International Journal of Clinical and Translational Medicine
https://www.sciltp.com/journals/ijctm

Review

Inflammation-Driven Tumorigenesis: Mechanisms, Immune Evasion, and Therapeutic Strategies

Vivek Singh [1], Mohmmad Kashif [2], Roma Pahwa [3,*] and Anand Singh [1,*]

[1] Thoracic Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA
[2] Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD 20852, USA
[3] Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA
* Correspondence: roma.pahwa@nih.gov (R.P.); anand.singh@nih.gov (A.S.)

How To Cite: Singh, V.; Kashif, M.; Pahwa, R.; et al. Inflammation-Driven Tumorigenesis: Mechanisms, Immune Evasion, and Therapeutic Strategies. *International Journal of Clinical and Translational Medicine* **2025**, *1*(3), 3. https://doi.org/10.53941/ijctm.2025.1000017.

Received: 11 March 2025
Accepted: 18 March 2025
Published: 2 July 2025

Abstract: Cancer is a complicated disease influenced by genetic, environmental, and immunological factors. Among these, chronic inflammation has emerged as a critical factor in tumor initiation, progression, and metastasis. The inflammatory tumor microenvironment, enriched with cytokines, chemokines, and immune cells, fosters immune evasion, angiogenesis, and genomic instability and key signaling pathways, including NF-κB, STAT3, and COX-2/PGE2, bridge inflammation and oncogenesis, making them promising therapeutic targets. Despite the tumor-promoting effects of chronic inflammation, the immune system also plays a crucial role in immunosurveillance, eliminating malignant cells. However, tumors develop escape mechanisms, such as immune checkpoint activation and recruitment of immunosuppressive cells, enabling survival and metastasis. Current therapeutic strategies target inflammation-driven tumorigenesis through nonsteroidal anti-inflammatory drugs (NSAIDs), cytokine inhibitors, immune checkpoint inhibitors, and combination therapies. Understanding the balance between pro- and antitumor immunity is essential for advancing novel therapeutic interventions. This review highlights recent findings on inflammation-driven cancer progression, the molecular mechanisms involved, and emerging strategies to harness inflammatory pathways for cancer treatment.

Keywords: inflammation; tumor microenvironment; immune evasion; cytokines and chemokines; NF-κB signaling

1. Introduction

Cancer development is a multifactorial process influenced by genetic, environmental, and immunological factors. Among these, chronic inflammation has emerged as a critical component of tumorigenesis, providing a favorable microenvironment for cancer initiation, progression, and metastasis. The link between inflammation and cancer dates back to Rudolf Virchow's 1863 hypothesis, which suggested that tumors arise from sites of chronic irritation and inflammation [1]. Recent research has validated this idea, demonstrating that inflammatory cells and their secreted mediators are pivotal in fostering tumor growth [2]. The immune system, a powerful force, largely shapes the tumor microenvironment, with inflammatory cells actively participating in the neoplastic process. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and chemokines and adhesion molecules, facilitate tumor cell proliferation, survival, and metastasis [3]. Additionally, tumor-associated macrophages (TAMs) have been shown to promote cancer progression by secreting growth factors, suppressing antitumor immunity, and enhancing angiogenesis [4]. Chronic inflammatory conditions, such as inflammatory bowel disease and chronic hepatitis, significantly increase the risk of colorectal and liver cancer,

respectively, by inducing persistent immune activation and DNA damage [5]. This intricate interplay between the immune system and cancer is a fascinating area of research that keeps the audience intrigued and engaged. While inflammation plays a central role in tumor progression, it also has the potential to suppress malignancy under specific conditions. This duality highlights the importance of understanding the balance between pro-tumorigenic and antitumorigenic immune responses [6]. For instance, in some cases, the immune system can recognize and eliminate cancer cells, a process known as immunosurveillance. By targeting key inflammatory pathways, novel therapeutic strategies, inclssuding nonsteroidal anti-inflammatory drugs (NSAIDs), immune checkpoint inhibitors, and cytokine-targeting therapies, offer promising avenues for cancer prevention and treatment [7]. The potential of these strategies, particularly immunotherapy, reassures the audience about the progress in cancer treatment and the hope they bring for the future.

2. Tumor-Associated Inflammation: The Dual Role of Tumor Suppressor Loss and Oncogene Activation

Several mechanisms contribute to the initiation of tumor-associated inflammatory responses driven by various stimuli. One of the hallmarks of cancer is the loss of tumor suppressor functions, which profoundly disrupts cellular homeostasis and immune regulation. Among the most frequently mutated tumor suppressors is Tp53, which encodes the p53 protein and is crucial for maintaining cellular balance and suppressing inflammatory pathways by antagonizing nuclear factor-κB (NF-κB) [8,9]. Since NF-κB is a key positive regulator of inflammation and remains constitutively active within the tumor microenvironment, the loss of p53 leads to unregulated NF-κB signaling and increased expression of NF-κB-dependent inflammatory genes. This inflammatory signature has been shown to drive tumor progression and metastasis in colorectal cancer [8,10,11]. Additionally, the loss of tumor suppressors compromises DNA repair mechanisms, promoting genomic instability and triggering DNA-damage-induced inflammatory pathways [12]. Understanding these molecular mechanisms is crucial for developing targeted therapies. Beyond tumor suppressor loss, oncogene activation is directly linked to increased inflammatory signaling, which fuels tumor progression. Many oncogenes stimulate the production of cytokines and chemokines, facilitating the recruitment of myeloid-derived immune cells that either support tumor growth or suppress antitumor immunity. For instance, oncogenic K-Ras signaling enhances the expression of C-X-C motif chemokine ligand 3 (CXCL3), a key factor in myeloid cell recruitment [13]. Moreover, K-Ras activation leads to the overproduction of cytokines and chemokines associated with the senescence-associated secretory phenotype (SASP), including IL-1α, IL-1β, C-C motif chemokine ligand 2 (CCL2), and CXCL1 [14]. The cooperative activation of K-Ras and c-Myc further amplifies inflammation by inducing CCL9, IL-23, and other inflammatory mediators in pancreatic cancer [15]. These findings highlight a common mechanism across cancers: oncogene activation and inflammatory cytokine overproduction establish a tumor-promoting inflammatory microenvironment.

