Nature Reviews Urology | Published online 27 January 2016; doi:10.1038/nrurol.2016.16

KIDNEY CANCER

When worlds collide — integrating metabolic and transcriptomic data in ccRCC

Stocktrek Images/Thinkstock

New research reveals the extensive alterations in the metabolic profile of clear cell renal cell carcinoma (ccRCC) in comparison with normal kidney tissue, showing that changes evolve with disease progression and correlate with cancer stage. Furthermore, integration of these metabolic data and results of transcriptomic studies reveals discordance between changes in metabolite and enzyme expression levels, highlighting that both approaches are required to enable comprehensive molecular characterization of ccRCC.

In the past few years, large-scale efforts, such as The Cancer Genome Atlas (TCGA) project, have been launched to profile different cancer types using omics approaches, including DNA and RNA sequencing and protein arrays. However, data on metabolic aberrations in cancers have rarely been collected in an extensive format, although evidence for the pervasiveness of dysregulated metabolism existed for several malignancies. The high complexity of cellular metabolic networks and previous technical challenges in metabolomic analysis might have been the main reasons precluding thorough assessment.

"Our participation in genomics data collection as part of the Kidney Renal Clear Cell Carcinoma project for TCGA led us to the concept that metabolic dysregulation can be instrumental in disease progression," explains James Hsieh from the Memorial Sloan Kettering Cancer Center, senior author of the new study in *Cancer Cell*. To investigate this hypothesis, the team collected 138 pairs of freshly frozen ccRCC tumour and adjacent normal tissues, along with pathological and patient characteristics. Mass spectrometry analyses detected 319 metabolites with differing amounts in malignant and normal tissues. Assignment of the alterations to metabolic pathways revealed that, in tumour samples, most increases occurred in carbohydrate metabolism pathways, whereas most decreases occurred in amino acid metabolism pathways.

Loss of VHL expression and accumulation of hypoxia-inducible factors are characteristics of ccRCC pathogenesis and should result in metabolic aberrations in glycolysis-related pathways. Through mapping of the detected changes in metabolite abundance to central carbon metabolism pathways, the researchers could indeed demonstrate differential metabolic alterations in glycolysis and the Krebs cycle of tumour tissues. The large number of samples and availability of pathological information then enabled the team to investigate associations between metabolic changes and ccRCC progression. Between stage I–II and stage III–IV tumours, amounts of 208 metabolites differed significantly; in high-stage samples, 73 compounds were more than twofold increased and only citrate was more than twofold decreased. Overall, elevated levels of dipeptides and compounds involved in glutathione metabolism were associated with high-stage tumours.

Next, the team examined how their metabolic data aligned with transcriptomic analyses from TCGA. "By combining our findings with expression data, we were able to compare changes in metabolites with analogous changes in gene expression levels of enzymes in a given pathway," summarizes Hsieh. Notably, the researchers found no correlation between the two and hypothesize that heterogeneity might be caused by the complex network of factors regulating metabolic flux, for example the distinct kinetic parameters of isoenzymes. Further interrogation of the datasets enabled them to link specific clusters of metabolite abundance and gene expression with patient survival data, demonstrating the potential value of incorporating metabolomic analyses in future studies. Finally, as analytical pipelines to integrate large sets of metabolomics and transcriptomics data are currently lacking, the researchers developed a new analytical tool, termed metabologram, to link and present omics and clinical data.

The team's current research focuses on investigating the genetic and epigenetic bases of identified metabolomic clusters and translation of the new knowledge into novel *in vivo* metabolic imaging studies. "Our aim is to evaluate effects of targeted therapeutics on cancer metabolism in real-time in patients with ccRCC," Hsieh concludes.

Clemens Thoma

ORIGINAL ARTICLE Hakimi, A. A. *et al.* An integrated metabolic atlas of clear cell renal cell carcinoma. *Cancer Cell* **29**, 104–116 (2016)