

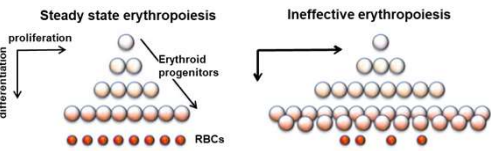
Targeting the EIF2AK1 Signaling Pathway Rescues Red Blood Cell Production in *SF3B1* Mutant Myelodysplastic Syndromes With Ringed Sideroblasts

Vera Adema, Feiyang Ma, Rashmi Kanagal-Shamanna, Natthakan Thongon, Guillermo Montalban-Bravo, Hui Yang, Scott A. Peslak, Feng Wang, Pamela Acha, Francesc Sole, Pamela Lockyer, Margherita Cassari, Jaroslaw P. Maciejewski, Valeria Visconte, Irene Gañán-Gómez, Yuanbin Song, Carlos Bueso-Ramos, Matteo Pellegrini, Tuyet M. Tan, Rafael Bejar, Jennifer S. Carew, Stephanie Halene, Valeria Santini, Gheath Al-Atrash, Karen Clise-Dwyer, Guillermo Garcia-Manero, Gerd A. Blobel, and **Simona Colla**

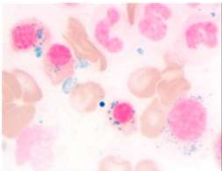
Leading Edge of Cancer Research Symposium
November 17-18, 2022

SF3B1^{MT} MDS-RS at the Single Cell Level

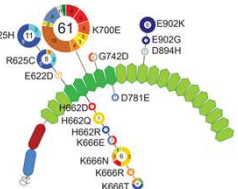
Ineffective erythropoiesis



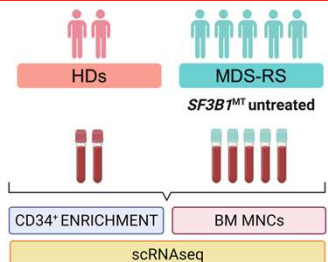
Ringed Sideroblasts



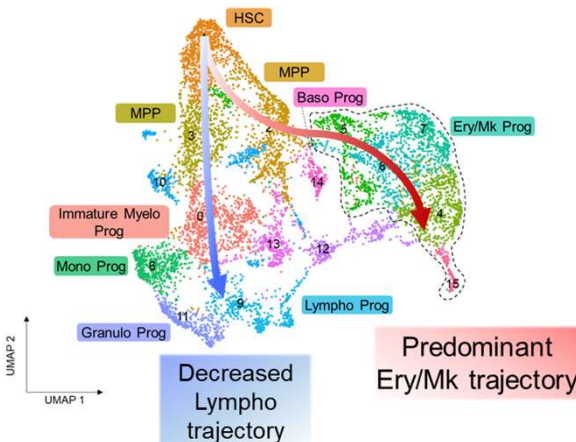
SF3B1^{MT}



We profiled the hematopoietic landscape of **SF3B1^{MT} MDS-RS** at the single-cell level



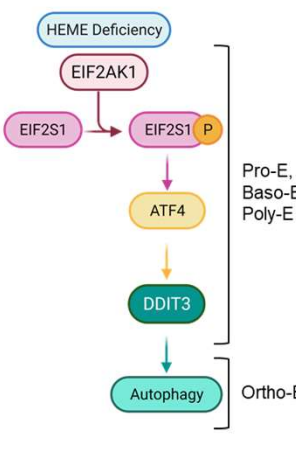
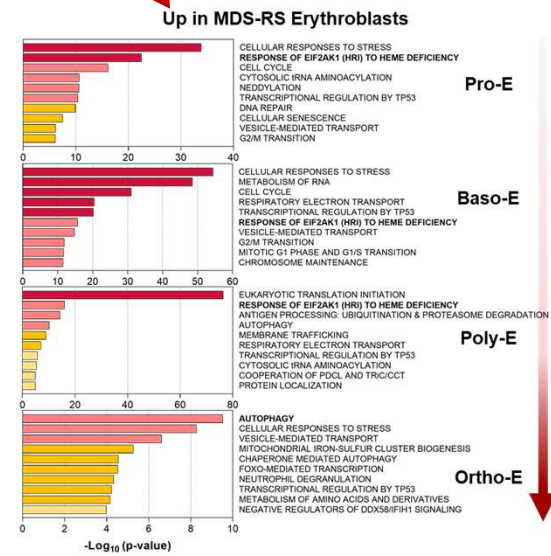
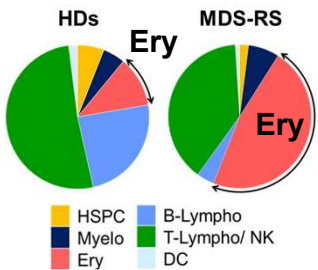
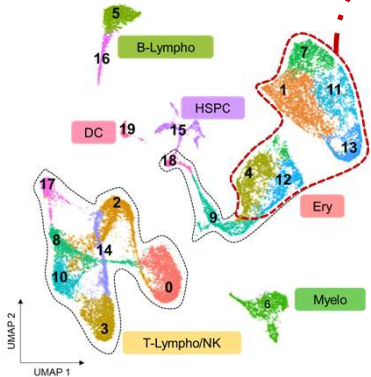
Lin-CD34⁺ HSPCs



