Cancer patients suffer from a variety of physical, affective, and cognitive symptoms caused either directly or indirectly by the cancer itself or its treatment. In this review, we focus on a common symptom cluster of fatigue, appetite loss, and sleep disruption, the causes of which are multidimensional. Although there may be disagreement as to what constitutes a symptom cluster, available data justify lumping together these particular symptoms for the purposes of our discussion.

The 'Sickness Behavior' Model and Symptom Clustering

Models for symptom production based on molecular mechanisms are well illustrated by the “sickness behavior” model, which hypothesizes that tumors, in conjunction with a host response, produce pro-inflammatory cytokines such as interleukin (IL)-1 and IL-6 and tumor necrosis factor-alpha (TNF-α). In this model, observed behaviors, such as decreased activity, appetite loss, and somnolence, can be induced in laboratory animals with the administration of lipopolysaccharide. Likewise, excessive production of pro-inflammatory cytokines in humans is thought to result in signaling cascades that upregulate brain cytokine levels, induce fever, and disrupt the hypothalamic-pituitary-adrenal (HPA) axis that contributes to symptom production. Clinical evidence for this hypothesis comes from the observation that elevated serum levels of IL-6 are associated with “B symptoms” (typically defined as fever and malaise) in patients with lymphomas (including Hodgkin’s disease), acute myelogenous leukemia, myelodysplastic syndromes, or pancreatic cancer who have a poor prognosis. Further support comes from the observations of mental changes such as neurologic fatigue clustered with a loss of motivation, lack of energy, and depression in cancer patients treated with interferon alfa (IFN-α) and/or IL-2, in which administration of IFN-α was associated with increased serum levels of IL-6 and IL-10, an anti-inflammatory cytokine produced in response to the production of pro-inflammatory cytokines. Other researchers have shown positive correlations between elevated levels of IL-6 or vascular endothelial growth factor (VEGF, thought to signal through the IL-6 pathway) and altered psychosocial, quality-of-life, and depression indices in untreated cancer patients.

The continued attraction of the pro-inflammatory cytokine hypothesis stems from the similarity...
Symptom Clusters and Their Relation to EGFR Ligand Modulation of the Circadian Axis

The central circadian system, described here in simplified form, has three major functional components. The first component is the central oscillator (represented by the clock in Figure 1) that produces electrophysiologic signals that arise from paired populations of neurons in the suprachiasmatic nuclei (SCN). Specialized “core and shell” neurons in the SCN produce an entrainable approximate 24-hour rhythm that is expressed in all mammals. Rhythmic output is produced even in the absence of environmental cues (such as the conditions prevailing in deep cave isolation studies) that result in “free-running” behavior. Another unique feature of the central oscillator’s output is constant periodicity over a wide temperature range.

The third component of the central circadian timing system is composed mainly of afferent nerve fiber groups projecting from the SCN to the hypothalamus and represents the output network. By relaying excitatory or inhibitory signals to other centers in the hypothalamus, these connections comprise an output network that modulates the synchronized, rhythmic physiology and behavior of the organism. Activation or inhibition of hypothalamic centers facilitates specific behaviors that are associated with rhythmic patterns of arousal and sleep, core body temperature, and appetite. Signals from these hypothalamic neuroendocrine centers regulate the secretion of reproductive, stress-axis, and physiology-regulating hormones, and by their effects on the parasympathetic and sympathetic autonomic centers in the brainstem, they help maintain physiologic balance.

LESSONS LEARNED FROM SCN ABLATION STUDIES

To better understand how the clock influences physiology and behavior, researchers have performed SCN ablation studies in an attempt to correlate loss of clock function with physiologic and behavioral changes in laboratory animals. SCN ablation causes permanent loss of rhythmic rest/activity, core body temperature, feeding, and sleep behavior patterns. Experimentally induced loss of circadian rhythms can be reversed by implanting embryonic SCN tissue into the area of the host’s ablated SCN or using encapsulated SCN preparations that prevent axonal connections but allow diffusion of secreted factors and partial restoration of clock function.

