Ischemic Stroke Activates Hematopoietic Bone Marrow Stem Cells

Gabriel Courties*, Fanny Herisson*, Hendrik B. Sager, Timo Heidt, Yuxiang Ye, Ying Wei, Yuan Sun, Nicolas Severe, Partha Dutta, Jennifer Scharff, David T. Scadden, Ralph Weissleder, Filip K. Swirski, Michael A. Moskowitz, Matthias Nahrendorf

From the Center for Systems Biology, Massachusetts General Hospital and Harvard Medical School, Boston (G.C., H.B.S., T.H., Y.Y., Y.S., P.D., J.S., R.W., F.K.S., M.N.); Stroke and Neurovascular Regulation Laboratory, Departments of Radiology and Neurology, Massachusetts General Hospital/Harvard Medical School, Charlestown (F.H., Y.W., M.A.M.); Center for Regenerative Medicine, Massachusetts General Hospital, Boston (N.S., D.T.S.); and Department of Systems Biology, Harvard Medical School, Boston, MA (R.W.).

Circulation Research. 2015;116:407-417

Background - what is known

- Stroke is the main complication of cerebral atherosclerosis leading to ischemic injury of the brain
- Microglia - the main resident immune cells of the central nervous system - proliferate and undergo inflammatory activation
- Ischemic stroke leads to blood monocytosis and neutrophilia
- Myeloid cells are recruited to the brain where they may contribute to the brain's recovery but also to reperfusion injury
- Increased levels of circulating cells may reflect demargination from tissue vascular beds or increased production

Gabriel Courties et al. Circulation Research. 2015;116:407-417

Question

How does stroke enhance the turnover of hematopoietic stem cells (HSC) to specifically generate myeloid cells ?

Gabriel Courties et al. Circulation Research. 2015;116:407-417

Experimental design

Experiments were undertaken using an established mouse stroke model, in which the middle cerebral artery is transiently occluded (tMCAO) to examine

- the source of increased innate immune cell numbers in the circulation and in the ischemic brain and
- the signals that regulate leukocyte supply after stroke

Gabriel Courties et al. Circulation Research. 2015;116:407-417

Hypothesis

Bone marrow (BM) hematopoietic stem cells (HSC), a source of neutrophils and monocytes in the steady state, increase their activity after transient middle cerebral artery occlusion (tMCAO) in mice.

