Proteogenomic analysis of multiple myeloma reveals therapeutic opportunities and predictive signatures

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Multiple myeloma is a plasma cell malignancy in the bone marrow and the second most frequent blood cancer. Although the introduction of better treatment options like lenalidomide and proteasome inhibitors greatly improved outcome, multiple myeloma remains an incurable disease due to acquired drug resistance. This stresses the need for complementary therapeutic strategies and improved molecular profiling of the disease. To this date, only very limited proteomic and integrated multi-omic datasets of multiple myeloma are available. Here, we used TMT-based, deep proteomic analyses in combination with RNA sequencing to identify new predictive markers, drug resistance mechanisms and therapeutic targets in multiple myeloma. This approach identified CDK6 upregulation on the protein, but not the transcriptional level, to be associated with treatment resistant disease. Functional studies revealed that the active kinase CDK6 mediates lenalidomide resistance in multiple myeloma cell line models. Targeting CDK6 with inhibitors or proteolysis targeting chimeras (PROTACs) reversed a CDK6-driven drug resistance protein signature and is highly synergistic with lenalidomide in cell line and animal models [1]. To identify additional therapeutic and diagnostic targets, we next aimed to further dissect the proteogenomic landscape of newly diagnosed multiple myeloma with a comprehensive multi-omic dataset of over 120 patient samples, covering all major cytogenetic and copy-number alterations. The analysis revealed both distinct proteomic profiles of recurrent cytogenetic abnormalities and a highly significant proteomic high-risk signature that is independent of cytogenetic risk status. Integrated comparisons to proteomic data of healthy bone marrow blood cell populations and CRISPR/Cas knock-out screens highlighted potential targets for pharmacological and immunological intervention. In conclusion, proteogenomic analysis of multiple myeloma uncovered actionable novel therapeutic targets for relapsed and newly diagnosed disease. Our dataset provides a valuable resource to identify additional therapeutic strategies and potential diagnostic markers in multiple myeloma.

100321, https://doi.org/10.1016/j.mcpro.2022.100358