



## Review Article

# Cancer and Inflammation: Immunologic Interplay, Translational Advances, and Clinical Strategies



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### Abstract

The association between chronic inflammation and cancer has reshaped our understanding of tumorigenesis and cancer therapy. Inflammatory responses can both promote and suppress cancer, depending on the context and timing. Key molecular players, such as nuclear factor kappa-light-chain-enhancer of activated B cells, interleukin-6, signal transducer and activator of transcription 3, and a variety of immune cell types, including tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T cells, orchestrate an environment conducive to tumor survival, angiogenesis, metastasis, and immune evasion. In recent years, immunotherapy, particularly immune checkpoint inhibitors, has revolutionized cancer treatment. However, its success varies across tumor types and patients, underscoring the need to understand the tumor microenvironment and inflammatory context. This review examines the mechanistic underpinnings of inflammation-driven cancer, discusses translational research efforts targeting inflammatory pathways, and explores clinical applications, including the integration of immunotherapy with anti-inflammatory agents and biomarkers for personalized treatment. Future directions in the field include the application of artificial intelligence, microbiome research, single-cell technologies, and gene editing tools to further tailor therapies and overcome resistance mechanisms.

### Introduction

The connection between inflammation and cancer dates back to the 19th century, when Rudolf Virchow proposed that tumors often arise at sites of chronic inflammation. While his theory was initially met with skepticism, modern molecular and cellular oncology has validated many of his insights.<sup>1</sup> Today, inflammation is recognized as one of the enabling characteristics of cancer development, integrated into the updated Hallmarks of Cancer framework by Hanahan and Weinberg.<sup>2</sup> Epidemiological and clinical data show that up to 20% of cancers are associated with chronic infections, autoimmune diseases, or environmental exposures that trigger persistent inflammation.<sup>3,4</sup> Recent global studies estimate that inflammation-related factors contribute to even higher proportions in specific regions, with chronic infections like *Helicobacter pylori* and hepatitis viruses accounting for over 15% of new cancer cases annually worldwide, particularly in low- and middle-income countries.<sup>5</sup>

Inflammation contributes to all stages of cancer development—

from initiation and promotion to progression and metastasis—through a complex interplay between immune cells, inflammatory mediators, and genetic alterations in epithelial or stromal cells. Key cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF- $\alpha$ ), transcription factors like nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) and signal transducer and activator of transcription 3 (STAT3), and cell types such as tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) modulate these processes, creating a tumor-supportive microenvironment.<sup>6,7</sup> Furthermore, inflammation not only drives cancer progression but also impacts therapeutic responses, particularly in the context of immunotherapy. Emerging evidence highlights how systemic inflammation can alter the efficacy of treatments by influencing immune cell trafficking and activation within the tumor microenvironment (TME). For instance, persistent inflammatory states can lead to T-cell exhaustion and reduced infiltration of effector cells, complicating responses to checkpoint blockade.<sup>8</sup> This dual role of inflammation, as both a driver of oncogenesis and a modulator of therapy, necessitates a deeper exploration of its mechanisms and clinical implications.

The connection between cancer and inflammation is increasingly robust, supported by mechanistic insights, translational research, and multiple lines of clinical evidence. A key example is the growing number of cross-disciplinary studies demonstrating that anticancer drugs are being successfully repurposed or applied for inflammatory diseases and vice versa (Table 1).<sup>9–28</sup> This

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Table 1. Approved or clinically investigated cancer drugs being used or explored for treating inflammation and vice versa<sup>9-28</sup>

