Asian Journal of Andrology (2014) 16, 661–663

www.asiaandro.com; www.ajandrology.com

Open Access

INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Lipogenic metabolism: a viable target for prostate cancer treatment?

Mengmeng Liang, David J Mulholland

Asian Journal of Andrology (2014) **16**, 661–663; doi: 10.4103/1008-682X.132947; published online: 20 June 2014

Cancer cells often depend on altered metabolism compared with their normal counterparts.[1–4] As observed in 1924 by Otto Warburg, cancer cells show preferential glucose consumption by way of aerobic glycolysis while normal cells generally assume mitochondrial oxidative phosphorylation.[4] Another metabolic hallmark of carcinogenesis is altered lipid metabolism, whereby cancer cells may adopt enhanced *de novo* lipid production (lipogenesis).[1–3] Enhanced lipid metabolism is also observed in individuals with metabolic syndromes potentially a consequence of increasing popularity of the Standard American Diet, composed of high levels of saturated fats and carbohydrates.[5] A growing body of epidemiological data indicates a positive correlation between the occurrence of metabolic syndromes, such as cardiovascular disease, obesity, type-2 diabetes and associated hyperinsulemia, with the aggressiveness of cancer.[6–9] Remarkably, it is estimated that for every 1% reduction in saturated fats, replaced by polyunsaturated, there would be a 2%–3% reduction in cardiovascular disease.[10] Thus, it is conceivable that an equally remarkable attenuation in cancer progression might be achieved with such a reduction in lipid accumulation.

Prostate cancer is the most diagnosed male malignancy and second-leading cause of cancer-related death in the United States.[11] Extensive research efforts are focused on understanding the progression of prostate cancer, in particular for incurable castration-resistant prostate cancer. Curiously, metabolic syndromes, such as hyperinsulemia, occur at a higher rate in prostate cancer patients undergoing long-term androgen deprivation therapy compared to hormone-naïve patients.[12] However, unlike many solid tumors, prostate cancers are generally less dependent on the Warburg effect and aerobic glycolysis, but rather, present with altered lipid metabolism with increased cholesterol synthesis and steroidgenesis.[1,2] With this, there is significant motivation to understand the biochemical alterations occurring during prostate cancer progression as a consequence of either changing systemic signaling factors or genetic aberrations.

In a recent publication in *Cell Metabolism*, Yue *et al.*[13] demonstrate an important role for lipogenesis in prostate cancer progression. The authors focus on lipid droplets (LDs) dynamic organelles serving as the hubs for lipid metabolism and are involved in a multitude of cellular functions.[14] On a structural level, LDs are composed of a phospholipid monolayer and a core of neutral lipids including sterol esters and triacylglycerols.[14] Previous studies have shown that LD content increases in cancers of the breast, colon and brain.[14,15] In this study, the authors employ an imaging technique termed compound "Raman spectromicroscopy" allowing the measurement of vibrational energy of cellular contents.

By combining high-speed vibrational imaging and quantitative spectral analysis,[16] the authors could accurately measure both LD composition and quantification within a single-cell level throughout prostate tissue samples. From large scale measurements of primary human samples at different stages of prostate cancer progression, the authors found cholesterol esters (CEs), within the LDs, to be significantly enriched in high-grade and metastatic specimens. Importantly, LD accumulation was not observed in normal prostate, benign prostatic hyperplasia, prostatitis, or prostatic intraepithelial neoplasia specimens. The aberrant activities of fatty acid synthase (FASN), the enzyme that catalyzes fatty acid production, in prostate cancer has been extensively studied. Elevated expression of FASN emerges early in prostate cancer development and is associated with progression to metastases.[17,18] Collectively, these data strongly suggest that CE-LDs serve as a critical fuel source for a lipogenic based metabolism in advanced prostate cancer. Raman spectromicroscopy is clearly a sophisticated imaging technique and is currently not a typical component of most clinical pathology labs. However, that distinct CE levels correspond to specific disease states suggests their potential clinical application to early diagnosis and treatment response and thus could accompany other biochemical tools such as PSA.[19]

