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# Lipid Metabolism Profiling and Bladder Cancer

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## Abstract

Current clinical studies on lipidomics have revealed some outcomes that could have a great effect on treating the possible pathophysiological mechanisms through new molecular targets rather than the phenotyping results of diseases. Bladder cancer is one of the leading cancers in the field of urology and a leading cause of cancer-related death. Beside its very common epidemiology, it is a highly heterogeneous disease. Non-muscle invasive bladder cancer definition includes a fully heterogeneous disease spectrum that involves Ta low grade and T1 high grade diseases, which are completely different for recurrence, progression and disease free survival rates. From this perspective, it is essential to research new target metabolites in an attempt to elucidate the underlying mechanisms to provide a more satisfactory and individualized approach in the diagnosis, treatment and prognosis for patients with bladder cancer. Lipids have many roles in cellular structure and function. They are structural scaffolds and mediators of signal transduction as well as serving as metabolic fuels. The development in lipidomic research are promising to identify new metabolites in this highly complex and heterogeneous cancer type but more studies are warranted to eluciadate the role of complex lipid metabolism in tumor pathophysiology as well as to find out targeted molecules for treatment and prognosis management in clinical settings.

**Keywords:** Bladder cancer; Lipidomics; Lipid metabolism profiling; Pathophysiology

## Introduction

Metabolomics is defined as quantitative measurement of the dynamic multiparametric responses of the livings to pathophysiologic stimuli or genetic modification [1-3]. Lipids are main structural scaffolds of the cell membrane and serve as structural element in steroid hormone and its precursors as well as their receptors. Furthermore, lipids have many functional tasks including providing electrical insulation of nerve cells, cell transporting systems and intracellular signal transmission. They also serve as metabolic fuels. It is well known that cancer is a metabolic disorder with highly complicated metabolic pathways many of which we need to explore to better comprehend and enhance our insights regarding underlying mechanisms. Bladder cancer (BC) is the fourth most common tumor in men and the eighth in women and it has high recurrence and progression rate due to the nature of the carcinoma [4-7]. 75–80% is non-muscle invasive with better survival rates compared to muscle invasive tumor but they are highly heterogeneous tumors with a wide spectrum involving *Ta* low grade and *T1* high grade tumors, which are completely different in terms of recurrence, progression and survival rates [8]. This highly heterogeneous disease certainly harbors very complex metabolic and carcinogenesis pathways and the alterations in lipid metabolism may give us new insights to understand and overcome the complexity of disease. Recent studies on lipidomics have advanced our understanding regarding the roles of lipids in carcinogenesis pathways as well as lipidomics offers great promise to define new molecular targets for treating the underlying molecular pathophysiology. Bladder cancer, which has very complicated wide spectrum phenotyping results (*Ta* low grade, *Ta* high grade, *T1* low grade, *T1* high grade, CIS…) surely justifies deep research with these aspects. The aim of this review is to search the literature regarding bladder carcinoma and lipid metabolism profiling and to contribute to our insights about the relationship between bladder cancer carcinogenesis and lipid metabolism profiling and lipidomics rather than emphasizing treatment options and resistance mechanisms.

## General lipid profiling in patients with bladder carcinoma

After the definition 'metabolomics' emerged, promising studies including the assessment of the whole metabolic process involving amino acids, lipids and carbohydrates have begun to be performed. The relevant studies regarding lipid metabolism profiling and bladder cancer has been demonstrated in Table 1.

## Glycerophospholipids, sphingolipids, fatty acids and bladder cancer

A comprehensive analysis conducted by Wittmann et al. [9] via global metabolomic profiling of urine revealed that metabolites related to lipid metabolism may be especially interesting biomarkers in bladder cancer. Palmitoyl sphingomyelin, phosphocholine and arachidonate were found to be enhanced in urine samples in subjects with bladder cancer (Table 1). Arachidonate is an unsaturated fatty acid and elevated levels of it may result from increased liberation of free fatty acids from phospholipids either in the tumor or in adjacent tissue. It is also a precursor of eicasonoids and has a potential role in inflammatory processes [10]. Phosphocholine is one of the most common glycerophospholipids in cell membrane and is also a component of sphingomyelin, which is another significant common component of the outer plasma membranes of cells. The elevated level of these lipid types may reflect a relatively higher tumor cell proliferation rate and increased lipid membrane remodeling. Similarly, Triphati et al. [11] conducted a study using HR-MAS NMR (high-resolution magic angle spinning nuclear magnetic resonance) and GC-MS (gas chromatography-mass spectrometry) methods. Twenty-six patients had benign disease and thirty-three patients had bladder cancer of which 17 patients were of *Ta-T1* and 16 patients had evidence of muscle invasion at diagnosis or during surveillance. Phosphocholine, choline and glycerophosphocholine were found to be enhanced in *Ta-T1* and muscle invasive subjects compared to benign tissues while triglyceride (TG) levels were found to be decreased (Table 1). No statistically significance was found between *Ta-T1* and muscle invasive tumor. The lower level of TG may result from the

