Review

NeuroImmunoModulation

Neuroimmunomodulation 2004;11:279–292
DOI: 10.1159/000079408

Received: July 23, 2003
Accepted: September 10, 2003

A Cytokine-Based Neuroimmunologic Mechanism of Cancer-Related Symptoms

Bang-Ning Lee[a] Robert Dantzer[h] Keith E. Langley[d] Gary J. Bennett[i]
Patrick M. Dougherty[b] Adrian J. Dunn[e] Christina A. Meyers[c] Andrew H. Miller[f]
Richard Payne[g] James M. Reuben[a] Xin Shelley Wang[b] Charles S. Cleeland[b]

[a]Department of Hematopathology, [b]Department of Symptom Research, [c]Department of Neuro-Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Tex., [d]Medical Writing Department, Amgen Inc., Thousand Oaks, Calif., [e]Department of Pharmacology, Louisiana State University Medical School, Shreveport, La., [f]Department of Psychiatry, Emory University, Atlanta, Ga., and [g]Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, N.Y., USA; [h]Laboratory of Integrative Neurobiology, University of Bordeaux 2, Bordeaux, France; [i]Department of Anesthesia, McGill University, Montreal, Canada

Key Words

Cytokines · Cancer · Cancer-related symptoms · Sickness behavior · Pain · Fatigue · Depression · Cognitive impairment · Nuclear factor-kappa B

Abstract

While many of the multiple symptoms that cancer patients have are due to the disease, it is increasingly recognized that pain, fatigue, sleep disturbance, cognitive dysfunction and affective symptoms are treatment related, and may lead to treatment delays or premature treatment termination. This symptom burden, a subjective counterpart of tumor burden, causes significant distress. Progress in understanding the mechanisms that underlie these symptoms may lead to new therapies for symptom control. Recently, some of these symptoms have been related to the actions of certain cytokines that produce a constellation of symptoms and behavioral signs when given exogenously to both humans and animals. The cytokine-induced sickness behavior that occurs in animals after the administration of infectious or inflammatory agents or certain proinflammatory cytokines has much in common with the symptoms experienced by cancer patients. Accordingly, we propose that cancer-related symptom clusters share common cytokine-based neuroimmunologic mechanisms. In this review, we provide evidence from clinical and animal studies that correlate the altered cytokine profile with cancer-related symptoms. We also propose that the expression of coexisting symptoms is linked to the deregulated activity of nuclear factor-kappa B, the transcription factor responsible for the production of cytokines and mediators of the inflammatory responses due to cancer and/or cancer treatment. These concepts open exciting new avenues for translational research in the pathophysiology and treatment of cancer-related symptoms.

Cancer-Related Symptoms

Cancer is the second leading cause of death in western countries. The symptoms of cancer are what patients report to clinicians as the subjective negative feelings of physical and mental changes produced by both disease

KARGER

Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1021–7401/04/0115–0279$21.00/0

Accessible online at:
www.karger.com/nim

Charles S. Cleeland, PhD
Department of Symptom Research, Box 221
The University of Texas M.D. Anderson Cancer Center
1100 Holcombe Boulevard, Houston, TX 77030 (USA)
Tel. +1 713 745 3470, Fax +1 713 745 3475, E-Mail ccleeland@mdanderson.org

and treatment [1]. These symptoms may be the side effects and toxicities of aggressive chemotherapy or radiotherapy, acute or chronic symptoms after surgery, and/or the direct effects of the disease process itself. They can include physical symptoms (pain, gastrointestinal symptoms, fatigue, shortness of breath), cognitive symptoms (memory problems, impaired concentration), and affective symptoms (especially depression and anxiety). In a study in 1994, Portenoy et al. [2] administered the Memorial Symptom Assessment Scale to a random sample of inpatients and outpatients with cancer. The most frequently reported symptoms for the sample were lack of energy, worry, feeling sad, and pain.

Common symptoms of cancer and cancer treatment have become a major health problem in their own right [1]. Pain is a good example: when pain is present, it adversely affects a patient's mood, activity, and ability to relate to others [3]. Similarly, fatigue, gastrointestinal symptoms, cachexia, anorexia, shortness of breath, and psychological distress add tremendously to the affliction that patients experience. Patients with cancer typically experience multiple symptoms at the same time. These symptoms frequently occur together in clusters. For example, pain, fatigue, and depression often co-occur [2, 4]. Cancer-related symptoms are a major aspect of disease-related morbidity [1, 5]. The quality of life of cancer patients and their families is profoundly affected by the presence of severe pain and other symptoms [3, 6–9]. Multiple and severe symptoms also present a significant challenge for the resources of those who manage cancer patients. Symptoms that are unrecognized by the treatment team may become so severe that an emergency room visit or hospitalization are required for management, adding substantially to the cost of treatment and to the disruption of the patients' routine and that of their family. Untreated symptoms may also negatively influence treatment effectiveness by interrupting treatment or causing treatment termination [10–12].

While it has been widely accepted that one symptom can give rise to another symptom (pain may cause depression, depression may cause fatigue), researchers are recognizing that shared biologic mechanisms may play a role in producing more than one symptom. For example, the collective signs of sickness behavior that develop when laboratory animals are treated with endotoxin or purified cytokines resemble some of the clusters of symptoms experienced by cancer patients. Sickness behavior refers to the co-occurring behavioral and physiologic responses in animals receiving exogenous cytokines, infectious agents or endotoxins [13–17]. These animal models can provide a direction for future symptom research, including the trajectory of cancer-related symptoms and the exploration of the relationship between these symptoms and laboratory measurements. We review here the current understanding of cancer-related symptoms, the animal models of sickness behavior, and the potential neuroimmunologic mechanism of cancer-related symptoms and sickness behavior.

Clinical Studies of Cancer Symptoms

Although some symptoms (such as cognitive impairment) must be identified by performance measures, most cancer-related symptoms are typically identified and evaluated by subjective reports from patients. The development of symptom assessment measures has progressed enough to allow credible epidemiologic studies of symptoms to be performed. However, several caveats must be emphasized regarding symptom assessment. Symptoms are often assessed and treated as discrete entities, whereas they undoubtedly interrelate in complex ways. Symptoms may persist for long periods of time, necessitating longitudinal rather than cross-sectional study [13]. Longitudinal studies are essential if we are to understand the relationship of symptoms to biologic mechanisms. Further, symptoms need to be evaluated after stratifying for disease type, disease treatment, and response to disease treatment.

As published by Cleeland et al. [4, 13], the relative distances and relations between major symptoms reported by patients receiving cancer treatment are shown in figure 1. The patients in this study were heterogeneous as to diagnosis and treatment. Hierarchical cluster analysis was used to identify groups of similar items. Using the average linkage (centroid method) between symptom items, clusters were formed and the distances between symptom items were calculated using squared Euclidian distances [18]. Symptoms that cluster earlier in the analysis (toward the left side) are identified by patients as occurring together. This analysis demonstrates a close correlation between clusters of affective and cognitive symptoms. The fatigue-related symptom cluster is more closely associated with affective disturbances and cognitive impairment than with gastrointestinal and respiratory symptoms. Pain and sleep disturbance tend to be reported relatively independently of other symptoms. The analysis in figure 1 is presented as preliminary rather than definitive as it is not stratified for the type of cancer or the type of treatment. Nevertheless, the clustering of symptoms favors the no-

