Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Biotarget. Author manuscript; available in PMC 2019 October 19.

Published in final edited form as:

Biotarget. 2019 August ; 3: . doi:10.21037/biotarget.2019.07.03.

Fatty acid oxidation (FAO) metabolic switch: metastasis in lymph nodes driven by yes-associated protein (YAP) activation

Thomas Wang[1,2], **Costa Frangou**[3], **Jianmin Zhang**[1]

[1]Department of Cancer Genetics and Genomics, Roswell Park Cancer Institute, Buffalo, NY 14263, USA

[2]The University of Western Ontario, London, Ontario, Canada

[3]Program in Molecular and Integrative Physiological Sciences, Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA

The Hippo signaling pathway, which was first discovered in *Drosophila*, guides organ growth in many multicellular organisms by regulating the proliferation, differentiation, and death of cells (1,2). Because this pathway offers potential targets for anticancer agents, it is of great interest in biomedical research. The key effectors of the mammalian Hippo pathway are the yes-associated protein (YAP) of proto-oncogenes and its paralog, transcriptional coactivator with PDZ-binding motif (TAZ). Upstream of YAP/TAZ is large tumor suppressor kinase 1/2 (LATS1/2), which is a kinase that inhibits YAP/TAZ with the help of adaptor proteins MOB kinase activator 1 A/B (MOB1A/B) by phosphorylating YAP/TAZ on serine residues. In the most basic model of this pathway, YAP/TAZ is targeted for degradation or sequestration in the cytoplasm when phosphorylated. When dephosphorylated, it becomes active and accumulates in the nucleus, where it partners with transcription factors such as TEA domain transcription factor (TEAD) to alter gene expression (3).

It has long been debated whether cancer spreads to distant sites through the lymphatic system (the Halstedian theory) or directly to the primary site (the systemic theory). The spectrum theory proposes that both the Halstedian and systemic theories are correct, but that traveling along the lymphatic system is a more effective means of spreading cancer (4,5). This conclusion is consistent with evidence from several recent studies using mouse models, which showed that metastasis that spreads through the lymphatic system results in more metastases than when it spreads directly from the primary tumor (6,7). The ability of malignant cancer cells to spread from the primary site to distant parts of the body through the lymphatic system may explain why the presence of metastasis in lymph nodes (LNs) can be used to predict cancer outcome. Higher LN ratios (an LN ratio being defined as the number of metastatic LNs divided by the number of examined nodes) have consistently been

Correspondence to: Jianmin Zhang. Department of Cancer Genetics and Genomics, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, USA. jianmin.zhang@roswellpark.org.

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

found to predict poorer outcomes for many types of cancers, including colon, pancreatic, head, and neck cancers (8,9).

A study using mouse models that was recently reported in *Science* (2019;363:644-9) found YAP to be responsible for metastasis in LNs through metabolic reprogramming, which causes tumors to shift from glycolysis to fatty acid oxidation (FAO) for energy production when metastasized to LNs (10). In this study, LN-metastatic tumors showed greater upregulation than primary tumors of genes involved in fatty acid metabolism, adipogenesis, bile acid metabolism, cholesterol homeostasis, and oxidative phosphorylation (OXPHOS). YAP activation alone triggered these changes, as shown by the fact that knockdown of YAP was sufficient to markedly reduce FAO. Etomoxir, an FAO inhibitor, was able to suppress LN metastasis and the growth of tumor cells directly implanted into LN while having no effect on the size of the primary tumor, thereby showing that LN-metastasized tumors depend on FAO for energy production.

The authors demonstrated mechanistically that elevated bile acid was responsible for the activation of YAP in LN metastatic tumors. The bile acid taurodeoxycholic acid (TDCA) was able to induce YAP dephosphorylation and activation in B16F10 within 30 minutes of treatment *in vitro*. Treatment with cholesterol, the precursor to all bile acids, was able to elicit the same response, albeit with slower kinetics. On the other hand, siRNA knockdown of cholesterol 7α-hydroxylase (CYP7A1), the only rate-limiting enzyme in bile acid synthesis (11), dramatically inhibited cholesterol-induced YAP activation. The authors also found that nuclear YAP localization in the metastatic LNs of melanoma patients correlated with a reduction in distant metastasis-free survival.

