

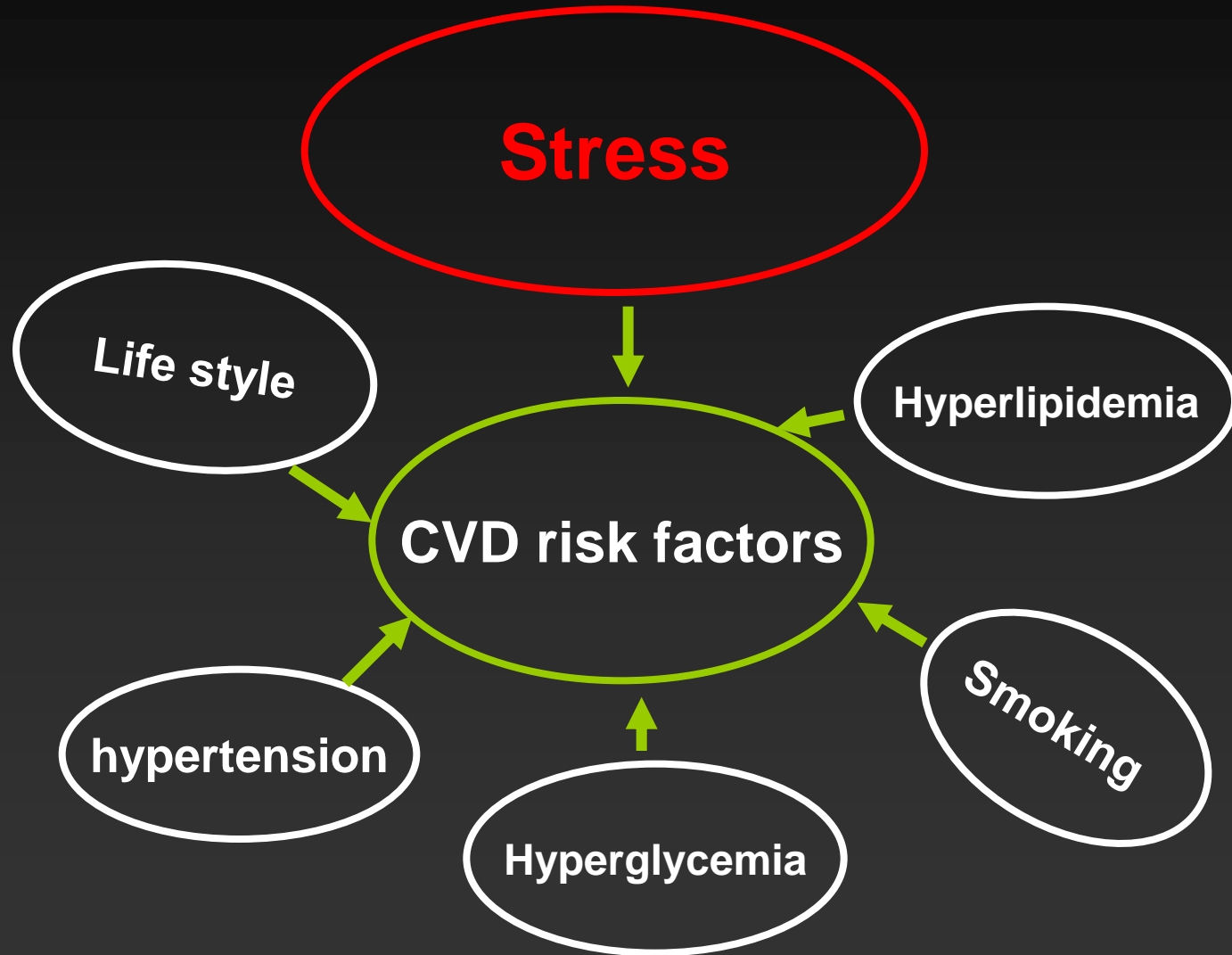
DPP4 Regulates Hematopoietic Stem Cell Activation in Response to Chronic stress

Yanbian University Hospital

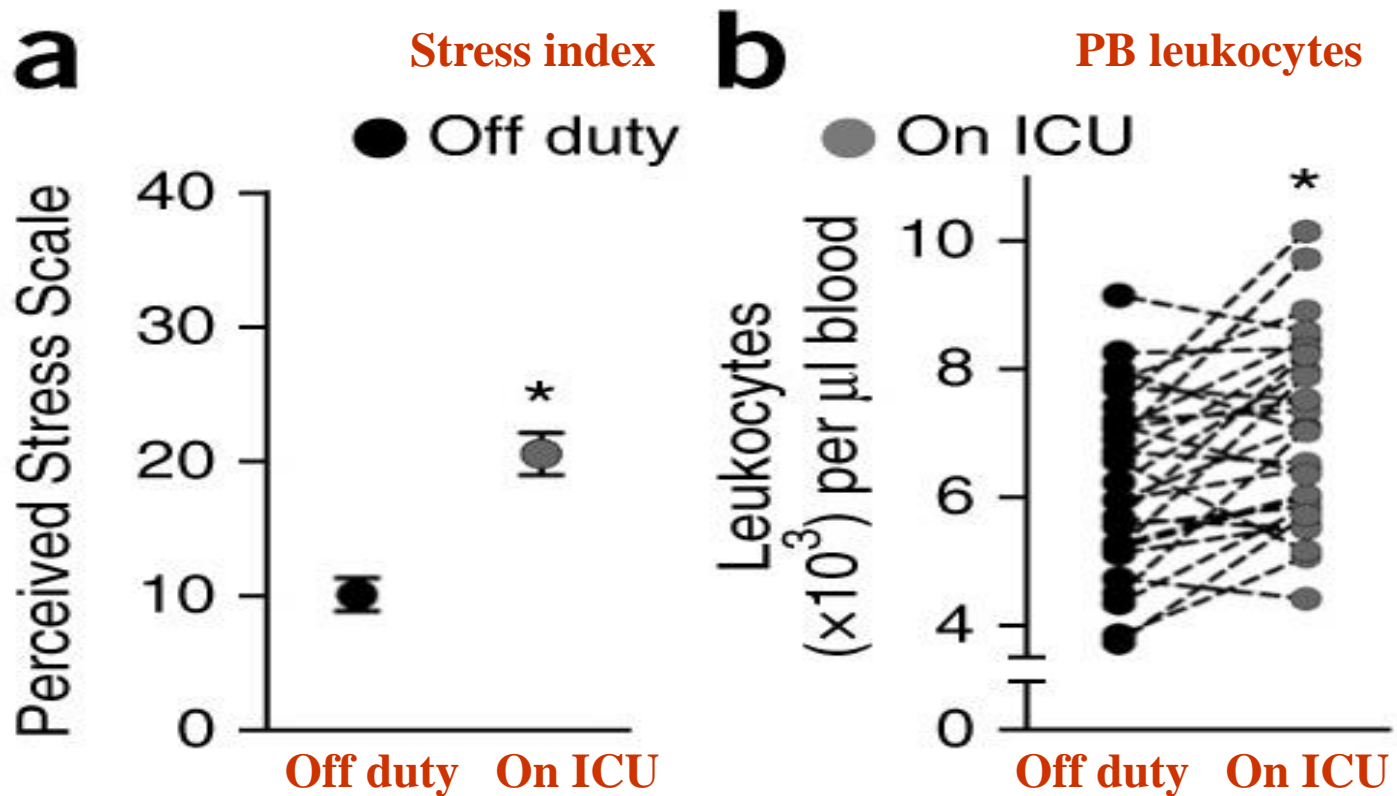
Enbo Zhu, MD, PhD; Xianwu Cheng, MD, PhD, FHA

