Targeting DNA2 Overcomes Metabolic Reprogramming in 1q21 Multiple Myeloma

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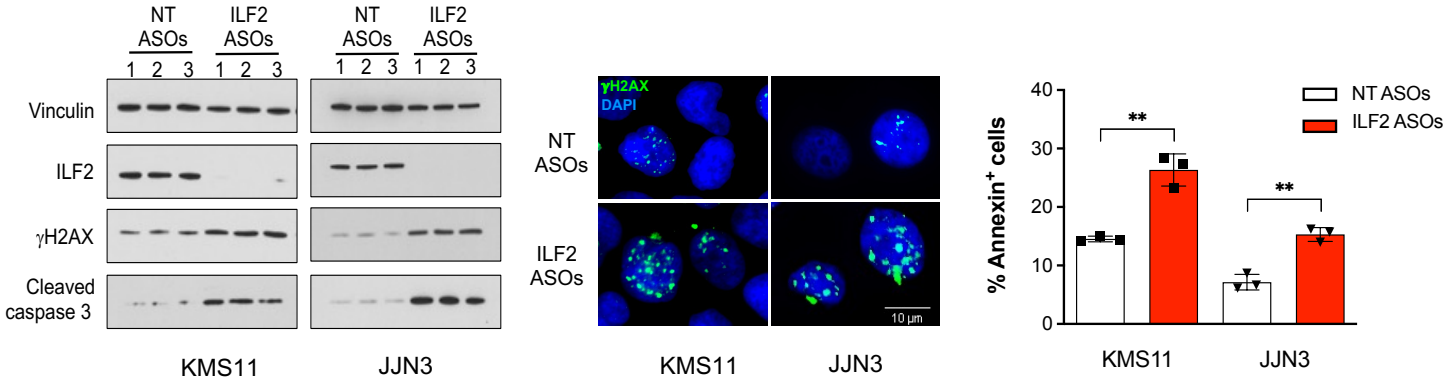
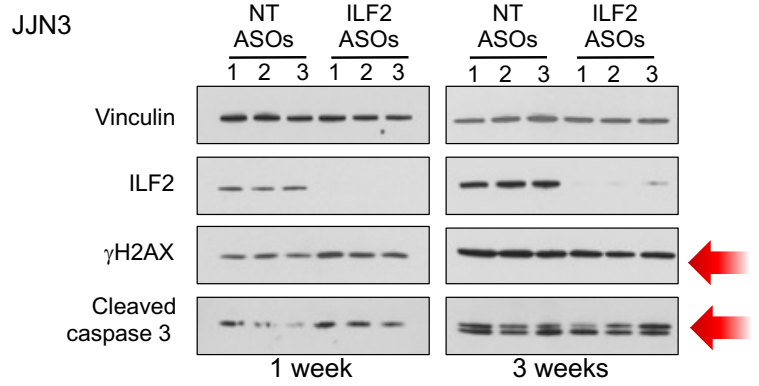
Antisense therapy targeting ILF2 (ILF2 ASOs) induces DNA damage in 1q21 MM cells.



Western blot (left), immunofluorescence (middle), and apoptosis (right) analyses in KMS11 and JJN3 cells treated with non-targeting (NT) or ILF2 ASOs for 1 week.

