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HPIP-HIF1a loop controls phenotypic plasticity in breast cancer cells

Human cancers display profound tumor heterogeneity, which is an important clinical determinant of drug resistance, tumor invasion and metastasis. Phenotypic plasticity, a property of tumor cells response to various microenvironmental cues, is one of the non-heritable factors to cause tumor heterogeneity. However the molecular mechanisms that defines the role of phenotypic plasticity accounting for tumor heterogeneity is largely unknown. We found that breast cancer cells display phenotypic plasticity when they are switched from hypoxic to normoxic microenvironments by operating a reciprocal positive feedback regulation between HPIP and HIF1α. PBXIP1/HPIP, an estrogen receptor interacting protein, is an upstream regulator of PI3K/AKT/mTOR signaling in cancer cells. How these signaling networks evoke phenotypic switching in breast cancer cells will be further discussed. Clinical data indicate that HPIP and HIF1 expression positively correlate in triple negative breast cancer subjects. Together this study revealed a novel signaling network controlling phenotypic plasticity in cancer cells, and further signifies considering this pathway as a novel therapeutic target to treat TNBCs.

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