Editorial: The Role of Hematopoietic Progenitors in Immune Regulation and Memory

Flora Zavala1*, César Nombela-Arrieta2, Moufida Ben Nasr3,4 and Paolo Fiorina3,4,5

1 Université de Paris, INSERM U1151, CNRS UMR8253, Institut Necker Enfants Malades, Paris, France, 2 Department of Medical Oncology and Hematology, University of Zurich and University Hospital Zurich, Zurich, Switzerland, 3 International Center for Type 1 Diabetes, Pediatric Clinical Research Center Romeo ed Enrica Invernizzi, Department of Biomedical and Clinical Science, Università di Milano, Milan, Italy, 4 Nephrology Division, Boston Children’s Hospital, Harvard Medical School, Boston, MA, United States, 5 Division of Endocrinology, Territorial Healthcare Company Fatebenefratelli-Sacco, Milan, Italy

Keywords: hematopoietic progenitors, transplantation, immune memory, hematopoietic niche, stromal cells, trained immunity, autoimmunity, graft versus host disease (GVHD)

Editorial on the Research Topic

The Role of Hematopoietic Progenitors in Immune Regulation and Memory

Hematopoietic stem cells and progenitors (HSPCs) represent an indispensable reservoir for the continuous replenishment of all immune and blood cells. HSPCs mostly reside within the bone marrow (BM) microenvironment in close interaction with a variety of stromal cell types that provide a regulatory infrastructure that controls quiescence or multilineage differentiation through the provision of instructive signals. The first part of this Research Topic focuses on the intricate nature of the cellular crosstalk between HSPCs and their niche, specifically, i) the functional and spatial complexity of hematopoietic niches, ii) the effects of infectious and inflammatory signals on the integrity of niches and hematopoiesis. The second set of articles explores the evidence suggesting that stimulation of HSPCs by various inflammatory or infectious signals can promote/enhance their trafficking and interaction with mature immune cells in peripheral tissues (1, 2), where they exert either an immune-enhancing effect or, conversely, an immunoregulatory effect on initiating or ongoing immune responses. Finally, several research papers characterize selective hematopoietic progenitor subsets with immunoregulatory properties in vitro as well as in experimental models of infection, autoimmune and alloimmune responses.

The complexity and overlapping roles of the hematopoietic and immune cell niches are reviewed in detail by Miao et al. The authors cast a special focus on the CXCR4/CXCL12 axis as a core pathway controlling quiescence and access of HSPCs to their niches and highlight the key functional roles of CXCL12-producing mesenchymal stromal cells (MSCs), in the replenishment of mature components of innate immunity in homeostasis as well as during stress. As the most prominent source of key cytokines instructing lineage specification, survival, and long-term maintenance of HSPCs, perturbations of their structural and functional integrity (3) underlie prototypical features of hematopoietic responses to infection and inflammation. As prime examples, the authors analyze the disruptive effects that WHIM syndrome, a combined immunodeficiency disease caused by a genetic mutation in the chemokine receptor gene CXCR4, myeloablative irradiation and leukemia, trigger in HSPC niches and the stromal infrastructure through the activation of a proinflammatory program. Such insults are known to cause defects in
hematopoietic cell development and recirculation, leading to immune deficiency and favoring malignant transformation.

In two related articles, Szévalyi et al. as well as Johnson et al., describe how infectious challenges or, conversely, antibiotic treatments affect hematopoiesis and the BM microenvironment. A number of recent exciting findings are highlighted in this context. Among them i) the emerging role of microbiota in fine-tuning hematopoiesis through the effects of circulating microbial molecules on BM resident hematopoietic and stromal cells ii) evidence suggesting the contribution of emergency granulopoiesis to anti-tumoral immunity (4), iii) the potential role of infection-mediated mobilization of HSCs from the BM through pathways involving downregulation of CXCL12 to the replenishment of empty niches in distal bones, iv) the detrimental effects of infections of stromal cells, such as the observed depletion of osteoblasts during sepsis, which leads to inefficient lymphopoiesis because of insufficient IL-7 production. Of major interest is the discussion on breakthroughs in our understanding on how microbial-dependent inflammation educates HSCs, induces a bias towards the myeloid lineages, and leads to the generation of monocytes and macrophages, presenting a primed state of hyper-responsiveness that enhances their innate immune function upon subsequent challenge. This type of unspecific, innate memory, termed trained immunity, is imprinted at the epigenetic and metabolic level in HSPCs, and has attracted major attention in recent times (5–7). Conversely, these reviews also describe studies showing how immunoregulatory properties are instructed by a variety of innate signals and pharmacological agents on specific HSPC subsets. This phenomenon could be fundamentally exploited for the control of immune responses by resetting an aberrant autoreactive immune system to a de novo self-tolerant immune system (8, 9).

