Published in final edited form as:

Nat Rev Clin Oncol. ; 9(7): 414–426. doi:10.1038/nrclinonc.2012.88.

Translational approaches to treatment-induced symptoms in cancer patients

Robert Dantzer¹, Mary W. Meagher², and Charles S. Cleeland¹

¹Department of Symptom Research, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1450, Houston, Texas TX77030, USA

²Department of Psychology, College of Liberal Arts, Texas A&M University, 515 Coke Street, College Station TX 77843-4235

Abstract

Cancer therapy makes patients sick. The therapies that are available to clinicians allow them to successfully control nausea, emesis, and pain. However, this is not the case for a number of other symptoms that include fatigue, distractibility, poor memory, and diminished interest in previously pleasurable activities. These symptoms cluster during the course of cancer therapy and impair patient quality of life, limit therapy options, and do not always resolve at the cessation of treatment. It is possible to describe the intensity and temporal features of symptoms and assess their relationship with the inflammatory response that is associated with cancer and cancer therapy. At the preclinical level, sophisticated animal models still need to be deployed to study the causal role of inflammation in specific components of cancer-related symptoms. Various approaches can be optimally combined in a translational symptom research pathway to provide a framework for assessing in a systematic manner the neurobehavioral toxicity of existing and newly developed cancer therapies. Ultimately this knowledge will allow derivation of mechanism-based interventions to prevent or alleviate cancer-related symptoms.

Introduction

Advances in cancer detection have allowed many people to be diagnosed relatively early in the disease process. After excision of even relatively small tumours, most patients will receive additional adjunctive therapy, which typically includes chemotherapy and/or radiation therapy to limit proliferation of residual cancer cells and prevent recurrence of the cancer. These therapies that aim to prevent cancer cell proliferation also damage normal tissues and impair homeostasis. As a result, many patients who felt reasonably healthy before diagnosis feel profoundly sick because of the treatments that are intended to cure them.

When patients learn that they have cancer they are concerned about the symptoms they will experience. These concerns are well-founded: approximately 70% of outpatients will experience pain or will take analgesics to manage pain. The prevalence of pain has remained

Robert Dantzer rdantzer@mdanderson.org.

Financial disclosure:

R. Dantzer has received recent honoraria from Lundbeck Laboratories and Janssen. He is also a consultant for Lundbeck Laboratories. Dr. C.S. Cleeland has been a consultant/advisor for Abbott, Genentech, Amgen, BMS-Bristol Myers Squibb, Exelixis, and Pfizer. Dr. Cleeland has received research funds from AstraZeneca.

R. Dantzer declares an association with the following company/organization: Janssen, Lundbeck Laboratories. C. S. Cleeland declares an association with the following companies: Abbott, Amgen, AstraZeneca, Bristol-Myers Squibb, Exelixis, Genentech, Pfizer. See the article online for full details of the relationships. M. W. Meagher declares no competing interests.

the same in studies conducted in patients almost two decades apart.(1, 2) Pain, however, is not an isolated symptom. Patients undergoing active therapy are more likely to report other symptoms as more severe than pain, including fatigue, inability to get things done, distress, worrying, and disturbed sleep.(3) A recent study of cancer survivors found that one in four patients reported high levels of symptoms 1 year after diagnosis, with pain, fatigue, inability to concentrate, and sleep disturbances being prominent symptoms. There was no difference in symptom burden between those who had recently completed and those who remained on therapy.(4)

Some cancer-related symptoms are the direct result of disease and may improve with effective cancer treatment. For example, reduction in pain may be an important outcome for curative therapies.(5) However, other symptoms, especially neuropathy, fatigue, sleep disturbance, cognitive dysfunction, and alterations in mood, dramatically increase during and immediately after cancer therapy.(3) As patients survive cancer for increasingly longer periods of time, persistent residual treatment-related symptoms are becoming more prevalent and pose an increasing barrier to the resumption of pre-disease functioning. Treatment-related symptoms can directly affect survival if they become so severe that patients abandon potentially curative therapies or if symptoms cause treatment delays. Post-treatment symptoms can also limit vocational activity and inhibit social recovery.(6) Conversely, effective control of treatment-related symptoms could enhance therapeutic outcomes by improving patient health status, minimizing toxicities that impair function, and increasing adherence to curative treatments. Such symptom control not only enhances or maintains health-related quality of life, but also potentially increases survival.

Cytotoxic therapies are expected to produce symptoms because normal tissue function is disrupted as cancer cells are killed. It was hoped that targeted anticancer therapies would destroy cancer cells specifically and, therefore, cause less general toxicity;(7) however, various toxic effects have emerged with these agents, such as hypertension, cardiac toxicity, thyroid dysfunction, and hand-foot skin reactions, in addition to the more-commonly seen nausea, diarrhea, and fatigue,(8) and each novel agent has its own unique toxicity profile. Fatigue is often a prominent common treatment-related symptom experienced by patients treated with targeted therapies, and it can prevent patients from adhering to chronic therapy, which is often essential to maintain molecular remission.

Patients undergoing treatment and experiencing symptoms are compelled to draw analogies with other conditions that present the same sorts of deficits, including clinical depression and dementia. Patients may also attribute their symptoms to the stress of having a life-threatening disease, the hectic schedule of treatment requirements, and changes in work and family life. There is increasing evidence that the symptoms cancer patients experience correspond to a collection of neurobehavioural symptoms or behavioural comorbidities,(9) which strongly suggests that treatment and/or cancer are perturbing central neuronal function.

We examine the nature of the behavioural comorbidities that are experienced by cancer patients and their mechanisms. We discuss how cancer-related symptoms develop and can remain after termination of curative treatment, and what can be done at the clinical and preclinical levels to better understand their mechanisms and identify appropriate treatments. We will draw from several disciplines, including clinical psychology, behavioral neuroscience, behavioral pharmacology, immunology, and psychoneuroimmunology.

Symptom measures and trajectories

Symptoms are defined as sensations or perceptions of changes related to health function that an individual experiences. Symptoms do not remain at the perceptual level. They give rise to

feelings of distress that can culminate in profoundly disturbing negative emotions in response to aggravating conditions. In clinical oncology, symptoms are usually not assessed by external observation. They are reported by patients in the form of health complaints. These complaints can be made more specific by asking patients to fill out standardized questionnaires on a given symptom or a set of symptoms. For instance, patients can rate the severity of a symptom such as fatigue or pain on a numeric rating scale from 0 (symptom not present) to 10 (the highest intensity of the symptom they can think of). Supplementary questionnaires can be used to assess the quality of the symptom, its temporal pattern and duration, and its interference with the patient's functioning.(10) While most agree that self-report is our best source of information about symptoms, other measures of performance (such as cognitive assessment, activity measures) can greatly supplement our understanding of symptoms. It is relatively standard practice in both clinical practice and clinical research for patients to rate a set of prevalent symptoms together on a single multi-symptom assessment measure, such as the M. D. Anderson Symptom Inventory (MDASI).(11)

Several common observations emerge from studies of symptoms in cancer patients (Box 1). What is immediately apparent with cancer patients is that they report several symptoms instead of only one symptom at any given time during cancer therapy. The intensity of these symptoms varies with time since the start of treatment, with the peak of treatment-related symptoms generally occurring a few weeks after the initiation of therapy (e.g., (12)). Variation of symptom type and severity over time corresponds to what is called the "symptom trajectory." In addition, subsets of symptoms have a higher probability of co-occurring. Multiple symptoms that follow the same time course in response to disease or treatment have been termed "symptom clusters."(13, 14) Symptom clusters vary according to the type of cancer and cancer therapy, and the time at which symptoms are assessed (Box 1). Symptom clustering also depends on the method of scoring and the mode of analysis of the data. In general, considering only the occurrence of symptoms gives less-sensitive clustering information than also including severity rating, mainly because of the dichotomous nature of occurrence.(15) As illustrated by the cluster analysis presented in Box 1, symptom items that represent negative effects (sadness, distress) are most often related to items that portray fatigue and lack of motivation. These subsets are also related to reports of cognitive slowing with difficulties in paying attention and remembering.(16)

We are far from understanding the mechanisms underlying the development of treatment-related symptom clusters. However, there is a growing awareness that common biological mechanisms (such as an inflammatory response produced by disease or treatment, endocrine impairment, haematopoietic dysfunction) may cause or contribute to some of these symptoms at the same time.(9, 17, 18)

Figure 1 presents an example of symptom trajectories in patients with colorectal cancer, oesophageal cancer, and non-small-cell lung cancer.(19) Fatigue emerges as the predominant symptom, followed by disturbed sleep, sore throat, lack of appetite, pain, and distress. An important aspect of symptom trajectories is their inter-individual variability. Despite the standardized cancer therapy that is administered nowadays in most cancer wards, some patients develop high levels of symptoms whereas others report very little variation in their symptom trajectory. This is illustrated in Figure 2 by an example taken from patients with head and neck cancer over the course of approximately seven weeks of chemotherapy, radiotherapy, or a combination of these treatments.(20) The reasons for these individual differences are not yet known, despite their importance for personalized care. We discuss this important issue later.

Pain has been the most intensively studied symptom in clinical oncology, in part because of its prevalence but also because it is such a well recognized symptom in medical care, in

terms of functional impact and medical insurance coverage. Several excellent reviews on pain in cancer patients and animal models of cancer pain are already available,(21–23) and we will not add to this abundant literature. Instead, we will focus on the symptom cluster that includes fatigue, insomnia, depressed mood, and cognitive impairment. The mechanisms and treatment of this symptom cluster remain elusive despite their very high prevalence both during and after cancer therapy.

