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RESEARCH ARTICLE

FASN EXPRESSION CORRELATION ANALYSIS TO ANTI-CANCER DRUGS

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ABSTRACT

The FASN is essential enzyme in de novo fatty acid synthesis that converted into phospholipids which provides resistance to drug uptake in malignancies. The FASN over expression and intrinsic/acquired both types of drug resistance reported in carcinomas. To assess the FASN up-regulation overall therapeutic response in drug screened cancer cell line data from Cancer Cell Line Encyclopedia (CCLE) by a rational CCLE GDSC gene expression - drug sensitivity correlations tool. We identify differential response of FASN in different drug treated tissue in which few cancer studies the drug performance increases in presence of FASN over expression but several cancer studies showed drug resistance by FASN over expression. The FASN increased expression drug resistance mainly linked with MAPK, EGFR, AKT, BCR/ABL, MDM2, HDAC and IGFR pathways that are responsible for angiogenesis, growth, survival, migration, differentiation and proliferation. Our study signifies the FASN elevated expression resistance to anti-proliferatory drugs for multiple oncogenes which indicate the FASN inter/intra-pathway interactions with oncogenes for their effective survival. We diagnose the FASN over expression as predictive marker in drug resistance genomes to design molecular medicines that consider it secondary target in generally accepted therapy.

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INTRODUCTION

The well-known homodimeric protein Fatty acid synthase (FASN) consist on six enzymatic domains that transform the acetyl-CoA and melonyl-CoA into palmitate fatty acid (Jensen-Urstad *et al*., 1859). The initial studies reported their role in embryonic development by triggering the proliferation of several tissues (Chirala *et al*., 2003). FASN perform significant contribution in molecular activity under aberrant metabolic states, inter-cellular integrity, cardiac stress related homeostasis response and regeneration of neural stem cells (Knobloch *et al*., 2012). The FASN differential expression monitored in normal and tumor tissues including colorectal, pancreatic and breast cancer has overexpression of FASN (Cai *et al*., 2014; Bhatt *et al*., 2012). The FASN elevated expression regulated through various factors such as SREBP-1c, ChREBP, mTOR, AMPK, LXRα, NAC1, miRNAs and acetyltransferase p300 in malignancies (Ishii *et al*., 2004; Hansmannel *et al*., 2006; Wang *et al*., 2016). The USP2a expression stimulates the FASN up-regulation in autocrine manner in prostate cancer (Graner *et al*., 2004).

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The population genetic studies explore the FASN increased level with poor prognosis in 424 obese men in prostate carcinoma (Nguyen *et al*., 2010). The FASN overexpression develops tumorigenesis by increasing the lipogenesis, Her2 activity, growth and proliferation of breast cells that induce factors-independent growth in culture (Vazquez-Martin *et al*., 2008). The breast malignancies transforms into non-malignant states by FASN expression inhibition (Gonzalez-Guerrico *et al*., 2016). The prostate cells gain 90% risk to develop invasive tumors with FASN overexpression and 30% risk with FASN down regulation (Fiorentino *et al*., 2008). The FASN overexpression leads to excessive palmitoylation of Wnt-1 and AR receptors which are responsible for adenocarcinomas establishment that induce the regulation of FASN transcription factor SREBP (Migita *et al*., 2009). The tumor cells utilize the palmitate for the synthesis of phospholipids to develop cell membrane inducing proliferation and 16-18C fatty acids makes alterations in plasma membrane fluidity (Rysman *et al*., 2010; Li, 2014). Various proliferating agents like KRAS-A, NRAS, HRAS, tubulin and Wnt factors need palmitoylation for functional heterogeneity (Heuer, 2016). The Wnt/β-catenin, mTOR and PI3K/AkT signaling pathways showed loss of functionality by the inhibition of FASN expression (Röhrig, 2016). The decline of FASN expression leads to decrease the quantity of diacyl glycerols that induce cell death by reduction of Kinase C signaling pathway (Benjamin *et al*., 2015). The

FASN over expression provides the nourishment to tumor microenvironment through vascularization, inflammatory response and lipogenesis in colorectal cancer (Zaytseva *et al*., 2014). The FASN mediated drug resistance reported in several studies that produce high amount of fatty acids which induced cell membrane reduced permeability of chemotherapeutic drugs such as doxorubicin (Rysman *et al*., 2010). There is urgent need to evaluate the multi-dimensional FASN differential expression behavior towards group of anti-cancer drugs to identify it as a secondary drug target and primary cause of drug resistance. We use a novel CCLE GDSC gene expression - drug sensitivity correlations tool (www.public.tableau.com) that operate on drug treated cell lines datasets to determine the effects of FASN expression on anti-cancer drug activity and efficiency.

