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POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Light Chain Amyloidosis Plasma Cells Show Specific Chromatin Accessibility and Transcriptome

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Immunoglobin light chain amyloidosis (AL) is a monoclonal gammopathy characterized by the accumulation of malignant plasma cells (PC) in the bone marrow. These PCs secrete misfolded immunoglobulin light chains fibrils, which deposit in various organs, leading to organ dysfunction. Unlike other monoclonal gammopathies such as Multiple Myeloma, both its rarity and the lower BM PC burden has limited the deep study of the tumor population. The aim of this study was to analyze the transcriptome and epigenome of the PC from patients with AL amyloidosis to identify the role of chromatin modifications in the pathogenesis of the disease.

Highly purified clonal PCs were obtained from bone marrow aspirates samples of 58 AL amyloidosis patients at diagnosis, 19 monoclonal gammopathy of undetermined significance (MGUS), 149 MM and 17 healthy donors. RNA was obtained from PCs and Illumina Stranded Total RNA-seq protocol was performed according to manufacturer's specifications. Accessible chromatin mapping was performed using FAST-ATACseq (Corces *et al*, 2016) with minor modifications. The data obtained were aligned with the GRCh38 version of the human genome and custom pipelines were used for computational analyses. Expression of immunoglobulin genes was removed for RNAseq analysis.

Unsupervised principal component analysis of the RNAseq and ATACseq data showed a clear distinction between PCs from AL patients, MM and HD. To obtain a reliable measure of the magnitude of epigenomic and transcriptome changes in AL, we compared the RNAseq and ATACseq data of AL with MM or HD. The RNAseq analysis showed some clear transcriptional programs (TPs) related to AL and different from MM and HD (Figure 1): TP1 showed 89 genes upregulated and associated with positive regulation of protein kinases and TP2 showed 274 genes downregulated and correlated with immunoregulatory interactions and mitotic regulation. On the other hand, TP3 included 560 downregulated genes associated with glutamate pathway and glycosylation of proteins and TP4 revealed 362 upregulated genes linked with B cell activation. Both patterns were identified in AL patients and HD in comparison with MM patients. Regarding chromatin accessibility, we detected a similar number of ATAC peaks between the AL and MGUS samples and with a significant difference compared to the MM samples (p=0.00014), suggesting that AL and PCs from MGUS have a lower chromatin accessibility (Figure 2). These results

provide evidence that the biological perturbations in the chromatin accessibility and transcriptome of PCs from AL patients are highly specific.

Although the results depicted in Figure 1 demonstrate that AL patients clustered together by relatively homogenous chromatin accessibility and transcriptome, compared with MM patients, we further investigated whether there were any discernible differences among AL patients themselves. To address this, we conducted an analysis of chromatin accessibility and transcriptome in relation to various factors, including age, gender, organ affected, light chain isotype, percentage of tumoral PCs, presence of t(11,14) or amp1q. Remarkably, we identified differences in the transcriptome between AL patients with and without t(11;14), identifying, 46 upregulated genes linked with T cell and lymphocyte apoptosis and inflammatory cytokines production and 257 downregulated genes linked with FGFR family ligand binding and activation and protein ubiquitination and phosphorylation, in t(11,14) positive AL patients. These results suggest that t(11;14) may exert a significant modulation on the transcriptome of PCs of AL patients. Finally, scRNAseq was performed to address the heterogeneity of PCs. Preliminary analysis has shown a remarkable homogeneity in malignant PCs from AL patients with very limited transcriptional differences between PCs clusters.

In summary, in this study we have characterized the PCs of AL patients revealing a homogeneous and specific chromatin accessibility and transcriptome that could contribute to explain the differences between AL and other gammopathies, such as MM. In addition, the identification of these epigenetic and transcriptomic alterations in AL will allow us to better understand the aberrant biology driving this disease, such as those AL with t(11;14). Moreover, these findings open new avenues for the development of innovative therapeutic strategies to improve the outcomes for AL patients.

