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Invited minireview

Circadian disruption in cancer: a neuroendocrine-immune pathway from stress to disease?

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Abstract

Psychosocial factors may modulate the course of cancer, but few data have been gathered on the biological mechanisms by which these effects may be mediated. We briefly review evidence of psychosocial effects on cancer progression and discuss one potential pathway that may underlie these effects: the disruption of neuroendocrine and immune circadian rhythms. Circadian system alterations occur in tumor tissue, tumor-bearing animals, and cancer patients with greater disruption seen in more advanced cases. Rhythm alterations include diminished amplitude, phase shifts, period changes, and erratic peaks and troughs in endocrine, metabolic, immunological, and rest- activity cycles. Psychosocial factors can engender dysregulation of circadian function. Cancer-related circadian dysregulation may also be driven by genetic factors, environmental and behavioral influences, and effects of the tumor on host clock regulation. There are several mechanisms by which circadian disruption might hasten tumor growth: via direct effects of altered hormone levels on tumor cells, effects on tumor versus host metabolism, neuroimmune effects resulting in cancer-relevant immunosuppression, or reduced efficacy and tolerability of cancer treatments for which the timing of administration is based upon the assumption of normal circadian rhythms. Emerging data in the human and animal literature suggest that circadian regulation may be an important prerequisite for the maintenance of host defenses against cancer. Thus, stress-related circadian disruption may have negative implications for cancer prognosis. Psychosocial effects on cancer progression may be measured, and possibly mediated, by disruption of circadian function.

1. Psychosocial effects on cancer progression

A growing body of evidence suggests that psychosocial factors have potentially powerful modulating effects on the course of cancer. While this notion has been a subject of some controversy, it is not implausible given the fact that variation in cancer progression is accounted for not only by tumor-related factors, but also by characteristics of the host. The aggressiveness of a tumor is determined by the source tissue, degree of dedifferentiation, functionality of apoptosis, DNA repair mechanisms, loss of contact inhibition, and its ability to induce a vascular supply and metastasize. In contrast, resistance of the host is dependent on immune competence and neuroendocrine regulation, which are subject to the influence of brain and behavior. Here we review one biological mechanism by which psychosocial effects on cancer progression may be mediated: stress-related disruption of circadian rhythms.

1.1. Psychosocial predictors of cancer outcomes

Research on social relationships and health shows mortality rates increase as a function of low quantity or

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quality of social relationships. Indeed, being well integrated socially reduces all-cause age-adjusted mortality by a factor of two, the same magnitude as the effect of having low serum cholesterol levels or being a nonsmoker (House et al., 1988), and the same effect has been observed specifically for cancer mortality (Reynolds and Kaplan, 1990). Psychosocial factors including social relationships, emotional expression, and personality have been associated with cancer progression in numerous studies. Emotional support has been associated with longer survival after diagnosis of breast, colorectal, or lung cancer, while social isolation conveys an elevated risk for cancer death (Reynolds and Kaplan, 1990). Shorter survival times have been reported among patients with few or poor social relationships, while married cancer patients are known to survive longer than unmarried persons (Maunsell et al., 1995). In general, research describing psychosocial influences on cancer progression suggests that expressive social activities and social support seem to be key factors in prolonging survival, while relatively rapid morbidity and mortality may occur among patients who demonstrate hopelessness/helplessness and depression (Spiegel, 2002). Thus, data provide evidence of a robust modulating effect of certain psychosocial variables on cancer progression, and therefore raise questions about potential mediating pathways.

1.2. Psychosocial intervention studies

Professionally directed psychosocial interventions that provide social support, cancer education, coping skills training, and opportunities for emotional expression have demonstrated benefits in terms of patient adjustment and quality of life. To date, 12 published studies have examined the effects of psychosocial intervention on cancer progression and survival. In 1989, our research group reported a beneficial effect of group psychotherapy on the survival of women with metastatic breast cancer. Since then, 10 other published clinical trials have tested the hypothesis that psychosocial intervention could affect survival time for patients with various types of cancer. Five of these showed a survival advantage for cancer patients who were given psychosocial support, whereas five showed no such effect (nine studies are reviewed in Spiegel, 2002, the 10th is presented in McCorkle et al., 2000). Another recent study that provides further evidence of a survival effect of psychosocial intervention is an extension of a previously published finding (Fawzy et al., 2003).