SF3B1^{MT} Lin-CD34⁺ HSPCs:

- ✓ Increased Ery/Mk differentiation
- ✓ Metabolic activation in SF3B1-mutant cells

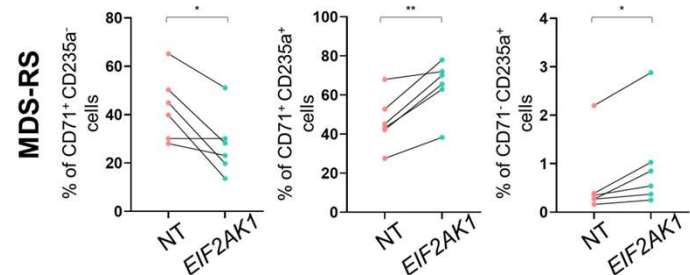
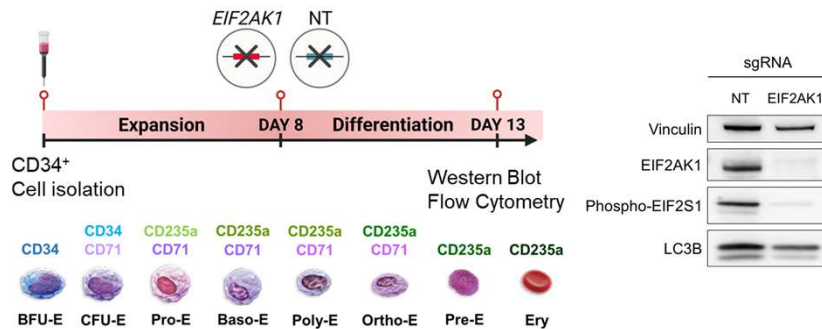
BM-MNCs



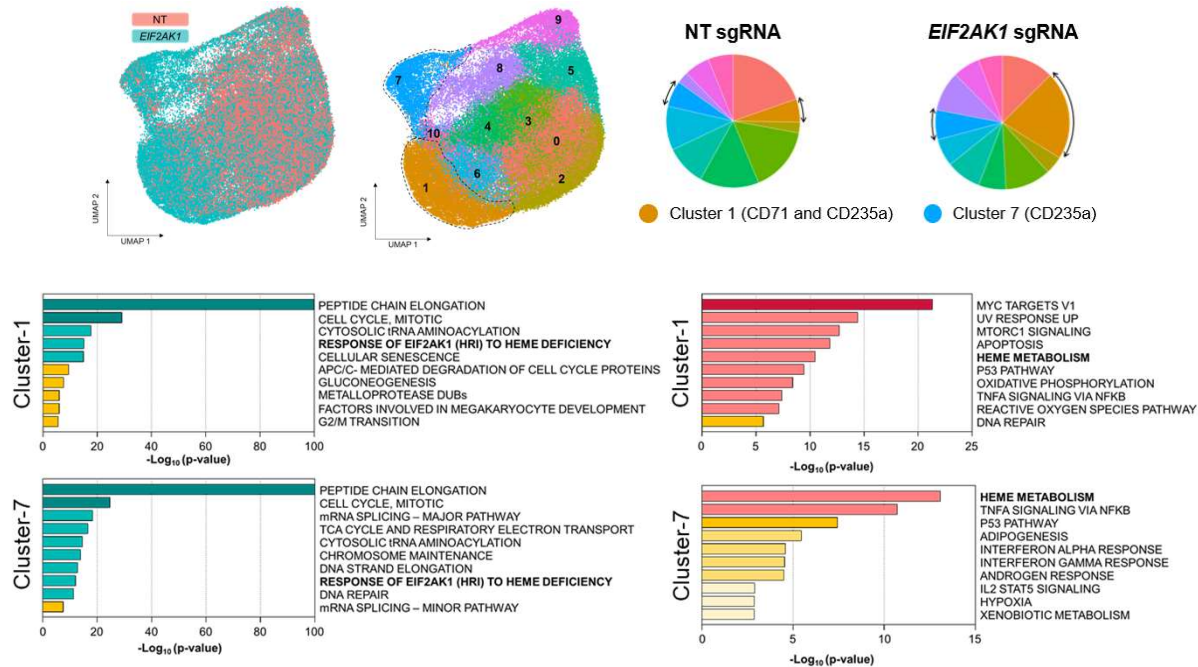
SF3B1^{MT} MNCs:

- ✓ Increased Erythroblast at the Orthochromatic stage

EIF2AK1 Depletion Overcomes SF3B1^{MT}- Induced Arrest in Terminal Erythroid Differentiation



Terminally differentiated cells



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

Summary