| Category                                         | Drug/Agent                                                    | Primary indication                                                                | Repurposed/<br>Applied for                                                                                    | Mechanism of Interplay<br>(highlighting immunologic/<br>translational links)                                                                                                                                          | Clinical status                                                                                                                                        | Brief clinical outcomes                                                                                                                                                                                                          |
|--------------------------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cancer<br>drugs for<br>inflam-<br>mation         | Metho-<br>trexate                                             | Cancer chemothe-<br>rapy (e.g., leukemia,<br>breast cancer)                       | Autoimmune/inflam-<br>matory diseases (e.g.,<br>rheumatoid arthri-<br>tis/RA, psoriasis)                      | Folate antagonist; suppresses<br>immune cell proliferation and<br>cytokine production (e.g., IL-6,<br>TNF-α), modulating NF-κB and<br>STAT3 pathways shared in tumori-<br>genesis and chronic inflammation            | FDA-approved for RA<br>and other autoimmune<br>conditions; low-dose<br>regimens common                                                                 | Low-dose (7.5–25 mg/week)<br>achieves 40–50% ACR20 re-<br>sponse in RA trials; sustained<br>remission >2 years in long-<br>term studies; folic acid supple-<br>mentation reduces toxicity <sup>9,10</sup>                        |
|                                                  | Rituximab                                                     | Oncology (e.g., non-<br>Hodgkin lymphoma,<br>chronic lympho-<br>cytic leukemia)   | Autoimmune diseases<br>(e.g., RA, vasculi-<br>tis, systemic lupus<br>erythematosus/SLE)                       | Anti-CD20 monoclonal antibody;<br>depletes B-cells, reducing autoan-<br>tibody production and inflamma-<br>tory responses while targeting<br>B-cell malignancies in cancer                                            | FDA-approved for RA<br>and other inflamma-<br>tory conditions                                                                                          | ACR20 response 51% vs.<br>18% placebo in RA (REFLEX<br>trial); sustained joint dam-<br>age inhibition over 2 years;<br>infusion reactions com-<br>mon but manageable <sup>11,12</sup>                                            |
|                                                  | Cyclophos-<br>phamide                                         | Cancer chemo-<br>therapy (e.g.,<br>breast, lymphoma)                              | Autoimmune diseases<br>(e.g., SLE, vasculitis)                                                                | Alkylating agent; induces im-<br>munosuppression by damaging<br>DNA in rapidly dividing immune<br>cells, intersecting with inflam-<br>matory pathways like NF-κB                                                      | FDA-approved for severe au-<br>toimmune conditions; used<br>off-label in rheumatology                                                                  | 73–90% 2-year remission<br>in SLE/vasculitis; reduces<br>renal progression in lupus<br>nephritis; bladder toxicity<br>mitigated by mesna <sup>13,14</sup>                                                                        |
|                                                  | Azathioprine                                                  | Cancer chemo-<br>therapy (originally;<br>now primarily im-<br>munosuppressant)    | Autoimmune diseases<br>(e.g., RA, inflammatory<br>bowel disease/IBD)                                          | Purine analog; inhibits DNA<br>synthesis, suppressing T- and<br>B-cell proliferation to control<br>inflammation, similar to its anti-<br>proliferative effects in cancer                                              | FDA-approved for RA and<br>organ transplant rejection<br>(anti-inflammatory context)                                                                   | Steroid-sparing in 60–70% of<br>IBD/RA patients; 30–50% re-<br>mission in UC; TPMT genotyp-<br>ing reduces myelotoxicity <sup>15,16</sup>                                                                                        |
|                                                  | PLK1 inhibi-<br>tors (e.g., vo-<br>lasertib)                  | Oncology (e.g., acute<br>myeloid leukemia)                                        | Inflammatory diseases<br>(e.g., gout, heart fail-<br>ure, cardiomyopathy,<br>airway inflammation)             | Inhibits Polo-like kinase 1 (PLK1);<br>dampens NLRP3 inflammasome<br>activation and airway smooth mus-<br>cle proliferation, reducing runaway<br>inflammation at lower doses than<br>for mitosis inhibition in cancer | In Phase III trials for cancer;<br>preclinical/early trials for<br>inflammation, including in<br>vivo models for asthma-like<br>conditions (2023–2025) | Preclinical: 50–70% reduc-<br>tion in NLRP3 activation in<br>gout/heart models; no recent<br>human trials; cancer Phase II:<br>20–30% response in AML but<br>neutropenia common <sup>17,18</sup>                                 |
| Anti-in-<br>flamma-<br>tory agents<br>for cancer | PLK1 in-<br>hibitors (e.g., small<br>molecule)<br>onvansertib | Oncology (e.g., small<br>cell lung cancer,<br>chronic myelomonocytic<br>leukemia) | Inflammatory diseases<br>(e.g., gout, cardiovas-<br>cular inflammation)                                       | PLK1 inhibition modulates im-<br>mune checkpoints and inflamma-<br>some responses, linking mitotic<br>control in cancer to cytokine storm<br>suppression in inflammation                                              | Phase II trials for cancer<br>(ongoing as of 2024); early<br>repurposing studies for in-<br>flammation show promise in<br>dampening NLRP3 (2023)       | Preclinical: 40–60% cytokine<br>reduction in gout models;<br>Phase II cancer: 25% ORR in<br>RAS-mCRC but trial discontin-<br>ued 2023 for lack of benefit in<br>bev-experienced; no inflam-<br>mation outcomes yet <sup>19</sup> |
|                                                  | Aspirin                                                       | Anti-inflammatory<br>(e.g., pain, fever)                                          | Cancer prevention/<br>treatment (e.g.,<br>colorectal cancer/<br>CRC risk reduction,<br>metastasis prevention) | COX-1/2 inhibition; reduces<br>prostaglandin E2, suppresses<br>NF-κB/STAT3, limits angiogenesis<br>and TME inflammation, enhanc-<br>ing immune surveillance                                                           | FDA-recommended for<br>CRC prevention in high-risk<br>adults; epidemiological sup-<br>port for reduced mortality<br>in breast/lung cancers             | Meta-analysis: 15–24% CRC<br>risk reduction; 35% lower CRC<br>mortality after 5–10 years;<br>no benefit for other cancers;<br>GI bleeding risk 1–2% <sup>20,21</sup>                                                             |

(continued)

