

Background

- High-grade serous ovarian carcinoma (HGSOC) is the most lethal gynecologic malignancy, mainly due to the persistence of dormant, drug-resistant cancer cells.
- More than 80% of cases, residual cancer cells express DIRAS3 and are undergoing autophagy.
- DIRAS3 is an imprinted tumor suppressor gene downregulated in 60% of primary ovarian cancers (OvC).
- DIRAS3 expression is associated with prolonged progression free survival, but not overall survival.

Hypothesis

Fibroblast Growth Factor Receptor (FGFR) inhibitors are selectively toxic to autophagic cancer cells and might eliminate dormant residual autophagic OvC.

Aim

Evaluate the selective toxicity of the FGFR inhibitor, Infigratinib, for autophagic OvC cells as a potential new therapy.

Methods

- Small-interfering RNA (siRNA) was used to knock down and confirm the potential targets.
- Autophagy was induced by **Doxycycline (DOX)** or Olaparib and was evaluated by Western blot analysis.
- The effect of Infigratinib on cell viability and cell proliferation was examined with sulforhodamine blue (SRB) assays and clonogenic assays, respectively.

Inhibition of Fibroblast Growth Factor Receptor (FGFR) inhibits cell growth of autophagic OvC cells

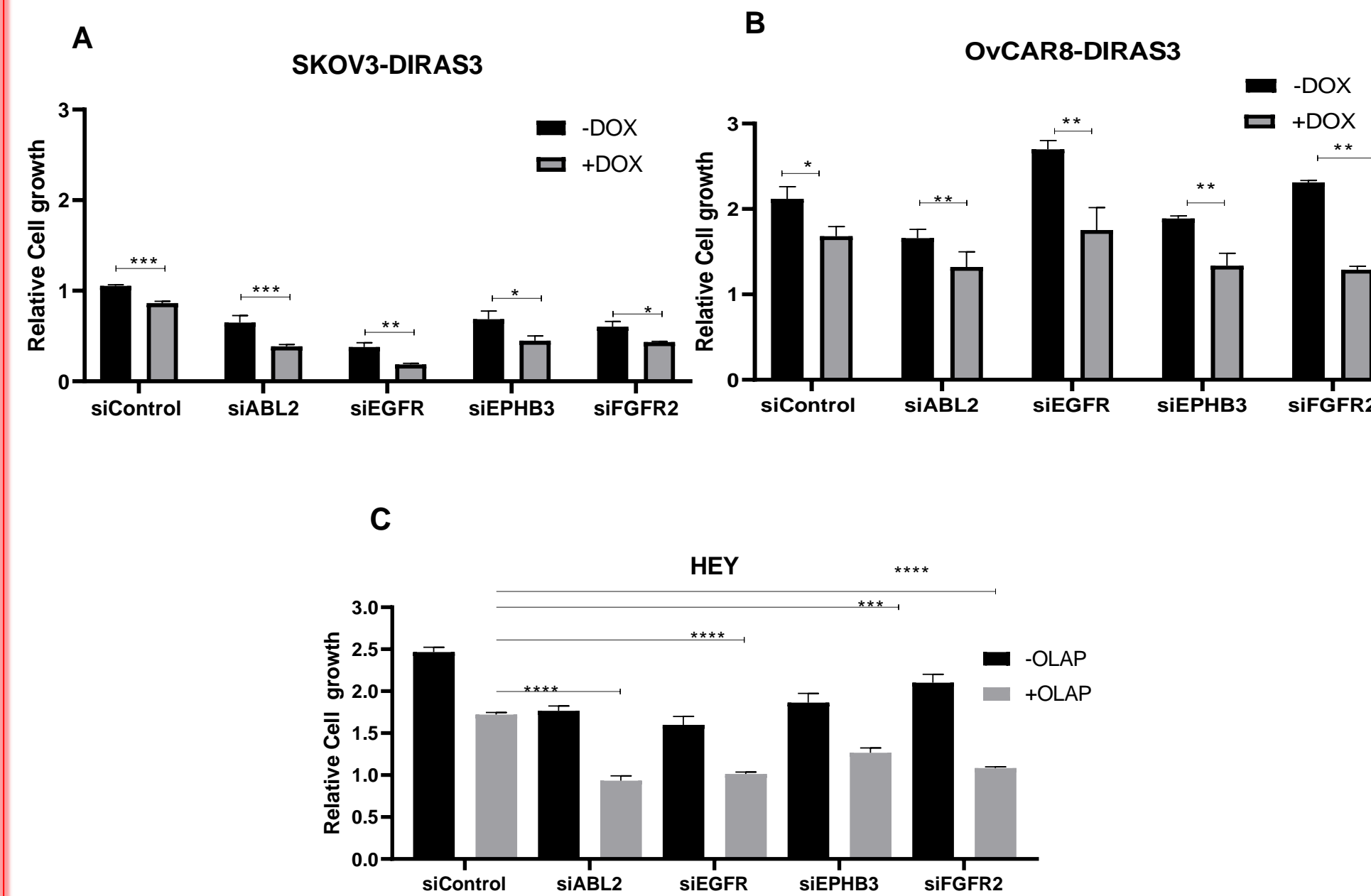


Figure 1. Prioritization of targets. SKOV3-DIRAS3 and OvCAR8-DIRAS3 OvC cells were incubated with each siRNA for 24hrs. DIRAS3 was then induced by incubating with DOX for 72hrs to produce autophagy before assaying cell viability with SRB assays. (C) HEY OvC cells were incubated with each siRNA for 24hrs. Autophagy was then induced by incubation with olaparib (Olap) for 5 days before assaying cell viability with SRB assays.