It is worth noting that the results of these studies are not randomly distributed. If results merely reflect random variation, only one in 20 trials should have produced a "false positive" result, and we would expect a roughly equal number of trials to demonstrate adverse effects on cancer survival (currently no published trial shows negative effects of psychosocial intervention on survival time). The disparate findings may be partly explained by differences in the cancer populations studied, types of interventions used (e.g., interventions based upon emotional expression versus patient education; individual versus group), and dose of intervention (e.g., time limited versus providing support to patients until death). Cancer treatments and the availability of social support have significantly improved during the 30-year span in which these studies have been conducted. Such advances may now claim much of the variation in survival time that was accounted for in earlier years by the stress-reducing effects of psychosocial intervention. Because psychosocial support available to cancer patients has improved considerably over the past three decades, both control and treatment patients involved in such trials today manage the difficulties of their illness in a very different social atmosphere than did participants in earlier trials. Despite the discrepancies among findings we can identify several components that are similar among studies in which survival benefits were found. These include: the provision of education, homogeneous groups, a supportive environment, coping skills, and stress management training (Spiegel, 2002). If nothing else, these studies challenge us to systematically examine the interaction of mind and body, to determine the aspects of therapeutic intervention that are most effective and the populations that are most likely to benefit.

1.3. Biological pathways that may underlie psychosocial effects on cancer progression

Psychosocial effects on cancer progression may be mediated by way of *behavioral* and/or *biological* pathways. Behavioral mechanisms include the patient's tendency to maintain a healthy lifestyle (e.g., diet, exercise, sleep, and smoking habits), their choice for or against physician-recommended treatments for cancer, and their adherence with those treatments. Biological pathways may begin with the numerous physical and emotional stresses imposed by a cancer diagnosis (e.g., medical treatments, anxiety about diagnosis/prognosis, and disruption of social functioning) that activate endocrine stress-response mechanisms including the hypothalamic–pituitary–adrenal (HPA) axis and the autonomic nervous system (ANS). Multiple modulatory effects of HPA and sympathetic nervous system (SNS) responses on immune function have been documented (Madden et al., 1995; Webster et al., 2002). Important aspects of anti-tumor immunity may be suppressed by stress-related increases in HPA and/or SNS activity and decreases in parasympathetic tone. Psychoneuroendocrine and psychoneuroimmune mechanisms with potential relevance to cancer have been reviewed previously (Andersen et al., 1994; Antoni, 2003; Cohen and Rabin,

1998; Kiecolt-Glaser et al., 2002; Turner-Cobb et al., 2001). Here we examine the possible role of another biological phenomenon as a marker and/or mediator of psychosocial effects on cancer progression: circadian rhythms.

2. Psychosocial factors and circadian rhythms

Thoughtful conceptualizations of the relationship between stress and disease emphasize the importance of the cumulative effect of stress on physiological response systems (McEwen, 1998). Chronic or repeated stress may cause prolonged reactivity resulting in states of heightened arousal (Sterling and Eyer, 1981), or activity outside the normal range of function of stress response systems. As a consequence, stress response systems may become dysregulated. Circadian rhythms are a potentially important indicator of the regulatory competence of stress response mechanisms because they reflect the capacity of a system to turn on and off appropriately. Chronic psychosocial stressors may cause the circadian rhythms of neuroendocrine stress response systems to become disrupted. For example, disruption of HPA axis rhythms has been linked with psychological distress including depression (Deuschle et al., 1997), post-traumatic stress disorder (Yehuda, 2002), chronic stress (Chrousos and Gold, 1998), and unemployment (Ockenfels et al., 1995). Research clearly supports links between psychosocial stress and disruption of circadian rhythms. In turn, disrupted circadian rhythms have been associated both with cancer incidence and cancer progression.

