

Guest editorial:

HIGHLIGHT REPORT: ROLE OF CHOLINE PHOSPHOLIPID METABOLISM IN TUMOR PROGRESSION

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Recently, Sonkar and colleagues published a comprehensive review about the glycerophosphocholine (GPC) pathway and its role in cancer biology (Sonkar et al., 2019). The authors address the enzymes of the GPC breakdown pathway; the oncogenic signaling pathways and transcription factors that regulate the GPC pathway; the interactions of the GPC pathway with other biochemical pathways such as glycolysis and triglyceride metabolism, and finally focus on non-invasive magnetic resonance spectroscopy techniques for detection of GPC in tumor tissue. Activation of choline metabolism is a critical step of cancer development and may lead to increased levels of phosphocholine, GPC and total choline-containing compounds (Hanan and Weinberg, 2011; Griffiths et al., 1981; Daly et al., 1987; Aboagye and Bhujwala, 1999; Gillies et al., 2002). These changes can be detected by magnetic resonance spectroscopy (Baek et al., 2008; Bolan et al., 2003; He et al., 2003-2004; Al-Saffar et al., 2017; Glunde et al., 2011). The glycerophosphodiesterase GPCPD1 is a key enzyme in choline metabolism that cleaves GPC to glycerol-3-phosphate (G3P) and choline (Stewart et al., 2012). This activity mediates integrin expression, tumor cell adhesion, spreading and migration (Lesjak et al., 2014; Marchan et al., 2012). Recently, glycerol-3-phosphate acyltransferase1, which further processes G3P to generate lysophosphatidic

acid (LPA) has been shown to promote tumor cell migration and is associated with poor survival in ovarian cancer (Marchan et al., 2017).

Besides phospholipid metabolism and metastasis tumor progression involves numerous further processes, such as proliferation (Schmidt et al., 2008; Hellwig et al., 2016; Siggelkow et al., 2012), immune cell infiltration (Edlund et al., 2019; Schmidt et al., 2012, 2018; Godoy et al., 2014), oxidative stress response (Cadenas et al., 2019; 2014; 2012). Studies in future will have to show if targeting members of the glycerophosphocholine pathway will delay tumor progression. The present review of Sonkar et al. gives a comprehensive summary of the state-of-the-art in this field and is of high value to anyone interested in how choline-phospholipid-metabolism is linked to tumor development.

Conflict of interest

The author declares no conflict of interest.

REFERENCES

- Aboagye EO, Bhujwala ZM. Malignant transformation alters membrane choline phospholipid metabolism of human mammary epithelial cells. *Cancer Res.* 1999;59:80-4.
- Al-Saffar NMS, Agliano A, Marshall LV, Jackson LE, Balarajah G, Sidhu J, et al. In vitro nuclear magnetic resonance spectroscopy metabolic biomarkers for the combination of temozolomide with PI3K inhibition in paediatric glioblastoma cells. *PLoS One.* 2017;12: e0180263.