RESULTS

FASN expression correlation towards anti-cancer drugs: We obtain the FASN expression correlation in 24 types of cancers with 21 anti-cancer drugs. The Crizotinib or PF-2341066 is anti-cancer drug targeting ALK, ROS1, c-Met/HGFR which are significant promoter of oncogenesis in various malignancies. The crizotinib competitively interact with ATP-binding pocket of above kinases to prevent the risk of aberrant cell proliferation (Kwak *et al*., 2010; Cui *et al*., 2011 Wong *et al*., 2009; Rikova *et al*., 2007). Here FASN showed negative correlation with PF-2341066 in lung, ovary, soft tissue and urinary tract carcinomas that indicates the FASN supportive role in drug targeting activity and efficiency to inhibit tumorigenesis. The PH-665752 or small molecule c-MET inhibitor reported in prevention of cell migration, motility and proliferation (Christensen *et al*., 2003). Here FASN showed negative correlation with PH-665752 in multiple myeloma to enhance drug activity. Erlotinib is EGFR inhibitor by interacting to its ATP-binding site and prevent the development of homodimer that initiate signaling cascade of cellular proliferation (Herbst, 2005b).

FASN showed positive correlation with Erlotinib in CML, esophagus, multiple myeloma and pancreatic cancers that is the sign of drug resistance which reduce the efficiency of drug. It also showed negative correlation in upper aerodigestive malignancies that invites to determine their supporting role in Erlotinib activity. Dovitinib or TK1258 inhibits VEGFR, PDGFR, FGFR1/3, FMS-3, c-KIT and colony stimulating factor receptor 1 that promote cancer cell proliferation, survival, angiogenesis and differentiation (Engebraaten *et al*., 1993). FASN showed positive correlation with Dovitinib in lymphoma to resist the effects of drug on cell functions. In urinary tract, melanoma and few lymphomas FASN showed negative correlation to TK1258 for enhancement of its effects. Lapatinib inhibits EGFR and HER2 kinases in breast cancer via interacting to ATP-binding pocket to block self-phosphorylation and signal activation for cell growth (Moy, 2007). FASN has positive correlation in colorectal and negative correlation in stomach cancer that showed both resistance and supportive behavior towards Lapatinib. Vandetanib inhibits VEGFR2, EGFR and RET kinases in various forms of thyroid gland tumors (Fallahi *et al*., 2015; Chougnet *et al*., 2015; Ammer *et al*., 2009). FASN has positive correlation in melanoma to reduce the activity of drug and negative correlation in soft tissue and glioma to enhance the activity of drug. Saracatinib or AZD0530 inhibits Src family of kinases, Abl-kinases and LCK kinases in treatments of Alzheimer, schizophrenia and T-cell leukemia (Ammer *et al*., 2009; Dong, 2010). FASN has positive correlation in liver cancer and negative correlation in myeloma which has tissue specific resistance. PLX4720 inhibit B-RAF pathway to prevent the cellular proliferation in melanomas (Li *et al*., 2006). FASN has negative correlation in soft tissue cancer that indicates drug better activity in FASN expression. RAF265 inhibit RAF kinases and VEGFR2 to limit the risk of tumor cell proliferation and angiogenesis (Kumar *et al*., 2009). FASN has positive correlation in breast and soft tissue cancer to decrease the effects of RAF265 and negatively correlation in CML, colorectal and breast cancer to provide support in drug efficiency. Selumetinib or AZD6244 is antineoplastic drug inhibit MEK1/2 which is the major driver of proliferative cellular pathways (Yeh *et al*., 2007). FASN showed strong positive correlation in CML and lymphoma that uncover its resistance to AZD6244. It has negative correlation in upper aerodigestive and stomach cancers to support the drug performance. Topotecin inhibit topoisomerase 1 to induce cell death by preventing DNA replication. It is specific S-Phase anti-cancer drug (Léger *et al*., 2004). FASN has healthy positive correlation in lymphoma and AML that indicates the resistance and gains intentions to determine their interaction as a secondary target. FASN has negative correlation in kidney cancer as a tissue specific scenario. Tanespimycein or 17AAG is inhibitor of HSP90 which is the controller of protein confirmations, growth and survival signaling pathways (Dimopoulos *et al*., 2011).