3. Innate Immune Signaling, Inflammation, and Myeloid Reprogramming in Tumor Progression

The innate immune system relies on key pathogen recognition receptor families, including Toll-like receptors (TLRs), NOD-like receptors (NLRs), and retinoic acid-inducible gene-like receptors (RLRs), to detect pathogenic and endogenous danger signals [16,17]. These receptors trigger intracellular signaling cascades, producing pro-inflammatory mediators such as cytokines, chemokines, leukotrienes, and eicosanoids, which contribute to inflammation and tumor progression [16]. TLRs, expressed either on the cell surface (TLR1, TLR2, TLR4, TLR5, TLR6, TLR10, TLR11) or within the cytoplasm (TLR3, TLR7, TLR9), recognize a variety of pathogens and inflammatory signals, initiating responses that can influence tumorigenesis. For example, TLR4 has been shown to promote tumor growth and metastasis in various cancers, including breast, lung, and colorectal cancer, by inducing the expression of pro-inflammatory cytokines and chemokines [16]. Structurally, TLRs share three major components: an extracellular leucine-rich domain, a transmembrane domain, and a Toll/interleukin-1 receptor (TIR) domain, essential for activating downstream pathways [18,19]. Upon activation, TLRs dimerize and interact with adaptors such as MyD88, IRAK, TRAF6, TAK1, TAB1, and TAB2, leading to NF-κB activation and the subsequent transcription of inflammatory genes [20,21]. TLR4 and TLR3 can also interact with TIRAP and TRIF, mediating MyD88-independent pathways [22,23]. NLRs, another class of pattern recognition receptors, are primarily located in the cytoplasm and are integral to immune responses against bacterial infections. Structurally, NLRs consist of a NACHT domain (for oligomerization and activation), an N-terminal protein-protein interaction domain (such as the CARD domain), and a C-terminal leucine-rich repeat (LRR) domain [24,25]. The NLR family comprises [20] intracellular receptors in monocytes, macrophages, T cells, B cells, and intestinal dendritic-like cells [26]. NOD1 and NOD2 receptors engage receptor-interacting protein (RIP)-2 via CARD-CARD interactions, subsequently activating NF-κB and MAPK pathways [27]. Some NLR members also contribute to inflammasome

formation, regulating caspase-1 activation and the maturation of pro-inflammatory cytokines such as IL-6, IL-10, IL12, IL23, IL-1β, IL-18, and IL-33 as shown in Figure 1 [28,29]. Inflammasome activation triggers cytokine production and induces pyroptosis, a form of inflammatory programmed cell death characterized by cell swelling, membrane rupture, and inflammatory mediator release [30,31]. Caspase-1 cleaves gasdermin D (GSDMD), regulating pyroptosis, which has been implicated in inflammatory diseases such as familial Mediterranean fever (FMF), neonatal inflammatory disorders, non-alcoholic steatohepatitis (NASH), and multiple sclerosis [32–37]. Additionally, inflammasome-mediated inflammation plays a role in tumor progression and resistance to therapy, with NLRP3 being implicated in inflammatory responses to anti-cancer drugs [38–43].

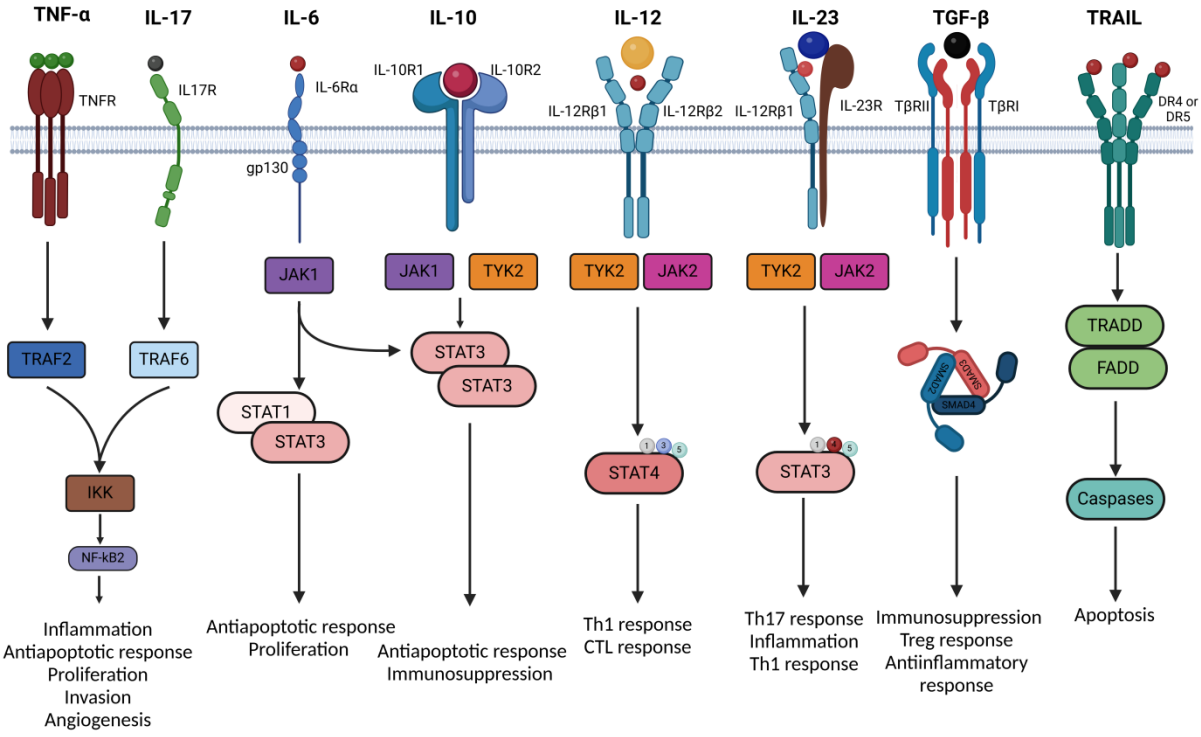

Figure 1. Inflammatory Signaling Pathways in Tumor Progression. The figure illustrates key inflammatory pathways contributing to tumor development and immune modulation. Pathways such as TNF-α, IL-6, IL-10, IL-12, IL-23, and TGF-β are shown with their downstream effectors, including JAK/STAT, SMAD, and NF-κB, which regulate processes like inflammation, immunosuppression, angiogenesis, and apoptosis. TRAIL-mediated caspase activation promotes tumor cell death, while other pathways facilitate immune evasion and tumor survival. The interplay of these signaling cascades highlights potential therapeutic targets for modulating inflammation in cancer treatment.

Immune cells within the tumor site can exhibit antitumorigenic or protumorigenic phenotypes. However, the tumor microenvironment (TME) often reprogrammes tumor-infiltrating immune cells, particularly myeloid cells, toward pro-tumor functions. These include suppressing antitumor immune responses and promoting angiogenesis [41–48]. Beyond modulating neutrophils, monocytes, and macrophages within the local TME, several tumors also trigger increased medullary and extramedullary myelopoiesis, a cancer-induced emergency myelopoiesis phenomenon. This process drives elevated bone marrow and/or splenic production of myeloid cells with immunosuppressive properties [49]. Such tumor-promoting myeloid cells, known as myeloid-derived suppressor cells (MDSCs), are defined by their ability to suppress immune responses. Several tumor-derived factors contribute to cancer-induced emergency myelopoiesis, including granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF, also known as CSF2), interleukin-6 (IL-6), and vascular endothelial growth factor A (VEGFA) [50–53]. Once produced, monocytes generated through this process are recruited into the TME, where they differentiate into tumor-associated macrophages (TAMs), further supporting tumor progression. A critical area of ongoing research is identifying where tumor-driven myeloid cell reprogramming occurs and elucidating the underlying mechanisms. Substantial evidence indicates that this reprogramming to a pro-tumor phenotype can occur within the TME. For instance, neutrophils undergo epigenetic modifications induced by tumors, leading to the expression of dcTRAIL-R1 (TNFRSF23), a neutrophil subset located in the hypoxic tumor core that enhances angiogenesis and tumor growth [46]. Similarly, in the colorectal

cancer microenvironment, neutrophils are transcriptionally reprogrammed to express Spp1 (encoding osteopontin) and Mmp14 (encoding a matrix metalloproteinase), promoting tumor vascularization [52]. Beyond the TME, tumor-mediated myeloid reprogramming can also originate in the bone marrow. Notably, IL-4 produced by basophils and eosinophils within the bone marrow has been shown to generate immunosuppressive, protumorigenic myeloid cells from progenitors [54]. Additionally, tumor-derived signals can drive hematopoietic stem and progenitor cells (HSPCs) toward differentiation into tumor-promoting MDSCs via chemokine receptor signaling through CCR1 and CCR5 as shown in Figure 2 [55].