Table 1. (continued)

| Category | Drug/Agent                         | Primary indication                               | Repurposed/<br>Applied for                                                                                             | Mechanism of Interplay<br>(highlighting immunologic/<br>translational links)                                                                                       | Clinical status                                                                                                                                                                                                                                                        | Brief clinical outcomes                                                                                                                                                      |
|----------|------------------------------------|--------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|          | Celecoxib                          | Anti-inflammatory (e.g., arthritis)              | Cancer therapy (e.g., familial adenomatous polyposis/FAP polyp regression, adjunct to chemo/radiation)                 | Selective COX-2 inhibition; induces apoptosis, reduces TME inflammation (e.g., TAMs/MDSCs), synergizes with ICI by modulating PD-L1                                | FDA-approved for FAP; Phase II/III trials as adjunct in breast/NSCLC; recent studies (2025) on blood test-guided use for prevention                                                                                                                                    | 28–30% polyp reduction in FAP (Phase III); no CRC incidence reduction in meta-analysis; CV risk with long-term use <sup>22,23</sup>                                          |
|          | Dexamethasone                      | Anti-inflammatory (e.g., allergies, arthritis)   | Cancer symptom management/treatment (e.g., edema, nausea; adjunct in lymphoma)                                         | Glucocorticoid; inhibits NF-κB/cytokine production (IL-6/TNF-α), reduces TME inflammation, enhances chemo efficacy while managing side effects                     | FDA-approved for cancer supportive care; used in protocols for brain tumors/NSCLC                                                                                                                                                                                      | QUARTZ trial: No OS/QoL benefit vs. supportive care in NSCLC brain mets; 8 mg dose improves fatigue in 40–50% of advanced cancer inpatients <sup>24</sup>                    |
|          | Prednisone                         | Anti-inflammatory (e.g., asthma, RA)             | Cancer treatment (e.g., lymphoma, prostate)                                                                            | Similar to dexamethasone; suppresses immune evasion in TME, induces apoptosis in lymphoid cells via glucocorticoid receptor signaling                              | FDA-approved in regimens like CHOP for lymphoma; supportive in hormone-sensitive cancers                                                                                                                                                                               | CHOP: 30–70% cure in aggressive NHL; intensified dose (100 mg/day x5) improves response but increases toxicity; no standalone benefit <sup>25</sup>                          |
|          | Infliximab                         | Anti-inflammatory (e.g., RA, IBD)                | Cancer therapy (e.g., colitis-associated CRC, metastatic breast; management of ICI side effects like colitis/cachexia) | Anti-TNF-α monoclonal antibody; blocks TNF-driven inflammation, reduces EMT/angiogenesis in TME, synergizes with chemotherapy and manages immunotherapy toxicities | In Phase II trials (e.g., with oxaliplatin for CRC); off-label exploratory use; recent Phase II for melanoma (with anti-PD-1, 2022–2025) and cachexia (placebo-controlled, 2020s).                                                                                     | Phase II cachexia: No weight gain vs. placebo in NSCLC/pancreatic; 85% response in ICI-colitis but 1 fatal event; no OS benefit in melanoma combo <sup>26</sup>              |
|          | Tocilizumab                        | Anti-inflammatory (e.g., RA)                     | Cancer therapy (e.g., ovarian cachexia, radioresistance in nasopharyngeal; adjunct in pancreatic, TNBC)                | Anti-IL-6 receptor; inhibits IL-6/STAT3 signaling, reprograms TME to overcome immunotherapy resistance and reduce MDSC accumulation.                               | In Phase II trials (e.g., for solid tumors); used for cytokine release syndrome in CAR-T therapy; recent Phase II additions include nab-paclitaxel/gemcitabine combo for pancreatic (2025), carboplatin for TNBC (2024), and with corticosteroids for cachexia (2024). | Phase II pancreatic: 18-month survival 40% vs. 20%; reduced muscle wasting but no OS/PFS gain; TNBC: 25% ORR in combo; cachexia: 30% weight stabilization                    |
|          | JAK inhibitors (e.g., tofacitinib) | Anti-inflammatory (e.g., RA, ulcerative colitis) | Cancer therapy (e.g., myelofibrosis, solid tumors with inflammatory TME)                                               | Inhibits JAK/STAT signaling; dampens chronic inflammation and cytokine storms, reducing tumor growth and enhancing immunotherapy in inflamed TMEs.                 | FDA-approved for myelofibrosis (ruxolitinib); recent trials (2020–2025) explore in solid tumors, showing tumor shrinkage via inflammation control.                                                                                                                     | Myelofibrosis: 28–32% spleen reduction; solid tumors: 20–40% response in Phase II (e.g., lung); anemia/thrombocytopenia in 10–20%; no OS data in solids yet <sup>27,28</sup> |