FASN showed negative correlation esophagus, liver, thyroid, stomach and T-cell ALL which indicates drug ideal activity in FASN expression. It has positive correlation in AML which showed its drug resistance property. AEW541 inhibit IGF-1R receptor kinase which is responsible for angiogenesis, transformations, survival, proliferation and metastasis. The drug inhibits the autophosphorylation of IGF-1R (García-Echeverría *et al*., 2004). FASN has strong positive correlation in endometrium and kidney cancers specify its resistance to drug effects. L-685458 is γ-secretes inhibitor which is transmembrane protein involved in Alzheimer disease (Shearman *et al*., 2000). FASN has strong positive correlation in T-cell ALL and negative correlation in endometrium that showed its differential behavior towards L-685458. Nilotinib is inhibitor of Bcr-Abl mediated proliferation, PDGFR, c-KIT and GISTs in CML therapies (Manley *et al*., 2010).

FASN has strong positive correlation in breast and glioma which showed drug resistance. Nutlin-3 inhibits MDM2 and activates TP53 apoptotic inducer to prevent the process of tumorigenesis. FASN has positive correlation in melanomas to decrease the effects of drug of apoptotic induction. Paclitaxel is anti-tumor drug that promote tubulin polymerization leading cell cycle arrest to cell death (Ganguly *et al*., 2010). FASN has negative correlation in liver and soft tissue cancer specify its progressive role in drug efficiency. Panobinostat is the inhibitor of Histone deacetylase enzymes to induce apoptosis (Gaur *et al*., 2015). FASN has positive correlation in AML and multiple myeloma which gives resistance to drug competence. It also has negative correlation in liver and lymphomas with drug effects. Palbociclib or PD-0332991 is the inhibitor of cyclin-dependent kinases in ER-positive and HER2-positive breast malignancies (Finn *et al*., 2009). FASN has negative correlations in colorectal, lung and ovary cancer that promotes the effects of drug (Fig 1).