December 9, 2017

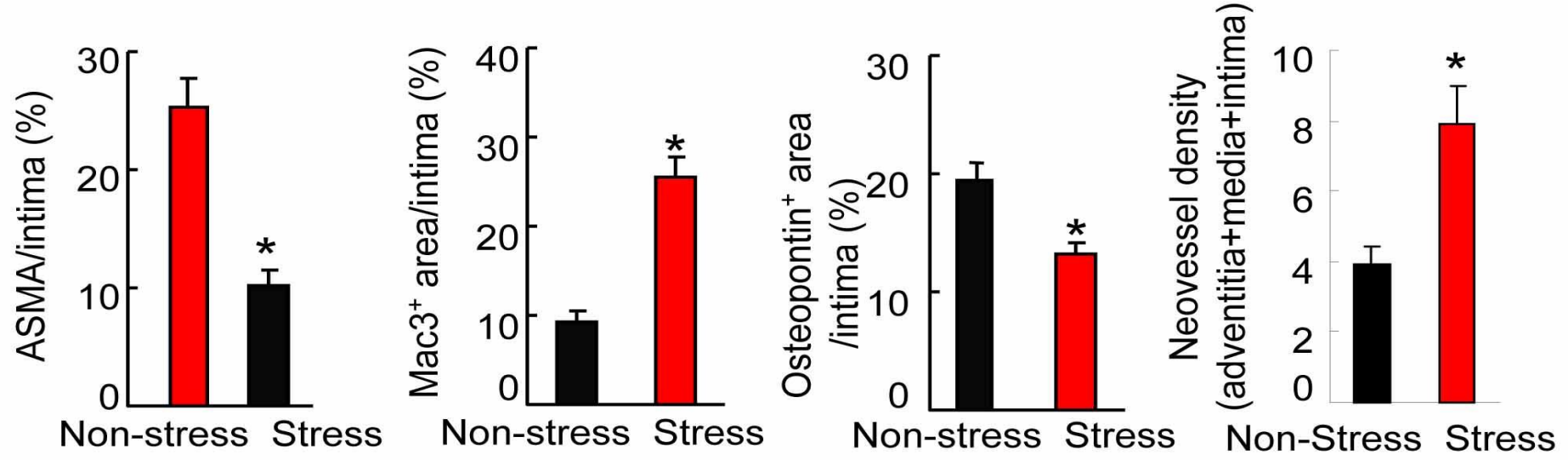
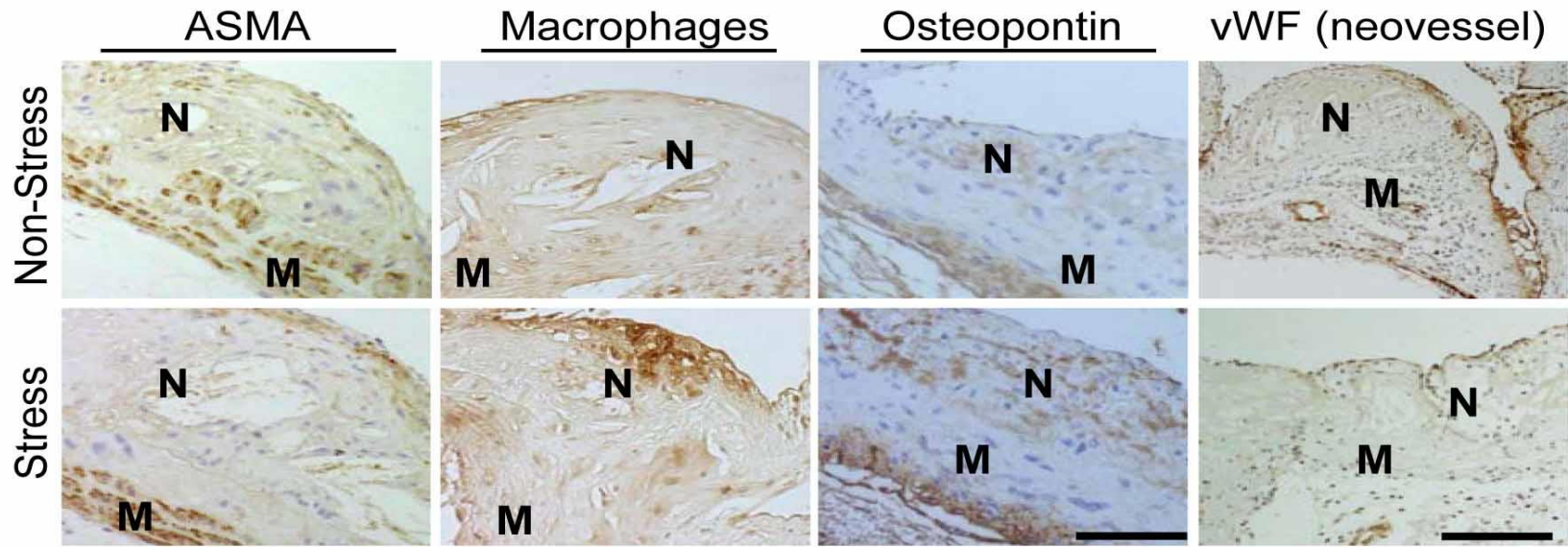
Cardiovascular risk factors



Chronic stress (night shift on ICU) increases peripheral blood leukocytes



Chronic stress accelerates atherosclerotic plaque growth



SDF1/Cxcl12 in HSC production

Published March 31, 2008

JEM

BRIEF DEFINITIVE REPORT

CXCR4 is required for the quiescence of **primitive hematopoietic cells**

Yuchun Nie, Yoon-Chi Han, and Yong-Rui Zou

From www.bloodjournal.org by guest on March 6, 2016. For personal use only.

Tzeng et al. Blood 2012

HEMATOPOIESIS AND STEM CELLS

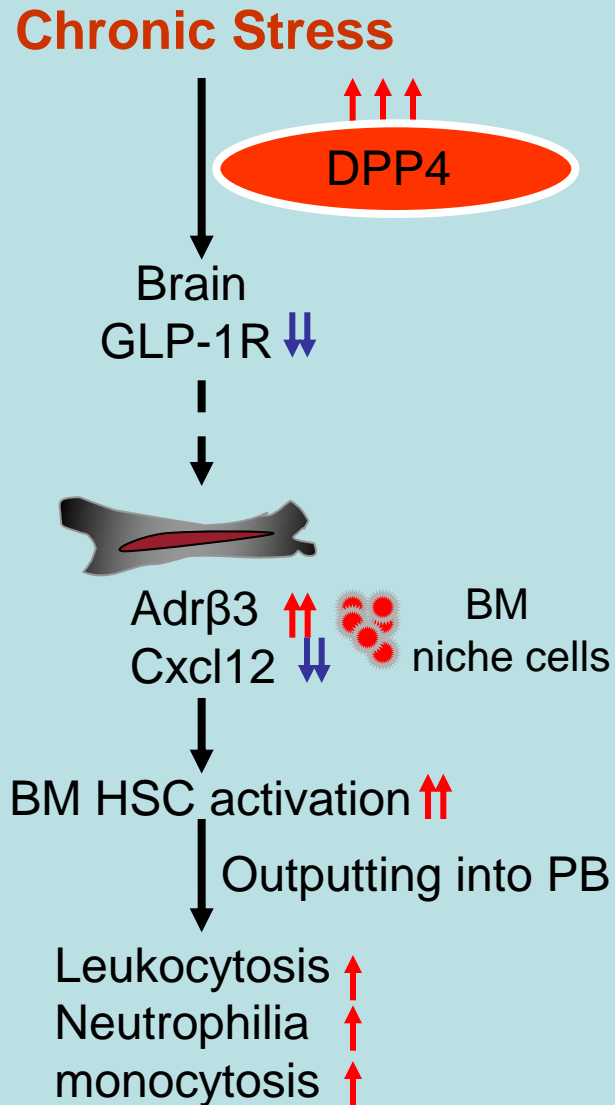
Loss of Cxcl12/Sdf-1 in adult mice decreases the quiescent state of hematopoietic stem/progenitor cells and alters the pattern of hematopoietic regeneration after myelosuppression

