KIDNEY CANCER

Metabolomics for targeted therapy

Metabolomics—the assessment of a complete set of small-molecule metabolite concentrations over time or in response to stimuli—is gaining popularity as a technique for identifying biomarkers and novel therapeutic targets for disease. In a paper published in *Cancer Research*, Ganti and colleagues present the findings of a systematic metabolomics analysis of multiple biofluids—tissue, plasma, and urine—from a xenograft mouse model of highly metastatic renal cell carcinoma (RCC) generated by subcapsular implantation of human Caki-1 cells.

Of the 267, 246, and 267 metabolic alterations detected in tissue, serum, and urine, respectively, 89 were ubiquitous for all three biofluids and the majority of these were altered in the same direction (upregulated or downregulated expression). The investigators constructed heat maps to show the expression of each individual metabolite in the metabolome (the complete set of metabolites) and showed that metabolite changes in blood serum more accurately reflected changes in tumour tissue than those identified in urine.

However, when asked whether this finding raises concerns regarding the utility of urinalysis for kidney cancer, Robert Weiss—the lead investigator of the study—was keen to stress otherwise. “As for abandoning urinalysis for RCC, I’m not ready to do this,” Weiss says. “In another project, we are investigating the metabolomics of urine samples from patients with RCC and we hope to get either a single marker or, more likely, a suite of metabolite markers that can be used to screen for RCC in a select high-risk population of patients.”

The individual metabolites that were the most significantly altered in all three matrices (fluids) in the mouse model were cinnamoylglycine, nicotinamide and cysteine-glutathione disulfide. Both cinnamoylglycine and nicotinamide, which were downregulated in mice implanted with tumour cells compared to sham surgery animals, are regulated by modulators of peroxisome proliferator-activated receptor α (PPAR α)—a protein that regulates key enzymes of the tryptophan pathway and has a role in fatty acid metabolism. Importantly, levels of tryptophan, as well as its downstream metabolite kynurenine, were also shown to be significantly altered. On the basis of these metabolic shifts, two pathways—the tryptophan metabolism pathway (linked to immunosuppression) and the peroxisome proliferator pathway—were selected for biological validation, with the aim of identifying potential therapeutic targets.

“The significance of this work lies not so much in the identification of individual RCC biomarkers, but in our use, for the first time, of metabolomics to discover a suite of biomarkers that can be used to identify novel potential therapeutic targets,” explains Weiss. “Identifying individual specific biomarkers for RCC, or indeed for any disease, can be highly problematic, but using metabolite expression levels as a signature of metabolic (or other pathologic) processes is more feasible. These processes can then be targeted during therapy.”

Following on from initial metabolomics analyses, Ganti *et al.* studied the effects of the PPAR α agonist Wy-14,643 and the PPAR α antagonist GW6471 on several RCC cell lines, Caki-1 cells, and ‘normal’ controls (HK-2 and NHK). Wy-14,643 increased cell proliferation in all cells, whereas GW6471 had the opposite effect, suggesting that PPAR α might be a viable target for RCC therapy. “The identification of PPAR α as a novel potential target for kidney cancer, along with our finding that levels of tryptophan metabolites are elevated, suggests that attenuation of PPAR α or tryptophan metabolism—for example, by 1-MT, which inhibits the upstream tryptophan catabolic enzyme indoleamine 2,3-dioxygenase—could be of therapeutic use,” Weiss elucidates. “We have started the process of validating these targets *in vitro* and we are currently performing *in vivo* animal studies. The next step in this project will be the clinical evaluation of these targets.”

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Original article Ganti, S. *et al.* Kidney tumor biomarkers revealed by simultaneous multiple matrix metabolomics analysis. *Cancer Res.* doi:10.1158/0008-5472.CAN-11-3105