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β-endorphin neuron transplantation
A possible novel therapy for cancer prevention

Changqing Zhang and Dipak K. Sarkar*

Rutgers Endocrine Program; Rutgers, The State University of New Jersey; New Brunswick, NJ USA

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Abbreviations: BEP, β-endorphin; PVN, paraventricular nucleus; cAMP, cyclic adenosine monophosphate; SNS, sympathetic nervous system

We summarize here our new discovery that the endogenous opioid peptide β-endorphin (BEP), by virtue of reducing body stress and maintaining active immune system, as well as, balancing the levels of pro-inflammatory and anti-inflammatory cytokines, destroys tumor cells and stops them from being transformed into metastatic cancer cells.

Body and mind interact extensively with each other in control of a person's health. Social and psychological stress can trigger or aggravate a wide variety of diseases and disorders. Accumulating data on animals and humans have shown the connection between the body's psychophysiologic reaction during stress and an increased incidence or relapse of cancer.[1] Activation of sympathetic nervous system, such as what happens in the "fight or flight" response, downregulates tumor-suppressive genes, inhibits immune function and promotes tumor growth. On the other hand, an optimistic attitude or psychological intervention helps cancer patients to survive longer. How this works is currently not clear. According to the research of our lab, this effect may be related to the β-endorphin (BEP), an endogenous peptide molecule, which has morphine-like activities.

BEP was first isolated by neurochemist Choh Hao Li at the University of California in San Francisco from dried camel pituitary. It was first found to have a strong effect in pain perception, 48 times more powerful than morphine when administered into the brain.[2] Now it is known that BEP has a profound effect in the inhibition of stress behavior and stress hormone production, production of analgesia and a feeling of well-being. In the brain, BEP producing perikarya are primarily found in the arcuate nucleus,[3] where they send projections to many brain areas, particularly within the hypothalamus.[4] It has been shown that BEP not only inhibits the stress response of hypothalamic-pituitary-adrenal axis through interaction with corticotrophin-releasing hormone neurons in the paraventricular nucleus (PVN), but also inhibits the sympathetic nervous system (SNS) through innervations of the PVN where these BEP molecules bind to δ- and μ-opioid receptors to modulate the neurotransmission in neurons of the autonomic nervous system. Abnormalities in BEP neuronal function are correlated with a higher incidence of cancers and infections in patients with schizophrenia, depression, fetal alcohol syndrome, and obesity.[5]

All these observations brought us the thought: whether an increase of BEP level will suppress the stress response, improve health, and most importantly, inhibit cancer? The answer was yes. Previous work from our lab showed that intracranial administration of BEP enhanced immune activity. BEP could enhance the production of interferon-gamma and granzyme B, promote splenic lymphocyte proliferation during an immune challenge, and increase cytotoxicity of natural killer cells through action on δ- and μ-opioid receptors.[6,7] The effect of intracranial infusion of BEP is transient. Therefore, we looked into further measures to establish a permanent source of BEP in the brain.

In light of this thinking, we have recently developed a method to differentiate β-endorphin neurons in vitro from hypothalamic neuronal stem cell using a cAMP analog. Previous study of alcohol-caused BEP neuronal death revealed that cAMP is critical for the survival and differentiation of hypothalamic BEP cells.[8] When a stable analog of cAMP is added to in vitro cultured hypothalamic neuronal stem cells, these cells could differentiate to a group of highly pure BEP neurons.[9] By transplanting these neurons into the PVN of the hypothalamus, we could increase both POMC gene expression and BEP production in the PVN. These transplanted neurons were shown to integrate well in the PVN, and could survive for at least 8 mo. During this period of time, these animals were shown to have decreased stress response to both immune challenge and behavior stressors, and increased peripheral innate immune cell function, such as higher natural killer cell cytotoxicity