Pastore et al. review the defects in HSC characterizing the murine model of spontaneous type 1 diabetes in the Non-Obese Diabetic (NOD) mouse, in which high CXCL12 BM levels alter the trafficking of HSCs and Tregs and favor T1D onset. The mixed-chimerism induced by HSC infusions resulted in autoreactive thymic T-cell deletion and delayed T1D onset. Moreover, infusions of ex vivo genetically engineered HSPCs, for instance, to express proinsulin or transgenically target MHC class II, successfully prevented T1D onset in NOD mice by reshaping the immune reservoir and facilitating tolerance towards auto-antigens. They further review clinical trials of HSCT in new-onset T1D patients (9, 10) that infected insulin independence for 4-6 years after HSCT and particularly delineated a selective subgroup of patients with a different immune profile that may benefit the most from AHSTC. However, HSCT required myeloablation, which may limit its clinical application. The alternative infusion of pharmacologically modulated or genetically engineered HSPCs, avoiding myeloablation, is advocated (9, 11–14).

Finally, several papers describe selective immature progenitor subsets endowed with immunoregulatory properties.

Marinascu et al. describe a BM subset contaminating MSCs at initial culture passages that exhibits a phenotype of anti-inflammatory macrophages and inhibits T-cell proliferation in vitro, but, unlike BM MSCs, does not exert anti-tumoral effects in vivo.

Elahi et al. and Mashhouri et al. focus on CD71+ erythroid progenitors, a prominent source of Reactive Oxygen Species (ROS) production in both mice and humans, more abundant in female than in male, with immunosuppressive properties that compromise immune response against systemic *Listeria monocytogenes* infection in neonatal mice. Their data underline the tight regulation of the immune system in newborns/infants.

Korniotis et al. and D’Aveni et al. focus on G-CSF mobilized multipotent MPP3 progenitors that display the property to selectively promote the proliferation of TCR-activated Foxp3+ Tregs in vitro and in vivo. This underlines their capacity to reduce autoimmune encephalomyelitis (EAE), a murine model of multiple sclerosis. Additionally, sustained beneficial effects comprised prevention of the onset of T1D in NOD mice (15) and also a reduction of Graft-versus-Host Disease (GVHD), a deleterious complication of allogeneic HSC transplantation observed in patients with hematological malignancies. The human counterpart of this suppressive mobilized MPP subset is characterized.

Overall, the contributions in this Research Topic focus on the use of ex vivo conditioned HSPCs as a potentially safer therapy than AHSTC, minimizing/eliminating the toxic conditioning that infers unacceptable risks for autoimmune patients. HSPCs have successfully rendered patients suffering from autoimmune diseases, disease-free. In addition, they may as well reduce the severity of GVHD post allogeneic HSCT in patients with hematological malignancies.

**AUTHOR CONTRIBUTIONS**

All authors contributed equally to the redaction of the research focus. All authors have seen and agree with the final version.

**FUNDING**

FZ was supported by core funding from CNRS and INSERM and by grants received from Fondation pour la Recherche sur la Sclérose en Plaques (ARSEP) and from The Secular Society (TSS). CN-A is supported by Swiss National Science Foundation (310030_185171). PF was supported by the Italian Ministry of Health grant RF-2016-02362512.