Inflammation-induced symptoms

Cleeland and his colleagues were among the first researchers to propose an analogy between behavioural comorbidities occurring in response to cancer treatment and the clinical signs of sickness caused by inflammation.(17) Sickness behaviour refers to the coordinated set of originally adaptive behavioral changes that develop in ill individuals during the course of an infection to promote survival.(24) These behavioural changes include lethargy, sleepiness, social withdrawal, loss of appetite, reduced body care, and decreased ability to concentrate. These changes are orchestrated in the brain and represent the expression of a motivational state that reorganizes the priorities of the organism to cope with infection or other insults targeting the immune system. The analogy made by Cleeland and his colleagues was not only in terms of clinical manifestations, but also in terms of mechanisms. It was proposed that cancer and cancer therapy trigger the release of inflammatory mediators that ultimately stimulate the brain to induce signs and feelings of sickness. The mechanisms of inflammation-induced sickness are summarized in Box 2.

The possibility that inflammation is the mediating process in the relationship between cancer therapy and symptoms is very much in line with the long history of the relationship between cancer and inflammation.(25) Inflammation is present at every stage of tumour progression. Chronic inflammation contributes to cancer initiation, promotion, and progression.(26) In addition to the reciprocal inflammatory relationships between neoplastic cells and other cell types in the microenvironment of the tumour, the trauma associated with the surgical procedure causes the release of inflammatory mediators. This is especially the case during visceral surgery,(27) but enhanced production of proinflammatory cytokines is also noted in patients submitted to various forms of breast reconstruction after mastectomy.(28) In recognizing the functional relationship between surgical trauma and inflammation, the inflammatory response to surgical trauma is currently examined as a possible cause for the post-operative delirium and cognitive dysfunction that commonly occurs during the post-operative period, especially in older patients.(29, 30) Chemotherapy and radiotherapy are known to induce a “cytokine storm” that involves many immune and non-immune cell types and various cytokines (for example, chemokines, proinflammatory cytokines, and growth factors).(31–33) Because this cytokine storm can lead to various forms of multi-organ failure, the administration of potent anti-inflammatory drugs, usually steroids, are required to limit its adverse consequences. The mechanisms that are at the origin of the cytokine storm induced by cancer therapy are not fully elucidated. They probably involve damage-associated molecules that are released into the extracellular space by necrotic and apoptotic cells (Box 2).

Cancer, cancer therapy, and inflammation can collectively result in profound alterations in physical and mental functioning. The proposed analogy between inflammation-induced sickness and cancer-related symptoms provided the necessary impetus for the clinical exploration of associations between biomarkers of inflammation and behavioral comorbidities in cancer patients. It was predicted that cancer patients with symptoms should present with higher levels of proinflammatory cytokines or other inflammatory mediators than individuals with no cancer. In addition, the association between symptoms and biomarkers of inflammation could last longer than the period of cancer therapy and be

present in cancer survivors afflicted with behavioural comorbidities. Both predictions were tested in patients with breast cancer by assessing the relationship between inflammation and symptoms in patients who underwent chemotherapy and/or radiotherapy.(9) The predictions turned out to be valid, despite the difficulties owing to the lack of standardization in the measurement of biomarkers of inflammation and to the fact that circulating cytokines do not reflect what is going in the organ(s) in which tumour cells are present or in the brain, where symptoms ultimately originate. In one study of women who had gone through primary and adjunctive treatment for early-stage breast cancer, 60% complained about fatigue and sleep disorders and 25% had elevated depressive symptoms.(34) Those women who had just finished chemotherapy had higher levels of all symptoms that were associated with increased levels of the soluble tumour necrosis factor (TNF) receptor II, a marker of TNF- α signaling.(34) Fatigue measured by the Fatigue Symptom Inventory, a 14-item valid and reliable scale developed for measuring symptoms of fatigue in cancer patients, was positively associated with this marker. In a study of patients treated with radiotherapy for breast or prostate cancer, changes in serum levels of C-reactive protein and interleukin (IL)-1 receptor antagonist were positively associated with increases in fatigue symptoms.(35)

Inflammatory cytokines act as intercellular autocrine, juxtacrine, and paracrine communication signals in the microenvironment in which they are produced. It is not clear whether circulating cytokines reflect “spillover” of molecules released locally from the site of inflammation or if they are part of an inflammatory milieu that influences tissue-specific activity. Most of the evidence is in favor of the “spillover” interpretation. Induction of bacterial peritonitis in mice, for instance, is associated with systemic inflammation as measured by circulating cytokines, but the subsequent development of inflammation in the lungs requires the local recruitment of polymorphonuclear leukocytes or the sequestration of neutrophils into the pulmonary vasculature.(36) In the same manner, the sustained release of proinflammatory cytokines into the systemic circulation that accompanies acute pancreatitis is associated with signs of inflammation only in the peritoneal compartment, whereas anti-inflammatory activity is present in the circulating compartment.(37) We have already mentioned that induction of sickness behavior in response to lipopolysaccharide is associated with a generalized inflammatory response (Box 2), but the propagation of peripheral inflammation to the brain does not occur via this general response pathway. Thus, circulating levels of cytokines can be used as biomarkers of inflammation but do not necessarily inform their functional role.

From a methodological viewpoint, the best approach to gain an insight on the relationship between inflammation and symptoms would be to measure cytokines in the tumour microenvironment. This is possible in some clinical situations such as ovarian cancer, in which cytokines can be assayed in the ascites fluid surrounding the tumour. In patients awaiting surgery for a pelvic mass suspected for ovarian cancer, the most discriminative measure between patients with tumours of low malignant potential and patients with advanced ovarian cancer was the vegetative dimension of depression assessed by the Center of Epidemiologic Studies Depression Scale.(38) Patients with earlystage ovarian cancer had an intermediate score on this scale. The dimension of vegetative depression includes an assessment of motivational components very similar to the psychological dimension of fatigue (for example, keeping your mind on what you are doing), in addition to items of reduced appetite and sleep loss.(39) In both the plasma and ascites of patients with invasive ovarian cancer, IL-6 levels were high, and patients with advanced ovarian cancer had the highest levels of IL-6. In addition, there was a positive correlation between IL-6 levels and vegetative depression.(38)

When the tumour microenvironment is not easily accessible, an alternative is to measure activation of intracellular cytokine signaling pathways in circulating immune cells or to assess the ability of these cells to produce cytokines in response to a standardized stimulation, such as lipopolysaccharide. This can be done on whole blood cell cultures or on isolated populations of peripheral blood mononuclear cells. Despite its relatively common use in other medical disciplines, such as biological psychiatry, this approach is rarely favoured in clinical oncology, probably because of the ease of measuring cytokines in serum or plasma of cancer patients.

The correlative nature of studies on inflammation and symptoms in cancer patients does not allow any causal inference. What is striking, however, is that very similar symptoms to those reported in response to cancer therapy have been observed in patients with kidney cancer or metastatic melanoma treated with interferon (IFN)- α and/or IL-2. In these patients, cytokine administration invariably induces the neurovegetative symptoms of depression, with a predominance of fatigue, decreased appetite, and sleep disorders. In about one third to one half of the patients, affective symptoms (decreased sensitivity to reward, feelings of guilt and worthlessness, suicidal thoughts) developed but only after several days or weeks of treatment.(40) It is important to note that the occurrence of symptoms of depression and fatigue is associated with inflammation-induced activation of enzymatic pathways involved in the biosynthesis of neurotransmitters (Box 3, Figure 3.1).

Animal models of cancer symptoms

There is plenty of evidence that tumours and cancer therapy lead to profound behavioral alterations in laboratory animals and that these behavioral alterations are associated with biomarkers of inflammation.(41) For instance, mammary tumours induced in rats by exposure to the carcinogen N-nitroso-N-methylurea were found to be associated with cognitive impairments in a radial-arm maze and an object-recognition memory test.(42) In the first test, rats must use environmental cues to orient themselves in a maze and find the arm of the maze in which a food reward is presented. In the second test, rats are presented with a novel object that they spontaneously explore, in contrast to an already familiar object. Recognition is inferred from the difference in the time spent assessing the two objects. Depressive-like behaviour can be measured by increased immobility in the forcedswim test. In this test, animals are put in a small bucket filled with water. Normal animals swim vigorously to try to find an escape, while “depressed” animals quickly stop swimming and just float with a minimum of movements to maintain their head out of the water. The anhedonic component of depressive-like behaviour can be assessed by reduced sucrose preference.(43) Both measures of depressive-like behaviour were also enhanced in rats with mammary tumours.(44) Female mice infected with syngeneic ovarian carcinoma cells displayed evidence of depressive-like behaviour as assessed by decreased sucrose preference.(45) In both cases altered behaviour was associated with increased expression of proinflammatory cytokines at the periphery and in the brain, although the causality was not tested.

Administration of chemotherapeutic agents, such as cisplatin, 5-fluorouracil, taxol, methothrexate, or adriamycin alone or in combination with cyclophosphamide, to naïve animals reduces spontaneous motor activity, decreases food intake, disturbs sleep patterns and nycthemeral rhythms, and induces cognitive dysfunction.(46–53) Various pharmacotherapies and supplements targeting oxidative stress and inflammation have been tested for their ability to alleviate the behavioural effects of chemotherapy.(48, 53, 54) The possibility of using stem-cell transplantation to alleviate cognitive dysfunction induced by cranial radiotherapy has even been examined in a recent study carried out in irradiated athymic nude rats.(55) However, since most intervention studies have been carried out in

naive animals there is still the caveat of a potential reduction in chemotherapeutic efficacy that needs to be considered before these results can be applied to the clinical condition.