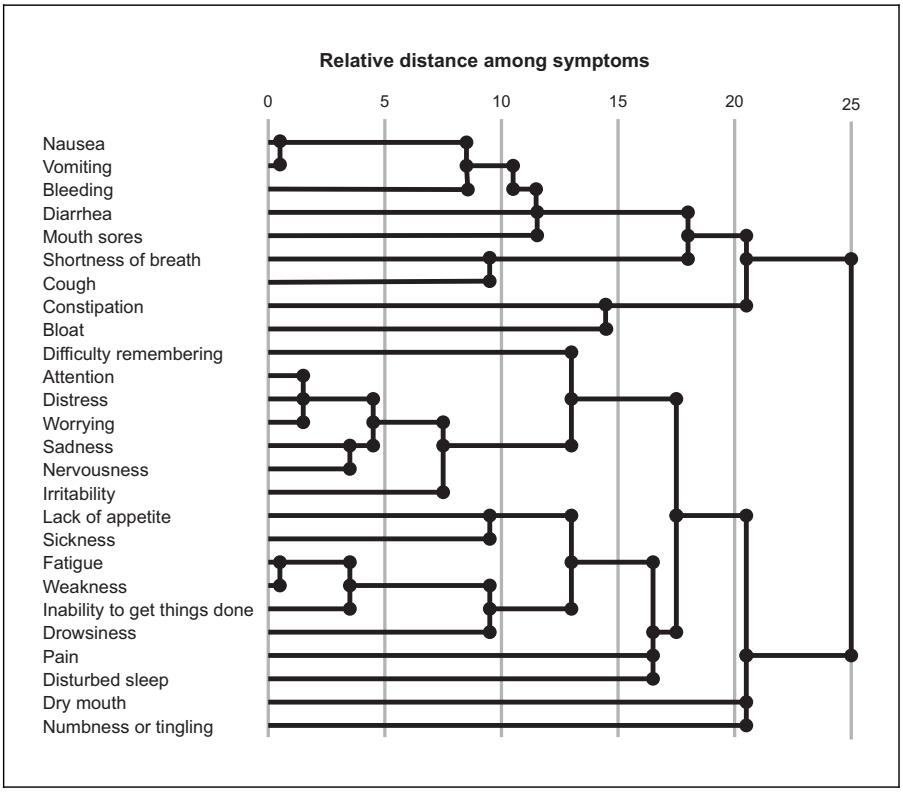

Fig. 1. Relative distance among symptoms associated with cancer and cancer treatment. This dendrogram shows the results of a cluster analysis of the self-reported symptoms of 527 outpatients undergoing therapy for various types of cancer at various stages. Hierarchical cluster analysis was used and clusters were formed using the average linkage (centroid method) between symptom items. The distances between symptoms were calculated using squared Euclidian distances. In this visual representation, the distance values of 0–25 represent relative distances; filled circles represent the point at which patients rated symptom items as very similar. Reading from left to right, vertical lines show the points at which symptom items join together. Symptoms that cluster earlier in the analysis are identified by patients as occurring together. For example, fatigue and weakness join immediately, suggesting the rating made by patients for one of these symptoms is almost identical to the rating for the other symptom. In contrast, pain and sleep disturbance remain separate from other symptoms for several steps in the analysis, indicating that patients identified them as occurring independently [4] (reprinted by permission of Wiley-Liss, Inc.).

tion that a given cluster may share underlying biologic mechanisms.

The most prevalent symptom associated with cancer and its treatment is fatigue. A recent study at The University of Texas M.D. Anderson Cancer Center indicated that over 40% of outpatients receiving chemotherapy experienced severe fatigue, resulting in significant impairment of their daily function [19]. Fatigue can be severely distressing for patients during and after cancer therapy, and can be a reason that patients stop treatment. Importantly, fatigue is commonly associated with many other symptoms, such as depression, lack of motivation, disturbed sleep, gastrointestinal symptoms, and difficulty thinking. Even so, there have been very few studies of the mechanisms that may underlie cancer-related fatigue and the other symptoms that tend to be associated with it.

Many cancer patients also experience impairments of neurocognitive function, including memory loss, distractibility, difficulty with multitasking, and mood disturbance. The etiologies of these problems are diverse and include direct effects of cancer within the central nervous system, indirect effects of certain cancers (the paraneoplastic disorders), and effects of cancer treatment on the brain. In addition to these cancer-related causes, patients may have coexisting neurologic or psychiatric disorders that affect their cognition and mood. Cognitive function studies performed on untreated cancer patients suggest that impairments tend to cluster. Such frontal subcortical

components as memory, motor dexterity, and executive functions tend to be impaired concurrently, although attention and psychomotor speed are not [20]; similarly, impairment is often found in working memory (the ability to process information and do multiple tasks) but not in hippocampal components of memory (retention and consolidation) [21]. Careful longitudinal assessment of patients complaining of neurocognitive or behavioral problems is essential to provide appropriate interventions and to maximize their quality of life.

Treatment-related neuropathic pain is also very distressing for cancer patients and is difficult to control. Chemotherapeutic agents such as vinca alkaloids, taxanes, and cisplatin are commonly associated with the development of neuropathic pain during treatment. Neuropathic pain has also been reported with immunotherapies [22, 23]. Since this symptom often persists long after treatment, it affects the return of cancer patients to productivity. Recent psychophysical studies have revealed that patients with neuropathic pain following treatment with vincristine, cisplatin, or taxol experience multiple zones of sensory disturbance [24, 25]. These psychophysical characteristics are similar to those observed in patients receiving cytokine therapy, even for neuropathies not associated with cancer [26, 27]. Nonetheless, little is known about the mechanistic and psychophysical characteristics of neuropathic pain.

It is likely that symptoms may have natural associations with each other that reflect the underlying mechanisms, yet descriptive studies of the symptoms of cancer patients are far from comprehensive. There is a need to explore symptom associations systematically and to design clinical studies so as to better understand possible common mechanisms for coexisting symptoms [13].

Roles for Cytokines in Cancer Patients: A Biologic Basis for Symptoms?

The hypothesis that proinflammatory cytokines might play a pivotal role in the pathophysiology of cancer-related symptoms comes from several convergent lines of experimental and clinical research not limited to the study of cancer. Inflammation is now recognized as a critical component of tumor progression not only because many cancers arise from sites of infection, chronic irritation, and inflammation, but also because tumor cells coopt some of the signaling molecules of the innate immune system for invasion, migration and metastasis [28]. Proinflammatory cytokines have been demonstrated to have very potent effects on brain functions. Immunotherapy with inflammatory cytokines is widely used in the treatment of chronic leukemia, renal cell carcinoma, and melanoma. In fact, more than half of patients receiving cytokine treatment have documented cognitive impairments, being considerably greater than the rate of cognitive dysfunction in patients treated with cytotoxic agents only [29]. Interferon (IFN)-α, the most widely used immunotherapy agent, has a broad array of effects on central nervous system function. Leukemia patients receiving IFN-α may develop cognitive deficits involving information-processing speed, verbal memory, and frontal lobe executive functions, a pattern suggestive of frontal-subcortical dysfunction [30]. Similar cognitive impairments appear in conjunction with the use of other cytokines in clinical trials against cancer [31]. Interleukin (IL)-2 and tumor necrosis factor (TNF)-α can cause memory deficits, difficulties with motivation and flexible thinking, motor dyscoordination, depression, and anorexia, while visuoperceptual and language functions tend not to be affected [32]. TNF-α causes such dose-dependent toxicities as decreased attentional abilities, verbal memory deficits, motor coordination impairments, and frontal lobe executive dysfunction. Headache, anorexia, stroke-like events (e.g. transient amnesia), and demyelination in the brain are also found as adverse effects of TNF-α. IL-1 and its receptors are found in many areas of the brain, particularly the hippocampus. IL-1 suppresses the influx of calcium into hippocampal neurons, which may explain the preponderance of memory impairments in patients with IL-1-associated toxicity [32].

Apart from the effect of cytokines on brain function, changes in serum concentrations of IL-1 receptor antagonist (IL-1RA), TNF-α, IL-6, IL-8, and epidermal growth factor are associated with fatigue and reduced quality of life in patients with myelodysplastic syndrome and acute leukemia prior to treatment [Meyers, unpubl. obs.]. Further evidence from women with breast cancer indicates that the hormone-ablative agent tamoxifen affects several neurotransmitters (e.g. seratonin, dopamine) and cytokines (e.g. IL-1, IL-6, IFN-α, TNF-α) implicated in cognitive functioning [33]. Major depression (which occurs in 1–15% of patients receiving tamoxifen) has been associated with increases in IL-1, IL-6, IL-2, TNF-α, and IFN-α and is associated with such symptoms as psychomotor retardation, malaise, lassitude, anxiety, anhedonia, and sleep disturbance [34].

IFN-induced proteins are elevated in the blood of patients suffering from chronic fatigue syndrome, which is related to such viral infections as Epstein-Barr virus,

human herpes virus-6, and cytomegalovirus [35]. Similarly, fluctuations in peripheral cytokines are associated with cancer-related fatigue [36]. For example, fatigued breast cancer survivors had significantly higher serum levels of IL-1RA, type 2 soluble TNF-α receptor, and neopterin than nonfatigued survivors [37]. Cancer-related fatigue may also be linked with anemia, low serum albumin and abnormal hemoglobin levels [38]. Further, high serum levels of IL-1, IL-6 and TNF-α were present in advanced-stage cancer patients, particularly in those with anorexia/cachexia syndrome [39]. The development of depression in colorectal patients with advanced disease was related to immune activation, as there was a positive correlation between the serum level of soluble IL-2 receptor alpha and the Hospital Anxiety and Depression Scale score [40].