3. Circadian rhythms and cancer incidence

The potential importance of circadian cycles with regard to cancer incidence has recently been brought to public attention by reports from two large-scale studies that demonstrated increased risk of breast cancer after extended nighttime shift work (Davis et al., 2001; Schernhammer et al., 2001). One hypothesized biological cause of this association is suppression of the nocturnal melatonin peak. Melatonin suppresses ovarian estrogen production. Women who are for years exposed to light at night during the time of the usual melatonin peak may have elevated estrogen production resulting in increased breast cancer incidence. Melatonin may serve as an antioxidant in tumor cells, and it stimulates cytokine release from activated T cells, aiding anti-tumor immunity (Davis et al., 2001; Schernhammer et al., 2001).

The relationship between shift work and breast cancer risk may alternatively be explained by other risk factors for cancer that are associated with circadian disruption. Shift work causes alterations of rest-activity cycles and sleep cycles. Chronic sleep debt has been linked with the disruption of numerous modulators of immune function including SNS hormones, HPA hormones, and cytokines (Vgontzas and Chrousos, 2002). However, the potential role of immunosuppression associated with chronic sleep debt has received little attention in studies of shift work and cancer incidence.

Shift work also induces changes in rhythms of HPA activity. The early morning transition from dim to bright light induces a marked elevation of cortisol levels (Leproult et al., 2001). Thus, exposure to light at night might activate the HPA axis during a time when it is normally suppressed. Sleep disruption coupled with exposure to light at night may interfere with the normal cortisol nadir. In support of the idea that an HPA pathway may contribute to the shift work–cancer relationship, patients at high risk for primary breast cancer show abnormal circadian patterns among an array of hormones including cortisol (Ticher et al., 1996). It is also noteworthy that HPA dysregulation has been associated with increased risk for a number of other human illnesses, including type 2 diabetes, stroke, and cardiovascular disease (Rosmond and Bjorntorp, 2000).

Recent animal studies shed further light on links between circadian rhythms and cancer incidence. It appears there is a tight connection between circadian clock genes, growth control and growth effector genes that are related to cancer. Mice with mutations in the mPer2 gene, which is critical for circadian rhythmicity, are more prone to tumor development and early death. Circadian disruption may be linked with the failure of DNA repair mechanisms and programmed cell death in mutated cells (Fu et al., 2002). These data suggest that cancer may be a consequence of the absence of circadian regulation.

In view of the animal data, it is indeed plausible that any factor causing general dysregulation among the systems that govern circadian endocrine, immune, and metabolic function may be linked with cancer incidence in humans. Whether that factor is behavioral or biological may be less important than the degree to which it disrupts normal circadian function. Indeed, data presented here support the idea that *both* behavioral (e.g., stress and sleep patterns) and biological (e.g., genetic and SCN) factors may favor cancer incidence by disrupting circadian rhythms.

4. Circadian rhythms and cancer progression

Numerous studies show that circadian system alterations are not only a risk factor for tumor incidence; they are also related to the progression of existing tumors. Circadian system alterations have been described in tumor tissue, tumor-bearing animals, and cancer patients. Murine tumor tissues demonstrate circadian

rhythms of cellular proliferation in vitro, with fast-growing, poorly differentiated tumors showing less pronounced rhythms than slow-growing, well-differentiated tumors. Rhythms in tumor tissue may also have lower amplitude (peak-to-trough difference) as compared with adjacent normal tissue (Mormont and Levi, 1997). Circadian rhythms of healthy tissue appear different in tumor-bearing animals as compared with control animals. For example, the circadian corticosterone rhythm in animals bearing hepatoma or osteosarcoma is altered with respect to amplitude, period, and 24-h mean levels (Mormont and Levi, 1997).

Among patients with breast, ovarian, prostate, stomach, and colon cancer, disruption of circadian function has been noted in endocrine (e.g., cortisol, melatonin, prolactin, TSH, GH, LH, and FSH), metabolic (e.g., temperature, proteins, and enzymes), and immunological (e.g., peripheral lymphocyte) rhythms, with greater disturbances in more advanced cases. Rhythm changes include diminished amplitude, phase shifts, period changes, and erratic peaks and troughs. Rhythms are most significantly altered in patients with large tumor burden, poor performance status, or liver metastases. Endocrine rhythms may be more markedly disrupted in patients with hormone-sensitive tumors (e.g., estrogen receptor positive versus estrogen receptor negative breast tumor) (Mormont and Levi, 1997).

