Catecholamines Mediate Psychologic Stress–Induced Cancer Progression

Daniel G. Bernabé

Catecholamines, which are involved in response to physical or emotional stress, have emerged as one of the main mediators of the relationship between chronic stress and cancer progression. The study in this issue of *Cancer Research* by Liu and colleagues reveals a new mechanism by which psychologic stress stimulates cancer progression through the D2 dopamine receptor and activation of the oxygen-independent HIF1α pathway. Although most investigations so far have focused on the action of the stress-related catecholamines norepinephrine and epinephrine on tumor cells, this study shows that dopamine and its receptor can be a potential therapeutic target. The findings broaden the understanding of the interaction of catecholamines with the tumor microenvironment and reinforces the need to look at psychologic stress as a modulator of cancer progression.

See related article by Liu et al., p. 5353

A growing body of evidence has brought scientific support to the long-standing premise that psychologic or emotional stress influences the growth of malignant tumors. Although the participation of psychologic stress in processes of tumorigenesis still lacks detailed mechanistic understanding, knowledge accumulated over time has attested to its role as a relevant modulating factor in cancer progression. In this context, catecholamines released in response to activation of the sympathetic nervous system (SNS) act in the cross-talk between psychologic stress and biological events related to tumor progression. In response to chronic stress, SNS fibers release the catecholamines norepinephrine, epinephrine, and dopamine in different tissues and organs. Although the neurotransmitters norepinephrine and epinephrine are the main catecholamines so far related to psychologic stress–induced cancer progression, in this issue of *Cancer Research*, Liu and colleagues shed light on a mechanism mediated by dopamine (1). Using *in vitro* and preclinical melanoma models they showed that the interaction between D2 dopamine receptor (DRD2) and von Hippel-Lindau (VHL) in the nucleus of neoplastic cells may establish a hypoxia-independent HIF1α pathway, which mediates the tumor progression induced by psychologic stress. The DRD2 antagonist trifluoperazine (TFP) reduced the stress-induced tumor growth in melanoma-bearing mice, an effect mediated by inhibition of the interaction between DRD2 and VHL and degradation of HIF1α. The transcription products of HIF1α (e.g., Twist1, VEGFA, and TGFβ1) have been linked with proliferation, migration, and invasiveness of tumor cells. Thus, the results suggest that chronic stress can lead to dopamine-induced DRD2 nuclear translocation, inhibition of HIF1α degradation, and consequently, increased expression of downstream genes and cancer progression.

Dopamine, which performs several functions in the brain and peripheral tissues, is a neurotransmitter precursor of norepinephrine and epinephrine. The family of dopamine receptors (DR) consists of five G protein–coupled receptors with differences in signal transduction and ligand affinity (2). The interest in studying the role of DRs in cancer progression grew after evidence that patients who used antipsychotic drugs, such as TFP, concurrently with cancer treatment had a better prognosis (3). Abnormal expression of DRs has been found in different tumors, which may have a clinical impact. The DRs are differentially expressed in several tumors, and interestingly, each type of tumor appears to have a specific pattern of receptor expression. For example, DRD3 and DRD4 are overexpressed in glioblastoma and acute myeloid leukemia, respectively (3). DRD2 in turn is expressed in several types of cancer and may promote the proliferation and invasion of neoplastic cells. In their article, Liu and colleagues (1) showed that DRD2 was highly expressed in stress-stimulated tumors and that the DRD2 inhibitor TFP evoked more robust antitumor effects in stressed mice than in the control group. However, it has been shown that DRD2 can also mediate antitumor effects by blocking angiogenesis and tumor cell proliferation (4), and both DRD2 agonists and antagonists have been reported to have inhibitory effects on cancer growth (3, 4). It is known that in noncancer biological models, chronic stress can modulate dopamine levels and the expression of DRs in the central nervous system (CNS) and peripheral tissues. An inhibitory effect of chronic stress on tumor dopamine levels has been reported in an orthotopic preclinical model of ovarian cancer (5). In this study, induction of restraint stress increased the dopamine concentrations after the first day but reduced the hormone levels after 3 and 14 days. This chronic stress–induced reduction in dopamine levels was accompanied by an increase in norepinephrine concentration and tumor growth, an effect that was reversed via DRD2 by dopamine replacement (5). Although Liu and colleagues in their study used a more elaborate model of chronic psychologic stress than restraint stress (1), systemic and local dopamine levels were not measured in the *in vivo* model, which makes it limited for the purpose of associating stress-induced overexpression of DRD2 with elevated levels of dopamine. In view of these findings, the effects of psychologic stress on cancer progression via DRs probably depend not only on the characteristic

Psychosomatic and Education Research Center, Oral Oncology Center, São Paulo State University (Unesp), School of Dentistry, Araçatuba, São Paulo, Brazil.

Corresponding Author: Daniel G. Bernabé, Psychosomatic Research Center, Oral Oncology Center, São Paulo State University (Unesp), Araçatuba, São Paulo SP 15050-015, Brazil. Phone: 5518-3636-3268/36363275; E-mail: daniel.bernabe@unesp.br

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and duration of stress, but also on the specific type of tumor and on the subtypes of DRs that are expressed in the tumor microenvironment.