The induction of proinflammatory cytokines around nerve endings may play a role in chemotherapy-induced peripheral neuropathy, as cytokines are released from tissues following exposure to chemotherapeutic drugs. Coadministration of vincristine and granulocyte-macrophage colony-stimulating factor (GM-CSF) markedly increases the severity and magnitude of treatment-induced pain and neurological impairment [41, 42]. The proinflammatory cytokines IFN-γ, TNF-α, and IL-1β are increased by cisplatin [43, 44] and taxol [45, 46]. Vincristine does not induce release of the same cytokines as taxol and cisplatin but rather induces an elevation of GM-CSF and downregulates TNF-α receptors [47]. Nevertheless, all three chemotherapeutic drugs directly activate the nuclear factor-kappa B (NF-κB) signaling pathway, which provides a link to the generation of pain as it is also activated in response to N-methyl-*D*-aspartate and substance P receptors in neural tissues [48, 49]. These are the key spinal neurotransmitter systems involved in the generation of cutaneous hyperalgesia [50].

Roles for Cytokines in Eliciting Sickness Behavior in Animals

There are few published studies that focus on symptoms using tumor-bearing mice and rats, other than those aimed at clarifying the role of cytokines in cachexia [51]. Nevertheless, cytokines such as IL-1β are thought to play important roles in the development of sickness behavior in animals by acting on targets in the peripheral and central nervous systems to elicit neuronal changes that lead to the development of sickness behaviors [52].

Anorexia, Nausea, and Cachexia

Illness-related reduction in feeding has been the most widely studied sickness behavior. It is observed in a variety of species and with a variety of different viral and bacterial infections [53–55], in the presence of tumors [56], in response to endotoxin [57], and following administration of certain purified cytokines. IL-1 is particularly potent, and is effective when administered intracerebrally or by one of many other routes [53, 54, 57, 58]. IL-6, TNF-α, and IFN-α have all been reported to reduce feeding [16, 54, 55], but the effects have been less consistent than with IL-1 and lipopolysaccharide (LPS), except when they were administered intracerebrally [59]. Peripheral administration of IL-6 failed to induce anorexia [60], although it is effective intracerebrally [59]. Peripheral administration of murine IFN-α and IFN-γ also induce reductions in food intake in mice [61]. Peripheral TNF-α administration has weak effects [60], but is more effective intracerebrally [59]. There is substantial evidence from antagonist studies that TNF-α is involved in the anorexia associated with cancer [51]. However, there is a rapid tolerance to this effect of TNF-α, and a major part of the anorexic response reflects a conditioned taste aversion [62].

LPS is perhaps the most studied anorexia inducer. Interestingly, although the anorexia induced by IL-1 is largely prevented by cyclooxygenase (COX) inhibitors [60, 63], the anorexic response to LPS is only slightly affected [58]. This suggests that the anorexic response to LPS is not mediated by IL-1. Consistent with this, LPS-induced anorexia is not prevented by IL-1RA [60] and it appears in IL-1 knockout mice [64]. However, combined treatment with antagonists to IL-1, IL-6 and TNF-α largely prevented LPS-induced anorexia, suggesting that each cytokine may be involved in a redundant manner [58]. The lack of sensitivity of illness-related anorexia to COX inhibitors extends to viral infections [58] and tumor models [65].

In addition to loss of appetite, cancer patients frequently experience nausea and vomiting. Since rodents do not vomit, they cannot be used to directly study the involvement of cytokines in nausea. Indirect approaches make use of the vagal-dependent effects of cytokines on gastric motility. For instance, the observation that the activation of the parasympathetic vagal excitatory pathways to the stomach by thyrotropin-releasing hormone was suppressed in urethane-anesthetized rats by a microinjection of TNF-α into the dorsal vagal complex was interpreted as evidence for a role of TNF-α on the vago-vagal reflex circuits that mediate the feelings of nausea [66]. In contrast to laboratory rodents, piglets vomit easily

and can therefore be used as a model to study the pathophysiology of emesis. Piglets consistently respond to cisplatin by acute and delayed emesis [67]. This response is sensitive to 5-HT3 receptor antagonists and to COX inhibitors [68]. LPS administered intraperitoneally also induces vomiting in piglets. This response is accompanied by increased circulating levels of TNF-α [69] and blocked by bilateral vagotomy and by COX inhibitors [68].

There is evidence that IL-6 plays a significant role in the development of cancer cachexia. As mentioned above, IL-6 has little effect of its own on food intake. However, its production is increased in the tumor microenvironment, and the neutralization of IL-6 by passive immunization or the antagonism of IL-6 receptor activation is accompanied by a significant reduction of the severity of cachexia in a murine model of colon cancer [70]. In the same model, an intratumoral injection of oligonucleotides to the NF-κB binding site that decreased the induction of IL-6 mRNA also significantly attenuated cachexia, without affecting the tumor burden [71].

Pain

That cytokines may contribute to cancer-related pain is suggested by animal models of hyperalgesia. The expression of IL-1β and TNF-α has been shown to be upregulated in the spinal cord of several rat mononeuropathy models [72]. Blocking the actions of IL-1β and TNF-α attenuates mechanical allodynia in a gender-specific manner in an L_5 spinal nerve transsection rodent model of neuropathic pain [73]. Structural damage to peripheral axons in the rat chronic constriction injury model led to an inflammatory reaction at the site of injury, and subsequently to neuropathic pain [74]. In a rat model of peripheral neuritis, the sciatic nerve was exposed to carrageenan, an immune stimulant, which caused the infiltration of inflammatory cells such as macrophages, neutrophils, and CD4+ and CD8+ T cells to the site, accompanied by increases in the concentrations of cytokines and the development of endoneural neuropathic pain [75].

Cytokines may cause symptoms by directly producing discharges of nerve fibers [76, 77], by altering neurotransmission [78], by altering the trafficking of growth factors along nerve fibers resulting in phenotypic changes in sensory endings [79], or by inducing an alteration of glial cell-mediated support of neural activities such as synaptic glutamate reuptake [80]. The cytokines IFN-α, TNF-α and IL-1 are inducible by cisplatin [43, 44] and taxol [45, 46], and also by irradiation [81–83]. Vincristine induces increased release of GM-CSF [47], suggesting that this agent causes peripheral neuropathy by a cytokine-mediated signaling pathway. Like humans, experimental animals develop hypersensitivity to cutaneous stimuli (i.e., peripheral neuropathy) following treatment with cisplatin [84], taxol [85, 86] and vincristine [87]. Both humans [88] and animals [89] often develop neuropathic pain-like syndromes and insensitivity to the analgesic properties of morphine upon exposure to gamma irradiation.

Cognitive Impairment

Earlier studies with transgenic mice have demonstrated distinct chronic-progressive neurologic disorders with neurodegeneration and cognitive decline associated with IL-6 expression, macrophage/microglial-mediated primary demyelination with motor impairment associated with IL-3 expression, and lymphocytic meningoencephalomyelitis with paralysis associated with TNF-α expression [90]. These findings indicate that specific cytokines produce specific neuropathologic alterations and functional impairments.

Examining cognitive assessment in animals in 1998, Gibertini [91] used the Morris water maze task with female C57BL/6 mice to study the dose effect of IL-1β on learning intensity and motivation. This study showed that IL-1β interfered with learning in a warm-water maze, but not in a cold-water maze. In general, treatments that elevate the levels of IL-1β in the brain are associated with learning impairment. This effect is apparently not due to a mere performance deficit since the forms of learning that are impaired are quite specific. For instance, the posttraining injection of IL-1β into the dorsal hippocampus of rats submitted to fear conditioning did not alter the freezing response to an auditory cue paired with electric shock, a form of memory that is independent of the hippocampal formation, but attenuated the fear response to the context, a form of memory that is dependent on the hippocampus [92]. In the same manner, IL-1β injected into the dorsal hippocampus of rats significantly increased the working memory errors in a three-panel runway setup but had no effect on the latency and the number of errors in the first trial [93]. A possible mechanism for these effects is the action of IL-1β on synaptic plasticity, since this cytokine is able to impair long-term potentiation in the hippocampus [94], a cellular model of learning.

IL-1β is not the only cytokine able to impair learning and memory. In another study, acute systemic administration of IL-2 did not influence spatial memory in mice as measured by performance in a water maze. In contrast, chronic administration of IL-2 impaired performance when the position of the escape platform varied over days but was without effect when the platform position was

fixed. The same treatment produced modest reductions in exploration and approach to a novel stimulus, effects not seen after acute treatment [95].