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Hypothesis

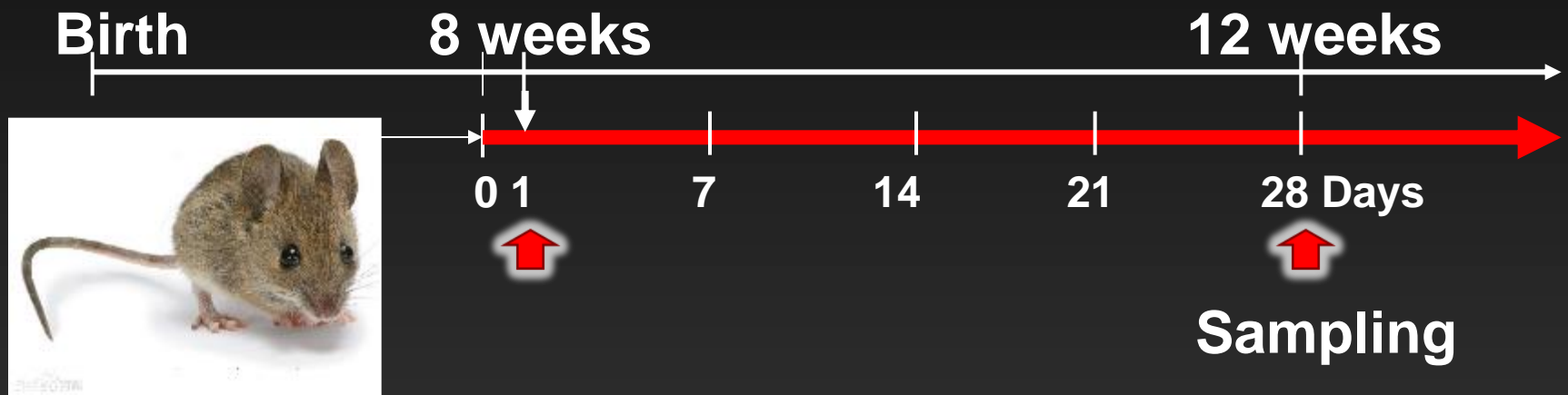


Purpose

- ❖ Given that interaction between the psyche and the immune system provides potential mechanism linking stress and disease initiation and progression, we investigated DPP4 inhibition-mediated benefits in chronic stress model with a special focus on HSC activation.

Protocol-Exp (1-1)

8-week-old male C57BL/6J mice

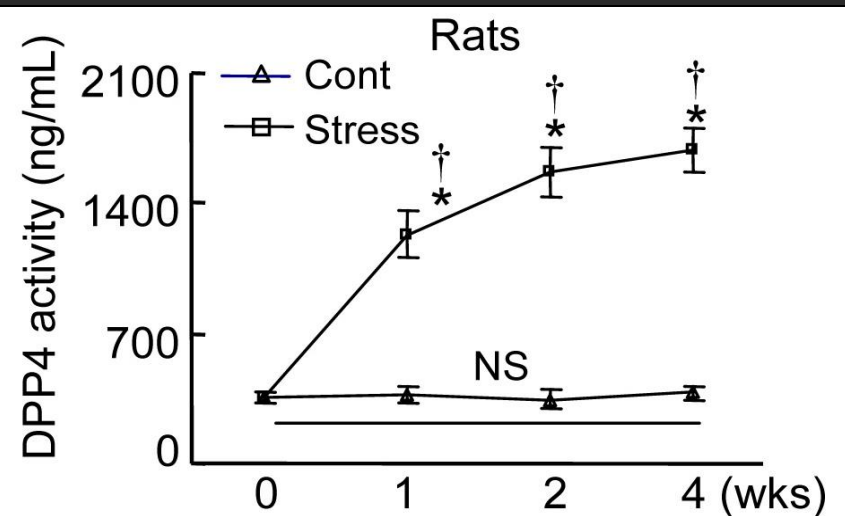
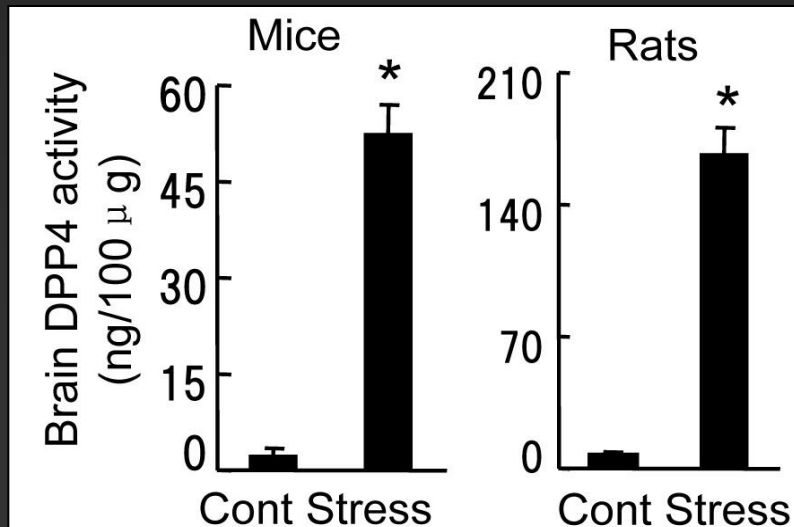
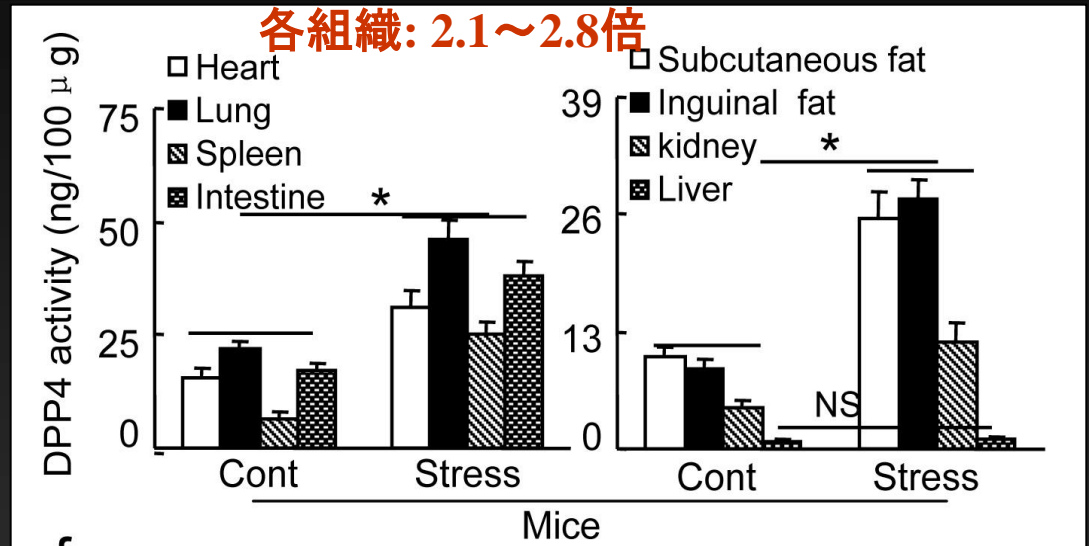
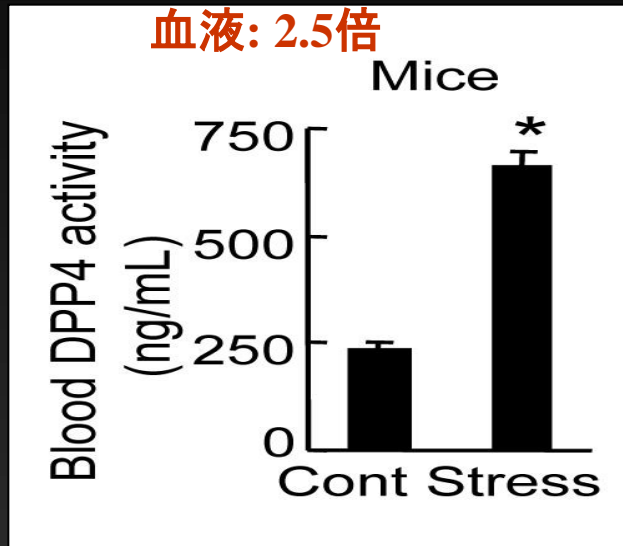


