX-682, which was designed to disrupt the trafficking of myeloid-derived suppressor cells (MDSCs) to tumours, is being tested in combination with pembrolizumab (an anti-PD-1 antibody) in a phase I/II trial involving patients with metastatic melanoma (NCT03161431). Additionally, data from the COMBAT trial (NCT02826486) indicate that the CXCR4 antagonist BL-8040 depletes MDSCs and increases the tumour infiltration of $CD8^+$ T cells, with evidence also indicating that this agent might cooperate with pembrolizumab to improve antitumour immune responses and chemotherapy efficacy in patients with PDAC[122].

Natural anti-inflammatory supplements

In addition to the drugs discussed above, some natural compounds might also help control inflammation and cancer. As an antioxidant and anti-inflammatory dietary supplement, vitamin C has been extensively explored for potential anticancer effects. However, contemporary data indicate that pharmacological vitamin C can enhance the cytotoxicity and therapeutic sensitivity of cancer cells only when administered intravenously at high doses and that it exerts anticancer effects primarily via pro-oxidant, rather than antioxidant, activity[123].

Vitamin D can regulate the host immune system to potentiate immune responses as well as to attenuate harmful inflammatory reactions[124]. The results of several prospective observational studies indicate that plasma levels of the major circulating form of vitamin D, 25-hydroxyvitamin D, are inversely associated with the risk of CRC and prostate cancer[125-127]. Pre-treatment vitamin D levels have also been associated with PFS and OS in patients with advanced-stage CRC or Hodgkin lymphoma who received first-line

chemotherapy[128,129]. However, a prophylactic benefit of vitamin D supplementation remains questionable. In 2,303 randomized postmenopausal women without a prior cancer diagnosis, nutritional supplementation with vitamin D and calcium did not reduce the risk of all-type cancer at 4 years compared with placebo[130]. In the VITAL (Vitamin D and Omega-3) trial, which involved a total of 25,871 cancer-free men and women (aged >50 years and >55 years, respectively), vitamin D supplementation (2,000 IU per day) for a median of 5.3 years was not associated with a reduced incidence of invasive cancer compared with placebo[131]. The findings of a meta-analysis of 52 RCTs involving 75,454 participants suggest that vitamin D supplementation could reduce the risk of cancer-related death by 16%[132]. Nonetheless, in the double-blind, phase II SUNSHINE trial involving patients with advanced-stage CRC, the addition of high-dose (8,000 IU per day for 14 days, followed by 4,000 IU per day) versus standard-dose (400 IU per day) vitamin D to standard chemotherapy resulted in no statistically significant difference in PFS (although a statistically significant difference in PFS was observed on multivariate analysis)[133]. Likewise, in the randomized single-centre AMATERASU trial in patients with digestive-tract cancers, postoperative vitamin D supplementation did not result in improved 5-year relapse-free survival or OS as compared with placebo[134]. In keeping with the anti-inflammatory properties of vitamin D, intake of this vitamin has been correlated with a reduced risk of ICI-related colitis[135].

The administration of long-chain omega-3 fatty acids, an anti-inflammatory nutritional supplement that is often tested in parallel with vitamin D, has not been found to be effective in cancer prevention[136,137]. However, omega-3 supplementation has been associated with a reduced risk of colorectal adenomas among individuals with low plasma levels of such fatty acids at baseline and in the African-American population (OR 0.59, 95% CI 0.35–1.00)[137]. Similarly, the seAFOod Polyp Prevention trial did not meet its primary end point (an improved adenoma detection rate) but did suggest that the omega-3 polyunsaturated fatty acid eicosapentaenoic acid has a chemopreventive effect in reducing recurrent adenoma multiplicity[138]. Of note, contradictory results have been obtained in trials investigating other dietary supplements, including β-carotene, α-tocopherol (vitamin E), selenium, vitamin B_{12} and folic acid, some of which were even associated with an increased cancer risk or diminished chemotherapy responses[38,137,139-143].

The antimicrobial, anti-platelet and lipid-lowering effects attributed to garlic supplements have earned these supplements a place in cancer prevention strategies. In a RCT conducted in a high-risk region for gastric cancer in Shandong, China, 3,365 participants were assigned to three different interventions (*H. pylori* treatment; vitamin C, vitamin E and selenium supplementation; or garlic extract and oil supplementation) or appropriate placebos; among these individuals, the use of garlic supplements for >7 years did not decrease the incidence of gastric cancer but did significantly reduce mortality from this disease (HR 0.66, 95% CI 0.43–1.00)[38].

As a plant-derived natural alkaloid with antioxidant and antimicrobial properties, berberine might have a wide range of therapeutic benefits for patients with digestive system or metabolic diseases. In a double-blind, placebo-controlled RCT, berberine at 0.3 g twice daily significantly decreased the recurrence rate of colorectal adenoma and polypoid lesions

after polypectomy (RR 0.77, 95% CI 0.66–0.91; P=0.001)[144]. Given the rather short follow-up duration of this study (2 years), the ability of berberine to prevent the occurrence of advanced colorectal adenomas or CRC remains to be determined.

Mechanisms of anti-inflammatory therapy

Suppression of oncogenic pathways

Targeting tumour cell-intrinsic pathways.—COX2-PGE_2 signalling can directly confer epithelial cells with protumorigenic traits, thus facilitating the development of inflammation-driven cancer (FIG. 2). COX2 can activate the AKT, mTOR and NF-κB pathways to support cancer cell proliferation either directly or via PGE_2 signalling. Consistently, aspirin and selective COX2 inhibitors have pro-apoptotic and antiproliferative effects on COX2-overexpressing cancer cells[145]. In addition, PGE_2 silences tumour-suppressor genes by reinforcing their promoter methylation through a EP4–DNA methyltransferase pathway[146]. Correspondingly, combined treatment with celecoxib and decitabine effectively mitigates intestinal tumour development in *Apc*$^{Min/+}$ mice[146]. Moreover, hepatic COX2 overexpression induces spontaneous HCC development in mice by reducing the expression of methylcytosine dioxygenase TET1 (a DNA demethylase), thereby resulting in increased DNA methylation, epigenetic silencing of tumour suppressor genes and in the activation of oncogenic pathways, which can be reversed by celecoxib treatment[40]. NSAID treatment can also neutralize a senescence-associated inflammatory response that promotes the growth and invasiveness of p53-deficient intestinal cells and thus prevents colorectal carcinogenesis[147]. Surprisingly, PGE_2 also promotes colon regeneration in preclinical models of colitis through feedforward activation of the transcriptional regulator YAP1, which can trigger tumorigenesis; accordingly, administration of the NSAID indomethacin or of an EP4 antagonist exacerbates colitis but can prevent colon tumorigenesis in mice[148].

Via competitive inhibition of HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway, statins can activate the AMPK and p38 MAPK pathways or suppress MYC phosphorylation to induce cell cycle arrest and apoptosis[149-151]. Similarly, metformin improves insulin sensitivity through the indirect activation of AMPK, which inhibits the activity of mTOR complex 1 (mTORC1), thereby leading to cell growth arrest and resulting in a broad cancer chemopreventive effect[152]. Metformin can also suppress cyclin D1 expression as well as the inflammatory responses associated with stem cell activation[152-154]. Consistent with the link between diabetes and cancer, hyperglycaemia impairs the AMPK-mediated phosphorylation and stabilization of TET2, leading to global DNA demethylation and the inhibition of tumour growth in mice; the anticancer effects of metformin might also depend on the reprogramming of a cancer-favourable epigenome via the activation of this AMPK-TET2 pathway[155]. Similarly, metformin has been shown to integrate metabolic and epigenetic signalling via an AMPK–SETD2–EZH2 axis, thereby suppressing prostate cancer metastasis[156]. Curiously, metformin impairs tumour growth only if administered during periods of fasting-induced hypoglycaemia in mice[157]. Mechanistically, the inhibition of CIP2A by metformin together with upregulation of the PP2A B subunit isoform B56δ

under low glucose conditions activates GSK3β signalling, which leads to reduced levels of the pro-survival protein MCL1 and, ultimately, cancer cell death[157] (FIG. 2).