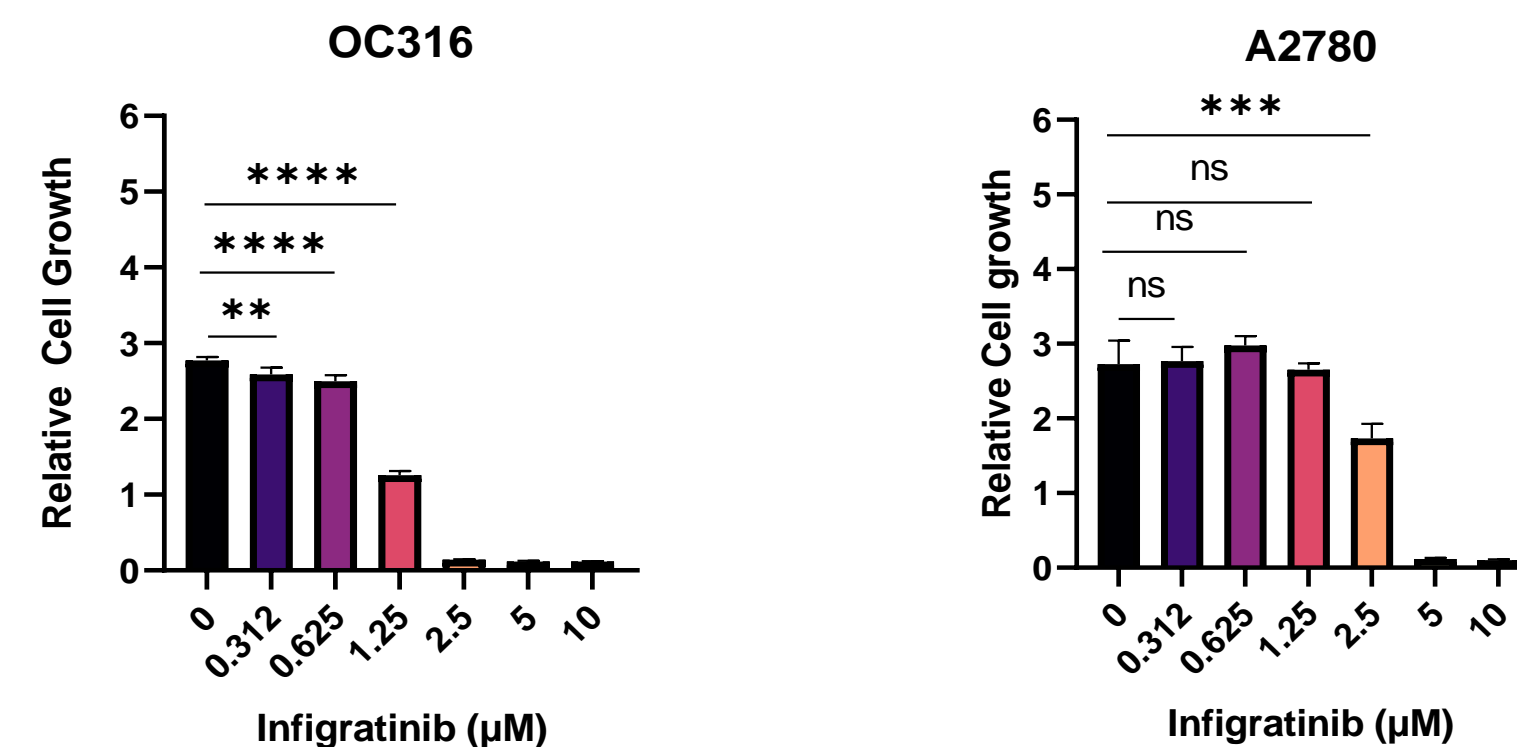


Figure 2. Dose dependent effect of Infigratinib on the growth of OvC cells. A2780 and OC316 were treated with different concentrations of Infigratinib for 5 days. Cell viability was evaluated with SRB assay.

Combined treatment of Infigratinib with DOX or Olaparib inhibits OvC cell growth

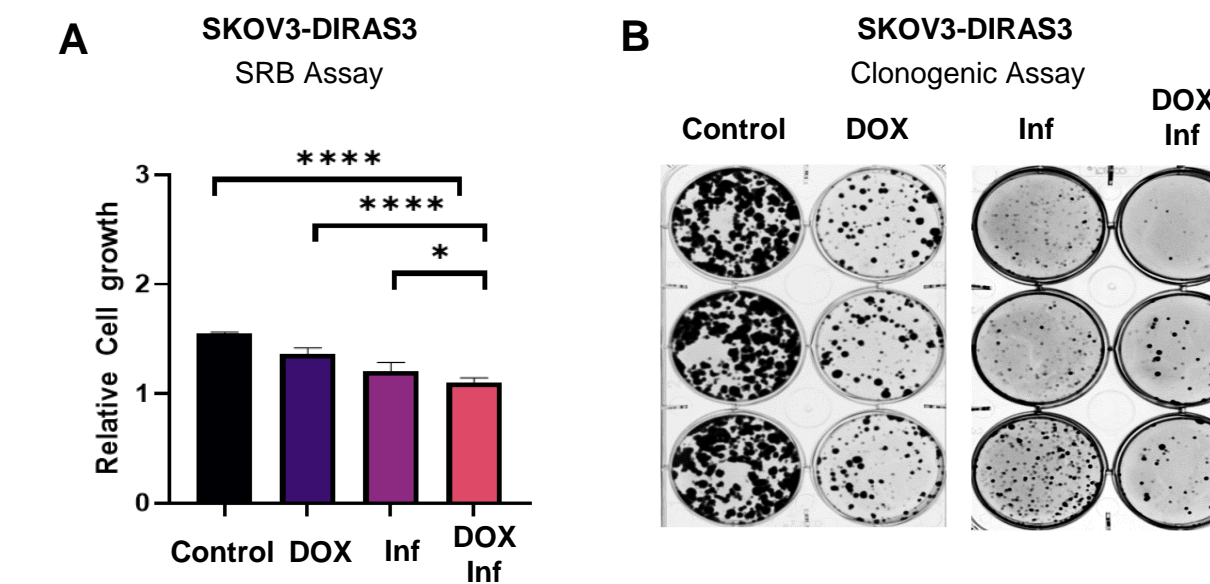


Figure 3. Infigratinib reduces cell viability and colony formation in autophagic OvC cells. (A) SKOV3-DIRAS3 inducible cells were treated with DOX (1ug/ml) to induce expression of DIRAS3 followed by treatment with Infigratinib (Inf) for 6 days. (B) Cells were seeded at 1000 cells/well and treated with DOX and 1uM of Infigratinib for 14 days.