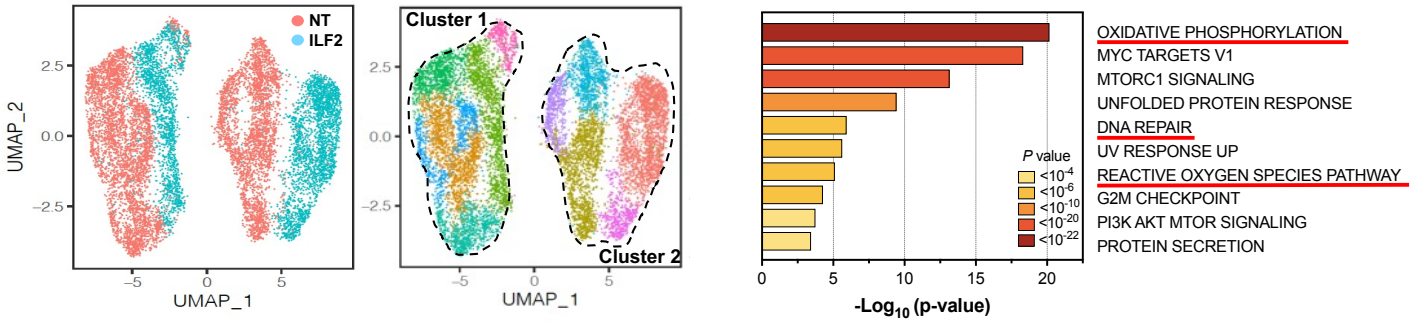
ILF2 ASOs
3 weeks

MM cells can overcome ILF2 ASO-induced DNA damage.



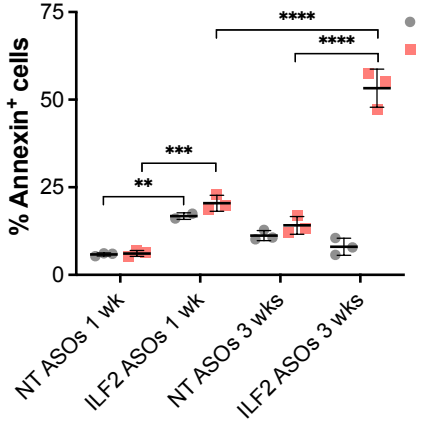
Aim #1: To dissect the molecular mechanisms by which MM cells overcome ILF2 ASO-induced DNA damage

- **Resistance to ILF2 ASOs is not induced by clonal selection (scRNA-seq)**
- **ILF2 ASO-resistant MM cells undergo metabolic switch and are dependent on oxidative phosphorylation to maintain survival (scRNA-seq and metabolomic analysis)**



Single cell RNA-seq and metabolomic analysis were performed in JJN3 treated with NT or ILF2 ASOs for 3 weeks.

OXPHOS mediates MM resistance to ILF2 ASOs.



ILF2 ASO-treated JJN3 for 1 wk or for 3 wks were further treated with the OXPHOS inhibitor IACS-010759 for 72 hours.

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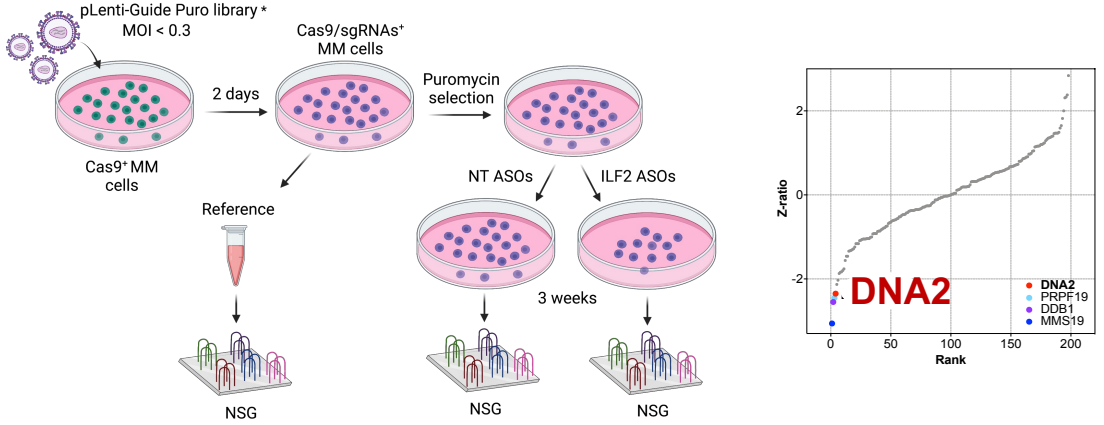
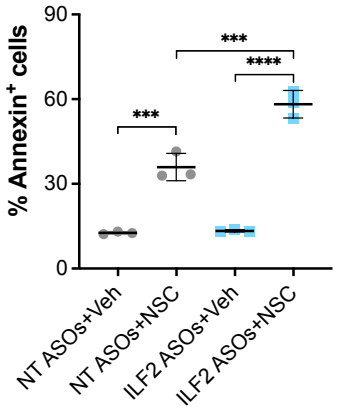
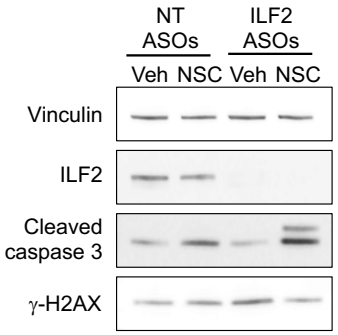
CRISPR/Cas9-based screening to identify DNA repair effectors whose loss of function suppresses MM cells' resistance to ILF2 ASO-induced DNA damage



