Li-Fraumeni Syndrome Patient-derived LFS50 Progression Cell Series as an Experimental Model for Breast Cancer Prevention Research

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Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome associated with germline mutations in the tumor suppressor gene TP53. Breast cancer (BC) is the most common tumor amongst women with LFS, who have increased risk for premenopausal BC before age 40 and a lifetime risk of 49% by the age of 60. Non-malignant, human mammary epithelial cells (HMECs) were derived from the contralateral breast tissue of LFS patient (LFS50) undergoing BC surgery. The LFS50 HMEC progression series comprises of pre-immortal (HME50), spontaneously immortalized (HME50-5E), hTERT-immortalized (HME50hTERT or HME50hT), and tumorigenic (HMET) which can be modeled to represent breast cancer progression. Gene expressions of the LFS50 series were profiled using HG-U133_Plus_2 Affymetrix chip. By hierarchical clustering, the LFS50 cells were observed to have significant differential expression of genes and ANOVA results revealed that EMT-related genes (e.g., epithelial membrane protein 3, p= 6.84911E-19; E-cadherin, p= 8.66098E-19; and Keratin 5, p= 9.73095E-19) to be the most differentially expressed amongst the LFS50 cells. Ingenuity Pathway Analysis (IPA) confirmed that E-cadherin and Keratin 5 were the top most differentially expressed genes as well as G2/M DNA Damage Checkpoint Regulation (p= 2.67E-05), Estrogen-mediated S-phase Entry (p=3.32E-04) Mitotic Roles of Polo-Like Kinase (p=5.5E-04) as few of the top canonical pathways. Furthermore, to identify the type of breast cancer that LFS50 series could model, the triple negative breast cancer (TNBC) subtyping database tool predicted that each of the LFS50 strains could be classified as a different subtype. Finally, as a proof of principle for drug targeting, treatment of the LFS50 series with PRIMA-1, a p53 rescue drug, using 3D cultures resulted in a reduction in acini size of the pre-invasive LFS50 cells (p<0.05). Therefore, this progression series can serve as a resource for drug target discovery and breast cancer prevention research.

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