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Depression stresses the immune response and promotes prostate cancer growth

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Summary:

Depression induces secretion of neuropeptide Y from prostate cancer cells which, in turn, recruits MDSCs to the tumor; tumor cells and MDSC secrete IL-6, which activates STAT3 within cancer cells. Prostate cancer samples from depressed patients reveal a similar phenotype, suggesting new treatment strategies based upon blockade of β_2 adrenergic receptors and/or neuropeptide Y.

In this issue of Clinical Cancer Research, Cheng et al., (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 (NE) which triggers release of NPY from prostate tumor cells through stimulation of the β_2 -adrenergic receptor on the tumor cell surface. Neuropeptide Y mediates recruitment of MDSC to the tumor microenvironment and these cells then produce IL-6. Additionally, NPY activates the IL-6/STAT-3 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 neuropeptide Y (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 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 anti-tumor immune response (3). Chronic stress suppresses anti-tumor immunity by several different mechanisms and, although these mechanisms remain to be fully identified, it is clear that stress increases the numbers and suppressive activity of myeloid/MDSC cells. A recent report by McKim et al., 2018 (4) has shown that psychological stress in mice mobilizes hematopoietic stem cell progenitor cells (HSPCs) which engraft in the spleen, and differentiate into several types of immunosuppressive cells, including MDSC. This process can be prevented by β -adrenergic

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receptor blockade. Similarly, Vamasetti et al (5) have also shown that SNS activation increases myeloid progenitor cell proliferation and differentiation. Specifically, NE increases proliferation of migrated granulocyte macrophage progenitors (GMPs) 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 et al now show that NPY induced by β 2-AR signaling in tumor cells increases MDSC recruitment from spleen to the tumor area (1).

The clinical relevance of these and other pre-clinical studies detailing the tumor-promoting effects of adrenergic stress in patients is currently coming into focus. One of the first reports linking stress and tumor progression in patients was from Lutgendorf's group who found that ovarian cancer patients experiencing a high degree of social isolation have elevated levels of NE in their tumors (6). Additionally, patients experiencing stress have higher levels of serum NPY and a myeloid cell growth factor (colony stimulating factor) compared to less stressed patients (7). Adding to this information, Cheng et al., now show that prostate cancer samples from depressed patients have higher numbers of TAMs (which likely result from rapid differentiation from MDSCs recruited to the tumor) and increased IL-6 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 co-incident use of " β -blockers" are beneficial to cancer outcomes. Multiple retrospective studies reviewing clinical outcomes of patients who are taking non-specific 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, use of β -blockers for other medical issues is associated with longer survival in melanoma patients given immunotherapy, including checkpoint blockade (9).

In considering the overall relevance of pre-clinical 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 papers 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 pre-clinical studies (11). For example, work from our lab and that of several others, shows that mandated sub-thermoneutral housing temperatures ($\sim 22^{\circ}\text{C}$) have a significant influence on modeling immune-mediated diseases in laboratory mice driving immunosuppression and resistance to cytotoxic and targeted cancer therapies compared to that seen in mice housed at thermoneutral temperatures ($\sim 30^{\circ}\text{C}$). 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 et al. 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 et al. 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: 1) inducing GMPs migration from bone marrow to spleen (4), 2) increasing GMP proliferation in spleen as new source of MDSCs (5), and 3) increasing MDSC recruitment to the tumor site through NPY (1). Moreover, the increased level of NE driven by chronic stress indirectly induces IL6/STAT-3 signaling in tumor cells through NPY. While the new evidence provided in the Cheng et al., paper is very informative, the role of NE in MDSC immunosuppressive function, migration, and metabolism remains to be clarified. Also, the downstream signaling mechanism of β 2-AR in MDSC is still unknown (Figure 1). Overall, the current work by Cheng et al highlights the fact that prostate cancer patients suffering from depression may experience many facets of the sympathetic stress response and may benefit from stress reduction and/or blockade of NE or NPY signaling.

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Figure 1: Psychological stress-induced neuropeptide Y (NPY) regulates MDSC recruitment to prostate tumors.

Psychological stress leads to release of norepinephrine (NE) from sympathetic nerves. High levels of NE induce GMP mobilization from bone marrow into spleen, increased GMP proliferation in spleen, and augment NPY secretion by prostate tumor cells through $\beta 2$ adrenergic receptor signaling. NPY increases MDSC accumulation at the tumor site as well as induces IL-6 release by tumor cells and MDSC. IL-6 activates STAT-3 transcription factor, which promotes tumor progression. However, there are still questions about the precise role of the $\beta 2$ adrenergic receptor ($\beta 2$ -AR) and neuropeptide Y receptor (NPYR) on MDSC that remain to be need to be addressed.