Immune microenvironment dysfunctions enable malignification at the onset of MDS

Ganan-Gomez I, Ma F, Chien KS, Yang H, Montalban-Bravo G, Wildeman BE, Kumar B, Kim YJ, Daher M, Takahashi K, Garcia-Manero G and Colla S

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

Background

- Myelodysplastic syndromes (MDS): clonal stem cell malignancies
- Standard therapy not curative, transient responses, poor prognosis
- *Are prevention or early intervention possible in MDS?*
- **Clonal cytopenias of undetermined significance (CCUS): aging-related premalignant state**, low-grade clonal hematologic disorders at high risk of progression to MDS and leukemia
- HSC-intrinsic alterations and extrinsic inflammatory factors cooperate to induce abnormal differentiation in CCUS (Ganan-Gomez et al. *ASH Meeting* 2021).

Aim

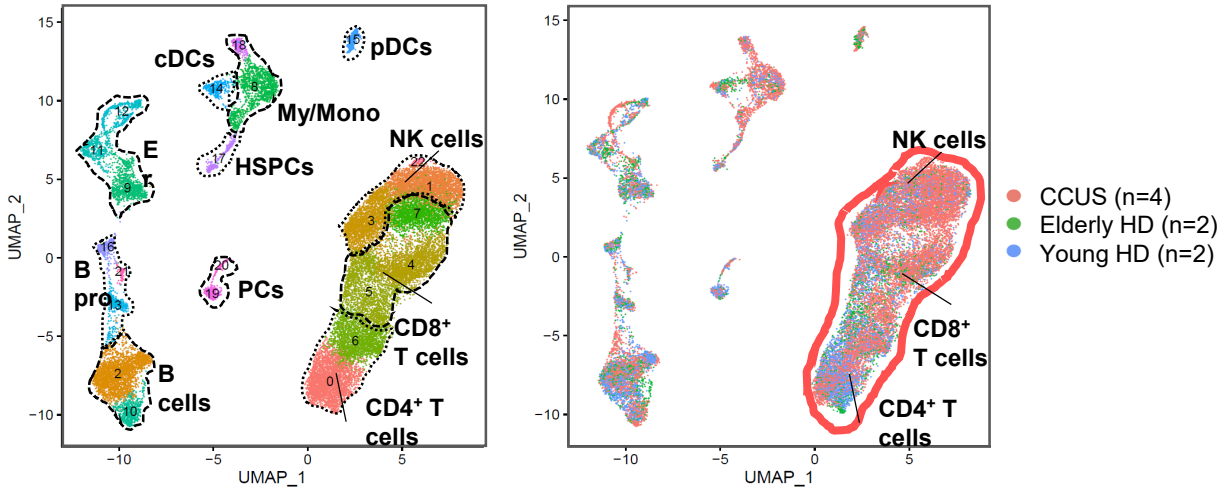
- Characterize early alterations in the bone marrow (BM) immune microenvironment that lead to the expansion of the MDS clone

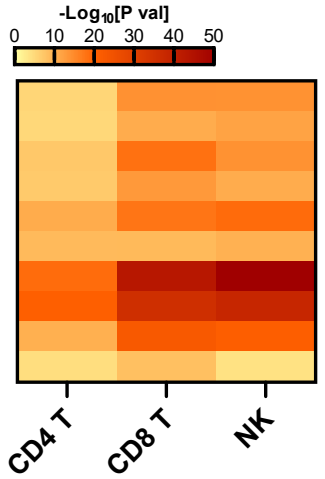
Methods

- BM mononuclear cells (MNCs) from patients with CCUS and young and elderly healthy donors (HDs)
- Single-cell transcriptomics (scRNA-seq)
- *In vitro* functional assays
- Single-cell genomics/antigen expression analysis (Tapestri)