This table summarizes approved or clinically investigated drugs demonstrating the interplay between cancer and inflammation. It includes cancer drugs repurposed for inflammatory diseases and anti-inflammatory agents applied to cancer treatment or prevention, highlighting shared immunologic mechanisms (e.g., NF-κB, IL-6, STAT3) and clinical outcomes from key trials (2020–2025 where available). ACR20, American College of Rheumatology 20% improvement criteria; AML, acute myeloid leukemia; CAR-T, chimeric antigen receptor T cell; CD20, cluster of differentiation 20; CHOP, a combination chemotherapy treatment for non-Hodgkin lymphoma that includes the drugs Cyclophosphamide, Hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and Prednisone; COX-1/2, cyclooxygenase-1/2; CRC, colorectal cancer; CV, cardiovascular; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; IL-6, interleukin-6; JAK, janus kinase; MDSC, myeloid-derived suppressor cell; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NLR family pyrin domain containing 3; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; QoL, quality of life; QUARTZ, quality of life after treatment for brain metastases; STAT3, signal transducer and activator of transcription 3; TAM, tumor-associated macrophage; TNBC, triple-negative breast cancer; TNF-α, tumor necrosis factor-alpha; TPMT, thiopurine S-methyltransferase; UC, ulcerative colitis;

comprehensive table summarizes approved or clinically investigated drugs that have recently demonstrated the interplay between cancer and inflammation. It includes cancer drugs repurposed for inflammatory diseases and anti-inflammatory agents applied to cancer treatment or prevention, highlighting shared immunologic mechanisms (e.g., NF- $\kappa$ B, IL-6, STAT3) and clinical outcomes from key trials (from 2020 to 2025, where available).

Recent advances have also underscored the role of lifestyle and environmental factors in exacerbating inflammation-linked cancer risk. Obesity, for example, induces low-grade chronic inflammation through adipose tissue-derived cytokines, increasing the incidence of cancers such as breast, colorectal, and endometrial cancers.<sup>29</sup> Similarly, tobacco smoke and air pollution trigger inflammatory pathways that promote lung carcinogenesis. These insights have spurred preventive strategies, including anti-inflammatory diets and chemoprevention with agents like aspirin, which have shown promise in reducing cancer incidence in high-risk populations.<sup>30</sup> As we delve further, this review will expand on these foundations, incorporating the latest mechanistic, translational, and clinical developments to provide a comprehensive overview.

## Mechanistic insights into cancer-associated inflammation

### Inflammatory signaling pathways

NF- $\kappa$ B is a central transcription factor activated in response to various stressors, including microbial products, cytokines, and oncogenic signals. Persistent NF- $\kappa$ B activation upregulates anti-apoptotic genes, cytokines, and chemokines such as IL-1, IL-6, and C-X-C motif chemokine ligand 8, facilitating tumor growth, angiogenesis, and immune evasion.<sup>31</sup> NF- $\kappa$ B also promotes epithelial-to-mesenchymal transition, a key step in metastasis.<sup>32</sup> Recent studies have elucidated how NF- $\kappa$ B interacts with other pathways, such as PI3K/AKT, to amplify inflammatory responses in hypoxic tumor environments, further driving resistance to apoptosis and therapy.<sup>33</sup>

STAT3, activated by IL-6 and other cytokines via the JAK pathway, supports tumorigenesis by promoting cell proliferation, survival, angiogenesis, and immunosuppression. STAT3 also inhibits the expression of pro-inflammatory signals needed for immune activation, establishing an immunosuppressive milieu.<sup>34,35</sup> In addition, STAT3 crosstalk with HIF-1 $\alpha$  under hypoxic conditions enhances metabolic reprogramming in cancer cells, favoring glycolysis and lactate production that sustains inflammation.<sup>36</sup>

Cyclooxygenase-2 (COX-2) and prostaglandins: The enzyme COX-2 is overexpressed in various cancers and contributes to tumor growth through the production of prostaglandin E2 (PGE2), which enhances cell proliferation, inhibits apoptosis, and suppresses immune responses.<sup>37</sup> Newer research links PGE2 to the recruitment of MDSCs and the polarization of macrophages toward an M2 phenotype, exacerbating immunosuppression.<sup>38</sup>

### Immune cell infiltrates in the TME

The TME is rich in immune and stromal cells whose polarization and function are shaped by inflammatory cues.

- TAMs often exhibit an M2-like phenotype characterized by IL-10 and transforming growth factor-beta (TGF- $\beta$ ) secretion, extracellular matrix remodeling, and promotion of angiogenesis. Their abundance is associated with poor prognosis in breast, ovarian, and pancreatic cancers.<sup>39</sup> Recent single-cell analyses reveal heterogeneity within TAM populations, with subsets expressing pro-inflammatory markers that could be reprogrammed for anti-tumor effects.<sup>40</sup>