Another important limitation of behavioural studies in laboratory animals is the difficulty of equating changes in behaviour observed in animals with symptoms reported by patients. In many cases, reasoning is by analogy or by successive elimination. In an attempt to model chemotherapy-related fatigue, mice were treated daily for five consecutive days with a sub-toxic dose of paclitaxel. Not surprisingly, paclitaxel-treated mice moved around less and did not use the running wheel during the first two or three weeks after treatment.(46) To support their claim that these behavioural alterations are equivalent to fatigue, the authors of this study took great care to show that the behavioural alterations observed in the third week post-treatment were not associated with differences in sleep patterns and in motor coordination, in contrast to the behavioural alterations that were observed in the first week post-treatment. However, they did not consider another possible confounding factor represented by the development of neuropathy in the paws of paclitaxel-treated mice.(56)

A similar approach based on pharmacological tools was used to dissociate malaise from fatigue in cisplatin-treated rats.(47, 54) Rats lack an emetic response but do engage in the consumption of kaolin clay when made sick by toxins, and this behaviour is antagonized by anti-emetic drugs. Cisplatin reduced food intake, stimulated kaolin consumption, decreased gastric emptying, and reduced locomotor activity. Administration of the 5-HT₃ receptor antagonist ondansetron, which is used to prevent nausea and emesis during cancer therapy, attenuated the effects of cisplatin on food intake and kaolin consumption but had no effect on gastric emptying and locomotor activity. Dexamethasone blocked all the behavioral effects of cisplatin and restored gastric emptying. These results indicate that reduced food intake and kaolin consumption are good indicators of cisplatin-induced malaise.

Measures of changes in spontaneous activities need to be complemented by assessment of sensory, motor, cognitive, and affective behaviors. Very sophisticated behavioral techniques have been developed by behaviourists, mainly in the context of behavioural phenotyping of transgenic mice, behavioural neuroscience, and behavioural pharmacology and toxicology. (57–59) These techniques can be easily applied to the study of symptoms induced by cancer and cancer therapy in laboratory rodents. For example, in the field of depression, researchers have developed animal models of depression that meet scientific criteria of validity, including construct validity (same causal factors as those for the human condition), face validity (similar clinical signs, such as anhedonia, in the animal model and the human condition), and predictive validity (treatments active in the animal model are able to reduce the symptoms in clinics).(60) The sensitivity of behavioural assays of depressive-like behaviour to the development of tumours induced by a carcinogen has been noted.(44) In the field of fatigue, most of the studies in exercise physiology have focused on the ability to withstand treadmill exercise with the implicit assumption that fatigue signals originate from peripheral sources. Run time to fatigue in mice is increased after muscle-damaging downhill exercise, and this symptom is associated with increased muscle inflammatory cytokines. However, the same cytokine response also occurs in the brain.(61) Furthermore, depletion of brain macrophages by intracerebroventricular injections of clodronate-filled liposomes that specifically kill brain macrophages was found to enhance treadmill performance after downhill runs.(62) These results demonstrate that there is an important central component in fatigue. This central component of fatigue has dimensions of affect and motivation that probably predate task failure and can be studied objectively in mice using appropriate behavioural techniques (Box 4).

Future perspectives

Given our discussion of the relationship between inflammation and cancer-related symptoms, it should be sufficient to give an anti-inflammatory treatment that targets proinflammatory cytokines to alleviate symptoms in cancer patients. However, this is not as easy as it appears. As of April 13, 2012, ClinicalTrials.gov lists five trials of minocycline for reducing symptom burden or neuropathy in cancer patients. Minocycline is a second-generation tetracycline that has interesting anti-inflammatory properties both at the periphery and in the central nervous system because of its ability to cross the blood-brain barrier. Its ability to down-regulate microglia activation confers some neuroprotective activity.(63) There is already evidence that the attenuation of microglial activation by minocycline prevents the development of neuropathic pain and inflammation-induced depressive-like behaviour in animal models.(56, 64–66) However, there is no evidence that minocycline can act in a curative manner. In the case of human immunodeficiency virus (HIV) infection, for instance, minocycline gave very encouraging results in the prevention of encephalitis and neurodegeneration in macaques infected with the simian equivalent of HIV.(67) However, minocycline treatment did not alleviate HIV-associated cognitive impairment(68) and had no effect on biomarkers of immune activation and inflammation in viremic human subjects.(69) On the basis of these findings, minocycline is probably a treatment of choice only when it can be initiated before the development of inflammation.

Another possibility is the use of anti-cytokine strategies. In the case of TNF- α , for instance, several antagonists (e.g., etanercept, infliximab, and adalimumab) have been developed for the treatment of rheumatoid arthritis and psoriasis. Their efficacy is supported by several randomized controlled studies and meta-analyses, despite their relatively moderate safety profile.(70, 71) These drugs have been tested for alleviation of symptom burden in cancer patients with very contrasting results.(72–74) An improvement in tolerability of dose-intensive chemotherapy with docetaxel in patients with advanced malignancies was reported with etanercept, particularly in terms of fatigue.(72) However, the combination of infliximab and docetaxel worsened fatigue and global quality of life scores in another trial carried out in patients with non-small cell lung cancer.(74) This trial had to be stopped because of lack of effect of infliximab on anorexia/cachexia, which was the primary outcome, and the possibility of severe side effects. The reasons for the discrepancies between these two trials are not immediately apparent.

Many pharmacological and non-pharmacological forms of intervention have been proposed for management of symptoms in cancer patients. In the case of fatigue, for instance, it is clear that none of the modalities that have been examined, from anti-inflammatory drugs to physical exercise via psychostimulants, dietary supplements, and psychosocial interventions, is fully effective.(75, 76) This state of affairs calls for a profound re-examination of the way symptoms are approached in clinical oncology. The current therapeutic landscape in cancer drug development is dominated by the search for drugs that suppress malignant and pre-malignant cells and prevent their dissemination. Much less importance is attached to treatment-related symptoms and toxicities despite their prevalence and their impact on adherence to anti-cancer treatment. There are still many barriers to research in symptom-management drug development, including the very limited knowledge on the biological processes that mediate symptom development and maintenance, the co-occurrence of multiple symptoms, and the difficulty of enrolling patients with high symptom burden into clinical trials.(77)

A new translational pathway to develop symptom-focused therapies is clearly needed. Its ingredients have already been listed and include: 1) focusing on treatment-related symptoms; 2) making use of individual differences in symptom expression to identify

genetic and epigenetic risk factors for developing severe symptom trajectories; 3) increasing efforts to produce animal models of cancer-related symptoms to test causality; and 4) investigating symptom interventions through controlled clinical trials.(78) An example of a successful strategy for addressing the research needs in translational symptom research is presented in Figure 3. It is based on the systematic studies of inflammation-induced depression that have been carried out during the last ten years and illustrates how clinical findings can be used to guide preclinical mechanistic experiments of which the results provide new leads for intervention studies in the clinic.(79, 80)

At the preclinical level, we have already seen that quite sophisticated animal models can be used to study the pathophysiology and treatment of cancer-related symptoms. On the clinical side, much still remains to be done to exploit the observation that not all patients who receive cancer therapy develop high levels of symptoms. The lower severity of symptoms in a significant proportion of cancer therapy-exposed patients challenges the notion that high symptom burden is a normative response to cancer therapy. It justifies the search for pre-existing risk factors, and the consideration of whether characteristics that differentiate patients with high symptoms from low symptoms reflect these risk factors.

A pharmacogenomic/toxicogenomic approach has been proposed for identification of patients at high and low risk of development of chemotherapy-induced peripheral neurotoxicity.(81) Genes of interest are those that have an important role in detoxification of drugs (such as glutathione S transferase P1, glutathione S-transferase M1 and M3, cytochrome P450 superfamily), in cancer cell resistance to platinum drugs (excision repair cross-complementing group 1), and in transport of drugs across extracellular and intracellular membranes (adenosine-5'-triphosphate (ATP)-binding cassette proteins). The results of this approach have so far been inconsistent. If inflammation is important in the development of behavioural co-morbidities in response to cancer therapy, the critical genes are not necessarily those that are involved in pharmacokinetics of the drugs and their penetration into the brain. Genes that influence intensity and duration of the inflammatory response and sensitivity of the central nervous system to inflammation should be more relevant.