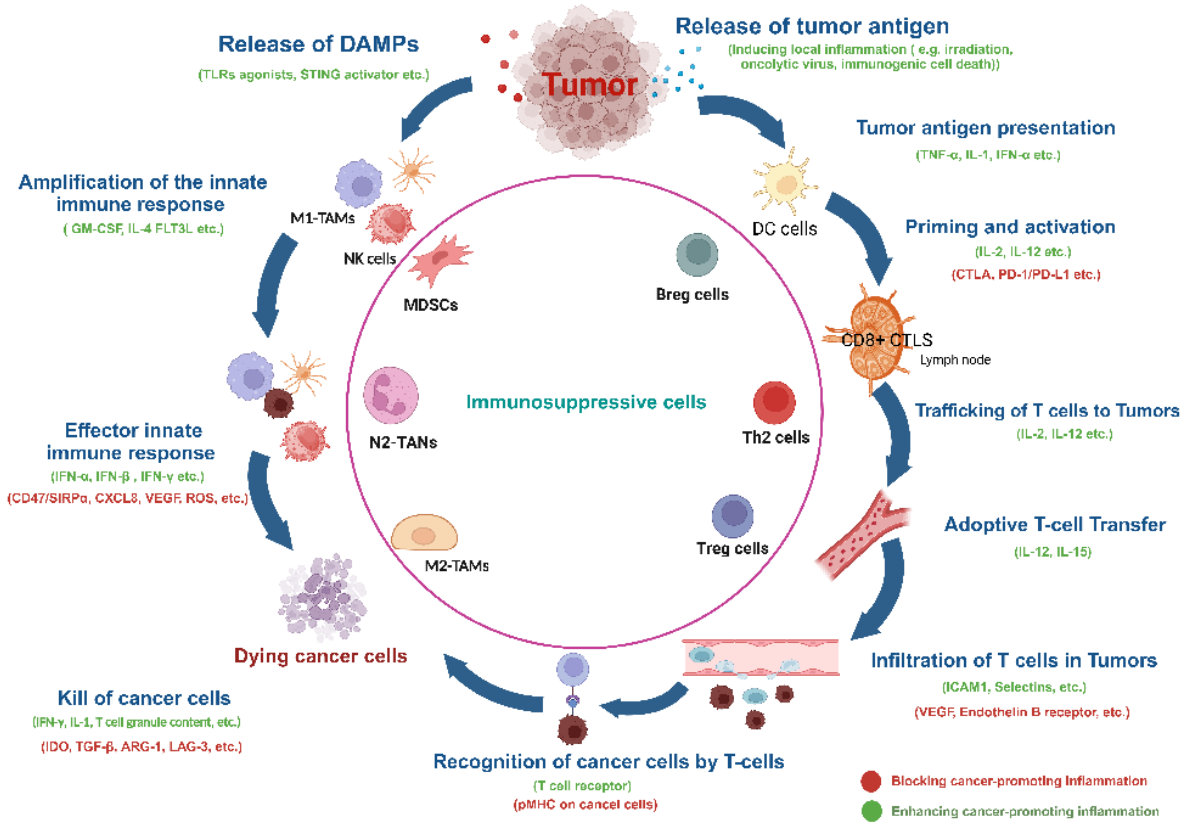

Figure 2. Harnessing Inflammation in Cancer Therapy: Balancing Pro- and Anti-Tumor Immune Responses. The figure represents the complex relationship between inflammation and cancer, balancing pro-tumorigenic and anti-tumorigenic immune responses. Inflammatory signals can support tumor immune evasion through MDSCs, Tregs, and M2 macrophages while facilitating anti-tumor immunity via CD8+ T cells, NK cells, and M1 macrophages. Strategies such as STING activation, immune checkpoint inhibition, cytokine modulation, and tumor antigen priming are shown as potential therapeutic interventions to optimize immune responses and enhance cancer immunotherapy.

4. Inflammation, Immune Surveillance, and Cancer Immunoediting: A Double-Edged Sword

The relationship between inflammation, immune surveillance, and cancer is complex and multifaceted. While the immune system detects and eliminates malignant cells, chronic inflammation can create a tumor-promoting environment. Cancer immunosurveillance was initially proposed to describe the immune system's role in preventing cancer development. However, tumors often evolve mechanisms to escape immune detection, leading to a dynamic process known as cancer immunoediting, which consists of three distinct phases: elimination, equilibrium, and escape [56]. In the elimination phase, immune cells such as natural killer (NK), cytotoxic CD8+ T lymphocytes, and dendritic cells recognize and destroy emerging cancer cells. This process is facilitated by releasing pro-inflammatory cytokines such as interferon-gamma (IFN-γ) and activating immune checkpoints that ensure effective immune responses. However, suppose a subset of tumor cells withstands immune-mediated destruction. In that case, they enter the equilibrium phase, where selective immune pressure allows for the survival and outgrowth of tumor variants with reduced immunogenicity [57]. Over time, these immune-resistant tumor cells accumulate mutations that further enable them to evade immune responses, progressing to the escape phase. In this final stage, tumors actively suppress immune responses through mechanisms such as loss of antigen presentation, secretion of immunosuppressive cytokines (TGF-β, IL-10), recruitment of regulatory T cells (Tregs),

and activation of immune checkpoints like PD-1/PD-L1 and CTLA-4. These adaptations help tumors grow unchecked despite an active immune system [58]. Chronic inflammation further exacerbates tumor progression by providing a microenvironment rich in growth factors, pro-inflammatory cytokines, and reactive oxygen species (ROS), contributing to DNA damage and genetic instability. Inflammatory mediators such as TNF-α, IL-6, and IL-1β have been implicated in promoting tumor growth by enhancing cell proliferation, angiogenesis, and resistance to apoptosis. Additionally, the tumor microenvironment (TME) is shaped by infiltrating immune cells such as tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and neutrophils, many of which exhibit pro-tumorigenic functions. TAMs, particularly those polarized toward the M2 phenotype, secrete immunosuppressive factors that support tumor survival and metastasis [59]. Moreover, danger signal receptors such as Toll-like receptors (TLRs) and inflammasomes play crucial roles in linking inflammation and cancer. TLR activation can promote both antitumor immunity and tumor progression, depending on the context. For example, while TLR4 activation can enhance dendritic cell maturation and antigen presentation, it has also been associated with increased tumor cell survival and metastasis. Similarly, inflammasomes contribute to inflammation-induced carcinogenesis by promoting the production of IL-1β and IL-18, which enhance immune cell recruitment and tumor-promoting inflammation [60]. Given the intricate interplay between inflammation, immune surveillance, and tumor evolution, therapeutic strategies targeting both immune evasion and chronic inflammation hold promise for cancer treatment. Immune checkpoint inhibitors (e.g., anti-PD-1, anti-CTLA-4), anti-inflammatory drugs (e.g., NSAIDs, COX-2 inhibitors), and cytokine-targeting therapies are being actively explored to enhance antitumor immunity. Understanding the balance between pro- and antitumor immune responses will be crucial for developing effective immunotherapies that harness the immune system while mitigating the tumor-promoting effects of chronic inflammation as shown in Figure 3 [61].