grammed for anti-tumor effects.<sup>40</sup>

- MDSCs expand under chronic inflammation and suppress T-cell responses via arginase, nitric oxide, and TGF- $\beta$  pathways. They are prominent in colon, breast, and lung cancers and correlate with resistance to checkpoint blockade.<sup>41</sup> Studies from 2024 indicate that MDSC-derived exosomes carry miRNAs that further dampen T-cell activation.<sup>42</sup>
- Regulatory T cells (Tregs) infiltrate the TME and secrete IL-10 and TGF- $\beta$ , inhibiting effector T-cell activity and facilitating immune escape. High Treg infiltration is a negative prognostic indicator in many cancers, including melanoma and hepatocellular carcinoma.<sup>43</sup> Emerging data suggest Tregs interact with cancer-associated fibroblasts to sustain fibrotic niches that impede drug penetration.
- Tumor-associated neutrophils can adopt an N2 phenotype that supports tumor growth, angiogenesis, and metastasis, particularly in lung and gastric cancers.<sup>44</sup> However, under certain inflammatory contexts, tumor-associated neutrophils can shift to an N1 anti-tumor state, highlighting the potential for therapeutic modulation.<sup>45</sup>

### Additional pathways and interactions

Beyond core pathways, the inflammasome—multiprotein complexes like NLR family pyrin domain containing 3 (NLRP3)—plays a pivotal role by activating caspase-1 and releasing IL-1 $\beta$  and IL-18, which can either promote or suppress tumor growth depending on context.<sup>46</sup> Inflammasome activation in response to cellular damage or microbial signals amplifies inflammation, contributing to pyroptosis, a form of inflammatory cell death that releases damage-associated molecular patterns to further fuel the cycle.<sup>47</sup> Moreover, epigenetic modifications, such as histone acetylation influenced by inflammatory cytokines, regulate gene expression in cancer cells, perpetuating oncogenic signaling.<sup>48</sup> These interactions underscore the multifaceted nature of inflammation in cancer, where feedback loops between signaling pathways and immune cells create resilient tumor ecosystems.

### Inflammation in specific cancer types

To better illustrate the immunologic interplay, this section examines inflammation's role in select cancers, drawing on recent evidence.

#### Colorectal cancer (CRC)

Chronic inflammation, often driven by inflammatory bowel disease or microbial dysbiosis, is a major risk factor for CRC. Dysregulated NF- $\kappa$ B and STAT3 signaling in epithelial cells promotes mutagenesis and proliferation, while TAMs and MDSCs foster an immunosuppressive TME.<sup>49</sup> Recent studies highlight how gut microbiota alterations exacerbate inflammation via lipopolysaccharide release, activating toll-like receptor 4 and perpetuating carcinogenesis.<sup>44</sup> In 2024, analyses showed that high NLRP3 inflammasome activity correlates with advanced stage and poor prognosis in CRC, suggesting targeted inhibitors as adjuncts to therapy.<sup>46</sup>

#### Lung cancer

In non-small cell lung cancer (NSCLC), tobacco-induced inflammation activates COX-2/PGE2 pathways, recruiting neutrophils and macrophages that support metastasis.<sup>50</sup> KRAS mutations further amplify inflammatory signaling, leading to IL-6/STAT3-driven immunosuppression.<sup>51</sup> Recent data from 2024 indicate that

air pollution particulates trigger sterile inflammation via NLRP3, linking environmental factors to increased incidence and resistance to immune checkpoint inhibitors (ICIs).<sup>50</sup>

### **Breast cancer**

In triple-negative breast cancer, inflammation via androgen receptor signaling promotes epithelial-to-mesenchymal transition and metastasis.<sup>52</sup> Obesity-related adipose inflammation releases leptin and IL-6, enhancing MDSC accumulation and Treg function.<sup>52</sup> Reviews from 2024 emphasize how inflammatory biomarkers like C-reactive protein (CRP) predict response to neoadjuvant therapy, guiding personalized approaches.

These examples demonstrate how inflammation's context-specific effects vary by cancer type, informing tailored interventions.

## **Immunotherapy and the inflammatory context**

### **Immune checkpoint inhibition**

Checkpoint molecules such as programmed death 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) act as physiological brakes on T-cell activation to prevent autoimmunity. Tumors exploit these pathways to avoid immune destruction. Checkpoint inhibitors targeting these molecules have revolutionized oncology, with approvals across melanoma, lung, bladder, kidney, and head and neck cancers.<sup>53,54</sup> Anti-PD-1 antibodies (e.g., nivolumab, pembrolizumab) and anti-PD-L1 antibodies (e.g., atezolizumab) have demonstrated durable responses in subsets of patients, though only 20–40% respond in many cancers.<sup>55</sup> Recent approvals in 2024–2025 include combinations with novel checkpoints like lymphocyte-activation gene 3 (LAG-3) (e.g., relatlimab) for melanoma, enhancing efficacy in inflamed tumors. Inflammatory markers such as high baseline IL-6 predict resistance, as they promote PD-L1 expression and T-cell exhaustion.<sup>56</sup>

