



SRC promotes lipogenesis: implications for obesity and breast cancer

Shu-Yong Lin ^{a,b} and Sheng-Cai Lin ^a

^aState Key Laboratory of Cellular Stress Biology, School of Life Sciences, Xiamen University, Xiamen, China; ^bDepartment of Digestive Diseases, School of Medicine, Xiamen University, Xiamen, China

ABSTRACT

Remodeling of lipid metabolism has been implicated in cancers; however, it remains obscure how the lipid metabolic pathways are altered by oncogenic signaling to affect tumor development. We have recently shown that proto-oncogene tyrosine-protein kinase Src interacts with and phosphorylates the lipogenesis enzyme phosphatidate phosphatase LPIN1 to promote breast cancer development.

ARTICLE HISTORY

Received 12 December 2020
Revised 15 December 2020
Accepted 17 December 2020

KEYWORDS

LPIN1; SRC;
phosphatidylethanolamine;
lipogenesis; breast cancer

Lipids comprise a huge family of bioactive molecules and biomembrane components in cells. Associations of obesity with the increased incidence and poorer prognosis of various cancers suggest that lipid metabolic reprogramming may play important roles in cancer.¹ Such relationship may be especially prominent for breast cancer cells that are exposed to high concentrations of fatty acids and adipokines secreted by surrounding adipocytes that are particularly abundant in breast tissues. Lipins are phosphatidic acid phosphatases (PAPs) that convert phosphatidic acids to diacylglycerols that serve as precursors for the synthesis of cellular triacylglycerols, and phospholipids alike. Posttranslational modifications including acetylation and serine phosphorylation have been reported to affect the PAP activity of LPIN1 (also known as lipin-1) through modulating intracellular translocation events.^{2,3}

In order to identify new regulatory mechanisms for LPIN1, we performed immunoprecipitation-mass spectrometry to screen for LPIN1-interacting proteins. To our surprise, the notorious proto-oncogene tyrosine protein kinase Src (SRC) was identified among the co-immunoprecipitated proteins. Three tyrosine residues of LPIN1 were found to be directly phosphorylated by SRC (Figure 1). LPIN1 phosphorylation was increased in several breast cancer cell lines when treated with pro-epidermal growth factor (EGF), platelet-derived growth factor (PDGF), insulin-like growth factor I (IGF1), insulin (INS) or leptin (LEP).⁴ As some of those growth factors or cytokines are key members of the molecular network in obesity, it is likely that SRC is often over-activated, particularly in breast cancers. For example, mammary tumors from MMTV-PyVT transgenic mice, a routinely utilized breast cancer model, show Src hyperactivity. In humans, SRC is upregulated in about one-fifth of breast cancer cases according to the Catalog of Somatic Mutations in Cancer. Importantly, we found that human breast tumor tissues of different subtypes uniformly exhibited dramatically elevated activation phosphorylation of SRC and tyrosine phosphorylation of LPIN1, both of which are usually very low or undetectable in adjacent normal tissues.

We then set to explore the biological consequences of SRC-mediated phosphorylation of LPIN1. It was found that phosphorylation by SRC enhances the catalytic activity of LPIN1, leading to increased production of glycerolipids. In contrast, the regulatory role of LPIN1 as a transcriptional coactivator involved in fatty acid oxidation was not affected. To further explore whether LPIN1 phosphorylation would affect cancer development, we used multiple tumor models and demonstrated that tyrosine phosphorylation of LPIN1 is crucial for promoting the progression of mammary tumor to malignancy. We showed that deletion of *Lpin1* reduced tumor weight and lung metastasis. We also found that the levels of LPIN1 tyrosine phosphorylation in tumor tissues significantly correlate with breast cancer malignancy and poorer prognosis. It is noteworthy that the depletion of *Lpin1* did not change tumor incidence and tumor onset.⁴ These data indicate that upregulation of lipogenesis plays an important part in tumor malignant transformation, but it may not be a driving force in tumor initiation.