1. BM Innate Immune Cells Are Activated in CCUS Patients

scRNA-seq in BM MNCs





Pathway analysis of significantly upregulated genes in CCUS

Formation of ATP by chemiosmotic coupling
Interferon alpha/beta signaling
Neutrophil degranulation
Mitochondrial translation initiation
Cytokine Signaling in Immune system
Membrane Trafficking
Eukaryotic Translation Elongation
Respiratory electron transport, ATP synthesis by chemiosmotic coupling
Adaptive Immune System
Parasite infection

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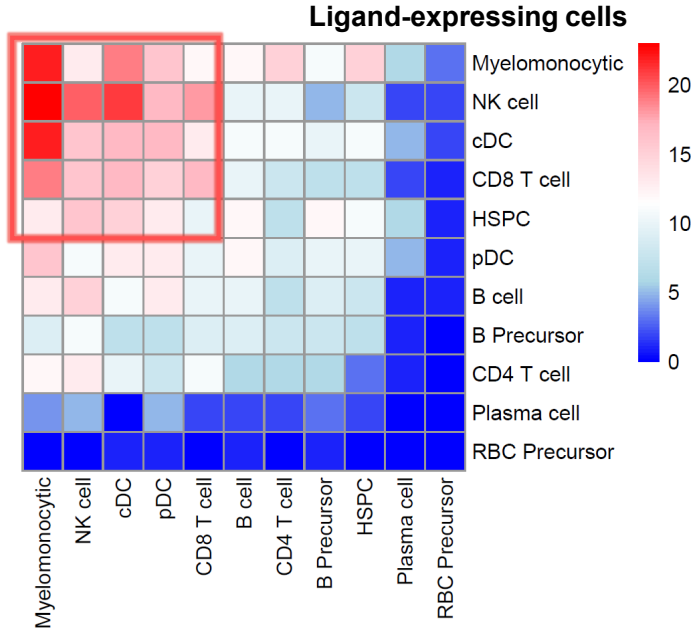
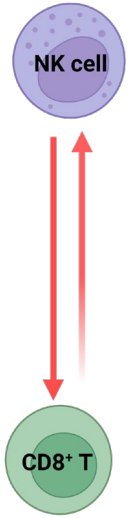
2. Inhibitory Crosstalk Predicted Between NK and CD8⁺ T Cells in CCUS

CellPhoneDB analysis of DEGs



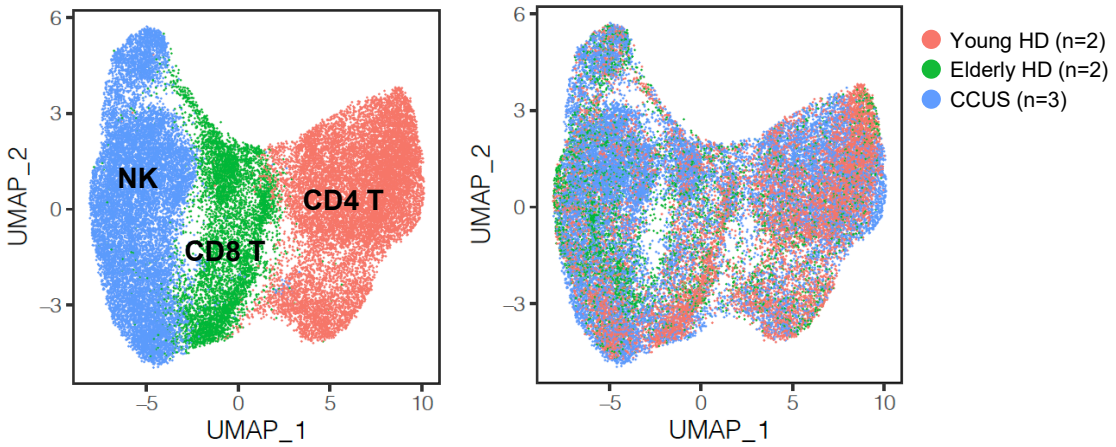
NK cell activation by CD8⁺ T cells
HLA-E:CD94/NKG2C
CD58:CD2
FASLG:TNFRSF1A



