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Extend Abstract

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Cancer Science 2018: Neuropeptide Y and its Y5 Receptor: Novel therapeutic targets linking stress and breast cancer progression - Dwayne N. Jackson - Associate Professor, Department of Medical Biophysics Medical Sciences Building, Canada

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Chronic stress is associated with elevated levels of sympathetic neurotransmitter release and immunosuppression. A growing body of evidence suggests that stress-related factors may contribute to the initiation, development and progression of breast cancer. We recently identified neuropeptide Y (NPY) as such a factor. Using the 4T1 murine breast cancer model, characterized NPY receptor expression in cancer cells and tumors annd observed positive NPY receptor (Y1R, Y2R and Y5R) expression. In vitro NPY treatment of 4T1 cells stimulated Y5R mediated increases in proliferation, whereas, NPY increased chemotaxis through Y2R and Y5R activation. We then tested whether NPY could function as an angiogenic factor by augmenting expression and secretion of the pro-angiogenic factor VEGF from breast cancer cells. We found that NPY functioned as a paracrine system with cancer cells to promote angiogenesis. Specifically, NPY Y5R activation of cancer cells (4T1 and MDA-MB-231) stimulated increased expression and release of VEGF. These novel findings served as motivation to develop an in vivo model in which the components of NPY system (i.e., nerves, ligands and receptors) could be functionally studied. We first demonstrated sympathetic neural innervation and NPY expression in 4T1 tumors. Secondly, when tumor sympathetic neural innervation was attenuated (via chemical sympathectomy), we observed a significant decrease in tumor growth and vascular development. Furthermore, we observed similar tumor growth-suppressing effects from oral Y5R antagonist treatment. Finally, we established a protocol for intravital microscopy imaging of tumors to investigate their neural innervation, cellular components, and microvasculature. Herein we provide novel evidence that: 1) NPY elicits proliferative, migratory, and angiogenic effects on breast cancer cells (via Y5R); 2) describes an in vivo murine model for functional studies examining the role of sympathetic nerves, neurotransmitters, cancer associated cells, and blood vessels, and 3) highlights the Y5R as a potential therapeutic target against breast cancer progression and metastasis.

NPY is a 36 amino-acid sympathetic neurotransmitter abundant in the brain and released from peripheral sympathetic neurons during their activation, e.g. by chronic stress or hypoxia (Zukowska-Grojec, 1995). Acting via its Y1-Y5 receptors (Y1R – Y5R), the peptide exerts pleiotropic effects that control various functions of the organism. Importantly, many of these actions of NPY, including stimulation of cell proliferation, migration and survival, as well as regulation of cell differentiation, are highly relevant to tumor growth and progression. Consequently, recent years brought significant progress in our understanding of the peptide's role in regulation of tumor growth, as well as some evidence for its contribution to cancer progression toward a metastatic and chemoresistant phenotype.

Keywords—Stress, Breast Cancer, Neuropeptide Y, Therapeutic Target.

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