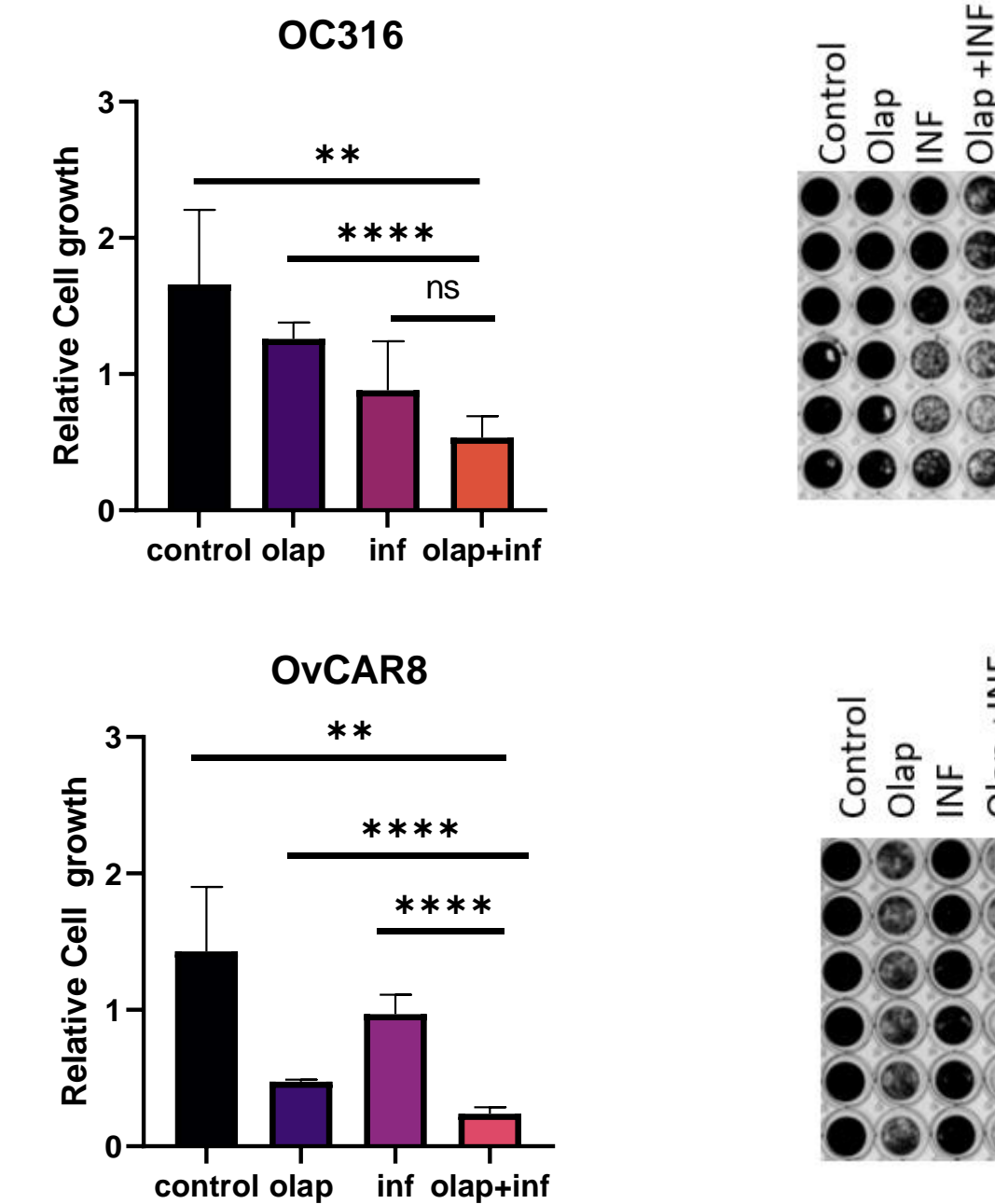


Figure 4. Combination of Olaparib and Infigratinib Decreases Cell Viability in OvC Cells. OC316 and OvCAR8 cells were treated with 5uM of olaparib and 1uM of Infigratinib for 5 days and SRB assays were performed to evaluate the effect of the combination on cell viability.

Conclusions

- Knockdown of FGFR significantly reduced cell viability of autophagic OvC cells compared to non-autophagic OvC cells.
- Treatment with Infigratinib significantly decreased cell viability and clonogenic growth of autophagic SKOV3-DIRAS3 cells.
- Treatment with Infigratinib and Olaparib significantly decreased cell viability of OvCAR8 and OC316 autophagic cells.

Future Directions

- Evaluate the expression of different FGFRs on several OvC cell lines.
- Evaluate the effect of Infigratinib on induction of apoptosis of autophagic cells.
- Determine the molecular mechanism(s) by which inhibition of FGFR decreases cell growth of autophagic cells.
- Examine the effect of the combination of olaparib and Infigratinib in other cell lines and ovarian cancer xenograft models.

Acknowledgments

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