Targeting tumour cell-extrinsic factors.—Early studies of diethylnitrosamine-induced HCC in mice have shown that IL-1α released by necrotic hepatocytes acts as an inflammatory switch that supports compensatory cell proliferation and HCC development, which could be counteracted using the IL-1R antagonist anakinra[158]. IL-6 is one of the central orchestrators of the inflammation-cancer interface, which directly enhances the proliferative and metastatic capacities of cancer cells[159]. Mouse models had revealed the therapeutic potential of drugs that target IL-6 or its receptor but, rather disappointingly, tocilizumab, clazakizumab and siltuximab had limited therapeutic activity in patients with cancer cachexia[109]. A novel IL-6 family member, leukaemia inhibitory factor (LIF), has been identified as a key pro-tumour paracrine factor secreted by activated pancreatic stellate cells; LIF blockade using a monoclonal antibody restricted the progression of PDAC in mice and augmented responses to chemotherapy by converting the cancer cells to a less aggressive and more drug-susceptible state[9]. In human and mouse prostate cancers, IL-23 produced by MDSCs can enhance androgen receptor (AR) activity in cancer cells, thus promoting a castration-resistant phenotype[10]. Accordingly, an anti-IL-23 antibody reversed resistance to androgen-deprivation therapy in a mouse model of prostate cancer[10].

Receptor activator of nuclear factor-κB (RANK) signalling governs osteoclastogenesis and bone resorption and has been examined as a therapeutic target in patients with breast or prostate cancer bone metastases[11]. Interestingly, RANK ligand (RANKL)-producing regulatory T cells also promote the spread of RANK-expressing mammary carcinoma cells to the lung in mouse models[160]. Accordingly, the administration of an antagonistic RANK–Fc fusion protein substantially reduces pulmonary metastasis in these models[160]. Myeloid cell-derived thymic stromal lymphopoietin promotes the survival of tumour cells through induction of the antiapoptotic molecule BCL-2 and a neutralizing antibody to thymic stromal lymphopoietin inhibits the growth of both primary tumours and lung metastases in mice[161].

CXCR4 is a chemokine receptor commonly expressed by multiple types of tumour cells; its ligand, CXCL12, is a component of the inflammatory TME and can enhance the survival and migration of tumour cells. Systemic administration of the CXCR4 antagonist plerixafor (AMD3100) inhibits the growth of intracranial glioblastoma and medulloblastoma xenografts in mice by reducing activation of the ERK and AKT signalling pathways[162]. Likewise, CXCR4 inhibition with motixafortide (BL-8040) restricts the growth of mouse neuroblastomas via the tumour-suppressive microRNAs miR-15a and miR-16-1, which silence BCL-2 and cyclin D1 expression[163]. Integrins, lectins and neuregulins are also known to contribute to the inflammatory TME and might therefore prove to be worthwhile therapeutic targets[164-166] if their oncogenic capacities can be inhibited using the corresponding antagonists.

Dietary vitamin D_3 and its analogue calcitriol regulate multiple genes by binding to the nuclear vitamin D receptor (VDR), a member of the steroid–thyroid–retinoid receptor superfamily of ligand-activated transcription factors. Theoretically, vitamin D and calcitriol

could suppress inflammation, cancer cell proliferation, invasion and metastasis; such anticancer effects have been validated in mouse xenograft models but, unfortunately, have not consistently been demonstrated in humans[125].

Disrupting the tumour-supporting stroma

Targeting inflammatory messengers.—Some soluble factors act as envoys by shuttling between the tumour and its stroma, thus constituting important targets for anti-inflammatory treatments (FIG. 3). In the aforementioned diethylnitrosamine-induced model of HCC, excessive production of reactive oxygen species (ROS) by inflammatory stromal cells results in oxidative DNA damage, hepatocyte death and compensatory cell proliferation[167]. Accordingly, oral administration of the chemical antioxidant butylated hydroxyanisole or vitamin E decreases ROS production and prevents diethylnitrosamine-induced HCC[167]. Similarly, butylated hydroxyanisole attenuates ROS-elicited TNF and IL-1β production by Kupffer cells and can prevent pre-malignant cholangiocellular lesions in mouse models of intrahepatic cholangiocarcinoma[168]. In addition, the antioxidant *N*-acetylcysteine prevents ROS-induced T cell death upon hepatic steatosis and delays HCC development in mice[169] (FIG. 3a).

IL-17 is implicated in the pathogenesis of both non-alcoholic steatohepatitis (NASH) and alcoholic steatohepatitis, including links with liver inflammation, fibrogenesis and carcinogenesis. In mice, targeting IL-17 or its upstream inducer IL-23 markedly suppressed the development of NASH-associated or alcoholic steatohepatitis-associated HCC[170,171]. Intriguingly, $CD4^+$ T cell-derived IL-17 was found to blunt the anticancer efficacy of chemotherapeutic agents in mice and this effect could be averted by blocking the IL-1β-IL-1R pathway[172] (FIG. 3b).

Complement component 3 (C3) is upregulated in mouse and human leptomeningeal metastatic cells and can activate C3a receptor (C3aR) signalling in the choroid plexus epithelium, which in turn can alter the composition of the cerebrospinal fluid in a manner that promotes tumour growth[173]. Correspondingly, a C3aR antagonist is effective in reducing breast and lung cancer leptomeningeal metastases in mice[173] (FIG. 3c).

The glycosaminoglycan hyaluronan (HA), a major component of the extracellular matrix, is abundant in the microenvironment of chronic inflammatory diseases as well as of several malignancies. In a genetically engineered mouse model (GEMM) of PDAC, HA has been identified as a crucial modifier of tumour vascular function and enzymatic depletion of HA using PEGylated human recombinant PH20 hyaluronidase (PEGPH20) substantially enhanced drug delivery and therapeutic efficacy with diminished tumour growth[174] (FIG. 3d). Unfortunately, however, the addition of PEGPH20 to standard chemotherapy was found to increase drug toxicity and thus to decrease treatment durations in patients with this disease[175].

Targeting inflammatory cells.—Macrophages are the dominant orchestrators of cancer-promoting inflammatory signals and an abundance of TAMs is associated with high-grade tumours and a poor prognosis[176]. The cytokine CSF1 has important roles in regulating macrophage recruitment and function through CSF1R signalling (FIG. 3e).

CSF1R inhibition can specifically deplete TAMs and suppresses glioma progression[177] and lung cancer brain metastasis[178] in mouse models. Increased CSF1 expression has been observed in patients with prostate cancers treated with radiotherapy or androgen-deprivation therapy; in mouse models, this upregulation of CSF1 culminates in acquired treatment resistance, which can be reversed through CSF1R inhibition[179,180]. In a different model, CSF1R inhibition does not affect mammary tumour growth or metastasis but rather sensitizes the tumours to chemotherapy[181]. Chemokines and chemokine receptors have been implicated in tumour infiltration by macrophages. Accordingly, antibodies targeting CCL2 or CCL5 impede tumour growth and dissemination in multiple preclinical models[176]. In a mouse model with excessive complement activation, the administration of a complement component C5a anaphylatoxin chemotactic receptor (C5aR) antagonist attenuates macrophage-mediated inflammation and tumorigenesis[182]. The G protein-coupled receptor 109A (GPR109A) has anti-inflammatory effects on colonic macrophages and dendritic cells (DCs) and is essential for the induction of IL-18 expression in colonic epithelium; the GPR109A agonists niacin (vitamin B_3) and butyrate efficiently suppress inflammation-induced and *Apc*$^{Min/+}$ intestinal tumours in mice[183].