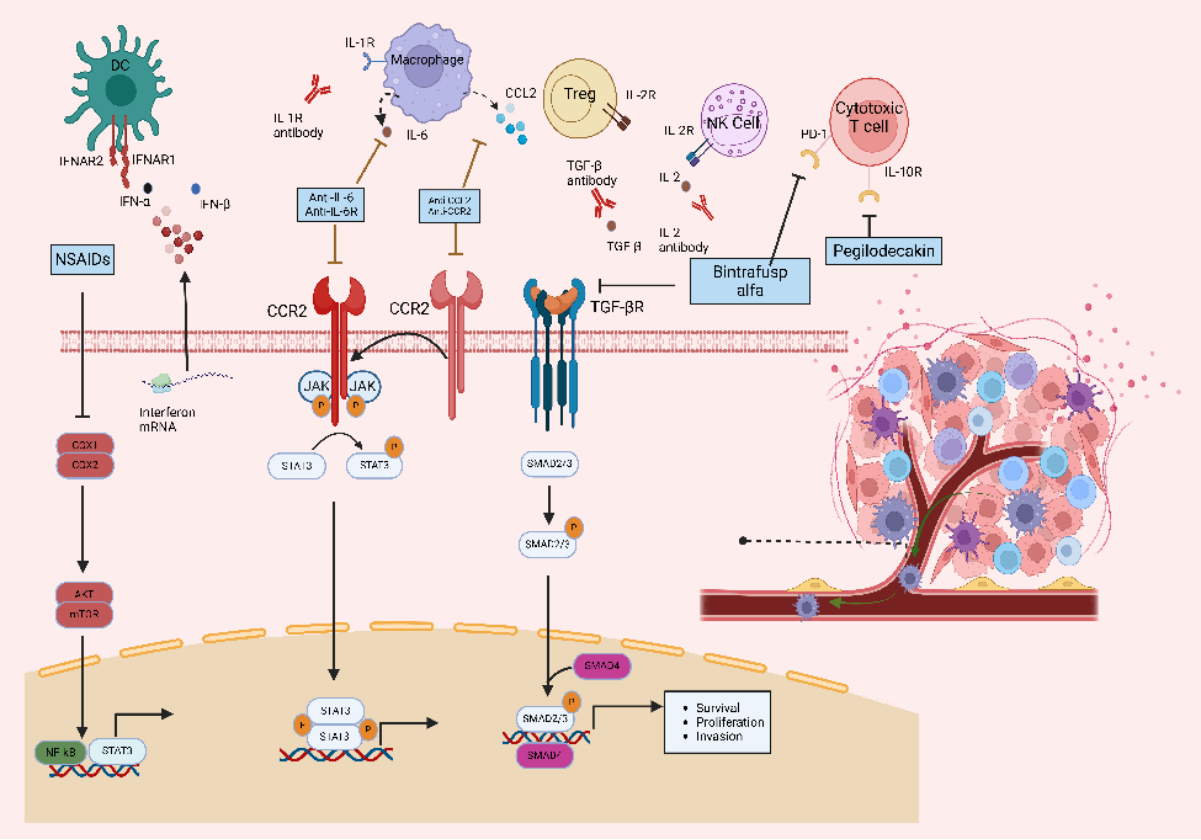

Figure 3. Targeting Inflammation in Cancer Therapy-Molecular Mechanisms and Therapeutic Strategies. Outlines of various therapeutic approaches targeting inflammation-driven cancer progression. NSAIDs and small molecule inhibitors of COX, JAK/STAT, and TGF-β pathways are depicted, highlighting their role in suppressing pro-inflammatory and immunosuppressive signaling. Therapeutic interventions such as IL-6/IL-6R blockade, CCR2 inhibitors, and IL-2/TGF-β modulation are shown to enhance immune surveillance and limit tumor proliferation, emphasizing the translational impact of inflammation-targeted strategies in cancer treatment.

5. Pathways Involved in Inflammation and Cancer as Potential Therapeutic Targets

Several signaling pathways mediate the complex relationship between inflammation and cancer, influencing tumor initiation, progression, and immune evasion. These pathways regulate inflammatory responses and provide viable therapeutic targets for cancer treatment as shown in Figures 1 and 3.

1. **NF-κB Pathway** [1]
   - Key Role: The nuclear factor-kappa B (NF-κB) pathway links inflammation to tumor progression. It is activated by inflammatory cytokines (TNF-α, IL-1β), microbial products (LPS), and stress signals.
   - Impact on Cancer: NF-κB promotes cell survival, proliferation, and immune evasion by upregulating anti-apoptotic genes (Bcl-XL, c-IAP1, c-IAP2) and pro-inflammatory mediators (IL-6, IL-8, COX-2). It also sustains chronic inflammation by recruiting tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs).
   - Therapeutic Targeting: IKK inhibitors (which block NF-κB activation) and TNF-α inhibitors are being explored for reducing tumor-associated inflammation.
2. **STAT3 Signaling** [62]
   - Key Role: Signal transducer and activator of transcription 3 (STAT3) is a key mediator of inflammation-driven carcinogenesis. It is activated by cytokines such as IL-6, IL-10, and IL-23, enhancing tumor survival.
   - Impact on Cancer: STAT3 activation leads to immune suppression by promoting Treg expansion and blocking cytotoxic T-cell responses. It also enhances angiogenesis via VEGF induction.
   - Therapeutic Targeting: JAK-STAT inhibitors (e.g., ruxolitinib) and IL-6 blockers (e.g., tocilizumab) are potential anti-cancer strategies targeting STAT3.
3. **COX-2/PGE2 Pathway** [63]
   - Key Role: Cyclooxygenase-2 (COX-2) is upregulated in response to inflammatory stimuli and produces prostaglandin E2 (PGE2), which modulates the immune response.
   - Impact on Cancer: COX-2 enhances tumor cell proliferation, immune evasion, and angiogenesis. It suppresses antitumor immunity by impairing T-cell function and recruiting MDSCs.
   - Therapeutic Targeting: COX-2 inhibitors (e.g., celecoxib, aspirin) have shown promise in cancer prevention and treatment.
4. **IL-1β/Inflammasome Pathway** [64]
   - Key Role: The inflammasome, primarily activated via NLRP3, produces IL-1β and IL-18, which drive chronic inflammation.
   - Impact on Cancer: IL-1β promotes tumor growth by inducing angiogenesis, epithelial-mesenchymal transition (EMT), and metastasis.
   - Therapeutic Targeting: IL-1β inhibitors (e.g., anakinra, canakinumab) are being investigated to reduce inflammation-driven cancer progression.
5. **TGF-β Signaling** [64]
   - Key Role: Transforming growth factor-beta (TGF-β) has a dual role. It initially acts as a tumor suppressor but later promotes tumor progression by inducing immunosuppression and metastasis.
   - Impact on Cancer: It promotes Treg expansion, fibroblast activation, and immune evasion, facilitating tumor escape.
   - Therapeutic Targeting: TGF-β inhibitors are under development to counteract its pro-tumorigenic effects.