Although the mechanisms related to the participation of dopamine and its receptors in the stress-related progression of malignant tumors are still poorly explored, the same cannot be said about norepinephrine and epinephrine. Secreted from sympathetic neurons and the adrenal medulla because of SNS activation, these catecholamines mediate the autonomous nervous system response to chronic stress and have been implicated in several molecular pathways associated with tumor growth. It is noteworthy that the participation of catecholamines in cancer growth is not a phenomenon that occurs strictly under the influence of chronic stress. Sympathetic and parasympathetic nerves from the peripheral nervous system stimulate tumor progression, and in reciprocation, cancer cells drive nerve outgrowth in a cross-talk that contributes to tumor growth (6). This phenomenon occurs with the participation of neurotransmitters such as catecholamines and acetylcholine (6) irrespective of the occurrence of a fight or flight reaction triggered by psychologic stress. In any case, when a rodent or human is under a stress condition, there is an uncontrolled overactivation of the communication between nerves and cancer cells, characterized by the exacerbated production of norepinephrine and epinephrine. Both stress-related catecholamines act by binding to G protein–coupled adrenergic receptors on the surface of the cancer cells and other cell types in the tumor microenvironment, such as endothelial cells, fibroblasts, and immune cells (7). The two main types of these receptors, α- and β-adrenergic receptors, share significant homology despite the higher affinity that α-adrenergic receptors have for norepinephrine and β-adrenergic receptors for epinephrine (7). The expression of adrenergic receptors has been observed in several types of cancer, such as breast, prostate, ovary, pancreas, lung, head and neck, skin, lymphoma, among others (7, 8). The effects of psychologic stress on the progression of these different tumor types are mainly mediated by the action of norepinephrine and epinephrine on β-adrenergic receptors. These catecholamines act on β1 and β2-adrenergic receptors inducing the activation of specific targets such as protein kinase A and gene expression by the transcription factor cAMP response element-binding protein (CREB; refs. 7, 8). Unlike dopamine, whose response to stress appears to be both inhibitory and stimulatory, the biological role of norepinephrine and epinephrine in response to stress is more clearly directed toward the potentiation of classical mechanisms of tumor progression. With rare exceptions, a large body of evidence has pointed out that the increased secretion of both norepinephrine and epinephrine as a result of chronic psychologic stress accelerates the proliferation, migration, and invasion of tumor cells, potentiating the occurrence of metastasis. In addition, the increased secretion of these catecholamines systemically and in the tumor microenvironment favors tumor angiogenesis, incitement to inflammation, suppression of adaptive immunity, inhibition of apoptosis, and resistance to chemotherapy and immunotherapy. These events are regulated by β-adrenergic receptors, mainly the β2-adrenergic subtype, which can activate several pathways including the MAPK, NFκB, Akt, HIF1α, and Stat3 pathways (7, 8). Reinforcing the participation of β-adrenergic receptors in cancer progression, an emerging set of epidemiologic studies has revealed an association between the use of their antagonists ("β-blockers") and reduced rates of progression for several cancers (8, 9). Furthermore, preclinical study by our group suggests that increased precarcinogenesis catecholamine levels in the normal microenvironment could be predictive of chemically induced cancer development and tumor progression related molecular events (10).

Although in the last decade, a robust body of preclinical studies has drawn attention to catecholamines as protagonists in the relationship between stress and cancer progression, extensive further work is still needed to advance understanding in this field. Few studies have yet focused attention on measuring systemic and tumor levels of norepinephrine, epinephrine, and dopamine in patients with cancer, as well as their interconnections with the psychologic status and their clinical implications. In general, assessment of the expression of DRs and adrenergic receptors in tumor tissue is more feasible than the measurement of catecholamines in the human biological fluids or tumor microenvironment. However, although mapping the expression of hormone receptors (or their polymorphisms) in the tumor microenvironment is a significant indicator for the sensitivity of the tumor to the action of catecholamines, it may have limited value if it is considered the only biological reference to measure the effects of the stress-related catecholamines on cancer progression. Further investigations may contemplate the combined analysis of tumor sensitivity to catecholamines via analysis of their receptors, with systemic and local levels of neurotransmitters. In addition, it would be very enriching to gain better understanding of the relationship of catecholamines with the psychologic characteristics of patients with cancer throughout treatment. Although we know that the patient may experience physical and emotional symptoms after cancer diagnosis (e.g., pain, anxiety, and depression), which can trigger stress, we still have a great deal to know about the interactions of these symptoms with SNS hyperactivity and the resulting secretion of catecholamines. The development of more sensitive protocols for the assessment of emotional stress throughout cancer diagnosis and treatment may help to understand how catecholamines secreted in the CNS and peripheral tissues interact with specific emotional characteristics of patients with cancer. In any case, given all the evidence we have so far, it is essential to consider stress-related catecholamines as potential targets for both therapeutic purposes and for the development of interdisciplinary protocols, with the aim of reducing emotional stress in patients with cancer.

Authors' Disclosures

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