Cytokines, Cancer and Depression: Connecting the Dots

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Commentary on "Are Inflammatory Cytokines the Common Link Between Cancer-associated Cachexia and Depression?" by James Illman, BS, Robert Corringham, MD, Don Robinson, Jr, MSPH, et al (page 37).

This review article by Illman et al highlights mechanisms that may lead to improved survival and quality of life for patients with cancer. Their overview of the literature suggests that, at a molecular level, cancer-related depression and cachexia are related through cytokines. Both depression and cachexia are associated with poorer survival and quality of life. As such, "connecting the dots" between cytokines, depression, and cachexia could lead to cytokine-mediated therapies, mitigation of symptoms, and better overall outcomes.

Cytokines are hormone-like proteins that act as immune system communicators, with apparent linkages to depression. Numerous studies demonstrate that individuals with depression, regardless of whether or not they have cancer, show elevated levels of cytokines, particularly interleukin-6 (IL-6) [1, 2]. Furthermore, there appears to be a causal relationship between cytokines and depression. Patients who receive cytokine-based therapies (eg, interferon-alpha [IFN-α]) may develop depressive symptoms after cytokine administration [3, 4]. Interestingly, there may be different cytokine pathways, thereby explaining why certain depressive symptoms seem to cluster together and have different responsiveness to antidepressant treatment [4, 5]. These results suggest that depression and depressive symptoms may not just be a reaction to a diagnosis of cancer but are in part related to immunological changes.

Cytokines and Depression/Fatigue

Numerous causal linkages have been suggested between cytokines and the induction of depressive symptoms. Possible mechanistic explanations include induction of neurotoxic metabolites [6]; disruption of serotonergic, noradrenaline, and dopamine neurotransmission [7]; and dysregulation of the hypothalamic-pituitary-adrenal axis [8]. Clearly, further research is needed to determine the exact mechanisms by which cytokines cause depression.

The evidence suggesting a role for endogenous cytokines such as IL-1, IL-6, and tumor necrosis factor-alpha (TNF-α) in the pathophysiology of depression in the medically ill combined with evidence that high levels of these endogenous cytokines are noted in patients with several common cancers (eg, pancreatic cancer) suggests that endogenous cytokines may play an important role in the etiology and phenomenology of depression in patients with cancer [2, 9–11]. Clinical researchers have long observed that depression in cancer patients (particularly in patients with pancreatic cancer) is unique in its phenomenology compared with classic depression seen in physically healthy populations [12].

Depressive symptoms sometimes precede the clinical diagnosis of certain malignancies (such as pancreatic cancer), suggesting an "organic" etiology for the depression. In these instances, the phenomenology of depressive illness involves primarily somatic or physical symptoms, with more prominent anhedonia, fatigue, and cognitive deficits. This clinical picture of depression in cancer suggests a syndrome that has been described as "cytokine induced sickness behavior" (Figure 1) [13]. This syndrome further suggests that clinical depression in patients with cancer may be unique in its phenomenology because of its association with cytokines.

Exogenous and endogenous cytokines are now postulated as etiologic factors in cancer-related fatigue, as well as treatment-induced mood and cognitive difficulties in patients receiving IFN or IL [2, 4, 11, 14–17]. Interestingly, some cancers, such as of the pancreas and lungs, have been reported to be associated with high levels of these very same proinflammatory cytokines.

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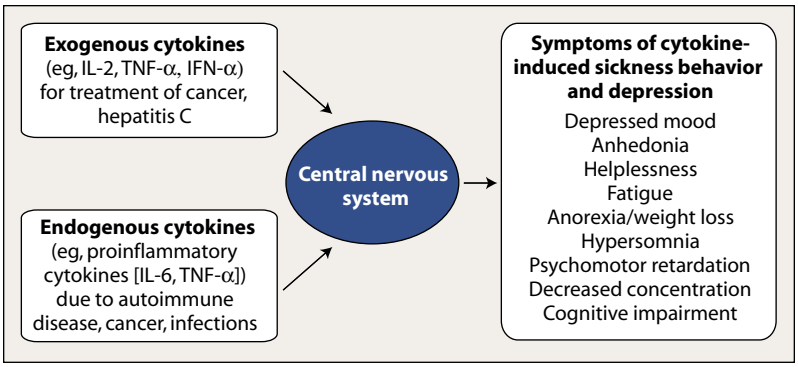

Figure 1 Role of Cytokines in Producing 'Sickness Behavior'/ Depressive Symptoms in the Medically Ill

Cytokines, Cachexia, and Depression

Cytokines and Cachexia

Cancer-related cachexia, a syndrome involving loss of adipose and skeletal muscle tissue, and one that is not responsive to increased caloric intake [18], also appears to be associated with the elevation of inflammatory cytokine levels, particularly IL-6 and TNF-α [19–21]. Moreover, diminishing or blocking IL-6 activity in animal models attenuates cachexia, further demonstrating the essential role IL-6 plays in the development of this syndrome [19, 21, 22].

