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Interconnected Dynamics Among Inflammation, Immunity, and Cancer–From Tumor Suppression to Tumor Onset, Promotion, and Progression

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Abstract

Inflammation serves as the body's defensive response to harmful stimuli. In the acute phase, immune cells such as neutrophils—which act as the principal responders—along with NK cells, DCs, and macrophages, secrete inflammatory mediators including cytokines, growth factors, and proteolytic enzymes, thereby facilitating tissue repair and regeneration. However, when this response becomes chronic, macrophages become the dominant immune population, succeeded by T and B cells, leading to the continuous release of cytokines, growth factors, and enzymatic mediators. This persistent inflammatory state initiates destructive effects on epithelial structures, immune cells, and vascular components, ultimately contributing to pro-tumoral processes. In the context of cancer, inflammation exhibits a dual nature: it can act as a protective mechanism or as a driving force behind tumor development. This dichotomy is largely regulated by key transcription factors such as nuclear factor-kappa beta (NF-KB) and signal transducer and activator of transcription-3 (STAT3), both of which are essential in modulating immune cell behavior and facilitating tumor progression at different stages of cancer. The present article focuses on the role of inflammatory mediators in both acute and chronic inflammatory microenvironments and their involvement in a wide array of cellular, immunological, and vascular alterations.

Keywords: Transforming growth factor -beta, Nuclear factor-kappa beta, Epidermal growth factor, Signal transducer and activator of transcription-3, Regulatory T cells, Vascular endothelial growth factor

Introduction

Cancer arises from the unrestrained and continuous multiplication of cells, which persists despite the elimination of the initiating cause. In nearly 90% of cases, this unregulated growth is linked to a combination of environmental exposures—such as physical or chemical substances (including methyl mercaptan, benzene, lead, and carbon monoxide), infectious organisms (notably HPV and EBV), and prolonged psychological stress. Among various cancer types, lung cancer holds the highest global incidence and mortality rate, followed closely by malignancies of the oral cavity, cervix, breast, and colon. A substantial proportion—roughly 25%—of cancer cases have been found to develop following long-standing inflammation or unresolved infections [1–3].

The present article focuses on the role of inflammatory mediators within both acute and chronic inflammatory microenvironments and their involvement in a wide array of cellular, immunological, and vascular alterations.

Materials and Methods

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A systematic collection of literature was performed using online research platforms such as PubMed, Medline, Scopus, Elsevier, and Google Scholar. Keywords and themes included both acute and chronic forms of inflammation, the roles of inflammatory and immune cells, functions of inflammatory mediators, and mechanisms of cancer defense and promotion. This article synthesizes outcomes from research papers, clinical evaluations, and academic reviews, along with findings derived from the author's investigative work.

Results and Discussion

Inflammation is a biological defense mechanism designed to counteract harmful insults. In its initial, short-term form, immune cells like neutrophils, DCs, and NK cells are mobilized to secrete mediators such as cytokines, enzymes, and growth factors, which drive processes essential for healing and cell restoration. However, when inflammation fails to resolve and instead becomes chronic—persistent, low-grade, and poorly regulated—it shifts toward a destructive state. During this phase, macrophages dominate the immune landscape, with T cells and B cells contributing to the sustained release of immune mediators including cytokines, growth factors, and proteolytic enzymes. This chronic inflammatory environment leads to cumulative tissue damage, immune dysfunction, and cellular stress, all of which set the stage for tumor initiation, promotion, and further progression. Central to these processes is the continual activation of Nuclear factor-kappa beta (NF-KB) and signal transducer and activator of transcription-3 (STAT3), two transcription factors that orchestrate immune cell dynamics and facilitate cancer development through each progressive stage.