The clustering of symptoms in cancer patients also suggests that a shared biologic mechanism exists for their production and that there may be a commonly shared neuroanatomic target within the central nervous system. In this review, a new hypothesis for symptom production is discussed that is based on targeted signaling by members of the epidermal growth factor receptor (EGFR) family that disrupt hypothalamic circadian modulation. The background for this idea is provided by studies emerging from the fields of chronobiology and the neurosciences, two disciplines that have seen a recent explosion in our understanding of the central molecular clock and its rhythmic output to downstream signaling networks within the hypothalamus that modulate circadian behavior. Data will be reviewed here supporting the continued investigation of symptom clusters in cancer patients that link disruption in rhythmic behavior of the 24-hour rest/activity pattern (as related to fatigue), feeding, and sleep to tumor-produced growth factors that appear to inhibit the hypothalamic relay stations involved in circadian signaling.

The Circadian Axis and Chronobiologic Regulation in Humans

The central circadian system, described here in simplified form, has three major functional components. The first component consists of signaling inputs, the most dominant of which is the timing of exposure to ambient light perceived by specialized sensors in the eye, that result in neurophysiologic changes in the central clock within the hypothalamus (Figure 1). The clock is also affected by the hormone melatonin, which participates in a feedback loop from the pineal gland to strengthen the darkness period of the circadian cycle. The light-dark cycle is considered the dominant input into the central oscillating apparatus that acts to entrain an imprecise clock that must be repeatedly reset. In addition, the central clock receives resetting input signals from other areas of the brain, as well as external signals. This input provides functional plasticity, allowing an organism to adapt to anticipated changes in the environment due, for example, to a shift in time zone with jet travel or shifting lighting conditions as the seasons progress.

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is this part of the recent story of circadian rhythm research that may be the key to understanding how symptom clusters in patients are related to circadian signaling. A thorough investigation of candidate factors secreted from the hamster SCN has identified three SCN peptides that are ligands of the EGFR: epidermal growth factor (EGF), transforming growth factor-alpha (TGF-α), and neuregulin-1 (NRG-1). Another diffusible factor produced in the SCN that may signal hypothalamic nuclei is prokineticin-2 (PK2). A molecule closely related to the VEGF found predominantly in endocrine tissues. In addition to the ligands of the EGFR and VEGF family, the last factor identified in the SCN is the cardiotoxin-like cytokine (Clt), a neuropeptide related to IL-6 that signals through the gp130 receptor. The functional activity of these ligands on circadian signaling in the hypothalamus has been evaluated using an intracerebroventricular infusion technique that delivers them through a microcatheter inserted directly into the third ventricle of the brain. These infusion studies show that all five peptides (EGF, TGF-α, NRG-1, PK2, and Clt) reversibly inhibit circadian body temperature rhythms, eliminate running-wheel activity, decrease feeding, and deregulate 24-hour sleep patterns.

DOWNSTREAM HYPOTHALAMIC MODULATION OF CIRCADIAN RHYTHMS

One concept put forth based on observations from ablative lesions created downstream from the SCN in the hypothalamus is that hypothalamic modulation of circadian time structure is an important function of these hypothalamic relay stations. There are important functional consequences of downstream SCN signal interruption at the sites of secondary and tertiary signal relay stations (Figure 2). For example, lesions to the subparaventricular zone (SPZ), at either the dorsal or ventral nuclei, can diminish circadian rhythms in rest/activity, sleep, and core body temperature, depending upon which of these two nuclei are damaged. Other laboratory investigations show that selective destruction of the dorsal medial nucleus (DMH) in the hypothalamus interrupts rhythmic feeding behavior. One important consequence of hypothalamic modulation is the ability to adapt to predominately diurnal or nocturnal activity despite the signal activity of the SCN clock always being highest during the light phase. This modulation of circadian rhythmicity can also sculpt behavior in optimal ways that can confer survival advantages on the organism. Clinical evidence supporting this argument is also provided by the finding of functional impairment similar to the behavioral and functional losses created by hypothalamic nuclei ablation studies described in the altered sleep/wake patterns of patients recovering from viral illness. The neuropathic behavior in these patients correlated with histologic destruction of areas of the anterior hypothalamus near the junction of the brainstem and the forebrain in the SPZ and DMH. These damaged sites coincide with the downstream circadian sleep/wake centers of the anterior hypothalamus and not the SCN.