These data suggest that endocrine, metabolic and immunological rhythms may serve as markers of tumor status. The tumor itself may influence these physiological systems, with greater rhythm disruption imposed by more advanced tumors. Alternatively, relationships between circadian function and tumor status may also be an epiphenomenon of factors related both to circadian rhythms and tumor progression. As disease progresses, pain, discomfort, or anxiety may become severe enough to interfere with sleep. Poor sleep has been linked with disruptions in endocrine and immune variables formerly associated with cancer progression (Vgontzas and Chrousos, 2002). Thus, behavioral variables related to cancer symptoms may partly account for relationships between circadian rhythms and tumor status. Because methods for distinguishing between tumor- and host-related cycles are rarely feasible among human subjects, little is known about the relative influence of these variables on circadian rhythms.

Regardless of the specific factors driving these relationships, circadian rhythms may not only serve as markers of tumor status, they may also have prognostic value.

5. Circadian rhythms and cancer prognosis

A few prospective studies have examined circadian rhythms as predictors of cancer outcome. Our group has demonstrated that circadian variation of salivary cortisol is prognostic of longer survival in patients with metastatic breast cancer (Sephton et al., 2000). In healthy individuals cortisol levels are often highest prior to awakening and decrease during the day, but 30–70% of patients with advanced breast cancer may have flattened circadian profiles, consistently high levels, or erratic fluctuations. Using data from a group of 104 women with metastatic breast cancer, we reported long-term prognostic significance for the salivary cortisol rhythm, with disrupted rhythms predicting early mortality up to 7 years after assessment (sample mortality 68%). Rhythm dysregulation was also associated with decrements of natural killer (NK) cell numbers and cytotoxic activity, and low absolute NK cell number was an independent predictor of early mortality. In concurrence with other studies showing more severe rhythm disruption with more advanced tumors, the most aberrant cortisol profiles were also associated with the presence of distant (e.g., bone and visceral) versus local (i.e., chest wall or adjacent lymph node) metastases. When other factors related to the progression of cancer symptoms (e.g., pain and sleep depression) were controlled in our analyses the predictive value of the cortisol rhythm for breast cancer survival remained intact (Sephton et al., 2000). Additional factors linked with abnormal cortisol rhythms included poor sleep (frequent nocturnal awakening) and prior marital disruption (separation, divorce, or widowhood), suggesting a possible mechanistic link between severe psychosocial stress and breast cancer progression.

Another study examined the prognostic value of the cortisol rhythm among 147 patients with metastatic colorectal cancer. The rhythm of serum total and salivary free cortisol was assessed, however, neither measure was prognostic for survival over a 4-year follow-up period during which the sample reached approximately 80% mortality (Mormont et al., 2002). It is possible that hormone-sensitive tumors (i.e., the majority of breast tumors were estrogen receptor positive) differ from less hormone-dependent (i.e., colorectal) tumors in their susceptibility to the influence of endocrine rhythms. Alternatively, methodological differences between the two studies may also explain the discrepancy in results. Mormont and colleagues assessed diurnal salivary cortisol using only two (versus four) time points over 2 (versus three) days with morning to evening ratio rather than diurnal slope as their prognostic variable, and relied primarily on categorical rather than continuous methods of data analysis.

These results raise important questions. First, is cortisol dysregulation per se, or rather, the effects of general circadian dysregulation more important in cancer outcomes? Second, it remains to be seen whether rhythm dysregulation is a mediator or a marker of advancing cancer.

