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Proinflammatory cytokine and cancer

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Abstract

Cytokines are a group of small proteins that are continuously released by several types of cells. These proteins are essential for communication between cells as they act as messengers. They are produced in response to various conditions, such as tissue damage, infection, or inflammatory stimuli. Cytokines possess various functions, including controlling and regulating fundamental physiological processes, such as inflammation, immunity, and hematopoiesis. Cytokines can be classified as proinflammatory or anti-inflammatory.

Proinflammatory cytokines act in response to external agents, such as tissue damage and infection, leading to an increase in inflammation in their target tissues. Some examples of proinflammatory cytokines are Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor alpha (TNF-α), and Interferon gamma (IFN-γ). All of these cytokines affect the influx of immune and inflammatory cells in the region of infection or tissue damage. Furthermore, proinflammatory cytokines can promote the secretion of acute-phase proteins by the liver, activation and proliferation of lymphocytes, induction of hematopoiesis, activation of the coagulation cascade, and a variety of other responses that take place during the acute-phase inflammatory response, such as the dramatic elevation of plasma cortisol concentration. Moreover, the continuous or excessive production of proinflammatory cytokines can lead to a variety of diseases, such as autoimmune, inflammatory, and neurodegenerative disorders.

On the other hand, anti-inflammatory cytokines down-regulate the expression and production of proinflammatory cytokines in response to the accumulation of proinflammatory cytokines, preventing hyperinflammation. A variety of cytokines possess anti-inflammatory activity, such as Interleukin-10 (IL-10), Transforming Growth Factor beta (TGF-β), and Interleukin-1 receptor antagonist (IL-1ra). The balance between proinflammatory and anti-inflammatory cytokines is fundamental to the control of inflammation-induced immune response.

Keywords: Cytokine; Cancer; IL-6; IL-1β; TNF-α

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Introduction

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inflammatory stimuli. Cytokines possess various functions, including controlling and regulating fundamental physiological processes, such as inflammation, immunity, and hematopoiesis. Cytokines can be classified as proinflammatory or anti-inflammatory. Proinflammatory cytokines act in response to external agents, such as tissue damage and infection, leading to an increase in inflammation in their target tissues. Some examples of proinflammatory cytokines are Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor alpha (TNF-α), and Interferon gamma (IFN-γ).

All of these cytokines affect the influx of immune and inflammatory cells in the region of infection or tissue damage. Furthermore, proinflammatory cytokines can promote the secretion of acute-phase proteins by the liver, activation and proliferation of lymphocytes, induction of hematopoiesis, activation of the coagulation cascade, and a variety of other responses that take place during the acute-phase inflammatory response, such as the dramatic elevation of plasma cortisol concentration. Moreover, the continuous or excessive production of proinflammatory cytokines can lead to a variety of diseases, such as autoimmune, inflammatory, and neurodegenerative disorders. On the other hand, anti-inflammatory cytokines down-regulate the expression and production of proinflammatory cytokines in response to the accumulation of proinflammatory cytokines, preventing hyperinflammation. A variety of cytokines possess anti-inflammatory activity, such as Interleukin-10 (IL-10), Transforming Growth Factor beta (TGF-β), and Interleukin-1 receptor antagonist (IL-1ra). The balance between proinflammatory and anti-inflammatory cytokines is fundamental to the control of inflammation-induced immune response.

Types of Proinflammatory Cytokines

Cytokines are small, secreted proteins that play an important role in cellular signaling. They mediate communication between different kinds of immune cells in both innate and adaptive immunity. Cytokines can be classified according to their structural, functional, and target cell specificity. They can also be classified as proinflammatory or anti-inflammatory. Proinflammatory cytokines are secreted by a variety of immune cells and induce inflammation. They are synthesized and released in response to an infection and increase the recruitment and activation of immune cells to the infection site. Proinflammatory cytokines are also involved in a variety of diseases, including autoimmune disorders, infectious diseases, and monogenic syndromes. Tumor necrosis factor was the first identified proinflammatory cytokine. It is a potent proinflammatory cytokine produced by various immune cells. It induces the biosynthesis of IL-1 and IL-6 and leads to the production of various adhesion molecules and chemokines. It is also involved in the development of cachexia by increasing basal metabolism and catabolism. IL-1, a family of proinflammatory cytokines, is produced mainly by activated macrophages. It initiates and amplifies the inflammatory process and induces other cytokines, including TNF and IL-6. IL-1 has a pro- and anti-tumorigenic role in different cancers. IL-6 is produced mainly by activated macrophages and fibroblasts and has similar properties to IL-1. IL-6 is a central