Other consequences of modulation of circadian rhythms by hypothalamic signaling downstream from the central oscillator is that circadian signaling can be subject to inputs from the brain’s visceral, limbic, and cortical systems. Rhythmic signaling can be modulated, amplified, or inhibited at these hypothalamic behavioral relay centers. This design feature theoretically allows for signal inputs from sources outside the brain, for example, by neurally active peptides (cytokines or growth factors) associated with infection, inflammation, cancer, and other disease states. Under these conditions, we postulate that the peripheral production of neurally active peptides can modify the SCN/hypothalamic signaling axis with potential consequences on physiological and behavioral drives such as arousal, feeding, and sleep. The production of the type of symptom clusters seen in cancer patients could thus be explained by inhibition of hypothalamic signaling pathways by products of the tumor itself.

Does Circadian Rhythm Dysregulation Occur in Cancer Patients?

The master clock mechanism illustrated in Figures 1 and 2 serves as the coordinator of physiologic and behavioral circadian periodicity through the generation of rhythmic signaling in the SCN and downstream modulation at paraventricular hypothalamic nuclei. However, a more complete picture of the cellular timing mechanism shows that the circadian system is composed of multiple peripheral oscillators, in addition to the central timing mechanism. This concept has grown out of an understanding of circadian rhythms based on the existence of a molecular autoregulatory transcription-translation feedback loop involving at least 15 “clock” genes. The core oscillator genes and downstream clock-controlled genes are found in all tissues; indeed, DNA microarray analysis has shown that transcription and translation of 10%–30% of the human genome undergo circadian oscillations.

Based on these findings, the circadian axis can be thought of as operating in a hierarchical fashion under the direction of a master clock that signals peripheral oscillators to synchronize and coordinate cellular function. The peripheral clocks are considered to be under the control of the central clock, functioning as local modulators of gene expression in each organ (eg, liver, heart, kidneys). This ubiquitous timekeeping mechanism tailors local gene-expression patterns differently in each tissue and organ while using the same set of clock genes that function in the SCN.

THE ROLE OF ‘CLOCK GENES’

Molecular clock gene studies show that several mutations are associated with changes in wakefulness, sleep, and adaptative behavior. The clock gene PER1 (homolog of Drosophila period 1 gene) has been well studied; polymorphisms of this gene are associated with advanced and delayed sleep-phase syndromes referred to as “morning lark” and “night owl” behavioral patterns. More details of these conditions are reviewed elsewhere. The relevance of these findings to cancer patients is unknown, since there are no known associated cancer...
ed is the relationship between the clock genes and proliferation described in oral mucosa studies from human volunteers. In these studies, serial biopsies of the oral mucosa showed significant correlations with clock-gene expression and progression through the cell cycle, as well as expression levels of cell-cycle checkpoint proteins (eg, cyclin A and E). Other molecular studies indicate a critical role in circadian control of the cell-cycle checkpoint at the transition from the G₂ phase to the M phase.

The consequences of disruption of circadian signaling at the level of the core clock or clock-controlled genes involved with syndromes in patients with these types of molecular clock disorders. Perhaps of greater importance regarding cancer research is the recent discovery that the core clock gene PER2 (homolog of the murine gene Per2) is a tumor suppressor gene described in a Per2 knockout system that results in a malignant phenotype in experimental animals. This finding is not surprising, given that the clock genes in peripheral tissues are closely tied to cell-cycle checkpoints, cellular proliferation, and apoptosis.