1. Control group : left undisturbed
2. Stress group : immobilized
(n = 10 for each group)

Methods

- Morphological analysis
- Biological and immunohistological assays
- Western blotting
- FACS
- ELISA

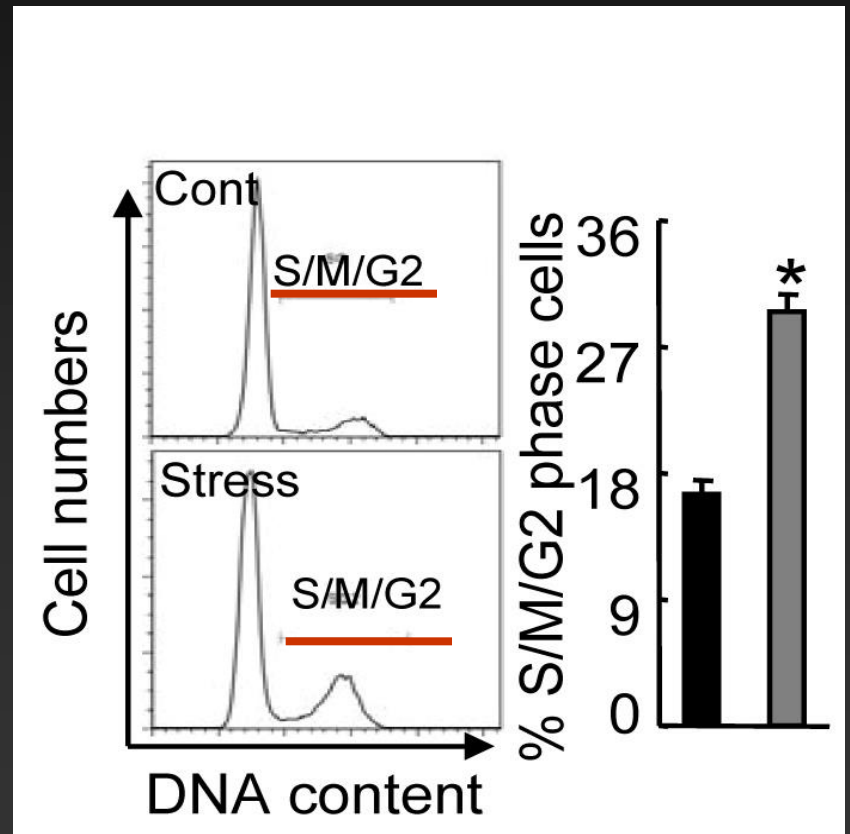
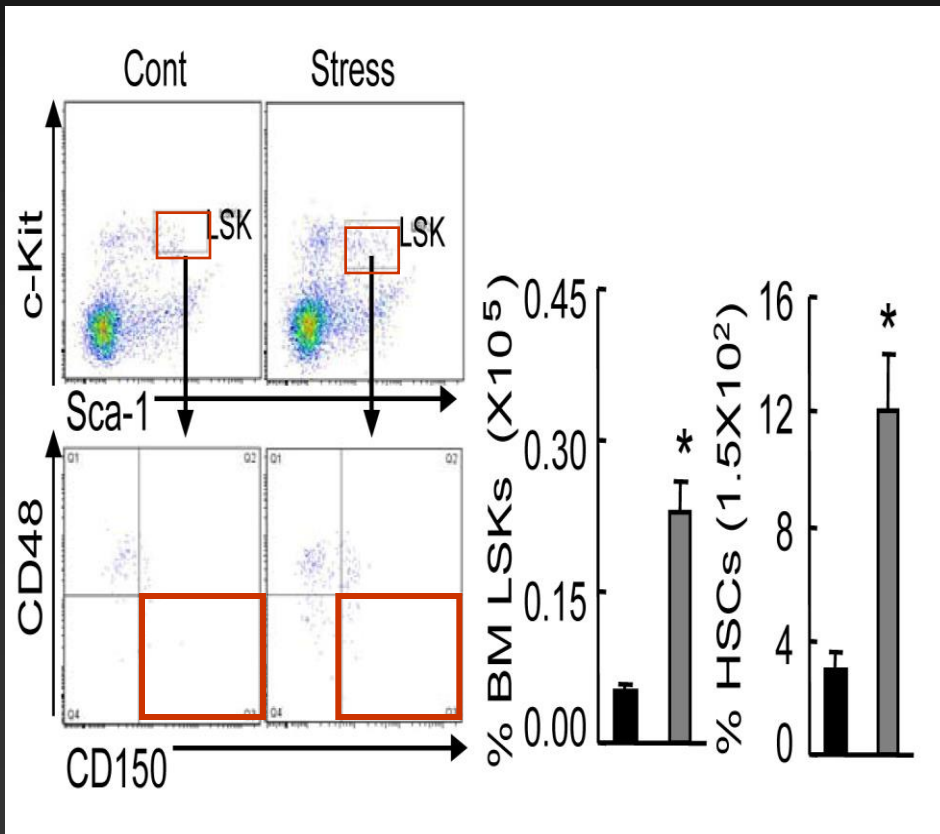
Stress decrease blood and tissue DPP4 levels



Chronic stress increased $\text{lin}^- \text{c-Kit}^{\text{high}} \text{sca-1}^{\text{high}} \text{CD48}^- / \text{CD150}^+$ HSC proliferation