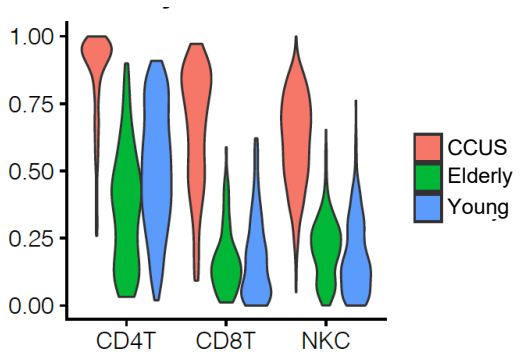
Immunosuppresion of CD8⁺ T cells by NK cells
CD48:CD244
TGFB1:TGFBR1

3. CCUS NK/T Cells Are Terminally Differentiated toward Exhaustion

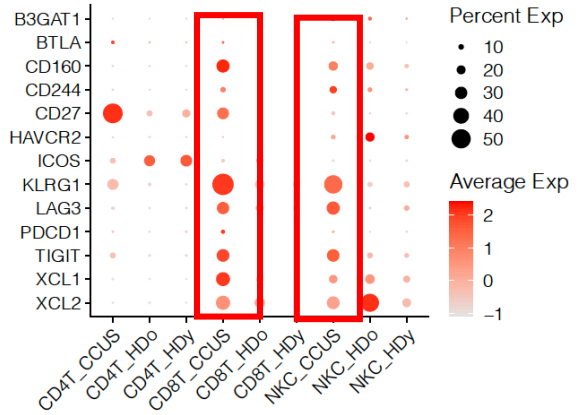
scRNA-seq in sorted CD3⁺ T and CD56⁺ NK cells