This has been found to be the case in the field of IFN- α -induced depression (Box 5). The probability of developing symptoms of depression was found to be a joint function of both cytokine and brain neurotransmitter risk factors.(82) There is preliminary evidence for a genetic association between IL-6 and TNF- α and the severity of sleep disturbance and morning fatigue in cancer patients.(83, 84) Other candidate genetic determinants for increased sensitivity of the brain to inflammatory injury involve the E4 allele of the apolipoprotein gene that compromises neuronal repair and plasticity, and polymorphism in the catechol-O-methyl transferase enzyme that regulates the amount of dopamine in the frontal cortex.(85) These genetic polymorphisms are associated with a higher risk of cognitive dysfunction in response to chemotherapy in breast cancer and lymphoma patients.(86)

In view of the several thousands of genes that are involved in the production and function of cytokines and their differences of expression between individuals and tissues, it is difficult to imagine being able to grasp the complexity of the relationship between inflammation and symptoms by focusing on a few candidate genes. Functional genomic strategies are certainly worth considering in this context. They have already proven useful to replace the problematic study of “stress-response genes,” which were hypothesized to be reliably associated with psychological states such as acute stress, post-traumatic stress disorders, and depression, by focusing on higher-order themes that involve the biological causes and consequences of gene transcription.(87) This type of approach has revealed the existence of

a biological residue manifested by decreased glucocorticoid and increased proinflammatory signalling in individuals with low early-life socio-economic status, which might explain the higher prevalence of chronic diseases associated with this condition.(88)

Mining the inflammation genome will not be sufficient to explain cancer-related symptoms. Epigenetic modifications need also to be considered, because environmentally-induced alterations in DNA methylation and histone acetylation can selectively activate or inactivate genes that control inflammation, such as the transcription factor nuclear factor-kappaB (NF- κ B). (89, 90)

Conclusions

Ultimately, the possibility of identifying genetic and epigenetic risk factors for developing symptoms in response to cancer therapy should allow personalization of cancer treatments as well as strategies for symptom control. Before this can be undertaken, it is necessary to make sure that the risk factors identified in patients are playing a causal role. This is where pre-clinical approaches have a vital role. Even if these two complementary approaches are feasible, it nonetheless remains that the present situation in which the causal factors and risk factors for developing symptoms in response to current cancer therapies are determined *a posteriori* is far from ideal. It would be much better to have an *a priori* knowledge of the exact mechanisms underlying neurobehavioral toxicities of cancer therapy. This remains to be accomplished.

Acknowledgments

The research described was supported by Award Numbers R01 MH079829 and R01 NS073939 to RD, P01 CA124787 and R01 CA026582 to CSC, and R01-NS060822 to MWM. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health

REFERENCES

1. Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, et al. Pain and its treatment in outpatients with metastatic cancer. The New England journal of medicine. 1994; 330(9):592–596. Epub 1994/03/03. [PubMed: 7508092]
2. Fisch MJ, Lee JW, Weiss M, Wagner L, Chang VT, Cella D, et al. Prospective observational study of pain and analgesic prescribing in medical oncology outpatients with breast, colorectal, lung, or prostate cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012 in press.
3. Cleeland CS. Cancer-related symptoms. Seminars in radiation oncology. 2000; 10(3):175–190. Epub 2000/10/18. [PubMed: 11034629]
4. Shi Q, Smith TG, Michonski JD, Stein KD, Kaw C, Cleeland CS. Symptom burden in cancer survivors 1 year after diagnosis: a report from the American Cancer Society's Studies of Cancer Survivors. Cancer. 2011; 117(12):2779–2790. Epub 2011/04/16. [PubMed: 21495026]
5. Cleeland CS, O'Mara A, Zagari M, Baas C. Integrating pain metrics into oncology clinical trials. Clinical cancer research : an official journal of the American Association for Cancer Research. 2011; 17(21):6646–6650. Epub 2011/11/03. [PubMed: 22046026]
6. Chang YJ, Lee JS, Lee CG, Lee WS, Lee KS, Bang SM, et al. Assessment of clinical relevant fatigue level in cancer. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2007; 15(7):891–896. Epub 2007/02/24. [PubMed: 17318593]
7. Segota E, Bukowski RM. The promise of targeted therapy: cancer drugs become more specific. Cleveland Clinic journal of medicine. 2004; 71(7):551–560. Epub 2004/08/24. [PubMed: 15320364]

8. Shepard DR, Garcia JA. Toxicity associated with the long-term use of targeted therapies in patients with advanced renal cell carcinoma. Expert review of anticancer therapy. 2009; 9(6):795–805. Epub 2009/06/06. [PubMed: 19496716]
9. Miller AH, Ancoli-Israel S, Bower JE, Capuron L, Irwin MR. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008; 26(6):971–982. Epub 2008/02/19. [PubMed: 18281672]
10. Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer. 1999; 85(5):1186–1196. Epub 1999/03/26. [PubMed: 10091805]
11. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer. 2000; 89(7):1634–1646. Epub 2000/10/03. [PubMed: 11013380]
12. Wang XS, Janjan NA, Guo H, Johnson BA, Engstrom MC, Crane CH, et al. Fatigue during preoperative chemoradiation for resectable rectal cancer. Cancer. 2001; 92(6 Suppl):1725–1732. Epub 2001/10/13. [PubMed: 11598894]
13. Cleeland CS. Symptom burden: multiple symptoms and their impact as patient-reported outcomes. Journal of the National Cancer Institute Monographs. 2007; (37):16–21. Epub 2007/10/24. [PubMed: 17951226]
14. Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status of patients with cancer. Oncology nursing forum. 2001; 28(3):465–470. Epub 2001/05/08. [PubMed: 11338755]
15. Kirkova J, Aktas A, Walsh D, Davis MP. Cancer symptom clusters: clinical and research methodology. Journal of palliative medicine. 2011; 14(10):1149–1166. Epub 2011/08/25. [PubMed: 21861613]
16. Nelson CJ, Nandy N, Roth AJ. Chemotherapy and cognitive deficits: mechanisms, findings, and potential interventions. Palliative & supportive care. 2007; 5(3):273–280. Epub 2007/11/01. [PubMed: 17969831]
17. Cleeland CS, Bennett GJ, Dantzer R, Dougherty PM, Dunn AJ, Meyers CA, et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. Cancer. 2003; 97(11):2919–2925. Epub 2003/05/27. [PubMed: 12767108]
18. Kim HJ, Barsevick AM, Fang CY, Miaskowski C. Common Biological Pathways Underlying the Psychoneurological Symptom Cluster in Cancer Patients. Cancer nursing. 2012 Epub 2012/01/10.
19. Wang XS, Johnson V, Williams LA, Mao L, Liao Z, Lui P, et al. Serum sTNF-R1 and IL-6 are associated with severity of symptom burden caused by concurrent chemoradiation therapy for patients with lung and gastrointestinal cancers. Brain, behavior, and immunity. 2009; 32(Suppl. 2):S61–S62.
20. Shi, Q.; Cleeland, CS. Genetic approaches to treating and preventing symptoms in patients with cancer. In: Cleeland, CS.; Fisch, MJ.; Dunn, AJ., editors. Cancer Symptom Science: Measurement and Management. Cambridge: Cambridge University Press; 2011. p. 192-205.
21. Pacharinsak C, Beitz A. Animal models of cancer pain. Comparative medicine. 2008; 58(3):220–233. Epub 2008/07/01. [PubMed: 18589864]
22. Chang, VT.; Portenoy, RK. The clinical science of cancer pain assessment and management. In: Cleeland, CS.; Fisch, MJ.; Dunn, AJ., editors. Cancer Symptom Science: Measurement, Mechanisms, and Management. Cambridge: Cambridge University Press; 2011. p. 18-30.
23. Zhang, H.; Dougherty, PM. The physiopathology of neuropathic pain. In: Cleeland, CS.; Fisch, MJ.; Dunn, AJ., editors. Cancer Symptom Science: Measurement, Mechanisms, and Management. Cambridge: Cambridge University Press; 2011. p. 41-50.
24. Dantzer R. Cytokine-induced sickness behavior: where do we stand? Brain, behavior, and immunity. 2001; 15(1):7–24. Epub 2001/03/22.
25. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002; 420(6917):860–867. Epub 2002/12/20. [PubMed: 12490959]

26. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008; 454(7203):436–444. Epub 2008/07/25. [PubMed: 18650914]
27. Wortel CH, van Deventer SJ, Aarden LA, Lygidakis NJ, Buller HR, Hoek FJ, et al. Interleukin-6 mediates host defense responses induced by abdominal surgery. *Surgery*. 1993; 114(3):564–570. Epub 1993/09/01. [PubMed: 7690162]
28. Schmidt A, Bengtsson A, Tylman M, Blomqvist L. Pro-inflammatory cytokines in elective flap surgery. *The Journal of surgical research*. 2007; 137(1):117–121. Epub 2006/11/07. [PubMed: 17084411]
29. Deiner S, Silverstein JH. Postoperative delirium and cognitive dysfunction. *British journal of anaesthesia*. 2009; 103(Suppl 1):i41–i46. Epub 2009/12/17. [PubMed: 20007989]
30. Cibelli M, Fidalgo AR, Terrando N, Ma D, Monaco C, Feldmann M, et al. Role of interleukin-1beta in postoperative cognitive dysfunction. *Annals of neurology*. 2010; 68(3):360–368. Epub 2010/09/08. [PubMed: 20818791]
31. Brode S, Cooke A. Immune-potentiating effects of the chemotherapeutic drug cyclophosphamide. *Critical reviews in immunology*. 2008; 28(2):109–126. Epub 2008/06/11. [PubMed: 18540827]
32. Hei TK, Zhou H, Chai Y, Ponnaiya B, Ivanov VN. Radiation induced non-targeted response: mechanism and potential clinical implications. *Current molecular pharmacology*. 2011; 4(2):96–105. Epub 2010/12/15. [PubMed: 21143185]
33. Tsavaris N, Kosmas C, Vadiaka M, Kanelopoulos P, Boulamatsis D. Immune changes in patients with advanced breast cancer undergoing chemotherapy with taxanes. *British journal of cancer*. 2002; 87(1):21–27. Epub 2002/06/27. [PubMed: 12085250]
34. Bower JE, Ganz PA, Irwin MR, Kwan L, Breen EC, Cole SW. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011; 29(26):3517–3522. Epub 2011/08/10. [PubMed: 21825266]
35. Bower JE, Ganz PA, Tao ML, Hu W, Belin TR, Sepah S, et al. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. *Clin Cancer Res*. 2009; 15(17):5534–5540. Epub 2009/08/27. [PubMed: 19706826]
36. Stamme C, Bundschuh DS, Hartung T, Gebert U, Wollin L, Nusing R, et al. Temporal sequence of pulmonary and systemic inflammatory responses to graded polymicrobial peritonitis in mice. *Infection and immunity*. 1999; 67(11):5642–5650. Epub 1999/10/26. [PubMed: 10531211]
37. Dugernier TL, Laterre PF, Wittebole X, Roeseler J, Latinne D, Reynaert MS, et al. Compartmentalization of the inflammatory response during acute pancreatitis: correlation with local and systemic complications. *American journal of respiratory and critical care medicine*. 2003; 168(2):148–157. Epub 2003/07/10. [PubMed: 12851244]
38. Lutgendorf SK, Weinrib AZ, Penedo F, Russell D, DeGeest K, Costanzo ES, et al. Interleukin-6, cortisol, and depressive symptoms in ovarian cancer patients. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008; 26(29):4820–4827. Epub 2008/09/10. [PubMed: 18779606]
39. Sheehan TJ, Fifield J, Reisine S, Tennen H. The measurement structure of the Center for Epidemiologic Studies Depression Scale. *Journal of personality assessment*. 1995; 64(3):507–521. Epub 1995/06/01. [PubMed: 7760258]
40. Capuron L, Miller AH. Cytokines and psychopathology: lessons from interferon-alpha. *Biological psychiatry*. 2004; 56(11):819–824. Epub 2004/12/04. [PubMed: 15576057]
41. Seigers R, Fardell JE. Neurobiological basis of chemotherapy-induced cognitive impairment: a review of rodent research. *Neuroscience and biobehavioral reviews*. 2011; 35(3):729–741. Epub 2010/09/28. [PubMed: 20869395]
42. Pyter LM, Cochrane SF, Ouwenga RL, Patel PN, Pinerros V, Prendergast BJ. Mammary tumors induce select cognitive impairments. *Brain, behavior, and immunity*. 24(6):903–907. Epub 2010/03/02.
43. Krishnan V, Nestler EJ. Animal models of depression: molecular perspectives. *Current topics in behavioral neurosciences*. 2011; 7:121–147. Epub 2011/01/13. [PubMed: 21225412]
44. Pyter LM, Pinerros V, Galang JA, McClintock MK, Prendergast BJ. Peripheral tumors induce depressive-like behaviors and cytokine production and alter hypothalamic-pituitary-adrenal axis

- regulation. *Proceedings of the National Academy of Sciences of the United States of America*. 2009; 106(22):9069–9074. Epub 2009/05/20. [PubMed: 19451634]
45. Lamkin DM, Lutgendorf SK, Lubaroff D, Sood AK, Beltz TG, Johnson AK. Cancer induces inflammation and depressive-like behavior in the mouse: modulation by social housing. *Brain, behavior, and immunity*. 25(3):555–564. Epub 2010/12/25.
 46. Ray MA, Trammell RA, Verhulst S, Ran S, Toth LA. Development of a mouse model for assessing fatigue during chemotherapy. *Comparative medicine*. 61(2):119–130. Epub 2011/05/04. [PubMed: 21535922]
 47. Malik NM, Moore GB, Smith G, Liu YL, Sanger GJ, Andrews PL. Behavioural and hypothalamic molecular effects of the anti-cancer agent cisplatin in the rat: A model of chemotherapy-related malaise? *Pharmacol Biochem Behav*. 2006; 83(1):9–20. Epub 2006/01/31. [PubMed: 16443263]
 48. Konat GW, Kraszpulski M, James I, Zhang HT, Abraham J. Cognitive dysfunction induced by chronic administration of common cancer chemotherapeutics in rats. *Metab Brain Dis*. 2008; 23(3):325–333. Epub 2008/08/12. [PubMed: 18690526]
 49. Wood LJ, Nail LM, Perrin NA, Elsea CR, Fischer A, Druker BJ. The cancer chemotherapy drug etoposide (VP-16) induces proinflammatory cytokine production and sickness behavior-like symptoms in a mouse model of cancer chemotherapy-related symptoms. *Biol Res Nurs*. 2006; 8(2):157–169. Epub 2006/09/28. [PubMed: 17003255]
 50. Seigers R, Schagen SB, Beerling W, Boogerd W, van Tellingen O, van Dam FS, et al. Long-lasting suppression of hippocampal cell proliferation and impaired cognitive performance by methotrexate in the rat. *Behavioural brain research*. 2008; 186(2):168–175. Epub 2007/09/15. [PubMed: 17854921]
 51. Gandal MJ, Ehrlichman RS, Rudnick ND, Siegel SJ. A novel electrophysiological model of chemotherapy-induced cognitive impairments in mice. *Neuroscience*. 2008; 157(1):95–104. Epub 2008/10/07. [PubMed: 18835334]
 52. Fardell JE, Vardy J, Logge W, Johnston I. Single high dose treatment with methotrexate causes long-lasting cognitive dysfunction in laboratory rodents. *Pharmacol Biochem Behav*. 97(2):333–339. Epub 2010/09/11. [PubMed: 20828582]
 53. Seigers R, Fardell JE. Neurobiological basis of chemotherapy-induced cognitive impairment: a review of rodent research. *Neurosci Biobehav Rev*. 35(3):729–741. Epub 2010/09/28. [PubMed: 20869395]
 54. Malik NM, Liu YL, Cole N, Sanger GJ, Andrews PL. Differential effects of dexamethasone, ondansetron and a tachykinin NK1 receptor antagonist (GR205171) on cisplatin-induced changes in behaviour, food intake, pica and gastric function in rats. *Eur J Pharmacol*. 2007; 555(2–3):164–173. Epub 2006/12/05. [PubMed: 17141213]
 55. Acharya MM, Christie LA, Lan ML, Giedzinski E, Fike JR, Rosi S, et al. Human neural stem cell transplantation ameliorates radiation-induced cognitive dysfunction. *Cancer research*. 2011; 71(14):4834–4845. Epub 2011/07/16. [PubMed: 21757460]
 56. Boyette-Davis J, Xin W, Zhang H, Dougherty PM. Intraepidermal nerve fiber loss corresponds to the development of taxol-induced hyperalgesia and can be prevented by treatment with minocycline. *Pain*. 2011; 152(2):308–313. Epub 2010/12/15. [PubMed: 21145656]
 57. Crawley JN. Behavioral phenotyping strategies for mutant mice. *Neuron*. 2008; 57(6):809–818. Epub 2008/03/28. [PubMed: 18367082]
 58. Dantzer R, Bluthé RM, LeMoal M. Experimental assessment of drug-induced changes in cognitive function: vasopressin as a case study. *Neurotoxicology*. 1988; 9(3):471–477. Epub 1988/01/01. [PubMed: 3059246]
 59. Ward RD, Simpson EH, Kandel ER, Balsam PD. Modeling motivational deficits in mouse models of schizophrenia: behavior analysis as a guide for neuroscience. *Behavioural processes*. 2011; 87(1):149–156. Epub 2011/02/23. [PubMed: 21338658]
 60. Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature*. 2008; 455(7215):894–902. Epub 2008/10/17. [PubMed: 18923511]
 61. Carmichael MD, Davis JM, Murphy EA, Brown AS, Carson JA, Mayer EP, et al. Role of brain IL-1 β on fatigue after exercise-induced muscle damage. *American journal of physiology*