### **Chimeric antigen receptor T-cell (CAR-T) cell therapy and beyond**

CAR-T therapies have achieved remarkable success in hematologic malignancies, notably B-cell leukemias and lymphomas. Solid tumors pose greater challenges due to antigen heterogeneity and immunosuppressive TMEs.<sup>57</sup> Next-generation CAR-T strategies include armored CARs, bispecific CARs, and switchable CARs. Clustered regularly interspaced short palindromic repeats (CRISPR)-edited CAR-T cells, with knocked-out PD-1 or enhanced cytokine secretion, have shown improved persistence in inflammatory TMEs, as demonstrated in 2024 trials for solid tumors.<sup>58</sup>

### **Cancer vaccines and oncolytic viruses**

Therapeutic vaccines such as Sipuleucel-T for prostate cancer aim to prime the immune system against tumor antigens. Personalized neoantigen vaccines are being trialed for melanoma and NSCLC.<sup>59</sup> Oncolytic viruses like talimogene laherparepvec selectively infect and kill cancer cells while stimulating immune responses. Recent 2024 studies combined vaccines with anti-inflammatory agents to mitigate suppressive effects in high-inflammation tumors.<sup>60</sup>

### **Tumor-infiltrating lymphocytes (TILs) and adoptive cell transfer**

TILs isolated from tumors and expanded *ex vivo* have shown efficacy in melanoma and cervical cancer. New methods using CRISPR to enhance T-cell persistence and resistance to exhaustion are in development.<sup>61</sup> In inflamed TMEs, TIL therapy benefits from

pre-treatment with IL-2 to counter MDSC suppression, with 2024 data showing improved outcomes in NSCLC.<sup>62</sup>

### **Emerging immunotherapies**

Bispecific T-cell engagers and antibody-drug conjugates (ADCs) target inflammatory markers for precise delivery. For instance, bispecific T-cell engagers against CD3 and tumor antigens recruit T cells despite suppressive inflammation.<sup>63</sup> These advances highlight how modulating inflammation can enhance immunotherapy efficacy.

## **Preclinical translational advances in inflammation-targeting therapies**

### **Drug repurposing: non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, and statins**

Epidemiological studies show reduced colorectal and breast cancer risk with long-term aspirin use. COX-2 inhibitors reduce polyp formation in familial adenomatous polyposis.<sup>30</sup> Statins may lower cancer risk by inhibiting mevalonate pathways linked to inflammation. Recent meta-analyses from 2024 confirm aspirin's role in preventing metastasis in inflamed tumors.<sup>64</sup>

### **Targeting cytokines: IL-6 and TNF- $\alpha$**

Tocilizumab (IL-6R inhibitor) and siltuximab (IL-6 antibody) are in trials for multiple myeloma and ovarian cancer. Anti-TNF agents such as infliximab have shown efficacy in inflammation-associated cancers but also carry risks of immunosuppression.<sup>65</sup> Trials in 2025 combine IL-6 blockers with ICIs to overcome resistance in pancreatic cancer.<sup>66</sup>

### **Blocking NF- $\kappa$ B and STAT3**

Inhibitors of I $\kappa$ B kinase and STAT3 are under preclinical and early-phase clinical investigation. Bortezomib, a proteasome inhibitor approved by the U.S. Food and Drug Administration for myeloma, suppresses NF- $\kappa$ B activation and inflammation-driven tumor growth.<sup>67</sup> Novel small-molecule STAT3 inhibitors show promise in reducing MDSC accumulation in preclinical models.<sup>68</sup>

### **Preclinical models and multi-omics platforms**

Humanized mouse models allow testing of human immune responses to inflammation-targeting therapies. Integrated multi-omics (genomics, transcriptomics, proteomics, metabolomics) provides deep insights into inflammatory pathways in individual tumors.<sup>69</sup> Single-cell multi-omics in 2024 revealed spatial heterogeneity in inflammatory niches, guiding targeted therapies.<sup>70</sup>

### **Nanomedicine and targeted delivery**

Nanoparticles engineered to deliver anti-inflammatory agents selectively to the TME minimize systemic toxicity. Lipid nanoparticles targeting TAMs reprogram them toward M1 phenotypes, as shown in 2024 studies on breast cancer.<sup>71</sup> This approach bridges translational gaps by enhancing drug bioavailability in inflamed tissues.

## **Clinical strategies and biomarker integration**

### **Inflammatory biomarkers**

CRP, IL-6, and the neutrophil-to-lymphocyte ratio are routinely evaluated for their prognostic and predictive value.<sup>72</sup> Elevated

CRP and IL-6 are associated with reduced ICI efficacy and survival in melanoma and NSCLC. Recent 2024 analyses identify the pan-immune-inflammation value as a superior predictor in advanced cancers.<sup>73</sup>

#### ***Predictive biomarkers for immunotherapy***

PD-L1 expression by IHC is used to guide ICI therapy in NSCLC, triple-negative breast cancer, and urothelial carcinoma. Tumor mutational burden and microsatellite instability also predict ICI responses.<sup>74</sup> Emerging biomarkers include circulating tumor DNA and gut microbiome signatures, with 2024 reviews emphasizing multi-omics integration for precision.<sup>75</sup>