CytoTRACE differentiation scores



Exhaustion marker expression



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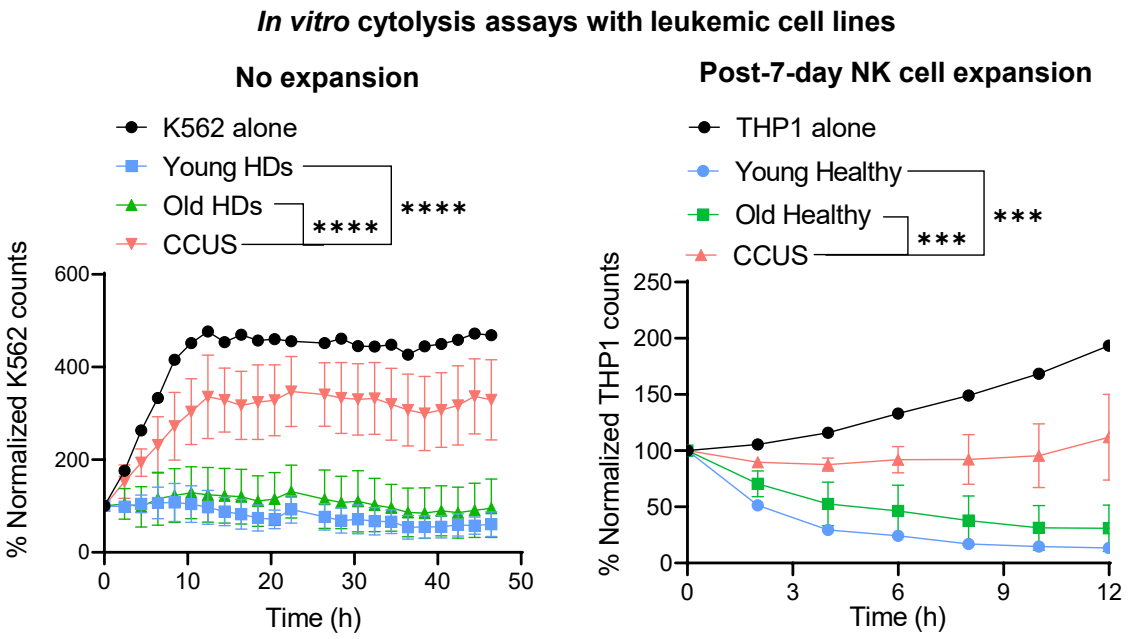
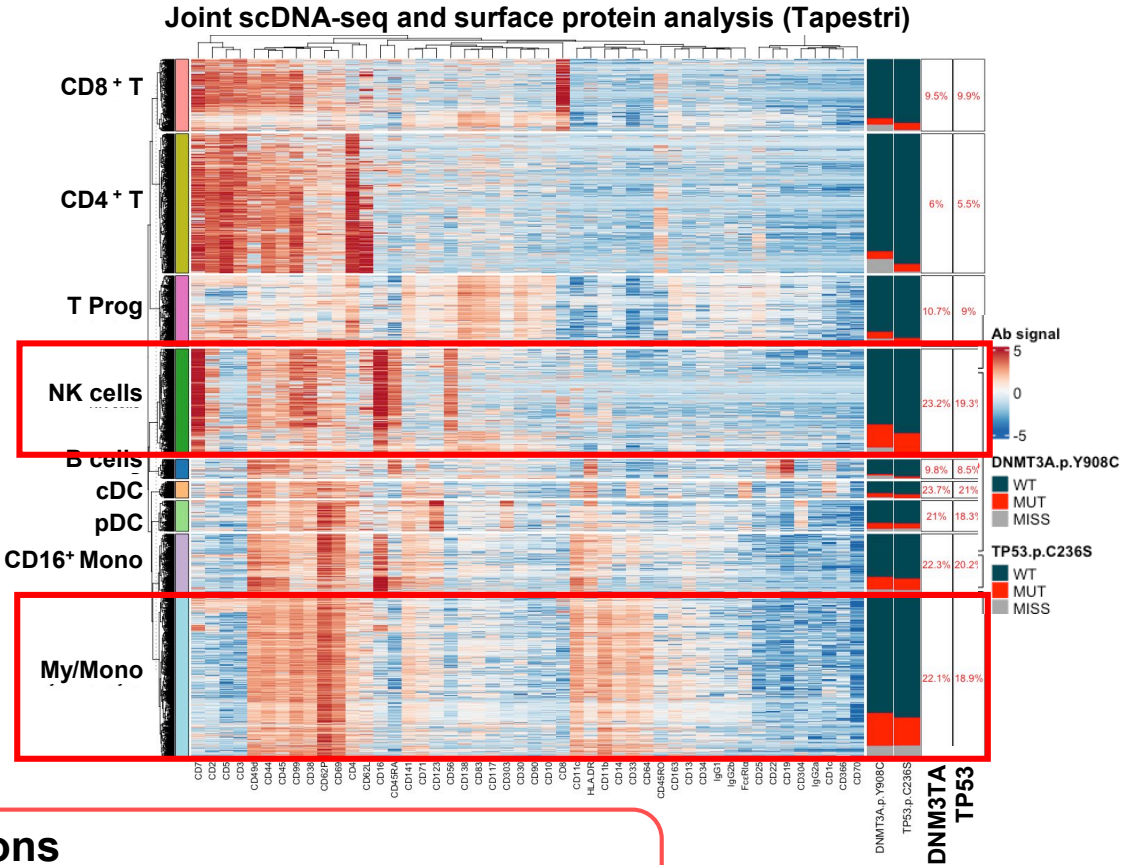
4. NK Cells from CCUS Patients Are Irreversibly Dysfunctional



5. NK Cells Are Part of the Mutant CCUS Clone



Conclusions

- The innate immune repertoire is molecularly and functionally altered in patients with CCUS
- **Immune evasion of premalignant clones may contribute to clonal evolution to MDS**
- Rationale for adoptive NK cell therapy in patients with CCUS or low-burden MDS to prevent/arrest MDS progression