*Correspondence to: Dipak K. Sarkar; Email: Sarkar@aesop.rutgers.edu
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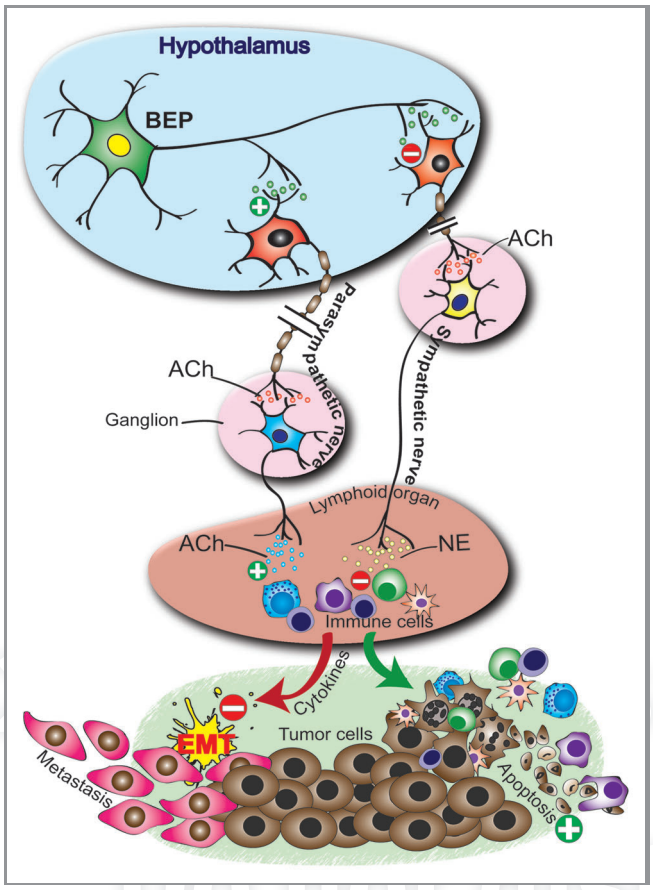

Figure 1. β-endorphin (BEP) neuron in the hypothalamus controls the growth and progression of tumor cells by modulating the neurotransmission in the autonomic nervous system and activating immune cell functions. Effects include the stimulation of parasympathetic nervous system and release of acetyl choline (Ach) and suppression of the sympathetic nervous system and release of norepinephrine (NE) leading to activation of innate immune cells (including macrophages and natural killer cells) of the lymphoid organ and an increase in cytotoxic immune cells and anti-inflammatory cytokines levels in the circulation. In a tumor microenvironment these immune cell and cytokine changes increase apoptotic death of tumor cells and reduce inflammation-mediated epithelial-mesenchymal transition (EMT), and thereby suppress cancer growth and progression. Collectively, these effects create an unfavorable environment for tumor initiation, growth and progression.

and macrophage migration activity. The anti-inflammatory cytokine levels were increased in their plasma, at the same time, inflammatory cytokine levels were found to be decreased.[5] As expected, BEP transplantation had an extensive effect in inhibition of tumor progression in several cancer models, including prostate cancer,[10] breast cancer and lung metastasis of mammary adenocarcinoma cells.[5]

This effect is possibly regulated through the action of BEP on the sympathetic and parasympathetic nervous system. Primary and secondary lymphoid organs, which include the thymus, spleen and lymph nodes, receive extensive autonomic input.[10] Administration of an opiate receptor blocker naloxone, a β-receptor agonist metaproterenol, or an acetylcholine receptor blocker methyllycaconitine all could inhibit the immune-enhancing and tumor-preventing effects by transplantation of BEP cells. These data indicate that BEP peptides in transplanted animals bind to opioid receptors, suppress the SNS and activate the parasympathetic nervous system, and finally, regulate immune function and tumor growth.

Current treatments of cancer focus on the physical removal of tumors and the destruction of dividing cells, such as chemotherapy and radiation therapy. These treatments are not specific, in that they also destroy normal cells that are programmed to be proliferating. This causes many side effects such as hair loss and nausea, and at the same time, weakens the body's defense against pathogens as well as tumors. These methods may also fail to kill cancer stem cells, which are in hibernation. Indeed, the body could recognize and kill cancerous cells by itself through immune surveillance. The transformed tumor cells express antigens that are not present in normal cells. Immune cells can recognize these foreign antigens and therefore attack and eliminate the tumor cells. The BEP cell transplantation procedure to treat cancer could potentially be valuable, because it utilizes and optimizes the body's own defense system to control abnormal cell proliferation, which is more specific, and bypasses the problem of current treatments.

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