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Chronic Inflammation: A Silent Trigger for Cancer

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ABSTRACT

Chronic inflammation is a central driver of cancer, influencing initiation, progression, metastasis, and response to therapy. Both intrinsic factors, including genomic instability and epithelial-to-mesenchymal transition (EMT), and extrinsic factors, such as infections, environmental exposures, and autoimmune disorders, disrupt tissue homeostasis and sustain inflammatory states. Inflammatory mediators, reactive oxygen species (ROS), and persistent activation of signaling pathways, such as Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and signal transducer and activator of transcription 3 (STAT3), promote tumor cell proliferation, survival, immune evasion, and therapy resistance. The tumor microenvironment, shaped by immune and stromal cells, amplifies these effects, while EMT contributes to metastatic potential and immunosuppression. Conventional cancer treatments - including chemotherapy, radiotherapy, and immunotherapy - can paradoxically enhance inflammation, further promoting tumor survival and resistance. A deeper understanding of the EMT-inflammation axis and its interaction with the immune system may reveal novel anti-inflammatory therapeutic strategies to prevent tumor progression and improve treatment outcomes.
Keywords: Chronic inflammation; epithelial-to-mesenchymal transition (EMT); immunosenescence; tumor microenvironment (TME).

INTRODUCTION

The concept that inflammation promotes cell proliferation dates back to 1863, when German physician Rudolf Virchow described leukocyte infiltration within tumors and proposed the possible relationship between inflammation and tumor development.[1] Recent findings clearly demonstrate that chronic inflammatory processes, as a fundamental innate immune response to perturbed tissue homeostasis, play a central role in tumorigenesis.[2,3] Cancer development requires intrinsic and extrinsic factors such as genomic instability, abnormalities in proliferation and senescence, reprogramming energy metabolism, evasion of immune destruction, and epithelial-mesenchymal transition (EMT). Only 5–10% of cancer cases are driven by germline mutations. In contrast, the rest of cancers are caused by acquired factors such as chronic infections, dietary factors, obesity, inhalation of pollutants, smoking, and autoimmune-related factors.[4] All these carcinogenic factors have standard features of disrupting tissue homeostasis and producing a continuous protective response – chronic inflammation.

Tissue damage and the consequent chronic inflammation caused by certain types of irritants enhance cell proliferation, which might potentiate neoplastic risk when orchestrated with other risk factors of cancer.[5] In addition, various pro-inflammatory mediators from immune cells or cancer cells can promote cancer development and drug resistance.[6] A chronic inflammatory state ensues if the acute inflammatory response fails to eliminate the pathogen.[7] Beyond persistent exposure to noxious stimuli such as pathogens, chronic inflammation may also arise from alternative sources of tissue injury, including autoimmune reactions and non-degradable foreign materials.[8] Increasing evidence shows that chronic inflammation can influence all aspects of cancer development along with the response to therapy.[9]

Chronic inflammation can impact each phase of cancer progression — from initiation and promotion to malignant transformation, invasion, and metastasis. The presence of an inflammatory microenvironment is now considered a defining feature of nearly all cancers, even those not directly linked to chronic inflammatory conditions.[2,3,10] Inflammation exerts a dual role in cancer biology. On one hand, it promotes tumor progression by generating a microenvironment enriched with cytokines and growth factors that support cancer cell survival and proliferation.[11-13] Many cells begin producing chemokines during transformation. As a result, they can use chemokines to help migrate to and survive at locations distant from the original tumor.[14-16] Medzhitov[8] demonstrated that inflammatory stimuli, such as Interleukin-6 (IL-6) and IL-1β, activate the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and signal transducer and activator of transcription 3 (STAT3) pathways, leading to dysregulated expression of oncogenic genes and enhanced cancer cell survival and proliferation.[17] On the other hand, inflammation can initiate antitumor immune responses — an effect leveraged in cancer immunotherapy.[11]

REVIEW

Inflammation and immunity: dual players in cancer progression

The link between Inflammation and cancer has long fascinated researchers, tracing back to Rudolf Virchow's 19th-century observation of leukocyte infiltration in tumor tissues.[18] Contemporary evidence firmly establishes Inflammation as a central driver of tumorigenesis, exerting influence across all stages of cancer progression, including initiation, promotion,

