Defining Gene Expression Programs of Amyloidogenic Clonal Plasma Cells Characterized by Single-Cell BCR and Transcriptomic Profiling

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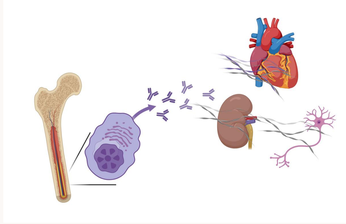
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PRISM
Plasma cell disease repertoire identification and single-cell mapping

Introduction

Primary light chain amyloidosis (pAL) is an uncommon plasma cell disease.

Clonal plasma cells produce misfolded immunoglobulin light chains that deposit in multiple organs.



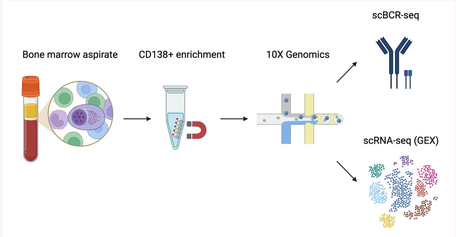
Objectives

To elucidate, at single-cell resolution, the gene programs underlying amyloidogenesis in clonal plasma cells in pAL.

Methods

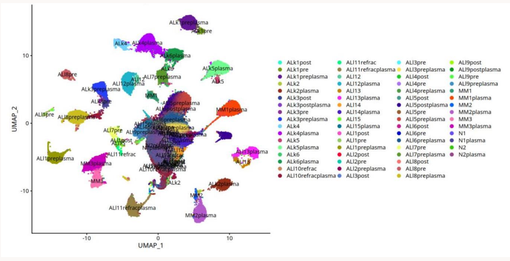
Cohort: 15 patients with lambda chain pAL, 6 with kappa chain pAL, 3 with LCMM, and 2 controls.

Analysis: With our *PRISM* framework.



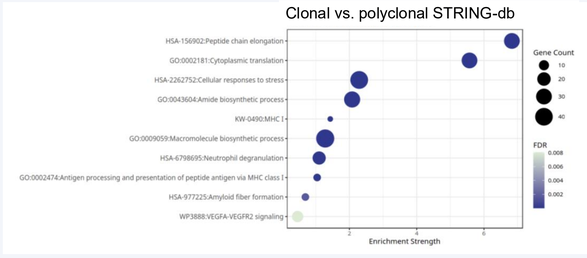
Results

pAL and LCMM plasma cell atlas: 168,045 single plasma cells with BCR-defined clonality, including amyloidogenic clones and polyclonal normal plasma cells.



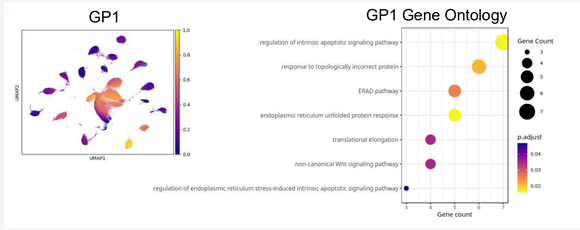
Results

Functional enrichment for amyloidogenic clonal plasma cells vs. polyclonal plasma cells.

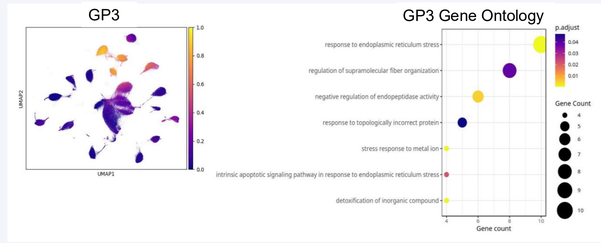


Non-negative matrix factorization revealed the gene programs in plasma cells.

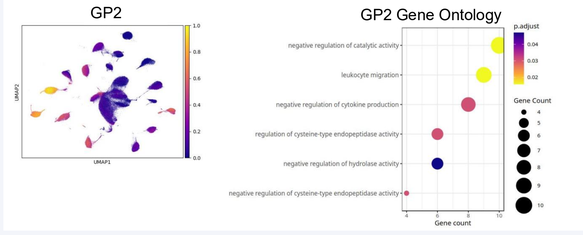
GP1 Misfolded Protein Response: XBP1, AGR2, SELENOS, etc.



GP3 Endoplasmic Reticulum Stress: TMSB4X, TRIB3, CEBPB, DDIT3, etc.

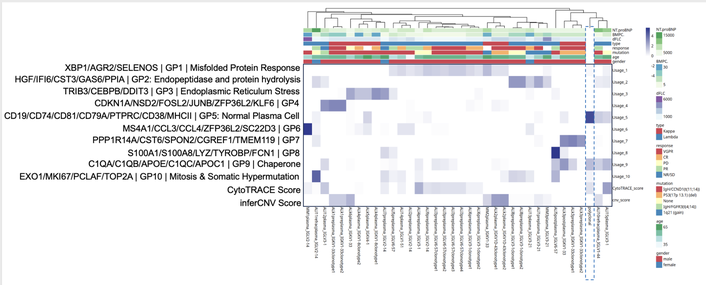


GP2: Endopeptidase and protein hydrolysis: HGF, IFI6, CST3, GAS6, PPIA, etc.



Summary

Amyloidogenic clonal plasma cells are characterized by restricted light chain production and downregulation of normal plasma cell gene programs, including MHC class II expression and B-cell receptor signaling. These cells show upregulation of MHC class I-mediated antigen presentation, activation of misfolded protein response pathways, endoplasmic reticulum stress–induced apoptosis, and dysregulation of endopeptidase activity.



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