Cancer cells face evolutionary pressures in the body just as organisms face evolutionary pressures in their environments. Cancer cells must compete for substrates and grow just as organisms must compete for food and occupy every niche in their ecosystems (12). In many scenarios, cancer cells are pressured to undergo metabolic reprogramming in order to maximize energy production on the basis of the types of substrates available in their microenvironments (13). As epithelial cancer cells begin spreading into sites further from their basement membranes, they have difficulty obtaining adequate amounts of oxygen and glucose (14). These hypoxic conditions select for cancer cells with upregulated genes related to glycolysis, i.e., the anaerobic conversion of glucose to pyruvate and then to lactate—as opposed to selection under aerobic conditions for cancer cells with upregulated genes related to full oxidation of glucose, which is a relatively inefficient and wasteful metabolic pathway. Requiring little oxygen, the cancer cells that thrive in hypoxic conditions are often more metastatic, for they can survive hypoxic and anoxic episodes during their migration. The glycolytic phenotypes selected for at the beginning of carcinogenesis are maintained even after normoxic conditions have been restored, as only glycolytic cancer cells can resist the toxic environments created by the waste products of glycolysis (15).

In environments where a particular energy substrate is more abundant than other energy substrates, it is to be expected that cancer cells adapted to metabolize the more abundant substrate will exhibit greater fitness than cancer cells not so adapted. Consistent with this hypothesis, ovarian and colon cancers have been found to upregulate genes involving lipid

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

uptake and metabolism in consequence of their proximity to adipocytes (16). In otherwise nutrient-deprived microenvironments, colon cancer cells have been able to transport and oxidize fatty acids from surrounding adipocytes (16,17). The lymphatic system plays important roles in immune defense and metabolic maintenance (18). Tumor cells grown in the microenvironment of the LN may undergo nutrient stress. The present study indicated that metastatic tumor cells in mice preferentially use fatty acids rather than glucose as a fuel source in the lipid-rich microenvironment of the LN (10).

Recently, it has been indicated that metabolic cues such as glucose, lipids, hormones, and other metabolic intermediates regulate YAP/TAZ activity (19). Cholesterol is derived from acetyl CoA through the mevalonate pathway. HMG-CoA reductase is the rate-limiting enzyme in this pathway and the target of statin drugs, which are most commonly used to treat high cholesterol and prevent cardiovascular events (20,21). Treatment of MDA-MB-231 breast cancer cells with statin drugs has been shown to induce cytoplasmic localization of YAP/TAZ by depleting geranylgeranyl pyrophosphate (GGPP) (20). One example of an oncogene controlled by the TEAD-YAP complex in a manner dependent on the mevalonate pathway is the receptor for hyaluronan-mediated motility (RHAMM), which functions as a hyaluronan receptor and mitotic spindle-binding protein that promotes microtubule instability and mitotic spindle integrity. Inhibition of the mevalonate pathway using simvastatin has led to the inhibition of RHAMM expression by way of the depletion of downstream GGPP, thus inactivating YAP (21). These findings suggest the potential for targeting components in the mevalonate pathway as a means of suppressing the YAP-mediated transcription of oncogenes. Similarly, the present study indicated that inhibition of YAP-driven FAO in LNs may help reduce tumor metastasis (10).

Further research will be needed to understand how YAP activation confers FAO and whether it is dependent on TEAD transcription factors. FAO confers a wide range of carcinogenic properties, including proliferation, angiogenesis, and metastasis. The FAO pathway represents a vulnerability in cancer with several potential upstream targets, including carnitine palmitoyltransferase 1 (CPT1) in FAO, HMG-CoA reductase in the mevalonic acid pathway, and YAP/TAZ activation. The therapeutic potential and clinical applications of small-molecule inhibitors that target these sites should be explored.

