

# REVIEW ARTICLE

## Renal cell carcinoma: a critical analysis of metabolomic biomarkers emerging from current model systems

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Metabolomics, an emerging field of “omics” sciences, has caught wide scientific attention in the area of biomarker research for cancers in which early diagnostic biomarkers have the potential to greatly improve patient outcome, such as renal cell carcinoma (RCC). Metabolomic approaches have been successfully applied to various human RCC model systems, mostly *ex vivo* neoplastic renal tissues and biofluids (urine and serum) from patients with RCC. Importantly, in contrast to other cancers, only a few studies have addressed the RCC metabolome using cancer cell culture-based *in vitro* models. Herein, we first carried out a comprehensive review of current metabolomic data in RCC, with emphasis on metabolite disturbances and dysregulated metabolic pathways identified in each of these experimental models. We then critically analyzed the consistency of evidence in this field and whether metabolites found altered in tumor cell and tissue microenvironment are reflected in biofluids, which constitute the rationale underlying the translation of discovered metabolic biomarkers into noninvasive diagnostic tools. Finally, dominant metabolic pathways and promising metabolites as biomarkers for diagnosis and prognosis of RCC are outlined. (Translational Research 2016; ■:1–11)

Abbreviations: ■ = ■■

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## METABOLOMIC RESEARCH ENDEAVORS IN RENAL CELL CARCINOMA

The most common type of kidney cancer is renal cell carcinoma (RCC), corresponding to the 13th most incident cancer worldwide.<sup>1,2</sup> RCC has one of the highest rates of mortality among urological cancers,<sup>3</sup> as it is responsible for nearly 90% of primary renal cancers.<sup>4</sup> Epidemiologic studies have pointed out some risk factors for this disease such as gender (higher risk in males), age (>55 years), smoking, obesity, diabetes,<sup>5,6</sup> and germline mutations in specific genes.<sup>7</sup> Individuals who suffer from hypertension or advanced chronic kidney disease, making dialysis a necessary therapy, are also at higher risk.<sup>3,8</sup>

RCC is a heterogeneous malignancy, both morphologically and genetically.<sup>7,9</sup> It is classified into different histologic subtypes,<sup>10</sup> the most common of which is clear cell RCC (ccRCC; 75%–80% of cases, characterized by alterations at chromosome 3p, mostly affecting the *VHL* locus) followed by papillary RCC (10%–15%, bearing multiple trisomies including those of chromosomes 7 and 17), chromophobe RCC (about 5%, displaying multiple chromosome losses, including Y, 1, 2, 6, 10, 13, 17, and 21), and other less common subtypes, some of which have only recently been recognized as distinct entities.<sup>10</sup>

In general, RCC develops and progresses asymptotically for a long period of time and its outcome is frequently unpredictable. Therefore, its diagnosis is often incidental (mostly because of the widespread use of medical imagiology) and when detected clinically it is frequently at an advanced stage and metastatic,<sup>11</sup> entailing a dismal prognosis. Furthermore, RCC is generally highly resistant to both chemotherapy and radiation treatments,<sup>12</sup> limiting the treatment options and their effectiveness, although targeted therapies provide some survival benefit.<sup>13</sup> Currently, diagnosis is dependent on imaging techniques but lacks early and cancer-specific methods. Thus far, studies have identified some candidate protein markers in human biofluids (eg, CA-IX,<sup>14</sup> TRAF-1,<sup>15</sup> SAA,<sup>16</sup> KIM-1,<sup>17</sup> AQP-1,<sup>18,19</sup> and PLIN2<sup>18,19</sup>), but mostly in the context of advanced RCC. However, none of them has been recommended for clinical practice because of their high cost-effectiveness ratio.<sup>20</sup> Thus, development of new approaches for early detection is needed and would certainly have a favorable impact on patient's survival.

Metabolomic approaches have shown promise in oncology, with the recognition of metabolic reprogramming as a central hallmark of cancer.<sup>21</sup> Consequently, metabolomics is increasingly being used in cancer research for the discovery and validation of biomarkers that might improve not only early detection but also

enable prediction of disease outcome and recurrence. Efforts have focused on the discovery of biomarker signatures in easily obtainable samples (such as blood and urine). RCCs are, in general, epithelial tumors in contact with the urinary space,<sup>22</sup> making this cancer well suited for a metabolomic approach through the analysis of urine. Concerning RCC metabolomic studies, some promising results have helped to improve the general understanding of RCC metabolic alterations. Most of the studies focused on the ccRCC subtype and, surprisingly, studies on tumor renal tissues and serum from RCC patients prevail over both in vitro cultured cells, despite their easily controllable setup,<sup>23</sup> and urine, despite its noninvasive collection and proximity to neoplastic renal cells.<sup>12,24,25</sup> Herein, we aimed at a comprehensive review of the literature on metabolomic studies in RCC, focusing on the identification of suitable metabolites as biomarkers for early diagnosis and prognosis (prediction of disease severity). The most promising metabolites from those studies are highlighted and the main metabolic pathways affected (illustrated in Fig 1). Studies with no metabolite characterization or lacking statistical data supporting the reported results, studies based on a sample size <10, and studies using animal models were excluded from this review (Supplementary Table S1). The characteristics and achievements of all included studies are summarized in Supplementary Tables S2–S4.

## METABOLOMIC STUDIES IN IN VITRO AND EX VIVO RCC MODEL SYSTEMS

**RCC metabolic signature and identification of diagnosis biomarkers.** Globally, RCC metabolic signature is characterized by alterations in metabolites associated with energy metabolism, especially those involved in glycolysis, amino acid metabolism, and fatty acid catabolism pathways, which are essential for cell growth and proliferation.<sup>26–28</sup>

**Glycolysis.** It is widely acknowledged that cancer cells rely on aerobic glycolysis (the Warburg effect) to provide sufficient energy for cell growth and survival.<sup>27,29,30</sup> In RCC, upregulation in the glycolytic flux manifests through the increase of some glycolysis-relevant metabolites, including glucose, pyruvate, and lactate (Table I). Because alterations in glycolysis are common among other cancers,<sup>31–33</sup> those metabolites lack specificity for RCC. Therefore, it would be pertinent to use them together with other metabolites.

Concerning glucose levels, trends vary significantly among in vitro studies, even when considering the extracellular medium alone,<sup>34,35</sup> and among ex vivo tissue studies,<sup>26–28,36,37</sup> most probably because of different

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