New Directions in Reducing Stress Effects on Cancer

Amal Melhem-Bertrandt and Anil K. Sood

Abstract
A growing body of evidence is now connecting neuroendocrine mediators of the stress response to cancer biology. Al-Wadei and colleagues report a study in this issue of the journal (beginning on page 189) that provides a new piece of this evidence, adding the inhibitory neurotransmitter γ-aminobutyric acid to this intricate pathway. Their mouse model study supports the hypothesis that stress mediators contribute to lung cancer progression and that known inhibitors of the stress pathway might block such effects, thus adding to the impetus for studying cancer prevention strategies targeting the stress pathway. Cancer Prev Res; 5(2); 147–9. ©2012 AACR.

There is growing recognition of the effects of the social environment on normal physiology, as well as on pathologic states (1), and social stress has emerged as a potential risk factor for cancer progression (2). Previous epidemiologic and clinical studies have shown it to be associated with poorer survival in certain cancer subtypes such as breast, head and neck, and lung cancer (3). The study of stress in the human context, however, has inherent difficulties, mainly pertaining to broad stress exposures but also to variable stress perceptions and physiologic responses across individuals. Furthermore, numerous confounding factors need to be accounted for, such as, for example, smoking, alcohol intake, obesity, and reluctance to seek care. Rigorous preclinical models of psychosocial stressors have been designed in an attempt to eliminate confounding variables and to standardize the effects of stress on tumor biology (4, 5). For the most part, these models have used rodents that have a reliable physiologic response to repeated social stressors (6, 7). Extending these studies, mechanistic insights into how social stress may affect tumor biology have emerged. Specifically, it has been shown that chronic stress influences the metastatic steps of angiogenesis, invasion, migration, proliferation, and, most recently, protection of cancer cells from a type of programmed cell death called anoikis (8). The effects of stress exposure on tumor biology may happen as early as the neonatal period with influences on normal tissue development (9).

The brain processes information gathered from exposure to acute or chronic social stress through a circuitry connecting the prefrontal cortex to the hippocampus and amygdala. This processing, in turn, leads to "modulation" of both the autonomic nervous system and the hypothalamic-pituitary-adrenal axis, causing a change in the levels of their respective mediators, catecholamines (norepinephrine and epinephrine), and glucocorticoids (cortisol; refs. 10, 11). Catecholamines are released predominantly from the sympathetic nervous system, which activates the adrenergic receptors (ARs) expressed on a variety of tissues. The main ARs involved in the stress response are the α-ARs (ARα) and β-ARs (ARβ; ref. 12).

With regard to tumor biology and the adrenergic system, the data so far seem to predominantly implicate the ARβs (13). These are a family of G-protein–coupled receptors, which, upon binding with their ligands, activate a number of signaling cascades through cyclic AMP (cAMP)-dependent and cAMP-independent phosphorylation events. A main signaling cascade activated by ARβs is the adenyl cyclase/cAMP/protein kinase A (PKA) pathway. This signaling pathway can be inhibited by the neurotransmitter γ-aminobutyric acid (GABA) via the inhibitory G-protein–coupled GABA receptor (14). GABA is synthesized primarily from glutamate by glutamate decarboxylase (GAD) and mediates its effects on cellular processes by the activation of traditional ionotropic (GABA_A) and metabotropic (GABA_B) receptors (15).

Prior in vitro studies by the Schuller group have shown that ARβ signaling may play a role in lung cancer progression (16). Human lung adenocarcinoma cells exposed to the ARβ agonist isoproterenol showed increased proliferation that was inhibited by the addition of the general β-blocker propranolol. This adrenergic signaling–induced proliferative effect was dependent on an ARβ-mediated increase in intracellular cAMP. Furthermore, nicotine--derived and highly carcinogenic nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNK) was found to be a high-affinity agonist for ARβ1 and ARβ2. This evidence suggested that activation of ARβ signaling may be linked to the development of smoking-associated cancers. NNK was found to stimulate the proliferation of human lung adenocarcinoma cells via a cAMP-dependent

Authors' Affiliations: Departments of 1Breast Medical Oncology, 2Gynecologic Oncology and Reproductive Medicine, 3Cancer Biology, and 4Center for RNA Interference and Non-Coding RNA, MD Anderson Cancer Center, Houston, Texas

Corresponding Author: Anil K. Sood, MD Anderson Cancer Center, Unit 1362, P.O. Box 301439, Houston, TX. Phone: 713-745-5266; Fax: 713-792-3643; E-mail: asood@mdanderson.org

doi: 10.1158/1940-6207.CAPR-11-0579
©2012 American Association for Cancer Research.
signaling cascade that involved activation of the transcription factor cAMP-response element binding protein (CREB) and PKA-dependent transactivation of the epidermal growth factor receptor (EGFR) pathway and its downstream effectors the extracellular signal–regulated protein kinase 1 (ERK1) and ERK2. This cross-talk between the ADRB and EGFR pathway, which is a major player in lung cancer, provides further mechanistic insight into the possible effects of social stress on tumor biology.