- Regulatory, integrative and comparative physiology. 2006; 291(5):R1344–R1348. Epub 2006/06/17.
62. Carmichael MD, Davis JM, Murphy EA, Carson JA, Van Rooijen N, Mayer E, et al. Role of brain macrophages on IL-1 β and fatigue following eccentric exercise-induced muscle damage. *Brain, behavior, and immunity*. 2010; 24(4):564–568. Epub 2010/01/07.
 63. Zemke D, Majid A. The potential of minocycline for neuroprotection in human neurologic disease. *Clinical neuropharmacology*. 2004; 27(6):293–298. Epub 2004/12/23. [PubMed: 15613934]
 64. O'Connor JC, Lawson MA, Andre C, Moreau M, Lestage J, Castanon N, et al. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Molecular psychiatry*. 2009; 14(5):511–522. Epub 2008/01/16. [PubMed: 18195714]
 65. Boyette-Davis J, Dougherty PM. Protection against oxaliplatin-induced mechanical hyperalgesia and intraepidermal nerve fiber loss by minocycline. *Experimental neurology*. 2011; 229(2):353–357. Epub 2011/03/10. [PubMed: 21385581]
 66. Willemen HL, Eijkelkamp N, Wang H, Dantzer R, Dorn GW 2nd, Kelley KW, et al. Microglial/macrophage GRK2 determines duration of peripheral IL-1 β -induced hyperalgesia: contribution of spinal cord CX3CR1, p38 and IL-1 signaling. *Pain*. 2010; 150(3):550–560. Epub 2010/07/09. [PubMed: 20609517]
 67. Zink MC, Uhrlaub J, DeWitt J, Voelker T, Bullock B, Mankowski J, et al. Neuroprotective and anti-human immunodeficiency virus activity of minocycline. *JAMA : the journal of the American Medical Association*. 2005; 293(16):2003–2011. Epub 2005/04/28. [PubMed: 15855434]
 68. Sacktor N, Miyahara S, Deng L, Evans S, Schifitto G, Cohen BA, et al. Minocycline treatment for HIV-associated cognitive impairment: results from a randomized trial. *Neurology*. 2011; 77(12):1135–1142. Epub 2011/09/09. [PubMed: 21900636]
 69. Ho EL, Spudich SS, Lee E, Fuchs D, Sinclair E, Price RW. Minocycline fails to modulate cerebrospinal fluid HIV infection or immune activation in chronic untreated HIV-1 infection: results of a pilot study. *AIDS research and therapy*. 2011; 8:17. Epub 2011/05/17. [PubMed: 21569420]
 70. Buch MH, Emery P. New therapies in the management of rheumatoid arthritis. *Current opinion in rheumatology*. 2011; 23(3):245–251. Epub 2011/03/24. [PubMed: 21427579]
 71. Numerof RP, Asadullah K. Cytokine and anti-cytokine therapies for psoriasis and atopic dermatitis. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy*. 2006; 20(2):93–103. Epub 2006/04/22.
 72. Monk JP, Phillips G, Waite R, Kuhn J, Schaaf LJ, Otterson GA, et al. Assessment of tumor necrosis factor alpha blockade as an intervention to improve tolerability of dose-intensive chemotherapy in cancer patients. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006; 24(12):1852–1859. Epub 2006/04/20. [PubMed: 16622259]
 73. Penna F, Minero VG, Costamagna D, Bonelli G, Baccino FM, Costelli P. Anti-cytokine strategies for the treatment of cancer-related anorexia and cachexia. *Expert opinion on biological therapy*. 2010; 10(8):1241–1250. Epub 2010/07/03. [PubMed: 20594117]
 74. Jatoi A, Ritter HL, Dueck A, Nguyen PL, Nikcevic DA, Luyun RF, et al. A placebo-controlled, double-blind trial of infliximab for cancer-associated weight loss in elderly and/or poor performance non-small cell lung cancer patients (N01C9). *Lung Cancer*. 2010; 68(2):234–239. Epub 2009/08/12. [PubMed: 19665818]
 75. Goedendorp MM, Gielissen MF, Verhagen CA, Bleijenberg G. Psychosocial interventions for reducing fatigue during cancer treatment in adults. *Cochrane Database Syst Rev*. 2009; (1):CD006953. Epub 2009/01/23. [PubMed: 19160308]
 76. Payne C, Wiffen PJ, Martin S. Interventions for fatigue and weight loss in adults with advanced progressive illness. *Cochrane Database Syst Rev*. 2012; 1:CD008427. Epub 2012/01/20. [PubMed: 22258985]
 77. Brell JM, Minasian LM. Developing symptom management drugs. In: Cleeland, CS, Fisch, MJ, Dunn, AJ, editors. *Cancer Symptom Science - Measurement, Mechanisms, and Management*. Cambridge: Cambridge University Press; 2011. p. 315–324.

78. Cleeland, CS.; Fisch, MJ.; Dunn, AJ. Symptom research: looking ahead. In: Cleeland, CS.; Fisch, MJ.; Dunn, AJ., editors. *Cancer Symptom Science: Measurement, Mechanisms, and Management*. Cambridge: Cambridge University Press; 2011. p. 341-348.
79. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews Neuroscience*. 2008; 9(1):46–56. Epub 2007/12/13.
80. Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacology & therapeutics*. 2011; 130(2):226–238. Epub 2011/02/22. [PubMed: 21334376]
81. Cavaletti G, Alberti P, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity in the era of pharmacogenomics. *The lancet oncology*. 2011; 12(12):1151–1161. Epub 2011/07/02. [PubMed: 21719347]
82. Bull SJ, Huezo-Diaz P, Binder EB, Cubells JF, Ranjith G, Maddock C, et al. Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon-alpha and ribavirin treatment. *Molecular psychiatry*. 2009; 14(12):1095–1104. Epub 2008/05/07. [PubMed: 18458677]
83. Aouizerat BE, Dodd M, Lee K, West C, Paul SM, Cooper BA, et al. Preliminary evidence of a genetic association between tumor necrosis factor alpha and the severity of sleep disturbance and morning fatigue. *Biological research for nursing*. 2009; 11(1):27–41. Epub 2009/05/08. [PubMed: 19419979]
84. Miaskowski C, Dodd M, Lee K, West C, Paul SM, Cooper BA, et al. Preliminary evidence of an association between a functional interleukin-6 polymorphism and fatigue and sleep disturbance in oncology patients and their family caregivers. *Journal of pain and symptom management*. 2010; 40(4):531–544. Epub 2010/06/24. [PubMed: 20570482]
85. Froklage FE, Reijneveld JC, Heimans JJ. Central neurotoxicity in cancer chemotherapy: pharmacogenetic insights. *Pharmacogenomics*. 2011; 12(3):379–395. Epub 2011/04/01. [PubMed: 21449677]
86. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. *Nature reviews Cancer*. 2007; 7(3):192–201. Epub 2007/02/24.
87. Cole SW. Elevating the perspective on human stress genomics. *Psychoneuroendocrinology*. 35(7): 955–962. Epub 2010/07/16. [PubMed: 20630660]
88. Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, et al. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. *Proc Natl Acad Sci U S A*. 2009; 106(34):14716–14721. Epub 2009/07/21. [PubMed: 19617551]
89. Greene WC, Chen LF. Regulation of NF-kappaB action by reversible acetylation. *Novartis Foundation symposium*. 2004; 259:208–217. discussion 18-25. Epub 2004/06/03. [PubMed: 15171256]
90. Lee H, Herrmann A, Deng JH, Kujawski M, Niu G, Li Z, et al. Persistently activated Stat3 maintains constitutive NF-kappaB activity in tumors. *Cancer cell*. 2009; 15(4):283–293. Epub 2009/04/07. [PubMed: 19345327]

Key points

- Overwhelming fatigue, distractibility, poor memory, and lack of interest in activities that used to be pleasurable are among the most distressing symptoms patients experience in response to cancer therapy
- The trajectory of these symptoms can be studied over time, together with their co-occurrence in the form of clusters and their impact on patients' daily functioning
- There is already evidence that the development of cancer-related symptoms is associated with an increased expression of inflammatory mediators
- Animal studies have confirmed that cancer therapy induces profound neurobehavioral changes that are associated with inflammation; however, no attempts have been made to model key symptoms in cancer patients
- Individual differences in the severity of symptoms in response to cancer therapy provides a unique perspective on symptoms genomics that should be incorporated in animal models of cancer-related symptoms
- Preclinical and clinical approaches can be combined in a translational research pathway that provides a framework for addressing the neurobehavioural toxicities of cancer therapies

Box 1 Prevalence and clustering of symptoms in cancer patients

The prevalence and severity of symptoms produced by cancer and its therapy vary. Pain, fatigue, sleep disturbances, emotional distress, and difficulties with concentration commonly co-occur or “cluster” across various diseases and treatments.(9, 48, 52) It has been postulated that this represents a symptom cluster that has common underlying mechanisms. An example of clustering of cancer-related symptoms is presented in Fig. 1.1 and is based on the data collected in one large study of patients undergoing treatment at a tertiary cancer centre. The 527 patients enrolled in this study had heterogeneous cancers and cancer treatment and completed the M. D. Anderson Symptom Inventory (MDASI). (1) The following symptoms were rated as being at least moderately severe (i.e., five or greater on the MDASI’s 0 to 10 scale): fatigue (59%), inability to get things done (51%), weakness (50%), worry (42%), distress (38%), disturbed sleep (41%), drowsiness (41%), lack of appetite (39%), sadness (32%), pain (34%), and difficulty remembering (30%). Another study analyzed the MDASI symptom ratings of 1,433 cancer patients from five different countries.(2) In each sample, fatigue was the most severe symptom. For the combined sample, highly rated symptoms included disturbed sleep, distress, lack of appetite, drowsiness, pain, and sadness. Symptom clustering is not always stable and depends on many factors, including occurrence versus severity of symptom, the instrument used, the type of cancer, the modalities of treatment, and the time points at which symptoms are evaluated. The general consensus in the field is that even if there is sufficient evidence for recognizing the co-occurrence of symptoms of fatigue, insomnia, pain, depression, and cognitive dysfunction, the way these symptoms cluster and the underlying mechanisms of clustering require further research.(4–8)

Box 1 References

1. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer*. 2000;89(7):1634-46. Epub 2000/10/03.
2. Wang XS, Cleeland CS, Mendoza TR, Yun YH, Wang Y, Okuyama T, et al. Impact of cultural and linguistic factors on symptom reporting by patients with cancer. *Journal of the National Cancer Institute*. 2010;102(10):732-8. Epub 2010/03/30.
4. Barsevick AM. The elusive concept of the symptom cluster. *Oncology nursing forum*. 2007;34(5):971-80. Epub 2007/09/20.
5. Kirkova J, Walsh D, Aktas A, Davis MP. Cancer symptom clusters: old concept but new data. *The American journal of hospice & palliative care*. 2010;27(4):282-8. Epub 2010/03/31.
6. Kim HJ, Barsevick AM, Fang CY, Miaskowski C. Common Biological Pathways Underlying the Psychoneurological Symptom Cluster in Cancer Patients. *Cancer nursing*. 2012. Epub 2012/01/10.
7. Aktas A, Walsh D, Rybicki L. Symptom clusters: myth or reality? *Palliative medicine*. 2010;24(4):373-85. Epub 2010/05/29.
8. Fan G, Filipczak L, Chow E. Symptom clusters in cancer patients: a review of the literature. *Curr Oncol*. 2007;14(5):173-9. Epub 2007/10/17.