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target in several cancers, including breast and prostate cancer. Other proinflammatory cytokines include IL-12, IL-15, IL-18, IL-23, IL-27, IL-33, CNTF, LIF, OSM, PTN, and TL1A. IL-12 is produced by macrophages and dendritic cells, and its activation promotes the differentiation of T cells. It is involved in the development of inflammatory bowel disease. IL-15 promotes the activation and proliferation of natural killer cells and memory T cells. It is involved in the development of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. IL-18 is produced by macrophages and is involved in the development of atherosclerosis and ischemic heart disease. IL-23 is produced mainly by dendritic cells and involved in the development of psoriasis. IL-27 is a member of the IL-6/IL-12 family of cytokines. It has a pro-inflammatory function and is involved in the development of type 1 diabetes and rheumatoid arthritis. IL-33 is involved in the development of asthma and allergic rhinitis.

Biological Functions and Signaling Pathways

Proinflammatory cytokines secreted by mast cells exist within tumor's microenvironment. Mast cells are known to induce cellular immunity in the early stages of inflammation and secrete a diverse array of cytokines and promote a subsequent T-helper 1 response through the production of IL-6. They also produce a variety of other cytokines, including IL-1, IL-2, IL-4, IL-9, etc., as well as several other cell types including endothelial cells, macrophages, and T-lymphocytes. Because mast cells have a relatively short life span of only a few days, they have the potential to promote the growth of tumors through the release of proinflammatory cytokines and the subsequent activation of protumor signaling pathways within the tumor's microenvironment. The actions of prostaglandin E2 can attenuate the capacity of T-lymphocytes to secrete a variety of cytokines, which largely reside within the T-helper 1 and cytotoxic T-lymphocyte lineages.

Relationship of proinflammatory cytokines and tumor. In some liver and colorectal cancer patients, circulating cytokine levels are higher than healthy control, and patients in these conditions display a comparably lower rate of progression, angiogenesis, and metastasis. Proinflammatory cytokines are tree-related to liver regeneration, but the fuel that generates this cytokine storm seems to be proinflammatory. Proinflammatory cytokines, IL-1 and TNF-α have been shown to act as tumor suppressors, whereas IL-6 showed protumor activity. Whether antitumor effects or protumor effects of proinflammatory cytokines are involved can be tissue-specific; it seems that growth suppressive effects are realized in T-cell-mediated apoptosis or activation of antiproliferative cytokines. The role of the balance between proinflammatory and anti-inflammatory signaling within the tumor microenvironment and whether alterations can suppress or enhance the development of these conditions remain to be understood.

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Cancer Biology Basics

Cancer is the second leading cause of death in developed countries, and with increased aging of the population, it is predicted that cancer incidence will rise. Cancer therapy has developed over recent years; however, many of the current treatments are ineffective in treating some forms of cancer, such as pancreatic cancer and brain tumors. In a cancer patient, the primary tumor gives rise to the majority of symptoms, including pain, discomfort due to ulcers, and storage of a large number of cancer cells in one location, hyperhidrosis, and others. However, none of these symptoms are the result of the action of cancerous cells themselves, but of the body's reaction to the tumor in the form of an inflammatory reaction and growth of new blood vessels into and around the tumor, leading to the release of certain molecules into general circulation. Early detection and the design of highly sensitive and efficient therapeutic agents with much lower side effects than the current options are highly desirable. The development and treatment of cancer is hindered by three particularities. The first is related to the body's response to the presence of cancer: secondary inflammation and release of subunits from dying cancer cells, which elicit secondary immune responses that weaken the body even before treatment begins. The second problem is tumor heterogeneity, with regard to genetic and transcriptomic profile, and morphology, all determined by the unique spatial and temporal aspects of the tumor's microenvironment. Finally, resistance to anti-cancer drugs is often a problem. This dictates the design of new therapeutic agents that are highly specific, efficient, and better tolerated in animal models. Sensitive molecular agents targeting inflammation, able to detect and monitor malignancy progress, will potentially allow treatment if introduced at the very first onset of the disease. This necessitates a complete deep understanding of these processes on the molecular level.

