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*Review Article*

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# Integrative Onco-Inflammatory Signaling Networks: A Comprehensive Review on the Role of Chronic Inflammation in Cancer Progression and Therapeutic Resistance

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**ABSTRACT**

Chronic inflammation has emerged as a crucial component in cancer biology, influencing various aspects of tumor progression, immune evasion, and resistance to therapeutic interventions. This review explores the molecular underpinnings of inflammation-driven oncogenesis, with a focus on key inflammatory pathways such as NF-κB, STAT3, and inflammasomes. These pathways not only regulate tumor cell survival and proliferation but also alter the tumor microenvironment (TME), enhancing cancer cell adaptability to treatments. Furthermore, the review discusses how these inflammatory processes contribute to resistance mechanisms in conventional, targeted, and immunotherapies, while highlighting emerging strategies for integrating inflammation-targeting therapies into precision oncology.

## Introduction

Cancer has traditionally been viewed through the lens of genetic mutations and tumor cell-autonomous mechanisms. However, increasing evidence has underscored the significant role of inflammation in cancer progression and response to treatment [1]. Chronic inflammation, characterized by sustained cytokine signaling and immune cell infiltration, creates a tumor-promoting environment, supporting malignant transformation, angiogenesis, and immune evasion [2]. Tumors exploit this inflammatory milieu to establish a pro-survival niche that enhances tumor cell proliferation while simultaneously thwarting immune surveillance [3].

In this review, we focus on the intersection between inflammatory signaling and cancer progression, particularly in the context of therapeutic resistance. We explore the molecular pathways that link inflammation with oncogenesis, provide insights into the mechanisms behind therapeutic failure, and discuss future directions in the development of therapies targeting the onco-inflammatory network.

## Molecular Mechanisms of Inflammation in Cancer

### NF-κB Pathway and Tumor Progression

The NF-κB signaling pathway plays a pivotal role in regulating the inflammatory response and is frequently upregulated in various cancers. It governs key processes such as cell survival, immune modulation, and angiogenesis, all of which are essential for tumor growth NF-κB activation in the TME promotes the secretion of pro-inflammatory cytokines like TNF-α and IL-1β, which, in turn, activate signaling cascades that foster tumorigenesis.

NF-κB also contributes to the recruitment and polarization of immune cells within the TME, particularly the induction of tumor-associated macrophages (TAMs) that have an immunosuppressive phenotype [4]. This immune landscape, characterized by the dominance of M2 macrophages and regulatory T cells (Tregs), hinders effective anti-tumor immune responses. Additionally, sustained NF-κB activation has been associated with resistance to chemotherapy and targeted therapies. For example, in breast cancer, NF-κB activation promotes resistance to chemotherapeutic agents such as doxorubicin.

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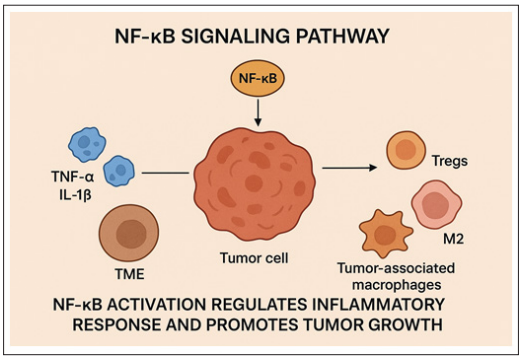
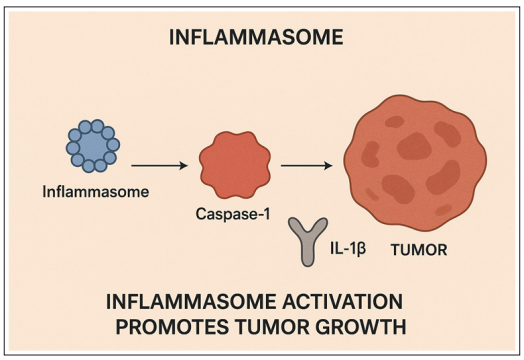
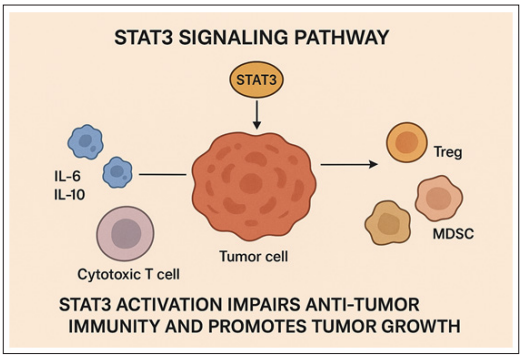