These questions are illuminated by the results of recent studies in humans and mice. The clocks that regulate circadian physiology are composed of interrelated pathways driven by at least nine genes and coordinated by the suprachiasmatic nucleus (SCN). Locomotor activity is thought to be a reliable indicator SCN-modulated circadian function in animals. Similarly, the human circadian rest-activity rhythm has been used as a marker of circadian function to modulate the timing of chemotherapy administration for best tolerability and efficacy (chronomodulated chemotherapy). A recent study of 192 patients with metastatic colorectal cancer demonstrated that marked rest-activity rhythms were prognostic of longer survival over a 2-year period (when the sample had reached 69% mortality) (Mormont et al., 2000). The rest-activity rhythm also predicted tumor response to chemotherapy treatment and provided prognostic information in addition to that obtained from clinical factors that reflect tumor burden. Rest activity rhythms were also associated with indicators of patient well-being including global quality of life, fatigue, appetite loss, and pain (Mormont et al., 2000). However, when quality of life factors were controlled in the analysis, these variables neither improved the predictive value of the model, nor obliterated the rhythm-survival effect (Mormont et al., 2000). These data suggest that some of the interindividual variance in response to medical treatment for cancer may be explained by individual differences in circadian rhythms. Specifically, among patients with poorly defined rhythms chronomodulated chemotherapy may not be effective. The relatively long-term prognostic significance of the cortisol rhythm for survival up to 7 years after assessment, and for rest-activity rhythm up to 2 years later, suggests these data do not simply reflect preterminal effects of the tumor on host physiology. Rather, they provide evidence that general circadian dysregulation is an important long-term marker of cancer prognosis.

6. Circadian disruption, a mediator of psychosocial effects on cancer progression?

Viewed in the light of long-standing data showing that poor social relationships convey an elevated cancer mortality risk (House et al., 1988; Reynolds and Kaplan, 1990), our data linking marital disruption with abnormal cortisol rhythms in cancer patients—and abnormal cortisol rhythms with early mortality (Sephton et al., 2000), raise an important question: Might circadian dysregulation actually mediate the effects of psychosocial factors on cancer progression?

Experimental manipulation of circadian rhythms in animals supports the notion that general circadian dysregulation may be a mediator of cancer outcomes. A mouse model of severe circadian dysfunction was obtained with sterotaxic destruction of the SCN, which eliminated circadian variation in locomotor acticity, corticosterone, body temperature and lymphocyte counts. After SCN ablation, mice that were implanted post-operatively with either a rapidly proliferating tumor (Glasgo osteosarcoma) or a more slow growing tumor (pancreatic adenocarcinoma) died significantly earlier than did sham-operated controls (Filipski et al., 2002).

In concurrence with the recent clinical studies, these data show that release from circadian regulation causes a dramatic acceleration in cancer progression. Viewed in combination with data suggesting a genetic link between circadian clock regulation and tumor incidence, these data provide evidence for a mediating role of circadian rhythm disruption in tumor incidence and progression. However, the findings do not illuminate the mechanism whereby circadian dysregulation may be related to early cancer mortality. Nor do they tell us whether it is HPA dysregulation or general circadian dysregulation that is more important in cancer outcomes. It is problematic that patients with altered rest-activity cycles and animals with SCN lesions are also likely to have dysregulated patterns of glucocorticoid release (Filipski et al., 2002). Furthermore, because glucocorticoids actually regulate circadian oscillation in a variety of peripheral tissues (Balsalobre et al., 2000), it is difficult to separate the potential effects of glucocorticoid rhythms from the effects of other circadian systems on tumor progression when dysregulation is widespread among systems. More research is needed to determine whether general circadian disruption or disturbances in specific circadian systems such as the HPA axis is more important in cancer outcomes. Animal research designed to examine the relative influence of endocrine, metabolic, immune, and sleep–wake or rest-activity rhythms may provide valuable information.

The fact that disruption of the circadian pacemaker in the SCN results in more rapid tumor growth (Filipski et al., 2002) and that the growth patterns of more aggressive tumors show reduced diurnal variation (Mormont and Levi, 1997) does provide plausible evidence for a mediating role of circadian rhythm disruption in tumor incidence and progression. However, little is known about how circadian dysregulation might hasten tumor growth.

