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RESEARCH HIGHLIGHT

Targeting psychoemotional stress to treat prostate cancer

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Earlier epidemiological studies identified diet as a primary environmental factor that determines substantial differences in prostate cancer incidence and mortality between East Asian and West European societies. New data from experiments performed in tissue culture and with animal models as well as epidemiological studies suggest that psychoemotional stress could be a second environmental component that influences prostate cancer progression by activation of epinephrine/beta(2)-adrenergic receptor signaling in the tumor cells. The emerging information on the role of stress in prostate cancer progression provides an additional incentive to actively treat anxiety and depression—frequent psychogenic comorbidities of prostate cancer. Given that almost 50% of men diagnosed with prostate cancer take medications to control hypertension, the choice of beta-blockers for these patients capable of antagonizing both beta(1)- and beta(2)-adrenergic receptors would provide a means of cancer therapy, whereas for men with normal blood pressure, using beta(2)-selective antagonists will help to minimize side effects.

The current path of civilization is characterized by an accelerated speed of change of the social environment. As a result, continuous emotional stress became prevalent in urbanized societies. At the same time, with increased life span and successes in treatments of infection and cardiovascular diseases, the chances of being diagnosed with cancer are increasing. The high incidences of stress-related conditions and cancer suggest that substantial numbers of patients will experience both. Furthermore, the cancer diagnosis itself invariably causes distress, and prostate cancer patients were reported to experience increased levels of stress and anxiety.[1]

Psychoemotional stress activates the hypothalamic–pituitary–adrenal axis and sympathetic nervous system that leads to release of glucocorticoids from the adrenal cortex and of epinephrine and norepinephrine from the adrenal medulla and sympathetic neurons.

The initial evidence that highlighted the importance of beta(2)-adrenergic receptor signaling in prostate cancer progression came from an epidemiological studies that found an 18% decrease in prostate cancer incidence among users of beta-blockers.[2] However, studies from other groups did not find correlation between beta-blockers use and prostate cancer incidence.[3] A recent report from Norwegian scientists showed increased survival in patients with advanced prostate cancer who take beta-blockers,[4] although this conclusion was contradicted by an earlier study.[5] Data on reduced mortality among beta-blocker users across multiple cancers including 20% reduction in mortality from male reproductive neoplasms based on analysis of the United States Food and Drug Administration Adverse Events Reporting System were also recently presented.[6] These results are consistent with the generalized conclusion from multiple studies which have shown that stress does not affect cancer incidence, but contributes to increased mortality from already established cancers.

Beta(2)-adrenergic receptors are expressed by normal and malignant prostate cancer cells. Injected norepinephrine increased migration and metastasis in prostate cancer xenografts, suggesting that signaling *via* beta(2)-adrenergic receptors may contribute to prostate cancer progression.[7] It was not clear, however, whether concentrations of catecholamines observed during stress could activate beta(2)-adrenergic receptors in prostate cancer cells and what signaling pathways are engaged. Recent experiments in tissue culture models demonstrated that epinephrine at concentrations over 1 nmol l^{-1}, observed during acute or chronic stress, protected prostate cancer cells from apoptosis, and identified beta(2)-adrenergic receptor/cAMP-dependent protein kinase/bcl-2-associated death promoter (ADRB2/PKA/BAD) signaling cascade responsible for the anti-apoptotic effect.[8] Subsequent studies in two distinct *in vivo* models of prostate cancer (C42Luc xenografts that represent metastatic cancer, and Hi-Myc mice that represent localized prostate cancer) demonstrated that stress induced by immobilization in the presence of fox scent activated anti-apoptotic signaling *via* epinephrine/ADRB2/PKA/BAD pathway in both prostate cancer xenografts and in primary prostate tumors. Activation of this signaling pathway increased therapy resistance and accelerated progression of prostate cancer in mice.[9] Earlier experiments in breast and ovarian cancer models demonstrated the importance of the tumor microenvironment (immune cells and angiogenesis) in mediating effects of stress on cancer progression.[6] Additional studies in mouse prostate cancer models will clarify whether these stress-activated mechanisms, identified in other cancers, operate in prostate cancer as well and whether anti-apoptotic signaling plays a leading role or is but one of several mechanisms through which stress influences prostate cancer.

These findings in animal models led us to propose that more attention should be given to analysis of interactions among stress, activation of the hypothalamic–pituitary–adrenal axis and ADRB2 signaling in prostate cancer progression in men. In fact, in 20% of prostate cancer patients, we observed increases of epinephrine over 1 nmol l^{-1}, a concentration that has been sufficient to activate the anti-apoptotic signaling pathway in tissue culture and in mouse prostates.[9]

Several issues should be taken into account when clinical tests of inhibiting the ADRB2

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pathway are planned. Is there a group of patients who consistently shows increased epinephrine levels, and are these patients characterized by nonproductive stress coping and anxiety? Are patients with increased circulating epinephrine also activating the ADRB2/PKA/BAD pathway in their prostates?

Answering these questions will allow selection of those patients most likely to benefit from targeting ADRB2 signaling. It will also aid in identifying biomarkers to detect activation of ADRB2 signing in prostates and determine the most effective ways to inhibit this signaling by psychological and pharmacological interventions that decrease stress and anxiety, by providing beta-blockers or by combination of both approaches.

In summary, advances in understanding mechanisms of stress–cancer interactions in animal models justify translational studies that will determine whether targeting neuroendocrine pathways will improve treatment outcomes for prostate cancer patients.

Design of individualized therapies that target stress-induced neuroedocrine signaling pathways requires collaborations among basic scientists with expertise in signal transduction, psychotherapists and clinical urologists. This interdisciplinary approach holds the promise of extending lives of patients with advanced prostate cancer for whom no effective treatments are currently available.

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