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## **American Liver Foundation Research Award: Apoptosis and Liver Fibrogenesis**

by Natalie J. Torok, MD

Liver fibrosis and cirrhosis are major causes of death worldwide, and are thought to be the result of a wound-healing process, marked by a cascade of events leading to scar formation, or fibrosis. Scar formation distorts the normal hepatic anatomy, and eventually cirrhosis develops.

It is striking that cirrhosis of the liver is a common consequence of chronic liver injury elicited by various agents including alcohol, viral infections and genetic damage to the liver cells. However, the relationship between chronic liver injury and fibrogenesis is not yet well understood. The aim of my research is to find a common process which could link chronic liver injury to fibrosis. It is well known that chronic liver injury causes ongoing loss of liver cells by programmed cell death, or apoptosis. We have found that particles from dead liver cells are “eaten up,” or phagocytosed, by other cells in the liver called stellate cells, which are known to be at the center of the scar-forming process. Stellate cells in a healthy liver are inactive and produce only small amounts of collagen which is the main component of the scar material. Upon activation during chronic liver injury, however, they begin producing increased amounts of collagen. We have directly demonstrated in cell culture studies that stellate cells following phagocytosis become activated and begin producing increased amounts of collagen. With these data we have described a novel mechanism of liver fibrogenesis, linking the key processes of chronic liver injury, cell death and fibrogenesis.

Based on these studies, we have developed a research program specifically aimed to further study the phagocytic process, to elucidate how collagen expression is “turned on” following phagocytosis and to study the intracellular signals leading to this. In addition, experiments have been designed to study the relevance of the phagocytosis-induced fibrogenesis in humans. The results of these studies will lead to exciting new information which will help us to better understand the development of liver fibrosis. The complexity of the signaling cascades and crosstalks provides an explanation of why current antifibrogenic approaches have so far been unsuccessful. Detailed analysis of the signaling pathways is necessary in order to pinpoint steps where intervention could be done without eliciting harmful effects (e.g. increased inflammation in the liver or possible tumor formation). Inhibition of apoptosis, phagocytosis of apoptotic bodies by stellate cells, or signaling events occurring as a result of the phagocytic process, may prove to be therapeutic strategies to inhibit liver fibrogenesis and cirrhosis, and delay or even avoid liver transplantation. Thus, by better understanding how cirrhosis develops from the initial liver injury, more rational treatments can be developed for all causes of liver disease.

*Dr. Torok is an Assistant Professor of Transplant Hepatology at the University of California, Davis. She received a \$150,000 Liver Scholar Award from the American Liver Foundation in 2004.*