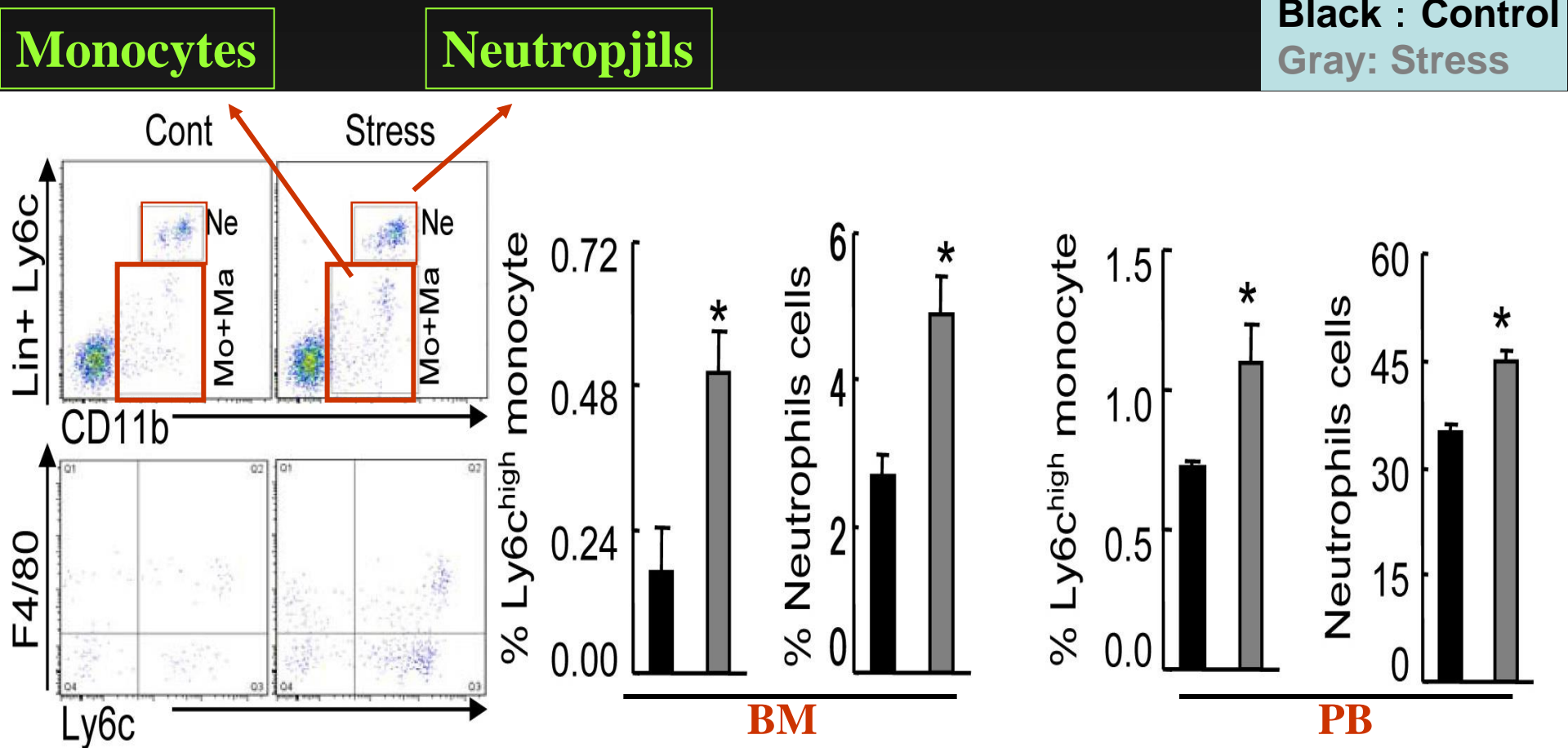
LSK: $\text{lineage}^- \text{c-Kit}^+ \text{sca-1}^+$

Black : Control
Gray: Stress



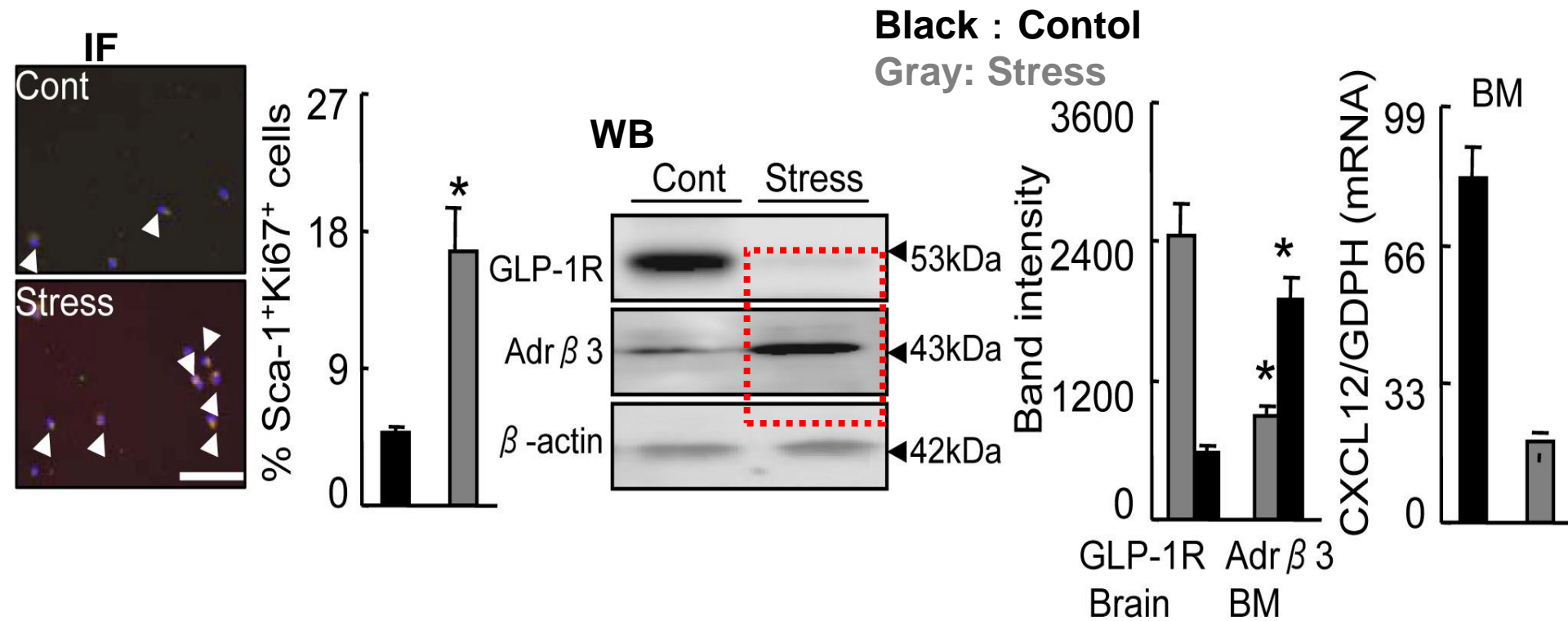
Cell cycle assay: FACSS
Propidium iodide (Invitrogen)