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fact that tumor cells utilize enhanced β-oxidation of fatty acids which are the skeleton of TG for rapid growth. Similar to these results, Lin et al. [12] found that patients with bladder cancer have enhanced level of phosphatidylcholine. In another study [13], canine bladder cancer tissue sections and adjacent normal tissues were imaged using desorption electrospray ionization (DESI) mass spectrometry and both glycerophospholipid and sphingolipid profiles between the tissue types differed, both in the intensities of the lipid signals present and the pattern of the lipid signals. While glycerophosphocholines, linoleic acid, oleic acid and arachidonic acid were demonstrated to be elevated in bladder cancer tissue, sphingomyelin was only found in normal bladder tissue (Table 1). In a study conducted by Bansal et al. [14], serum metabolism profiling of 36 low grades BC and 32 high grades BC patients were compared with 32 healthy subjects using H-NMR analytical method. Malonate level was found significantly higher in patients with BC. It was also found to be enhanced in high grade patients compared to low grade subjects. Malonate level is based on the concentrations of malonyl-CoA which is the commitment step for fatty acid synthesis. Fatty acids are incorporated into phospholipids and sphingolipids which are essential components of cell membranes and they also serve as metabolic fuels. This study also enabled us to get some tips on the biological events that take place at the high and low-grade bladder tumor carcinogenesis. In another study Pasikanti et al. [15] demonstrated down regulation of glycerol in patients with BC compared with non-BC control subjects (Table 1).

## TCA cycle, ketone bodies and bladder cancer

Fatty acid β-oxidation is the substantial pathway for the production of energy for tumor cells in the fasted state. However if the acetyl-CoA which is mostly derived from β-oxidation is not well accommodated by the tricarboxylic acid (TCA) cycle, ketogenesis will take place and ketone bodies, including β-hydroxybutyrate, acetoacetate, and acetone will be generated.

A study [16] which was performed using H nuclear magnetic resonance (NMR)-based metabolomic analysis on serum samples from low-grade bladder cancer patients, high-grade bladder cancer patients; pre- and post-transurethral resection of bladder tumor patients; urinary tract calculi patients with the similar clinic sign of hematuria as bladder cancer patients and healthy subjects revealed that patients with bladder cancer have elevated level of V/LDL compared with those from healthy and calculi subjects. This may result from the fact that lipogenesis is an essential process for cell growth and proliferation as it is the origin of membrane biosynthesis. In that study acetoacetate level was found to be elevated in patients with bladder cancer (Table 1). When taking into account the fact that the main precursor of ketone bodies-acetyl-CoA- is mostly derived from β-oxidation of fatty acids, high level of acetoacetate could reflect enhanced utilization of β-oxidation pathway in bladder tumor cells.

Meanwhile, in a canine model study conducted by Zhang et al. [17] elevated level of β-hydroxybutyrate and acetone were found in invasive bladder cancer urine samples compared with healthy dogs (Table-1). These findings suggest that cancer cells can alter their energy supply by switching from active glycolysis to fatty acid oxidation with an associated increase in Krebs cycle activity and oxidative phosphorylation [18].

## Carnitine derivatives and bladder cancer

Carnitine is required for the transport of fatty acids from the intermembraneous space into the mitochondria during the breakdown of lipids for the generation of metabolic energy. The altered level of it may be implicated in the carcinogenesis of bladder cancer.

Jin et al. [19] conducted a study including 83 non-muscle invasive BC, 55 muscle invasive BC patients. For control groups, 69 healthy subjects and 5 patients with hematuria with non-malignant disease were included. Several acylcarnitines were found to contribute to the differentiation between the cancer and control groups (Table 1). Furthermore carnitine palmitoyltransferase, which is a key protein that uses carnitine to transfer fatty acid into mitochondria for oxidation was found to be expressed significantly higher in BC tissues ($p$=0.0084). In addition, the increase was more significant in muscle-invasive bladder cancer (MIBC) ($p$=0.0003) than non- muscle-invasive bladder cancer (NMIBC) ($p$=0.089), and its level was significantly different between the two types of cancer ($p$=0.028). Carnitine acylcarnitine translocase-like protein (CACL), another enzyme involved in fatty acid transport into mitochondria was also found to be expressed significantly higher in both MIBCs and NMIBCs than control tissues, but no significant difference was found between two cancer type groups. These results suggest that β-oxidation may play an important role in BC tumorigenesis and possibly aggressiveness. Another study conducted by Putluri et al. [20] also revealed that patients with BC have higher level of carnitine (Table 1).