The importance of metabolic deregulation in cancer cells has gained an appreciation since cell biologists acknowledged the cross-talk between lipid metabolism and signaling pathways in cancer cells. Previous works have shown phosphoinositide 3-kinase (PI3K)/Akt and mitogen-activated protein kinase (MAPK) signaling to positively regulate lipogenic enzymes such as FASN.[20] Activation of the PI3K/Akt signaling pathway occurs in the majority of advanced prostate cancers[21] and may occur both through extracellular growth factor stimulation or cell autonomous genetic aberrations. The authors elect to focus on the potential regulatory role of PTEN loss, a frequent event occurring both in primary and metastatic prostate cancers that parallels heightened PI3K/Akt signaling.[21] The authors conducted a series of biochemical studies to address the mechanism by which PTEN loss could potentiate production of CE rich LDs. They determined that with

Icahn School of Medicine at Mount Sinai, New York, NY, USA.
Correspondence: Dr. DJ Mulholland (david.mulholland@mssm.edu)

PTEN loss, CE accumulation was catalyzed in prostate cancer cells by the enzyme acetyl-CoA acetyltransferase (ACAT).[14] Similarly, introduction of wild-type PTEN into PTEN deficient PC3 prostate cancer cells could reverse CE accumulation. The authors then examined sterol response element binding proteins (SREBPs), as a potential mediator of PI3K/Akt signaling and lipogenic metabolism. They observed that elevated PI3K/Akt signaling could enhance SREBP leading to increased expression of the low density lipid receptor (LDLr) and a resulting increase in hydrolysis of LDL to free fatty acids. Importantly, increased expression of the transcription factor SREBP not only regulates syntheses of fatty acids, triglycerides, cholesterol and the expression of FASN[1] but may increase in expression in advanced prostate cancer.[1,22,23] Thus, SREBPs serve as a bridge for the enhanced lipogenic activities with oncogenic/tumor suppressor pathways in cancer cells.[22,23]

While PI3K/Akt signaling was shown to induce CE-SREBP production, curiously, androgen signaling was not. As a therapeutic alternative, the authors explored the potential for targeting ACAT, the enzyme responsible for the conversion of free cholesterol to the CEs found in LDs. Yue *et al.*[13] found that by inhibiting ACAT-1 activity, using Avasimibe, significant suppression of prostate cancer cell growth was achieved both *in vitro* and *in vivo* and presented with only minor toxicity in mice. Interestingly, ACAT-1 inhibitors have been previously used to treat atherosclerosis.[24] These results together provide the possibility that impairing CE accumulation by ACAT inhibitors may act as an effective treatment for advanced prostate cancers, particularly those with PI3K/Akt activation. Down regulation of SREBPs by small interfering ribonucleic acid reduced the exogenous LDL uptake in prostate cancer cells. Thus, it would be of great interest to test if CE accumulation and PI3K/Akt would be affected by abrogating the activity of SREBPs using specific inhibitors. Together, this suggests that for patients treated with antiandrogen therapies, such as enzalutamide or abiraterone acetate,[25] lipogenic metabolism may be poorly responsive. However, PI3K/Akt or dual PI3K-mammalian target of rapamycin (mTOR) inhibitors may achieve a reduction in SREBP which, when combined with currently approved taxane or anti-androgen therapies, may provide superior clinical outcomes.

The relationship between lipid metabolism, signaling pathways likely extends well beyond the apparent regulatory role of PTEN. PI3K/Akt signaling is regulated by a multitude of intracellular factors, including extracellular cytokines, insulin-like growth factors (IGFs) and insulin. With the rise in metabolic syndromes including type-2 diabetes and associated high systemic insulin levels (hyperinsulemia) there is increased potential for receptor tyrosine kinase activation to promote PI3K/Akt signaling and a resulting enhancement of SREBP function. Intracellular mediators of prostate cancer lipogenesis may also extend to the MAPK-ERK and LKBI-AMPK signaling cascades both of which have been shown to orchestrate with SREBPs to regulate the expression of lipogenic enzymes.[1] Application of pathway specific therapies will help determine potential therapeutic responses. Finally, it further remains to be determined whether the accumulation of CEs is restricted to prostate cancers or whether other PI3K-dependent cancers, such as breast and brain, display enhanced lipogenesis.