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malignant transformation, invasion, and metastatic dissemination.[2,3,19,20]

The role of the immune system in cancer remains complex and not fully understood, as it mediates both antitumor responses and immune evasion.[21] Notably, antitumor immunity differs between younger and older patients, although the mechanisms underlying these age-related differences remain unclear.[22]

The immune system undergoes progressive modifications throughout the human lifespan, beginning with the ontogeny of innate and adaptive immune responses during infancy and childhood. Peak immunocompetence is typically achieved in adolescence and early adulthood, followed by a gradual onset of immunosenescence in later life.[23]

Immunosenescence is a multifaceted, progressive process involving structural remodeling of immune organs and extensive regulatory changes at the cellular and molecular levels.[24] These alterations culminate in reduced immune competence, resulting in diminished pathogen clearance and suboptimal vaccine responsiveness in older adults.

A defining feature of immunosenescence is inflammaging—a persistent, low-grade systemic inflammatory state characterized by elevated circulating pro-inflammatory mediators and recognized as a fundamental driver of the aging process.[20,24]

With advancing age, the immune system undergoes metabolic reprogramming, characterized by increased glycolysis, progressive mitochondrial dysfunction, and excessive production of reactive oxygen species (ROS).[25,26] These metabolic alterations, integral to immunosenescence, contribute to chronic Inflammation and impaired immune regulation. Consequently, they are strongly associated with increased morbidity and mortality from age-related diseases, including cardiovascular disorders, neurodegenerative diseases, autoimmune disorders, metabolic syndromes, and various cancers.[27,28]

Chronic Inflammation, driven by persistent immune cell activation and dysregulated molecular signaling networks, has been recognized as a critical predisposing factor for tumorigenesis. Epidemiological analyses indicate that approximately one-quarter of human cancers arise in the context of chronic inflammatory disorders; however, the mechanistic underpinnings of this association remain incompletely elucidated, involving complex interactions between cytokine signaling, genomic instability, and the tumor microenvironment.[29]

Inflammatory microenvironment as a driver of tumorigenesis

An inflammatory tumor microenvironment (TME) is strongly linked to increased cancer incidence.[30] The accumulation of senescent suppressive cells within the TME enhances the secretion of inhibitory cytokines, thereby promoting cancer growth and progression.[31,32]

Greten and Grivennikov (2019)[33] reported that inflammation-rich environments containing cytokines and DNA damage promote mutational accumulation in epithelial cells, leading to uncontrolled proliferation and tumor initiation. Over the past decade, research on differentiated thyroid cancers (DTCs) has consistently demonstrated a strong association between chronic Inflammation and elevated DTC risk. Chronic inflammatory states appear to drive cellular transformation, tumor initiation, and progression.[34-37]

Chronic Inflammation caused by infections, environmental insults, or autoimmune diseases contributes to tumorigenesis by shaping a microenvironment enriched with cytokines, chemokines, growth factors, and reactive oxygen/nitrogen species. This milieu induces genomic instability, DNA damage, and excessive proliferation while persistently activating NF-κB, STAT3, and cyclooxygenase-2 (COX-2) pathways. These pathways promote oncogene expression, suppress tumor suppressor functions, and enhance angiogenesis.[38-43] ROS not only damage DNA but also drive epithelial–mesenchymal transition (EMT), thereby facilitating tumor invasion and metastasis.[44]

The immune infiltrate in tumors arises from both resident and bone marrow–derived cells. Resident cells include endothelial cells, cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), and dendritic cells, while bone marrow recruits neutrophils, macrophages, and immunosuppressive myeloid-derived suppressor cells (MDSCs).[45] Chronic Inflammation–driven immunosuppression is carried primarily by regulatory dendritic cells (DCregs), regulatory T cells (Tregs), and effector T-cell exhaustion mediated by immune checkpoints.[46,47]

During tumorigenesis, cancer cells, innate immune cells (such as dendritic cells and TAMs), and activated stromal cells (such as CAFs and endothelial cells) release a wide range of cytokines and chemokines in response to tumor-derived danger signals. These mediators recruit additional bone marrow–derived immune cells, fueling a so-called “cytokine storm.”[48]

