ABSTRACT

Background: Prevention of estrogen receptor–negative (ER–) breast cancer is an unmet challenge, although tamoxifen and aromatase inhibitors can successfully decrease the incidence of ER-positive (ER+) breast cancer.

Hypothesis: Blocking PIK3 pathway by genetic knockdown or using a clinically applicable PI3K inhibitor (GDC-0941) can inhibit ER+ tumor initiation and progression.

Results:
- PI3K pathway is significantly activated in premalignant ER+ breast cancer.
- Genetic knockdown of PI3K and low dose GDC-0941 intervention reversed the disorganized 3-dimensional growth of semi-transformed human ER- mammary epithelial cells in vitro.
- Low-dose GDC-0941 treatment significantly delayed mammary tumor initiation in the MMTV-neu mouse model without exhibiting discernable adverse effects.
- Increased CD4+ GZMB+ T-cells were detected in mammary tissue after GDC-0941 treatment, suggesting enhanced immune surveillance.
- Mechanistically, elevated expression of potent T-cell chemo-attractants, including CCL5 and CXCL10, were detected both in vitro and in vivo after GDC-0941 treatment. Inhibition of PI3K significantly increased T-cell recruitment in a CCL5/CXCL10-dependent manner.

RESULTS

Figure 1. Blocking PIK3CA prevents the dysplasia phenotype of 10A.B2 mammary epithelial cells.

Figure 2. Targeting PI3K/Akt by GDC-0941 inhibited tumor initiation in MMTV-neu mice.

Figure 3. Low-dose GDC-0941 increases T-cell infiltration in mammary tissues of MMTV-neu mice.

CONCLUSIONS

- Our study demonstrated that PI3K/Akt activation as a potential target for ER- breast cancer prevention and showed that inhibiting the PI3K/Akt pathway by low-dose GDC-0941 effectively suppressed abnormal acini growth of semi-transformed mammary epithelial cells in vitro and delayed ER+ mammary tumor initiation in vivo.
- Low dose of PI3K inhibitor also significantly enhanced T-cell recruitment in a CCL5 and CXCL10–dependent manner.

REFERENCES