Gabriel Courties et al. Circulation Research. 2015;116:407-417

Ankersmit Laboratory

for Diagnosis & Regeneration in Thoracic Diseases & Applied Immunology

MEDIZINISCHE UNIVERSITÄT WIEN

Stroke increases BM progenitor activity

Enhanced proliferation of myeloid progenitors

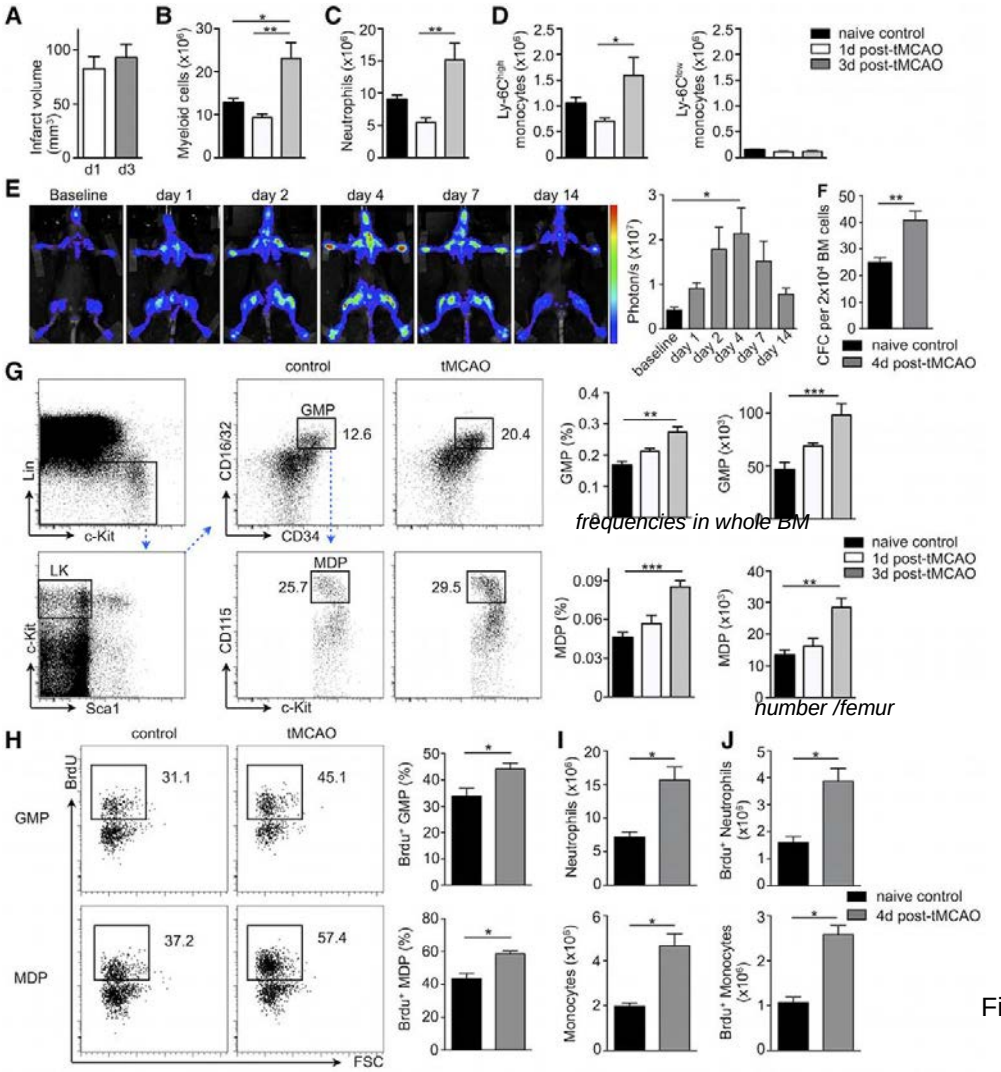


Figure 1

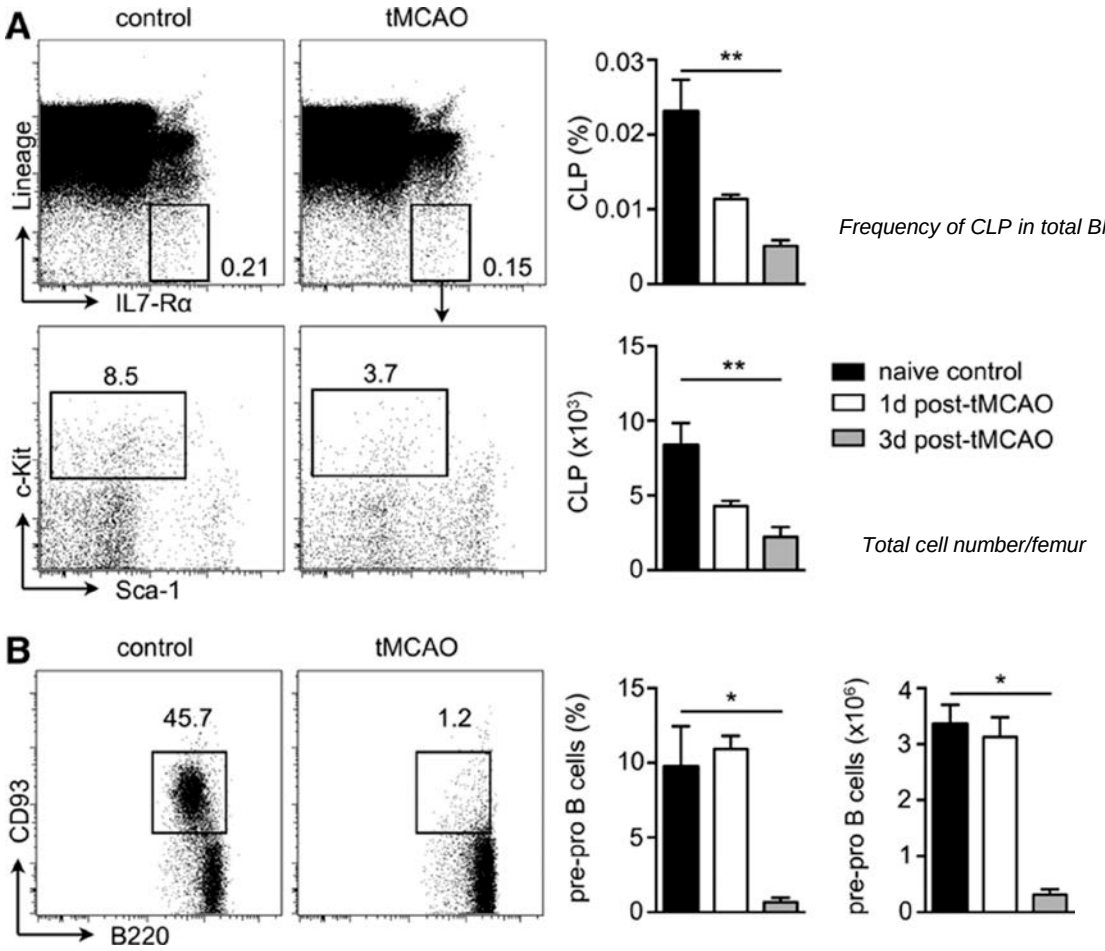
Gabriel Courties et al. Circulation Research. 2015;116:407-417