## Possible relevant mechanisms regarding lipid metabolism and bladder cancer

### Oxidative stress-modification on lipid structure of cell membranes

Oxidative stress which is the cumulative effect of free oxygen radicals, is one of the most important pathophysiological events implicated in several human pathologies, including cancer [21,22]. There has been increased interest in research of the role of free radicals in carcinogenesis and the role of antioxidant materials in the prevention, treatment, and alleviation of therapy related side effects of cancer [23,24]. Reactive oxygen species (ROS) can damage many different macromolecules including DNA, amino acids, lipid, and carbohydrate. Beside reactive oxygen species, there are intrinsic enzymatic and non-enzymatic antioxidants detoxifying mechanisms that help to diminish the extent of ROS-induced damage. Superoxide dismutase, which catalyses the dismutation of superoxide anions to $H_2O_2$ catalase, which converts $H_2O_2$ into molecular oxygen and water, and selenium-dependent glutathione peroxidase (GSH-Px) that reduces $H_2O_2$ to water and molecular oxygen, are among the enzymes involved in these defense mechanisms. GSH-Px is the key enzyme responsible for the detoxification of cellular hydrogen peroxide; it exists in two forms, selenium-dependent and–independent [25]. Given that lipids are major components of cell membranes, the peroxidation of lipids is a significant implication in the pathogenesis of oxidative stress. In a study conducted by Yalcın et al. [25] the levels of erythrocyte glutathione peroxidase (GSH-Px) and the serum levels of antioxidant vitamins (A, E and C), selenium and malondialdehyde (MDA) in patients with transitional cell carcinoma (TCC) of the bladder were assessed. While the serum levels of vitamin A, E and C, and selenium were significantly lower ($P$<0.05) in patients with bladder cancer, erythrocyte GSH-Px activities ($P$<0.05) and serum MDA levels ($P$<0.01) were significantly higher. Malondialdehyde (MDA), the major aldehyde end product of lipid peroxidation of membrane polyunsaturated fatty acids by free radicals, is an indicator of oxidative stress [23] and high level of it may be explained by the fact that lipid peroxidation is implicated in carcinogenesis. There are many studies [26,27] examining the lipid

| Author (year) | Analytical Method | Sample Source | Subjects with bladder cancer(n) | Controls (n) | Up-regulated lipid metabolites | Down-regulated lipid metabolites | Ref |
|---|---|---|---|---|---|---|---|
| Dill et al. (2009) | DESI-MS | Tissue (canine) | 4 | Adjacent normal bladder tissue (4) | GlycerophosphocholinesLinoleic acid, Oleic acid Arachidonic acid | Sphingomyelin | [13] |
| Putluri et al. (2011) | LC-MS | Urine (human) Tissues(human) Bladder cancer (BC) cell lines | 83 | Adjacent normal bladder tissue (51) | Carnitine, Oleic acid Palmitic acid | Lauric acid | [20] |
| Cao et al. (2012) | H-NMR | Serum (human) | LGBC (15) HGBC (22) | Healthy subjects (25) Calculi patient (28) Post-TURBT patient (20) | V/LDL Acetoacetate | | [16] |
| Lin et al. (2012) | RPLC-MS HILIC- MS | Serum (human) | 13 | Healthy subjects (20) Nephrolit hiasis (8) BPH (10) | Phosphatidylcholine | | [12] |
| Zhang et al. (2012) | H-NMR | Urine (canine) | Invasive BC (40) | Healthy dogs (42) | Choline, β hydroxybutyrate Acetone | | [17] |
| Pasikanti et al. (2013) | GC×GC−TOFMS | Urine (human) | 38 | Non-BC subjects (61) | | Glycerol | [15] |
| Triphati et al. (2013) | HR-MAS NMR GC-MS | Tissue (human) | BC: Ta-T1(17) BC: ≥ T2 (16) | Benign diseases (26) | Phosphocholine, Choline Glycerophosphocholine | Triglicerides | [11] |
| Bansal et al. (2013) | H-NMR | Serum (human) | LGBC (36) HGBC (31) | Healthy subjects (32) | Malonyl-CoA | | [14] |
| Jin et al. (2014) | HPLC-QTOFMS | Urine (human) | NMIBC (83) MIBC (55) | Healthy subjects (69) Hematuria due to non-malignant disease (5) | Carnitine, Isovalerylcarnitine Octenoylcarnitine, Acetyl-CoA Carnitine palmitoyltransferase Carnitine acylcarnitine translocase like protein (CACL) | Glutarylcarnitine Decanoylcarnitine | [19] |
| Wittmann et al. (2015) | UHPLC-MS/MS GC-MS | Urine(human) | Retrospective (cohort 1) | | Palmitoyl sphingomyelin Phosphocholine | | [9] |
| | | | BC (66) | Non-BC subjects (266) | | | |
| | | | Prospective (cohort 2) | | Arachidonate | | |
| | | | BC (29) | Non-BC subjects (79) | | | |

