Chapter 15

The Possible Role of Cytokines in Chemotherapy-Induced Cognitive Deficits

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Abstract

Proinflammatory cytokines play a significant role in the body's immune response to pathogens, including malignant cells. Proinflammatory cytokines are associated with tumor invasion and progressive disease and are released in response to many antineoplastic agents. Exogenous administration and endogenous production of cytokines is related to a pattern of behaviors known as sickness behavior that has a significant impact on patients' quality of life. The behavioral patterns associated with sickness behavior include inability to concentrate and impaired learning. Identification of sequelae specific to individual cytokine activity provides novel targets for investigation.

The Role of Proinflammatory Cytokines

The release of proinflammatory cytokines is one of several mechanisms hypothesized to play a role in the cognitive changes seen in patients receiving chemotherapy for treatment of malignancy. Proinflammatory cytokines are an integral component of the immune response and are released as a result of tissue injury related to tumor growth as well as the administration of antineoplastic agents.[1-5] The side effects that result have been referred to as sickness behavior, an adaptive response to disease and injury.[6,7] Further understanding of the sequela related to proinflammatory cytokine release will be important to the identification of patients at risk and the development of appropriate interventions.

Overview of Cytokines

Cytokines are small proteins involved in intracellular signaling. The term cytokine refers to both proinflammatory and anti-inflammatory signaling molecules that have autocrine, paracrine and endocrine activity. Cytokines are pleiotrophic, in that the same cytokine may be secreted by a number of different cell types and any one cytokine may act on multiple cell types. The primary function of cytokines is the mediation and regulation of immunity, inflammation and hematopoiesis.[8]

The Immune Response

The body's first line of defense against an invading pathogen (or antigen) is the macrophages which phagocytize the offending bacteria or virus (recognized as "not self" by the body's immune system).[9] This process is referred to as nonspecific immunity and ultimately results in the presentation of antigenic components to circulating T-cells. Antigen recognition results and additional specific T-cells are produced, leading to direct antigen cell death by cytotoxic T-cells.

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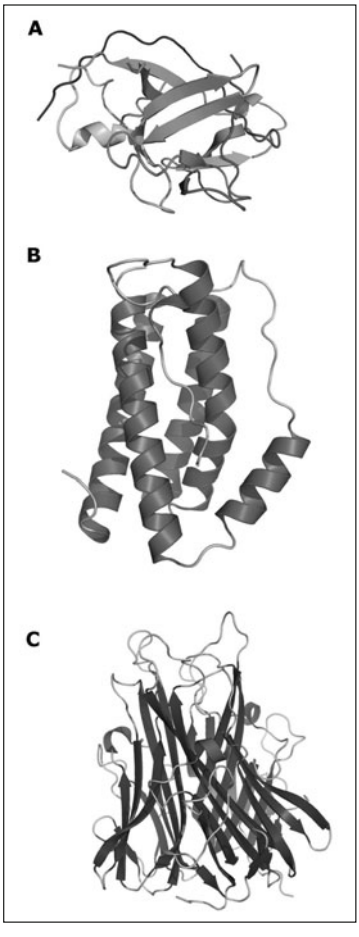

Figure 1. Crystal Structures of (A) Interleukin-1, (B) Interleukin-6 and (C) TNF-alpha. Reprinted with permission from Wikipedia. Retrieved on April 16, 2009 from http://en.wikipedia.org/wiki/File:2ILA.png.

Additionally, T-helper cells stimulate B-cell production associated with the secretion of antibody to destroy the antigen. Macrophages, T-helper cells and B-cells secrete a number of cytokines involved in the stimulation of cellular interactions needed for antibody production. The macrophages synthesize and release proinflammatory cytokines, including interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) (Fig. 1).[9] Proinflammatory cytokine release attracts additional immune cells to mount the immune response (referred to as specific immunity).

Proinflammatory Cytokines and Cancer

Release of proinflammatory cytokines is associated with the body's response to cancer and the tissue damage caused by malignancy.[2] Aberrant production of endogenous cytokines can serve as autocrine growth factors and are indicators of an immune response to tumor invasion.[10] Some tumor cells have been shown to secrete cytokines as invasion of surrounding tissues and metastasis occurs.[11,12] TNF-α is produced by tumor cells (such as ovarian and renal cancer). TNF-α is associated with poor prognosis, loss of hormone responsiveness, cachexia/asthenia and

can promote tumor spread. Interleukin 1 beta (IL-1β) promotes angiogenic factor production and is associated with increased tumor invasiveness and metastasis.[13] Chronic inflammation, seen in inflammatory diseases such as Helobacter pylori infection (gastric) and inflammatory bowel disease (colon) has been associated with progression to malignancy.[13] Elevations of IL-6 are seen in diffuse large B-cell lymphoma and pancreatic cancer.[10] Increased levels of cytokines as well as cognitive impairment have been seen in patients with leukemia and myelodysplastic syndrome prior to receiving antineoplastic therapy.[14]

Proinflammatory Cytokines and Antineoplastic Agents

Proinflammatory cytokine release in vitro has been associated with a number of antineoplastic agents.[3-5,15] Animal studies have shown production of cytokines following etoposide administration. Subsequent decreases in food intake and physical activity were observed.[7] Increased levels of IL-6, IL-8 and IL-10 have been associated with the taxanes (paclitaxel and docetaxel).[16] Chemotherapy-induced side effects are very similar to those associated with sickness behavior.[7]