Depression

Several authors have pointed out that the symptoms of sickness behavior resemble those of depression [57, 96, 97]. A majority of depressed patients exhibit elevated plasma concentrations of cortisol, which is characteristic of infections [98] and is induced by the administration of IL-1 and LPS [99]. In 1996, Yirmiya [57] demonstrated that rats treated with LPS expressed an apparent anhedonia (decreased preference for saccharin), one of the cardinal symptoms of depression. Interestingly, this effect of LPS was largely prevented by chronic (but not acute) treatment with the antidepressant imipramine. In an attempt to dissociate the anhedonic from the anorexic effects of cytokines, Merali et al. [100], in 2003, showed that chronic pretreatment of rats with fluoxetine did not alter IL-1β-induced reduction of freely available lab chow, but attenuated the IL-1β-induced decrease in responding for a sucrose reward on a progressive ratio schedule in which rats had to progressively increase their number of operant responses in order to get the reward. The antidepressant effect does not appear to occur in mice, and may reflect peripheral mechanisms [101–103]. Limited evidence points to the possibility that antidepressants may alter the balance between proinflammatory and anti-inflammatory cytokines [104]. A role for cytokines in depression has been further proposed, based on the synergy between the brain effects of cytokines and those of psychogenic and neurogenic stressors, and the sensitization that develops upon repeated exposure to cytokine treatments [105].

Fatigue

Fatigue symptoms are multifactorial and are influenced by motivational state, muscle mass and strength, motor unit reorganization, and metabolic status. Proinflammatory cytokines can act at all these levels to induce fatigue. In rats and mice, fatigue is usually measured by the amount of wheel running or treadmill running that animals engage in. Based on these criteria, infection and other conditions associated with an increase in proinflammatory cytokines are accompanied by signs of extreme fatigue. For instance, intravenous injection of killed *Brucella abortus* caused an immediate decrease in voluntary running for a few days followed by a gradual return to baseline over the next 2–4 weeks, albeit with substantial interindividual differences in the rate of recovery [106]. In another study, a significant difference in running activity between two mice strains was observed after *Corynebacterium parvum* antigen inoculation: C57BL/6 mice showed a significant reduction in running activity compared to preinjection levels and slower recovery to baseline than Balb/c mice [107]. Further, increased TNF-α and IL-1β mRNA expression was found in the brains of C57BL/6 mice compared to that seen in Balb/c mice at 6, 10, and 15 days after *C. parvum* antigen injection. IFNs are also involved in fatigue. Mice acclimated to treadmill running showed a decreased run time to fatigue when injected with the pathogen-associated molecule polyinosinic polycytidylic acid; this was attenuated by passive immunization against IFN-α/β [108].

Summary

It is clear from the evidence presented above that proinflammatory cytokines have the potential to mediate cancer-related symptoms. However, most of the behavioral effects of cytokines have been described in conditions of acute administration of cytokines or cytokine inducers. There is therefore a need for longer-term studies. It will also be necessary to delineate the exact cytokines that mediate each category of symptoms if the apparent specificity in the activity of each component of the cytokine network is confirmed (e.g. IL-6 for cachexia, IL-1β for cognitive impairment, IFN-α for fatigue). Last but not least, the mechanisms that are involved need to be worked out in relation to the intracellular signaling pathways and the role of intermediate mediators such as prostaglandins and nitric oxide. The animal models of sickness behavior discussed above allow us to address some of these questions. Yet, additional animal models of cognitive impairment and depression need to be applied to our understanding of cancer-related symptoms. Existing models considered to represent these symptoms may not correspond accurately to human symptoms, either operationally or behaviorally, giving rise to a unique challenge. For example, human cognitive impairment often seems to affect working memory capacity and efficient memory retrieval, while animal models are designed to assess declarative and nondeclarative memory. Animal fatigue models are particularly lacking and will require careful attention to distinguish locomotor deficits from fatigue per se [13]. Researchers would benefit from the input of clinical and basic scientists, who could identify operational definitions for cancer-related symptoms and propose component animal behaviors that might represent these definitions. Finally, researchers could apply this framework to animal models of various types of cancer in order

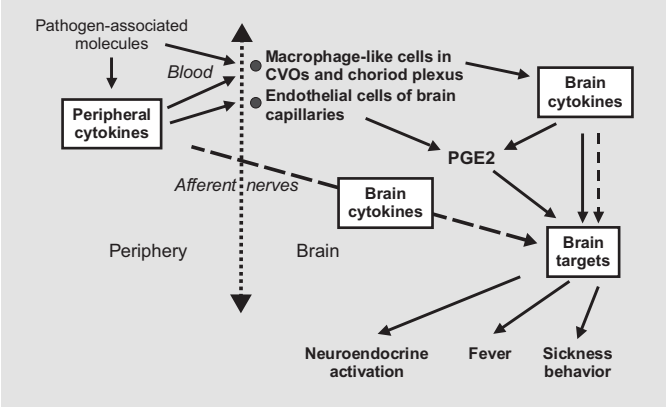

Fig. 2. A schematic drawing of a proposed mechanism of action for cytokines on the brain. Peripheral cytokines are produced by accessory immune cells in response to various pathogen-associated molecules. IL-1, in particular, activates afferent nerves locally and can, under certain conditions, enter the blood in sufficiently high concentrations to reach the CVOs and the choroid plexus. Note that circulating pathogen-associated molecules can also reach the same targets in the CVOs and choroid plexus to induce the synthesis of cytokines. We propose that activation of afferent nerves leads to the induction of the expression of brain cytokines. Cytokines can also act on endothelial cells of brain capillaries to induce the synthesis of prostaglandins (PGE_2) that can freely diffuse into the brain parenchyma and activate neuronal targets. Cytokines produced in the brain or in the CVOs and choroid plexus can enter the brain parenchyma and activate directly or indirectly various neuronal targets to induce components of sickness behavior. The dotted lines represent neural pathways of transmission, while the solid lines represent humoral pathways.

to validate the mechanisms proposed in this review and to seek additional potential moderators.

Cytokines as a Mechanistic Framework for Cancer-Related Symptoms

Cytokines are thought to be among the mediators that bridge the neuroendocrine and immune systems. Cytokines produced by activated immune cells can alter neural activity [78, 109], while hormones and neurotransmitters released by the nervous system can bind to receptors expressed by immune cells [15, 110]. Based on the potent effects of IL-1β on the brain and the association between pathological states of immune activation and depression, Smith [96], in 1991, proposed that excessive secretion of IL-1 and other macrophage products causes depression. This has been supported by studies showing the presence of a moderate activation of the innate immune system in depressed patients and the normalizing action of antidepressant therapy [111]. Although there are many problems associated with biologic psychiatry approaches, including the relevance of circulating cytokines to mental states, a recent study demonstrated that levels of IL-1β in the cerebrospinal fluid of 13 hospitalized patients with acute untreated severe depression were higher than those of normal subjects [112].

Peripheral cytokines can induce brain effects in multiple ways [52, 113]: they can induce the synthesis of prostaglandins (PGE) by endothelial cells in brain capillaries, they can act on cells in the circumventricular organs (CVOs) and the choroid plexus, and/or they may induce the expression of cytokines in the brain by activating afferent nerves. PGE and locally produced cytokines diffuse into the brain parenchyma and ultimately act directly or indirectly on different neuronal targets to induce sickness behavior, neuroendocrine activation and changes in body temperature. As depicted in figure 2, the dotted line represents neural pathways of transmission, while the solid line represents humoral pathways. Circulating pathogen-associated molecular patterns that activate accessory immune cells at the periphery can also reach the same targets in the CVOs and choroid plexus to induce the synthesis of cytokines. It is noteworthy that cancer-related symptoms also correlate with changes in the concentrations of other potential mediators induced by proinflammatory cytokines (e.g. acute-phase proteins and tryptophan). In non-Hodgkin's lymphoma and leukemia patients, fatigue strongly correlates with decreased circulating concentrations of albumin [38]. Immunotherapy-induced depression has been correlated with increased plasma concentration of IL-10 (an anti-inflammatory cytokine) and decreased plasma concentrations of tryptophan [114]. The decrease in plasma tryptophan is mainly a consequence of the activation by IFN-γ of indolamine 2,3-dioxygenase, an enzyme that catabolizes the degradation of tryptophan along the kynurenine pathway, resulting in a decrease in brain serotonin [114].