**REFERENCES**

1. Massberg S, Schaerli P, Knezevic-Maramica I, Kollnberger M, Tubo N, Moseman EA, et al. Immunosurveillance by Hematopoietic Progenitor Cells Trafficking Through Blood, Lymph, and Peripheral Tissues. *Cell* (2007) 131:994–1008. doi: 10.1016/j.cell.2007.09.047

2. Murphy DM, Mills KHG, Basdeo SA. The Effects of Trained Innate Immunity on T Cell Responses; Clinical Implications and Knowledge Gaps for Future Research. *Front Immunol* (2021) 12:706583. doi: 10.3389/fimmu.2021.706583

3. Gomari A, Hellbing PM, Isringhausen S, Suessbier U, Becker A, Boss A, et al. Quantitative Spatial Analysis of Haematopoiesis-Regulating Stromal Cells in the Bone Marrow Microenvironment by 3D Microscopy. *Nat Commun* (2018) 9:2532. doi: 10.1038/s41467-018-04770-z
4. Kalafati L, Kourtzelis I, Schulte-Schrepping J, Li X, Hatzioannou A, Grinenko T, et al. Innate Immune Training of Granulopoiesis Promotes Anti-Tumor Activity. *Cell* (2020) 183:771–85.e12. doi: 10.1016/j.cell.2020.09.058
5. Mitroula I, Ruppova K, Wang B, Chen L-S, Geyrak M, Grinenko T, et al. Modulation of Myelopoiesis Progenitors is an Integral Component of Trained Immunity. *Cell* (2018) 172:147–61.e12. doi: 10.1016/j.cell.2017.11.034
6. Cirovic B, de Bree LCJ, Groh L, Blok BA, Chan J, van der Velden WJFM, et al. BCG Vaccination in Humans Elicits Trained Immunity via the Hematopoietic Progenitor Compartment. *Cell Host Microbe* (2020) 28:322–34.e5. doi: 10.1016/j.chom.2020.05.014
7. Netea MG, Dominguez-Andrés J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E, et al. Defining Trained Immunity and Its Role in Health and Disease. *Nat Rev Immunol* (2020) 20:375–88. doi: 10.1038/s41577-020-0285-6
8. Cunningham KT, Mills KHG. Trained Innate Immunity in Hematopoietic Stem Cell and Solid Organ Transplantation. *Transplantation* (2021) 105:1666–76. doi: 10.1097/TP.0000000000003673
9. Ben Nasr M, Bassi R, Usuelli V, Valderrama-Vasquez A, Tezza S, D’Addio F, et al. The Use of Hematopoietic Stem Cells in Autoimmune Diseases. *Regener Med* (2016) 11:395–405. doi: 10.2217/rme-2015-0057
10. D’Addio F, Valderrama Vasquez A, Ben Nasr M, Franek E, Zhu D, Li L, et al. Autologous Nonmyeloablative Hematopoietic Stem Cell Transplantation in New-Onset Type 1 Diabetes: A Multicenter Analysis. *Diabetes* (2014) 63:3041–6. doi: 10.2337/db14-0295
11. Ben Nasr M, D’Addio F, Malvandi AM, Faravelli S, Castillo-Leon E, Usuelli V, et al. Prostaglandin E2 Stimulates the Expansion of Regulatory Hematopoietic Stem and Progenitor Cells in Type 1 Diabetes. *Front Immunol* (2018) 9:1387. doi: 10.3389/fimmu.2018.01387
12. Ben Nasr M, Tezza S, D’Addio F, Marnelli C, Usuelli V, Maestroni A, et al. PD-L1 Genetic Overexpression or Pharmacological Restoration in Hematopoietic Stem and Progenitor Cells Reverses Autoimmune Diabetes. *Sci Transl Med* (2017) 9(416):eaam7543. doi: 10.1126/scitranslmed.aam7543
13. Montandon R, Korniotis S, Layseca-Espinosa E, Gras C, Mégret J, Ezine S, et al. Innate Pro-B-Cell Progenitors Protect Against Type 1 Diabetes by Regulating Autoimmune Effector T Cells. *Proc Natl Acad Sci USA* (2013) 110: E2199–208. doi: 10.1073/pnas.1222446110
14. Korniotis S, Gras C, Letscher H, Montandon R, Mégret J, Siegert S, et al. Treatment of Ongoing Autoimmune Encephalomyelitis With Activated B-Cell Progenitors Maturing Into Regulatory B Cells. *Nat Commun* (2016) 7:12134. doi: 10.1038/ncomms12134
15. Kared H, Adle-Biassette H, Fois E, Masson A, Bach J-F, Chatenoud L, et al. Jagged2-Expressing Hematopoietic Progenitors Promote Regulatory T Cell Expansion in the Periphery Through Notch Signaling. *Immunity* (2006) 25:823–34. doi: 10.1016/j.immuni.2006.09.008

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Zavala, Nombela-Arrieta, Ben Nasr and Fiorina. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.