Doxorubicin administration in animal models has been associated with an increase in circulating levels of TNF-α.[17] TNF-α has been shown to penetrate the blood brain barrier (BBB) and activate glial cells to produce TNF-α in the brain. Nitric oxide synthase is induced, nitric oxide is generated and central nervous system (CNS) injury results.[18] Oxidative stress is related to a number of additional antineoplastic agents in addition to the anthracyclines, such as cyclophosphamide, cisplatin, busulfan, mitomycin, fluorouracil, cytosine arabinoside and bleomycin.[17]

Proinflammatory Cytokines and Sickness Behavior

The behavioral patterns of animals and humans in response to the onset of infectious diseases has been referred to as sickness behavior.[6] The patterns included: lethargy, depression, anorexia, reduction in grooming, increased sleep, seeking warmth, conservation of energy, weakness, inability to concentrate, decreased interest in surroundings, decreased social and sexual interaction, decreased ability to experience pleasure, enhanced pain perception and impaired learning.[6,12,19-21] The febrile response is associated with many of these behaviors.[19]

Much of the knowledge about the role of cytokines in sickness behavior is credited to experience with the endogenous administration of cytokines as a component of cancer therapy. Treatment with immunomodulating agents such as interferon-α, TNF and IL-2 are associated with a side effect called "flu-like syndrome" that is similar to the behaviors associated with sickness behavior.[22] Fever, chills, lethargy, anorexia and cognitive impairment have been observed. Animal research has been conducted to evaluate the effects of endogenously administered IL-1β. The resultant hippocampal production of IL-1β was shown to interfere with memory formulation.[15]

The behavioral reaction to endogenous cytokines, such as fever, raised the question of how cytokine release in the peripheral blood would have an effect on the CNS.[23] The CNS is considered to be an immunoprivileged site due to the almost complete absence of T and B lymphocytes and the protection from foreign substances provided by the BBB. Cytokines are large molecules that should be unable to pass through the tight junctions of the BBB. Recent studies have demonstrated significant cross talk and bidirectional communication between the CNS and the immune system as well as the presence of cytokine receptors in the brain.[15,23-25] Proinflammatory cytokines (IL-1, IL-6, TNF-α) have been shown to penetrate the BBB in spite of their large molecular size. Additionally, some cytokines are produced in the CNS (TNF-α, IL-1β).

A number of mechanisms have been proposed for the BBB penetration. IL-1α is known to cross the BBB via a saturable transport system. Evidence also suggests this humoral route for IL-1β, IL-6 and TNF.[1,15] In some areas of the brain, the BBB is weak or absent such as the organum vasculosum lateralis terminalis, subfornical organ, median eminence, area postrema and choroid plexus.[15] Cytokines are able to cross the BBB at these circumventricular organs.

Neural routes are activated to project cytokine signaling to distant target regions within the brain through the use of mediators such as prostaglandin E2 and neurotransmitters.[1,9,15] The vagus nerve carries efferent signals from the periphery to the brain. Innervation of the lungs (a

typical site of pathogen entry) and the lymp nodes (tissue involved with the immune response) may explain why severing the vagus nerve eliminates many of the behavioral responses associated with exogenously administered cytokines.[1,26]

One of the cytokines produced in the brain is IL-1β. Production is thought to occur from microglial cells, perivascular and meningeal macrophages.[27] Once the cytokines are produced, they are postulated to travel to the periphery and initiate a neural cascade of brain-mediated host responses.[1]

Proinflammatory Cytokines and Other Symptoms

A number of additional symptoms have been associated with chemotherapy-induced proinflammatory cytokine release such as peripheral neuropathy.[12] Cisplatin and paclitaxel increase serum levels of IL-1β, interferon γ and TNF-α. Vincristine is associated with increased levels of TNF-α. Nuclear factor-κB is hypothesized to be the link between inflammatory cytokines and cancer-related symptoms due to its role in the stimulation of cytokine release for the immune and stress responses.[12] Cisplatin, paclitaxel and vincristine directly activate the nuclear factor-κB signaling pathway associated with neural tissue pain activation.[12]

Proinflammatory cytokine release has been linked to fatigue and cachexia.[12,28] Cachexia is associated with both IL-6 and TNF-α. Close linkages between depression and cachexia have been observed in patients with cancer.[28] Recent research has been devoted to clusters of symptoms that occur concurrently in patients with cancer.[29-31] Sickness behavior has been described as a symptom cluster[12,14] as have pain, fatigue and depression.[32]

Future Implications

A number of pharmaceutical agents are being evaluated for efficacy in minimizing the negative effects of proinflammatory cytokine release by targeting or antagonizing the action of cytokines. Many of these agents are being studied in chronic inflammatory diseases as well as malignancy.

Etanercept is a TNF receptor antagonist being studied in rheumatoid arthritis as well as cancer. This receptor-antibody fusion protein has been studied in combination with IL-2. Decreased levels of TNF-α and partial suppression of IL-1, IL-6, IL-8 and C-reactive protein were demonstrated. Etanercept also is being studied in cancer-related cahexia.[28] Infliximab is a TNF-α antibody approved for use in rheumatoid arthritis, Crohn's disease and ankylosing spondylitis. Some efficacy has been seen in the treatment of cachexia.[28]

Other anticytokine strategies under evaluation include: cytokine synthesis inhibitors, soluble cytokine receptors, cytokine receptor antibodies, cytokine receptor antagonists, IL-6 inhibitors and nuclear factor-κB inhibitors.[12,28]

Conclusion

Success in the area of cytokine inhibition has the potential for a major impact on quality of life in patients with malignancies. Much work remains to be done to determine the impact of specific cytokines, identify appropriate targets for therapy and demonstrate effectiveness of therapies to control or prevent the effects of cytokine-induced inflammatory response.

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