Box 2 Inflammation-induced sickness

Inflammation-induced sickness has been studied mainly in the context of peripheral activation of the innate immune system by pathogen-associated molecules such as lipopolysaccharide (LPS) that target toll-like receptors (TLRs) at the membrane of innate immune cells. (1) Activation of TLRs induces production of inflammatory cytokines via activation of nuclear factor (NF)- κ B and mitogen-activated protein kinase (MAPK). In the context of chemotherapy and radiotherapy, the inflammatory response is triggered by molecules released by necrotic and apoptotic cells. These molecules include high mobility group box protein 1, heat shock proteins, and S100 proteins. They engage TLRs and the receptor for advanced glycation end products (RAGE) that signal through NF - κ B pathways. (2) The resulting inflammation propagates to the brain via several parallel immune-to-brain communication pathways (Figure 2.1). The relative importance of each of these pathways depends on the response to inflammation. Behavioural responses are mediated by afferent neural pathways, whereas neuroendocrine and fever responses are mediated by humoral pathways involving circulating pathogen -associated molecular patterns. Cytokines are ultimately responsible for the changes in behaviour, endocrine functions and metabolism that characterize the host response to inflammation. (4) The neurocircuitry of inflammation-induced sickness has been studied in animals injected with LPS and in humans given low doses of endotoxin or typhoid vaccine. Intra - peritoneal administration of LPS to rats signals the brain via the vagus nerves and activates viscerosensory nuclei that are located in the caudal brainstem. (10, 11) The activation of stress-related brain areas contrasts with the deactivation of brain areas that are involved in positively-mediated behaviour, which include the motor cortex, piriform and cingulate cortex, together with the nucleus accumbens and locus coeruleus. (12) Fatigue and/or lethargy appear to be associated with reduced activation of dopaminergic neurons in the ventral tegmental area, histaminergic neurons in the ventral tuberomammillary nucleus, and orexin neurons in the lateral hypothalamus. (10, 13)

Activation of innate immune cells by damage-associated molecular patterns leads to the production and release of proinflammatory cytokines. This peripheral immune message is relayed to the central nervous system (CNS) via several communication pathways, including activation of the sensory nerves at the site of inflammation. This results in the local production of proinflammatory cytokines by CNS perivascular macrophages and microglia. These cytokines or the prostaglandins they induce ultimately affect neuronal functions to induce symptoms of sickness, together with alterations in metabolism and neuroendocrine activity.

Box 2 References

1. Imler JL, Hoffmann JA. Toll receptors in innate immunity. *Trends Cell Biol.* 2001 Jul; 11(7):304-11.
2. Sims GP, Rowe DC, Rietdijk ST, Herbst R, Coyle AJ. HMGB1 and RAGE in inflammation and cancer. *Annu Rev Immunol.* [Review]. 2010 Mar;28:367-88.
4. Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: mechanisms and implications. *Trends Neurosci.* [Review]. 2002 Mar;25(3):154-9.
10. Gaykema RP, Goehler LE. Ascending caudal medullary catecholamine pathways drive sickness-induced deficits in exploratory behavior: brain substrates for fatigue? *Brain Behav Immun.* 2011 Mar;25(3):443-60.
11. Konsman JP, Veeneman J, Combe C, Poole S, Luheshi GN, Dantzer R. Central nervous action of interleukin-1 mediates activation of limbic structures and behavioural

depression in response to peripheral administration of bacterial lipopolysaccharide. *Eur J Neurosci*. 2008 Dec;28(12):2499-510.

12. Stone EA, Lehmann ML, Lin Y, Quartermain D. Depressive behavior in mice due to immune stimulation is accompanied by reduced neural activity in brain regions involved in positively motivated behavior. *Biol Psychiatry*. 2006 Oct 15;60(8):803-11.

13. Grossberg AJ, Zhu X, Leininger GM, Levasseur PR, Braun TP, Myers MG, Jr., et al. Inflammation-induced lethargy is mediated by suppression of orexin neuron activity. *J Neurosci*. 2011 Aug 3;31(31):11376-86.

\$watermark-text

\$watermark-text

\$watermark-text

Box 3 The biochemistry of inflammation-induced depression and fatigue

Inflammation induces depression and fatigue. Different mechanisms downstream of inflammation probably mediate depression and fatigue. There is evidence that inflammation-associated depression is mediated by activation of the tryptophan - degradation pathway, which affects glutamatergic neurotransmission. By contrast, inflammation-associated fatigue is mediated by a relative deficit in tetrahydrobiopterin that ultimately affects dopaminergic neurotransmission. Proinflammatory cytokines activate genes controlling cellular proliferation, differentiation of cells, and genes that regulate metabolism. Low-grade inflammation activates both indoleamine 2,3-dioxygenase (IDO), which targets tryptophan metabolism, and guanosine triphosphate cyclohydrolase-1 (GTP-CH1), which indirectly targets tryptophan and phenylalanine metabolism. Both enzymes are expressed in a variety of immune and non-immune cells. IDO degrades the essential amino acid tryptophan along the kynurenine pathway. The degradation of tryptophan also generates neurotoxic metabolites such as 3-hydroxykynurenine and quinolinic acid. Activation of IDO, as measured by decreased circulating levels of tryptophan and increased levels of kynurenine, is associated with lower quality of life in patients with colorectal cancer.(5) The same enzyme is activated in cancer patients treated with interferon (IFN)- α , and the lower the concentrations of circulating tryptophan, the higher the symptoms of depression.(6) In mice, inflammation-induced depressive-behavior is abrogated by antagonism of IDO.(7, 8) These findings are strongly suggestive of a causal role of IDO in inflammation-associated depression. (9) Deficit in the biosynthesis of dopamine, evidenced indirectly by an increase in the ratio of phenylalanine to tyrosine, has been documented in cancer patients treated with IFN- α , and this could be responsible for psychomotor retardation.(11) It is also found in older patients with low-grade inflammation and it has been correlated with neurovegetative symptoms, including sleep disturbances, digestive symptoms, fatigue, sickness, and motor symptoms. In the same population, increased tryptophan degradation was associated with the depressive symptoms of lassitude, reduced motivation, anorexia, and pessimism.(12)

Box 3 References

5. Huang A, Fuchs D, Widner B, Glover C, Henderson DC, Allen-Mersh TG. Serum tryptophan decrease correlates with immune activation and impaired quality of life in colorectal cancer. *British journal of cancer*. 2002;86(11):1691-6. Epub 2002/06/28.
6. Capuron L, Neirauter G, Musselman DL, Lawson DH, Nemeroff CB, Fuchs D, et al. Interferon-alpha-induced changes in tryptophan metabolism. relationship to depression and paroxetine treatment. *Biological psychiatry*. 2003;54(9):906-14. Epub 2003/10/24.
7. O'Connor JC, Lawson MA, Andre C, Moreau M, Lestage J, Castanon N, et al. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Molecular psychiatry*. 2009;14(5):511-22. Epub 2008/01/16.
8. O'Connor JC, Andre C, Wang Y, Lawson MA, Szegedi SS, Lestage J, et al. Interferon-gamma and tumor necrosis factor-alpha mediate the upregulation of indoleamine 2,3-dioxygenase and the induction of depressive-like behavior in mice in response to bacillus Calmette-Guerin. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2009;29(13):4200-9. Epub 2009/04/03.
9. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews Neuroscience*. 2008;9(1):46-56. Epub 2007/12/13.

11. Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacology & therapeutics*. 2011;130(2): 226-38. Epub 2011/02/22.
12. Capuron L, Schroecksnadel S, Feart C, Aubert A, Higuieret D, Barberger-Gateau P, et al. Chronic low-grade inflammation in elderly persons is associated with altered tryptophan and tyrosine metabolism: role in neuropsychiatric symptoms. *Biological psychiatry*. 2011;70(2):175-82. Epub 2011/02/01.

\$watermark-text

\$watermark-text

\$watermark-text

Box 4 Parsing components of cancer-related symptoms

To study the mechanisms of cancer-related symptoms, it is necessary to translate them into objective behavioural and physiological measures (Figure 4.1). Animal models are useful because they can be designed to measure the various dimensions of symptoms. This approach is illustrated by two behavioural tests used to study motivation: a progressive ratio test (Figure 4.2) and a concurrent choice task (Fig. 4.3). Both tests evaluate the cost an animal is ready to pay to get access to a given commodity (here, a food reward). Although impaired performance in these tasks would suggest a motivational deficit, additional behavioral tests would be needed to evaluate alternative explanations. Chemotherapy could induce a motor impairment that makes the animal unable to respond quickly or to sustain effort. This can be examined using tests of motor function. Chemotherapy could also alter the affective or hedonic response to the preferred food, resulting in a less -valued outcome and, consequently, decreased effort. To evaluate the latter hypothesis, additional tests that assess emotional “liking/disliking,” as listed in the second column of Fig. 4.1 (e.g., response vigor, facial affect, drug discrimination), would be needed.(4–6) The inflammatory changes induced by cancer and its treatment can affect any or all of the psychobiological processes depicted in Fig. 4.1, and an alteration in just one component is sufficient to modify behavior in several tasks. It can therefore be predicted that various cancer therapies sharing the same neuroimmune mechanisms will induce a similar pattern or spectrum of behavioral changes and, *a contrario*, that cancer therapies with different mechanisms of action will induce distinct patterns of behavioral change. These patterns can be further used to study the mechanisms of action of cancer therapy on symptoms and to test the efficacy of preventive and curative treatments.