Hallmarks of Cancer

Cancer cells were initially described by Hanahan and Weinberg based on their extraordinary characteristics associated with advancing the development of cancer. Initially, hallmarks of cancer were proposed and these included: unlimited replicative potential (telomerase reactivation), ability to escape programmed cell death (inactivation of TP53), tissue invasion and metastasis (inactivation of CDKN2A or over-expression of cyclin E), self-sufficient growth and proliferation (growth signaling pathways), induction of angiogenesis, stimulation of the formation of an inflammatory stromal microenvironment, and constant activation of cell proliferation by avoiding immune surveillance. The acquisition of additional characteristics was discussed in other review studies. However, recent large-scale analyses have revealed that the majority of these attributes are neither extraordinary nor representative of the diseases being considered. The development of the hallmarks has influenced our understanding of cancer but can also tarnish this discussion by slightly derogating the efforts made in using the "insights" concept as a unifying strategy.

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One of these new candidate characteristics that has been proposed is the role of pro-inflammatory cytokines in cancer development and progression. Some of these cytokines are involved in traditional cancer-progression steps, suggesting that their induction is part of the genetic program for at least one inflammatory feature considered to be part of the definition of cancer. Cancer-associated pathology results from the host reaction or inflammation driven by the presence of the tumor. The proteinaceous tumor microenvironment itself can contain virus-induced antigens, mutated cellular antigens, and myeloid-derived suppressor cells. It is essential for tumor growth and transformation and has a key role in many of the so-called "hallmarks of cancer". The tumor secretome contributes to these traits. During transformation, neoplastic cells use cytokines, protect themselves from cellular damage, reprogram surrounding stromal cells, avoid immunity-induced cytotoxicity, survive, proliferate, migrate and settle in distant organs, initiate an angiogenic switch, and finally create the pre-metastatic niche.

Tumor Microenvironment

The tumor microenvironment (TME) is involved in different biological processes, such as tumor progression, growth, metastasis, and drug resistance. TME includes various immune cells, endothelial cells, fibroblasts, and has a unique TME phenotype. Proinflammatory cytokines are highly expressed in the solid TME. Cytokines, such as IL-6, IL-1β, IL-8, and TNF-α, secreted from immune cells, cancer cells, and stromal cells in the cancer TME, can enhance cancer cell transformation and proliferation and suppress cell apoptosis. The complex relationship between cytokines, tumor cells, and TME plays an important role in programming the functions of TME. In the study of TME, cytokines are identified and found to affect biological functions in cancer cells and TME. Simultaneously, the concentration of these identified cytokines is found to increase in the cancer microenvironment. Consequently, these redundant cytokines create a proinflammatory TME, which can promote cancer development and progression. Moreover, preclinical and clinical studies provide some targets and treatment methods for cancer treatment. Targeted therapy that uses critical inhibitors to downregulate the expression of proinflammatory cytokines can reverse the biological processes and inhibit cancer progression.

Interplay Between Proinflammatory Cytokines and Cancer

Proinflammatory cytokines are vital for inducing inflammation and the innate immune response. Cancer cells also interact with cells in the tumor microenvironment to modulate these immunologic routes in a bid to escape the immune system and thrive. This intervolved process involves a complex network of proinflammatory cytokines related to innate immunity, including IL-1β, IL-6, and tumor necrosis factor-α (TNF-α). This review appraises the operations of the IL-1 axis, IL-6–STAT3 signaling, and TNF-α in terms of their roles in cancer cell survival, immune cell infiltration, cell plasticity, and adaptation to stress. Targeting proinflammatory cytokines could thus be a strategy where cancer, inflammation, and immunology can be integrated to deter cancer cells' plasticity and improve the antitumor response.

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Promotion of Tumorigenesis

Cytokines, proinflammatory cytokines in particular, play a central role in promoting tumorigenesis in a number of ways. Tumor development and progression involve genetic mutations, chronic inflammatory stress, increased intratumoral and oxidative-nitrative stress, angiogenesis, and persistent infections due to the chronic wound healing process. Increased cell proliferation, survival, angiogenesis, invasion, and metastasis are all tumor cell responses mediated by a variety of factors released by cells at the site of the tumor and taking part in the wound healing process to restore homeostasis. These factors include hormones, growth factors, proteolytic enzymes, angiogenic factors, receptors, adhesion molecules, enzyme regulators, extracellular matrix (ECM) and components of the cytoskeleton, and adhesion molecules. The production of cytokines and growth factors can increase in malignant tumors for a number of reasons, such as, for example, fibroblasts located near the tumor secreting cytokines that can affect both intratumoral as well as adjacent tumor determinations, both intratumoral and normal cells secreting some type of cytokine or growth factor, including cancer cells themselves. These molecules affect tumor cell growth in an autocrine or paracrine manner, with the height of their concentration affecting the activation and sensitivity of both tumor and stromal cells in a complex manner. Upregulated cytokines and growth factors will greatly increase the lesion, with numerous gene alterations in cancer cells predisposing them to hyperactivation, which is selective due to the mitogenic action of the particular cytokine or growth factor, as well as proinvasive through the secretion of stromal cells that help remodel the extracellular matrix and infiltrate and metastasize at distal and microvasculature sites. These cytokines activate complex networks including multiple intracellular signaling pathways both within the tumor cell and stromal cell subsets. To date, tumor cells are targeted through biochemical agents and antibodies recognizing the tumor and its activated genes, and chemical compounds from plant nutrients, making it possible to examine the configuration and behavior on different occasions using different techniques. Differentiable circuits that proceed simultaneously and over time according to a method we refer to as cytokinetic signaling drive neoplastic transformation, carcinogenesis, tumor progression, recruitment of cell reprogramming, and the construction of a rich vascular network and niche that will promote angiogenesis, invasiveness, and metastasis by stromal cell determinations, and sustain the growth and expansion of the lesion.

