Individual adverse drug responses could be predicted by a simple blood test

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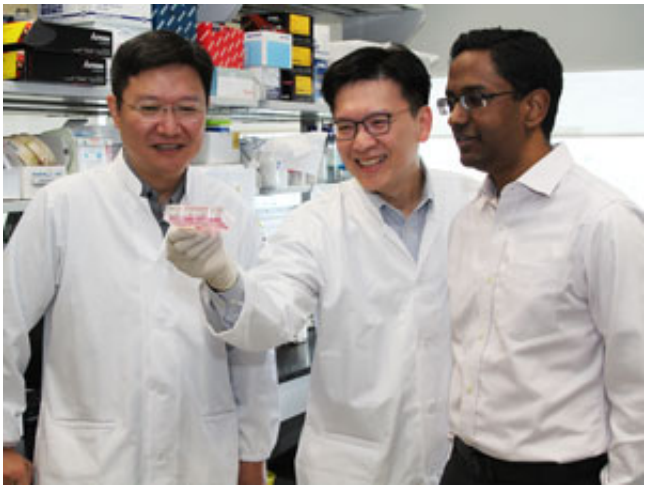

Researchers from the Institute of Bioengineering and Nanotechnology and the National Cancer Centre Singapore who discovered the approach of using patients' stem cells to test for side effects of drugs. From left: Hanry Yu, Min-Han Tan and Ravindran Kanesvaran. Credit: A*STAR Institute of Bioengineering and Nanotechnology

Severe illnesses sometimes require treatment regimens carrying grave risks, including organ failure. Now, a non-invasive technique developed at A*STAR could help predict patient vulnerability to potentially toxic drugs.

Therapeutics can induce organ damage via mechanisms that vary between individuals. These idiosyncratic drug reactions are a common

reason for the withdrawal of new drugs, and can be a significant problem during disease treatment.

Research led by Min-Han Tan and Hanry Yu from the Institute of Bioengineering and Nanotechnology, and National Cancer Centre shows how cells derived from a patient's blood offer the first opportunity to test an individual's susceptibility to idiosyncratic liver damage, known as hepatotoxicity; in this case, from the cancer drug, pazopanib.

Currently there is no easy way to predict idiosyncratic harm from the drug, "Pazopanib causes idiosyncratic hepatotoxicity, and liver biopsies are not commonly undertaken due to their invasive nature and potential risks," says Tan.

The researchers took white blood cells from five patients receiving pazopanib for metastatic renal cell cancer, three of whom exhibited hepatotoxicity. They converted these white blood cells into stem cells, and then into 'hepatocyte-like cells' (HLCs). This created a population of cells that retained the genetics and morphology of each patient's native liver cells, without the risks of a biopsy. The stem cells were then treated with pazopanib.

After 24 hours, the HLCs taken from the three patients exhibiting hepatotoxicity also experienced significantly more cell death than those from the two patients without liver damage. This validated that the test can model the individually-mediated effects of pazopanib on the liver.

"Currently, new drugs are tested for toxicity using generic liver cells, which cannot model patient-specific reaction. Establishing patient-specific HLCs with characteristics that are representative of genetic variation will be valuable for pharmaceutical drug testing," says Yu.

The team also discovered the mechanism by which pazopanib causes

injury by evaluating the changes in HLC gene expression following drug administration. In cells from both groups of patients, gene expression changes indicated a response to drug-induced stress. HLCs from hepatotoxicity-susceptible individuals, however, also showed evidence of differential iron metabolism as well as other genetic variations from non-susceptible HLCs. This probably contributes to the greater levels of cellular damage and death and provides the first experimental evidence of pazopanib's mechanism of action in idiosyncratic hepatotoxicity.

Tan hopes his team's research could be used in future to predict an individual's response to a proposed treatment. "We plan to expand the approach to different drugs and organs, and determine the nature of drug toxicity," explains Tan. "Our ultimate goal is to benefit patients and clinicians by gaining a better understanding of toxicity."

More information: Yukti Choudhury et al. Patient-specific hepatocyte-like cells derived from induced pluripotent stem cells model pazopanib-mediated hepatotoxicity, *Scientific Reports* (2017). DOI: 10.1038/srep41238

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