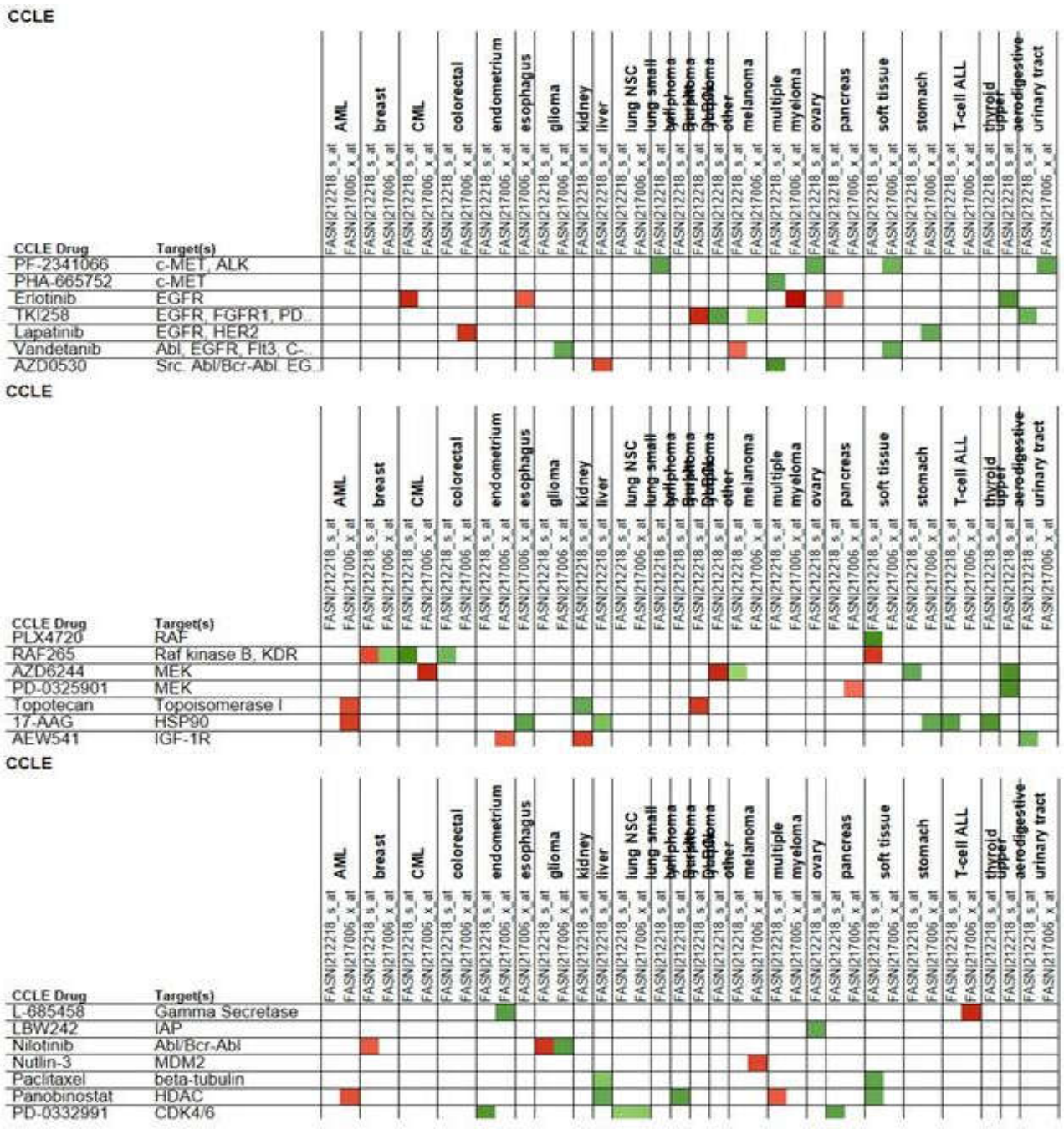

Fig. 1. FASN therapeutic response in 24 cancers with 21 anti-cancers drugs

DISCUSSION

FASN has two types i.e. cytosolic and mitochondrial both are capable to synthesize lipid contents but mitochondrial FASN induced fatty acid synthesis played significant role in mitochondrial physiology (Lee *et al*., 2013; Menendez , 2004). The cytosolic FASN is 270 KDa multi-dimensional polypeptide protein that has 6 catalytic domains including KS, MAT, DH, ER, KR, TE and ACP that gives the X shape to FASN protein (Zeng *et al*., 2011). The cancer cell synthesizes de novo fatty acids that develop into phospholipids which initiate signaling cascade (Kuhajda, 2006). Various studies reported the FASN overexpression resistance correlation with chemotherapeutics such as its elevated expression increased the resistance in doxorubicin-targeted breast cancer cell lines (Milgraum *et al*., 1997). In pancreatic cancer cells FASN up-regulation acquired gemsitabine resistance that shared its post-translational regulation (Buchholz *et al*., 2005).

The FASN knockout studies in cancer cell lines determine that cancer cells become sensitized to anti-cancer drugs such as Trastuzumab, 5-FU, γ-irradiation, TRAIL and DNA-damaging drugs (Ventura *et al*., 2015; Alò *et al*., 1999; Puig , 2011). In this study we determine the FASN overall therapeutic response to anti-cancer drugs and evaluate the resistance to various drugs in multiple tissues in a single approach. The FASN overexpression provides strong resistance to Erlotinib, TK1258, Lapatinib and Vandetanib anti-cancer drugs which mainly target the EGFR that modulate the signaling pathways of growth, survival, migration, adhesion and differentiation of tumor cells (Yewale *et al*., 2013). The EGFR activation stimulated by ligand-induced SH2 and PTB domains receptor dimerization that further trigger STAT, AKT, PI3K and MAPAK pathway that leads to cell adhesion, survival, migration and proliferation (Cargnello *et al*., 2011; Lim, 2006). The anti-EGFR drugs normally inhibit intracellular