sgRNAs targeting *MMS19*, ***DNA2***, and *DDB1* genes were significantly depleted in ILF2 ASO-treated JJN3 cells but not KMS11 cells after 3 weeks of ASO-treatment. DNA2 is the only druggable target.

Targeting DNA2 enhances ILF2 ASO-induced apoptosis in JJN3 cells.

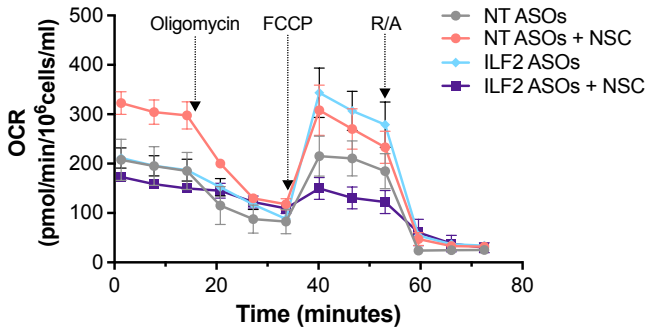


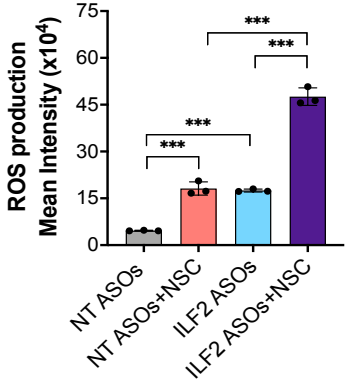


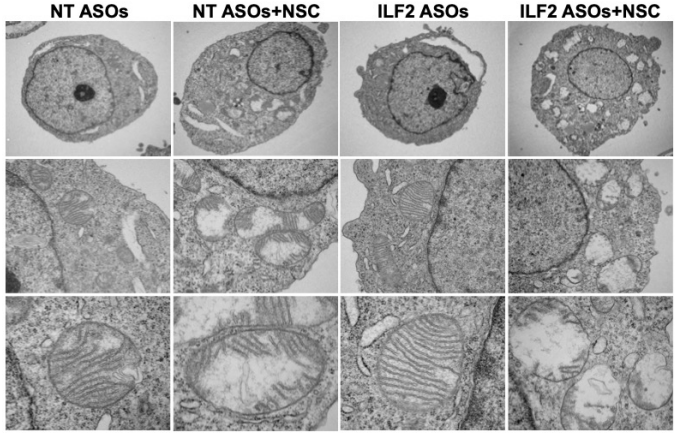
Western blot (left) and apoptosis (right) analyses were performed in JJN3 cells treated with vehicle (Veh) or the DNA2 inhibitor NSC105808 (NSC; 1μM) for 48 hours after long-term exposure to NT or ILF2 ASOs.

Aim #2: To dissect the mechanisms of DNA2 inhibition-induced synthetic lethality in MM cells undergoing metabolic reprogramming in the context of ILF2 depletion

DNA2 inhibition decreases the oxygen consumption rate and increases ROS production in ILF2-depleted cells.







