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

CRISPR-Based Gene-Editing Screens Revealed Modulators of Dexamethasone Sensitivity in Multiple Myeloma

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Background: Multiple myeloma (MM) is an incurable plasma cell malignancy that accounts for 10% of hematologic malignancies. Despite improved prognosis due to advances in treatment, most patients ultimately develop therapy resistance and relapse. The glucocorticoid dexamethasone is a potent anti-myeloma agent used in combination with proteasome inhibitors and Immunomodulatory drugs (IMIDs) as frontline treatment. Dexamethasone binds to the glucocorticoid receptor (GR), which induces apoptosis by driving an apoptotic transcriptional program. The mechanisms of Dexamethasone resistance in MM remain poorly understood.
Aim: To define cellular processes that modulate dexamethasone sensitivity in MM.
Methods: We performed loss-of-function CRISPR screens in the t(4;14), NSD2 overexpressing, MM cell lines KMS11 and LP1 using the genome-wide Brunello sgRNA library.
Results: The screens identified genes whose loss altered MM cell sensitivity to dexamethasone, most being cell type-specific suggesting heterogeneity in mechanisms influencing dexamethasone cytotoxicity across MM patients. In KMS11 cells, disruption of the IL10/JAK/STAT signaling pathway and glycosaminoglycans/heparan sulfate synthesis pathway increases sensitivity to dexamethasone. By contrast, loss of chromatin remodeling factors including the polycomb group member EPC1 and the SWI/SNF complex components BRD7 and BRD9, altered dexamethasone response exclusively in LP1 cells. Perturbations resulting in dexamethasone resistance in both cell lines include the GR and its co-chaperone PTGES3 in addition to members of the NFKB inhibitor family (NFKBIA, NFKBIB). By contrast, disruption of the druggable GR co-chaperone FKBP5 or the histone deacetylase HDAC8 increased sensitivity to dexamethasone. In addition, the GID/CTLH E3 ubiquitin ligase complex was also identified as a general determinant of dexamethasone resistance in MM cells as disruption of several constituents of this complex resulted in increased dexamethasone sensitivity in both cell lines. The mechanism by which the GID/CTLH complex confers dexamethasone tolerance in MM cells is currently under investigation.
Conclusions: Multiple cellular processes contribute to modulating the cytotoxic effect of dexamethasone in MM. Such processes often regulate expression, stability, or localization of the GR. NFKB signaling and the GID/CTLH E3 ubiquitin ligase activity are key determinants of dexamethasone resistance. Targeting these processes can increase the therapeutic effect of dexamethasone in MM.

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