Targeting DNA2 Overcomes Metabolic Reprogramming in 1q21 Multiple Myeloma

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

MM cells can overcome ILF2 ASO-induced DNA damage.

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.

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)

OXPHOS mediates MM resistance to ILF2 ASOs.

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

**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.
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DNA2 is essential to maintain oxidative phosphorylation and metabolic reprogramming 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.