DESI-MS: Desorption Electrospray İonization-Mass Spectrometry; LC-MS: Liquid Chromatography-Mass Spectrometry; BC: Bladder Cancer; H-NMR: H Nuclear Magnetic Resonance; LGBC: Low Grade Bladder Cancer; HBC: High Grade Bladder Cancer; TURBT: Transurethral Resection of Bladder Tumor; RPLC-MS: Reversed Phase Liquid Chromatography-Mass Spectrometry; HILIC-MS: Hydrophilic İnteraction Chromatography-Mass Spectrometry; BPH: Benign Prostate Hyperplasia; GC×GC−TOFMS: Gas Chromatography Time of-Flight Mass Spectrometry; HR-MAS NMR: High-Resolution Magic Angle Spinning Nuclear Magnetic Resonance; GC-MS: Gas Chromatography-Mass Spectrometry; HPLC-QTOFMS: High-Performance Liquid Chromatography-Quadrupole Time-Of-Flight Mass Spectrometry; NMIBC: Non-Muscle Invasive Bladder Cancer; UHPLC-MS/MS: Ultrahigh-Performance Liquid Chromatography/Tandem Mass Spectrometry

**Table 1:** Relevant studies regarding the association between lipid metabolism profiling and bladder cancer.

peroxidation and antioxidant enzyme activities in cancerous bladder tissue and they obtained similar results indicating lipid oxidative stress is a strong effector on carcinogenesis enhancing lipid peroxidation as well as lowering antioxidant enzymes. Furthermore, bladder cancer is a disease of the middle-aged and aged populations and the accumulation of oxidative stress in cells of this population may be a potential risk factor for transforming normal urothelial cells to cancer cells

## FGFR3 and bladder cancer

Fibroblast growth factor receptor 3 (FGFR3) is one of four members of the tyrosine kinases receptor family that have critical roles in cell proliferation, differentiation, survival and angiogenesis. Since the activation of FGFR3 trigger many pathways, one of the most important of which is the Ras pathway, the mutations of Ras and FGFR3 are considered to result in similar alterations to phenotype via mutual interactions [28]. While FGFR3 mutations are available at the higher rate of 70% in non-muscle invasive low grade papillary tumors, this rate is only 10-20% in muscle invasive bladder cancer [29]. Although FGFR3 mutations induce cell proliferation, the regulation of cell cycle and apoptotic mechanisms are not much impaired. This may be the explanation behind the reduced proliferation potential of low grade tumors compared to high grade and muscle invasive tumors. However, there are still some points that should be explored more regarding this complex pathway. Recently a study conducted by Xiangnan Du et al. [30] shed light on the issue regarding FGFR3 and lipid metabolism. It was found that FGFR3 signaling promotes the cleavage and activation of the master transcriptional regulator of lipogenesis, and sterol regulatory element-binding protein 1

(SREBP1/SREBF1) which regulates the expression of key lipogenic enzymes, including stearoyl CoA desaturase 1 (SCD1/SCD). It was also demonstrated that pharmacologic inhibition of SCD1 blocked fatty acid desaturation and also exerted antitumor activity. These findings reveal a previously unrecognized role of FGFR3 in regulating lipid metabolism to maintain tumor growth and survival, and also identify SCD1 as a potential therapeutic target for bladder cancer.

## Conclusion

The alterations of lipid metabolism in cancer cells lead us to review lipid profiles of the patients with bladder cancer. Although some promising evidence is available in literature, lipidomic studies comprising lipid profiles of serum, urine and the histopathology of bladder tissue are warranted to explore the role of complex lipid metabolism involved in pathways implicated in bladder carcinogenesis with the goal of finding out targeted molecules for treatment and prognosis management in clinical settings.

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