Computational networks linking ECM-integrin interactions to tumor cell metabolism

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***Short Abstract* — Interactions of extracellular matrix (ECM) and integrins play a role in the proliferation, survival, apoptosis, migration and invasion of tumor cells. In our study, laminin-332 (Ln-332) loss (by γ2 subunit knockdown) in a carcinoma cell line produced 50 times larger tumors in mice and overexpression of cell surface Glut-1 *in vitro*. In addition, these knockdown cells increased their glucose uptake and lactate secretion (Warburg effect). We hypothesize that Ln-332 interactions with its integrin receptor α3β1 influence PI3-kinase/Akt pathway (frequently aberrant in cancer and involved in Warburg) via a novel mechanism that we are mapping by network modeling, primary tumor data regression analyses and network perturbation studies.**

***Keywords* - Laminin, Ln-5, Ln-332, Warburg, integrin, cancer, metabolism, network, Akt, PI3kinase.**

MOST cancers are of epithelial cell origin, making basement membranes (BM), the specialized ECM structure, their immediate microenvironment. Ln-332, an essential molecule in the BM, actively impacts cell processes, such as proliferation, migration, and invasion. It consists of α3 (LAMA3), β3 (LAMB3) and γ2 (LAMC2) subunits, of which β3 and γ2 are unique to Ln-332. Ln-332 initiates several signaling pathways through its integrin receptors, α6β4 and α3β1, as well as epidermal growth factor receptor[1]. Ln-332 expression is widely altered in various cancers, though data from various reports show diverging trends with increased Ln-332 expression in colon[2], cervical[3], and oral cancers[4]; while decreased Ln-332 expression is reported in basal cell carcinoma[5], lung[5], breast[6], prostate[7] and bladder cancers[7].

A consistent feature of cancer cell metabolism is the Warburg effect - cancer cells consume significantly larger amounts of glucose than normal cells, among which a large portion is converted to lactic acid by fermentation in the cell cytosol, rather than being oxidized in the mitochondria, even in the presence of oxygen[8]. There are several proposed advantages for this preference, including: 1) high flux of glucose through glycolysis generates high flux ATP and abundant intermediates for biosynthesis[9,10], and 3) lactic acid produced during this process acidifies the microenvironment, which jeopardizes survival of normal cells[11,12] and activates pH-dependent proteases that facilitate cancer cell invasion[13]. The PI3kinase-Akt signaling pathway is often aberrant in carcinomas and plays a role in tumor metabolism by favoring the Warburg effect [14,15].

Herein, we report the unexpected finding that the BM-associated ECM macromolecule, Ln-332, can repress the Warburg effect in cancer cells. Our findings indicate that removal of secreted Ln-332 by knockdown in carcinoma cells leads to the translocation of the glucose transporter, GLUT1, to the plasma membrane and initiation of Warburg effect. This process depends upon one of the Ln-332 receptors, integrin α3β1, and is reversible. This is the first proof of ECM interactions influencing cancer cell metabolism. We are now using network modeling, patient tumor data correlations and network perturbation studies, to prove our hypothesis that PI3K-Akt pathway is indeed a downstream effector of the Ln-332/α3β1 pathway and serves as an important node in intertwined roles of Ln-332 in cancer cell proliferation, survival, migration, invasion and now metabolism.

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