7. How can circadian disruption influence tumor growth?

Fig. 1 provides a conceptual model of potential pathways by which circadian disruption may mediate the effects of psychosocial factors in human cancer. Research illustrating relationships between psychological stress (e.g., depression and unemployment) and alterations of circadian cortisol rhythms (Chrousos and

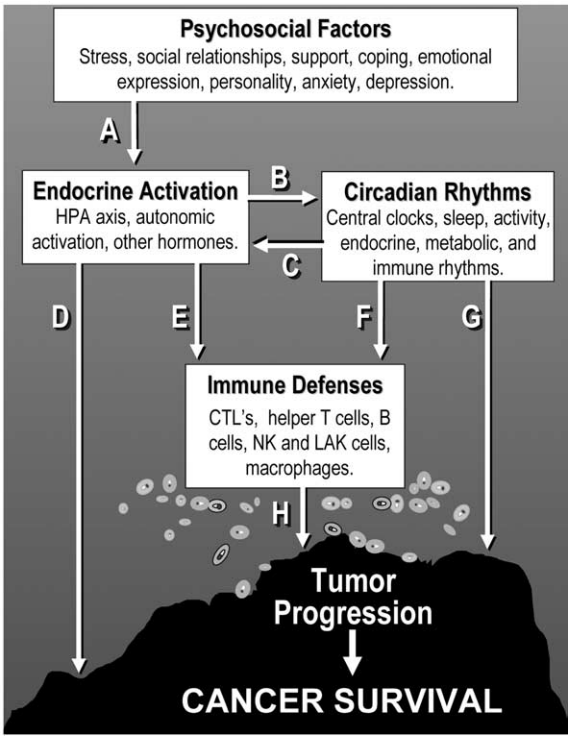

Fig. 1. Potential pathways by which circadian dysregulation may mediate psychosocial effects on cancer progression. Arrow (A) represents activation of endocrine stress-responses associated with psychological distress and other psychosocial factors. Repeated stress-response activation may hypothetically lead to dysregulation of circadian rhythms (B), while aberrations in sleep–wake cycles, rest-activity rhythms, genetic, or suprachiasmatic control of circadian rhythms would engender endocrine abnormalities (C). Hypotheses regarding direct effects of hormones on tumor growth involve metabolic pathways or influences on oncogene expression (D). Neuroimmune effects are widespread and include modulation of innate immunity, T and B cell function, cytokine and adhesion molecule expression, cell trafficking, and immune cell differentiation (E). Circadian rhythm aberration is associated with abnormalities of immune cell trafficking and cell proliferation cycles (F). It has been hypothesized that circadian clock genes are tightly linked with genes related to tumor growth and that tumors may be a direct consequence of circadian dysregulation (G). Immune defenses against tumor growth include both specific mechanisms (e.g., killing by cytotoxic T lymphocytes aided by helper T cells, B cell-mediated antibody-dependent lysis) and non-specific immunity (e.g., lytic activity of NK, LAK, and A-NK cells, macrophages, and granulocytes; H).

Gold, 1998) support the notion that repeated stress-response activation may result in circadian endocrine disruption (McEwen, 1998) (Fig. 1, arrows A and B), while central circadian clocks play a major role in modulating endocrine circadian rhythms (arrow C).

Direct endocrine pathways may mediate effects of rhythm dysregulation on tumor growth (arrow D). There is evidence for facilitative effects on tumor growth by stress hormones by way of metabolic pathways. For example, although glucocorticoids normally inhibit glucose uptake, tumor cells may become resistant to this effect and therefore have a metabolic advantage. Glucocorticoids may differentially affect gluconeogenesis in healthy versus tumor cells and tumor cells may develop resistance to catabolic actions of stress hormones. Thus, energy may be preferentially shunted to the tumor and away from normal cells when the HPA axis is activated (studies reviewed by Turner-Cobb et al. (2001)).

Psychoneuroimmune pathways may convey effects of rhythm dysregulation on tumor growth (arrows E and H). Multiple pathways exist by which the sustained alteration of glucocorticoids levels seen with rhythm dysregulation could influence anti-cancer immunity. Immune defenses against tumors include both specific mechanisms (e.g., killing by cytotoxic T lymphocytes aided by helper T cells, B cell-mediated antibody-dependent lysis) and non-specific immunity (e.g., lytic activity of NK, LAK and A-NK cells, macrophages, and granulocytes). Neuroendocrine-immune effects are widespread and include modulation of innate immunity, T and B cell function, cytokine and adhesion molecule expression, cell trafficking, and immune cell differentiation by HPA and SNS hormones (Madden et al., 1995; Webster et al., 2002). Natural killer (NK) cells can kill tumor cells of many different types, and there is evidence that progression of breast cancer is associated with declines in NK cell cytotoxicity (Levy et al., 1991). We also observed that NK cell number predicts survival time in breast cancer. Furthermore, we found that abnormal cortisol rhythms were associated with reduced natural killer cell numbers and lower NK cytotoxicity. It is possible that the connection between cortisol rhythm and disease progression may be mediated by impaired natural killer cell number and function. There may be many other interactive effects of glucocorticoid dysregulation and selective immunosuppression that can allow for more rapid cancer progression. Psychoneuroimmune interactions have been extensively researched, but the relevance of these relationships in cancer progression has not been proven, and further research is needed (Cohen and Rabin, 1998).