By targeting these inflammatory pathways, novel cancer therapies can reduce tumor-promoting inflammation while preserving antitumor immune responses, offering a promising direction for treatment.

6. Therapeutic Strategies Targeting Inflammation in Cancer

Inflammation is a key driver of tumor progression, influencing cancer cell survival, metastasis, and immune evasion. Various therapeutic strategies have been explored to mitigate cancer-promoting inflammation, including anti-inflammatory drugs, immune modulators, cytokine-targeting therapies, and combination strategies with immunotherapy or chemotherapy as shown in Figure 2. Below are the major therapeutic approaches discussed in the article:

6.1. Anti-Inflammatory Agents for Cancer Prevention and Treatment

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs, particularly aspirin and COX-2 inhibitors, have been widely studied for their cancer-preventive and therapeutic effects[61].

- Aspirin: Long-term aspirin use has been associated with a lower risk of colorectal, esophageal, gastric, and hepatobiliary cancers. It exerts anti-inflammatory effects by inhibiting COX-2 and reducing prostaglandin E2 (PGE2) production, which is implicated in tumor progression.
- COX-2 Inhibitors (Celecoxib, Rofecoxib): These drugs have shown efficacy in reducing colorectal adenomas but are not routinely used due to cardiovascular risks.
- Challenges: NSAIDs primarily delay tumor growth rather than eradicating cancer cells, and long-term use is associated with gastrointestinal bleeding and cardiovascular side effects.

6.2. Targeted Anti-Inflammatory Therapies

6.2.1. IL-1 Inhibitors

IL-1β is a pro-inflammatory cytokine that promotes tumor growth, immune evasion, and metastasis.

- Canakinumab (IL-1β monoclonal antibody) significantly reduced lung cancer incidence and mortality in the CANTOS trial, originally designed to prevent cardiovascular diseases.
- MABp1 (IL-1α monoclonal antibody) has been studied in colorectal cancer and has shown potential benefits in improving disease stabilization [65–67].

6.2.2. IL-6 Inhibitors

IL-6 plays a key role in cancer-related inflammation and immunosuppression.

- Tocilizumab (anti-IL-6R), Clazakizumab, and Siltuximab (anti-IL-6 antibodies) have been tested in prostate, lung, and multiple myeloma patients. However, clinical responses have been modest, indicating limited efficacy as monotherapies.
- Potential Use: IL-6 blockade may enhance immunotherapy responses by reducing tumor-induced immune suppression [65–67].

6.2.3. TNF-α Inhibitors

TNF-α promotes cancer cell survival, angiogenesis, and immune evasion.

- Infliximab (anti-TNF-α) and Etanercept (TNF receptor blocker) have been tested in advanced cancer patients but showed limited efficacy.
- However, TNF blockade is beneficial in managing immune-related adverse events (irAEs) from immunotherapy, particularly colitis induced by checkpoint inhibitors [65–67].

6.2.4. TGF-β Inhibitors

TGF-β suppresses early-stage tumors but later promotes immune evasion and metastasis.

- Galunisertib (TGF-βR1 kinase inhibitor) showed potential in combination with gemcitabine for pancreatic cancer and sorafenib for hepatocellular carcinoma (HCC).
- Other bi-functional antibodies (anti-PD-L1-TGFβR2 inhibitors) are in early clinical trials [65–67].

6.3. Combination Therapies: Anti-Inflammatory Drugs with Immunotherapy

Targeting Tumor-Associated Macrophages (TAMs) and Myeloid-Derived Suppressor Cells (MDSCs)

6.3.1. Inflammation-Associated Myeloid Cells Contribute to Immune Suppression and Therapy Resistance

- CSF1R Inhibitors: Depleting TAMs through CSF1R blockade improves responses to checkpoint inhibitors.
- CCR2 and CCR5 Antagonists: Inhibiting these chemokine receptors enhances the efficacy of PD-1 inhibitors in pancreatic and colorectal cancer models.
- CXCR1/2 Inhibitors (SX-682, BL-8040): These agents reduce MDSC infiltration and are tested in melanoma and pancreatic cancer with immune checkpoint inhibitors (ICIs).

6.3.2. Modulating Tumor Microenvironment (TME) for Enhanced Immunotherapy

Inflammatory mediators in the TME often lead to checkpoint inhibitor resistance.

- NSAIDs with Checkpoint Inhibitors: Aspirin or Celecoxib enhances anti-PD-1 responses by reversing immune suppression via PGE2 blockade.
- IL-1β Inhibitors with ICIs: Blocking IL-1β reduces myeloid cell-mediated immune suppression, improving anti-PD-1 efficacy.
- TGF-β Inhibitors with ICIs: TGF-β blockade remodels the TME, making tumors more susceptible to immune attack [68].

6.4. Metabolic and Lifestyle-Associated Anti-Inflammatory Strategies

6.4.1. Statins (Lipid-Lowering Drugs)

Statins have anti-inflammatory effects beyond cholesterol reduction.

- Studies suggest that statins lower colorectal and hepatocellular cancer risks, particularly in patients with viral hepatitis or diabetes.
- However, statins may induce epithelial-mesenchymal transition (EMT), potentially promoting tumor progression in some cases [63,67].

6.4.2. Metformin (Diabetes Drug with Anti-Inflammatory Effects)

Metformin improves insulin sensitivity and suppresses tumor growth via AMPK activation.

- It reduces IL-6 and TNF-α production, suppressing cancer-associated inflammation.
- Clinical Trials: Ongoing trials are testing metformin in combination with aspirin for colorectal cancer prevention [63,67].

6.4.3. Vitamin D and Omega-3 Fatty Acids

- Vitamin D has immune-modulatory and anti-inflammatory properties but has not consistently shown cancer-preventive benefits in clinical trials.
- Omega-3 fatty acids may reduce colorectal adenoma recurrence, but their role in cancer prevention remains unclear [63,67].

7. Harnessing T-Cell Immunotherapy in Inflammation-Driven Cancers: The Role of CAR-T Cell Therapy

T-cell-mediated therapeutic strategies, particularly chimeric antigen receptor (CAR)-T cell therapy, have gained significant attention in inflammation-driven cancers due to their potential to enhance antitumor immunity. Chronic inflammation plays a dual role in cancer, promoting tumor progression while also activating immune surveillance mechanisms. However, tumors often exploit inflammatory pathways to evade immune responses, recruiting immunosuppressive cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which dampen T-cell activity [69]. CAR-T cell therapy, which genetically engineers T cells to recognize tumor-specific antigens, has shown remarkable success in hematologic malignancies but faces challenges in solid tumors, where the inflammatory tumor microenvironment suppresses cytotoxic T-cell responses. However, the potential of combining CAR-T cell therapy with anti-inflammatory strategies, such as immune checkpoint inhibitors, cytokine modulation, or targeted inhibition of NF-κB and STAT3 pathways, to enhance T-cell infiltration and function within tumors is a promising avenue. This integrative approach could help counteract inflammation-mediated immune suppression, a significant step forward in the fight against cancer, making CAR-T therapy a promising avenue for treating inflammation-associated cancers [70,71].