#### ***Combination approaches***

Combining ICIs with anti-inflammatory drugs (e.g., aspirin), VEGF inhibitors (e.g., bevacizumab), chemotherapy, or radiation has improved efficacy in several trials. These regimens aim to overcome primary or acquired resistance.<sup>76</sup> Trials in 2024 on CRC combine ICIs with microbiome modulators to reduce inflammation and boost responses.<sup>77</sup>

#### ***Managing immune-related adverse events (IRAEs)***

IRAEs can affect any organ system. Endocrinopathies, pneumonitis, and colitis are among the most common. Early identification and immunosuppression with corticosteroids or TNF inhibitors are critical for management.<sup>78</sup> Protein biomarkers like sCD25 predict IRAE risk, enabling proactive monitoring.<sup>79</sup>

#### ***Personalized medicine frameworks***

Artificial intelligence (AI)-driven models integrate biomarkers to stratify patients, predicting inflammation-driven resistance and guiding combinations. Platforms in 2024 use machine learning on multi-omics data for real-time adjustments.<sup>80</sup>

### **Future perspectives**

#### ***Microbiome and inflammation***

The gut microbiota profoundly influences systemic immunity and ICI outcomes. Specific microbial taxa, such as *Bifidobacterium* and *Akkermansia*, are associated with better responses. Clinical trials using probiotics and fecal microbiota transplantation are ongoing.<sup>81</sup> 2024 research links microbiome dysbiosis to heightened inflammation and lung cancer progression, with metabolites like short-chain fatty acids modulating TME immunosuppression.<sup>51</sup> Future interventions may include microbiome editing via CRISPR to enhance anti-tumor immunity.<sup>58</sup>

#### ***AI and machine learning***

AI models can integrate complex biomarker data to predict treatment responses and IRAE risks. Algorithms trained on genomic, transcriptomic, and clinical data are being validated in prospective studies.<sup>82</sup> In 2024, Stanford-developed AI predicts cancer prognosis by analyzing inflammation patterns in imaging and text data. Machine learning also optimizes CAR-T design by forecasting inflammatory resistance.<sup>58</sup>

#### ***Gene editing and synthetic biology***

CRISPR-Cas9 allows precise editing of immune checkpoints and cytokine pathways in T cells. Synthetic circuits enable real-time modulation of immune responses. These tools hold potential for next-generation cell therapies.<sup>83</sup> 2024 reviews detail CRISPR's

role in enhancing CAR-T efficacy by editing exhaustion genes in inflammatory TMEs.<sup>84</sup> RNA-editing variants offer reversible modifications to tune inflammation without permanent changes.<sup>85</sup>

#### ***Single-cell and spatial omics***

Single-cell RNA sequencing and spatial transcriptomics reveal the heterogeneity of immune and inflammatory cells within tumors. These technologies are key to identifying new therapeutic targets and resistance mechanisms. 2024 studies using single-cell multi-omics uncovered vulnerabilities in immunotherapy-resistant TMEs, such as MDSC clusters driven by inflammation. Integrating these with AI will enable dynamic mapping of inflammatory evolution.

#### ***Nanotechnology and liquid biopsies***

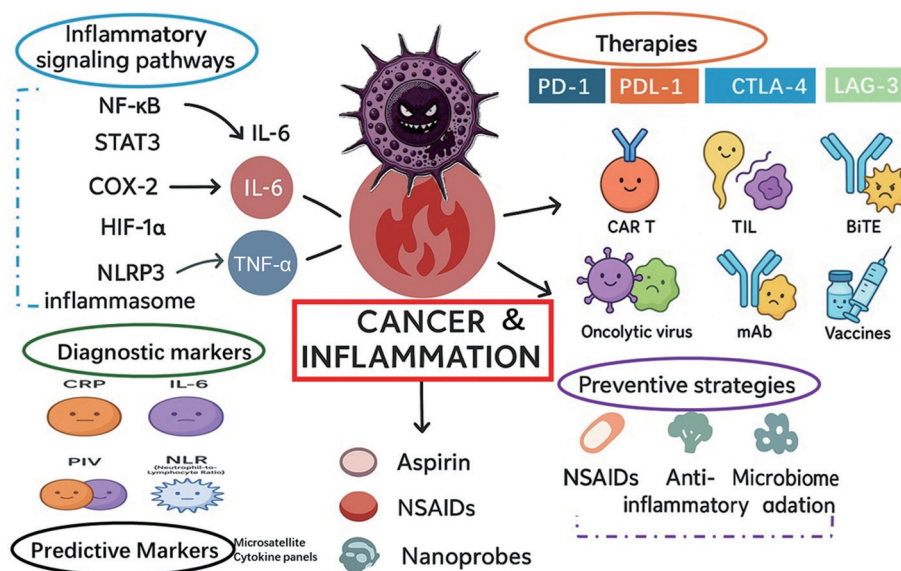
Nanoprobes targeting inflammatory markers could enable real-time TME monitoring. Liquid biopsies detecting inflammatory circulating tumor DNA signatures predict responses noninvasively, as per 2024 advancements.<sup>86</sup> These innovations promise to bridge gaps in current therapies.