Disclosures Palladini: *Sebia:* Honoraria; *Prothena:* Consultancy, Honoraria; *Pfizer:* Honoraria; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Argobio, GSK:* Consultancy; *Siemens:* Honoraria. **Paiva:** *Gilead:* Honoraria; *Roche Glycart AG:* Honoraria, Research Funding; *Amgen:* Honoraria; *Adaptive:* Honoraria; *GSK:* Honoraria, Research Funding; *EngMab:* Research Funding; *Takeda:* Honoraria, Research Funding; *Sanofi:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria; *Bristol-Myers Squibb:* Consultancy, Honoraria, Research Funding; *Oncopeptides:* Honoraria. **San-Miguel:** *Amgen:* Consultancy, Other: Advisory Board; *Abbvie:* Consultancy, Other: Advisory Board; *BMS:* Other: Advisory Board; *GSK:* Other: Advisory Board; *Celgene:* Other: Advisory Board; *Janssen-Cilag:* Other: Advisory Board; *Haemalogix:* Other: Advisory Board; *Regeneron:* Other: Advisory Board; *Takeda:* Other: Advisory Board; *Novartis:* Other; *MSD:* Other: Advisory Board; *Karyopharm:* Other: Advisory Board; *Roche:* Other: Advisory Board; *Sanofi:* Other: Advisory Board; *SecuraBio:* Other: Advisory Board. **Nuvolone:** *Jannsen:* Honoraria.

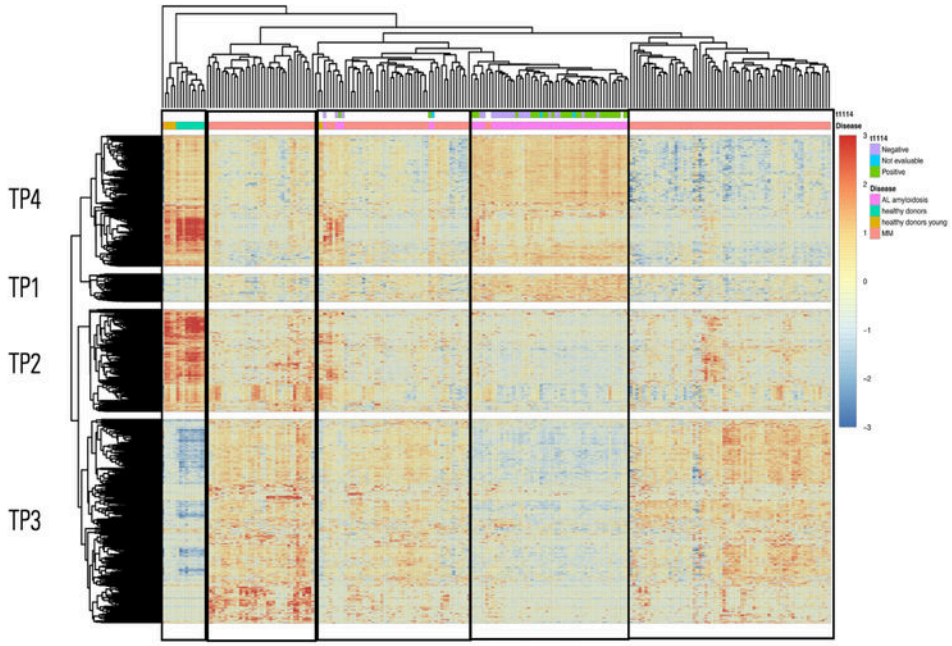

Figure 1. Heatmap representing the differential expressed genes between AL, MM and HD, in which there are 4 different trascriptional programs (TPs) and 5 different patient groups according to their expression patterns.

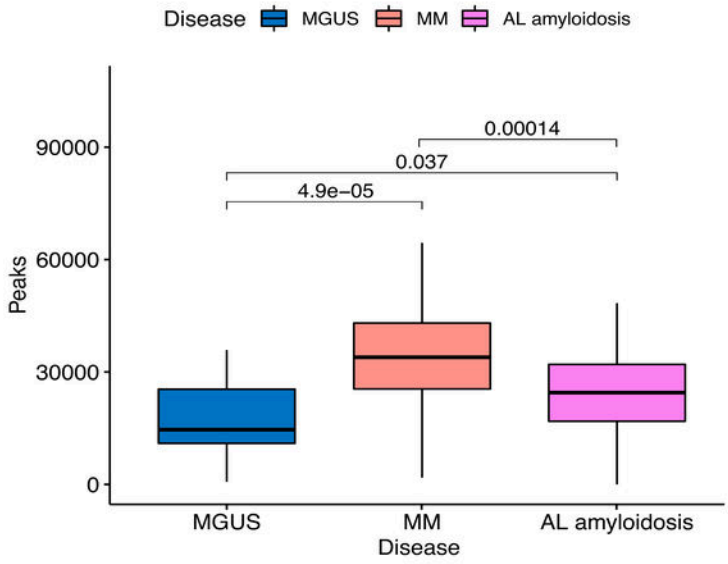

Figure 2. Repressentation of number of peaks in each disease group (MGUS, MM and AL), in which statistical differences can be seen between MGUS - MM and MM - AL.

Figure 1

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