The capacity for oncogenic signaling to regulate the accumulation of LDs, raises the potential importance of diet and systemic metabolism. Adult mammalian cells take up lipids either as free fatty acids or are assembled in lipoproteins such as low-density lipoproteins (LDLs). These lipids can be acquired from dietary sources or can be synthesized *de novo* in the liver.[2] The potential for whole-body lipid metabolism to regulate oncogenic potential is compelling. Obesity and insulin resistance can lead to greater production of insulin by pancreatic beta-cells and enhanced availability of IGF-1.[26] Inflammatory cytokines produced by adipocytes can lead to transformation and proliferation of cancer cells.[27] Polyunsaturated fatty acids obtained from dietary sources are composed of two main types: omega-6 and omega-3.[1] Linoleic acid, a common omega-6, is converted to arachidonic acid and can promote cell proliferation via activation of the PI3K/Akt/mTOR pathway in prostate cancer.[28] LDLs can also function as the primary carrier for the "bad cholesterol" and arachidonic acid.[15] Thus, it is tempting to speculate that dietary restriction and therapeutic maintenance of systemic insulin may allow control over oncogenic signaling potentiation of lipogenic signaling – an increasingly attractive therapeutic target in prostate cancer?

This study integrates the roles of dietary restriction, oncogenic signaling pathways and metabolic reprogramming. This study also provides a novel mechanism by which a carcinogenic process is exacerbated by the intertwined network of exogenous lipids uptake, altered cholesterol metabolism and mutated tumor suppressor signaling pathway. In normal cells, exogenous LDLs are hydrolyzed to free fatty acids and cholesterol. Cellular free cholesterol then inhibits the activity of SREBPs which in turn reduce lipogenesis and exogenous lipid uptake. In contrast, high grade and metastatic prostate cancer cells with PTEN loss and hyperactive PI3k/Akt/mTOR signaling pathways drive CE accumulation which functions to provide a buffer against toxicity from excess cholesterol[14] and maintain the constitutive activity of SREBPs. The overall effect is an oncogenic lipid based metabolism that provides significant fuel for prostate cancer progression.

COMPETING INTERESTS

The authors declare no competing interests.

REFERENCES

1 Zadra G, Photopoulos C, Loda M. The fat side of prostate cancer. *Biochim Biophys Acta* 2013; 1831: 1518–32.
2 Santos CR, Schulze A. Lipid metabolism in cancer. *FEBS J* 2012; 279: 2610–23.
3 Currie E, Schulze A, Zechner R, Walther TC, Farese RV Jr. Cellular fatty acid metabolism and cancer. *Cell Metab* 2013; 18: 153–61.
4 Warburg O. On the origin of cancer cells. *Science* 1956; 123: 309–14.
5 Last AR, Wilson SA. Low-carbohydrate diets. *Am Fam Physician* 2006; 73: 1942–8.
6 Adami HO, Chow WH, Nyrén O, Berne C, Linet MS, *et al.* Excess risk of primary liver cancer in patients with diabetes mellitus. *J Natl Cancer Inst* 1996; 88: 1472–7.
7 Chow WH, Gridley G, Nyrén O, Linet MS, Ekbom A, *et al.* Risk of pancreatic cancer following diabetes mellitus: a nationwide cohort study in Sweden. *J Natl Cancer Inst* 1995; 87: 930–1.
8 Will JC, Vinicor F, Calle EE. Is diabetes mellitus associated with prostate cancer incidence and survival? *Epidemiology* 1999; 10: 313–8.
9 Nicolucci A. Epidemiological aspects of neoplasms in diabetes. *Acta Diabetol* 2010; 47: 87–95.
10 Astrup A, Dyerberg J, Elwood P, Hermansen K, Hu FB, *et al.* The role of reducing intakes of saturated fat in the prevention of cardiovascular disease: where does the evidence stand in 2010? *Am J Clin Nutr* 2011; 93: 684–8.
11 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; 62: 10–29.
12 Nobes JP, Langley SE, Laing RW. Metabolic syndrome and prostate cancer: a review. *Clin Oncol (R Coll Radiol)* 2009; 21: 183–91.
13 Yue S, Li J, Lee SY, Lee HJ, Shao T, *et al.* Cholesteryl ester accumulation induced by PTEN loss and PI3K/AKT activation underlies human prostate cancer aggressiveness. *Cell Metab* 2014; 19: 393–406.
14 Farese RV Jr, Walther TC. Lipid droplets finally get a little R-E-S-P-E-C-T. *Cell* 2009; 139: 855–60.
15 Bozza PT, Viola JP. Lipid droplets in inflammation and cancer. *Prostaglandins Leukot Essent Fatty Acids* 2010; 82: 243–50.
16 Slipchenko MN, Le TT, Chen H, Cheng JX. High-speed vibrational imaging and spectral analysis of lipid bodies by compound Raman microscopy. *J Phys Chem B* 2009; 113: 7681–6.
17 Swinnen JV, Vanderhoydonc F, Elgamal AA, Eelen M, Vercaeren I, *et al.* Selective activation of the fatty acid

