



Abstract Title: Whole Proteome Analysis of Multiple Myeloma Patient Samples Provides New Insights into IMiD/CELMoD Resistance

ABSTRACT PREVIEW: WHOLE PROTEOME ANALYSIS OF MULTIPLE MYELOMA PATIENT SAMPLES PROVIDES NEW INSIGHTS INTO IMiD/CELMOD RESISTANCE

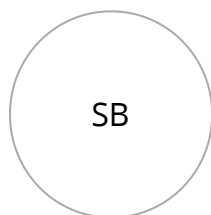
Whole Proteome Analysis of Multiple Myeloma Patient Samples Provides New Insights into IMiD/CELMoD Resistance

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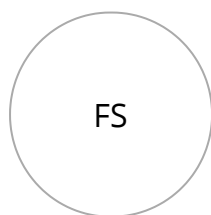
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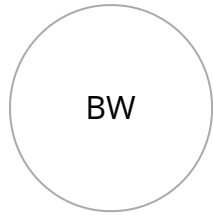
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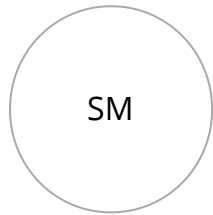
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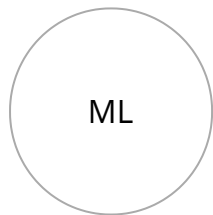
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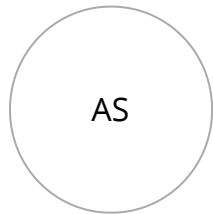
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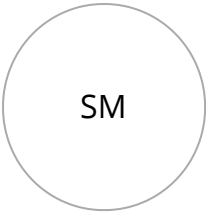
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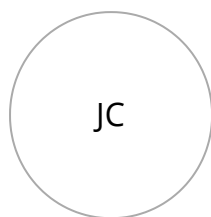
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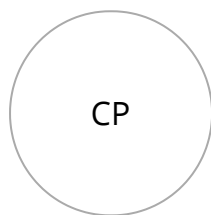
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Abstract Track

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Introduction

Analyses of large cohorts of primary samples from MM patients to understand resistance mechanisms have mostly been undertaken at the DNA/RNA level. However, whole proteome analysis is highly pertinent to understanding resistance to protein degraders such as immunomodulatory drugs (IMiDs) and next generation agents (CELMoDs), which are central to many MM treatment regimens.

Methods

We analysed proteomic changes associated with relapse on lenalidomide (Len) therapy using paired baseline and relapse CD138+ samples from patients enrolled in the Myeloma XI trial. In a separate analysis we explored degradation profiles in patient MM cells (CD138+ samples from IMiD sensitive and resistant patients) treated *ex vivo* with IMiDs/CELMoDs (Len 10uM, pomalidomide [Pom] 10uM, iberdomide [Iber] 1uM and/or mezigdomide [Mezi] 1uM vs DMSO control over 4h). All samples were analysed by TMT-labelled quantitative mass spectrometry. RNA expression and outcome were explored in the CoMMpass dataset for key proteins.

Results

Paired baseline and relapse samples from 14 patients enrolled in Myeloma XI were analysed with ~7500 proteins identified. At relapse on Len, the expression levels of 91 proteins were upregulated ($\log_2FC \geq 0.5$, $p < 0.01$) and of 272 were downregulated ($\log_2FC \leq -0.5$, $p < 0.01$). The top 5 upregulated proteins were CHAF1B, CTAG1B/CTAG1A, DHFR, NCAPD2 and RAPGEF1 and downregulated were FAM241B, HSP90AA4P, PIQG, SMPD2 and TMEM19.

High RNA expression of DHFR, CHAF1B and CTAG1A at diagnosis was associated with significantly shorter PFS and high expression of CHAF1B, CTAG1A and CTAG1B with significantly shorter OS in the CoMMpass dataset, suggesting a key role in MM resistance.

Ex vivo samples from 19 patients (6 clinically sensitive/unexposed to IMiDs, 13 resistant, none exposed to CELMoDs) were analysed with ~7000 proteins identified. Degradation of Ikaros and/or Aiolos was demonstrated in all IMiD sensitive patients (6/6) but in resistant patients 8/13 (62%) degraded with Len and Mezi, 2/13 (15%) degraded with Mezi but not Len and 3/13 (23%) showed no degradation with either. This suggests loss of CRBN function led to resistance in a subset of patients, whilst in the remainder resistance arose through alternate mechanisms.

To explore the full degradome in the primary sample context for the first time, the 16 patients demonstrating degradation were analysed. Degradation of Ikaros/Aiolos was confirmed with all IMiDs/CELMoDs and of ZFP91 with Pom, Iber and Mezi. The expected increase in magnitude of

degradation of Ikaros/Aiolos was demonstrated with CELMoDs compared to IMiDs. Analysis of potential novel neosubstrates and differences in the degradome between clinically sensitive and resistant patients is ongoing.

Conclusions

Exploring the whole proteome of primary patient samples enhances our understanding of mechanisms of resistance and has highlighted potential novel therapeutic targets in IMiD resistance such as CTAG1B/CTAG1A, for which TCR engineered T cells have been studied in solid tumours.

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