As reported in this issue of the journal, Al-Wadei and colleagues (the Schaller group) tested GABA for its in vivo effects on stress-mediated lung cancer growth and signaling (17). Specifically, they used male nude mice exposed to a validated chronic stress procedure consisting of repeatedly changing group composition (6). Following 4 weeks of stress exposure, these mice were then separated into 2 groups, one inoculated with the human lung adenocarcinoma cell line NCI-H322 (containing an activating K-ras mutation), and the other with the human adenocarcinoma cell line NCI-H441 (no K-ras mutation). Stress exposure then resumed. These mice were compared with nonstress–exposed controls inoculated with the same cancer cell lines. Mice from all these groups were then treated with i.p. injections of GABA for another 30 days prior to a relatively nonstressful method of euthanasia (CO2 inhalation). Serum levels of the stress mediators noradrenaline, adrenaline, and cortisol were significantly increased in stressed mice compared with nonstressed mice (untreated with GABA); conversely, serum GABA levels were reduced in the stressed versus nonstressed mice. These effects were also seen in xenograft tumor tissues. Associated with an increase in stress hormones and a reduction in GABA, a significantly increased tumor size occurred in stressed mice compared with controls. Furthermore, cAMP intracellular levels were increased in xenografts from stressed mice, and the level of the proposed downstream signaling cascade, mainly phospho­rylated CREB and ERK, increased. Most striking, treatment with GABA seemed to reverse these effects, reducing tumor volume in stressed mice as well as nonstressed controls. GABA also reduced cAMP levels, as well as downstream CREB and ERK phosphorylation, in stressed and nonstressed mice. The presence of a K-ras–activating mutation did not seem to affect the stress response or the reaction to GABA. A downstream effector of EGFR and implicated in resistance to lung cancer therapy, K-ras may well could have influenced response to GABA. In this study, however, the response to GABA regardless of K-ras may mean that the proposed antitumor effects of GABA could circumvent the K-ras–mediated mechanism of resistance.

Al-Wadei and colleagues convincingly show that social stress in mice accelerates tumor growth, an effect that is reversed by GABA. It is interesting to note, however, that nonstressed mice also had a reduction in tumor volume following GABA treatment, pointing to the possibility of additional tumor-related pathways that may be modulated by GABA besides the stress pathway. Pursuing this possibility further by comparing the effects of adrenergic antagonists, glucocorticoid antagonists, and GABA on lung cancer growth may strengthen the case for the use of GABA in this setting. It is unclear whether GABA would offer any advantage over β-blockers, which have been associated with decreased cancer recurrence in retrospective studies of breast cancer and melanoma (18–22).

As shown in this study, however, GABA has the potential to more broadly inhibit the stress response (both the glucocorticoid and adrenergic pathways). Previous preclinical studies have shown that GABA acts as a developmental signal in both embryonic and adult developing tissues and affects the proliferation of many different cell types, including stem cells (15, 23). These effects support a role for GABA beyond that of a mere inhibitory neurotransmitter or antagonist of the stress response. In addition, as stated by Al-Wadei and colleagues, GABA is available as a relatively safe, low cost nutritional supplement, making the case for using GABA even more appealing. GABA supplements have been in use since the 1960s and began being tested clinically (in trials for neurologic disorders) that were reported in the 1980s. GABA studies subsequently branched out to use the GABA derivative Baclofen, and the completed phase 1 studies of GABA have been done in noncancer diseases (24, 25).

Many questions would need to be addressed before using GABA or related substances in clinical cancer prevention or therapy settings. For example, which individuals are most likely to benefit from such an intervention? Should the proposed antitumor effects of GABA be considered only within the context of stress? Moreover, factors related to oral
absorption, dosing, and surrogate markers of biological activity would need to be addressed.

Our understanding of the effects of behavioral stress on cancer biology is expanding. The strongest links with this stress seem to center on cancer progression rather than initiation, as indicated by prior epidemiologic studies and meta-analysis (3). The few clinical trials examining the role of psychosocial interventions in slowing cancer progression have to date been inconclusive, pointing to the complexity of carrying out such studies (2). A deeper understanding of the underlying pathways responsible for mediating the effects of stress will undoubtedly improve the design of such trials and lead to new opportunities for cancer prevention and treatment (26). The study by Al-Wadei, coupled with many other recent studies, is paving a path toward such opportunities. The pipeline for possible interventions includes behavioral interventions with or without pharmacologic agents such as β-adrenergic blockers and glucocorticoid antagonists and now perhaps GABA alone or combined with behavioral interventions. Most important, the in vivo evidence presented by Al-Wadei and colleagues in this issue of the journal supports the hypothesis that stress mediators contribute to tumor progression and that known inhibitors of the stress response oppose it (Fig. 1). This evidence further confirms that our attempts to decipher the connections between the neuroendocrine mediators of stress and cancer are heading in the right direction.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received November 17, 2011; revised December 12, 2011; accepted December 28, 2011; published online February 3, 2012.

References

23. Young SZ, Bordey A. GABA’s control of stem and cancer cell proliferation in adult neural and peripheral niches. Physiology (Bethesda) 2009;24:171–85.
New Directions in Reducing Stress Effects on Cancer

Amal Melhem-Bertrandt and Anil K. Sood


Updated version
Access the most recent version of this article at:
http://cancerpreventionresearch.aacrjournals.org/content/5/2/147

Supplementary Material
Access the most recent supplemental material at:
http://cancerpreventionresearch.aacrjournals.org/content/suppl/2012/02/07/5.2.147.DC1

Cited articles
This article cites 25 articles, 10 of which you can access for free at:
http://cancerpreventionresearch.aacrjournals.org/content/5/2/147.full.html#ref-list-1

Citing articles
This article has been cited by 3 HighWire-hosted articles. Access the articles at:
/content/5/2/147.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.