Neutrophils often accumulate in both primary tumours and pre-metastatic niches in response to diverse inflammatory milieus[184]. Moreover, the neutrophil-depleting antibody anti-Ly6G effectively prevents tumour cell dissemination to distant organs in mice[185] (FIG. 3e). Pro-inflammatory molecules, such as high mobility group box 1 (HMGB1), IL-1β, IL-17 and G-CSF, help shape the tumour-promoting phenotypes of neutrophils; thus, the neutralization or inhibition of these factors is effective in reducing metastasis in preclinical models[186,187]. Additionally, pharmacological inhibition of the leukotriene-generating enzyme arachidonate 5-lipoxygenase or neutrophil extracellular trap-associated signals (the latter using anti-CCDC25 antibodies) interferes with the pro-metastatic functions of neutrophils in many settings[188-190].

Fibroblasts are typically the most abundant stromal component within solid tumours and these cells can become activated during tissue inflammation and fibrogenesis. As such, cancer-associated fibroblasts (CAFs) are integrally involved in cancer-promoting inflammation. CAF-targeting therapies, including fibroblast activation protein-neutralizing antibodies, CXCL12–CXCR4 pathway antagonists, all-*trans* retinoic acid, the VDR ligand calcipotriol, and the immunomodulatory and anti-inflammatory agent ursodeoxycholic acid, have demonstrated anticancer activities in preclinical models[191,192] (FIG. 3e).

Platelets are hypothesized to promote tumour cell dissemination. For example, platelet accumulation and tumour angiogenesis is markedly inhibited using antiplatelet or anti-IL-6 antibodies, which enhances the therapeutic efficacy of paclitaxel in a mouse model of ovarian cancer[193]. Moreover, suppression of platelet activation and aggregation using aspirin and clopidogrel can abrogate HBV-associated or NASH-associated inflammation and carcinogenesis[194,195] (FIG. 3e).

Promotion of antitumour immunity

Using conventional anti-inflammatory drugs.—Mounting evidence from preclinical studies indicates that conventional anti-inflammatory drugs exert immunomodulatory

functions (FIG. 3f,g). Notably, COX inhibition synergizes with PD-1 inhibition in eradicating mouse tumours[68,196]. Mechanistically, tumour-derived PGE_2 impairs the natural killer cell-mediated recruitment of conventional type 1 DCs, thus culminating in tumour immune evasion, which could be reversed by treatment with aspirin or celecoxib[68,196] (FIG. 3g). Consistent with its immunosuppressive properties, PGE_2 produced by senescent hepatic stellate cells directly compromises T cell function in mice with HCC induced by a high-fat diet[197]. Accordingly, an EP4 antagonist restores antitumour immunity and attenuates HCC development in this model[197]. PGE_2 has also been implicated in the M2 polarization of macrophages[198].

Metformin triggers AMPK activation and consequently silences hypoxia-inducible factor-α, which is a transcription factor crucial in inducing CD39 and CD73 expression on MDSCs; CD39 and CD73 mediate production of the immunosuppressive factor adenosine; therefore, suppression of the expression of these proteins by metformin reinvigorated the antitumour activity of $CD8^+$ T cells in patients with ovarian cancer[199] (FIG. 3g). Interestingly, metformin-induced AMPK activation can directly cause PD-L1 phosphorylation, which results in abnormal glycosylation, endoplasmic reticulum accumulation and endoplasmic reticulum-associated protein degradation, thereby manifesting a potential mechanism for increased T cell activity and, thus, immunotherapy efficacy[200] (FIG. 3f). Furthermore, increased infiltration of $CD8^+$ T cells and other immune cells into the TME has been observed in patients with ESCC receiving low-dose metformin[201].

The modulation of cholesterol metabolism can also potentiate T cell receptor signalling and prevent T cell exhaustion. Specifically, the disruption of cholesterol esterification using the acyl-CoA cholesterol acyltransferase 1 inhibitor avasimibe potentiates the antitumour effect of PD-1 inhibition in preclinical models[202,203]. Moreover, conventional anti-platelet agents can improve T cell-based therapy in mouse models in which platelets constrain T cell-mediated anticancer immunity through a glycoprotein A repetitions predominant (GARP)–TGFβ axis[204] (FIG. 3g).

Using targeted agents.—Targeted anti-inflammatory agents might also harness the host immune system to fight cancer and many of these agents depend on the manipulation of myeloid cell plasticity (FIG. 3). CSF1R inhibition directly depletes or reprogrammes immunosuppressive TAMs and consequently improves antitumour immune responses in many preclinical models[205-208]. TAMs can also have an important role in antibody-based cancer therapy through antibody-dependent cellular phagocytosis. Surprisingly, when phagocytosing tumour DNA, TAMs impart immunosuppression through the upregulation of PD-L1 and indoleamine 2,3-dioxygenase (IDO) expression, which is dependent on inflammasome activation and IL-1β production; therefore, treatment with an anti-IL-1β antibody substantially improves the efficacy of anti-HER2 therapy in immunocompetent mice bearing $HER2^+$ breast cancer cells[209]. In another model of breast cancer[210], genetic deficiency of IL-1β expression increases the intratumoural DC to macrophage ratio and anti-IL-1β antibodies synergize with anti-PD-1 treatment in tumour elimination. In response to inflammatory stimulation or chemoattraction, $CD11b^+Gr1^+$ myeloid cells frequently infiltrate tumour sites and exert an immunosuppressive effect in various mouse models; the pharmacological depletion or segregation of these cells (which are typically referred

to as MDSCs) from tumours using an anti-Gr1 antibody or a CXCR1/2 antagonist, respectively, restored antitumour immunity[211-214]. Notably, the overexpression of IL-1β led to MDSC mobilization and activation in the early stage of gastric carcinogenesis and, therefore, anti-IL-1β therapy might prevent cancer development by stimulating turnover of the immunosuppressive environment of neoplastic tissues[215].

Remarkably, studies using human CRC samples have revealed that inflammatory DCs can induce IL-17-producing γδT (γδT17) cells in an IL-23-dependent manner[216]. In addition to IL-17, these γδT17 cells also secrete TNF, IL-8 and GM-CSF, all of which can attract MDSCs and sustain their immunosuppressive activity, which is reversible with IL-23 neutralization[216] (FIG. 3g). Furthermore, in a GEMM of inflammatory lung cancer, co-blockade of IL-23 and CCL9 abrogated MYC-induced immune exclusion and tumour progression[217].

The C5a–C5aR axis contributes to the immunosuppressive effects of myeloid cells. For example, C5a generated locally in the TME can recruit MDSCs and promote their production of ROS and reactive nitrogen species, which hamper the antitumour activity of $CD8^+$ T cells. Preclinically, the pharmacological inhibition or genetic ablation of C5aR impairs tumour growth via increases in the abundance and cytotoxicity of $CD8^+$ T cells[218]. Furthermore, the C5aR antagonist PMX-53 improves the antitumour efficacy of immunotherapy or chemotherapy in various mouse models[219,220]. A phase I trial of the C5aR1 monoclonal antibody IPH5401 in combination with the anti-PD-L1 antibody durvalumab in patients with advanced-stage solid tumours is ongoing[221] (STELLAR-001; NCT03665129). Phagocytosis checkpoint proteins, such as CD47, are additional novel targets for cancer immunotherapy[222] and might provide more opportunities for combinations with anti-inflammatory agents.

In addition to myeloid cells, CAFs, B cells, γδT cells, type 1 innate lymphoid cells (ILC1) and mucosal-associated invariant T cells can also curtail antitumour immune responses under certain inflammatory conditions[191,223-227] Nonetheless, specific anti-inflammatory strategies for targeting these cell types are lacking, with the possible exception of CAFs. For instance, CXCR4 inhibition can render tumours responsive to immunotherapy by overcoming the fibrotic and immunosuppressive TME in both HCC and PDAC models[228,229].

