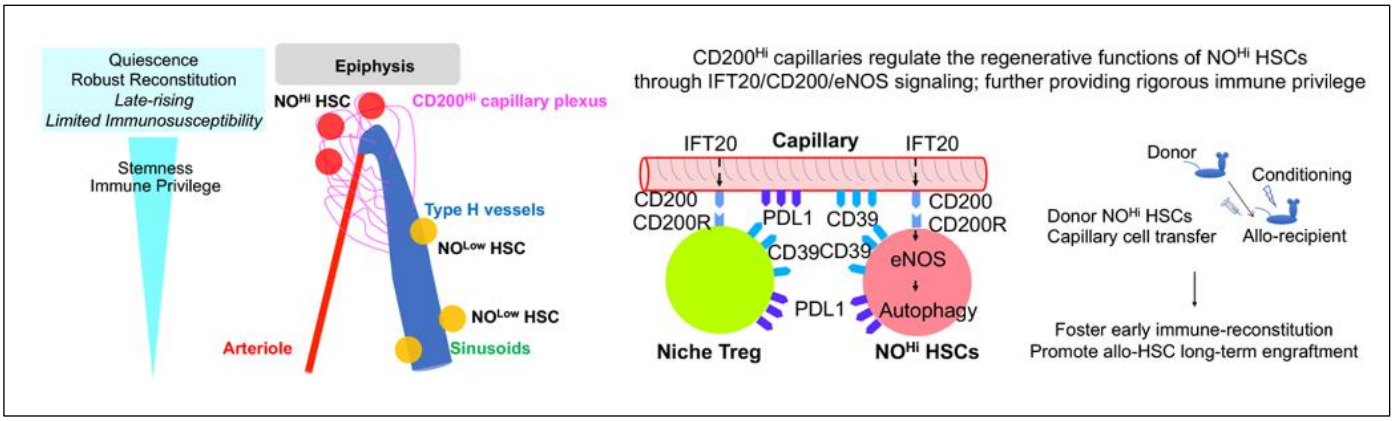
News Release

Bone marrow niches orchestrate stem cell hierarchy and immune tolerance



Key Points

- NO^{Hi} haematopoietic stem cells (NO^{Hi}HSCs), which are less susceptible to immune attack, are 'dormant' in a steady state and show robust long-term regenerative potential upon transplantation.
- NO^{Hi}HSCs reside in a capillary plexus characterized by positive primary cilia, which are shear stress sensors, and high levels of the immune checkpoint molecule CD200. This vascular plexus is predominantly in the epiphyseal space.
- CD200-high expressing capillaries maintain the high stemness of NO^{Hi}HSCs through primary ciliated protein IFT20/CD200/eNOS/autophagy signaling, which further induces immune protection.

Summary

Stem cells reside in specialized microenvironments, termed niches, at several different locations within tissues. The differential functions of heterogeneous stem cells and niches are important given increasing clinical applications of stem cell transplantation and immunotherapy. It remains unknown whether hierarchical structures amongst stem cells at distinct niches exist, and further control aspects of immune tolerance.

This study was performed in collaboration with Kazuhiro Furuhashi, Lecturer, Shoichi Maruyama, Professor, Department of Nephrology, Nagoya University Graduate School of Medicine, Miwako Kakiuchi, Postdoctoral Fellow, Columbia University, Ryosuke Ueda, Postdoctoral Fellow, Harvard Medical School, Simon C. Robson, Professor, Harvard Medical School and Joshi Fujisaki, Associate Professor, Harvard Medical School. Here, we propose novel hierarchical

arrangements within hematopoietic stem cells (HSCs) and bone marrow (BM) niches, that dictate both regenerative potential and immune privilege. High level nitric oxide-generating (NOHi) HSCs are refractory to immune attack and exhibit “delayed” albeit robust long-term reconstitution. Such highly immune privileged, primitive NOHi HSCs colocalize with distinctive capillaries, characterized by primary ciliated endothelium and high levels of the immune checkpoint molecule CD200. These capillaries regulate the regenerative functions of NOHi HSCs through ciliary protein IFT20/CD200/eNOS/autophagy signals, further mediating immune protection. Our studies suggest the niche may orchestrate hierarchy in stem cells and immune tolerance, delineating future immunotherapeutic targets.

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Research Background

Heterogeneity within somatic stem cells may be linked to their respective niches. Different sites within the brain, gastrointestinal tract, liver, lung, and BM, have been reported to serve as niches. Earlier reports suggested HSC colocalization with endosteum osteoblasts, while more recent studies have demonstrated HSCs at central marrow sinusoids. Still, others have suggested that HSCs co-localize with BM arterioles or metaphyseal Type H vessels. It remains largely unclear whether such discrepancies are, at least in part, explained by possible hierarchical structures within stem cells, and can be further linked to any differential immunological properties.

The testis, placenta, and hair follicles act as immunological sanctuaries, termed immune-privileged sites; where multiple mechanisms inhibit or prevent immune responses to stem cells. Such protective mechanisms enable tolerance and the long-term persistence of transplanted allogeneic (allo-) or xenogeneic grafts without exogenous immunosuppression.

While it has remained unclear whether somatic stem cells are broadly immunosuppressive, our recent studies indicate HSCs possess immune privilege. BM HSCs co-localize with unique $FoxP3^{+}$ regulatory T cells (Tregs) characterized by high levels of an HSC marker, CD150. These niche Tregs enable allo-HSC persistence in non-conditioned, immunocompetent mice.

Whether immune privilege is dictated by the heterogeneous nature of HSCs or any particular niche sites remains unknown. Here, we have tested whether immune privilege helps define hierarchical structures within previously described HSCs, and further characterizes these niches. We identify highly immune-privileged and highly potent HSCs, amongst other stem cells, and characterize highly immunoprotective niches within the BM.

