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Cell division typically associated with cancer may also protect the liver from injury

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Researchers at Oregon Health & Science University have discovered that a form of cell division typically associated with cancer called multipolar mitosis can yield diverse, viable cells capable of protecting the liver from injury and poisonous substances, such as pesticides, carcinogens or drugs. Their findings are published online in the journal *Nature*.

"Our findings show that the liver, which is known to have a tremendous capacity for regeneration, also has an amazing degree of diversity. A better understanding of this process may reveal why some individuals are more susceptible to different forms of liver injury than others, which could lead to new therapies for the treatment of liver disease," said Andrew Duncan, Ph.D., principal investigator and postdoctoral researcher in the lab of Markus Grompe, M.D., Papé Family Pediatric Institute, OHSU Doernbecher Children's Hospital; and the Oregon Stem Cell Center at OHSU.

The liver comprises a pool of genetically distinct hepatocytes, the primary functional cell type in the liver. Duncan and colleagues' work suggests that in response to liver injury that is toxic to most hepatocytes, a subset of select hepatocytes may respond favorably, thereby preventing liver failure and ensuring survival of the organism.

Unique among other cells in the body, hepatocytes in humans and rodents contain either a single nucleus with one set of DNA, called diploid hepatocytes, or one-two nuclei with multiple sets of DNA, called polyploid hepatocytes, explained Duncan. The functional significance of

hepatic polyploidy is unknown.

Duncan and colleagues endeavored to study the function of mouse polyploid hepatocytes using multiple approaches, including therapeutic liver repopulation, live cell imaging and cytogenetic analysis. While most polyploid hepatocytes underwent normal cell division to generate two identical daughter cells, approximately 4 percent of polyploid hepatocytes underwent specialized cell divisions, or multipolar mitosis, generating genetically distinct daughter cells. These unique daughter hepatocytes contained either chromosomal gains/losses, known as aneuploidy, or one-half DNA content of the parental polyploid hepatocyte.

The research team characterized the extent of hepatocyte aneuploidy in livers from healthy adult mice and found chromosomal gains and/or losses in more than 60 percent of hepatocytes. Together, the data show that hepatocyte proliferation involves a cycle of polyploidization, "ploidy reversal"— the opposite of polyploidization — and aneuploidy. The researchers call this dynamic process the "ploidy conveyor."

"Aneuploidy is most often associated with cancer, therefore our finding of pervasive aneuploidy in the liver is very surprising. Despite the high prevalence of numerical chromosome abnormalities, spontaneous liver cancer is rare in wild-type mice. We believe aneuploidy is a normal characteristic of hepatocytes. Furthermore, we speculate aneuploidy may be common in many different tissues. Studies are currently under way to characterize aneuploidy in human hepatocytes and other normal tissues in rodents and humans," said Duncan.

Although it is well known that hepatocytes become polyploid, the function of polyploid hepatocytes has been unknown. Andrew and colleagues suggest that proliferating hepatocytes polyploidize and undergo ploidy reversal, that is the ploidy conveyor, to specifically

generate unique hepatocytes with different mixtures of chromosomes. This genetic diversity may operate as an adaptive mechanism, serving as a substrate for selection of those hepatocytes most resistant to foreign compounds, Duncan explained. In response to liver injury that is toxic to most hepatocytes, a subset of select hepatocytes may respond favorably, thereby preventing liver failure and ensuring survival of the organism.

Provided by Oregon Health & Science University