Targeting the EIF2AK1 Signaling Pathway Rescues Red Blood Cell Production in SF3B1 Mutant Myelodysplastic Syndromes With Ringed Sideroblasts

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**SF3B1<sup>MT</sup> MDS-RS at the Single Cell Level**

Ineffective erythropoiesis  
Ringed Sideroblasts  
SF3B1<sup>MT</sup>

We profiled the hematopoietic landscape of **SF3B1<sup>MT</sup> MDS-RS at the single-cell level**

**Lin<sup>-</sup>CD34<sup>+</sup> HSPCs:**
- Increased Ery/Mk differentiation
- Metabolic activation in SF3B1-mutant cells

**BM-MNCs:**

**SF3B1<sup>MT</sup> MNCs:**
- Increased Erythroblast at the Orthochromatic stage
**EIF2AK1 depletion overcomes $SF3B1^{MT}$-induced arrest in terminal erythroid differentiation**

Depletion of EIF2AK1 induces differentiation of ringed sideroblasts. EIF2AK1 as a new pharmacological target for patients with MDS-RS with $SF3B1$ mutations
Summary

BFU-E
CFU-E
Pro-E
Baso-E
Poly-E
Ortho-E

RS survival

Heme deficiency

Heme biosynthesis

Heme

SF3B1<sup>mt</sup>

Hemoglobin

Globin chains

Globin mRNA

Heme biosynthesis genes and mitochondrial iron transporters

Autophagy

ATF4

elF2α

elF2α

Differentiation

VF2AK1

active

inactive

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