Crosstalk among inflammatory mediators, immune cells, epithelial elements, and stromal components in the acute inflammatory tumor microenvironment

The biological process of inflammation represents the body's immediate response to harmful insults. In the early phase, neutrophils are the primary immune responders, with subsequent involvement of dendritic cells (DCs), natural killer (NK) cells, macrophages, and mast cells [4, 5]. Chemokines secreted by leukocytes facilitate the targeted migration of these immune cells toward the inflamed region. Neutrophils, macrophages, and epithelial cells collaboratively engage in tissue regeneration and antimicrobial defense by producing controlled levels of hydrogen peroxide (H_2O_2) [6, 7].

Various growth factors—including epidermal growth factor (EGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF)—are secreted by immune cells and play pivotal roles in promoting angiogenesis, fibroblast-mediated collagen production, and cellular proliferation. These regenerative processes are orchestrated through the activation of Nuclear factor-kappa beta (NF-KB) and Signal transducer and activator of transcription-3 (STAT3) transcription factors [8, 9]. NK cells, functioning independently of antigen priming, exert cytotoxic effects via the secretion of opsonin, granzyme-B, and IFN-ϒ, contributing to antiviral, anti-inflammatory, and tumor-suppressive responses [10, 11]. Innate immune cells such as DCs and macrophages are integral to the development of long-term immunological memory and are involved in initiating antibody production [12, 13]. The release of pro-inflammatory cytokines like IL-1, TNF-α, and IL-6 triggers NF-KB activation—a transcription factor crucial in balancing immune-stimulatory and anti-inflammatory effects through the release of IL-2, IL-12, and IFN-ϒ. This promotes the development and maturation of cells from both innate and adaptive immune lineages [7–9].

Cellular and molecular interactions in the chronic inflammatory tumor microenvironment

When inflammation becomes prolonged and escapes regulatory control, it takes on a persistent and pathological nature, marked by the sustained and abnormal activation of NF-KB. This dysregulated transcriptional activity leads to the continuous expression of inflammatory mediators, establishing a tumor-promoting microenvironment [10, 11, 14]. Macrophages dominate this chronic setting, followed by T and B lymphocytes, all of which contribute to the secretion of cytokines, growth factors, and proteolytic enzymes. These agents induce cellular damage, promote immune evasion, disrupt genomic integrity, and drive tumor cell survival, proliferation, and angiogenic activity.

The simultaneous and uncontrolled activation of both NF-KB and STAT3 transcription factors facilitates a wide spectrum of cancer-enabling processes. These include cell cycle progression via cyclins D and E, resistance to apoptosis through BCL-2 and BCL-XL, angiogenesis via IL-8, COX-2, HIF-1α, and VEGF, and

destabilization of the genome through mediators like ROS, RNS, AID, and Arginase1. Additionally, immune modulation is amplified by cytokines such as IL-3, IL-4, IL-5, IL-13, IL-15, and IL-17, while invasion and metastasis are promoted through the actions of UPA and matrix metalloproteinases (MMPs) [15–18].

In this chronic inflammatory context, adaptive immune regulation is mediated by inducible T regulatory cells (A Tregs), which are derived from Th1 cells under the influence of TGF-β and IL-10. Regulatory B cells (Bregs), which also secrete IL-10 under TGF-β influence, play a parallel role in modulating immune responses. NF-KB, beyond its regulatory role in inflammation, governs the transcription of over 500 genes and acts in functional opposition to the tumor-suppressor gene p53, whose mutation can be driven by nitric oxide (NO), reactive nitrogen species (RNS), and reactive oxygen species (ROS), all of which are associated with chronic inflammation [19–21].

Conclusion

In its early stages, inflammation acts as a protective mechanism; however, when it becomes chronic, it shifts toward a harmful and tumor-promoting role. The complex dynamics among inflammatory mediators, immune cells, and their interactions with epithelial and vascular tissues play a pivotal role in transitioning from tissue regeneration and healing to processes that involve cell damage, vascular alterations, and immune dysfunction—ultimately facilitating tumor development and advancement. A comprehensive grasp of the distinct roles played by acute versus chronic inflammatory microenvironments, as well as the mediators and cellular participants involved, is essential for improving approaches to cancer prevention, therapeutic targeting, and prognosis, thus enhancing overall patient care outcomes.

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