The Transcription Factor: NF-κB, a Possible Link between Proinflammatory Cytokines and Cancer-Related Symptoms

NF-κB regulates both innate and adaptive immune responses. A large variety of danger signals, including bacteria and viruses, can lead to the activation of NF-κB, which in turn controls the expression of many inflammatory cytokines, chemokines, immune receptors, and cell

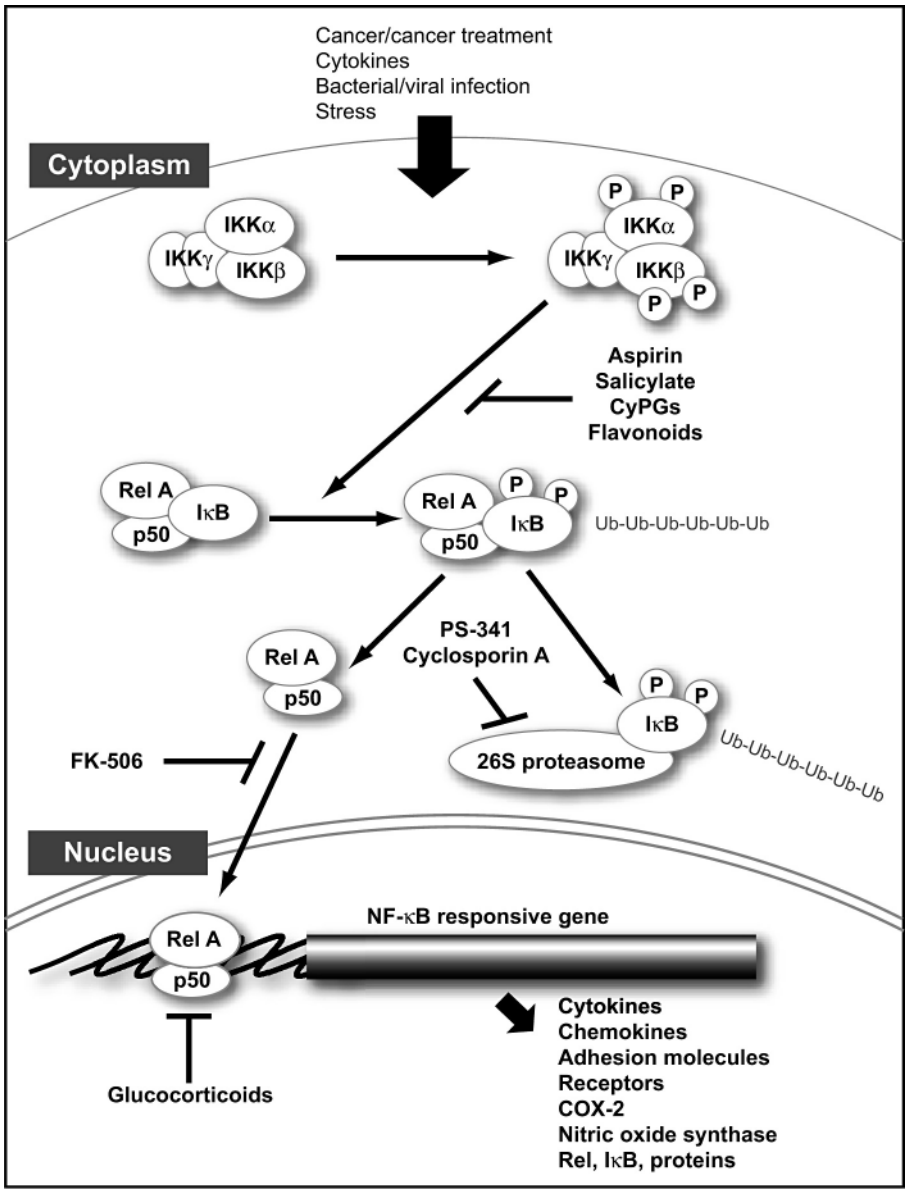

Fig. 3. Inhibition of the NF-κB pathway by therapeutic agents. NF-κB can be the target for new types of treatment to block the inflammatory responses due to cancer and its therapy. Numerous drugs including glucocorticoids, NSAIDs (aspirin, salicylate), cyclopentenone prostaglandins (CyPGs), and natural products (flavonoids) can act at several of these steps to interfere with NF-κB activation. In addition, specific molecules such as PS-341 (a potent inhibitor of proteasome function) and FK-506 (an immunosuppressive agent blocking the c-Rel translocation) can prevent IκB degradation and transcription of NF-κB-responsive genes, respectively [115] (adapted with permission from *The Journal of Clinical Investigation*).

surface adhesion molecules. Recent studies have shown that NF-κB can also regulate stress responses, since different stressful conditions, including physical stress, oxidative stress, and exposure to certain chemicals, also lead to NF-κB activation. In particular, IL-1β and TNF-α produced by an NF-κB-dependent mechanism can also directly activate the NF-κB pathway, thus establishing a positive autoregulatory loop [115]. In addition, NF-κB activates the expression of genes coding for enzymes involved in the pathogenesis of the inflammatory process, including inducible nitric oxide synthase and inducible COX-2 [116]. COX-2 enables prostaglandin formation (phospholipase A_2 initiates the cascade), and the active products of the arachidonate metabolism produced by the cerebral microvasculature have critical roles in initiating the neuronal responses and the neurophysiological outcomes that take place during immunogenic stimuli, including sickness behaviors, fever and increased activity in the hypothalamic-pituitary-adrenal axis [117]. Therefore, the activation of NF-κB is a potential link between the expression of inflammatory cytokines and the production of cancer-related symptoms.

NF-κB is constitutively activated in various types of cancer, including leukemia, lymphoma, breast cancer, and colorectal cancer [118]; it is also directly activated by multiple chemotherapeutic drugs including the vinca alkaloids, the taxanes, and the platinum compounds [119]. Therefore, inhibitors of this signaling pathway may act to correct cancer-related symptoms. A schematic illustration of the steps involved in the inhibition of the NF-κB pathway as described by Yamamoto and Gaynor [115] (adapted with permission) is depicted in figure 3. Glucocorticoids, such as dexamethasone and prednisone, and nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and salicylate, are widely used for their anti-inflammatory and immunosuppressive properties, and there are several proposed mechanisms to explain the inhibitory effects on the NF-κB pathway [120]. Other than glucocorticoids and NSAIDs, cyclopentenone prostaglandins and natural products (flavonoids) can interfere with NF-κB activation. In addition, specific molecules such as PS-341 (a potent inhibitor of proteasome function) and FK-506 (an immunosuppressive agent blocking the c-Rel translocation) can prevent IκB degradation and transcription of NF-κB-responsive genes, respectively. Whether or not cancer treatment involving the inhibition of the NF-κB activation pathway will lead to the inhibition of cytokines and possibly to a reduction in symptoms needs further investigation. In addition, the establishment of animal models will allow us to study how potential inhibitors of this signaling pathway may act to correct sickness behaviors.

Pharmacological Agents Used in Animal Models

A wide range of animal models of pain and affective disorders has contributed significantly to the development of pharmacological agents. The most common pharmacological agents used to antagonize sickness behaviors in animals are the NSAIDs [121], which include aspirin, acetaminophen, ibuprofen and the COX-2-selective inhibitors [122]. However, most of the effects of NSAIDs take place at the periphery, and the ability of these drugs to abrogate centrally mediated sickness behaviors is still unclear. The effect of any one NSAID or glucocorticoid varies considerably with its concentration, the presence of other regulatory molecules, the type of target cells, and the extracellular environment. Anti-inflammatory cytokines such as IL-10 and IL-1RA have potent downregulatory effects on the expression and action of cytokines in the brain [123]. Others, such as IL-4 and IL-13, have more complex effects since their administration can worsen sickness behavior depending on when they are administered [124, 125]. Taking advantage of these agents in animal models may be crucial to establishing the mechanisms implicated in the development of cancer-related symptoms.

Future Directions and Conclusion

In the search for underlying mechanisms, laboratory researchers must collaborate with clinicians to better understand the symptoms presented by cancer patients, so that such symptoms may be appropriately modeled in animals. Effective translational research is needed to identify outcome measures (usually behavioral assessments) that maximize the generalizability of animal findings to patient studies. Animal researchers should seek common denominators for behavioral assessment and make use of cytokine antagonists to control behavioral changes. Potential therapeutic agents can then be translated from bedside to bench in order to gain insight into the pathophysiology of symptom development and control. For example, researchers need to know whether different cerebral mechanisms are involved in different sickness behaviors. The existence of differences would allow selective manipulation of a particular symptom. When dealing with animal experiments, assessment of symptoms or behaviors should be repeated at fixed intervals so that changes in symptom severity and patterns related to both disease and treatment can be identified. Further, data on potential biologic markers of symptoms need to be collected from a large set of patients. Longitudinal and multivariate statistical modeling can then be applied to identify patterns of symptoms that cluster and thus suggest shared biologic mechanisms.

The hypothesis that cytokines play a mechanistic role in the production of cancer-related symptoms could potentially stimulate new approaches to symptom treatment. Systematic, multi-institutional cooperation is needed to develop and standardize the assessment of multiple symptoms and physiologic and biologic correlates within a framework for hypothesis generating and testing. To complement descriptive studies of symptom evolution and to probe mechanistic pathways, well-designed clinical trials can be undertaken. Basic science studies using the established animal models of cancer-related symptoms need to continue. Animal models for pain are presently the best-developed and most useful for generating and

testing hypotheses because pain mechanisms are more physiologically definable and behaviorally measurable than the mechanisms for other symptoms. Other animal models of cancer-related symptoms will help define the cellular and molecular mechanisms of symptom development.

