Depression Stresses the Immune Response and Promotes Prostate Cancer Growth

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Depression induces secretion of neuropeptide Y from prostate cancer cells, which, in turn, recruits myeloid-derived suppressor cells (MDSC) to the tumor; tumor cells and MDSCs secrete IL6, which activates STAT3 within cancer cells. Prostate cancer samples from depressed patients reveal a similar phenotype, suggesting new treatment strategies based upon blockade of β2-adrenergic receptors and/or neuropeptide Y.

In this issue of *Clinical Cancer Research*, Cheng and colleagues (1) show that subjecting mice with prostate cancer to chronic unpredictable mild stress (CUMS), to model depression, significantly increases numbers of myeloid-derived suppressor cells (MDSC) in the tumor and spleen. This increase is driven by stress-induced norepinephrine, which triggers release of neuropeptide Y (NPY) from prostate tumor cells through stimulation of the β2-adrenergic receptor on the tumor cell surface. NPY mediates recruitment of MDSCs to the tumor microenvironment and these cells then produce IL6. In addition, NPY activates the IL6/STAT3 signaling pathway in tumor cells, which stimulates prostate cancer growth. These results align with previous reports that prostate cancer cells that have undergone neuroendocrine differentiation also secrete NPY (2).

The mechanistic connections between chronic stress (such as that associated with depression), immune dysregulation, and diseases such as cancer are currently unclear and, if clarified, could provide new therapeutic targets. We know that adrenergic receptors for sympathetic nervous system (SNS) catecholamines are present on tumor cells and provide a direct mechanism by which chronic stress–induced catecholamines promote tumor cell proliferation, survival, and expression of proangiogenic factors. Furthermore, immune cells also express adrenergic receptors and are prone to SNS-mediated suppression of the antitumor immune response (3). Chronic stress suppresses antitumor immunity by several different mechanisms and, although these mechanisms remain to be fully identified, it is clear that stress increases the numbers and expressive activity of myeloid cells/MDSCs. A recent report by McKim and colleagues (4) has shown that psychological stress in mice mobilizes hematopoietic stem cell progenitor cells, which engraft in the spleen, and differentiate into several types of immunosuppressive cells, including MDSCs. This process can be prevented by β-adrenergic receptor blockade. Similarly, Vamasetti and colleagues (5) have also shown that SNS activation increases myeloid progenitor cell proliferation and differentiation. Specifically, norepinephrine increases proliferation of migrated granulocyte macrophage progenitors (GMP) in the spleen. As might be expected, ablation of splenic SNS signaling diminishes progenitor proliferation and myeloid cell development (5). Adding to our understanding of how stress-induced neurotransmitters suppress the immune response, Cheng and colleagues now show that NPY induced by β2-adrenergic receptor signaling in tumor cells increases MDSC recruitment from spleen to the tumor area (1).

The clinical relevance of these and other preclinical studies detailing the tumor-promoting effects of adrenergic stress in patients are currently coming into focus. One of the first reports linking stress and tumor progression in patients was from Lutgendorf and colleagues who found that patients with ovarian cancer experiencing a high degree of social isolation have elevated levels of norepinephrine in their tumors (6). In addition, patients experiencing stress have higher levels of serum NPY and a myeloid cell growth factor (colony stimulating factor) compared with less stressed patients (7). Adding to this information, Cheng and colleagues now show that prostate cancer samples from depressed patients have higher numbers of tumor-associated macrophages (which likely result from rapid differentiation from MDSCs recruited to the tumor) and increased IL6 suggesting that adrenergic blockade and/or NPY inhibition could be helpful as a strategy for treatment of prostate cancer in depressed patients. This fits well with other findings supporting the idea that coincident use of “β-blockers” are beneficial to cancer outcomes. Multiple retrospective studies reviewing clinical outcomes of patients who are taking nonspecific β-adrenergic receptor antagonists for other medical issues (e.g., hypertension) have been conducted. This includes data from several different cancers including breast, ovarian, colorectal, prostate, and melanoma (8). Importantly, none of the β-blockers for other medical issues is associated with longer survival in patients with melanoma given immunotherapy, including checkpoint blockade (9).

In considering the overall relevance of preclinical studies of stress and depression in mice to the potential for development of therapeutic strategies in patients, recent work raises a note of caution. Several articles over the last decade have concluded that “control” laboratory mice are chronically stressed due to many mandated aspects of their housing.
conditions (10) and it is not yet understood how this baseline chronic stress affects the stress response of mice to subsequent stresses such as CUMS or other imposed stresses used in preclinical studies (11). For example, work from our laboratory and that of several others, shows that mandated sub-thermoneutral housing temperatures (22°C) have a significant influence on modeling immune-mediated diseases in laboratory mice driving immunosuppression and resistance to cytotoxic and targeted cancer therapies compared with that seen in mice housed at thermoneutral temperatures (24°C). We have also recently shown that adrenergic stress resulting from cool housing reduces the ability of T cells to become fully activated (3). The expression of inflammatory cytokines, which can significantly influence the degree of immunosuppression seen in mice, is also significantly skewed by cool housing, for example, the differences seen in modeling inflammation and atherosclerosis in mice housed at different temperatures (12). Nevertheless, the patient data reported by Cheng and colleagues appears to support the conclusions drawn from the murine studies. Furthermore, treatment of tumor-bearing mice housed under standard cool housing with the pan-β-blocker propranolol (11) was shown to significantly increase the response to checkpoint blockade immunotherapy indicating that blocking adrenergic receptors may generally reduce the ability of various forms of adrenergic stress to induce immunosuppression. This may hold true for blockade of NPY as well.

In summary, the work by Cheng and colleagues adds to our growing body of information revealing the tumor growth–promoting role of adrenergic stress. Figure 1 highlights some information which is accumulating regarding the mechanisms by which chronic stress influences tumor growth by: (i) inducing GMP migration from bone marrow to spleen (4), (ii) increasing GMP proliferation in spleen as new source of MDSCs (5), and (iii) increasing MDSC recruitment to the tumor site through NPY (1). Moreover, the increased level of norepinephrine driven by chronic stress indirectly induces IL6/STAT3 signaling in tumor cells through NPY. While the new evidence provided in the Cheng and colleagues’ article is very informative, the role of norepinephrine in MDSC immunosuppressive function, migration, and metabolism remains to be clarified. Also, the downstream signaling mechanism of β2-adrenergic receptors in MDSC is still unknown (Fig. 1). Overall, this work by Cheng and colleagues highlights the fact that patients with prostate cancer suffering from depression may experience many facets of the sympathetic stress response and
may benefit from stress reduction and/or blockade of norepinephrine or NPY signaling.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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