Acknowledgments

Funding: This work was supported by the Roswell Park Cancer Institute and the National Cancer Institute, grant P30 CA016056; the Roswell Park Alliance Foundation; the National Cancer Institute, grant R01 CA207504; and the American Cancer Society, grant RSG-14-214-01-TBE (to J Zhang).

References

1. Pan D. The hippo signaling pathway in development and cancer. Dev Cell 2010;19:491–505. [PubMed: 20951342]
2. Zanconato F, Cordenonsi M, Piccolo S. YAP/TAZ at the Roots of Cancer. Cancer Cell 2016;29:783–803. [PubMed: 27300434]
3. Yu FX, Zhao B, Guan KL. Hippo Pathway in Organ Size Control, Tissue Homeostasis, and Cancer. Cell 2015;163:811–28. [PubMed: 26544935]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

4. Podgrabinska S, Skobe M. Role of lymphatic vasculature in regional and distant metastases. Microvasc Res 2014;95:46–52. [PubMed: 25026412]
5. Alitalo K. The lymphatic vasculature in disease. Nat Med 2011;17:1371–80. [PubMed: 22064427]
6. Brown M, Assen FP, Leithner A, et al. Lymph node blood vessels provide exit routes for metastatic tumor cell dissemination in mice. Science 2018;359:1408–11. [PubMed: 29567714]
7. Pereira ER Kedrin D, Seano G, et al. Lymph node metastases can invade local blood vessels, exit the node, and colonize distant organs in mice. Science 2018;359:1403–7. [PubMed: 29567713]
8. Riediger H, Keck T, Wellner U, et al. The lymph node ratio is the strongest prognostic factor after resection of pancreatic cancer. J Gastrointest Surg 2009;13:1337–44. [PubMed: 19418101]
9. Berger AC, Sigurdson ER LeVoyer T, et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. J Clin Oncol 2005;23:8706–12. [PubMed: 16314630]
10. Lee CK, Jeong SH, Jang C, et al. Tumor metastasis to lymph nodes requires YAP-dependent metabolic adaptation. Science 2019;363:644–9. [PubMed: 30733421]
11. Chiang JY. Bile acid metabolism and signaling. Compr Physiol 2013;3:1191–212. [PubMed: 23897684]
12. Boroughs LK, DeBerardinis RJ. Metabolic pathways promoting cancer cell survival and growth. Nat Cell Biol 2015;17:351–9. [PubMed: 25774832]
13. Sullivan LB, Gui DY, Vander Heiden MG. Altered metabolite levels in cancer: implications for tumour biology and cancer therapy. Nat Rev Cancer 2016;16:680–93. [PubMed: 27658530]
14. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74. [PubMed: 21376230]
15. DeBerardinis RJ, Lum JJ, Hatzivassiliou G, et al. The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. Cell Metab 2008;7:11–20. [PubMed: 18177721]
16. Wen YA, Xing X, Harris JW, et al. Adipocytes activate mitochondrial fatty acid oxidation and autophagy to promote tumor growth in colon cancer. Cell Death Dis 2017;8:e2593. [PubMed: 28151470]
17. Nieman KM, Kenny HA, Penicka CV, et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. Nat Med 2011;17:1498–503. [PubMed: 22037646]
18. von der Weid PY, Rainey KJ. Review article: lymphatic system and associated adipose tissue in the development of inflammatory bowel disease. Aliment Pharmacol Ther 2010;32:697–711. [PubMed: 20636483]
19. Koo JH, Guan KL. Interplay between YAP/TAZ and Metabolism. Cell Metab 2018;28:196–206. [PubMed: 30089241]
20. Sorrentino G, Ruggeri N, Specchia V et al. Metabolic control of YAP and TAZ by the mevalonate pathway. Nat Cell Biol 2014;16:357–66. [PubMed: 24658687]
21. Wang Z, Wu Y, Wang H, et al. Interplay of mevalonate and Hippo pathways regulates RHAMM transcription via YAP to modulate breast cancer cell motility. Proc Natl Acad Sci U S A 2014;111:E89–98. [PubMed: 24367099]