In conclusion, mounting evidence indicates that some cancer-related symptoms are produced by common biologic mechanisms, and that alterations in cytokines and other neuroimmunological processes may be critical to symptom production. Such evidence is provided by animal models of sickness behavior that resemble the human expression of cancer symptoms, and by our increasing understanding of the ways that symptoms correlate and cluster. Modulating cytokines and their receptors may suppress and perhaps even protect against the development of at least some cancer-related symptoms. With ample subjects to stratify for such factors as cancer type, treatment, and response to treatment, large-scale clinical studies examining the relationship of symptoms and inflammatory markers could provide critical leads in developing more targeted therapy for symptom control.

Acknowledgments

We thank Dr. Perry Fuchs of The University of Texas at Arlington for comments on the animal models for cognitive impairment, and Jeanie F. Woodruff of M.D. Anderson Cancer Center for editorial support. This publication is supported by an educational grant from Amgen, Inc.

References

1 Cleeland CS: Cancer-related symptoms. Semin Radiat Oncol 2000;10:175–190.
2 Portenoy RK, Thaler HT, Kornblith AB, Lepore JM, Friedlander-Klar H, Coyle N, Smart-Curley T, Kemeny N, Norton L, Hoskins W: Symptom prevalence, characteristics and distress in a cancer population. Qual Life Res 1994;3:183–189.
3 Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS: When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain 1995; 61:277–284.
4 Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, Engstrom MC: Assessing symptom distress in cancer: The M.D. Anderson Symptom Inventory. Cancer 2000; 89:1634–1646.
5 Brescia FJ, Portenoy RK, Ryan M, Krasnoff L, Gray G: Pain, opioid use, and survival in hospitalized patients with advanced cancer. J Clin Oncol 1992;10:149–155.
6 Cain JM, Hammes BJ: Ethics and pain management: Respecting patient wishes. J Pain Symptom Manage 1994;9:160–165.
7 Hammes BJ, Cain JM: The ethics of pain management for cancer patients: Case studies and analysis. J Pain Symptom Manage 1994;9:166–170.
8 Cella DF: Quality of life: Concepts and definition. J Pain Symptom Manage 1994;9:186–192.
9 Wang XS, Cleeland CS, Mendoza TR, Engstrom MC, Liu S, Xu G, Hao X, Wang Y, Ren XS: The effects of pain severity on health-related quality of life: A study of Chinese cancer patients. Cancer 1999;86:1848–1855.
10 Borden EC, Parkinson D: A perspective on the clinical effectiveness and tolerance of interferon-alpha. Semin Oncol 1998;25(1 suppl 1): 3–8.
11 Parsons JT, Bova FJ, Million RR: A re-evaluation of split-course technique for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1980;6:1645–1652.
12 Parsons JT, Thar TL, Bova FJ, Million RR: An evaluation of split-course irradiation for pelvic malignancies. Int J Radiat Oncol Biol Phys 1980;6:175–181.
13 Cleeland CS, Bennett GJ, Dantzer R, Dougherty PM, Dunn AJ, Meyers CA, Miller AH, Payne R, Reuben JM, Wang XS, Lee BN: Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? Cancer 2003;97:2919–2925.
14 Dantzer R, Bluthe RM, Laye S, Bret-Dibat JL, Parnet P, Kelley KW: Cytokines and sickness behavior. Ann N Y Acad Sci 1998;840:586–590.
15 Dantzer R, Konsman JP, Bluthe RM, Kelley KW: Neural and humoral pathways of communication from the immune system to the brain: Parallel or convergent? Auton Neurosci 2000; 85:60–65.
16 Larson SJ, Dunn AJ: Behavioral effects of cytokines. Brain Behav Immun 2001;15:371–387.
17 Watkins LR, Maier SF: The pain of being sick: implications of immune-to-brain communication for understanding pain. Ann Rev Psychol 2000;51:29–57.
18 Johnson SC: Hierarchical clustering schemes. Psychometrika 1967;32:241–254.
19 Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, Huber SL: The rapid assessment of fatigue severity in cancer patients: Use of the Brief Fatigue Inventory. Cancer 1999;85:1186–1196.
20 Meyers CA, Byrne KS, Komaki R: Cognitive deficits in patients with small cell lung cancer before and after chemotherapy. Lung Cancer 1995;12:231–235.
21 Scheibel RS, Valentine AD, O'Brien S, Meyers CA: Cognitive dysfunction and depression during treatment with interferon-alpha and chemotherapy. J Neuropsychiatry Clin Neurosci, in press.
22 Slart R, Yu AL, Yaksh TL, Sorkin LS: An animal model of pain produced by systemic administration of an immunotherapeutic anti-ganglioside antibody. Pain 1997;69:119–125.
23 Garber K: Cancer research. Taking garbage in, tossing cancer out? Science 2002;295:612–613.
24 Dougherty PM, Cordella JV, Weng HR: Chemotherapy-induced hypersensitivity is accompanied by a decrease in spontaneous locomotor activity (abstract). Soc Neurosci 31st Annu Meet, San Diego, 2001, 506.5.
25 Dougherty PM, Weng H-R, Burton A, Reddy S: Psychophysical findings in patients with chemotherapy-induced peripheral neuropathy. J Pain 2002;3(Suppl 1):17.
26 Brenard R: Practical management of patients treated with alpha interferon. Acta Gastroenterol Belg 1997;60:211–213.
27 Bridge TP: Neuropsychiatrically active lymphokines and AIDS. Clin Neuropharmacol 1986;9:473–475.
28 Coussens LM, Werb Z: Inflammation and cancer. Nature 2002;420:860–867.
29 Meyers CA, Abbruzzese JL: Cognitive functioning in cancer patients: Effect of previous treatment. Neurology 1992;42:434–436.
30 Pavol MA, Meyers CA, Rexer JL, Valentine AD, Mattis PJ, Talpaz M: Pattern of neurobehavioral deficits associated with interferon-alpha therapy for leukemia. Neurology 1995; 45:947–950.
31 Meyers CA, Valentine AD, Wong FC, Leeds NE: Reversible neurotoxicity of interleukin-2 and tumor necrosis factor: Correlation of SPECT with neuropsychological testing. J Neuropsychiatry Clin Neurosci 1994;6:285–288.