#### ***Other areas where the interplay between cancer and inflammation may prove significant in the future***

First, emerging technologies such as nanotechnology and ADCs could facilitate tumor-specific delivery of anti-inflammatory agents. These technologies provide targeted approaches by utilizing nanoparticles to deliver anti-inflammatory agents directly to the TME, thereby reducing systemic toxicity. Additionally, ADCs can be engineered to bind specifically to tumor-associated antigens, releasing anti-inflammatory payloads only upon internalization by cancer cells, thus enhancing precision and efficacy. Secondly, rational combination therapies can be designed based on pharmacological principles such as synergy and overcoming resistance. This approach can leverage pharmacological synergy by pairing anti-inflammatory agents with immunotherapies, including checkpoint inhibitors, to boost immune responses while mitigating inflammation-driven resistance. Furthermore, sequential or dose-adjusted combinations can target multiple pathways, such as NF- $\kappa$ B and STAT3, to prevent tumor adaptation and improve therapeutic outcomes. Lastly, patient genetic profiles may be employed to predict the efficacy and toxicity of anti-inflammatory drugs. Genetic profiling can identify polymorphisms in cytokine pathways or drug-metabolizing enzymes, such as CYP450, to forecast individual responses and customize anti-inflammatory treatments accordingly. Moreover, analyzing genetic markers linked to immune-related adverse events can help anticipate toxicity risks, enabling personalized dosing strategies to optimize both safety and efficacy.

### **Conclusions**

Cancer-related inflammation acts as a double-edged sword—while it can prime anti-tumor immunity, chronic and unresolved inflammation fosters tumorigenesis, immune evasion, and therapy resistance. Integrating inflammation-targeting strategies with immunotherapy and biomarker-driven approaches offers a promising path toward personalized and durable cancer treatment. As summarized in a schematic illustration (Fig. 1), this review provides a comprehensive overview of the intricate bidirectional relationship between cancer and inflammation, encompassing signaling pathways, therapeutic selections, biomarkers, preventive strategies, and emerging technologies. Numerous lines of clinical evidence have established a solid foundation for this linkage, and thorough



**Fig. 1. A schematic illustration presenting a comprehensive overview of the intricate bidirectional relationship between cancer and inflammation.** The linkages between cancer and inflammation are built around various aspects, including signaling pathways, therapeutic selections, biomarkers, preventive strategies, and emerging technologies. Key inflammatory signaling pathways (NF- $\kappa$ B, STAT3, COX-2, HIF-1 $\alpha$ , NLRP3 inflammasome) and cytokines (IL-6, TNF- $\alpha$ ) drive tumorigenesis and immune evasion. The figure highlights diagnostic markers (CRP, IL-6, NLR, PIV) and predictive indicators (microsatellites), alongside therapeutic strategies, including immunotherapies (PD-1, PD-L1, CTLA-4, CAR-T, LAG-3, vaccines, BiTEs, TILs), and preventive approaches (aspirin, NSAIDs, anti-inflammatory agents, microbiome modulation). Translational advances and clinical applications, such as integrating immunotherapy with anti-inflammatory agents, are emphasized to underscore personalized treatment and resistance management. BiTEs, bispecific T-cell engagers; CAR-T, chimeric antigen receptor T-cell; COX-2, cyclooxygenase-2; CRP, C-reactive protein; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HIF-1 $\alpha$ , hypoxia-inducible factor-1 $\alpha$ ; IL-6, interleukin-6; LAG-3, lymphocyte-activation gene 3; mAb, monoclonal antibody; NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NLR, neutrophil-to-lymphocyte ratio; NLRP3 inflammasome, NOD-, LRR-, and pyrin domain-containing protein 3 inflammasome; NSAIDs, non-steroidal anti-inflammatory drugs; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; PIV, pan-immune-inflammation value; STAT3, signal transducer and activator of transcription 3; TILs, tumor-infiltrating lymphocytes; TNF- $\alpha$ , tumor necrosis factor-alpha.

investigation into this topic could yield an in-depth understanding of the mechanisms of action, ultimately leading to improved therapeutics and interventions for both conditions. With recent advances in microbiome modulation, AI prediction, gene editing, and single-cell technologies, the field is poised for transformative progress. Continued investment in mechanistic research, translational innovation, and clinical validation is essential to fully realize the therapeutic potential of modulating inflammation in oncology, ultimately improving patient outcomes across diverse cancer types.

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## Conflict of interest

WY is employed by ClinBridge Biotechnology Co. Ltd. The author declares no other conflicts of interest.

## Author contributions

WY is the sole author of the manuscript.

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