8. Conclusions and Future Perspectives

Inflammation plays a dual role in cancer, acting as both a facilitator of tumor progression and a mechanism for immune-mediated tumor elimination. While inflammation-driven carcinogenesis has been well established, its intricate molecular interactions continue to be explored. Advances in targeting inflammatory pathways have paved the way for novel therapeutic approaches, such as combining immune checkpoint inhibitors with anti-inflammatory agents to enhance antitumor immunity. However, several challenges remain, including therapy resistance, off-target effects, and patient-specific responses. Future research should focus on precision medicine approaches, integrating genomic, proteomic, and immunological data to tailor inflammation-targeted therapies.

Additionally, investigating the role of gut microbiota, metabolic pathways, and systemic inflammation in cancer progression may provide new avenues for intervention. As our understanding of the inflammation-cancer nexus deepens, developing effective, personalized treatments will be crucial for improving patient outcomes and transforming cancer management.

Author Contributions

V.S., M.K. and R.P.: conducted the article search, interpreted the data, writing of text and drawing Figures 1–3, and editing. V.S., R.P. and A.S.: conceived the idea and proposed the scope. A.S.: writing, revision and editing, study design and direction. All authors have read and agreed to the published version of the manuscript.

Funding

Not Applicable.

Institutional Review Board Statement

Not Applicable.

Informed Consent Statement

Not Applicable.

Data Availability Statement

Not Applicable.

Acknowledgments

Elements of Figures 1–3 were created using BioRender.com.

Conflicts of Interest

The authors declare that they have no competing interests.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

References

1. Balkwill, F.; Mantovani, A. Inflammation and Cancer: Back to Virchow? *Lancet* **2001**, *357*, 539–545. https://doi.org/10.1016/S0140-6736(00)04046-0.
2. Dvorak, H.F. Tumors: Wounds That Do Not Heal. Similarities between Tumor Stroma Generation and Wound Healing. *N. Engl. J. Med.* **1986**, *315*, 1650–1659. https://doi.org/10.1056/NEJM198612253152606.
3. Coussens, L.M.; Werb, Z. Inflammation and Cancer. *Nature* **2002**, *420*, 860–867. https://doi.org/10.1038/nature01322.
4. Kuper, H.; Adami, H.O.; Trichopoulos, D. Infections as a Major Preventable Cause of Human Cancer. *J. Intern. Med.* **2000**, *248*, 171–183. https://doi.org/10.1046/j.1365-2796.2000.00742.x.
5. Shacter, E.; Weitzman, S.A. Chronic Inflammation and Cancer. *Oncology* **2002**, *16*, 217–226.
6. Ernst, P.B.; Gold, B.D. The Disease Spectrum of Helicobacter Pylori: The Immunopathogenesis of Gastroduodenal Ulcer and Gastric Cancer. *Annu. Rev. Microbiol.* **2000**, *54*, 615–640. https://doi.org/10.1146/annurev.micro.54.1.615.
7. Borsig, L.; Wong, R.; Hynes, R.O.; et al. Synergistic Effects of L- and P-Selectin in Facilitating Tumor Metastasis Can Involve Non-Mucin Ligands and Implicate Leukocytes as Enhancers of Metastasis. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 2193–2198. https://doi.org/10.1073/pnas.261704098.
8. Schwitalla, S.; Ziegler, P.K.; Horst, D.; et al. Loss of P53 in Enterocytes Generates an Inflammatory Microenvironment Enabling Invasion and Lymph Node Metastasis of Carcinogen-Induced Colorectal Tumors. *Cancer Cell* **2013**, *23*, 93–106. https://doi.org/10.1016/j.ccr.2012.11.014.
9. Komarova, E.A.; Krivokrysenko, V.; Wang, K.; et al. P53 Is a Suppressor of Inflammatory Response in Mice. *FASEB J.* **2005**, *19*, 1030–1032. https://doi.org/10.1096/fj.04-3213fje.
10. Pribluda, A.; Elyada, E.; Wiener, Z.; et al. A Senescence-Inflammatory Switch from Cancer-Inhibitory to Cancer-Promoting Mechanism. *Cancer Cell* **2013**, *24*, 242–256. https://doi.org/10.1016/j.ccr.2013.06.005.
11. Elyada, E.; Pribluda, A.; Goldstein, R.E.; et al. CKIα Ablation Highlights a Critical Role for P53 in Invasiveness Control. *Nature* **2011**, *470*, 409–413. https://doi.org/10.1038/nature09673.