Inflammatory mediators further modulate epigenetic programs regulating gene expression. For example, TNF-α induces ROS generation in epithelial cells, while cytokines such as IL-6 and IL-23 activate NF-κB and STAT3. Persistent activation of these transcription factors supports cell survival, proliferation, angiogenesis, and immune evasion, ultimately fostering tumor initiation and progression.[33,49,50]

One of the most important biological features contributing to cancer metastasis is EMT. EMT loosens cell–cell adhesion complexes and enhances migratory ability. Cancer cells undergoing EMT exhibit stem-like properties and resistance to apoptosis.[45]

Preclinical evidence demonstrates a strong link between EMT and immune suppression. In murine non-small-cell lung cancer (NSCLC), tumor cells undergoing EMT upregulate programmed death-ligand 1 (PD-L1) via ZEB1, suppressing T-cell function and enhancing metastasis.[46] Similarly, human breast cancer cells undergoing EMT express PD-L1 in a ZEB1–microRNA-200–dependent manner.[51] Extensive literature

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highlights the involvement of the EMT-inflammation axis in early tumor formation, metastatic progression, poor prognosis,[52-54] and therapy resistance. In lung cancer, erlotinib-induced IL-8 production triggers EMT and resistance via p38 MAPK activation, while IL-8 neutralization restores epithelial features and drug sensitivity.[55] De Cock et al[56] showed that Inflammation enhances metastatic outgrowth in breast cancer, and Rao et al[57] demonstrated that mast cells promote EMT-dependent metastasis.

Taken together, these findings underscore the intricate interplay between Inflammation and EMT in cancer progression. Targeting the EMT-inflammation axis holds significant promise for innovative anti-inflammatory cancer therapies.

The dual role of cancer therapy: tumor suppression and resistance induction

Surgery, chemotherapy, radiotherapy, and immunotherapy remain the primary treatment modalities for cancer. However, these therapies often induce the release of pro-inflammatory mediators that recruit immunosuppressive cells into the TME, amplifying chronic Inflammation, enriching cancer stem cells (CSCs), and promoting therapy resistance.[58]

Therapy-induced Inflammation plays a dual role in tumor biology. Chemotherapy and radiotherapy cause extensive tissue damage, leading to the release of damage-associated molecular patterns (DAMPs) that activate inflammatory signaling.[59,60] While this response can enhance tumor antigen presentation and antitumor immune activation, it can also paradoxically promote tumor survival by activating prosurvival pathways.[61,62]

Dying cancer cells release abundant DAMPs following treatment.[63] Within the TME, these molecules act as ligands for Toll-like receptors (TLRs) on immune cells, stimulating cytokine production and T-cell activation.[64] However, tumor-derived DAMPs can also directly activate TLRs expressed on cancer cells, inducing chemoresistance and metastasis.[65,66] In parallel, chronic DAMP-induced Inflammation enhances infiltration of immunosuppressive M2 macrophages, MDSCs, and Tregs.[67-69]

Therapy resistance is further reinforced by persistent activation of prosurvival signaling pathways, particularly NF-κB and STAT3, which allow residual cancer cells to survive, adapt, and repopulate following treatment.[62,70,71]

Thus, conventional cancer therapies exert a dual role: they induce tumor cell death and antitumor immunity, but also trigger inflammatory responses that foster CSC enrichment, epithelial plasticity, and resistance via NF-κB and STAT3 signaling.

CONCLUSIONS

The intricate relationship between chronic Inflammation, EMT, and the immune system is shaping cancer progression. Chronic Inflammation represents a fundamental link between aging, immune dysfunction, and cancer development. Immunosenescence and inflammaging progressively impair immune regulation, foster metabolic dysregulation, and promote a tumor-supportive microenvironment. Targeting this axis—by disrupting inflammatory signaling, reprogramming the tumor microenvironment, or blocking EMT-driven immunosuppression - represents a promising strategy to reduce tumor aggressiveness and overcome therapy resistance. A deeper understanding of these interactions will be crucial for developing novel anti-inflammatory interventions that not only prevent tumor initiation but also improve therapeutic outcomes.

AUTHOR AFFILIATION

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