32 Meyers CA, Valentine AD: Neurological and psychiatric adverse effects of immunological therapy. CNS Drugs 1995;3:56–68.
33 Erlanger DM, Kutner KC, Jacobs AR: Hormones and cognition: Current concepts and issues in neuropsychology. Neuropsychol Rev 1999;9:175–207.
34 Dantzer R, Wollman EE, Vitkovic L, Yirmiya R: Cytokines, stress, and depression: Conclusion and perspectives; in Dantzer R, Wollman EE, Yirmiya R (eds): Cytokines, Stress, and Depression. New York, Kluwer Academic/Plenum, 1999, pp 317–329.
35 Vojdani A, Lapp CW: Interferon-induced proteins are elevated in blood samples of patients with chemically or virally induced chronic fatigue syndrome. Immunopharmacol Immunotoxicol 1999;21:175–202.
36 Kurzrock R: The role of cytokines in cancer-related fatigue. Cancer 2001;92(6 suppl):1684–1688.
37 Bower JE, Ganz PA, Aziz N, Fahey JL: Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med 2002; 64:604–611.
38 Wang XS, Giralt SA, Mendoza TR, Engstrom MC, Johnson BA, Peterson N, Broemeling LD, Cleeland CS: Clinical factors associated with cancer-related fatigue in patients being treated for leukemia and non-Hodgkin's lymphoma. J Clin Oncol 2002;20:1319–1328.
39 Mantovani G, Maccio A, Lai P, Massa E, Ghiani M, Assantona MC: Cytokine involvement in cancer anorexia/cachexia: Role of megestrol acetate and medroxyprogesterone acetate on cytokine downregulation and improvement of clinical symptoms. Crit Rev Oncog 1998;9:99–106.
40 Allen-Mersh TG, Glover C, Henderson DC, Vavies M: Relation between depression and circulating immune products in patients with advanced colorectal cancer. J R Soc Med 1998; 91:408–413.
41 Rowinsky EK, Chaudhry V, Forastiere AA, Sartorius SE, Ettinger DS, Grochow LB, Lubejko BG, Cornblath DR, Donehower RC: Phase I and pharmacologic study of paclitaxel and cisplatin with granulocyte colony-stimulating factor: Neuromuscular toxicity is dose-limiting. J Clin Oncol 1993;11:2010–2020.
42 Weintraub M, Adde MA, Venzon DJ, Shad AT, Horak ID, Neely JE, Seibel NL, Gootenberg J, Arndt C, Nieder ML, Magrath IT: Severe atypical neuropathy associated with administration of hematopoietic colony-stimulating factors and vincristine. J Clin Oncol 1996; 14:935–940.
43 Basu S, Sodhi A: Increased release of interleukin-1 and tumor necrosis factor by interleukin-2-induced lymphokine-activated killer cells in the presence of cisplatin and FK-565. Immunol Cell Biol 1992;70:15–24.
44 Gan XH, Jewett A, Bonavida B: Activation of human peripheral blood-derived monocytes by cis-diamminedichloroplatinum: enhanced tumoricidal activity and secretion of tumor necrosis factor-alpha. Nat Immun 1992;11:144–155.
45 O'Brien Jr. JM, Wewers MD, Moore SA, Allen JN: Taxol and colchicine increase LPS-induced pro-IL-1 beta production, but do not increase IL-1 beta secretion. A role for microtubules in the regulation of IL-1 beta production. J Immunol 1995;154:4113–4122.
46 Zaks-Zilberman M, Zaks TZ, Vogal SN: Induction of proinflammatory and chemokine genes by lipopolysaccharide and paclitaxel (Taxol) in murine and human breast cancer cell lines. Cytokine 2001;15:156–165.
47 Ogura K, Ohta S, Ohmori T, Takeuchi H, Hirose T, Horichi N, Okuda K, Ike M, Ozawa T, Siba K, Kasahara K, Sasaki Y, Nakajima H, Adachi M: Vinca alkaloids induce granulocyte-macrophage colony stimulating factor in human peripheral blood mononuclear cells. Anticancer Res 2000;20:2383–2388.
48 Lieb K, Fiebich BL, Berger M, Bauer J, Schulze-Osthoff K: The neuropeptide substance P activates transcription factor NF-kB and kB-dependent gene expression in human astrocytoma cells. J Immunol 1997;159:4952–4958.
49 Shen W, Zhang C, Zhang G: Nuclear factor kB activation is mediated by NMDA and non-NMDA receptor and L-type voltage gated Ca^{2+} channel following severe global ischemia in rat hippocampus. Brain Res 2002;933:23–30.
50 Dougherty PM, Palecek J, Paleckova V, Sorkin LS, Willis WD: The role of NMDA and non-NMDA excitatory amino acid receptors in the excitation of primate spinothalamic tract neurons by mechanical, thermal, chemical, and electrical stimuli. J Neurosci 1992;12:3025–3041.
51 Torelli GF, Meguid MM, Moldawer LL, Edwards CK, Kim H-J, Carter JL, Laviano A, Fanelli FR: Use of recombinant human soluble TNF receptor in anorectic tumor-bearing rats. Am J Physiol 1999;46:R850–R855.
52 Konsman JP, Parnet P, Dantzer R: Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci 2002;25:154–159.
53 McCarthy DO, Kluger MJ, Vander AJ: Suppression of food intake during infections: Is interleukin-1 involved? Amer J Clin Nutr 1985;42:1179–1182.
54 Weingarten HP: Cytokines and food intake: The relevance of the immune system to the student of ingestive behavior. Neurosci Biobehav Rev 1996;20:163–170.
55 Dantzer R: Cytokine-induced sickness behavior: Where do we stand? Brain Behav Immun 2001;15:7–24.
56 Chance WT, Cao L, Nelson JL, Foley-Nelson T, Fischer JE: Reversal of neurochemical aberrations after tumor resection in rats. Am J Surg 1988;155:124–129.
57 Yirmiya R: Endotoxin produces a depressive-like episode in rats. Brain Res 1996;711:163–174.
58 Swiergiel AH, Smagin GN, Dunn AJ: Influenza virus infection of mice induces anorexia: comparison with endotoxin and interleukin-1 and the effects of indomethacin. Pharmacol Biochem Behav 1997;57:389–396.
59 Plata-Salamán CR, Sonti G, Borkoski JP, Wilson CD, French-Mullen JMH: Anorexia induced by chronic central administration of cytokines at estimated pathophysiological concentrations. Physiol Behav 1996;60:867–875.
60 Swiergiel AH, Smagin GN, Johnson LJ, Dunn AJ: The role of cytokines in the behavioral responses to endotoxin and influenza virus infection in mice: Effects of acute and chronic administration of the interleukin-1-receptor antagonist (IL-1ra). Brain Res 1997;776:96–104.
61 Crnic LS, Segall MA: Behavioral effects of mouse interferon-α and interferon-γ and human interferon-α in mice. Brain Res 1992;590: 277–284.
62 Bernstein IL: Neutral mediation of food aversions and anorexia induced by tumor necrosis factor and tumors. Neurosci Biobehav Rev 1996;20:177–181.
63 Uehara A, Ishikawa Y, Okumura T, Okamura K, Sekiya C, Takasugi Y, Namiki M: Indomethacin blocks the anorexic action of interleukin-1. Eur J Pharmacol 1989;170:257–260.
64 Kozak W, Zheng H, Conn CA, Soszynski D, Van Der Ploeg LHT, Kluger MJ: Thermal and behavioral effects of lipopolysaccharide and influenza in interleukin-1β-deficient mice. Am J Physiol 1995;38:969–977.
65 McCarthy DO, Daun JM: The effects of cyclooxygenase inhibitors on tumor-induced anorexia in rats. Cancer 1993;71:486–492.
66 Hermann G, Rogers RC: Tumor necrosis factor-alpha in the dorsal vagal complex suppresses gastric motility. Neuroimmunomodulation 1995;2:74–81.
67 Milano S, Blower P, Romain D, Grelot L: The piglet as a suitable animal model for studying the delayed phase of cisplatin-induced emesis. J Pharmacol Exp Ther 1995;274:951–961.
68 Girod V, Dapzol J, Bouvier M, Grelot L: The COX inhibitors indomethacin and meloxicam exhibit anti-emetic activity against cisplatin-induced emesis in piglets. Neuropharmacology 2002;42:428–436.
69 Kanitz E, Tuchscherer M, Tuchscherer A, Stabenow B, Manteuffel G: Neuroendocrine and immune responses to acute endotoxemia in suckling and weaned piglets. Biol Neonate 2002;81:203–209.
70 Strassmann G, Kambayashi T: Inhibition of experimental cancer cachexia by anti-cytokine and anti-cytokine-receptor therapy. Cytokines Mol Ther 1995;1:107–113.
71 Kawamura I, Morishita R, Tomita N, Lacey E, Aketa M, Tsujimoto S, Manda T, Tomoi M, Kida I, Higaki J, Kaneda Y, Shimomura K, Ogihara T: Intratumoral injection of oligonucleotides to the NF kappa B binding site inhibits cachexia in a mouse tumor model. Gene Ther 1999;6:91–97.