TNF can directly trigger activation-induced death of T cells, whereas TGFβ hampers cytotoxic immune cell function (FIG. 3g). Hence, targeting either of these cytokines using etanercept or galunisertib, respectively, enhances the antitumour effects of ICIs[108,116]. Oncogenic pathways also impart unconventional inflammatory signals to directly suppress cytotoxic lymphocytes. For example, loss of the tumour suppressors APC in intestinal tumour cells or of PTEN in melanoma cells causes them to secrete Dickkopf-related protein 2 (DKK2), which impedes signal transducer and activator of transcription 5 (STAT5) activation within immune cells via binding to LDL receptor-related protein 5 (LRP5)[230]. Accordingly, an anti-DKK2 antibody reactivates tumour-infiltrating natural killer cells and $CD8^+$ T cells and potentiates responses to PD-1 inhibition in mouse models of these cancers[230].

Mitigating irAEs.—Anti-inflammatory agents also have indispensable roles in attenuating irAEs. As discussed, judicious use of an anti-IL-6R antibody can attenuate CAR T cell-induced CRS, which can otherwise limit the therapeutic value of this innovative immunotherapy[231]. IL-1R antagonism via anakinra or CAR T cell engineering is also capable of abrogating CRS-related mortality in mouse models[231]. Likewise, prophylactic use of TNF antagonists can ameliorate immune-related colitis associated with dual anti-CTLA4 and anti-PD-1 inhibition in a mouse model of colon cancer[108]. Of importance, these anti-inflammatory therapies can further enhance immunotherapy efficacy and prolong survival in preclinical models, which are desirable characteristics for clinical use.

Pro-tumour perils of anti-inflammatories

Increasing clinical and preclinical evidence supports the broad therapeutic activity of metformin across a wide range of cancer types. However, *BRAF*-mutant melanoma has been demonstrated to escape the growth-inhibitory stress imposed by metformin[232]. The dual-specificity phosphatase DUSP6 negatively regulates ERK activity downstream of oncogenic BRAF, and AMPK hyperactivation by metformin results in the targeting of DUSP6 for degradation and thereby potentiates the ERK-driven expression of VEGFA, which bypasses the inhibitory effects of metformin and AMPK on mTORC1 signalling; thus, metformin counterproductively stimulates angiogenesis and accelerates tumour growth[232]. Inhibitors of mTOR (the kinase component of mTORC1) have long been considered as potential cancer treatments. As an immunosuppressive drug, however, the mTOR inhibitor rapamycin was found to activate the pro-tumorigenic factor STAT3 in a mouse model of steatotic HCC. Mechanistically, hepatocyte-specific loss of mTORC1 activity promoted hepatocarcinogenesis through the hyperactivation of AKT owing to the disruption of a negative feedback loop[233]. Another potential peril associated with metformin use relates to the consequent increases in circulating levels of growth/differentiation factor 15 (GDF15), which induces weight loss and correlates with cachexia and poor survival outcomes in patients with cancer[234,235].

With statin treatment for PDAC, the disruption of cholesterol biosynthesis can induce the sterol response element-binding protein (SREBP)-dependent expression of TGFβ and the epithehal-to-mesenchymal transition in cancer cells[236], which might promote disease progression. Glucocorticoids are generally used as anti-inflammatory and immunosuppressive agents for treating chemotherapy-related or immunotherapy-induced adverse events in patients with advanced-stage cancer. Multiomics data from patient-derived xenograft models indicate that these agents can activate glucocorticoid receptor signalling at distant metastatic sites, which in turn increases metastatic colonization and reduces mouse survival via upregulation of the tyrosine-protein kinase transmembrane receptor ROR1 (REF.[237]). The intravasation of tumour cells is a key process involved in metastatic dissemination to distant organs. Accordingly, the anticoagulant warfarin has been shown to increase vascular leakiness in mammary tumours, which was accompanied by substantial increases in the numbers of circulating tumour cells and lung metastases[238].

Cytokine-specific or cytokine receptor-specific therapeutic agents have been tested in proof-of-concept trials across many cancer types; however, paradoxical findings underscore the

importance of careful clinical application and further interrogation into their molecular mechanism. Despite the reported clinical benefits of anti-IL-1β therapy[98], IL-1β is essential for cancer immunosurveillance in various contexts (FIG. 4). First, immunogenic cell death in established tumours is associated with the activation of DCs with an intact inflammasome machinery to secrete IL-1β, which primes tumour-specific T cell responses[239]. Conversely, the anticancer effects of chemotherapeutic agents are dampened with the coadministration of an IL-1β-neutralizing antibody[239]. Second, the IL-1β-STAT1-interferon regulatory factor 1 (IRF1) axis is fundamental for IL-9 and IL-21 production by T helper 9 (T_H9) cells, as demonstrated by the downregulation of *Irf1, Il9* and *Il21* expression in tumour-infiltrating T_H9 cells following treatment with an IL-1R antagonist; this pathway was found to be crucial for the anticancer functions of T_H9 cells in mice[240]. Third, in an *Apc*-based mouse model of CRC, IL-1R signalling in epithelial cells and T cells has pro-tumorigenic effects, whereas myeloid cell-specific IL-1R signalling counteracts tumour-promoting dysbiosis and inflammation[241]. Fourth, in mouse models of breast cancer, a systemic IL-1β-mediated inflammatory response has been shown to prevent metastasis-initiating cell differentiation and colonization of distant tissues, and the inhibition of IL-1R signalling at the primary tumour site results in metastatic progression[242]. In keeping with these preclinical findings, patients with breast cancer expressing high levels of IL-1β have been found to have better survival outcomes than those with low IL-1β expression[242]. Similarly, several different counterintuitive effects might explain the disappointing clinical outcomes achieved to date with agents targeting CSF1R. For example, in a GEMM of glioblastoma, macrophages that persist following CSF1R inhibition produce insulin-like growth factor 1 (IGF1), which can drive tumour recurrence through PI3K activation[12]. Surprisingly, CSF1R inhibition can also affect CAFs and, in particular, causes these cells to express the granulocyte-specific chemokine CXCL1, which initiates an immune inhibitory circuit[243]. Compelling evidence from single cell-based analyses of CRCs from mice indicates that antagonism of CSF1R depletes inflammatory $F4/80^{hi}$ myeloid cell populations, while sparing those with pro-angiogenic and immunosuppressive properties[13]. In mouse models of breast cancer, treatment with a CCL2 antagonist reduces the abundance of TAMs and metastases by retaining inflammatory monocytes in the bone marrow, but cessation of such treatment results in a lethal rebound effect mediated by IL-6 and VEGF secretion[244].

Conceivably, neutrophil-targeting strategies might also have poor anticancer efficacy because neutrophils have immunostimulatory activities in certain scenarios[245,246]. Likewise, the complement system might enhance the clinical responses to various cancer treatments, including monoclonal antibodies, vaccines and radiotherapy, reminiscent of the risks associated with complement-targeted therapeutics[221,247]. The depletion of CAFs might also induce immune evasion, for example, by increasing the abundance of regulatory T cells in the TME of PDAC[248].

Antioxidants are believed to exert anticancer effects owing primarily to interference with pro-tumorigenic redox signalling. Paradoxically, in some preclinical models, antioxidant treatments accelerate tumour progression and metastasis through the inactivation of tumour suppressors or metabolic reprogramming[249-252], mirroring outcomes observed in the clinical setting[143].

Given the extensive molecular intersections and crosstalk, cellular adaptability, and organ-specific contexture, anti-inflammatory therapy targeting a single immunomodulatory factor might lead to tumour evolution or TME remodelling. Together, the paradoxical findings discussed above should prompt special caution when translating anti-inflammatory therapies into clinical use.

