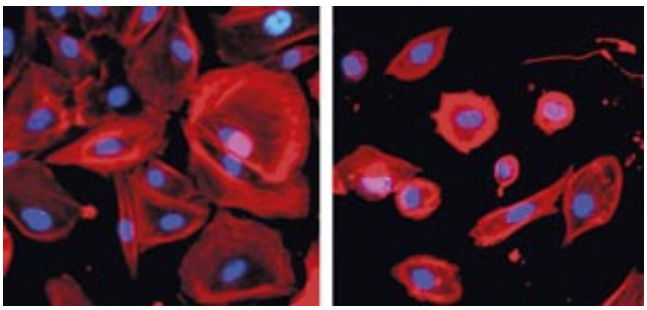
A cell imaging-based screening approach predicts toxic effects of chemicals on the human kidney

June 2 2016



Human renal proximal tubule cells treated with Dexamethasone (non toxic, left) and Bismuth Oxide (toxic, right). Credit: A*STAR Bioinformatics Institute and the Institute of Bioengineering and Nanotechnology

Thousands of new drug candidates and compounds must be tested every year to ensure their safety for humans, and toxicity is one of the main reasons for their failure. Animal models are widely used for this purpose, but they offer low efficiency. A*STAR researchers have now combined cell biology and computational expertise to find alternative, animal-free, toxicity testing methods.

Daniele Zink and Lit-Hsin Loo from the A*STAR Institute of Bioengineering and Nanotechnology and Bioinformatics Institute, respectively, are co-lead authors of a study that describes an approach for screening large numbers of compounds for toxic effects in human

renal proximal tubular cells (PTCs). These cells have key roles in kidney function and act to eliminate drugs and chemicals from the body. PTCs are often damaged in patients with compound-induced kidney injury, but little is known about the early mechanisms and markers of injury. To predict compound toxicity, the researchers treated laboratory-grown PTCs with a range of reference chemicals and developed an automated procedure to identify the first signs of damage.

Using machine-learning techniques to automatically analyse 129 image-based cell features, the researchers were able to predict PTC toxicity in humans with more than 80 per cent accuracy, irrespective of any knowledge of the compounds' chemical structure. "We were surprised that it worked so well," says Zink. "The screening results tell us, in an unbiased way, a lot about the cellular injury occurring in the samples," she adds.

The results indicate that most PTC-toxic compounds cause damage to the cells' DNA, despite the fact that many of them have not been found to directly target DNA. "We suspect that DNA damage may be a common response to different PTC injury-causing agents," explains Loo.

This animal-free model to predict kidney toxicity in humans will be especially useful during the initial stages of product development, where the safety of potential chemical ingredients must be evaluated. The researchers are now collaborating with the US Environmental Protection Agency to predict the kidney toxicity of hundreds of environmental chemicals, and they are developing a similar approach to predict liver- and lung-specific toxicities.

The next step will involve obtaining regulatory approval, which as Zink remarks "would be important for putting Singapore on the map as a global player in the rapidly growing in vitro safety testing market."

More information: Ran Su et al. High-throughput imaging-based nephrotoxicity prediction for xenobiotics with diverse chemical structures, *Archives of Toxicology* (2015). DOI: 10.1007/s00204-015-1638-y