Researchers develop new approach to treat acute liver failure

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Acute liver failure is a life-threatening disease, characterized by a sudden, massive death of liver cells. Unfortunately, few treatment options exist, especially for advanced-stage liver failure. As a last resort a liver transplant may be the only remaining option. Now the physician Dr. Junfeng An of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch and Dr. Stefan Donath, a specialist in internal medicine and cardiology, also of the MDC and Helios Klinikum Berlin-Buch, have developed a new treatment approach based on a mouse model. In their current study published in *Hepatology*, the liver failure was reversed and the mice recovered completely. The researchers hope to soon be able to test their new approach in clinical trials with patients.

According to an estimate published in a 2011 issue of the "Deutsche Ärzteblatt", a professional journal for German physicians, between 200 and 500 patients suffer from acute liver failure in Germany each year. Poisoning from mushrooms or drugs is one of the main causes of this serious liver disease. In Southern Europe, Africa and Asia an acute infection with the hepatitis B virus is considered to be the most important cause.

For their treatment approach the two researchers utilized the recently discovered protein ARC (apoptosis repressor with caspase recruitment domain), which serves as the body's own survival switch. ARC is expressed in heart and skeletal muscle and in the brain, but not in the liver. In 2006 Dr. Donath showed that apoptosis is the cause for the death of myocardial cells during heart failure, but that ARC stopped the

myocardial cells from being destroyed.

Apoptosis protects the body from diseased or defective cells. In tumor cells apoptosis is deactivated, allowing the cancer cells to proliferate uncontrollably. Cancer researchers are therefore striving to utilize apoptosis to develop a treatment. They are looking for ways to reactivate apoptosis to drive the proliferating cancer cells into programmed suicide. However, in acute liver failure the problem is not too little but rather too much apoptosis. Physicians administer drugs in an attempt to halt the destruction of the cells, but only with modest success.

Now Dr. Donath and his colleagues have fused ARC to a noninfectious fragment of the human immunodeficiency virus (HIV), called TAT for short. The researchers used TAT as a shuttle to transfer this survival-switch construct into the liver. Mice with acute liver failure were given an intravenous or intraperitoneal injection with the construct. "Within just a few minutes the fusion protein TAT-ARC reached the liver of the animals and immediately began to take effect. ARC was able to stop the apoptosis of the liver cells, and all of the animals completely recovered," Dr. Donath said. "ARC is very fast acting, and this is a huge advantage, because in an emergency there is not much time for treatment. And when the massive damage is over, the liver is quite capable of regenerating itself. In addition, ARC reaches other organs via the bloodstream, not only the liver. "Moreover," he pointed out, "since TAT-ARC only has to be administered for a short time, a cancer risk can be largely excluded."

During their studies, the researchers also discovered a new active mechanism of ARC, which apparently is responsible for the protective function of this protein in the liver. It inhibits the activity of a molecule (JNK), which is activated in immune cells of the liver and causes abnormal processes, whereby another molecule (TNF alpha) is released that causes the liver cells to die. ARC thus protects the liver cells from

destruction. The researchers hope to soon be able to test their new approach in clinical trials with patients.

Dr. Donath and the MDC have patented the fusion protein TAT-ARC for the indication of acute liver failure. The research project was funded by the MDC Pre-Go-Bio project, an internal project fund of the MDC that supports the transfer of diagnostic or therapeutic procedures obtained in basic research into clinical applications.

More information: TAT-ARC protein transduction rescues mice from fulminant liver failure, *Hepatology*, doi:101002/hep.25697 ; Vol. 56, No. 2, August 2012

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