Editorial Commentary

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

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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 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 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.

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Footnote

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.

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