Enhanced Cancer Cell Proliferation and Survival

There are two main pathways that can mediate enhanced proliferation and/or survival to support the overall role of proinflammatory cytokines in increasing cancer development and progression as shown in Figure 2. First, signaling through proinflammatory cytokines can support increased cellular survival and decreased apoptosis. In many cases, the extrinsic death-receptor pathway is used by proinflammatory cytokines to prevent cytokine-induced

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apoptosis. Signaling through the proinflammatory cytokine receptors can result in transcription-dependent or -independent regulation of Bcl-2 family member proteins. Second, proinflammatory cytokines have been shown to overcome cell cycle checkpoints or promote growth signaling in cancer cells. For example, many reports have implicated a role for the proinflammatory cytokines in mediating resistance to endocrine therapy. Together, the effects of proinflammatory cytokines on cancer involve interference with cell cycle regulation, controlling signaling pathways, or effecting senescence.

Clinical Implications and Therapeutic Strategies

Ovarian cancer remains the most lethal gynecologic malignancy in the United States and the fifth-most common malignancy in women, affecting 1 in 57. Ovarian cancer is typically diagnosed at an advanced stage with most patients having widely disseminated intraabdominal metastases and large-volume ascites and is treated with surgery, a platinum agent, and frequently a taxane, to which the original tumor usually responds well. However, about 75% of women with advanced disease will develop recurrent cancer and ultimately succumb to their disease. The high mortality of ovarian cancer is related to late diagnosis and the development of platinum/taxane-resistant disease. Ovarian tumors characteristically have high levels of IL-6, IL-6R, and paracrine gp130 signaling, which is also significantly increased in ovarian tumors. The occurrence of this proinflammatory cytokine pathway is critical for a tumor-associated inflammatory feedback loop or autocrine or even paracrine tumor growth pathway and supports aggressive human cancer cell growth. Current treatment for advanced-stage ovarian cancer has not changed significantly over the past few decades. Although aberrant JAK-signaling pathway mutations occur frequently in ovarian cancer, especially in low-grade serous ovarian cancer, JAK inhibitors are only efficacious in the context of activated STAT3 proteins and are just beginning to be tested in clinical trials.

Currently, there are only a few STAT3 inhibitors in phase I trials and none in ovarian cancer. Targeting these specific molecules with inhibitors that have advanced to large clinical trials in other cancers and that are more widely available in early clinical trials in ovarian cancer may provide a different treatment target for ovarian cancer that is currently treated with traditional chemotherapy. Combination small molecule inhibitors aimed at both the cancer stem cells that cause cancer relapse and the more differentiated tumor cells that are heavily dependent on paracrine/autocrine activation of STAT3 signaling may enhance the effectiveness of ovarian cancer treatment.

Cytokine-Targeted Therapies

The first reported attempt to use drugs to modify the balance between the levels of anti- and proinflammatory cytokines was the administration of recombinant human IL-10 in patients with advanced cancer. Subsequently, an attempt was made to reduce the production of IL-6 by stromal cells in inflamed liver tissues in hepatocellular carcinoma using the immunosuppressive

agent rapamycin, with the hope of attenuating the inflammation-induced formation of hepatocellular carcinoma. The effect of IL-6R blockade has been evaluated in patients with advanced solid tumors and in a dose-escalation study of patients with various types of cancer. Tocilizumab monotherapy was found to be ineffective in terms of classical Response Evaluation Criteria in Solid Tumors, but it showed clinical activity in six out of 20 peripheral T-cell lymphoma patients who were evaluated from two different centers. The development of ramucirumab was initiated based on anti-VEGF-resistant lung cancer that had been confirmed by the results of two phase III studies.

