967 Hematopoietic Stem Cell Function in β-Thalassemia Is Impaired and Is Rescued By Targeting the Bone Marrow Niche

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Hall B, Level 2 (Orange County Convention Center)

Annamaria Aprile, PhD[1], *Alessandro Gulino, PhD*[2*], *Isabella Villa, PhD*[3*], *Stefano Beretta, PhD*[4*], *Ivan Merelli, PhD*[5*], *Alessandro Rubinacci, MD*[3*], *Maurilio Ponzoni, MD*[6], *Sarah Marktel, MD*[7*], *Claudio Tripodo, MD*[8*], *Maria Rosa Lidonnici, PhD*[1*] *and Giuliana Ferrari, PhD*[9]

[1]*San Raffaele-Telethon Institute for Gene Therapy (SR-TIGET), IRCCS San Raffaele Scientific Institute, Milan, Italy*
[2]*Department of Health Science, Human Pathology Section, Tumor Immunology Unit, University of Palermo, Palermo, Italy*
[3]*Bone Metabolism Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy*
[4]*Institute For Biomedical Technologies, National Research Council, Segrate, Italy*
[5]*Institute for Biomedical Technologies, National Research Council and San Raffaele-Telethon Institute for Gene Therpay (SR-TIGET), IRCCS San Raffaele Scientific Institute, Milan, Italy*
[6]*Pathology Unit, IRCCS San Raffaele Scientific Institute and Università Vita-Salute San Raffaele, Milan, Italy*
[7]*Hematology and Bone Marrow Transplantation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy*
[8]*Department of Health Science, Human Pathology Section, Tumor Immunology Unit, University of Palermo, Palermo, Italy*
[9]*San Raffaele-Telethon Institute for Gene Therapy (SR-TIGET), IRCCS San Raffaele Scientific Institute and Università Vita-Salute San Raffaele, Milan, Italy*

Hematopoietic stem cells (HSC) are regulated by signals from the bone marrow (BM) niche and little is known about their fate in altered hematological conditions associated to non-malignant diseases. In β-thalassemia ineffective erythropoiesis and secondary alterations, as abnormal regulation of bone metabolism, iron overload and hormonal factors, induce changes in the BM homeostasis with a potential impact on HSC-niche interaction. We addressed these unexplored issues in the murine disease model and in patients' cells.

We investigated hematopoiesis in thalassemic $Hbb^{th3/+}$ (*th3*) mutant mice and we found lower frequency, reduced quiescence and reconstituting potential of HSC. *th3* HSC have impaired self-renewal, which is rescued upon transplantation in a normal BM, proving an active role of the niche microenvironment. Both stromal and hematopoietic components of the BM niche are altered in *th3* mice. Consistently with the common finding of osteoporosis in patients, we found reduced bone deposition with decreased levels of parathyroid hormone (PTH), which is a key regulator of bone metabolism but also of HSC activity. Low PTH negatively affects bone deposition and expression of the Notch-ligand Jag1 by *th3* mesenchymal and osteolineage cells, thus reducing the activation of Notch1 in HSC and consequently impairing their function. *In vivo* activation of PTH signaling through the reestablished Jag1-Notch1 pathway restores the functional pool of *th3* HSC by correcting HSC-niche crosstalk.

In addition to the stromal component of the BM, hematopoietic cells with a key role in regulating the fate of HSC, such as megakaryocytes (Mk), were found defective in maturation, possibly due to reduced circulating levels of thrombopoietin (TPO). We are currently investigating the molecular causes of dysmegakaryopoiesis and the Mk-HSC interaction in thalassemic mice.

Strikingly, reduced HSC quiescence was confirmed in samples from patients affected by β-thalassemia, along with impaired stromal niche and megakaryopoiesis, thus highlighting the clinical relevance of our findings. Further investigation will unravel the multiple molecular mechanisms that affect *in trans* HSC functions in the complexity of the stressed thalassemic BM microenvironment. Our results uncover a defect of HSC in β-thalassemia, induced by an altered BM niche and provide new relevant insight for improving transplantation and gene therapy approaches.