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POSTER ABSTRACTS

112.THALASSEMIA AND GLOBIN GENE REGULATION

FGF23 Inhibition Improves Hematopoietic Stem Cell Transplantation in β-Thalassemia

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Clinical evidence has established a link between anemias and skeletal abnormalities, although the underlying molecular mechanisms remain elusive. β-thalassemia (βThal) represents a valuable model for studying congenital anemia and associated bone and bone marrow (BM) microenvironment defects. Osteoporosis has a high morbidity in βThal patients, and we demonstrated that impaired hematopoietic stem cell (HSC) function is due to the prolonged persistence in an altered βThal BM niche (*Aprile et al, 2020*). The correction of the genetic cause of βThal, mutations in the β-globin gene, is achieved by transplantation of HSCs from healthy donors or autologous HSCs from patients upon gene therapy. In both scenarios, a comprehensive understanding of HSCs and the BM niche is crucial to obtain successful outcomes. Our research focused on the role of fibroblast growth factor 23 (FGF23), a phosphaturic hormone at the crossroads of bone and erythropoiesis. We demonstrated that the elevated erythropoietin characteristic of the disease, leads to increased FGF23 production in both the βThal mouse model (*th3*) and βThal patients, negatively affecting bone homeostasis and the interaction between HSCs and the stromal niche. Notably, *in vivo* FGF23 inhibition by cFGF23 peptide in *th3* mice fully rescued bone defects, BM niche and HSC function (*Aprile, Raggi et al, 2023*). To mimic the allogenic transplantation, we transplanted wt and *th3* cells in a competitive setting into untreated *th3* or *th3*+cFGF23 recipients. We observed partially enhanced engraftment in the cFGF23-treated mice indicating that FGF23 inhibition improves the supportive capacity of the damaged niche. We hypothesized that prolonged cFGF23 administration to recipient mice after transplantation could further restore the BM niche and boost the graft, thus achieving therapeutic outcomes.

To establish the proper dose regimen with withdrawal periods for prolonged cFGF23 treatment, we analyzed bone mineral density (BMD) and HSC cell cycle at 1 and 2 weeks after discontinuing cFGF23 administration. Our results showed that rescued BMD was sustained after the discontinuation of treatment for 1 and 2 weeks (*th3* vs. *th3*+cFGF23 _1wk vs. *th3*+cFGF23_2wks: 125.9±3.8 vs. 181±19.9 vs. 142±1.6 mg/cm ^{3}, $p<0.01$). Ongoing histomorphometric analysis will provide a better characterization of bone quality. Additionally, we observed the restoration of defective quiescence in *th3* HSCs after 1- and 2 weeks (*th3* vs. *th3*+cFGF23 _1wk vs. *th3*+cFGF23_2wks: 77.8±1,4 vs. 92.1±1.8 vs. 87.8±0.9 on Lin ^{neg} BM cells, $p<0.001$).

To test autologous transplantation upon gene therapy, we transduced *th3* Lin ^{neg} BM cells with a lentiviral vector carrying the β-globin gene (GLOBE LV) at MOI 5 resulted in a mean vector copy number of 1 and a transduction efficiency of 50%. We performed competitive transplantation using 1x10 ^{5} (CD45.1) transduced donor *th3* cells and 1x10 ^{5} (CD45.2) competitor mock-transduced *th3* cells into busulfan-conditioned (CD45.2) untreated *th3* or *th3*+cFGF23 recipient mice. The treated recipient mice received two doses of cFGF23 every 2 weeks as a maintenance regimen. We observed higher engraftment of transduced cells in the peripheral blood of cFGF23-treated mice at 8 weeks post-transplant (*th3* vs. *th3*+cFGF23: 4.9±1.1 vs. 10.7±1.9 % of CD45.1 engrafted cells, $p<0.05$). Comparative evaluation of hematological parameters and molecular analysis of transduced cells are ongoing.

Targeting FGF23 signaling provides a promising strategy to improve bone defects and HSC-niche alterations in βThal. Here, we show that the use of FGF23 inhibition in the transplantation setting in β-thalassemia results in superior engraftment of donor cells in treated recipients, indicating a potential application to ameliorate the clinical outcome.

Disclosures No relevant conflicts of interest to declare.

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