EGLN1 is a synthetic lethal target in ARID1A-mutant ovarian cancer

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ABSTRACT

The successful use of PARP inhibitors for the treatment of BRCA-mutant ovarian cancer underscores the importance of synthetic lethality as a therapeutic opportunity for patients with loss-of-function mutations in tumor suppressor genes. Ovarian cancer ranks as the fifth deadliness cancer among women, and one ovarian cancer subtypes, clear cell carcinoma, is particularly underserved. The most frequent genetic alteration in ovarian clear cell carcinoma is loss-of-function mutation of the SWI/SNF-A complex subunit, ARID1A. We interrogated the data published by Project Achilles to determine candidate synthetic lethal partners with ARID1A in ovarian cancer, and identified EGLN1, a member of the EGLN-family of prolyl hydroxylases. Inhibition of EGLN1, either genetically or pharmacologically, leads to decreased viability in ovarian cancer cell lines. Pharmacological inhibition of EGLN1 is clinically achievable as evidenced by several well-tolerated, small molecule inhibitors currently in clinical trials for the treatment of anemia in the context of chronic kidney disease. The synthetic lethal interaction of ARID1A and EGLN1 may provide a therapeutic opportunity for patients diagnosed with ovarian clear cell carcinoma.

EGLN proteins regulate HIFα stability

ARID1A is commonly mutated in OCCC

ARID1A-mutant ovarian cancer cell lines are EGLN1-dependent

ARID1A-mutant ovarian cancer cell lines are sensitive to pharmacological EGLN inhibition

PI3Kα inhibitor is synergistic with EGLN inhibitor in ARID1A/PIK3CA-mutant ovarian cancer

ABSTRACT

SUMMARY

REFERENCES

1. EGLN1 is a synthetic lethal target in ARID1A-mutant ovarian cancer

2. ARID1A-mutant ovarian cancer cell lines are sensitive to a pan-EGLN inhibitor

3. Sensitivity to pan-EGLN inhibitor is HIF-dependent

4. EGLN inhibition is synergistic with PI3K inhibition

5. Pharmacological inhibition of EGLN prolyl hydroxylases is well-tolerated in mammals

6. EGLN inhibitors may be efficacious in the treatment of ARID1A-mutant OCCC

REFERENCES