Ankersmit Laboratory

for Diagnosis & Regeneration in Thoracic Diseases & Applied Immunology

MEDIZINISCHE UNIVERSITÄT WIEN

Stroke decreases activity of Lin⁻ IL7Rα ⁺ c-Kit^{int} Sca-1^{int} lymphoid progenitors in the BM



Significant decrease of early immature B cells (Lin⁻ B220^{int} CD93⁺) in the BM of tMCAO mice

Figure 2

Gabriel Courties et al. Circulation Research. 2015;116:407-417

BM Lin⁻ c-Kit+ Sca-1+ (LKS) cells exhibit a myeloid bias after stroke

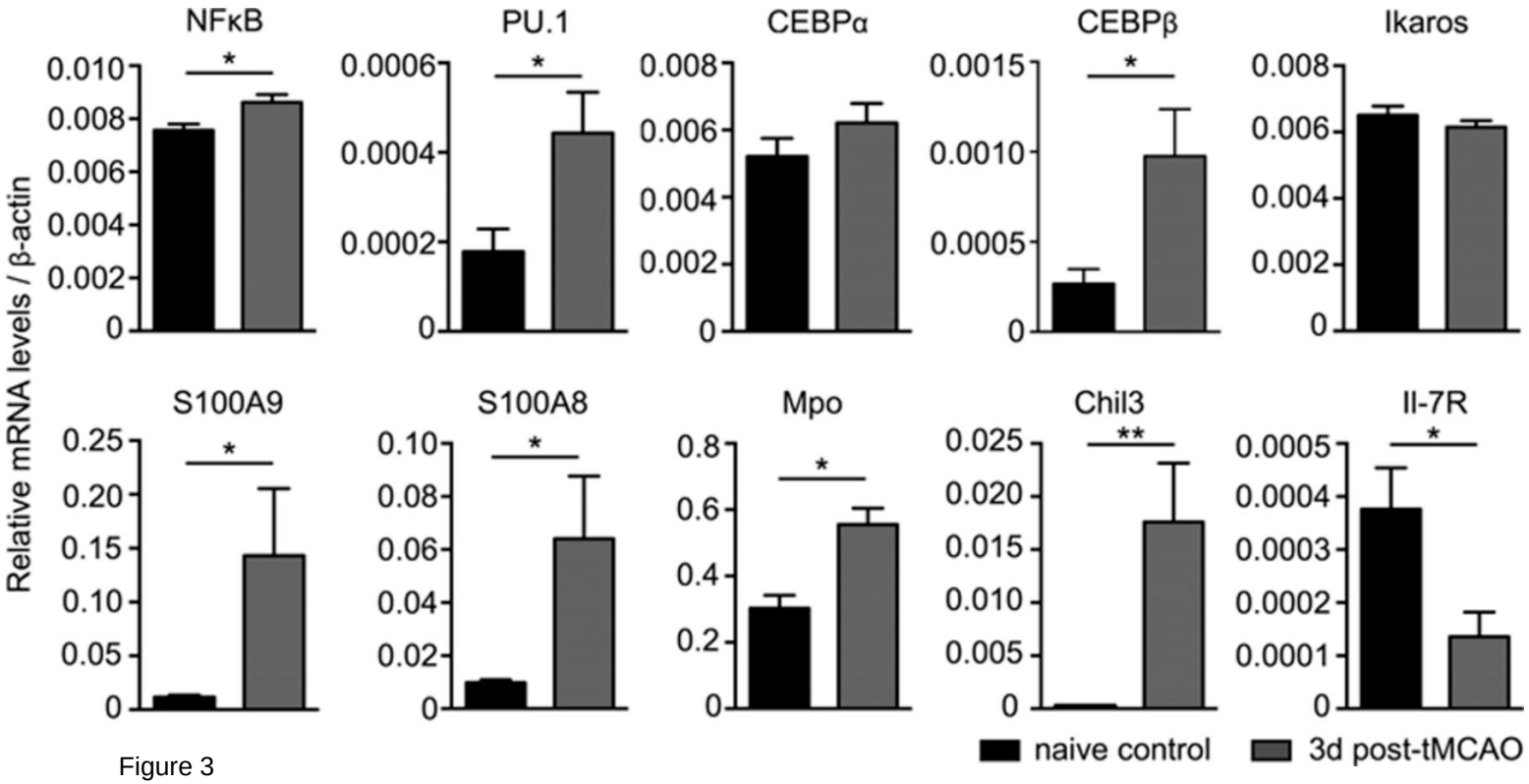


Figure 3

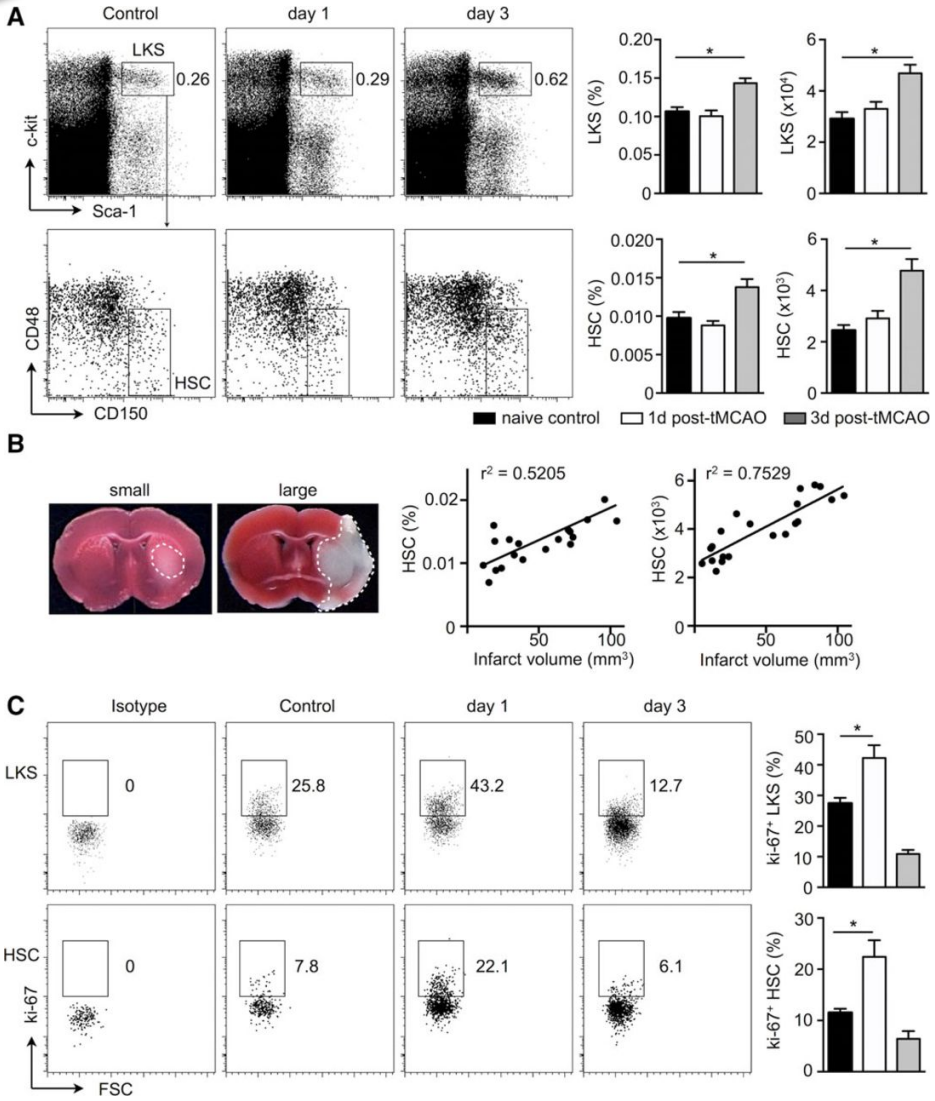
Gabriel Courties et al. Circulation Research. 2015;116:407-417