Chronic stress increased BM and PB neutrophils and Ly6c^{high} monocytes



BM: Bone-marrow
PB: Peripheral blood

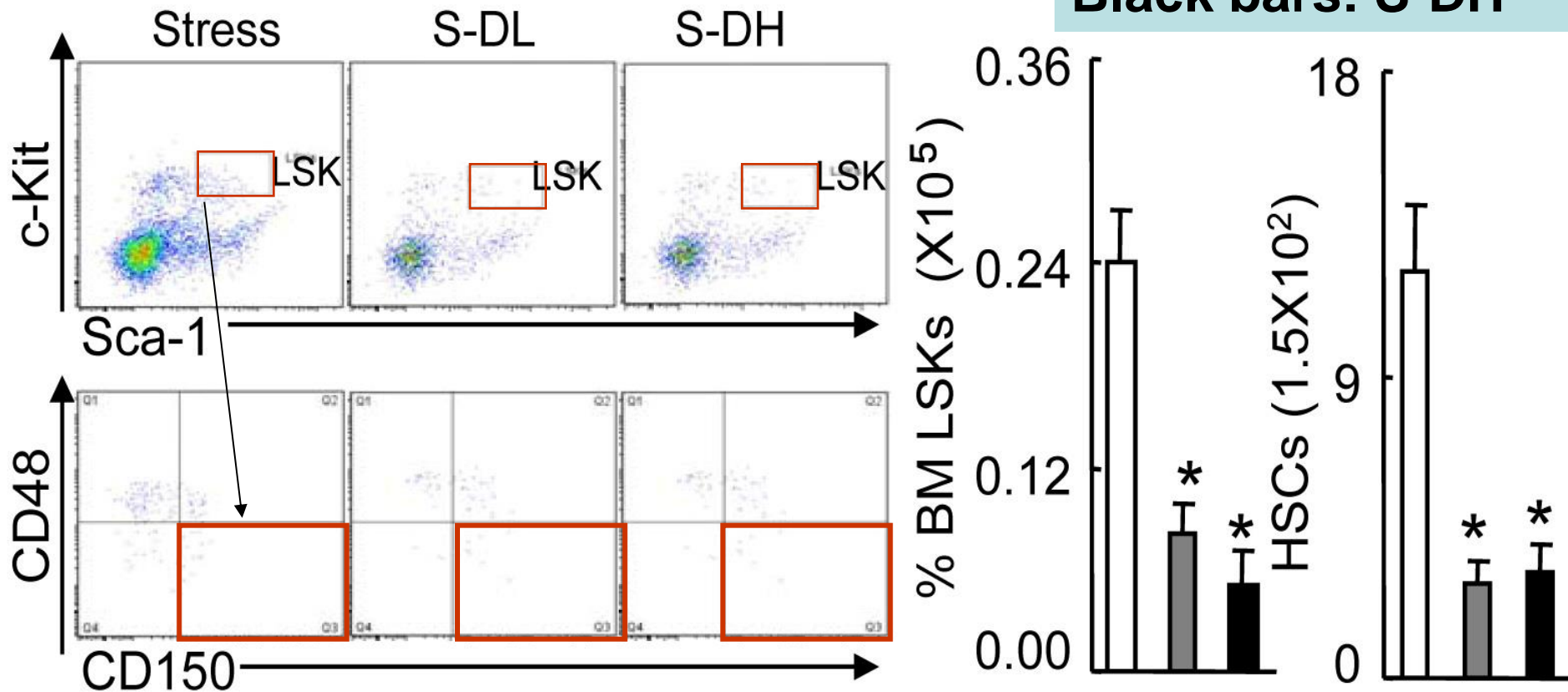
Chronic stress affects proliferation and targeted protein expression BM c-Kit⁺ cells



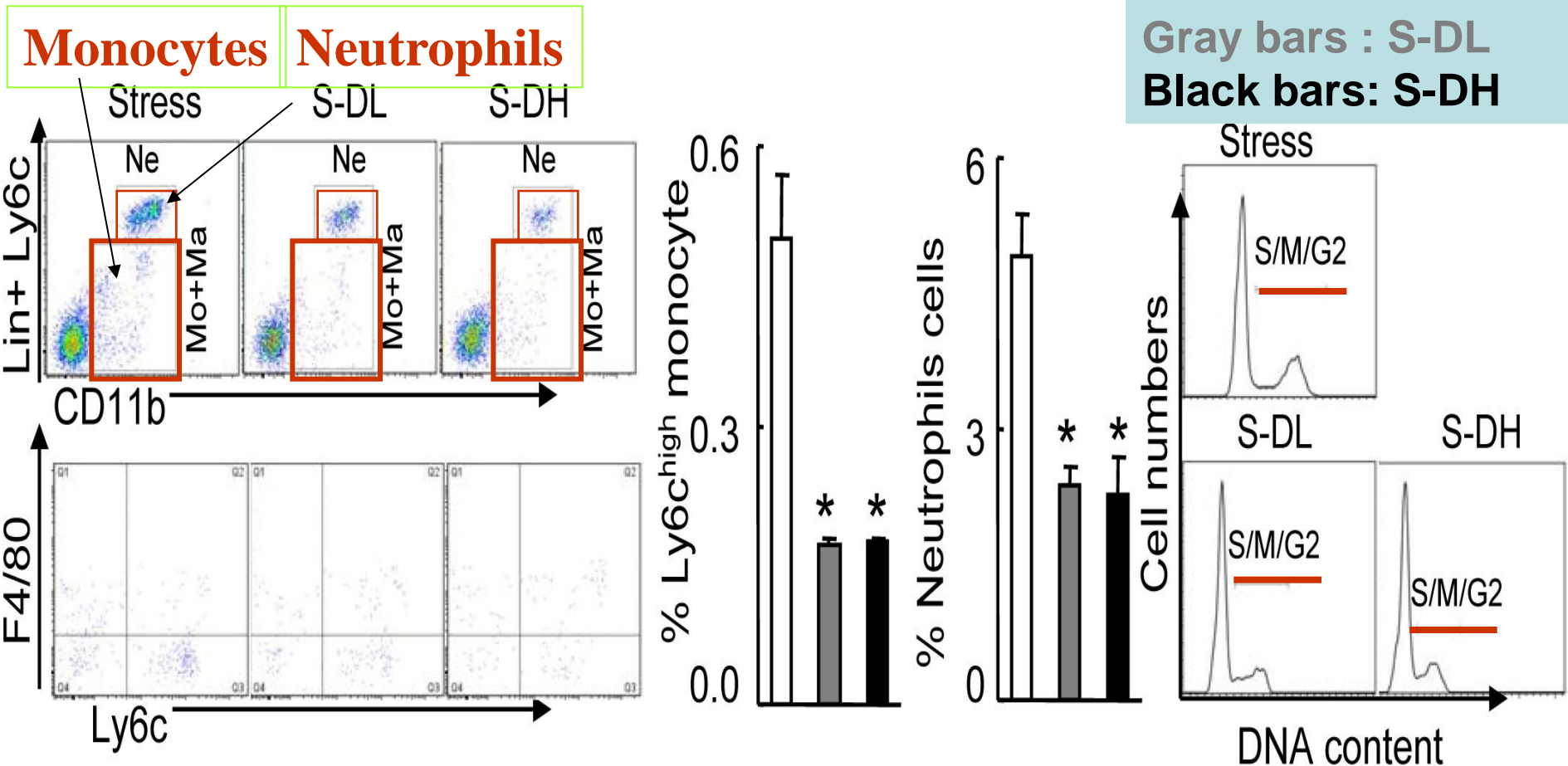
DPP4 inhibitor mitigates BM $\text{lin}^- \text{c-Kit}^{\text{high}} \text{sca-1}^{\text{high}} \text{CD48}^- / \text{CD150}^+$ HSC proliferation

