Targeting Semaphorin 7a Signaling in ER+ Breast Cancer

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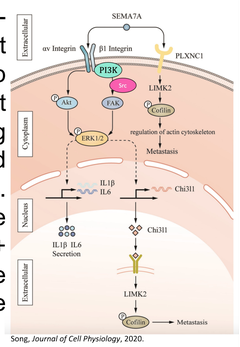
Abstract

Endocrine receptor-positive (ER+) breast cancer (BC) makes up over 70% of all breast cancers and is the leading cause of BC-related deaths in females. Despite available therapies against ER+ BC, disease recurrence arises primarily due to the development of therapeutic resistance. Besides ER+ status, our lab has found that Semaphorin 7a (SEMA7A) expression is elevated (SEMA7A+) in BC patient tumors compared to normal breast tumor. Importantly, increased SEMA7A (1.1-1.4-fold) is associated with increased recurrence and decreased survival in ER+ BC patients. SEMA7A is a membrane-bound protein that can activate cell survival pathways via integrin-mediated activation of PI3K signaling. Our lab has shown that SEMA7A-overexpressing (OE) ER+ BC cells are resistant to the selective ER degrader, Fulvestrant, which is likely due to increased PI3K survival signaling and other pro-tumor effects of high SEMA7A expression.



Hypothesis

SEMA7A+ ER+ BC cells are sensitive to PI3K inhibition via Alpelisib, SEMA7A monoclonal antibody (SmAb), or these treatments in combination with Fulvestrant.

SEMA7A-expressing cells are sensitive to PI3K inhibitor Alpelisib

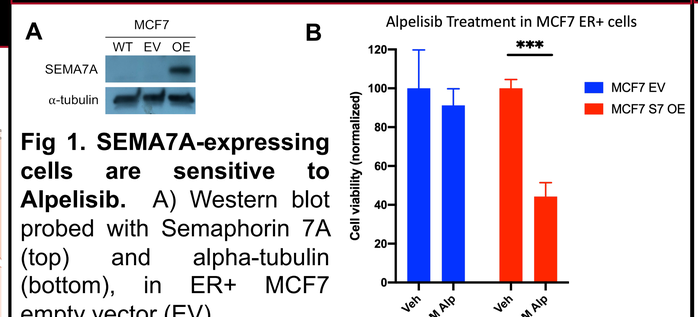


Fig 1. SEMA7A-expressing cells are sensitive to Alpelisib. A) Western blot probed with Semaphorin 7A (top) and alpha-tubulin (bottom), in ER+ MCF7 empty vector (EV), SEMA7A-overexpressing (OE) and wild type (WT) cell lines. B) MCF7 empty vector (EV) or SEMA7A-overexpressing (OE) cell lines treated with vehicle (veh) or 1uM of Alpelisib.

Combining Alp with endocrine therapy is efficacious in ER+ SEMA7A OE cells

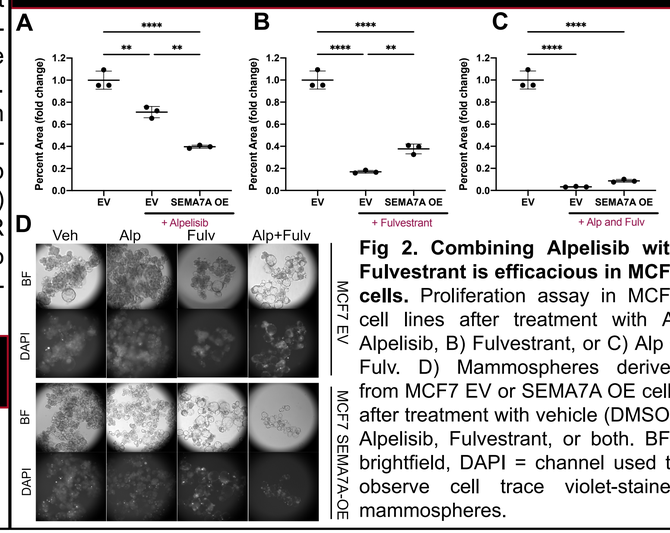


Fig 2. Combining Alpelisib with Fulvestrant is efficacious in MCF7 cells. Proliferation assay in MCF7 cell lines after treatment with A) Alpelisib, B) Fulvestrant, or C) Alp + Fulv. D) Mammospheres derived from MCF7 EV or SEMA7A OE cells after treatment with vehicle (DMSO), Alpelisib, Fulvestrant, or both. BF= brightfield, DAPI = channel used to observe cell trace violet-stained mammospheres.

The addition of SmAb to Alp inhibits tumor cell growth

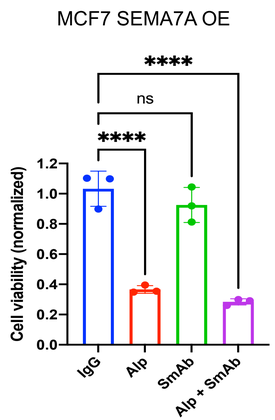


Fig 3. The combination of anti-SEMA7A treatment with PI3K inhibitor Alpelisib is efficacious in ER+ SEMA7A+ cell lines. Human ER+ MCF7 SEMA7A OE were treated with either IgG as a control, 1uM Alpelisib, 500uM anti-SEMA7A monoclonal antibody (SmAb) or the combination of Alp and SmAb. (Fold change, as compared to IgG control. One-way ANOVA, Multiple Comparisons analysis.

SEMA7A-expressing cells are sensitive to a combination of SmAb and Fulvestrant

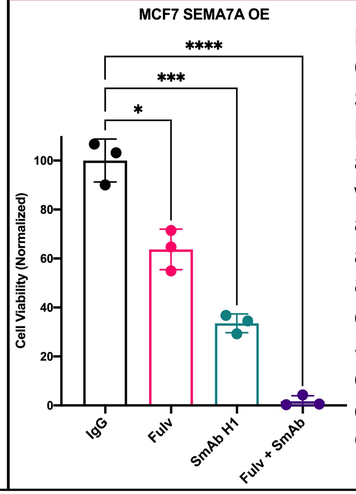


Fig 4. MCF7 ER+ SEMA7A OE cells are sensitive to SmAb in combination with Fulvestrant. Proliferation assay after 48-hour treatment with vehicle (DMSO), 500uM anti-SEMA7A monoclonal antibody treatment (SmAb), 8nM Fulvestrant, or the combination in MCF7 SEMA7A-OE cells (Percent cell viability, normalized to control). Multiple comparisons, One-way ANOVA analysis.

Conclusions

- SEMA7A-overexpressing ER+ BC cells are sensitive to inhibition by Alpelisib
- The addition of SmAb to Alp further enhances inhibition of tumor growth
- SEMA7A-overexpressing ER+ cells are sensitive to treatment with combinations of Alpelisib plus Fulvestrant or SmAb plus Fulvestrant, and the combinations are more effective than each single treatment alone

Future Directions

- Establish ER+ syngeneic mouse model for evaluating SEMA7A+ BC *in vivo*
- in ER+ BC patient samples
- Do *in vivo* experiments: Alpelisib or SmAb +/- Fulvestrant in ER+ SEMA7A+ BC
- Test other PI3K inhibitors (eg. Ipatasertib)
- Find SEMA7A/ER correlation in patient samples

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