One interesting matter regarding the lipid species affected by the SRC-LPIN1 axis is that phosphatidylethanolamines (PEs) are increased most prominently among the lipid species tested in various experimental conditions.⁴ This finding is consistent with a previous study demonstrating stronger upregulation of PE than the other phospholipid species in malignant breast cancer.⁵ We also found that blocking the increase of PE alone has stronger inhibitory effect on the proliferation of breast cancer cells than inhibition of triacylglycerol synthesis.⁴ It is thus likely that PE synthesis is favored by the SRC-LPIN1 axis to propel breast cancer progression (Figure 1). There are some clues why PE is unique among phospholipids for tumor development (Figure 1). First, as the second most abundant phospholipid in animal cells, PE is particularly enriched in the inner membrane of mitochondria and is essential for mitochondrial functions such as production of energy.⁶ Reduction of mitochondrial PE synthesis inhibits the proliferation of breast cancer cells.⁷ Second, the microtubule-associated

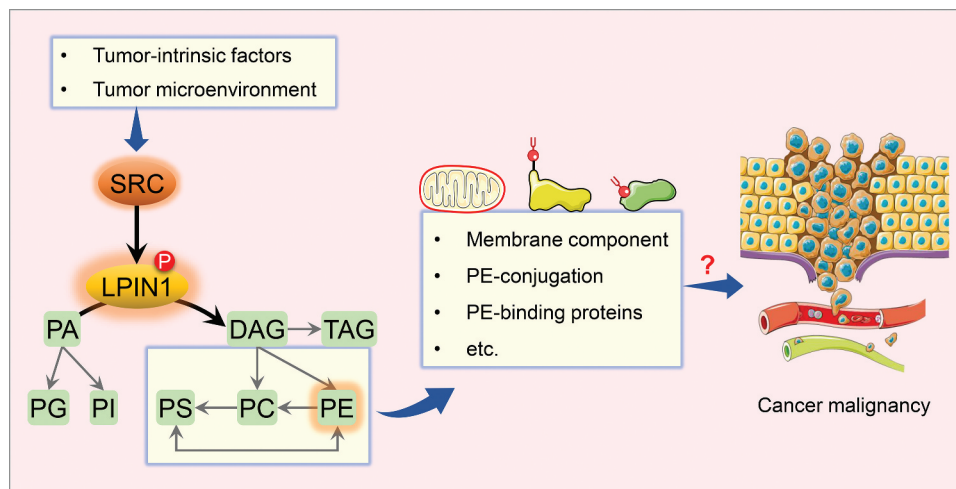


Figure 1. SRC-mediated LPIN1 phosphorylation and mammary oncogenesis. Tumor-intrinsic oncogene activation and/or obese-associated extracellular stimuli impinge upon the proto-oncogene tyrosine protein kinase Src (SRC)-phosphatidate phosphatase LPIN1 axis, leading to increased production of lipids. It is possible that SRC may also modulate the conversion between phospholipids, which ultimately leads to preferential accumulation of phosphatidylethanolamine (PE). PA, phosphatidic acid; PG, phosphatidylglycerol; PI, phosphatidylinositol; DAG, diacylglycerol; TAG, triacylglycerol; PS, phosphatidylserine; PC, phosphatidylcholine. The disproportional increase in PE may in turn contribute to cancer malignancy through mechanisms that are yet to be defined. Several elements of this image were adopted and modified from Servier Medical Art by Servier (<https://smart.servier.com/>) licensed under a Creative Commons Attribution 3.0 Unported License (<https://creativecommons.org/licenses/by/3.0/>).

protein 1 light chain 3 (LC3)-PE conjugation system is the core machinery for autophagy, the network of which interfaces with multiple aspects of cancer malignancy.⁸ Third, PE-binding proteins that could serve as direct sensors for PE have been implicated in the metastasis of breast cancer.⁹ More studies have to be conducted to pinpoint the exact roles of PE with relation to cancer malignancy.

