Elucidating the Role of Natural Killer Cells in Antibody Breadth During HIV Infection

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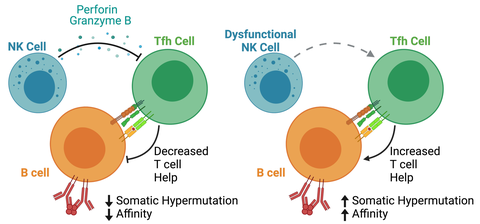
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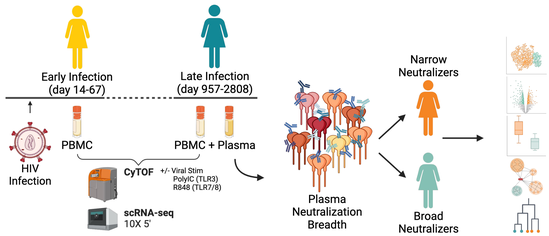
INTRODUCTION

- Understanding drivers of antibody breadth is critical to the development of an HIV vaccine
- Natural Killer (NK) cells are underappreciated regulators of antibody responses
- NK cells can kill T follicular helper (Tfh) cells and decrease antibody response in mice[1]
- Dysfunctional NK Cells are associated with bnAbs[2] in chronic HIV infection
- We investigate differences in peripheral immune response between broad vs narrow neutralizers
- Matched early and late infection samples give us additional insight into immune trajectory

HYPOTHESIS

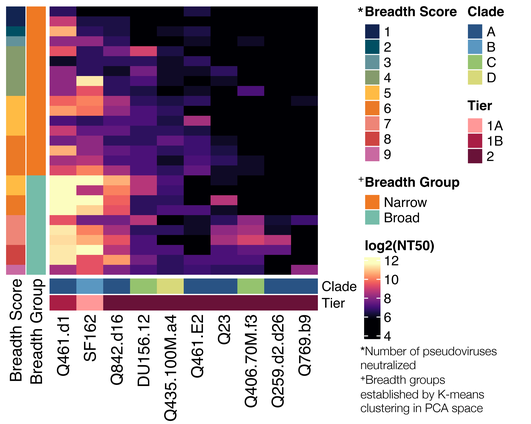


COHORT AND STUDY DESIGN



- Mombasa Sex Worker Cohort is the longest running cohort of HIV positive women (est. 1993)
- Seroconverters are asked to donate samples, creating a unique longitudinal sample bank
  - Samples were banked before ART treatment in Mombasa
- 22 individuals with matched early and late infection samples profiled:
  - Pseudovirus neutralization breadth
  - 10X 5' scRNA-seq
  - Mass cytometry by time of flight (CyTOF)

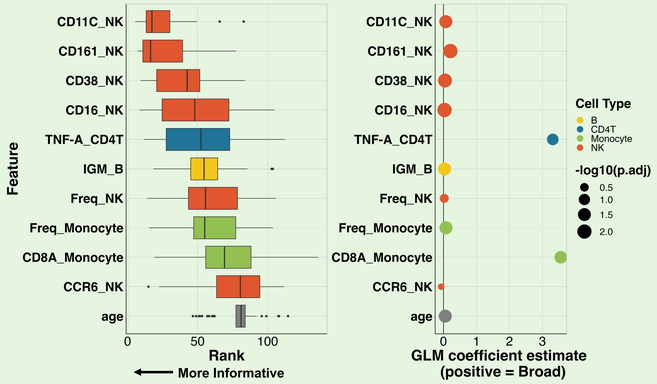
COHORT NEUTRALIZATION BREADTH



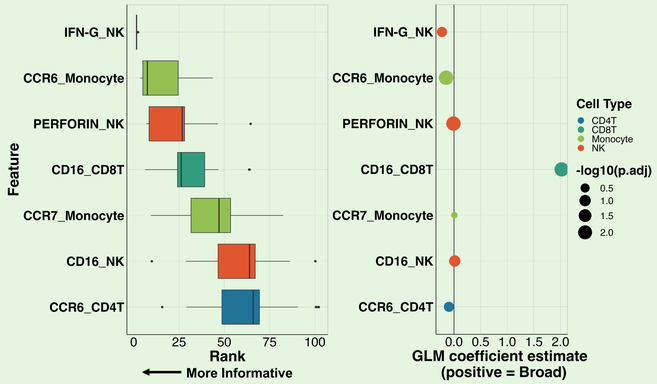
*Number of pseudoviruses neutralized
+Breadth groups established by K-means clustering in PCA space

Unbiased Variable Selection Identifies NK Cell Features Associated with Breadth in Early and Late Infection

