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POSTER ABSTRACTS

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

Differential Chromatin Organization between t(4;14) and Non-t(4;14) Multiple Myeloma Driven By the Histone Methyltransferase NSD2

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Background: The incidence of multiple myeloma (MM) with t(4;14) translocation is ~15% of newly diagnosed MM (NDMM), and is associated with poor prognosis and high-risk disease. Recent analysis of t(4;14) genomics indicate that the location of the chromosome 4 (chr4) breakpoint can significantly segregate patient outcome regardless of therapeutic intervention. Translocation of IGH regulatory elements from chr14, drive the expression of NSD2 (chr4), a histone (H3) methyltransferase responsible for di-methylation of H3 lysine 36 (H3K36me2), a mark of active chromatin. Depending upon the location of the chr4 breakpoint, different isoforms of NSD2 are expressed, including full-length (NSD2-FL) and various N-terminus truncations (NSD2-TR). The mechanisms of how the location of the chr4 breakpoint and the functionalities of NSD2 isoforms may contribute to a higher risk biology in t(4;14) MM patients is not known. Here we compare and contrast the 3D chromosomal organization of t(4;14)-NSD2-FL, t(4;14)-NSD2-TR and non-t(4;14) in pre-clinical MM models.

Results: Comparative analysis of chromosome conformation capture (Hi-C) indicates that there is a decrease in medium-to-long range chromosomal looping interactions accompanied by an increase in short-range interactions from t(4;14) vs. non-t(4;14) models (Figure A). Accordingly, relative quantification of chromosomal contact probabilities of intra-chromosomal (cis) contacts increase in frequency from non-t(4;14) (77%) vs. t(4;14)-NSD2-FL (87%) vs. t(4;14)-NSD2-TR (89%). Evaluation of active/inactive (A/B) 3D genomic compartments between non-t(4;14) and t(4;14) models suggest significant compartment switches (~30% genome; combined A-to-B and B-to-A). Analysis of gene neighborhoods through topologically associated domains (TADs) suggests that there are decreases in contacts at the TAD boundary regions in t(4;14)-NSD2-TR vs. t(4;14)-NSD2-FL vs. non-t(4;14) models. TAD sizes are also generally smaller in size, from t(4;14)-NSD2-TR vs. t(4;14)-NSD2-FL vs. non-t(4;14). Complimentary analysis of activity by contact (ABC) to assess the potential influence of proximal and distal enhancers on gene activity confirms there is a decrease in ABC scores when comparing t(4;14) vs. non-t(4;14).

Assessment of global chromatin accessibility (ATAC-Seq) indicate significant consensus open peaks (~135k), differentially accessible (DA) peaks (~2.6k), and differential closed peaks (~8.8k) in t(4;14) vs. non-t(4;14). Principal component (PC) analysis demonstrated a unique grouping of t(4;14) models compared to a very heterogenous distribution of non-t(4;14) models. DA regions in t(4;14) were found to be primarily more enriched in both intronic and intergenic regions, and within proximal and distal promoters.

Analysis of histone marks was used to assess differences in global active enhancers (H3K4me1, H3K27ac), repressive chromatin (H3K9me3, H3K27me3), and active transcription (H3K36me2/3, H3K4me3) between non-t(4;14) and t(4;14). Active marks were shown to be increased, and repressive marks decreased in t(4;14) vs. non-t(4;14) models that also correlated with DA peaks. Enhancer ranking suggests the frequency of potentially poised superenhancers increase in t(4;14) vs. non-t(4;14).

Differential expression (DE) analysis between t(4;14) and non-t(4;14) was highly correlative with DA peaks (Figure B). In addition, distinctive transcriptional signatures between non-t(4;14), t(4;14)-NSD2-FL, and t(4;14)-NSD2-TR were identified. Conservative (DA+DE) pathway enrichment suggests multiple and distinct biological processes including cell adhesion through adherens junctions, cell-cycle regulation through mitotic checkpoints, chromosomal reorganization through depolymerization of the nuclear lamina, and epithelial to mesenchymal transition.

Conclusions: Systematic chromosomal re-arrangement and accessibility driven by differential epigenetic deposition of histone regulatory marks, differentiates t(4;14) from non-t(4;14) MM biology. These analyses suggest that given the nature of the

translocation, and additionally the location of the chr4 breakpoint, result in major 3D chromosomal structural rearrangement, mediating biological programs that may explain the differences between successful and poor interventional therapies for this subset of MM disease.

Disclosures Bjorklund: *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Zhao:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Jain:** *BMS:* Current Employment. **Shtraizent:** *BMS:* Current Employment, Current equity holder in publicly-traded company. **Ortiz:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Mukherjee:** *BMS:* Current Employment. **Hagner:** *BMS:* Current Employment, Current equity holder in publicly-traded company. **Gandhi:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company.

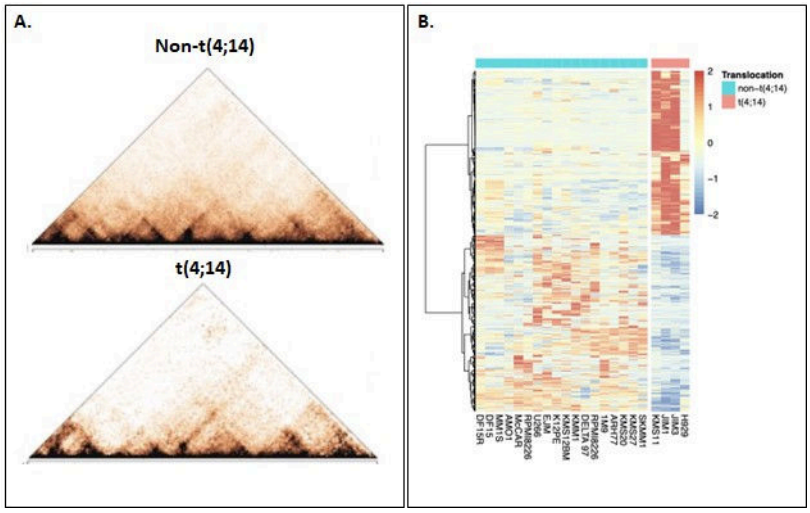

Figure 1

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