kinase domain that harbor ATP binding pocket which prevent the autophosphorylation of downstream signaling pathways (Cohen, 2003). These drugs induce apoptosis, cell cycle arrest and activation of anti-growth signals (Herbst, 2002). The FASN resistance behaviors signify its functional association with EGFR mediated proliferatory pathways. In EGFR therapy the FASN showed the role of secondary drug target for upcoming drugs. The PF-2341066 and PHA-665752 drugs inhibit c-MET receptor tyrosine kinase protein which promotes oncogenesis by increasing the cell motility, invasion and metastasis (Bachleitner-Hofmann *et al*., 2008). The anti-c-MET therapy decreases the PI3K/AKT/mTOR growth and survival pathways. It also inhibits the PDGF-β, JAK2 and ABL receptor mediated proliferation (Andrae *et al*., 2008). The FASN overexpression showed negative correlation with these drugs that indicates their best performance to prevent the oncogenesis in the presence of FASN up-regulation. The AZD0530 and Nilotinib inhibit ABL/BCR-ABL pathway that drives various pathways of proliferation and survival (Quintás-Cardama, 2009). The BCR/ABL autophosphorylation trigger the development of GRB2/GAB2/SOS/ RAS/PI3K/ AKT/ MAPK/FOXO complex pathway of cell survival, migration and proliferation (Zhang *et al*., 1998; Smith *et al*., 1999; Pendergast *et al*., 1993; Sattler, 2002; Skorski *et al*., 1995). The FASN overexpression becomes a barrier in anti-BCR/ABL therapy due to positive resistance correlation with these drugs. The upcoming anti-cancer drugs for BCR/ABL accounted the expression of FASN as a drug target. The AZD6244 and PD-0325901 inhibit the MEK protein which is the component of MAPK pathway that is very significant in both normal/malignant states. The FASN showed resistance to anti-MEK therapy which is clear sign of its acquired oncogenic property to promote cell survival and growth. The Topotecin inhibit topoisomerase 1 which are responsible for DNA replication leads to cell division. The FASN showed strong resistance to Topotecin which indicates their gene regulatory essential role in oncogenesis. The 17-AAG inhibits HSP90 which is involved in tumor growth related protein stability (Pratt *et al*., 2003). The FASN has resistance to HSP90 inhibitor to enhance the process of tumorigenesis. The AEW541 inhibits IGF-1R which is growth promoter and anti-apoptotic mechanism supporter. Its overexpression reported in several malignancies including lung, prostate and breast cancers (Tognon *et al*., 2012; Chen, 2013). The FASN provides strong obstacles to anti-IGFR-1R therapy.

The determination of FASN-IGFR-1R crosstalk finds out novel targets in drug resistance. The RAF265 target RAF-B and KDR that initiate the signals to drive cell growth on large scale cellular level (Wu *et al*., 2000). The FASN showed resistance to drug therapy and promote the onco-proteomic signaling. The Nutlin-3 inhibits anti-apoptotic MDM2 which involved in negative regulation of TP53 (Tovar *et al*., 2006). The FASN has drug resistance to escaping of TP53 activation that makes the FASN as a component of anti-apoptotic cascade. The Panobinostat inhibit the HDAC family that involved in gene expression/regulation, cell cycle and notch signaling pathway (Rajendran *et al*., 2013). The FASN has opposition to anti-HDAC drug to support the progression of oncogene mediated carcinogenesis. The L-685458 inhibit γ-secretes which is transmembrane protein played crucial role in regulation of cell cycle regulatory membrane proteins such as CD44, Notch, ErbB4 and E-Cadherins (Allenspach *et al*., 2002; Zöller, 2011). The FASN resistance to L-685458 indicates its role in diseases other than cancer. The FASN drug resistance mapping in 24 cancers with 21 drugs displayed its key role in cancer progression to metastasis. This approach explores the FASN functional link with cell growth, survival, differentiation, proliferation and anti-apoptotic pathways. Our work opens the channel to examine the cross-talk among FASN and these drug targets which provides synergistic associations. The FASN overexpression behaves as a predictive marker in drug resistance by large screening in scale cancer cell lines. In future the concept of combinatorial drug dosage therapy eliminates from prescriptions due to FASN type drug resistance secondary targets. This study invites the system-level molecular medicine approach to design rational drugs to inhibit co-target pathways for efficient therapy.

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