LSK: lineage- $\text{c-Kit}^+ \text{sca-1}^+$

White bars: control
Gray bars : S-DL
Black bars: S-DH

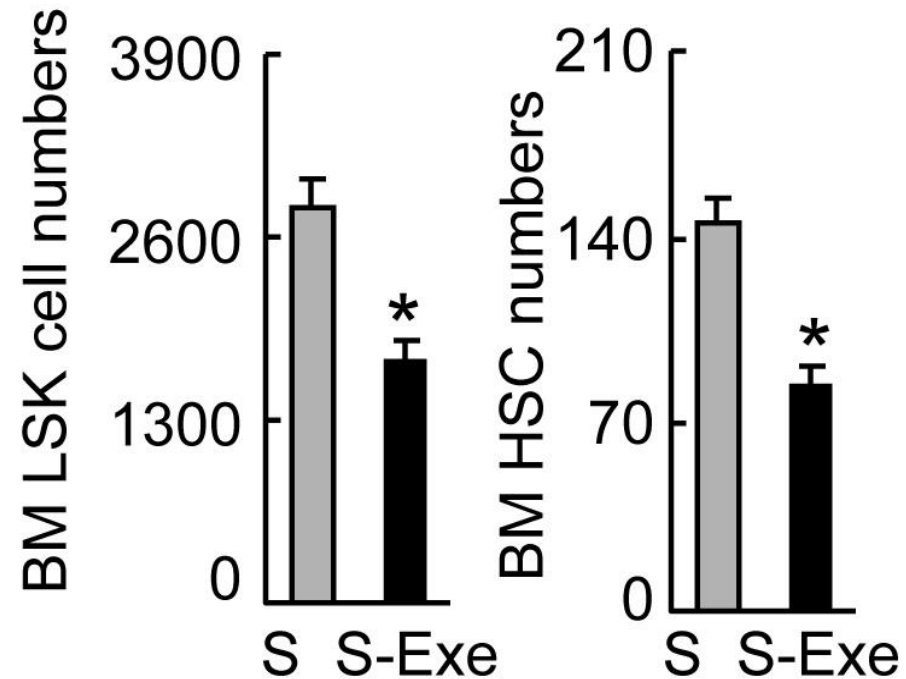
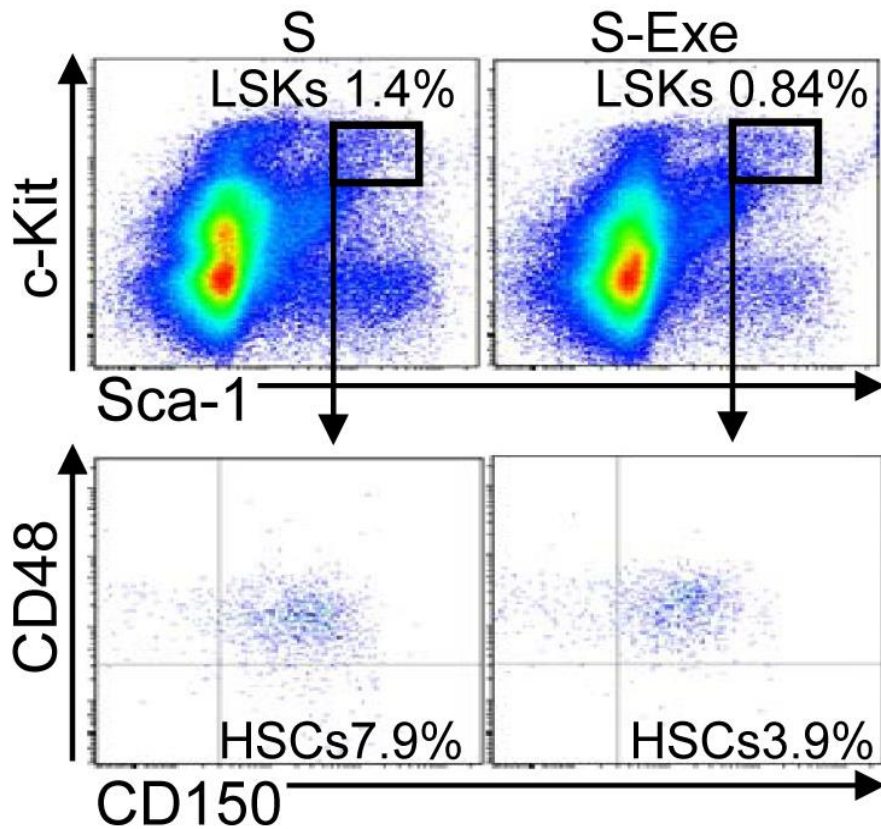


DPP4 inhibition ameliorated BM neutrophils and Ly6c^{high} monocytes productions

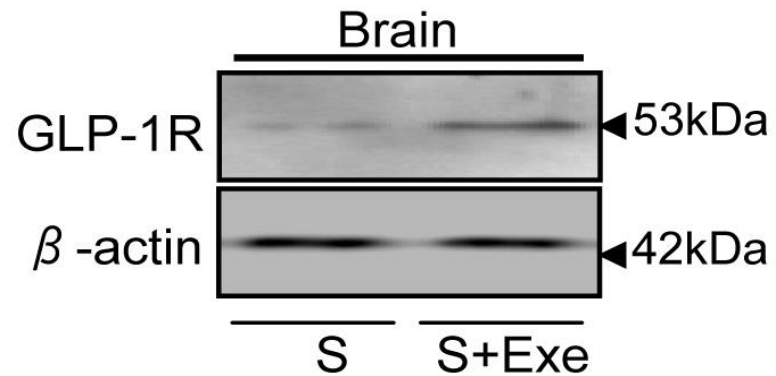
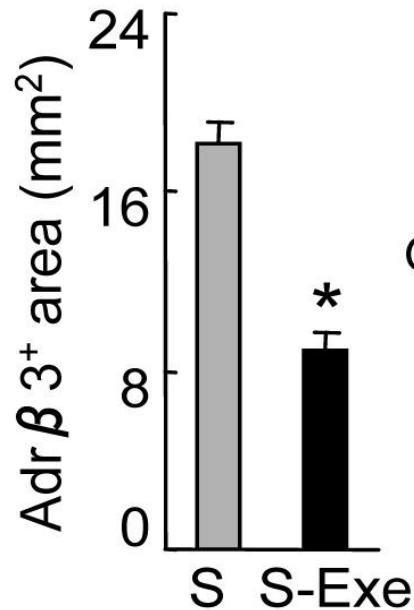
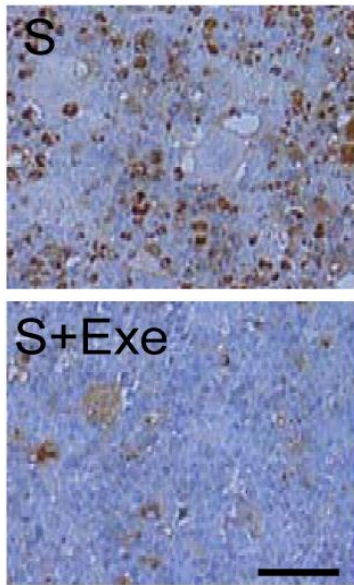