Ankersmit Laboratory

for Diagnosis & Regeneration in Thoracic Diseases & Applied Immunology

MEDIZINISCHE UNIVERSITÄT WIEN

The BM response after stroke occurs at the most upstream hematopoietic stem cell level ……

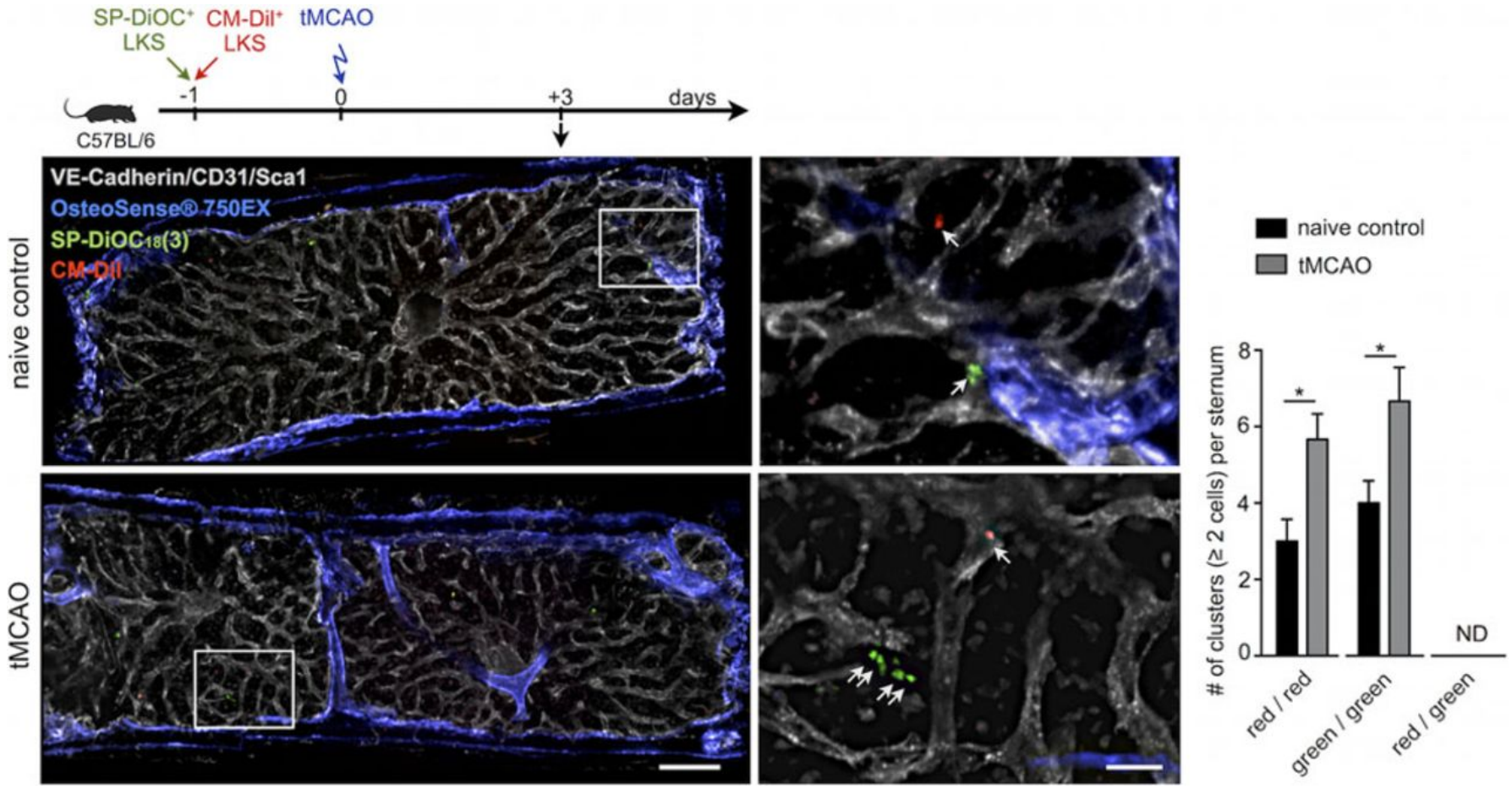


…..and correlates with injury size

Figure 4

Gabriel Courties et al. Circulation Research. 2015;116:407-417

Confocal imaging of Lin− c-Kit+ Sca-1+ (LKS) progenitor expansion in the BM of mice with stroke