The precise roles these clock genes play in regard to cancer are still largely unknown, but one aspect that has been elucidated is the relationship between the clock genes and proliferation described in oral mucosa studies from human volunteers. In these studies, serial biopsies of the oral mucosa showed significant correlations with clock-gene expression and progression through the cell cycle, as well as expression levels of cell-cycle checkpoint proteins (eg, cyclin A and E). Other molecular studies indicate a critical role in circadian control of the cell-cycle checkpoint at the transition from the G₂ phase to the M phase. The consequences of disruption of circadian signaling at the level of the core clock or clock-controlled genes involved with

Figure 2  Hypothalamic Modulation of Circadian Behavior
Signals emanating from the suprachiasmatic nucleus (SCN) are modulated in the hypothalamic nuclei, resulting in the modification, amplification, or inhibition of circadian behavior and physiology: (A) thermoregulation; (B) cortisol secretion; (C) wakefulness, appetite; (D) melatonin secretion. One mechanism that theoretically can contribute to altered behavior is the inhibitory effects produced by transforming growth factor-alpha (TGF-α) on the epidermal growth factor receptor (EGFR) at the level of the ventral nuclei of the subparaventricular zone (vSPZ).

Abbreviations: ARC = arcuate nucleus of the hypothalamus; CRH = corticotropin-releasing hormone; DMH = dorsomedial hypothalamus; dSPZ = dorsal nuclei of the subparaventricular zone; GABA = gamma-aminobutyric acid; LHA = lateral hypothalamic area; MCH = melanin-concentrating hormone; MPO = medial preoptic nucleus of the hypothalamus; PVHd = paraventricular nucleus of the hypothalamus, descending division; PVHm = paraventricular nucleus of the hypothalamus, magnocellular division; TRH = thyrotropin-releasing hormone; VLPO = ventrolateral preoptic area of the hypothalamus; VMH = dorsomedial hypothalamus.

Adapted, with permission, from Saper et al.
proliferation and apoptosis could be important to cancer induction and promotion and are areas under active investigation.

ALTERED CIRCADIAN RHYTHMS IN CANCER PATIENTS

In addition to the new knowledge describing the molecular actions of the central and peripheral clocks, there is an abundant older literature regarding rhythmic physiology and behavior in cancer patients. Both laboratory and clinical studies show that a variety of circadian parameters may be altered in patients with cancer, including peripheral blood cells; bone marrow proliferation; hormone levels (typically, serum melatonin and cortisol levels); and miscellaneous parameters such as body temperature, urinary volume, and levels of tumor markers.

In general, early-stage cancer patients exhibit little or no measurable differences in circadian rhythms compared with those in normal populations or people with diseases other than cancer. Patients with advanced primary cancers or metastatic disease, however, show disrupted chemical, physiologic, and behavioral rhythms, including amplitude dampening, phase shifts, and/or period changes with ultradian rhythms, or rhythms that occur more frequently than every 24 hours. Although disrupted rhythmic physiologic and behavior patterns are observed in cancer populations, the question can be raised of whether circadian disruption is a marker for advanced disease or whether there is a mechanistic relationship between circadian disruption and cancer progression and prognosis.

CORTISOL RHYTHMS

Approaches to answer this question have involved measurement of two circadian parameters in cancer patients that have mechanistic underpinnings. One method is the evaluation of cortisol rhythms as measured in either saliva or serum; one report showed that a significant correlation exists between dampened circadian rhythm of salivary cortisol levels and prognosis in patients with metastatic breast cancer. A flatter cortisol rhythm was associated with the presence of distant metastasis versus local/regional disease, and this finding remained significant for survival even when other prognostic factors were controlled for in the study.

This correlation was further strengthened by a second study that compared cortisol rhythms in age-matched healthy controls with those in cancer patients. These data suggest that cancer patients with high “allostatic loads” from stress and disease have a disrupted HPA axis, which, in turn, results in poor outcomes because of detrimental effects on natural killer cells and lymphocytes in combating cancer. The cortisol rhythm data suggest that disruption to the HPA axis, a mechanistic centerpiece for the sickness behavior model, produces physiologic, neurologic, and immunologic alterations that might directly contribute to poor outcomes in cancer patients.

REST/ACTIVITY PATTERNS

Other rhythmic behavior data can be obtained in cancer patients with the assessment of 24-hour rest/activity patterns (an example of an actigram is shown in Figure 3) obtained with a wrist-worn accelerometer. This device detects circadian rhythms and is a well-accepted research tool in human sleep and circadian biology. Prospective measurement of rest/activity patterns by wrist actigraphy has been correlated with poor outcomes in patients with metastatic colorectal cancer, where dampened motor-activity rhythms were associated with significant levels of fatigue and appetite loss and poor survival.