**STAT3 as a Key Regulator in Cancer**

STAT3 is another central mediator of inflammatory responses in cancer. Upon activation by cytokines such as IL-6 and IL-10, STAT3 translocates to the nucleus, driving the expression of genes that promote cell survival, proliferation, and immune evasion. In cancers like colorectal, liver, and breast, constitutive STAT3 activation is a hallmark feature that contributes to both tumorigenesis and therapeutic resistance.

STAT3 has been shown to impair anti-tumor immunity by promoting the differentiation of Tregs and MDSCs while suppressing the function of cytotoxic T cells. In addition to its role in immune modulation, STAT3 also facilitates resistance to targeted therapies such as EGFR inhibitors. In non-small cell lung cancer (NSCLC), IL-6-driven STAT3 activation contributes to resistance to EGFR-targeted therapies, indicating that STAT3 inhibitors may be a valuable adjunct in overcoming resistance.




**Inflammasomes and Pyroptosis in Cancer**

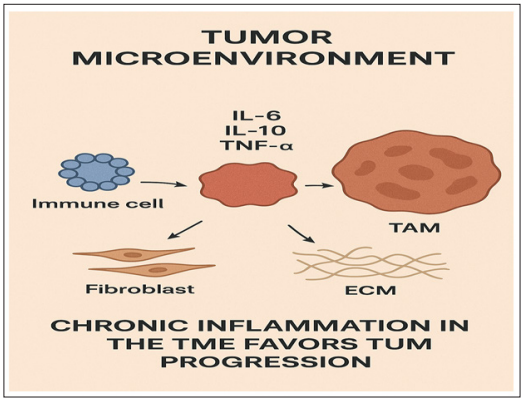
Inflammasomes are multi-protein complexes that mediate the activation of caspase-1 and the secretion of pro-inflammatory cytokines like IL-1β [5]. The NLRP3 inflammasome, in particular, has gained attention for its dual role in both promoting and suppressing tumorigenesis. While inflammasome activation can drive immune responses that limit tumor growth, chronic activation of NLRP3 and the subsequent release of IL-1β can foster tumor progression by promoting angiogenesis, tissue remodeling, and immune evasion.

Interestingly, inflammasome-mediated pyroptosis, a form of cell death associated with inflammation, can also affect tumor cell survival. In early tumorigenesis, inflammasome activation may serve as a tumor-suppressive mechanism by inducing inflammatory cell death [6]. However, sustained inflammasome activation can enhance cancer cell survival by creating a pro-inflammatory environment that supports tumor growth.

Tumor Microenvironment (TME) and Inflammation

The TME consists of various cellular and non-cellular components, including tumor cells, immune cells, fibroblasts, and extracellular matrix components. Chronic inflammation in the TME plays a critical role in remodeling this environment to favor tumor progression. Inflammatory cytokines such as IL-6, IL-10, and TNF-α contribute to the recruitment of immune cells, including TAMs and MDSCs, which suppress anti-tumor immunity and promote immune tolerance.

The recruitment of M2-like TAMs is particularly detrimental, as these macrophages secrete pro-tumorigenic factors that support angiogenesis and metastasis. Additionally, inflammatory cytokines can induce epithelial-to-mesenchymal transition (EMT), a process that enhances the migratory and invasive properties of tumor cells, further contributing to metastasis [7]. This inflammatory network within the TME significantly complicates the treatment of cancer, as it not only fosters tumor survival but also creates barriers to effective immune responses.