12. Andriani, G.A.; Vijg, J.; Montagna, C. Mechanisms and Consequences of Aneuploidy and Chromosome Instability in the Aging Brain. *Mech. Ageing Dev.* **2017**, *161 Pt. A*, 19–36. https://doi.org/10.1016/j.mad.2016.03.007.
13. Liao, W.; Overman, M.J.; Boutin, A.T.; et al. KRAS-IRF2 Axis Drives Immune Suppression and Immune Therapy Resistance in Colorectal Cancer. *Cancer Cell* **2019**, *35*, 559–572.e7. https://doi.org/10.1016/j.ccell.2019.02.008.
14. Quadiri, A.; Prakash, S.; Dhanushkodi, N.R.; et al. Therapeutic Prime/Pull Vaccination of HSV-2-Infected Guinea Pigs with the Ribonucleotide Reductase 2 (RR2) Protein and CXCL11 Chemokine Boosts Antiviral Local Tissue-Resident and Effector Memory $CD4^+$ and $CD8^+$ T Cells and Protects against Recurrent Genital Herpes. *J. Virol.* **2024**, *98*, e01596-23. https://doi.org/10.1128/jvi.01596-23.
15. Kortlever, R.M.; Sodir, N.M.; Wilson, C.H.; et al. Myc Cooperates with Ras by Programming Inflammation and Immune Suppression. *Cell* **2017**, *171*, 1301–1315.e14. https://doi.org/10.1016/j.cell.2017.11.013.
16. Si, Y.; Zhang, Y.; Chen, Z.; et al. Posttranslational Modification Control of Inflammatory Signaling. *Adv. Exp. Med. Biol.* **2017**, *1024*, 37–61. https://doi.org/10.1007/978-981-10-5987-2_2.
17. Fekete, T.; Bencze, D.; Szabo, A.; et al. Regulatory NLRs Control the RLR-Mediated Type I Interferon and Inflammatory Responses in Human Dendritic Cells. *Front. Immunol.* **2018**, *9*, 2314. https://doi.org/10.3389/fimmu.2018.02314.
18. Dolasia, K.; Bisht, M.K.; Pradhan, G.; et al. TLRs/NLRs: Shaping the Landscape of Host Immunity. *Int. Rev. Immunol.* **2018**, *37*, 3–19. https://doi.org/10.1080/08830185.2017.1397656.
19. Istomin, A.Y.; Godzik, A. Understanding Diversity of Human Innate Immunity Receptors: Analysis of Surface Features of Leucine-Rich Repeat Domains in NLRs and TLRs. *BMC Immunol.* **2009**, *10*, 48. https://doi.org/10.1186/1471-2172-10-48.
20. Wieland, C.W.; Florquin, S.; Maris, N.A.; et al. The MyD88-Dependent, but Not the MyD88-Independent, Pathway of TLR4 Signaling Is Important in Clearing Nontypeable Haemophilus Influenzae from the Mouse Lung. *J. Immunol.* **2005**, *175*, 6042–6049. https://doi.org/10.4049/jimmunol.175.9.6042.
21. Broad, A.; Kirby, J.A.; Jones, D.E.J.; et al. Toll-like Receptor Interactions: Tolerance of MyD88-Dependent Cytokines but Enhancement of MyD88-Independent Interferon-Beta Production. *Immunology* **2007**, *120*, 103–111. https://doi.org/10.1111/j.1365-2567.2006.02485.x.
22. Triantafilou, M.; Gamper, F.G.J.; Haston, R.M.; et al. Membrane Sorting of Toll-like Receptor (TLR)-2/6 and TLR2/1 Heterodimers at the Cell Surface Determines Heterotypic Associations with CD36 and Intracellular Targeting. *J. Biol. Chem.* **2006**, *281*, 31002–31011. https://doi.org/10.1074/jbc.M602794200.
23. Karnati, H.K.; Pasupuleti, S.R.; Kandi, R.; et al. TLR-4 Signalling Pathway: MyD88 Independent Pathway up-Regulation in Chicken Breeds upon LPS Treatment. *Vet. Res. Commun.* **2015**, *39*, 73–78. https://doi.org/10.1007/s11259-014-9621-2.
24. Chamaillard, M.; Girardin, S.E.; Viala, J.; et al. Nods, Nalps and Naip: Intracellular Regulators of Bacterial-Induced Inflammation. *Cell. Microbiol.* **2003**, *5*, 581–592. https://doi.org/10.1046/j.1462-5822.2003.00304.x.
25. Inohara, N.; Nuñez, G. NODs: Intracellular Proteins Involved in Inflammation and Apoptosis. *Nat. Rev. Immunol.* **2003**, *3*, 371–382. https://doi.org/10.1038/nri1086.
26. Ting, J.P.-Y.; Lovering, R.C.; Alnemri, E.S.; et al. The NLR Gene Family: A Standard Nomenclature. *Immunity* **2008**, *28*, 285–287. https://doi.org/10.1016/j.immuni.2008.02.005.
27. Wagner, R.N.; Proell, M.; Kufer, T.A.; et al. Evaluation of Nod-like Receptor (NLR) Effector Domain Interactions. *PLoS ONE* **2009**, *4*, e4931. https://doi.org/10.1371/journal.pone.0004931.
28. Zhou, R.; Tardivel, A.; Thorens, B.; et al. Thioredoxin-Interacting Protein Links Oxidative Stress to Inflammasome Activation. *Nat. Immunol.* **2010**, *11*, 136–140. https://doi.org/10.1038/ni.1831.
29. Davis, B.K.; Wen, H.; Ting, J.P.-Y. The inflammasome NLRs in immunity, inflammation, and associated diseases. *Annu. Rev. Immunol.* **2011**, *29*, 707–735.
30. Man, S.M.; Karki, R.; Kanneganti, T.-D. Molecular Mechanisms and Functions of Pyroptosis, Inflammatory Caspases and Inflammasomes in Infectious Diseases. *Immunol. Rev.* **2017**, *277*, 61–75. https://doi.org/10.1111/imr.12534.
31. Schroder, K.; Tschopp, J. The Inflammasomes. *Cell* **2010**, *140*, 821–832. https://doi.org/10.1016/j.cell.2010.01.040.
32. Hu, B.; Elinav, E.; Huber, S.; et al. Inflammation-Induced Tumorigenesis in the Colon Is Regulated by Caspase-1 and NLRC4. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 21635–21640. https://doi.org/10.1073/pnas.1016814108.
33. Xu, B.; Jiang, M.; Chu, Y.; et al. Gasdermin D Plays a Key Role as a Pyroptosis Executor of Non-Alcoholic Steatohepatitis in Humans and Mice. *J. Hepatol.* **2018**, *68*, 773–782. https://doi.org/10.1016/j.jhep.2017.11.040.
34. Xiao, J.; Wang, C.; Yao, J.-C.; et al. Gasdermin D Mediates the Pathogenesis of Neonatal-Onset Multisystem Inflammatory Disease in Mice. *PLoS Biol.* **2018**, *16*, e3000047. https://doi.org/10.1371/journal.pbio.3000047.
35. Kanneganti, A.; Malireddi, R.K.S.; Saavedra, P.H. V.; et al. GSDMD Is Critical for Autoinflammatory Pathology in a Mouse Model of Familial Mediterranean Fever. *J. Exp. Med.* **2018**, *215*, 1519–1529. https://doi.org/10.1084/jem.20172060.
36. Feng, S.; Fox, D.; Man, S.M. Mechanisms of Gasdermin Family Members in Inflammasome Signaling and Cell Death. *J. Mol. Biol.* **2018**, *430*, 3068–3080. https://doi.org/10.1016/j.jmb.2018.07.002.

