Harnessing antibody-based therapies for treating triple-negative breast cancer

**Description:** Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer that has a poor prognosis and high rate of relapse. This type of breast cancer cannot be treated with hormone therapies or therapies targeting the growth factor receptor HER2. Recent research indicates that another growth factor receptor, the epidermal growth factor receptor (EGFR), is expressed and active in TNBC. This receptor increases the growth and metastasis of TNBC and thus represents a therapeutic target for the treatment of this disease.

**Relevance:** Currently, TNBC can be treated only with standard chemotherapy and radiation, thus, the need for more advanced treatment options is urgent. Studies by the Wheeler laboratory indicate that nuclear EGFR enhances TNBC growth and cannot be blocked by anti-EGFR antibody therapies such as cetuximab. The results of this study revealed that blocking EGFR trafficking to the nucleus could increase the efficacy of cetuximab in TNBC providing a new treatment option for patients.

**Results:** Therapies that inhibit the EGFR have been used for decades to treat several cancers. One such therapy, cetuximab, is an antibody that can bind to the EGFR on the cell surface to prevent its activation. However, clinical trials testing the efficacy of cetuximab have yielded minor benefits.

Research in Dr. Wheeler’s laboratory may explain why TNBC cells do not respond to cetuximab. In approximately 20 percent of TNBC patients, the researchers found the EGFR localized inside the tumor cells’ nucleus, a cellular compartment that cannot be penetrated by antibody-based therapies such as cetuximab. Inside the nucleus, the EGFR can promote tumor cell growth and survival, which may lead to decreased overall survival of breast cancer patients.

Further studies indicated that a group of enzymes in TNBC cells called Src Family Kinases (SFKs) regulated nuclear EGFR translocation. Researchers found that inhibition of SFK activity blocked nuclear EGFR trafficking and led to an accumulation of EGFR on the cell surface. On the cell surface, the EGFR can be blocked by antibody-based therapies; thus, researchers observed an increase in tumor sensitivity to cetuximab. Collectively, these data indicate that targeting both nuclear EGFR and cell surface EGFR simultaneously may be a viable approach for treating patients with TNBC.

**Publications:**