**Inflammation and Therapeutic Resistance**

Inflammation is a critical driver of therapeutic resistance in cancer. In chemotherapy, the pro-inflammatory cytokines IL-6 and TNF-α can enhance tumor cell survival and promote the development of chemoresistance. Additionally, inflammation-induced signaling, such as the activation of NF-κB and STAT3, has been linked to resistance against targeted therapies, including EGFR inhibitors in NSCLC and HER2-targeted therapies in breast cancer.

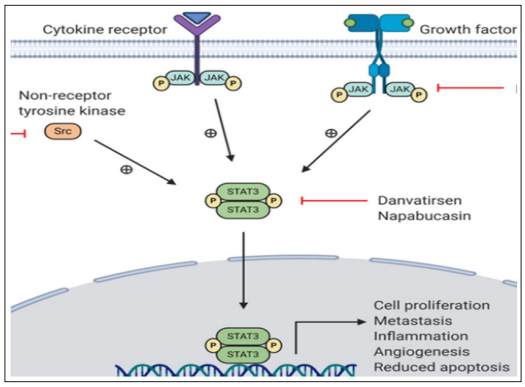
In immunotherapy, the TME's inflammatory milieu also contributes to resistance. Chronic inflammation in tumors can upregulate immune checkpoint molecules like PD-L1, thereby dampening the efficacy of immune checkpoint inhibitors [7]. Furthermore, inflammatory cytokines can promote the differentiation of immunosuppressive Tregs and MDSCs,

limiting the effectiveness of T-cell-mediated anti-tumor responses.

### Targeting Inflammation in Precision Medicine

In light of the growing recognition of inflammation's role in cancer progression and therapy resistance, there has been an increased focus on developing targeted therapies that modulate the onco-inflammatory network. Several promising approaches include:

- **JAK/STAT Inhibitors:** Agents like ruxolitinib, which inhibit the IL-6/STAT3 signaling axis, are being tested in clinical trials for their ability to reduce inflammation-driven tumor progression and overcome resistance to immunotherapies.
- **Inflammasome Inhibition:** NLRP3 inhibitors, such as MCC950, have demonstrated potential in preclinical models of cancer by blocking inflammasome-driven tumor progression.
- **Combination Therapies:** Combining immune checkpoint inhibitors with anti-inflammatory agents or JAK inhibitors is an emerging strategy to enhance anti-tumor immunity and overcome resistance.
- **Microbiome Modulation:** Manipulating the gut microbiota to alter systemic inflammation holds promise in enhancing responses to immunotherapy [9].




The JAK/STAT3 and Src signaling pathways play central roles in pancreatic cancer progression and therapeutic resistance. Current clinical trials are investigating agents such as **ruxolitinib** (JAK inhibitor), **danvatirsen** and **napabucasin** (STAT3 inhibitors), and dasatinib (Src inhibitor) for their ability to block STAT3 activation and disrupt tumor-promoting inflammation. Emerging strategies also focus on combining these inhibitors with immunotherapies or chemotherapy to enhance anti-tumor responses and overcome resistance mechanisms.

These approaches underscore the potential of integrating inflammation-modulating therapies into the personalized cancer treatment landscape, offering new avenues for overcoming therapeutic resistance [10,11].

### Conclusion

Chronic inflammation is a critical factor in cancer progression and therapeutic resistance. The molecular interplay between inflammatory pathways and tumor cells contributes to tumor survival, immune evasion, and metastasis. By targeting the onco-inflammatory axis, new therapeutic strategies hold promise for improving treatment outcomes, particularly in the context of precision oncology. However, more research is needed to fully understand the complex role of inflammation in cancer and develop effective, personalized treatments that can overcome both primary and acquired resistance.

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