Cachexia may also be related to the role of acute phase proteins. The acute phase response and production of acute phase proteins (eg, C-reactive protein [CRP]) are mediated by IL-6 [20, 23]. Studies correlate elevated levels of IL-6 to elevated levels of acute phase proteins, which, interestingly, are also associated with increased weight loss and decreased survival [20, 23, 24]. Thus, with elevated IL-6 levels, amino acid metabolism is directed away from peripheral tissues to the liver for production of acute phase proteins. This in turn leads to muscle wasting, which is a component of cachexia. Accordingly, the cytokine-induced acute phase response may be a primary component of cancer-related cachexia.

Possible Targets for Treatment

A causal pathway between depression, cachexia, and cytokines opens the possibility of therapeutic opportunities. Numerous agents are discussed in this review, including nonsteroidal anti-inflammatory drugs, melatonin, thalidomide (Thalomid), progesterone, and eicosapentaenoic acid, as well as their potential therapeutic effect. Studies demonstrate that these agents, which are shown to decrease weight loss, either modulate the production of acute phase proteins or decrease the level of circulating cytokines [17, 25–28]. Their effects on depression, however, are not reviewed. Regarding depression, only antidepressants, which are effective in treating cancer-related depression, are highlighted [29].

Currently available anticytokine biologics may prove to be essential cancer treatment modalities. Etanercept (Enbrel) is a receptor-antibody fusion protein that binds TNF-α, decreases TNF activity, and suppresses the elevation of IL-1, IL-6, IL-8, and CRP [30]. Infliximab (Remicade), a mouse/human chimeric anti-TNF monoclonal antibody, also blocks the action of TNF and decreases weight loss in mice [31]. Currently, studies are being performed to determine the effect of infliximab and etanercept on cancer-related cachexia.

IL-6–targeted treatments have also been studied. As previously mentioned, IL-6 antibodies decrease the amount of weight loss in animal models [19, 21, 22]. Antibodies to IL-6 have also been studied in humans. BE-8 and CNTO 328, both anti–IL-6 monoclonal antibodies, reduce the synthesis of CRP and the incidence of cachexia in cancer and HIV patients with lymphoma [32]. Thus, one might expect decreased weight loss and improved survival [20, 23, 24]. As such, further research into IL-6 antibodies and their benefits regarding cancer-related depression and cachexia is warranted.

The importance of this research is underscored by the fact that depression among cancer patients is not infrequent, with some studies quoting prevalence rates as high as 50% [29]. Cancer-related depression is associated with poor outcomes, including decreased survival time, reduced compliance with treatments, and an overall decreased quality of life [29]. Similarly, cancer-related cachexia carries a poor prognosis for cancer patients, associated with a substantial decrease in survival time, decreased response to chemotherapy, and an overall decreased quality of life [20–22, 24, 26]. In fact, cachexia is responsible for 30% of cancer-related deaths, irrespective of tumor burden [33]. These findings are especially important for those cancers—such as pancreatic cancer—with limited treatment options and an association with higher rates of depression and weight loss [24, 29]. In these instances, the potential benefits of interventions targeting depression and cachexia are self-evident.

Understanding cytokines may also elucidate issues of diagnosis and the assessment of prognosis. For example, it has been demonstrated that cancer patients with higher serum levels of IL-6 have a shorter interval of time between diagnosis of a primary tumor and metastasis [23], as well

as more progressive disease after treatment [23]. In addition, cytokine levels may be used to detect occult metastatic disease [34] or may be used as tumor markers [35]. Future research will no doubt help to elucidate these important linkages.

The review article by Illman et al highlights exciting opportunities for basic mechanistic understanding and novel therapeutic alternatives. Further research is needed, however, to examine the effects of anticytokine therapy and its effects on depression. Additionally, understanding the exact causal linkages among cytokines, cachexia, and depression, and mapping distinct cytokine pathways that may be symptom specific, could help in shaping appropriate, effective treatment approaches, with the ultimate goal of reducing suffering and improving the quality of life for patients living with advanced disease.

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