Research Results

We observed that allogeneic HSCs exhibit a unique distribution pattern in the bone marrow. Although differentiated cells are rejected, allogeneic HSCs survived in the bone marrow without exogenous immunosuppression. Specialized capillaries forming sharp hairpin-curved structures were localized at this location. Such structures may induce shear stress and increase nitric oxide (NO) levels. Prior studies using global eNOS knockout suggested NO regulates hematopoiesis. Yet, it is unclear whether NO defines hierarchy within HSCs and niches or controls immune privilege. We hypothesized NO defines and regulates highly immune-privileged, potent HSCs associated with the specialized vascular niche and tested this proposition. We identified unique, high-level NO-expressing (NO^{Hi}) HSCs, comprising 10–15% of BM $CD150^{+}CD48^{-}Lin^{-}Sca1^{+}cKit^{+}$ HSCs. NO^{Hi} HSCs expressed high levels of immunomodulatory molecules, CD200 receptor (CD200R). Importantly, NO^{Hi} HSCs were more frequently quiescent. The ability of NO^{Hi}HSCs as stem cells was then demonstrated by bone marrow transplantation, where NO^{Hi}HSCs were shown to have high stem cell capacity as they efficiently reconstitute haematopoietic cells, and are also quiescent, regenerative stem cells that show proliferation over time or finally in a second transplant. NO^{Hi}HSC express CD200R, whose ligand CD200 is strongly expressed in the epiphyseal region. Furthermore, NO^{Hi}HSC are in CD200- strongly expressing vascular plexus. The CD200-strongly expressing vessels also express primary cilia, which are shear stress sensors. Therefore, we demonstrated whether CD200-high expressing capillaries regulate the regenerative function of NO^{Hi}HSCs through primary ciliary protein IFT20/CD200/eNOS signalling and further induce immune defence, using mice lacking vascular endothelium-specific CD200 or primary cilia.

In summary, this work identifies highly immune-privileged, late-rising primitive HSCs; and characterizes highly immunoprotective capillary niches. We demonstrate evidence for the innovative IFT20/CD200/eNOS/autophagy axis

in HSCs. These studies highlight the functionality of NO^{Hi} HSCs and $CD200^{Hi}$ capillaries in mediating immune privilege and facilitating allo-HSC transplantation. These stem-immunology studies provide fundamental insights into stem cell hierarchy, niches, and immune tolerance for stem cells. Novel hierarchical arrangements within HSCs and their niches are described that dictate both regenerative potential and immune privilege.

Research Summary and Future Perspective

We found that blood flow-generated shear stress regulates the expression of immunoregulatory molecules in the stem cell niche and maintains the regenerative capacity and quiescence of the stem cells. As stem cells are present in various tissues, the regulation of vascular and perivascular cells can be developed from the regulation of tissue stem cells to tissue regeneration. Furthermore, the presence of similar cancer stem cells in cancer tissue, surrounded by blood vessels, could be applied to new cancer therapies that radically cure cancer from its upstream cells. In addition, the enhancement of immunomodulatory molecules in vessels with high shear stress is involved in local inflammation control and homeostasis, so this concept can be applied to the development of new immunosuppressive and inflammation-controlling treatments.

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Author Names and Affiliations:

Kazuhiro Furuhashi [2, 3, 10, 11], Miwako Kakiuchi [2, 3], Ryosuke Ueda [1, 2, 3], Hiroko Oda [1], Simone Ummarino [4, 5, 6, 7], Alexander K. Ebralidze [4, 5, 6, 7], Mahmoud A. Bassal [5, 7, 8], Chen Meng [1, 9], Tatsuyuki Sato [1], Jing Lyu [1, 9], Min-guk Han [1], Shoichi Maruyama [10], Yu Watanabe [10], Yuriko Sawa [10], Daisuke Kato [12], Hiroaki Wake [12], Boris Reizis [13], John A. Frangos [14], David M. Owens [15, 16], Daniel G. Tenen [4, 5, 6, 7, 8], Ionita C. Ghiran [1], Simon C. Robson [1], Joji Fujisaki [*1, 2, 3, 17, 18]

[1] Center for Inflammation Research, Department of Anesthesia, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA

[2] Columbia Center for Translational Immunology, Department of Medicine, Columbia University, Vagelos College of Physicians and Surgeons, New York, USA

[3] Columbia Stem Cell Initiatives, Columbia University, Vagelos College of Physicians and Surgeons, New York, USA
[4] Harvard Medical School Initiative for RNA Medicine, Harvard Medical School, Boston, USA
[5] Harvard Stem Cell Institute, Harvard Medical School, Boston, USA
[6] Cancer Research Institute, Beth Israel Deaconess Medical Center, Boston, 330 Brookline Avenue Boston, USA
[7] Division of Hematology and Oncology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, USA
[8] Cancer Science Institute of Singapore, National University of Singapore, Singapore
[9] Department of Anesthesiology, Taihe Hospital, Hubei University of Medicine, Shiyan, Hubei, China
[10] Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, JAPAN
[11] Nagoya University Institute for Advanced Research, Nagoya, Aichi, JAPAN
[12] Department of Anatomy and Molecular Cell Biology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, JAPAN
[13] Translational Immunology Center, Department of Pathology, New York University, NY, USA
[14] La Jolla Bioengineering Institute, La Jolla, USA
[15] Department of Dermatology, Columbia University Irving Medical Center, Vagelos College of Physicians & Surgeons, New York, USA
[16] Department of Pathology & Cell Biology, Columbia University Irving Medical Center, Vagelos College of Physicians & Surgeons, New York, USA
[17] Division of Clinical Immunology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA

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