Box 4 References

1. Meagher MW. Developing translational animal models of cancer-related fatigue. In: Cleeland CS, Fisch MJ, Dunn AJ, editors. Cancer Symptom Science: Measurement, Mechanisms, and Management. Cambridge: Cambridge University Press; 2011. p. 124-41.
2. Larson SJ, Romanoff RL, Dunn AJ, Glowa JR. Effects of interleukin-1beta on food-maintained behavior in the mouse. Brain, behavior, and immunity. 2002;16(4):398-410. Epub 2002/07/05.
3. Salamone JD, Correa M, Farrar A, Mingote SM. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. Psychopharmacology. 2007;191(3):461-82. Epub 2007/01/17.
4. Berridge KC, Robinson TE. Parsing reward. Trends in neurosciences. 2003;26(9): 507-13. Epub 2003/09/02.
5. Bluthé RM, Dantzer R, Le Moal M. Peripheral injections of vasopressin control behavior by way of interoceptive signals for hypertension. Behavioural brain research. 1985;18(1):31-9. Epub 1985/10/01.
6. Aubert A, Dantzer R. The taste of sickness: lipopolysaccharide-induced finickiness in rats. Physiology & behavior. 2005;84(3):437-44. Epub 2005/03/15.

Box 5 – Genetic risk factors for the development of interferon- α -induced depression

Only one third to one half of the patients treated with interferon (IFN)- α develop a major depressive episode within a few weeks after the initiation of treatment.(1) Studies of genetic risk factors for IFN- α -induced depression are carried out in patients with chronic hepatitis C rather than cancer patients because the chronic hepatitis C patients are very numerous and easily accessible for epidemiological studies. Functional polymorphisms in candidate genes that regulate the brain response to insults and the immune response have been examined. Interestingly, the short/short genotype in the serotonin transporter length promoter region (5-HTTLPR) that was proposed to increase risk for depression in subjects possibly exposed in stressful life events was found to increase vulnerability to IFN- α - induced depression in hepatitis C patients.(2) The long/long serotonin transporter genotype does not necessarily act alone, as it was found to interact with a low IL-6 synthesizing genotype to increase resilience to depressive symptoms in a different population of hepatitis C patients.(3) The “A” allele in a promoter region of the tumour necrosis factor (TNF)- α gene that is associated with higher TNF- α plasma levels increased vulnerability to IFN- α -induced labile anger,(4) which is another psychiatric feature of IFN- α -treated patients with hepatitis C.(5)

Box 5 References

1. Raison CL, Demetrashvili M, Capuron L, Miller AH. Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS drugs*. 2005;19(2):105-23. Epub 2005/02/09.
2. Lotrich FE, Ferrell RE, Rabinovitz M, Pollock BG. Risk for depression during interferon-alpha treatment is affected by the serotonin transporter polymorphism. *Biological psychiatry*. 2009;65(4):344-8. Epub 2008/09/20.
3. Bull SJ, Huezio-Diaz P, Binder EB, Cubells JF, Ranjith G, Maddock C, et al. Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon-alpha and ribavirin treatment. *Mol Psychiatry*. 2009;14(12):1095-104. Epub 2008/05/07.
4. Lotrich FE, Ferrell RE, Rabinovitz M, Pollock BG. Labile anger during interferon alfa treatment is associated with a polymorphism in tumor necrosis factor alpha. *Clin Neuropsychopharmacol*. 2010;33(4):191-7. Epub 2010/07/28.
5. Constant A, Castera L, Dantzer R, Couzigou P, de Ledinghen V, Demotes-Mainard J, et al. Mood alterations during interferon-alpha therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms. *J Clin Psychiatry*. 2005;66(8):1050-7. Epub 2005/08/10.

Figure 1.

Symptom severity over time in patients receiving chemotherapy. Symptoms were measured by MDASI over the course of several cycles of chemotherapy in 44 patients with colorectal cancer, 53 patients with esophageal cancer, and 62 patients with non-small cell lung cancer. Symptom trajectories are represented as Lowess curves, which are smoothed estimates of average symptom severity as a function of time. Note that fatigue (green) is the dominant symptom for all patient cohorts, followed by drowsiness (yellow), pain (dark blue) and disturbed sleep (red). Other symptoms include distress (tan), lack of appetite (dark magenta), diarrhea (cyan), difficulty swallowing (gray) and shortness of breath (lilac).

Top Five Symptoms, by Week

Figure 2.

Individual variation in symptom burden during chemotherapy in 182 patients with head and neck cancer or breast cancer over 10 weeks of chemotherapy. Symptoms were assessed repeatedly on the MDASI's 0–10 numeric rating scale. The score represented on the vertical axis is a composite score that includes the five most severe MDASI symptoms (pain, fatigue, disturbed sleep, lack of appetite, and drowsiness). Note that 78 patients (43%) experienced no or mild symptom burden over the course of treatment, whereas the remaining 104 patients (57%) were asymptomatic at the beginning of treatment but suffered increasing symptom burden as treatment progressed.

Figure 3.

Translational strategy for elucidating the pathophysiology of inflammation-associated depression. Clinical needs were identified on the basis of the high prevalence of symptoms of depression in patients with chronic inflammation. Measurement strategies were then identified to assess the phenomenology and time course of symptoms in a target population with a high prevalence of inflammation-induced depression. Cancer patients with metastatic kidney cancer or melanoma and treated chronically with IFN- α and/or IL-2 were selected for this purpose. Clinical biochemistry revealed that immune stimulation was associated with activation of a tryptophan-degrading pathway that was tentatively ascribed to activation of indoleamine 2,3 dioxygenase. Mechanistic studies in animal models of depression confirmed the causative role of inflammation in the development of depressive-like behavior and the mediating role of indoleamine 2,3 dioxygenase activation. Similar associations between inflammation and activation of tryptophan-degrading pathway have now been confirmed in other disease conditions characterized by chronic inflammation. The possibility of targeting tryptophan-degrading pathways for treating inflammation-associated symptoms of depression is currently under investigation.

Figure 1.1. The dendrogram presents the relationship of patient ratings on the severity of 26 symptoms used in the development of the MDASI. The sample represents ratings made by 547 patients with various cancers undergoing a variety of treatments at a tertiary cancer center. The figure is read from left to right. The figure represents the probability of co-reporting of the symptoms in this set. The nodes in the diagram represent linkages among the symptoms. Clusters of symptoms are color coded. One cluster (orange) represents fatigue and decreased motivation. A second cluster (green) combines ratings of cognitive impairment and emotional distress. These two clusters combine, along with pain and sleep disturbance. (Adapted from Cleeland CS, Mendoza TR, Wang XS, et al. *CANCER* 89(7). Copyright © 2000 American Cancer Society. Reprinted with permission of John Wiley and Sons. (1)).

Figure 2.1.
Immune-to-brain communication pathways.

Fig. 3.1.

Effects of inflammatory cytokines on enzymatic pathways responsible for tryptophan degradation and neopterin/tetrahydrobiopterin formation. The compounds in red are those of which the concentrations are relatively increased during chronic inflammation, whereas those in blue are those of which the concentrations are relatively decreased. See the text for the abbreviations.

Figure 4.1. Schematic representation of how cancer-related symptoms are modeled in animals. The first row delineates six constructs that contribute to the cluster of cancer - related symptoms, including motivation, emotion, learning and memory, executive function, and biological clocks. Each construct contains different psychobiological components (middle row) that are governed by different psychological processes and neural mechanisms. Behavioral tests and measures that are sensitive indicators of the each of these psychobiological components are listed in the third row. These measures can be used to characterize the behavioral syndrome induced by cancer and its treatment in laboratory animals (adapted from (1))

Figure 4.2.

Acute administration of interleukin (IL)-1 β decreases the motivation to work for sweetened milk in mice in a progressive ratio test. In order to get access to a few drops of sweetened milk, mice have to insert their nose in the hole that is at the right of the feeder. When this is done 10 times in a row, mice get access to the milk and they can repeat this during a 30 min test (fixed ratio 10). In this test, IL-1 β does not alter the response rate in doses varying from 10 to 300 ng (left diagram). In the progressive ratio 10 (right diagram), mice have to respond 10 times for the first reward, 20 times for the second reward, and so on with an increment of 10 after each reward. Saline-treated mice normally stop responding when they reach a ratio of 110 responses for a food reward. IL-1 β administered at a dose of 100 or 300 ng decreases the maximum ratio mice are willing to work for (adapted from Brain, Behavior and Immunity, 16/4, Larson SJ, Romanoff RL, Dunn AJ, Glowa JR, Effects of interleukin-1beta on food-maintained behavior in the mouse, 398-410, copyright © 2002, with permission from Elsevier. (2)). It is expected that chemotherapy will produce the same type of deficit.

Figure 4.3.

Cancer-related fatigue and effort-related decision making.

The two upper figures show the apparatus used to assess effort-related decisions based upon cost-benefit analyses. The rat is put in a chamber that allows access to a highly palatable food (condensed sweetened milk), providing it presses the left lever five times, while a less preferred food (lab chow) is freely available at the same time (top left and right). With a ratio requirement of 5, control rats get most of their food from lever pressing (bottom left). By contrast, rats that have received chemotherapy and experience fatigue are expected to shift behaviour away from lever pressing and increase their consumption of lab food (bottom right) (adapted from *Psychopharmacology*, 191/3, Salamone JD, Correa M, Farrar A, Mingote SM, Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits, 461-482, copyright © 2007, with permission from Springer (3)).