The regulatory T cell (Treg) inducibility of both and has thus become an issue of concern. In the case of standard molecularly targeted drugs, it may be possible to mitigate the occurrence of hyperprogression by incorporating immune checkpoint inhibitors in the treatment, but no specific immunotherapies have been developed to date. Sorafenib, or the combined use of lenvatinib and pembrolizumab, may be effective in treating HCC by the same mechanism, but there is still a need for the development of drugs with other biological properties. There are certain modes of cytokine action that exhibit immunosuppressive effects, not only by inhibiting the inflammatory response, but also by selectively targeting effector T cells. Identifying those modes could lead to the creation of a novel, effective interventional strategy. The evodiamine diacetylformat derivative compound (CHS-828) is cytotoxic to TNF-overexpressing cancer cells, and its main action mechanism is related to the production of NO.

Immunotherapy Approaches

In addition to standard clinical therapy, the methods of immunotherapy are evaluated very actively. They are based on stimulation of the immune system against the cancer cells. The various directions of applied immunotherapy (i.e., activation of a tumor-specific T cell response) and further modification targeting of lymphocytes at the tumor site include recruitment of T cells to tumor cells, elimination of suppression of effector function of T cells, direct killing of the tumor, etc. Immunotherapy for treatment of multiple cancers is based on antibodies that bind to proteins on the surface of so-called immune checkpoint cells. One of the most powerful regulators of the immune response are the so-called negative control molecules. After an immune response begins to be formed, the cells of the immune system produce the molecules that inhibit the effector immune cells. Then the generation of the immune response finishes and the negative controls are abolished. After that, the effector immune cells can implement their functions. In many cases, cancer cells take advantage of these protective molecules to escape the immune response by inhibitory checkpoints. Conventional negative regulator molecules, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) and its ligand (PD-L1), play a role in immune response injuries. CTLA-4 is detected on the surface of a small selection of regulatory T cells and on the surface of effector T cells during the activation phase. These increase the immune response by blocking the CD28-B7 amplification during the immune response. As for PD-1, it becomes active on

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activated T, B, and NK cells, particularly during the inflammation phase. Interaction of PD-1 with PD-L1 or PD-L2 (its major ligand) inhibits the activity of PI3-kinase, which then slows the phosphorylation of the phosphatidylinositol triphosphate (PIP3) and then reduces the activity of AKT in cells. This means that T cells that respond to the cancer cells and thus stop killing them. PD-L1 is produced by many types of cancer cells and some other types of cells, such as immune cells. Not only does immunotherapy that targets PD-L1 pathways allow to restore the cytotoxic activity of CD8+ T cells, but also the activation of CD4+ cells maintains the immune response.

Research Opportunities

Given the growing body of literature evidence for a relationship between chronic inflammation and the development and progression of several types of human cancer, blocking the inflammatory pathways at different stages might require a personalized and adaptable approach. Various cancers will require intervention at different stages, and for some patients, an effective, well-tolerated alternative to lifelong exposure to nonsteroidal anti-inflammatory drugs might be an attractive option. Concurrent with the identification and further development of well-selected pharmacological agents targeting specific stages of cancer-related inflammation, the use of predictive and prognostic biomarkers will be critical for identifying at-risk patients and tracking whether the agents successfully arrest or reverse the inflammation.

From a clinical applications perspective, we envision the development and application of new multiplexed serum/protein biomarker panels representing biomarkers and their products at inflammatory sites to predict response to therapeutic interventions as a primary focus of future research. We forewarn that with the exception of distinct inflammation-blockers such as corticosteroids, cyclo-oxygenase-2 inhibitors, or expensive/biologically targeted therapies, small-molecule pharmacological agents with similar or combined gene targets may not provide long-term anti-inflammatory effects. Furthermore, they may not target the sources of chronic inflammation as effectively as stringent discipline-based lifestyle modifications. We recognize the general reprehension of clinical studies on nutrition and cancer about the totality of disconcerting messages generated by ambiguous results and apparent inconsistencies. However, in our opinion, the beneficial effects of lifestyle modifications approach broader applicability and significance beyond primary cancer prevention. Nevertheless, clinical studies should strive to identify the effects and effectiveness of these modifications on specific patient populations. For instance, GI tolerability is a realistic concern in patients who are to commence long-term anti-inflammatory therapy such as PPIs. It would be advisable to select a specific group of patients such as current smokers, alcoholics; patients with esophagitis or gastritis or infected with H. pylori to minimize treatment-naïve costs and make the preparation for the interventional studies feasible and more effective.

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Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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