synthesis pathway in human prostate cancer. *Int J Cancer* 2000; 88: 176–9.
18 Hamada S, Horiguchi A, Kuroda K, Ito K, Asano T, *et al*. Elevated fatty acid synthase expression in prostate needle biopsy cores predicts upgraded Gleason score in radical prostatectomy specimens. *Prostate* 2014; 74: 90–6.
19 Djulbegovic M, Neuberger MM, Dahm P. Prostate-cancer mortality after PSA screening. *N Engl J Med* 2012; 366: 2228–9.
20 Yang YA, Han WF, Morin PJ, Chrest FJ, Pizer ES. Activation of fatty acid synthesis during neoplastic transformation: role of mitogen-activated protein kinase and phosphatidylinositol 3-kinase. *Exp Cell Res* 2002; 279: 80–9.
21 Taylor BS, Schultz N, Hieronymus H, Gopalan A, Xiao Y, *et al*. Integrative genomic profiling of human prostate cancer. *Cancer Cell* 2010; 18: 11–22.
22 Shao W, Espenshade PJ. Expanding roles for SREBP in metabolism. *Cell Metab* 2012; 16: 414–9.
23 Krycer JR, Sharpe LJ, Luu W, Brown AJ. The Akt-SREBP nexus: cell signaling meets lipid metabolism. *Trends Endocrinol Metab* 2010; 21: 268–76.
24 Llaverías G, Laguna JC, Alegret M. Pharmacology of the ACAT inhibitor avasimibe (CI-1011). *Cardiovasc Drug Rev* 2003; 21: 33–50.
25 Chen Y, Clegg NJ, Scher HI. Anti-androgens and androgen-depleting therapies in prostate cancer: new agents for an established target. *Lancet Oncol* 2009; 10: 981–91.
26 Renehan AG, Frystyk J, Flyvbjerg A. Obesity and cancer risk: the role of the insulin-IGF axis. *Trends Endocrinol Metab* 2006; 17: 328–36.
27 Rosenzweig SA, Atreya HS. Defining the pathway to insulin-like growth factor system targeting in cancer. *Biochem Pharmacol* 2010; 80: 1115–24.
28 Hughes-Fulford M, Li CF, Boonyaratanakornkit J, Sayyah S. Arachidonic acid activates phosphatidylinositol 3-kinase signaling and induces gene expression in prostate cancer. *Cancer Res* 2006; 66: 1427–33.

How to cite this article: Liang M, Mulholland DJ. Lipogenic metabolism: a viable target for prostate cancer treatment?. *Asian J Androl* 20 June 2014. doi: 10.4103/1008-682X.132947. [Epub ahead of print]