Additionally, we examined for any differential manifestation of the SRC-LPIN1 axis in luminal, receptor tyrosine-protein kinase erbB-2 (ERBB2, best known as HER2)-overexpressing and triple-negative breast cancer (TNBC) subtypes by using various cell lines, animal models and clinical samples. It was found that the SRC-LPIN1 axis intersected by diverse extracellular and intracellular cues seems to be ubiquitously activated and plays a general role among all the breast cancer subtypes.⁴ However, statistically significant correlation between body mass index (BMI) and the levels of tyrosine phosphorylation of LPIN1 in tumors was found only in the luminal A subtype (data not shown). This result concurs with reports showing varied influence of obesity on breast cancer prognosis according to different subtypes.¹⁰ The lack of correlation between obesity and LPIN1 tyrosine phosphorylation in the other breast cancer subtypes could be caused by robust tumor-intrinsic mitogenic signaling in those tumors. HER2 in the HER2-overexpressing subtype, and epidermal growth factor receptor (EGFR) overexpressed in TNBC are likely among the confounding factors that shadow the effect of obesity. Larger clinical sample sizes and more obese animal models in different genetic backgrounds may help delineate the relative contributions to cancer development of tumor-intrinsic factors and tumor-extrinsic factors such as obesity, which converge to activate the SRC-LPIN1 axis (Figure 1).

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by the National Natural Science Foundation of China under Grants [#31822027, #31690101, #31871168]; the Fundamental Research Funds for the Central Universities under Grand [#20720190084]; the Natural Science Foundation of Fujian Province of China under Grand [#2020J02003] and the Youth Innovation Fund of Xiamen under Grand [#3502Z20206028].

ORCID

Shu-Yong Lin  <http://orcid.org/0000-0002-4419-1713>
Sheng-Cai Lin  <http://orcid.org/0000-0003-1993-8376>

References

1. The Lancet Diabetes Endocrinology. The obesity-cancer link: of increasing concern. *Lancet Diabetes Endocrinol.* 2020;8:175. doi:10.1016/S2213-8587(20)30031-0.
2. Zhang P, Reue K. Lipin proteins and glycerolipid metabolism: roles at the ER membrane and beyond. *Biochim Biophys Acta Biomembr.* 2017;1859:1583–1595. doi:10.1016/j.bbmembr.2017.04.007.
3. Li TY, Song L, Sun Y, Li J, Yi C, Lam SM, Xu D, Zhou L, Li X, Yang Y, et al. Tip60-mediated lipin 1 acetylation and ER translocation determine triacylglycerol synthesis rate. *Nat Commun.* 2018;9:1916. doi:10.1038/s41467-018-04363-w.
4. Song L, Liu Z, Hu HH, Yang Y, Li TY, Lin ZZ, Ye J, Chen J, Huang X, Liu DT, et al. Proto-oncogene Src links lipogenesis via lipin-1 to breast cancer malignancy. *Nat Commun.* 2020;11:5842. doi:10.1038/s41467-020-19694-w.
5. Merchant TE, Meneses P, Gierke LW, Den Otter W, Glonek T. 31P magnetic resonance phospholipid profiles of neoplastic human breast tissues. *Br J Cancer.* 1991;63:693–698. doi:10.1038/bjc.1991.157.

6. Vance JE. Phospholipid synthesis and transport in mammalian cells. *Traffic*. 2015;16:1–18. doi:10.1111/tra.12230.
7. Keckesova Z, Donaher JL, De Cock J, Freinkman E, Lingrell S, Bachovchin DA, Bieri B, Tischler V, Noske A, Okondo MC, et al. LACTB is a tumour suppressor that modulates lipid metabolism and cell state. *Nature*. 2017;543:681–686. doi:10.1038/nature21408.
8. Rybstein MD, Bravo-San Pedro JM, Kroemer G, Galluzzi L. The autophagic network and cancer. *Nat Cell Biol*. 2018;20:243–251. doi:10.1038/s41556-018-0042-2.
9. Li H, Huang F, Fan L, Jiang Y, Wang X, Li J, Wang Q, Pan H, Sun J, Cao X, et al. Phosphatidylethanolamine-binding protein 4 is associated with breast cancer metastasis through Src-mediated Akt tyrosine phosphorylation. *Oncogene*. 2014;33:4589–4598. doi:10.1038/onc.2013.408.
10. Jiralerspong S, Goodwin PJ. Obesity and breast cancer prognosis: evidence, challenges, and opportunities. *J Clin Oncol*. 2016;34:4203–4216. doi:10.1200/JCO.2016.68.4480.