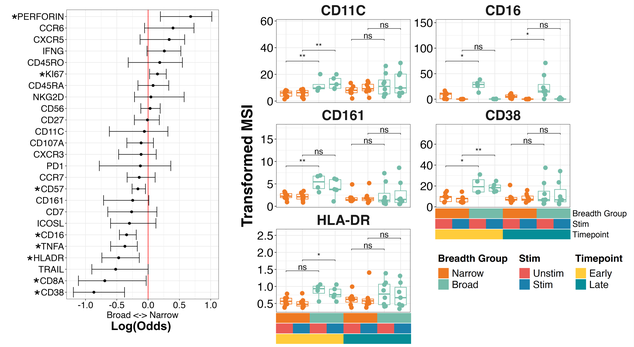
Early Infection



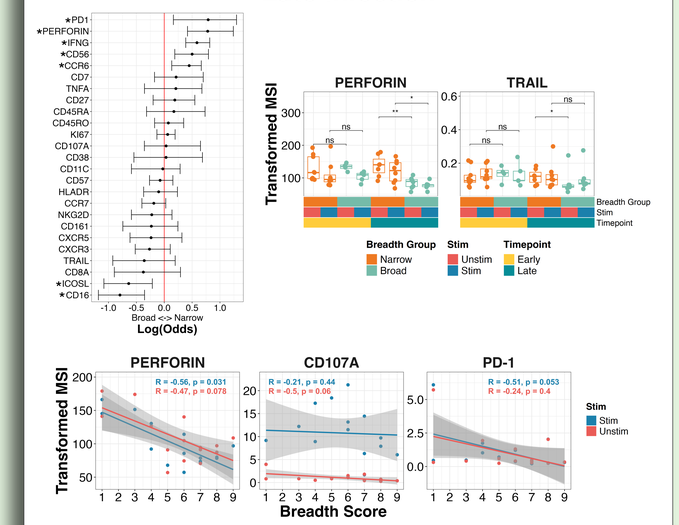
Late Infection



Broad Neutralizers Exhibit Activated NK Cells in Early Infection



Markers of Cytotoxicity are Associated with Narrow Neutralizers and Low Breadth Score in Late Infection



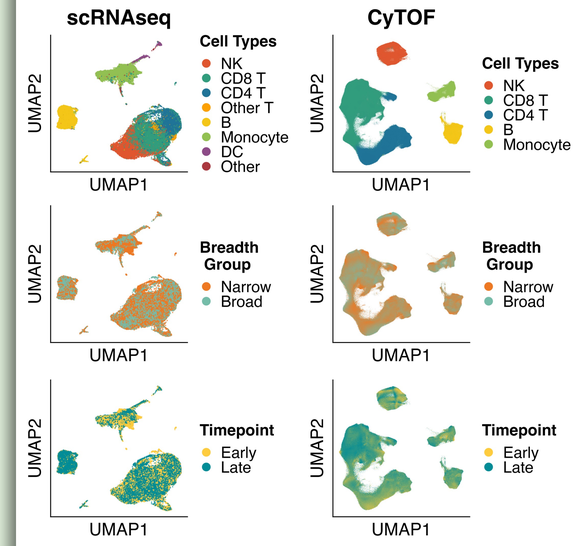
REFERENCES

1. Rydynski et al. Cell Rep. 2018. 2. Bradley et al. Cell. 2018.
Graphics created with Biorender.

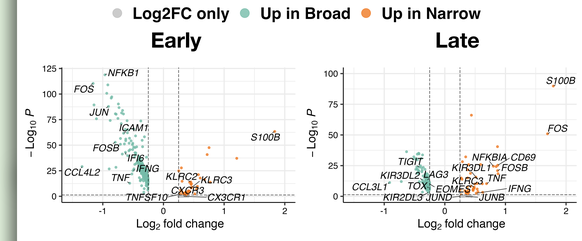


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UMAP EMBEDDINGS



DIFFERENTIAL EXPRESSION



CONCLUSION

- NK cell features are strongly correlated with breadth in both early and late infection
  - Unbiased selection identified markers of NK cell activation in early infection associated with increased breadth measured in late infection
  - Markers of NK cell cytotoxicity associated with decreased breadth in late infection
- Further targeted analysis of NK compartment shows upregulation of activation and ADCC markers in broad neutralizers on the patient level
  - Upregulation of cytotoxic markers in late infection
  - Negative correlation between cytotoxic markers and Breadth Score in late infection
- Differential expression analysis in RNA space supports NK phenotype on protein level

FUTURE DIRECTIONS

- Investigate cell-cell communication that may influence NK cell phenotype
- Analysis of somatic hypermutation and BCR sequences of narrow and broad groups

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