Gabriel Courties et al. Circulation Research. 2015;116:407-417

Figure 5

Ankersmit Laboratory

for Diagnosis & Regeneration in Thoracic Diseases & Applied Immunology

MEDIZINISCHE UNIVERSITÄT WIEN

Serial intravital microscopy reports increased hematopoietic stem cells (HSC) expansion in the BM of mice with stroke

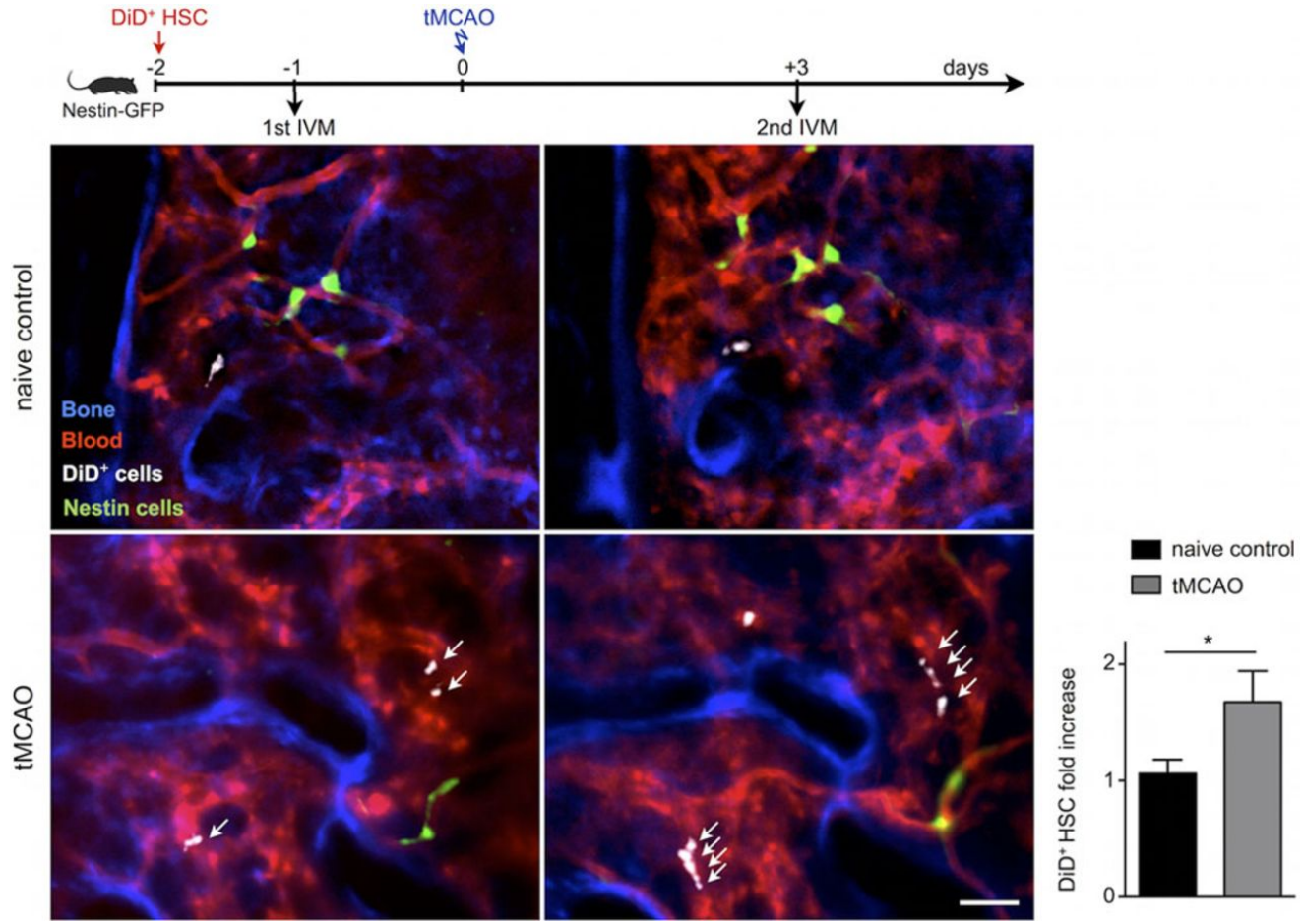


Figure 6

Gabriel Courties et al. Circulation Research. 2015;116:407-417

