Role of neuropeptide Y in the bone marrow hematopoietic stem cell microenvironment

Min Hee Park1,2,3,*, Woo-Kie Min4,*, Hee Kyung Jin1,5 & Jae-sung Bae1,2,3,*

1Stem Cell Neuroplasticity Research Group, Kyungpook National University, 2Department of Physiology, Cell and Matrix Research Institute, School of Medicine, Kyungpook National University, 3Department of Biomedical Science, BK21 Plus KNU Biomedical Convergence Program, Kyungpook National University, 4Department of Orthopaedic Surgery, Kyungpook National University Hospital, Daegu 41944, Korea, 5Department of Laboratory Animal Medicine, College of Veterinary Medicine, Kyungpook National University, Daegu 41566, Korea

The sympathetic nervous system (SNS) or neurotransmitters in the bone marrow microenvironment has been known to regulate hematopoietic stem cell (HSC) functions such as self-renewal, proliferation and differentiation. However, the specific role of neuropeptide Y (NPY) in this process remains relatively unexplored. In this study, we demonstrated that NPY deficient mice have significantly reduced HSC numbers and impaired bone marrow regeneration due to apoptotic destruction of SNS fibers and/or endothelial cells. Moreover, NPY treatment prevented bone marrow impairments in a mouse model of chemotherapy-induced SNS injury, while conditional knockout mice lacking the Y1 receptor in macrophages did not restore bone marrow dysfunction in spite of NPY injection. Transforming growth factor-beta (TGF-β) secreted by NPY-mediated Y1 receptor stimulation in macrophages plays a key role in neuroprotection and HSC survival in the bone marrow. Therefore, this study reveals a new role of NPY in bone marrow HSC microenvironment, and provides an insight into the therapeutic application of this neuropeptide. [BMB Reports 2015; 48(12): 645-646]

*Corresponding author. E-mail: jsbae@knu.ac.kr
#These authors contributed equally to this work.

http://dx.doi.org/10.5483/BMBRep.2015.48.12.227

Received 2 November 2015

Keywords: Bone marrow microenvironment, Hematopoietic stem cell, Neuropeptide Y, Regeneration, Sympathetic nervous system

Abbreviations: NPY, Neuropeptide Y; SNS, Sympathetic nervous system; HSCs, Hematopoietic stem cells; BM, Bone marrow; MSCs, Mesenchymal stem cells; ECs, Endothelial cells; TGF-β, Transforming growth factor-beta; CM, conditioned medium

Perspective to: Min Hee Park et al. (2015). Neuropeptide Y regulates the hematopoietic stem cell microenvironment and prevents nerve injury in the bone marrow, EMBO J, 34(12):1648-1660, doi: 10.15252/embj.201490174.
Role of neuropeptide Y in the bone marrow hematopoietic stem cell microenvironment
Min Hee Park, et al.

Fig. 1. Model of NPY mediated regulation of HSC microenvironment. Under homeostatic conditions of bone marrow, HSCs reside in the perivascular niche. SNS regulates EC and Nestin+ MSCs associated with HSC retention in perivascular niche. (1) Under condition of NPY deficiency in the bone marrow environment, (A) destruction of SNS fibers and endothelial cell death occurs, and (B) nestin+ MSCs decrease, since macrophages expressing Y1 receptor cannot support these niche cell survival. Thus, (C) survival of HSCs residing in the perivascular niche is reduced. (2) In mouse model of NPY deficiency or chemotherapy-induced SNS nerve injury, NPY treatment promotes neuroprotection from SNS fiber destruction by TGF-β secreted from macrophage through the Y1 receptor, resulting in prevention of HSC loss.

that bone marrow microenvironment cells were related to HSC survival in NPY deficient bone marrow. The BM of NPY deficient mice showed increased p53-dependent apoptosis of SNS fibers and CD31+ ECs, resulting in a reduction of these cells. Therefore, these findings indicated that NPY deficiency caused impairment of HSC survival and bone marrow regeneration by reducing the bone marrow microenvironment cells such as SNS fibers and CD31+ ECs. NPY or a Y1 agonist treatment into NPY deficient mice significantly prevented the loss of HSCs in the BM, and the reduction of SNS fiber and CD31+ ECs was also protected. In contrast, the pharmacological Y1 receptor-blockade in mice, by treating with Y1 antagonist, showed reduction in mouse survival, impairment of HSCs and bone marrow microenvironment cell survival after 5FU treatment, which causes ablation of most hematopoietic cells. Overall, these results suggested that an interaction of NPY and the Y1 receptor could mediate the survival of HSCs residing in the perivascular microenvironment by regulation of bone marrow SNS nerves and ECs.

Chemotherapy-induced neuropathy is one of the severe side effects of cancer therapy. Moreover, chronic bone marrow damage by chemotherapy accompanies impaired HSC function or hematopoietic regeneration, and this leads to reduced recovery of bone marrow microenvironment cells. In particular, chemotherapy drugs such as cisplatin induces sympathetic neuropathy by reducing the expression of Th fibers. In our study, cisplatin-induced bone marrow dysfunction and SNS injury were prevented by NPY treatment, which reduced cisplatin-induced apoptosis of BM cells. This protective effect of NPY was not found in conditional Y1 receptor knockout mice in macrophages. To explore the specific mechanism of NPY/Y1 receptor-mediated improvement of cisplatin-induced bone marrow dysfunction, we performed an in vitro experiment evaluating the differentiation of PC12 cells into neurons. PC12 cells exposed to conditioned medium (CM), derived from the NPY-treated control macrophages, showed neural differentiation capacity, but not in Y1 receptor deficient macrophages treated with NPY. Taken together, these results highlight the fact that NPY has a potential therapeutic value for chemotherapy-induced bone marrow abnormalities, and the trophic or bioactive factors secreted from macrophages through NPY/Y1 regulation mediates neural protection. Transforming growth factor-beta (TGF-β) has been known to play a key role in the regulation of neuronal survival, differentiation and repair processes in the nervous system. We confirmed that the PI3K/Akt/mTOR/eIL4E signaling pathway, which produces TGF-β, was activated in macrophages with NPY treatment, resulting in an up-regulation of TGF-β secretion or expression in macrophages. Therefore, these results indicate that TGF-β released by NPY-mediated Y1 receptor stimulation in macrophages is responsible for neuroprotection and HSC survival in bone marrow.

In conclusion, our findings suggest a new role of NPY as a regulator for bone marrow HSC microenvironment (Fig. 1). Moreover, we suggest that NPY or Y1 agonists have a potential clinical utility as neuroprotective agents for patients treated with chemotherapy. With an increase in patients suffering from cancer, the development of drugs is important for reduction of chemotherapy-induced side effects. NPY has a high clinical value to improve bone marrow impairments by chemotherapy, due to a stable peptide that is synthesized naturally. Therefore, the modulation of the endogenous bone marrow HSC microenvironment by NPY could be an effective therapeutic approach. Further studies investigating the functional role of NPY on bone marrow HSC microenvironment under pathological conditions may provide more valuable information on the mechanisms of interaction with the nervous system and HSC microenvironment.

ACKNOWLEDGEMENTS

This work was supported by Biomedical Research Institute grant, Kyungpook National University Hospital (2012).