Cell cycle assay: FACS
 Propidium iodide (Invitrogen)

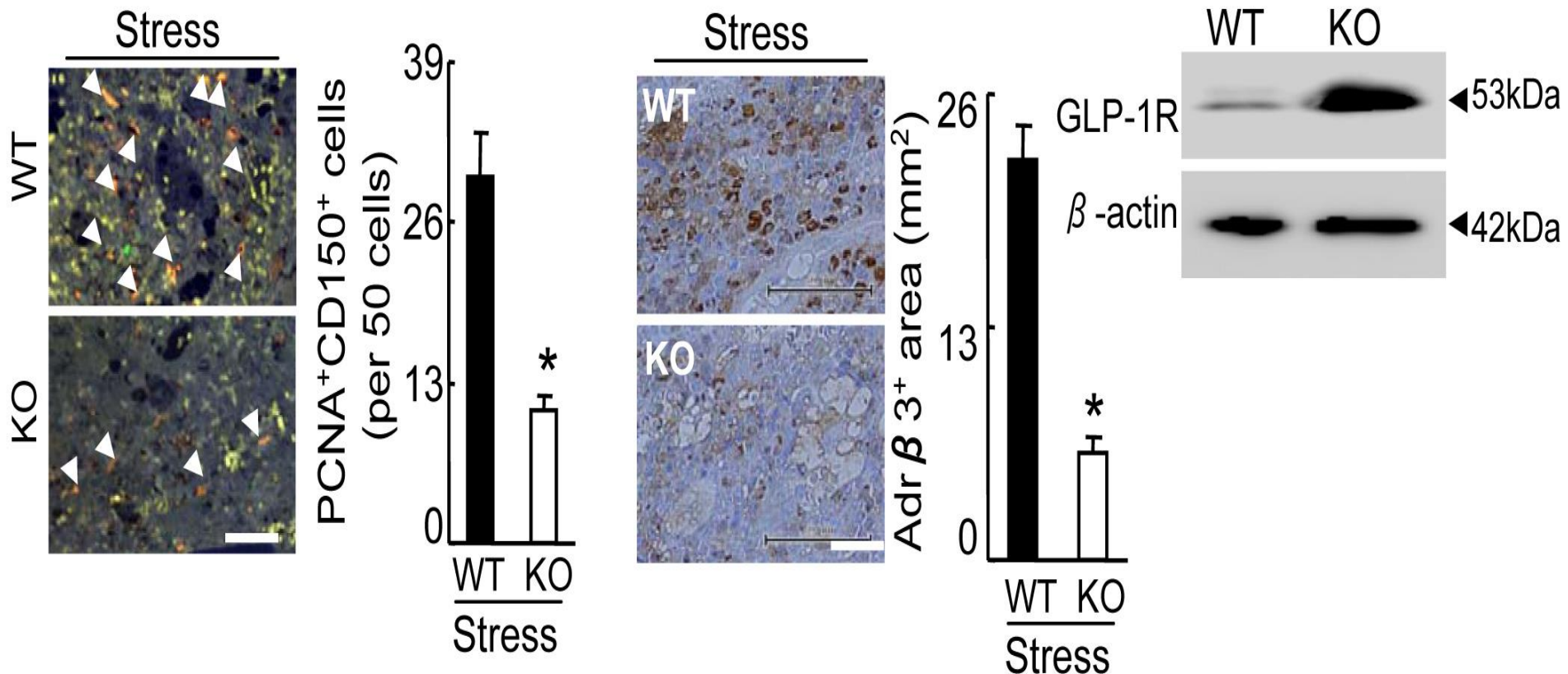
Exenatide mitigates BM $\text{lin}^- \text{c-Kit}^{\text{high}} \text{sca-1}^{\text{high}} \text{CD48}^- / \text{CD150}^+$ HSC proliferation



Exenatide mitigates Adr β 3 and GLP-1R protein expressions in BM lin-c-Kit^{high}

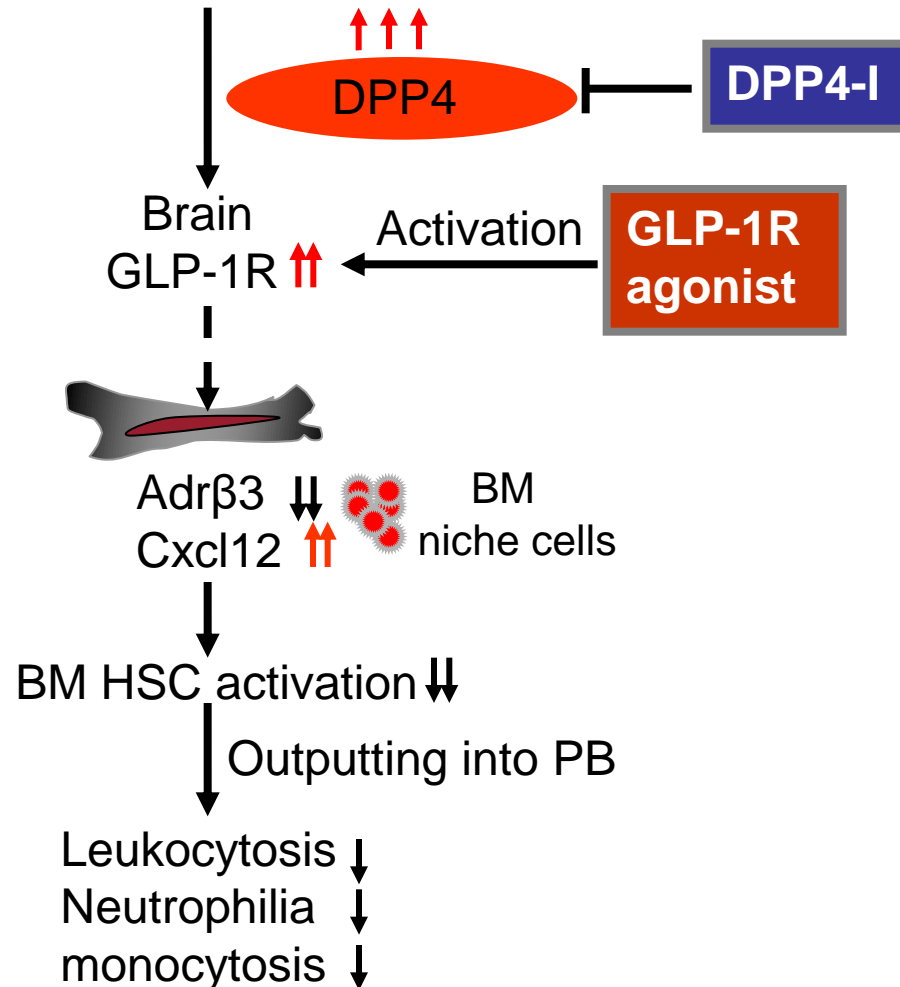


DPP4KO inhibits BM proliferating CD150⁺ cells and Adr β R3 and GLP-1R protein expression



Proposed mechanism of how DPP4 inhibition and GLP-1R activation prevent HSC activation and leukocytosis in response to chronic stress

Chronic Stress



Conclusions

This study demonstrated that DPP4 inhibition appears to improve BM HSC activation in response to chronic stress via $Ad\beta 3/Cxcl12$ -dependent mechanism that is mediated GLP-1/GLP-1R axis, suggesting a novel therapeutic strategy for the management of stress-related cardiovascular disease.