37. Xue, Y.; Enosi Tuipulotu, D.; Tan, W.H.; et al. Emerging Activators and Regulators of Inflammasomes and Pyroptosis. *Trends Immunol.* **2019**, *40*, 1035–1052. https://doi.org/10.1016/j.it.2019.09.005.
38. Pikarsky, E.; Porat, R.M.; Stein, I.; et al. NF-KappaB Functions as a Tumour Promoter in Inflammation-Associated Cancer. *Nature* **2004**, *431*, 461–466. https://doi.org/10.1038/nature02924.
39. Chen, L.; Huang, C.-F.; Li, Y.-C.; et al. Blockage of the NLRP3 Inflammasome by MCC950 Improves Anti-Tumor Immune Responses in Head and Neck Squamous Cell Carcinoma. *Cell. Mol. Life Sci.* **2018**, *75*, 2045–2058. https://doi.org/10.1007/s00018-017-2720-9.
40. Feng, X.; Luo, Q.; Zhang, H.; et al. The Role of NLRP3 Inflammasome in 5-Fluorouracil Resistance of Oral Squamous Cell Carcinoma. *J. Exp. Clin. Cancer Res.* **2017**, *36*, 81. https://doi.org/10.1186/s13046-017-0553-x.
41. McAllister, S.S.; Weinberg, R.A. The Tumour-Induced Systemic Environment as a Critical Regulator of Cancer Progression and Metastasis. *Nat. Cell Biol.* **2014**, *16*, 717–727. https://doi.org/10.1038/ncb3015.
42. Lega, I.C.; Lipscombe, L.L. Review: Diabetes, Obesity, and Cancer-Pathophysiology and Clinical Implications. *Endocr. Rev.* **2020**, *41*, 33–52. https://doi.org/10.1210/endrev/bnz014.
43. Greten, F.R.; Grivennikov, S.I. Inflammation and Cancer: Triggers, Mechanisms, and Consequences. *Immunity* **2019**, *51*, 27–41. https://doi.org/10.1016/j.immuni.2019.06.025.
44. Wildes, T.J.; DiVita Dean, B.; Flores, C.T. Myelopoiesis during Solid Cancers and Strategies for Immunotherapy. *Cells* **2021**, *10*, 968. https://doi.org/10.3390/cells10050968.
45. Zhou, J.; Tang, Z.; Gao, S.; et al. Tumor-Associated Macrophages: Recent Insights and Therapies. *Front. Oncol.* **2020**, *10*, 188. https://doi.org/10.3389/fonc.2020.00188.
46. Ng, M.S.F.; Kwok, I.; Tan, L.; et al. Deterministic Reprogramming of Neutrophils within Tumors. *Science* **2024**, *383*, eadf6493. https://doi.org/10.1126/science.adf6493.
47. Fridman, W.H.; Zitvogel, L.; Sautès-Fridman, C.; et al. The Immune Contexture in Cancer Prognosis and Treatment. *Nat. Rev. Clin. Oncol.* **2017**, *14*, 717–734. https://doi.org/10.1038/nrclinonc.2017.101.
48. Singh, V.; Singh, R.; Kushwaha, R.; et al. The Molecular Role of HIF1α Is Elucidated in Chronic Myeloid Leukemia. *Front. Oncol.* **2022**, *12*, 912942. https://doi.org/10.3389/fonc.2022.912942.
49. Kashif, M.; Quadiri, A.; Singh, A.P. Essential Role of a Plasmodium Berghei Heat Shock Protein (PBANKA_0938300) in Gametocyte Development. *Sci. Rep.* **2021**, *11*, 23640. https://doi.org/10.1038/s41598-021-03059-4.
50. Veglia, F.; Sanseviero, E.; Gabrilovich, D.I. Myeloid-Derived Suppressor Cells in the Era of Increasing Myeloid Cell Diversity. *Nat. Rev. Immunol.* **2021**, *21*, 485–498. https://doi.org/10.1038/s41577-020-00490-y.
51. Aliazis, K.; Yenyuwadee, S.; Phikulsod, P.; et al. Emergency Myelopoiesis in Solid Cancers. *Br. J. Haematol.* **2024**, *205*, 798–811. https://doi.org/10.1111/bjh.19656.
52. Bui, T.M.; Yalom, L.K.; Ning, E.; et al. Tissue-Specific Reprogramming Leads to Angiogenic Neutrophil Specialization and Tumor Vascularization in Colorectal Cancer. *J. Clin. Investig.* **2024**, *134*. https://doi.org/10.1172/JCI174545.
53. Singh, V.; Singh, R.; Mahdi, A.A.; et al. The Bioengineered HALOA Complex Induces Anoikis in Chronic Myeloid Leukemia Cells by Targeting the BCR-ABL/Notch/Ikaros/Redox/Inflammation Axis. *J. Med. Life* **2022**, *15*, 606–616. https://doi.org/10.25122/jml-2021-0230.
54. LaMarche, N.M.; Hegde, S.; Park, M.D.; et al. An IL-4 Signalling Axis in Bone Marrow Drives pro-Tumorigenic Myelopoiesis. *Nature* **2024**, *625*, 166–174. https://doi.org/10.1038/s41586-023-06797-9.
55. Zilio, S.; Bicciato, S.; Weed, D.; et al. CCR1 and CCR5 Mediate Cancer-Induced Myelopoiesis and Differentiation of Myeloid Cells in the Tumor. *J. Immunother. Cancer* **2022**, *10*. https://doi.org/10.1136/jitc-2021-003131.
56. Dunn, G.P.; Bruce, A.T.; Ikeda, H.; et al. Cancer Immunoediting: From Immunosurveillance to Tumor Escape. *Nat. Immunol.* **2002**, *3*, 991–998. https://doi.org/10.1038/ni1102-991.
57. Shankaran, V.; Ikeda, H.; Bruce, A.T.; et al. IFNgamma and Lymphocytes Prevent Primary Tumour Development and Shape Tumour Immunogenicity. *Nature* **2001**, *410*, 1107–1111. https://doi.org/10.1038/35074122.
58. Kaplan, D.H.; Shankaran, V.; Dighe, A.S.; et al. Demonstration of an Interferon Gamma-Dependent Tumor Surveillance System in Immunocompetent Mice. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 7556–7561. https://doi.org/10.1073/pnas.95.13.7556.
59. Koebel, C.M.; Vermi, W.; Swann, J.B.; et al. Adaptive Immunity Maintains Occult Cancer in an Equilibrium State. *Nature* **2007**, *450*, 903–907. https://doi.org/10.1038/nature06309.
60. Swann, J.B.; Vesely, M.D.; Silva, A.; et al. Demonstration of Inflammation-Induced Cancer and Cancer Immunoediting during Primary Tumorigenesis. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 652–656. https://doi.org/10.1073/pnas.0708594105.
61. Grivennikov, S.I.; Greten, F.R.; Karin, M. Immunity, Inflammation, and Cancer. *Cell* **2010**, *140*, 883–899. https://doi.org/10.1016/j.cell.2010.01.025.
62. Smyth, M.J.; Thia, K.Y.; Street, S.E.; et al. Differential Tumor Surveillance by Natural Killer (NK) and NKT Cells. *J. Exp. Med.* **2000**, *191*, 661–668. https://doi.org/10.1084/jem.191.4.661.

63. Ben-Baruch, A. Inflammation-Associated Immune Suppression in Cancer: The Roles Played by Cytokines, Chemokines and Additional Mediators. *Semin. Cancer Biol.* **2006**, *16*, 38–52. https://doi.org/10.1016/j.semcancer.2005.07.006.
64. Ghiringhelli, F.; Apetoh, L.; Tesniere, A.; et al. Activation of the NLRP3 Inflammasome in Dendritic Cells Induces IL-1beta-Dependent Adaptive Immunity against Tumors. *Nat. Med.* **2009**, *15*, 1170–1178. https://doi.org/10.1038/nm.2028.
65. Bosetti, C.; Santucci, C.; Gallus, S.; et al. Aspirin and the Risk of Colorectal and Other Digestive Tract Cancers: An Updated Meta-Analysis through 2019. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **2020**, *31*, 558–568. https://doi.org/10.1016/j.annonc.2020.02.012.
66. Diakos, C.I.; Charles, K.A.; McMillan, D.C.; et al. Cancer-Related Inflammation and Treatment Effectiveness. *Lancet Oncol.* **2014**, *15*, e493–e503. https://doi.org/10.1016/S1470-2045(14)70263-3.
67. Yang, J.D.; Hainaut, P.; Gores, G.J.; et al. A Global View of Hepatocellular Carcinoma: Trends, Risk, Prevention and Management. *Nat. Rev. Gastroenterol. Hepatol.* **2019**, *16*, 589–604. https://doi.org/10.1038/s41575-019-0186-y.
68. Germano, G.; Lamba, S.; Rospo, G.; et al. Inactivation of DNA Repair Triggers Neoantigen Generation and Impairs Tumour Growth. *Nature* **2017**, *552*, 116–120. https://doi.org/10.1038/nature24673.
69. Zhou, X.; Tu, S.; Wang, C.; et al. Phase I trial of fourth-generation anti-CD19 chimeric antigen receptor T cells against relapsed or refractory B cell non-Hodgkin lymphomas. *Front. Immunol.* **2020**, *11*, 564099.
70. Pitt, J.M.; Vétizou, M.; Daillère, R.; et al. Resistance mechanisms to immune-checkpoint blockade in cancer: tumor-intrinsic and-extrinsic factors. *Immunity* **2016**, *44*, 1255–1269.
71. June, C.H.; O'Connor, R.S.; Kawalekar, O.U.; et al. CAR T cell immunotherapy for human cancer. *Science* **2018**, *359*, 1361–1365.