Stroke increases the sympathetic nervous activity in the BM

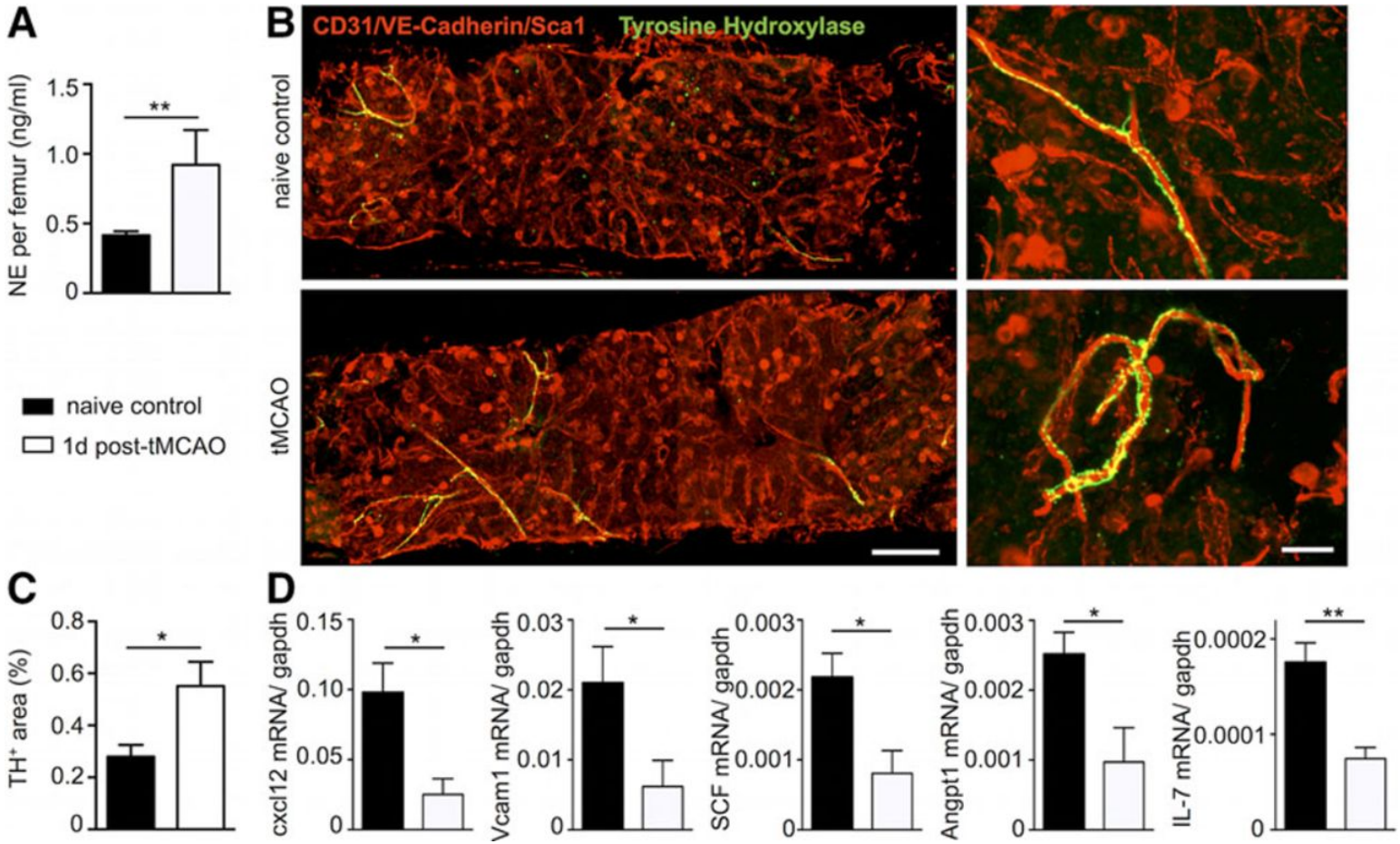


Figure 7

Gabriel Courties et al. Circulation Research. 2015;116:407-417

Ankersmit Laboratory

for Diagnosis & Regeneration in Thoracic Diseases & Applied Immunology

MEDIZINISCHE UNIVERSITÄT WIEN

Adrenergic signaling regulates hematopoietic stem cell activation after stroke via the β3 adrenergic receptor

