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## STAR-RELATED LIPID TRANSFER PROTEIN 10 AS NOVEL KEY PLAYER IN ETHANOL-INDUCED ERBB2 BREAST CANCER PROGRESSION

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**Propose:** Epidemiological studies demonstrated that ethanol administration promotes breast cancer development and metastasis. Human breast cancer cells with a high expression of ErbB-2 Receptor Tyrosine Kinase 2 (ErbB2) exhibited an enhanced response to ethanol-stimulated cell invasion in vitro triggering the phosphorylation status of mitogen-activated protein kinase (MAPKs). ErbB2 amplification and/or overexpression has been described in 20-30% of human breast cancers and correlates with poor prognosis. StarD-related lipid transfer protein 10 (StarD10) is a member of the StarD protein family and lipid transfer protein with selective binding site to phosphatidylcholine (PC) and phosphatidylethanolamine (PE), two potential precursors for lipid metabolism and a major constituent of cell membranes. Choline metabolism and its derived metabolites can produce extensive alterations on phospholipid membrane composition that usually occurs before the morphological tumorigenic changes. StarD10 is highly expressed in 35% of ErbB2-positive breast cancer suggesting a selective growth advantage and cellular transformation for tumor expressing both proteins. The goal of this study is to investigate the role of StarD10 and ErbB2 cross-talk in breast cancer as consequence of ethanol administration and elucidate the molecular mechanisms.

**Methods:** The experiments were performed using MCF-7 and SKBR-3 human carcinoma cell lines. mRNA and protein levels were analyzed by Real-Time PCR and Western Blotting, respectively. *StarD10* promoter activity and cell proliferation were performed by promoter reporter and MTT assay, respectively. Phosphatidylcholine level was measured using an enzyme-coupled assay.

**Results:** Cells treated with 100mM ethanol for 48 hours showed increased expression of StarD10 and ErbB2. Consistently, ErbB2 overexpression caused an increase of StarD10 expression. Using PROMO program to predict transcription factor binding sites in DNA sequences, we found out that p65, c-MYC, c-FOS and c-JUN, well known to be transcription factors (TFs) ErbB2 downstream targets, are highly predicted to bind *StarD10* promoter sequence. Overexpression of all predicted TFs induced StarD10 promoter activity mimicking ErbB2 trigger function. Also, we demonstrated that StarD10 and ErbB2 positively regulate each other's expression. Moreover, ethanol increased phosphatidylcholine level supporting the proposed role of StarD10 as player on tumorigenesis via its lipid transporter function. Interesting, we found that both StarD10 overexpression and silencing induced cell growth and migration in MCF-7 and SKBR-3 cells. This data validated the hypothesis of StarD10 is a key protein on induced-ethanol breast cancer development accordingly with its pathophysiological level. High level of secreted PC was found in ethanol-treated cells media, while *StarD10* silencing completely prevented it. In contrast, *StarD10* overexpression promoted PC secretion and induced it further in co-treatment with ethanol. This finding could help us to explain how potentially StarD10 controls the changes in cell membrane properties during malignancy may be modulating the membrane fluidity.

**Conclusions:** The ability of StarD10 to influence ErbB2 expression and activity may be involve both dependent and independent lipid binding function. This is the first report demonstrating that ethanol can modulate in dynamic manner the ErbB2 role through StarD10 involvement in breast cancer.

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