In other studies where rest/activity patterns were measured prior to treatment, actigraphy showed that disruption of these patterns was independently associated with poor performance status and quality of life and revealed a flattening of circadian rest/activity patterns in patients receiving chemotherapy. Other actigraphy studies have confirmed a high degree of correlation of disturbed rest/activity patterns with quality-of-life indices and symptom clusters of fatigue, change in appetite, and sleep disruption.

These studies provide further evidence that disruption of rhythmic physiologic processes contributes to poor prognosis in cancer patients. A molecular mechanism to explain these findings has not been available until recently. It is discussed in the following section.

Symptom Production in Cancer Patients and the EGFR Ligand Hypothesis

The importance of the EGFR in the cancer process and EGFR inhibition as a therapeutic intervention is a well-established success story in the management of several solid human tumors. EGFR signaling occurs through the dimerization of a pair of members of the EGFR family that communicate extra-
were originally evaluated for chronomodulated chemotherapy. Therapeutic intervention based on targeted inhibition of this pathway with monoclonal antibodies or tyrosine kinase inhibitors has improved the outcomes of patients with cancer of the head and neck, breast, lungs, colon, rectum, and pancreas.75–79

One area of the EGFR story that has been relatively undeveloped is a fuller understanding of the role the EGFR ligands themselves may play in cancer prognosis. For example, there is evidence that patients with lung, pancreatic, colorectal, or breast cancer whose tumors overexpress EGFR and who have high levels of the EGFR ligand TGF-α have a particularly poor prognosis.80–82 One reason for their worse prognosis may be related to the increased autoregulatory mechanism of self-stimulation by locally produced EGFR ligands like TGF-α where these growth-signaling pathways produce agonistic effects on growth and angiogenesis, as has been demonstrated in patients with pancreatic and non-small cell lung cancer.81,82

### DISRUPTION OF CIRCADIAN RHYTHMS BY EGFR LIGANDS

An additional reason for the poor prognosis in these patients may be related to the inhibition of hypothalamic modulation of circadian rhythms by TGF-α, which, in turn, accounts for the symptom clustering of fatigue, appetite loss, and sleep disruption observed in cancer patients. The studies with intracerebroventricular infusions of TGF-α described earlier in this review show it is an SCN locomotor inhibitor and targets EGFR-positive cells at the level of the circadian relay stations in the SPZ.13,14 Although TGF-α has been localized in the adjacent glial cells and not in the neurons in the SCN, that does not necessarily negate its participation as a “diffusible signaling” substance in the SCN that can disrupt circadian rhythmicity when infused into the third ventricle. Our hypothesis is that patients with elevated serum levels of TGF-α would be expected to show loss of motor activity (ie, fatigue), have poor appetite, and display other symptoms, such as sleep disruption, associated with interference of hypothalamic circadian signaling.

This hypothesis has been examined in a retrospective clinical study of 80 patients with metastatic colorectal cancer who were originally evaluated for chronomodulated chemotherapy and assessed prior to treatment with a battery of quality-of-life studies and measurement of 24-hour rest/activity patterns by wrist actigraphy.83 As shown in Table 1,83 a significant correlation was found in these patients between dampened circadian rhythm (low r24), poor quality-of-life scores, high serum levels of the pro-inflammatory cytokines IL-6, TNF-α, and TGF-α and flattened cortisol rhythms. These data support the EGFR-ligand hypothesis and are currently being validated with new correlative studies.

### CAN EGFR INHIBITION REVERSE THESE EFFECTS?

As a means of cross-validating the hypothesis that EGFR ligands produce symptom clusters in cancer patients, it would be logical to ask if there are data from therapeutic interventions with EGFR inhibitors that are associated with symptom changes in cancer patients. One might expect that EGFR inhibition would lead to improvement in those symptoms that are related to TGF-α blockade of the circadian signals emanating from the hypothalamus. Studies of the tyrosine kinase inhibitor gefitinib (Iressa) in metastatic non-small cell lung cancer have shown a rapid improvement in quality-of-life indices that is four-fold higher than the objective tumor response in the same patients.84,85 Although some of this effect on quality of life could be explained by a direct antitumor effect, mentation and appetite rapidly improved in these patients, suggesting an effect of gefitinib independent of tumor response. The mechanism for this effect is not entirely understood, but the findings are consistent with the EGFR hypothesis that some human cancers produce neurally active peptides that produce symptom clusters.