Conclusions

To date, many drugs and drug candidates have been used both preclinically and clinically to curtail the inflammatory conditions that fuel cancer development and progression. Numerous preclinical studies have provided insights into the mechanisms underlying the intricate interactions between cancer, inflammation and immunity, which should eventually lead to more innovative anti-inflammatory cancer therapies reaching the clinic. Considering the advances outlined herein, researchers and oncologists working together should be capable of developing successful strategies to inhibit cancer-related inflammation and of making such an approach a main-stay of modern cancer therapy. So far, anti-inflammatory strategies have proven rather effective in cancer prevention and conventional drugs such as aspirin have led to a much larger reduction in cancer mortality than novel and far more sophisticated targeted therapies. Given our improved understanding of the TME, research tools and animal models, we are hopeful that, in the next decade, several anti-inflammatory therapies will advance to the clinic and prove effective in preventing or treating cancer.

The numerous and diverse links between cancer and inflammation all present therapeutic opportunities, especially when the concept of ‘inflammation’ is broadened to include viral, bacterial and fungal infections. However, numerous hurdles and uncertainties remain in every step of translating an anti-inflammatory agent into clinical use. First, whether the inflammatory redundancies identified in preclinical models are targetable and druggable remains unclear. Second, the heterogeneity and plasticity of the TME present problems in targeting a single cytokine or even a single cell type. The effects of disrupted negative feedback loops and the activation of compensatory pathways is also hard to predict. Third, given that patients with cancer are typically assigned to conventional treatments, a need exists to identify more specific inflammatory targets that are responsible for therapy resistance or adverse events. Fourth, contrary to other targeted therapies, clinically applicable biomarkers for the selection of anti-inflammatory agents and assessment of their anticancer effects are lacking. Fifth, the effects of endogenous factors, such as the patients age and microbiota, on the magnitude of inflammatory responses and on the outcomes of anti-inflammatory treatments remain to be determined[253,254]. Notably, the composition of the microbiota has been shown to affect immunotherapy efficacy, suggesting that microbial interventions could potentially be leveraged to improve cancer prevention or treatment[255,256]. By necessity, defining a therapeutic paradigm for anti-inflammatory treatments would require optimized pharmaceutical programmes as well as appropriate animal models and clinical trial designs. In addition, integrative high-resolution analyses using multiomics, single-cell and/or spatial-based technologies should provide deeper insights into local therapeutic responses and the exact cellular and molecular consequences of anti-inflammatory treatments. Finally, the deployment of personalized, multi-agent, anti-

inflammatory regimens in the era of immunotherapy is possibly another key to treating cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The work of the authors is supported by grants from the National Key Research and Development Program of China (2016YFC0905900 to B.S.), the State Key Program of the National Natural Science Foundation (81930086 to B.S.; 81871970 and 81672801 to J.H.) and the US NIH (U01AA027681, R01CA211794, R01CA234128, P01CA128814, R01CA198103 and Tower Cancer Research Grant to M.K.). The work of J.H. is also supported by the Hundred Talent Program of Sun Yat-sen University. Figures in this review were drafted with the assistance of Dr Haiyan Zhang (Sun Yat-sen University Cancer Center).

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Key points

- Inflammation-related biological processes influence all stages of cancer development and treatment; environmental risk factors and both tumour-extrinsic and tumour-intrinsic inflammatory processes have been linked to tumour initiation, promotion and progression.
- Several conventional drugs with anti-inflammatory properties have demonstrated protective effects against cancer but are yet to be deployed in at-risk populations and properly evaluated for therapeutic applicability.
- Cytokine-specific agents with anti-inflammatory activities have antitumour efficacy in preclinical studies but evidence demonstrating activity against solid tumours in clinical trials is scarce.
- Preclinical studies have revealed that anti-inflammatory drugs can suppress cancer development through multiple mechanisms.
- Monotherapy with anti-inflammatory agents can elicit cell adaptability and/or affect tumour evolution in heterogeneous cancer types, leading to therapy resistance or even accelerated disease progression.
- Overcoming current obstacles to the clinical introduction of anti-inflammatory therapy will require the development of effective combination regimens and the identification of reliable response biomarkers.

Box 1|

Antitumour immunity versus cancer-promoting inflammation

External stimuli, host-specific endogenous factors and therapeutic interventions can promote the recruitment and activation of various types of inflammatory and/or immune cells that shape the tumour microenvironment[18]. Short-term inflammation, such as that induced by immune adjuvants used in vaccination approaches, can potentiate anticancer immunity through the enhancement of T cell priming; such effects can shape the course of early tumour development (through immune elimination and immunoediting) but can also enhance responses to immunotherapy[257]. By contrast, chronic inflammation is immunosuppressive and thus cancer promoting[15]. Accordingly, so-called ‘hot’ tumours that harbour extensive inflammatory infiltrates are not necessarily responsive to immunotherapy, unless immunosuppressive inflammation is attenuated. Not surprisingly, inducers of antitumour immunity, such as infectious or commensal microbes, as well as danger-associated molecular patterns can also trigger cancer-related inflammation and contribute to a refractory phenotype[258-260].

The cancer-immunity cycle hypothesis[261] posits that an optimal anticancer immune response relies on the iterative cooperation between immune cells, host factors and tumour antigens. This cycle is initiated by the release of tumour antigens and their presentation to T cells and is terminated upon the clearance of tumour cells by cytotoxic T lymphocytes. Unless efficiently initiated and precisely maintained, the cancer-immunity cycle can be broken and replaced by inflammation-promoted tumour progression[2]. By exploiting self-tolerance mechanisms and microenvironmental assistance, cancer cells can escape cytotoxic T lymphocyte-mediated killing, often by downregulating MHC class I-dependent antigen presentation[262], but also through the production of immunosuppressive factors[18]. Thus, tumour cell-autonomous inflammatory traits alter the molecular circuits and cellular interactions that form the basis for antitumour immunity, such that they are highjacked to support malignant progression[14].

When treating an immune ‘hot’ tumour, consideration of the common mechanisms underlying anticancer immunity and cancer-promoting inflammation is required. Hopefully, anti-inflammatory therapies will be found effective not only in abrogating tumour growth and progression but also in boosting anticancer immunity in synergy with other immunotherapies, such as immune-checkpoint inhibitors.