- Baek HM, Chen JH, Nalcioglu O, Su MY. Choline as a biomarker for cell proliferation: do the results from proton MR spectroscopy show difference between HER2/neu positive and negative breast cancers? *Int J Cancer*. 2008;123:1219-21.
- Bolan PJ, Meisamy S, Baker EH, Lin J, Emory T, Nelson M, et al. In vivo quantification of choline compounds in the breast with 1H MR spectroscopy. *Magn Reson Med*. 2003;50:1134-43.
- Cadenas C, Vosbeck S, Hein EM, Hellwig B, Langer A, Hayen H, et al. Glycerophospholipid profile in oncogene-induced senescence. *Biochim Biophys Acta*. 2012;1821:1256-68.
- Cadenas C, van de Sandt L, Edlund K, Lohr M, Hellwig B, Marchan R, et al. Loss of circadian clock gene expression is associated with tumor progression in breast cancer. *Cell Cycle*. 2014;13:3282-91.
- Cadenas C, Vosbeck S, Edlund K, Grgas K, Madjar K, Hellwig B, et al. LIPG-promoted lipid storage mediates adaptation to oxidative stress in breast cancer. *Int J Cancer*. 2019;145:901-15.
- Daly PF, Lyon RC, Faustino PJ, Cohen JS. Phospholipid metabolism in cancer cells monitored by 31P NMR spectroscopy. *J Biol Chem*. 1987;262:14875-8.
- Edlund K, Madjar K, Mattsson JSM, Djureinovic D, Lindskog C, Brunnström H, et al. Prognostic impact of tumor cell programmed death ligand 1 expression and immune cell infiltration in NSCLC. *J Thorac Oncol*. 2019;14:628-640.
- Gillies RJ, Raghunand N, Karczmar GS, Bhujwala ZM. MRI of the tumor microenvironment. *J Magn Reson Imaging*. 2002;16:430-50.
- Glunde K, Bhujwala ZM, Ronen SM. Choline metabolism in malignant transformation. *Nat Rev Cancer*. 2011;11:835-48.
- Godoy P, Cadenas C, Hellwig B, Marchan R, Stewart J, Reif R, et al. Interferon-inducible guanylate binding protein (GBP2) is associated with better prognosis in breast cancer and indicates an efficient T cell response. *Breast Cancer*. 2014;21:491-9.
- Griffiths JR, Stevens AN, Iles RA, Gordon RE, Shaw D. 31P-NMR investigation of solid tumours in the living rat. *Biosci Rep*. 1981;1:319-25.
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646-74.
- He Q, Xu RZ, Shkarin P, Pizzorno G, Lee-French CH, Rothman DL, et al. Magnetic resonance spectroscopic imaging of tumor metabolic markers for cancer diagnosis, metabolic phenotyping, and characterization of tumor microenvironment. *Dis Markers*. 2003-2004;19:69-94.
- Hellwig B, Madjar K, Edlund K, Marchan R, Cadenas C, Heimes AS, et al. Epsin family member 3 and ribosome-related genes are associated with late metastasis in estrogen receptor-positive breast cancer and long-term survival in non-small cell lung cancer using a genome-wide identification and validation strategy. *PLoS One*. 2016;11:e0167585.
- Lesjak MS, Marchan R, Stewart JD, Rempel E, Rahnenführer J, Hengstler JG. EDI3 links choline metabolism to integrin expression, cell adhesion and spreading. *Cell Adh Migr*. 2014;8:499-508.
- Marchan R, Lesjak MS, Stewart JD, Winter R, Seeliger J, Hengstler JG. Choline-releasing glycerophosphodiesterase EDI3 links the tumor metabolome to signaling network activities. *Cell Cycle*. 2012;11:4499-506.
- Marchan R, Büttner B, Lambert J, Edlund K, Glaeser I, Blaszkewicz M, et al. Glycerol-3-phosphate acyltransferase 1 promotes tumor cell migration and poor survival in ovarian carcinoma. *Cancer Res*. 2017;77:4589-601.
- Schmidt M, Böhm D, von Törne C, Steiner E, Puhl A, Pilch H, et al. The humoral immune system has a key prognostic impact in node-negative breast cancer. *Cancer Res*. 2008;68:5405-13.
- Schmidt M, Hellwig B, Hammad S, Othman A, Lohr M, Chen Z, et al. A comprehensive analysis of human gene expression profiles identifies stromal immunoglobulin κ C as a compatible prognostic marker in human solid tumors. *Clin Cancer Res*. 2012;18:2695-703.
- Schmidt M, Weyer-Elberich V, Hengstler JG, Heimes AS, Almstedt K, Gerhold-Ay A, et al. Prognostic impact of CD4-positive T cell subsets in early breast cancer: a study based on the FinHer trial patient population. *Breast Cancer Res*. 2018;20:15.
- Siggelkow W, Boehm D, Gebhard S, Battista M, Sickling I, Lebrecht A, et al. Expression of aurora kinase A is associated with metastasis-free survival in node-negative breast cancer patients. *BMC Cancer*. 2012;12:562.
- Sonkar K, Ayyappan V, Tressler CM, Adelaja O, Cai R, Cheng M, et al. Focus on the glycerophosphocholine pathway in choline phospholipid metabolism of cancer. *NMR Biomed*. 2019;32:e4112.
- Stewart JD, Marchan R, Lesjak MS, Lambert J, Hergenroeder R, Ellis JK, et al. Choline-releasing glycerophosphodiesterase EDI3 drives tumor cell migration and metastasis. *Proc Natl Acad Sci U S A*. 2012;109:8155-60.