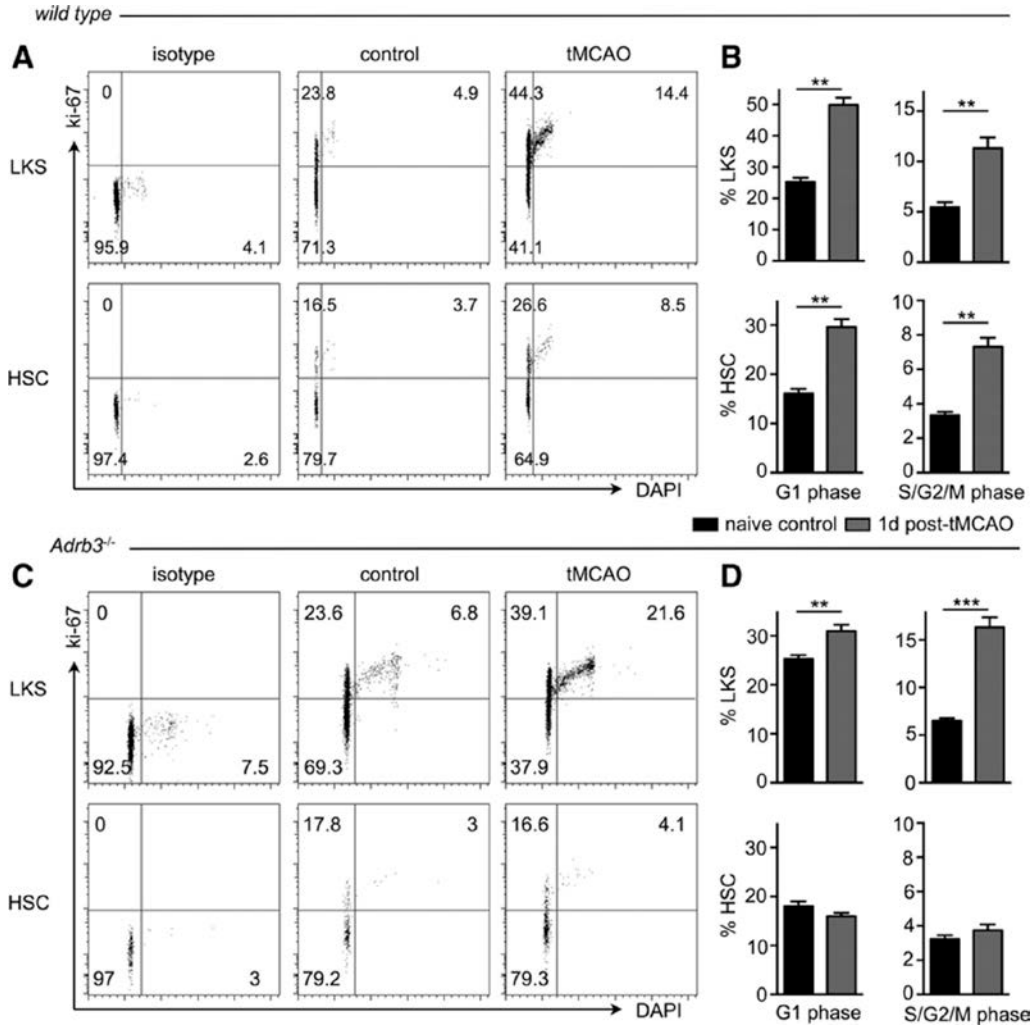


Figure 8

Gabriel Courties et al. Circulation Research. 2015;116:407-417

Conclusion

- After ischemic stroke the BM provides increased numbers of monocytes and neutrophils through increase myelopoiesis, whereas lymphoid progenitors are less active
- Indirect sympathetic signaling to the BM niche cells leads to the activation of most upstream hematopoietic stem cells
- Stroke increases BM noradrenaline levels that alter the hematopoietic niche by signaling through β3 adrenergic receptors

Gabriel Courties et al. Circulation Research. 2015;116:407-417

Comments

- Compelling concept that adrenergic signaling controls the BM
- Prior to the current report, the same group showed that
  - this mechanism causes monocytosis during myocardial infarction and chronic stress and
  - that BM-derived monocytes infiltrate the atherosclerotic wall, aggravate local and systemic inflammation, and eventually enhance the probability of subsequent myocardial infarction

  → evidence for the existence of a psycho-cellular *vicious circle*, in which pain, anxiety, stress are potent drivers of BM-derived monocytosis and HSC release with a myeloid bias
- Elegant *in vitro* and *in vivo* imaging approaches directly visualize the inside of the BM niche – context-dependent methods add complexity
- Inflammation is associated with increased GCSF levels which enhance the turnover of hematopoietic cells in the BM – the interaction of GCSF and adrenergic signaling in this model would be interesting