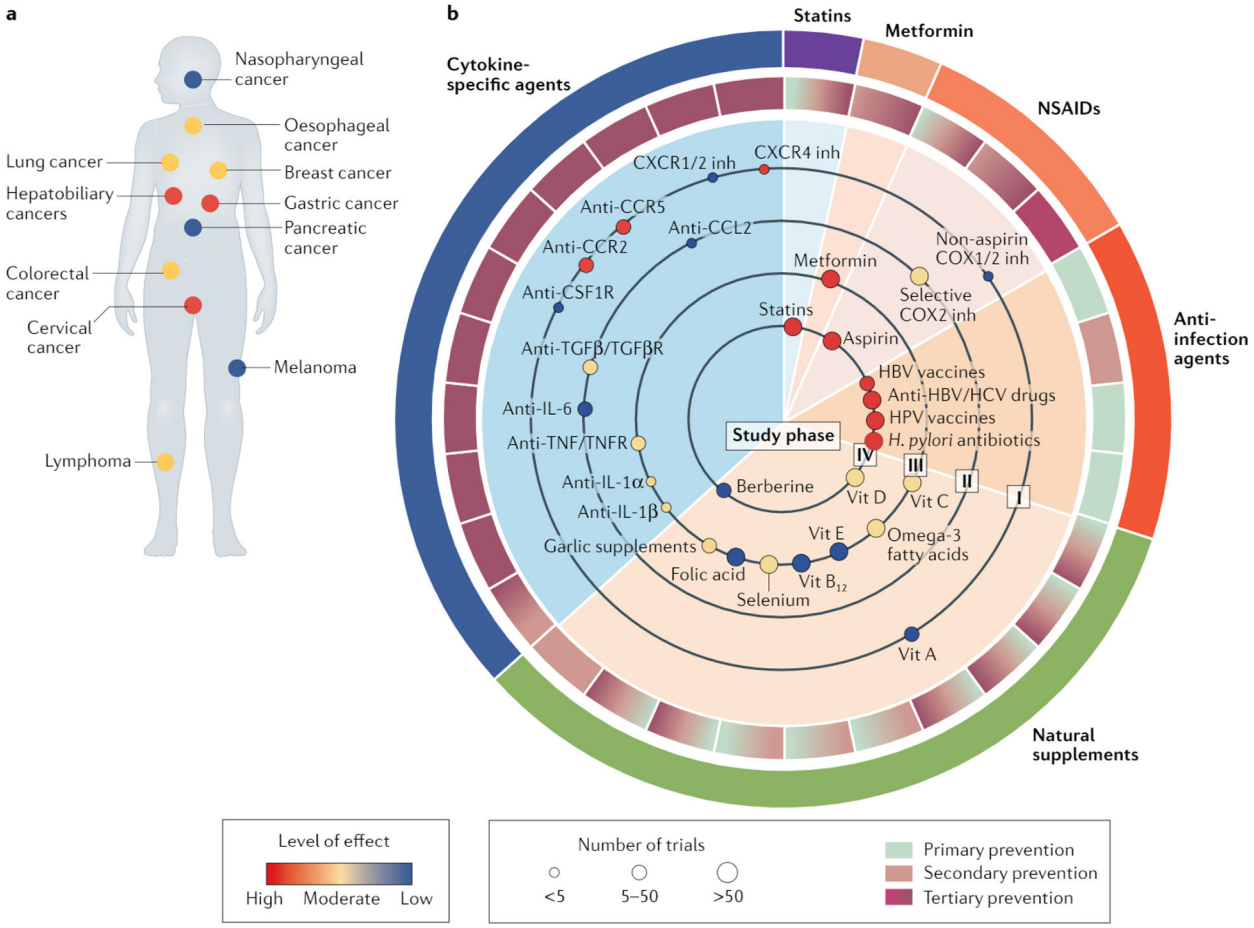

Fig. 1 | Evidence grading for anti-inflammatory agents in cancer prevention.

a | Statistics of anti-inflammatory treatments assigned to patients with different cancer types. Each small circle represents a cancer type for which anti-inflammatory treatments have been examined. The colour of the circles reflects the level of effect defined based on the number of positive versus negative prospective trials registered in the ClinicalTrials.gov database. **b** | Anti-inflammatory treatments using various anti-infective agents or modalities, nonsteroidal anti-inflammatory drugs (NSAIDs), statins, metformin, cytokine-specific drugs, and natural supplements are illustrated according to levels of evidence and efficacy in the management of cancer. The arcs in the outer circle surrounding the central pie chart indicate the various categories of therapeutic agents. The shading in each portion of the inner circle surrounding the pie chart represents the preventive applications in which each respective agent (or class of agent) shown within the body of the pie chart has been evaluated: primary prevention to deduce the aetiological role of the therapeutic target, secondary prevention to mitigate development of the disease in at-risk populations or tertiary prevention for the treatment of cancer following diagnosis. Each small circle in the inner sectors of the pie chart reflects the clinical evidence for each agent, indicating the level of effect (circle colour), the number of clinical studies performed (circle size) and the phase of clinical testing (as indicated by the ‘study phase’ designation on each large circle within the pie chart). Ongoing trials are summarized in Supplementary Table 1. CCR, CC-chemokine receptor; COX,

cyclooxygenase; CSF1R, colony stimulating factor 1 receptor; CXCR, CXC-chemokine receptor; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; inh, inhibitor; TGFβ, transforming growth factor-β; TGFβR, TGFβ receptor; TNF, tumour necrosis factor; TNFR, TNF receptor; Vit, vitamin.

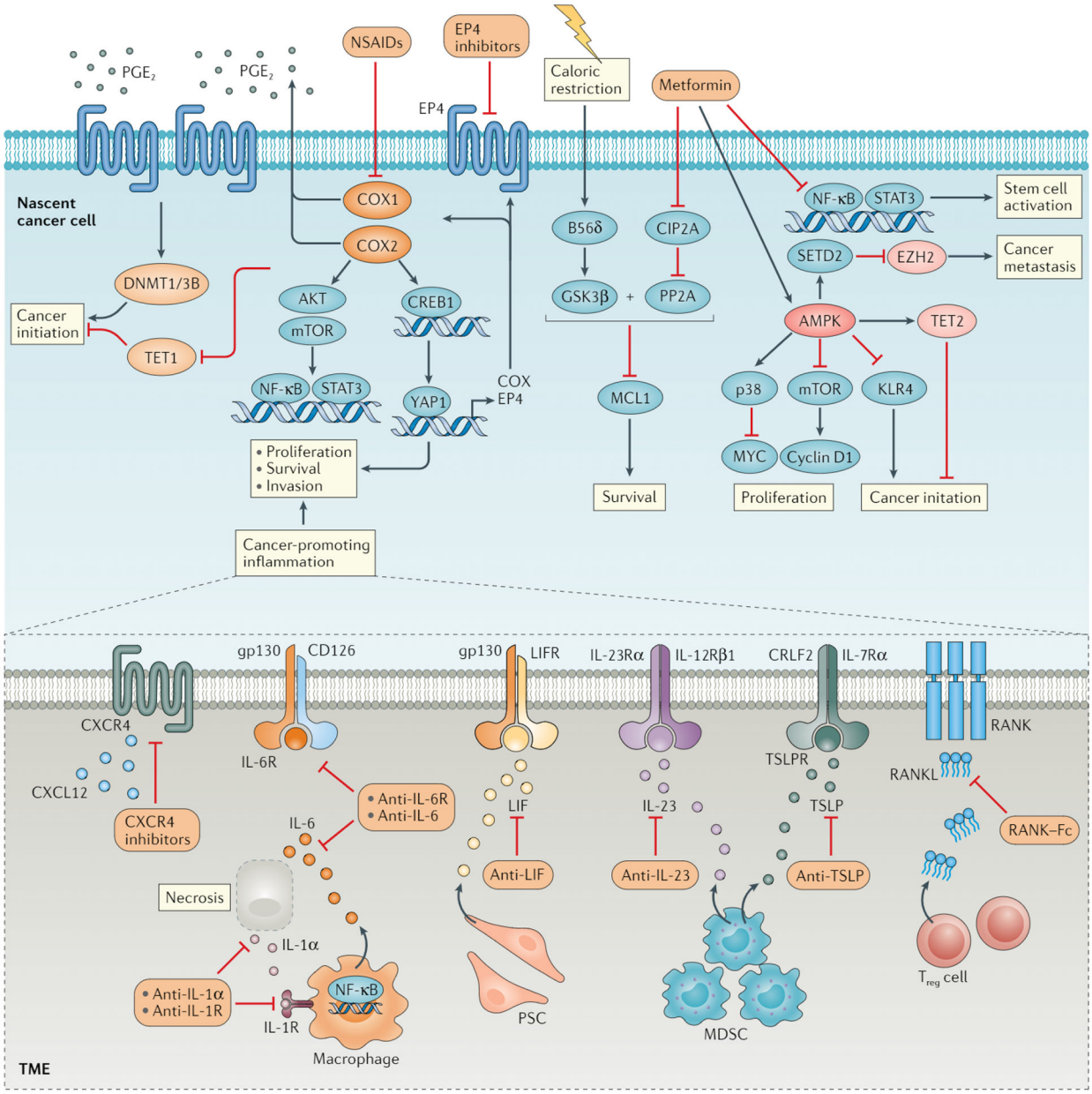

Fig. 2 |. Impact of anti-inflammatory agents on oncogenic pathways.

