The current issue in the treatment of lung cancer patients harboring the activating epidermal growth factor receptor (EGFR) mutation is a spiral of the drug-resistance and novel EGFR-TKI development. Here, Saito and colleagues identified mitochondrial p14ARF as a specific effector at the downstream of EGFR signaling in response to gefitinib in non–small cell lung cancers. Based on that, a peptide that restores the impaired p14A reaction was created. This peptide was able to restore the sensitivity of gefitinib-resistant tumor cells to the same level as the gefitinib-sensitive cells. The identification of p14ARF and its antitumor peptide could be useful in the therapeutics of gefitinib-resistant cancers.

Activation of the phosphatidylinositol 3-kinase (PI3K) pathway is frequently observed in basal-like breast cancer, an aggressive subtype for which targeted therapies are lacking. Using patient-derived xenograft models of basal-like breast cancer, Xu and colleagues showed that the mTOR inhibitor MK-8669 and the AKT inhibitor MK-2206 inhibited tumor growth and cell proliferation synergistically in tumors with activated PI3K signaling. PTEN knockdown in a basal-like breast cancer cell line derived from a patient-derived xenograft model rendered cancer cells susceptible to mTOR and AKT inhibition in vivo. These results provided evidence of the PI3K pathway as a therapeutic target for basal-like breast cancer.

The efficacy of paclitaxel, a widely used chemotherapeutic drug, is often limited by tumor resistance that may relate to the ability of this drug to activate Toll-like receptor-4 (TLR4). Activation of the TLR4 pathway leads to upregulation of prosurvival genes that abolish the benefits of anticancer therapy. Using breast cancer models, Rajput and colleagues showed the in vitro and in vivo evidence that TLR4 depletion substantially reduced tumor recurrence, whereas its overexpression enhanced resistance to chemotherapy. These findings suggest that blocking TLR4 may significantly improve the efficacy of anticancer cytotoxic therapy.
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