Seahorse experiments (left) were performed in JJN3 cells treated with ASOs for 7 days prior to receiving NSC for 72 hours. Quantification of ROS production (middle) and transmission electron microscopy (right) were performed in JJN3 cells treated with ASOs for 7 days prior to receiving NSC for 48 hours.

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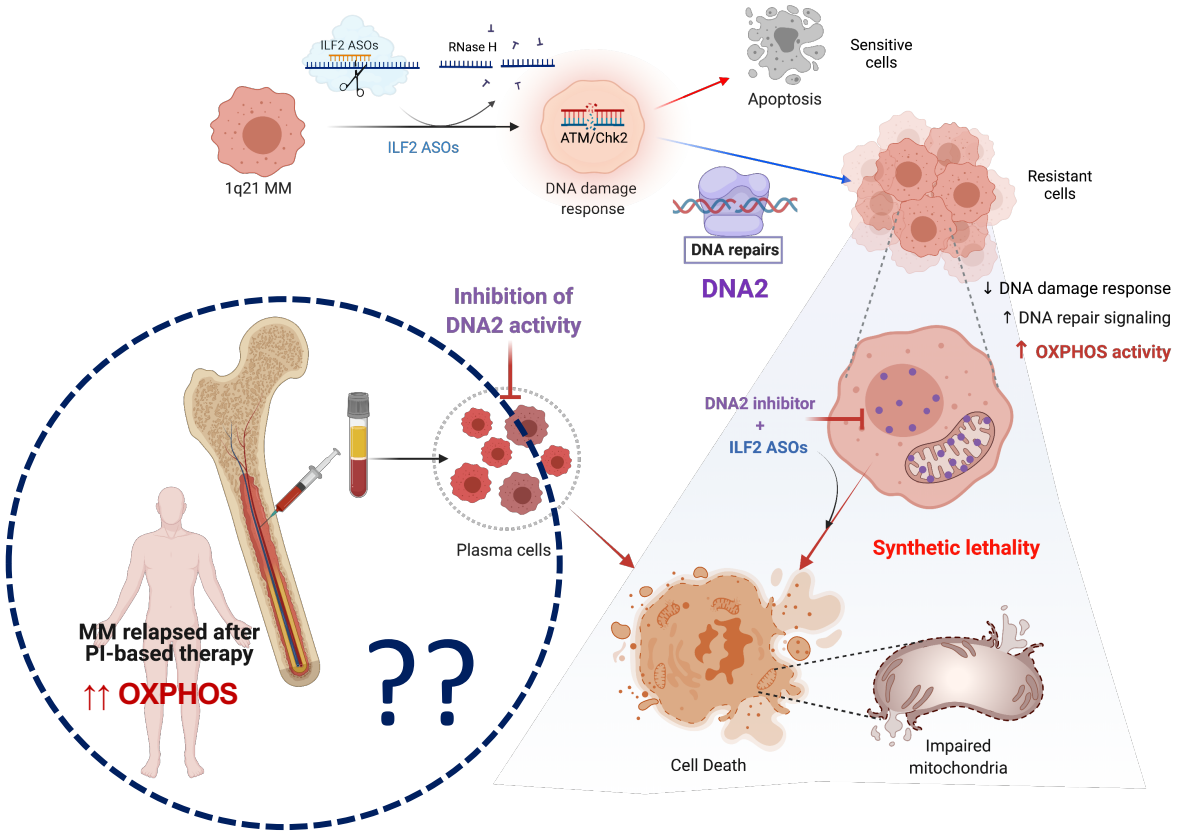
Working model & Conclusion



- ✓ DNA2 is essential to maintain oxidative phosphorylation and metabolic reprograming in MM cells.
- ✓ DNA2 inhibition is a synthetic lethal approach to targeting 1q21 MM cells in the setting of ILF2 depletion-induced DNA damage.

Future direction

- To evaluate whether inhibition of DNA2 activity is synthetically lethal in MM plasma cells from patients whose disease failed previous therapies, such as therapy with proteasome inhibitors.

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