Cyclooxygenase 1 (COX1) and COX2, which are the targets of nonsteroidal anti-inflammatory drugs (NSAIDs), can activate AKT, mTOR and NF-κB to support cancer cell survival and proliferation, either directly or via the production of prostaglandin E_2(PGE_2). PGE_2 produced in a COX2-dependent manner can bind to the PGE_2 receptor EP4 and induce intracellular signal transduction. Whereas COX2 functions to downregulate the expression of DNA demethylase TET1, EP4 signalling upregulates the expression of DNA (cytosine 5)-methyltransferase 1 and/or 3B (DNMT1/3B). The altered expression of both of these epigenetic regulators results in silencing of tumour suppressor genes and thus promotes cancer initiation, which could potentially be prevented through treatment with the NSAID COX2 inhibitor celecoxib. PGE_2-EP4 signalling can also activate a

positive feedforward loop for tumour initiation and promotion involving upregulation of the transcriptional coactivator YAP1, which in turn upregulates the expression of COX enzymes and EP4. NSAIDs or EP4 antagonists might effectively disrupt this inflammation-driven process. The anticancer effects of metformin largely depend on the activation of AMPK, which negatively regulates downstream signalling cascades involved in cancer initiation. In addition, AMPK activation confers a tumour-suppressive epigenome via the stabilization of TET2 and/or degradation of the histone-lysine *N*-methyltransferase EZH2. In an AMPK-independent fashion, metformin attenuates an NF-κB-mediated inflammatory response required for stem cell function and can activate a protein phosphatase 2A (PP2A) pathway to exert control over cell survival via inhibition of the antiapoptotic protein MCL1. The latter mechanism is otherwise ineffective for cancer prevention in mice without GSK3β activation through caloric restriction. Various cytokines present in the inflammatory tumour microenvironment (TME), including IL-6, IL-23, leukaemia inhibitory factor (LIF), receptor activator of nuclear factor-κB ligand (RANKL), thymic stromal lymphopoietin (TSLP) and CXC-chemokine ligand 12 (CXCL12), can induce pro-tumorigenic signals via cognate receptors expressed by cancer cells themselves. Therefore, inhibitory antibodies or other antagonists targeting these cytokines or their receptors might have anticancer effects. These cytokines are derived from distinct immune cells, including macrophages, myeloid-derived suppressor cells (MDSCs) and regulatory T (T_{reg}) cells or stromal cells, such as pancreatic stellate cells (PSCs), in a context-dependent manner. For instance, IL-6 can be produced abundantly by macrophages in response to necrotic tumour cells and IL-1α. Hence, the blockade of IL-1α signalling might prevent downstream tumorigenic events. B56δ, PP2A B subunit isoform B56δ; CIP2A, cancerous inhibitor of protein phosphatase 2A; CREB1, cAMP-responsive element-binding protein 1; CXCR4, CXC-chemokine receptor 4; STAT3, signal transducer and activator of transcription 3.

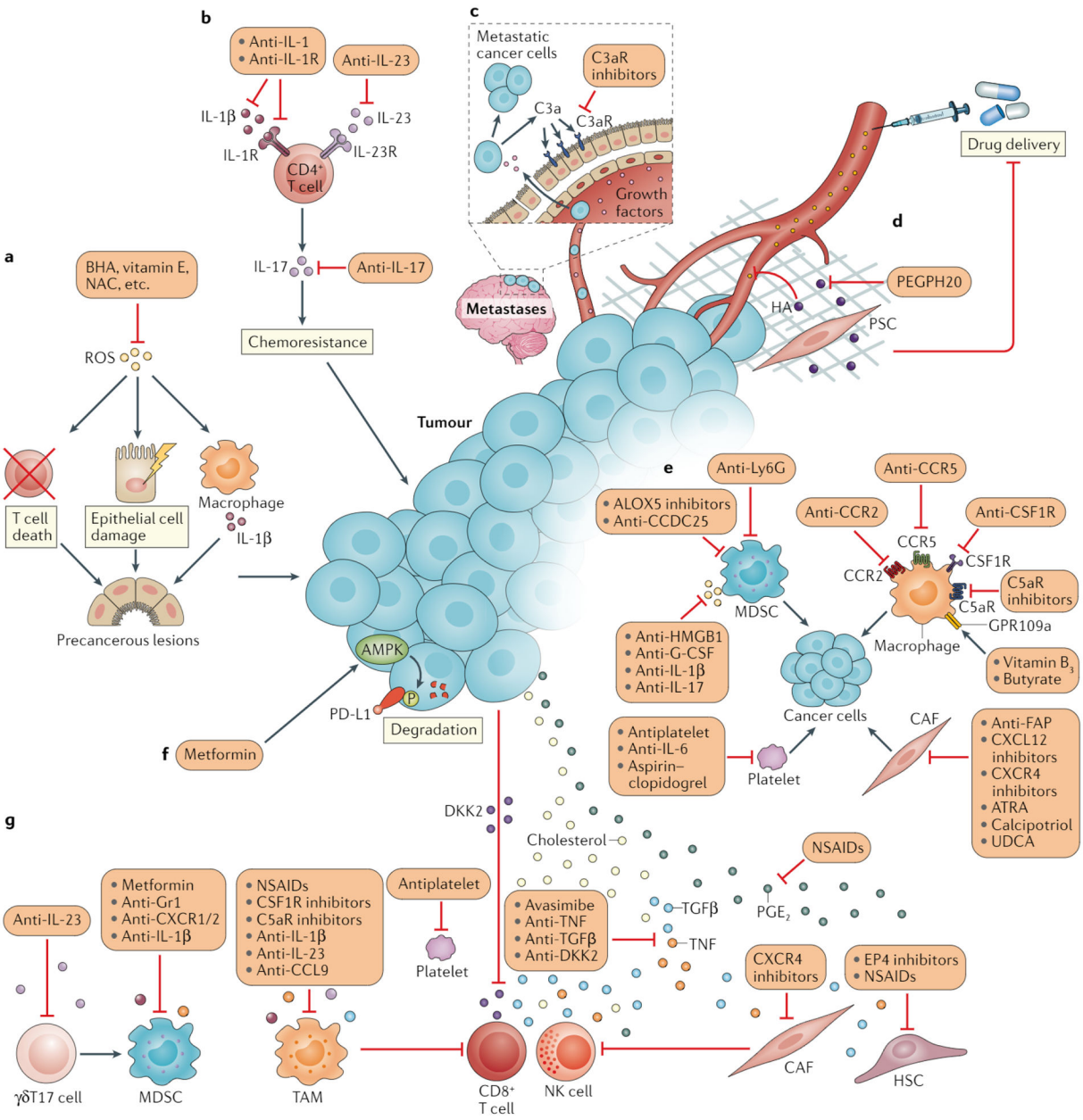

Fig. 3 |. Approaches to resolving cancer-associated inflammation and normalizing antitumour immunity.

