Editorial

Fatty acids: from adipocytes to cancer cells

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Cancer cells have re-programmed metabolism which acquires them competitive advantages. The most renowned discovery is the Warburg effect which refers to the production of lactic acid from glucose in cancer cells even under non-hypoxic conditions. Otto Warburg concluded this phenomenon was the result of damaged mitochondria and impaired respiration in cancer cells. Until recently emerging evidence show that such a conclusion is erroneous because cancer cells do have functional mitochondria. Since then, lipid metabolism in cancer cells has attracted much attention.

Lipid metabolism in cancer cells is dysregulated with enhanced *de novo* fatty acid synthesis and increased fatty acid uptake, which directly affects cancer growth. Fatty acids are involved in many aspects of tumorigenesis and tumor progression by providing energy, macromolecules for membrane synthesis, and lipid signals during cancer progression (1-3).

In the tumor microenvironment, adipocytes serve as a fatty acid reservoir for some cancers due to the anatomic locations, including cancers of ovarian, prostate, breast and melanoma. Studies have demonstrated that enhanced lipolysis in adipocytes provide cancer cells fatty acids for beta-oxidation (4,5). The visualization of lipid transfer from adipocytes to cancer cells mainly rely on cell models. Early in 2007, it was proven that lipid can be translocated between adipocytes and prostate cancer cells using FTIR imaging microspectroscopy (6). Additionally, it has also been demonstrated in a co-cultured system whereby labeled fatty acid BODIPY® FLC16 fluorescent signal was detected in melanoma cells after co-cultured with the adipocytes that had been loaded with the BODIPY dye (7).

A recent study further demonstrates the direct transfer of fatty acids from adipocytes to melanoma cells in an *in vivo* model (8). Zhang *et al.* used a $BRAF^{V600E}$ driven transgenic zebrafish model of melanoma that resembles the genetic background of the human disease. With plin2-tdTomato transgenic line to indicate the location of the depot of subcutaneous fat in the ventral and dorsal skin of the fish, the team transplanted a GFP-labeled melanoma cell line ZMEL2 into the zebrafish adipocyte fat pad, and the lipids were then stained with BODIPY 558/568 dye. Results clearly showed that the transplanted melanoma cells had lipid accumulation but not the melanoma cells in the adipocyte-free areas of the fish.

Establishing zebrafish as a model for cancer study is an alternative approach to mouse model. Owing to their small size, short maturation time, zebrafish has become an important model of cancer in the past decades.

Although several challenges face the development of zebrafish as a cancer model, such as difference in tumor spectrum, incidence and onset from human cancers, zebrafish has been commonly used for the study of many cancer types including cancers of the digestive system, the skin, muscle, vasculature and testis. It mainly serves as a model for the study of tumor angiogenesis and tumor metastasis. Zhang *et al.* is at the forefront of using zebrafish as an *in vivo* model to study the tumor microenvironment and has clearly demonstrated lipid transfer from adipocytes to cancer cells, which is difficult, if not impossible, to study in a mouse model.

Cancer cells may have elevated expression of fatty acid binding proteins (FABPs) (9), which is a group of proteins that that serves as intracellular fatty acid transporters. For example, it has been shown that compared to the

primary ovarian tumors, FABP4 is upregulated in omental metastases, and FABP4 expression is detected in ovarian cancer cells at the adipocyte-tumor cell interface (4). FABP4 is essential for the metastatic tumor growth in mice (4).

Blockers for FABP can be developed to interrupt the lipid transport in cancer cells so as to reduce the tumorigenic effect of adipocytes in the tumor microenvironment. However, FABPs are cytosolic proteins but not the "gatekeeper" that guards the uptake of fatty acids into the cancer cells.

The gatekeeper that is involved in the "import" of exogenous fatty acids into the cells is the fatty acid transport proteins (FATPs). FATPs are classified as members of the Solute Carrier 27 (Slc27) family of protein and they promote the import of exogenous fatty acids in different cell types. The stunning finding in the study by Zhang *et al.* is the identification of FATP-1 in mediating the transport of fatty acids into the melanoma cells from adipocytes, which is another piece of strong evidence to suggest fatty acids are transported from adipocytes to the cancer cells. The team overexpressed FATP-1 in zebrafish with mosaic transgenic system in which FATP-1 was inserted and expressed coordinately with $BRAF^{V600E}$ under the melanocyte-specific mitfa promoter. This ensured melanocyte-specific $BRAF^{V600E}$ and FATP-1 expression are limited in melanocytes to eliminate the off-target effect in other cell types. The melanoma development markedly increased in the fish with FATP-1 overexpression and these melanoma cells had pronounced lipid accumulation, in contrast to those without FATP-1 overexpression. The team has also used mouse xenograft model to further suggest the involvement of FATP-1 in this fatty acid transport.

We do not know yet the involvement of other FATPs in the adipocyte-mediated fatty acid transport in other cancer types, or whether the expression of FATPs is cancer specific or regulated by adipokines, cytokines or other immune cells in the tumor microenvironment, which warrants further investigation.

Another aspect of research to explore would be the development of FATPs blockers to inhibit the fatty acid transport process. The blockers can serve as adjuvant therapy to combat cancer especially obesity-associated cancers. A mere inhibition of endogenous fatty acid synthesis by fatty acid synthase inhibitor Orlistat (Xenical) has been proved to be inadequate to significantly reduce the fatty acid levels in cancer cells. Up to the present, the well-known FATP inhibitor is Lipofermata, 5'-bromo-5-phenyl-spiro[3H-1,3,4-thiadiazole-2,3'-indoline]-2'-one, which is designed to reduce FATP2-mediated fatty acid transport. However, Lipofermata has a short half-life *in vivo* which hinders its clinical application. Zhang *et al.* has applied this compound directly to tumor to bypass the liver clearance in the zebrafish model; and systemic administration of Lipofermata failed to show its inhibitory effect in mouse model, which was a shortfall in Zhang's study. FATP has been implicated in many diseases. Recent studies have characterized FATP mutant in Drosophila and C. elegans, and established new models of cardiomyopathy, retinal degeneration, fat storage disease and dermopathies (10). To date, FATP-1, FATP-2 and FATP-4 have been used as targets in the selection of small molecule inhibitors to treat insulin resistance and attenuate dietary absorption of fatty acids (11).

Perhaps, our goal is to have therapeutic agents for cancers targeting the dysregulated metabolism, to further Otto Warburg's contribution in this field.

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Footnote

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