Stress pathway involving beta-adrenergic receptors fuels tumor growth

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Stress can have a significant negative effect on health, but our understanding of how stress impacts the development and progression of cancer is just beginning. A team from Roswell Park Comprehensive Cancer Center has identified an important mechanism by which chronic stress weakens immunity and promotes tumor growth. Their findings,

just published in *Cell Reports*, point to the beta-adrenergic receptor (β-AR) as a driver of immune suppression and cancer growth in response to stress, opening the possibility of targeting this receptor in cancer therapy and prevention.

Using a preclinical model of triple-negative breast cancer, a research team led by Hemn Mohammadpour, Ph.D., DVM, a postdoctoral research affiliate in the lab of Elizabeth Repasky, Ph.D., and Dr. Repasky, who is Co-Leader of the Cell Stress and Biophysical Therapies Program and the Dr. William Huebsch Professor in Immunology at Roswell Park, found that as tumors grow, they become more sensitive to stress signals coming from the nervous system. Specifically, the researchers discovered that a population of immune cells known as myeloid derived suppressor cells (MDSCs) show an increase in the expression of β-AR, a molecule that controls the function of key immune cells.

The findings will help researchers better understand why prolonged exposure to stress often makes our immune system less effective, and build on Roswell Park's pioneering research into the relationship between stress and cancer.

"This increase in β-AR expression on myeloid-derived suppressor cells allows these cells to be stimulated by the stress hormone norepinephrine, which fosters an immunosuppressed environment that promotes tumor growth by increasing MDSCs' ability to generate and process energy and suppress anti-tumor immune response," says Dr. Mohammadpour, the paper's first author. "This study provides some very important clues that help explain the specific mechanisms by which prolonged stress stimulates tumor growth and decreases lifespan."

While there has been a longstanding recognition that long periods of stress, or chronic activation of nerves, are harmful to overall health,

details about how this occurs are unclear, especially in the setting of cancer. A better understanding of the specific ways in which stress influences cancer, particularly in terms of lowering immunity against tumor cells, could be used to design new drugs or therapies that can help to minimize negative effects of chronic stress and boost cancer immunotherapy.

Based on these findings, Dr. Repasky's team is planning new clinical and laboratory studies to identify therapies—including existing therapies already approved for other applications—that can block these harmful stress signals and stop the negative cycle of cancer growth and metastasis. "This is especially important for cancer patients, who frequently endure greatly increased levels of stress after their diagnosis, including anxiety, depression and worry about factors like finances and family interactions," adds Dr. Mohammadpour.

Several clinical trials are planned or underway to investigate which interventions are most effective at mitigating the effects of stress in patients with cancer. Roswell Park is currently studying the effects of combining the β-AR blocker propranolol, which is traditionally used to treat migraine headache and various heart problems, with immunotherapy.

More information: Hemn Mohammadpour et al, β2-adrenergic receptor signaling regulates metabolic pathways critical to myeloid-derived suppressor cell function within the TME, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.109883

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