a | Reactive oxygen species (ROS) can cause epithelial cell damage, immune cell death, unresolved inflammation and subsequent precancerous lesions. ROS and their effects can be counteracted by antioxidants, such as butylated hydroxyanisole (BHA), vitamin E and *N*-acetylcysteine (NAC). **b** | IL-17 has a pivotal role in inflammation-driven cancer initiation as well as in angiogenesis and chemotherapy resistance. IL-17 is generally produced by $CD4^+$ T cells in response to IL-23 or IL-1β. Accordingly, antagonistic antibodies targeting IL-17, IL-23 or IL-1β receptor (IL-1R) have substantial therapeutic anticancer effects in mice[170-172]. **c** | Leptomeningeal metastatic cells can secret complement component 3 (C3a), which activates the C3a receptor (C3aR) expressed on the choroid plexus epithelium and

thereby enables circulating growth factors to enter the leptomeningeal space via disruption of the blood–brain barrier. C3aR antagonism might therefore interrupt the nutrition supply to metastatic cells in the cerebrospinal fluid. **d** | The glycosaminoglycan hyaluronan (HA) is a central component of the extracellular matrix, fostering tissue stiffness and restricting drug perfusion. A PEGylated form of PH20 hyaluronidase (PEGPH20), which can degrade HA in the tumour microenvironment, is capable of enhancing chemotherapeutic efficacy[174]. **e** | Tumour-associated macrophages (TAMs), neutrophils or myeloid-derived suppressor cells (MDSCs), cancer-associated fibroblasts (CAFs) and platelets directly communicate with cancer cells and supply them with various pro-tumorigenic signals, which can be interrupted by targeting the corresponding inflammatory stimulants or their receptors. **f** | Tumour cells often express the inhibitory immune-checkpoint protein PD-L1 to avoid elimination by $CD8^+$ T cells; AMPK can catalyse the phosphorylation and thus promote the degradation of PD-L1, and this process can be activated by metformin. **g** | Moreover, cholesterol, prostaglandin E_2 (PGE_2), tumour necrosis factor (TNF), transforming growth factor-β (TGFβ) and oncoproteins such as Dickkopf-related protein 2 (DKK2) present in the tumour-associated inflammatory milieu can directly suppress the function of $CD8^+$ T cells and natural killer (NK) cells; therefore, the cholesterol acyltransferase inhibitor avasimibe, nonsteroidal anti-inflammatory drugs (NSAIDs), PGE_2 receptor EP4 antagonists, and cytokine-specific antibodies or antagonists might reinforce the antitumour effects of these cytotoxic lymphocytes. TAMs, MDSCs, CAFs (or hepatic stellate cells (HSCs)), platelets and other cell types that coordinate the inflammatory responses within the tumour microenvironment also frequently produce factors that are suppressive to effector lymphocytes. Other pro-inflammatory cells, such as IL-17-producting γδT (γδT17) cells, can further strengthen the immunosuppressive phenotype of MDSCs. Anti-inflammatory strategies for depleting or reprogramming these cells might restore the cancer–immunity cycle. ALOX5, arachidonate 5-lipoxygenase; ATRA, all-*trans* retinoic acid; CCDC25, coiled-coil domain containing protein 25; CCL, CC-chemokine ligand; CCR, CC-chemokine receptor; CSF1R, colony-stimulating factor 1 receptor; CXCL, CXC-chemokine ligand; CXCR, CXC-chemokine receptor; C5aR, complement component 5a receptor; FAR fibroblast activation protein; G-CSF, granulocyte colony-stimulating factor; GPR109A, G protein-coupled receptor 109A; HMGB1, high mobility group box1; Ly6G, lymphocyte antigen 6G (also known as Gr1); UDCA, ursodeoxycholic acid.

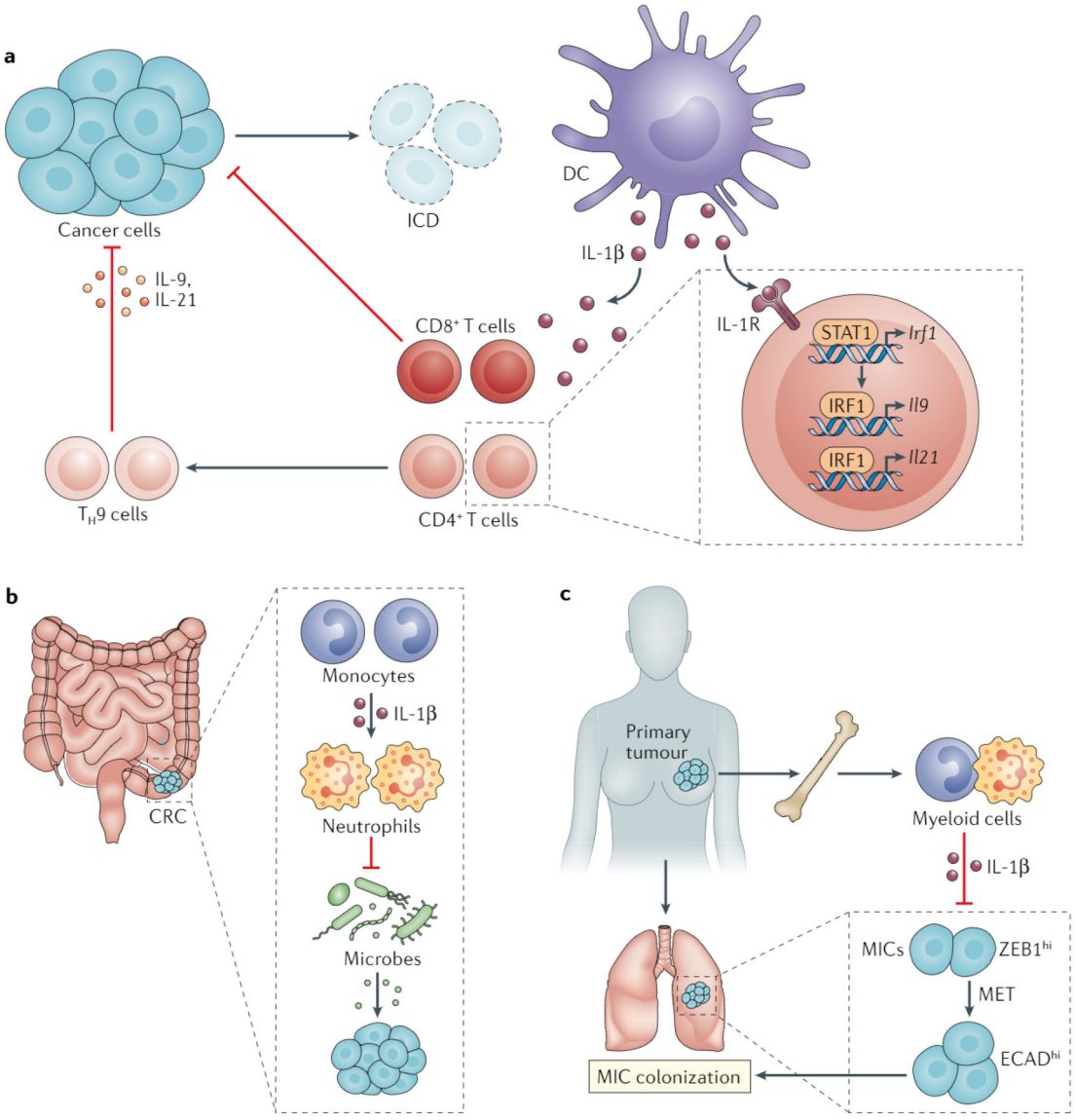

Fig. 4 |. Potential perils of anti-IL-1β therapy for cancer.

The discovery of important roles for IL-1 in promoting antitumour immunity and suppressing cancer-promoting inflammation warrants careful consideration in approaches to targeting this cytokine for cancer therapy. **a** | Chemotherapy-induced immunogenic cell death (ICD) of cancer cells activates dendritic cells (DCs) and thereby results in the production of IL-1β, which is mandatory for the cross-priming of antitumour $CD8^+$ T cells. IL-1β also dictates the anticancer effect of T helper 9 (T_H9) cells by upregulating IL-9 and IL-21 expression in these $CD4^+$ T cells via signal transducer and activator of transcription 1 (STAT1) and interferon regulatory factor 1 (IRF1)[240]. **b** | In a mouse model of colorectal cancer (CRC), monocyte-derived IL-1β imparts an anti-inflammatory phenotype in neutrophils, which attenuate intestinal dysbiosis and cancer progression[241]. **c** | In models of breast cancer, primary tumours elicit a systemic inflammatory response that includes the expansion of bone marrow and circulating myeloid cells and the production of IL-1β

by these myeloid cells suppresses metastatic colonization by preventing mesenchymal-to-epithelial transition (MET) of metastasis-initiating cells (MICs)[242]. ECAD, E-cadherin; ZEB1, zinc finger E-box binding homeobox 1.