### The Future: Targeted Therapy for Symptom Management?

Our understanding of the mechanisms by which rhythmic physiologic processes and behavior are regulated on the molecular level has improved with the discovery of the details of cellular timekeeping and the activity of a family of core and clock-controlled genes involved with metabolism, the cell cycle, proliferation, and apoptosis. Recent discoveries in chronobiology and the neurosciences regarding the location and mechanisms of circadian signaling downstream from the SCN in the hypothalamus have also shed new light on how rhythmic behavior of the organism is regulated. The EGFR ligand

| Table 1 Correlation of Circadian Rhythms With Clinical Indices, Pro-Inflammatory Cytokines, and EGFR Ligand Levels in 80 Patients With Metastatic Colorectal Cancer |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| ASSESSMENT OF INDIVIDUAL PATIENT CIRCADIAN RHYTHM BY ACTIGRAPHY | CORTISOL RATIO (SLOPE) | SERUM LEVEL OF TGF-α | SERUM LEVEL OF IL-6 | CLINICAL INDICES |
| Robust rhythm* (autocorrelation > 0.47) (n = 40) | 1.72 (steep) | Low | Low | Less fatigue and appetite loss |
| Dampered rhythm (autocorrelation < 0.35) (n = 40) | 1.60 (flat) | High | High | More fatigue and appetite loss |

* Differences in cortisol ratio, serum levels of TGF-α and IL-6, and clinical indices are statistically significant.

Abbreviations: EGFR = epidermal growth factor receptor; IL-6 = interleukin-6; TGF-α = transforming growth factor-alpha

Adapted from Rich et al81

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hypothesis overlaps areas of behavioral research, symptom research, and cancer biology in new and testable ways.

LIMITATIONS OF THE EGFR HYPOTHESIS

One of the shortcomings of the EGFR ligand hypothesis is that there are several other neurally active molecules that might contribute to symptom clustering in cancer patients besides the members of the EGFR family. First, there are at least four SCN locomotor inhibitors that have been identified in the brain infusion model, and although two of these are also members of the EGFR family, such as TGF-α, two others also have connections to cancer since one of them is PK2 (a form of VEGF) and the other is Clec, which is related to the proinflammatory cytokine IL-6. This last finding overlaps with our clinical observations in metastatic colorectal cancer patients, in whom altered circadian rhythms correlated with higher symptom levels and poorer survival in those patients with elevated levels of IL-6. In theory, cross-signaling could occur between these ligand’s families, since IL-6 is a pleiotropic cytokine that has been associated with proinflammatory conditions, poor survival, and the production of sleep dysfunction and other symptoms. Additional correlative studies with multiple biologic markers for the sickness behavior model and the EGFR ligands are therefore indicated.

The fields of symptom management and chronobiology are driven today with discoveries regarding the timing of processes involving molecular biologic events regulating intracellular and intercellular signaling. The studies discussed here suggest that symptoms in cancer patients can be produced by signaling molecules produced by either the tumor or the host. The pro-inflammatory and growth factor hypotheses each share similarities, since each relies on the production of neurally active molecules that interfere with brain signaling. Application of this knowledge might someday translate into new mechanistically based therapeutic interventions for humans suffering from cancer-related symptoms.

CIRCADIAN-BASED PROGNOSTIC MARKERS

One approach, especially for the assessment of the circadian axis, would be to measure rhythmic chemical and activity levels in cancer patients to identify those patients with dampened rhythms, since it appears that this would segregate patients into unique groups with different prognoses. This approach is now being done with actigraphy but could soon include other non-invasive or minimally invasive means of monitoring a person’s biorhythms that would allow quantification of behaviors that may be useful for fine-tuning host performance status. Circadian-based prognostic markers could also be used for the testing of new hypotheses, with individualized cancer therapy having a specific and targeted biologic basis.

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