72 Bennett GJ, Xie YK: A peripheral mononeuropathy in rat that produces disorder of pain sensation like those seen in man. Pain 1988;33:87–107.
73 Sweitzer S, Martin D, DeLeo JA: Intrathecal interleukin-1 receptor antagonist in combination with soluble tumor necrosis factor receptor exhibits an anti-allodynic action in a rat model of neuropathic pain. Neuroscience 2001;103:529–539.
74 Miletic G, Miletic V: Increases in the concentration of brain derived neurotrophic factor in the lumbar spinal dorsal horn are associated with pain behavior following chronic constriction injury in rats. Neurosci Lett 2002;319:137–140.
75 Eliav E, Herzberg U, Ruda MA, Bennett GJ: Neuropathic pain from an experimental neuritis of the rat sciatic nerve. Pain 1999;83:169–182.
76 Oh SB, Tran PB, Gillard SE, Hurley RW, Hammond DL, Miller RJ: Chemokines and glycoprotein 120 produce pain hypersensitivity by directly exciting primary nociceptive neurons. J Neurosci 2001;21:5027–5035.
77 Sorkin LS, Doom CM: Epineurial application of TNF elicits an acute mechanical hyperalgesia in the awake rat. J Peripher Nerv Syst 2000;5:96–100.
78 Dunn AJ: Effects of cytokines and infections on brain neurochemistry; in Ader R, Felten DL, Cohen N (eds): Psychoneuroimmunology, ed 3. New York, Academic Press, 2001, pp 649–666.
79 Neumann S, Doubell TP, Leslie T, Woolf CJ: Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. Nature 1996;384:360–364.
80 Honore P, Rogers SD, Schwei MJ, Salak-Johnson JL, Luger NM, Sabino MC, Clohisy DR, Mantyh PW: Murine models of inflammatory, neuropathic and cancer pain each generates a unique set of neurochemical changes in the spinal cord and sensory neurons. Neuroscience 2000;98:585–598.
81 Galdiero M, Cipollaro DI, Folgore A, Cappello M, Giobbe A, Sasso FS: Effects of irradiation doses on alterations in cytokine release by monocytes and lymphocytes. J Med 1994;25:23–40.
82 Ibuki Y, Goto R: Contribution of inflammatory cytokine release to activation of resident peritoneal macrophages after in vivo low-dose gamma-irradiation. J Radiat Res 1999;40:253–262.
83 Wasserman J, Petrini B, Wolk G, Vedin I, Las U, Blomgren H, Ekre HP, Strannegard O: Cytokine release from mononuclear cells in patients irradiated for breast cancer. Anticancer Res 1991;11:461–464.
84 Authier N, Fialip J, Eschalier A, Coudore F: Assessment of allodynia and hyperalgesia after cisplatin administration to rats. Neurosci Lett 2000;291:73–76.
85 Cavaletti G, Tredici G, Braga M, Tazzari S: Experimental peripheral neuropathy induced in adult rats by repeated intraperitoneal administration of taxol. Exp Neurol 1995;133:64–72.
86 Polomano RC, Mannes AJ, Clark US, Bennett GJ: A painful peripheral neuropathy in the rat produced by the chemotherapeutic drug, paclitaxel. Pain 2001;93:293–304.
87 Aley KO, Reichling DB, Levine JD: Vincristine hyperalgesia in the rat: A model of painful vincristine neuropathy in humans. Neuroscience 1996;73:259–265.
88 Gale RP: Immediate medical consequences of nuclear accidents. Lessons from Chernobyl. JAMA 1987;258:625–628.
89 Dougherty PM, Aronowski J, Samorajski T, Dafny N: Opiate antinociception is altered by immune modification: the effect of interferon, cyclosporine and radiation-induced immune suppression upon acute and long-term morphine activity. Brain Res 1986;385:401–404.
90 Campbell IL, Stalder AK, Chiang CS, Bellinger R, Heyser CJ, Steffensen S, Masliah E, Powell HC, Gold LH, Henriksen SJ, Siggins GR: Transgenic models to assess the pathogenic actions of cytokines in the central nervous system. Mol Psychiatry 1997;2:125–129.
91 Gibertini M: Cytokines and cognitive behavior. Neuroimmunomodulation 1998;5:160–165.
92 Rachal Pugh C, Fleshner M, Watkins LR, Maier SF, Rudy JW: The immune system and memory consolidation: a role for the cytokine IL-1beta. Neurosci Biobehav Rev 2001;25:29–41.
93 Matsumoto Y, Yoshida M, Watanabe S, Yamamoto T: Involvement of cholinergic and glutamatergic functions in working memory impairment induced by interleukin-1beta in rats. Eur J Pharmacol 2001;430:283–288.
94 Lynch MA: Age-related impairment in long-term potentiation in hippocampus: a role for the cytokine, interleukin-1beta? Prog Neurobiol 1998;56:571–589.
95 Lacosta S, Merali Z, Anisman H: Influence of acute and repeated interleukin-2 administration on spatial learning, locomotor activity, exploratory behaviors, and anxiety. Behav Neurosci 1999;113:1030–1041.
96 Smith RS: The macrophage theory of depression. Med Hypotheses 1991;35:298–306.
97 Charlton BG: The malaise theory of depression: Major depression disorder is sickness behavior and antidepressants are analgesic. Med Hypotheses 2000;54:126–130.
98 Dunn AJ, Powell ML, Meitin C, Small PA: Virus infection as a stressor: Influenza virus elevates plasma concentrations of corticosterone, and brain concentrations of MHPG and tryptophan. Physiol Behav 1989;45:591–594.
99 Besedovsky HO, del Rey A, Sorkin E, Dinarello CA: Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. Science 1986;233:652–654.
100 Merali Z, Brennan K, Brau P, Anisman H: Dissociating anorexia and anhedonia elicited by interleukin-1beta: antidepressant and gender effects on responding for 'free chow' and 'earned' sucrose intake. Psychopharmacology (Berl) 2003;165:413–418.
101 Connor TJ, Leonard BE: Depression, stress and immunological activation: The role of cytokines in depressive disorders. Life Sci 1998;62:583–606.
102 Connor TJ, Harkin A, Kelly JP, Leonard BE: Olfactory bulbectomy provokes a suppression of interleukin-1beta and tumour necrosis factor-alpha production in response to an in vivo challenge with lipopolysaccharide: Effect of chronic desipramine treatment. Neuroimmunomodulation 2000;7:27–35.
103 Dunn AJ, Swiergiel AH: The reductions in sweetened milk intake induced by interleukin-1 and endotoxin are not prevented by chronic antidepressant treatment. Neuroimmunomodulation 2001;9:163–169.
104 Dantzer R, Wollman EE, Yirmiya R: Cytokines and depression: An update. Brain Behav Immun 2002;16:501–502.
105 Anisman H, Merali Z, Hayley S: Sensitization associated with stressors and cytokine treatments. Brain Behav Immun 2003;17:86–93.
106 Ottenweller JE, Natelson BH, Gause WC, Carroll KK, Beldowicz D, Zhou XD, LaManca JJ: Mouse running activity is lowered by *Brucella abortus* treatment: A potential model to study chronic fatigue. Physiol Behav 1998;63:795–801.
107 Sheng WS, Hu S, Lamkin A, Peterson PK, Chao CC: Susceptibility to immunologically mediated fatigue in C57BL/6 versus Balb/c mice. Clin Immunol Immunopathol 1996;81:161–167.
108 Davis JM, Weaver JA, Kohut ML, Colbert LH, Ghaffar A, Mayer EP: Immune system activation and fatigue during treadmill running: role of interferon. Med Sci Sports Exerc 1998;30:863–868.
109 Saphier D: Neurophysiological and endocrine consequences of immune activity. Psychoneuroendocrinology 1989;14:63–87.
110 Vitkovic L, Bockaert J, Jacque C: 'Inflammatory' cytokine: Neuromodulators in normal brain? J Neurochem 2000;74:457–471.
111 Maes M: Major depression and activation of the inflammatory response system. Adv Exp Med Biol 1999;461:25–46.
112 Levine J, Barak Y, Chengappa KN, Rapoport A, Rebey M, Barak V: Cerebrospinal cytokine levels in patients with acute depression. Neuropsychobiology 1999;40:171–176.
113 Dunn AJ: Mechanisms by which cytokines signal the brain; in Clow A, Hucklebridge F (eds): Neurobiology of the immune system. New York, Academic Press, 2002, pp 43–65.
114 Capuron L, Ravaud A, Neveu PJ, Miller AH, Maes M, Dantzer R: Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. Mol Psychiatry 2002;7:468–473.

115 Yamamoto Y, Gaynor RB: Therapeutic potential of inhibition of the NF-κB pathway in the treatment of inflammation and cancer. J Clin Invest 2001;107:134–142.
116 Surh YJ, Chun KS, Cha HH, Han SS, Keum YS, Park KK, Lee SS: Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: down-regulation of COX-2 and iNOS through suppression of NF-kappa B activation. Mutat Res 2001;480–481:243–268.
117 Rivest S: What is the cellular source of prostaglandins in the brain in response to systemic inflammation? Facts and controversies. Mol Psychiatry 1999;4:500–507.
118 Karin M, Cao Y, Greten FR, Li ZW: NF-κB in cancer: From innocent bystander to major culprit. Nat Rev Cancer 2002;2:301–310.
119 Das KC, White CW: Activation of NF-κB by antineoplastic agents. J Biol Chem 1997;272: 14914–14920.
120 Lanza L, Scudeletti M, Monaco E, Monetti M, Puppo F, Filaci G, Indiveri F: Possible differences in the mechanism(s) of action of different glucocorticoid hormone compounds. Ann NY Acad Sci 1999;876:193–197.
121 Okamoto T: NSAID zaltoprofen improves the decrease in body weight in rodent sickness behavior models: Proposed new applications of NSAIDs. Int J Mol Med 2002;9:369–372.
122 Raz A: Is inhibition of cyclooxygenase required for the anti-tumorigenic effects of nonsteroidal, anti-inflammatory drugs (NSAIDs)? In vitro versus in vivo results and the relevance for the prevention and treatment of cancer. Biochem Pharmacol 2002;63: 343–347.
123 Bluthé RM, Castanon N, Pousset F, Bristow A, Ball C, Lestage J, Michaud B, Kelley KW, Dantzer R: Central injection of IL-10 antagonizes the behavioural effects of lipopolysaccharide in rats. Psychoneuroendocrinology 1999;24:301–311.
124 Bluthé RM, Bristow A, Lestage J, Imbs C, Dantzer R: Central injection of interleukin-13 potentiates LPS-induced sickness behavior in rats. Neuroreport 2001;12:3979–3983.
125 Bluthé RM, Lestage J, Rees G, Bristow A, Dantzer R: Dual effect of central injection of recombinant rat interleukin-4 on lipopolysaccharide-induced sickness behavior in rats. Neuropsychopharmacology 2002;26:86–93.