Disruption of sleep–wake rhythms and associated sleep debt may suppress immune cancer defenses (Vgontzas and Chrousos, 2002). Further, circadian rhythms of immune factors may be driven by endocrine rhythms or other circadian systems, with consequential effects on tumor growth and responses to medical treatments for cancer (arrow F). As noted, circadian rhythm aberration has been associated with abnormalities of immune cell trafficking and cell proliferation cycles. When endocrine rhythms are aberrant, dysregulated patterns of immune activity and immune cell trafficking also emerge (Mormont and Levi, 1997). The efficacy of

immune cancer defenses may be diminished if adequate numbers of immune cells are not at the tumor site due to effects of altered circadian rhythms on cell trafficking, or if there are persistent alterations in cytokine expression, immune cell differentiation or cytotoxicity.

Circadian dysregulation may also reduce the efficacy of cancer treatments. Chronomodulated administration of chemotherapy is becoming more common. The intent is to administer chemotherapy during the hours when toxicity will be lowest and efficacy will be highest based on predictable circadian changes in cellular metabolism and proliferation. Chronomodulation is of real potential importance: studies suggest that survival may be significantly improved with evening rather than morning administration of maintenance chemotherapy in children with leukemia, and animal studies show that survival may vary from 2- to 8-fold as a function of the timing of a high dose of an anticancer agent (Levi, 2002). Because individual differences in circadian rhythmicity may not be taken into account in the planning of treatment administration, cancer patients with altered rhythms may be unlikely to benefit. The results of studies now underway may support the use of individual circadian rhythms in the planning of chemotherapy administration (Levi, 2002).

Lastly, control of circadian clocks may be tightly linked with control of genes related to the initiation of tumors and the progression of cancer. Indeed, animal studies show existing tumors grow faster (Filipski et al., 2002), and new tumors may actually arise, as a consequence of circadian dysregulation (Fu et al., 2002) (arrow G).

Circadian disruption in cancer is probably mediated both by behavioral and biological factors. Nevertheless, the psychosocial characteristics of the cancer patient are potentially important determinants of disease outcomes including survival time as well as quality of life. There is accumulating evidence that psychosocial factors that may lead to disruption of circadian endocrine and immune rhythms may also contribute to risk of cancer incidence and more rapid progression. The role of circadian rhythms as markers or mediators of effects of psychosocial factors on cancer progression remains to be clarified. Pathways by which circadian disruption may impact cancer progression include direct effects of altered hormone levels on tumor cells, psychoneuroimmune effects that may interfere with tumor defenses, or reduced efficacy and tolerability of cancer treatments for which the timing of administration is based upon the assumption of normal circadian rhythms.

More research is needed to characterize how psychosocial variables influence disease course and response to treatment and to examine the relevance of various biological pathways in these outcomes. It is possible that psychosocial interventions may ameliorate effects of cancer-related stress on circadian function; however, little data exist to support or refute this idea.

Regardless of whether or not psychosocial treatments have survival value, there is a pressing need for well-honed interventions to help patients and their families confront the changes imposed by a cancer diagnosis and ameliorate the profound effects of medical treatment on quality of life. Circadian rhythms may have importance for the effectiveness of both psychosocial and biomedical interventions, and provide a means of analyzing clinically meaningful interactions between the endocrine and immune systems. Studies that gather data on relationships between psychosocial factors and potential biological mediators of disease outcome will provide important information for the design of interventions that address cancer patient's psychological, social and behavioral needs in ways that more specifically provide a positive impact on health outcome.

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