'Stimulated' stem cells stop donor organ rejection

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(Medical Xpress) -- Johns Hopkins researchers have developed a way to stimulate a rat's stem cells after a liver transplant as a means of preventing rejection of the new organ without the need for lifelong immunosuppressant drugs. The need for anti-rejection medicines, which carry serious side effects, is a major obstacle to successful long-term transplant survival in people.

With a combination of a very low, short-term dose of an immunosuppressive drug to prevent immediate rejection and four doses of a medication that frees the recipient's stem cells from the bone marrow to seek out and populate the donor organ, the rats lived more than 180 days with good liver function despite stopping both drugs after one week. The researchers are also testing the method on other transplanted organs, including kidneys, in rats and other larger animals.

Essentially, the Hopkins scientists transformed the donor liver from a foreign object under attack by the rat's immune system into an organ tolerated by the recipient's immune system — all in a matter of three months from the date of transplant, they report.

The technique, if replicated in humans, could mark a major shift in the process of organ transplantation, the researchers say. An article describing the experiment appears in the current issue of the *American Journal of Transplantation.*

"It is the dream for all scientists in the transplant field to erase the need

for lifelong immunosuppressant drugs," says study leader Zhaoli Sun, M.D., Ph.D., an associate professor of surgery at the Johns Hopkins University School of Medicine. "Currently, if a patient survives for 10 or 20 years with a new liver, that organ is still seen as foreign inside its new body because immunosuppression puts blinders on the immune system that must stay on to prevent rejection. Our idea was to find a way to turn that organ into something that 'belongs' and is never at risk of rejection."

Although thousands of people with end-stage liver disease have gotten lifesaving liver transplants in recent years, rejection remains a chronic risk. And the expensive immunosuppressant drugs they need increase the chance of developing severe infections and many kinds of cancers. Some patients have difficulty sticking to the cocktail of drugs, which must be taken every day.

For their study, researchers transplanted portions of the livers of one kind of rat (dark agouti, or DA) into another (Lewis-type). For seven days after transplantation, the Lewis rats were treated with low-dose tacrolimus (an immunosuppressant), plerifaxor (a stem-cell stimulator) or a combination of the two. Twelve of the 13 rats that received a combination of the two drugs had long-term liver function and survived more than 180 days, while nearly all of the remaining rats rejected their new livers after 12 days.

"This short-term treatment had long-term results," says Sun, who also is director of Hopkins' Transplant Biology Research Center.

Typically, organ transplant recipients receive full doses of immunosuppressant drugs, such as tacrolimus, immediately after they receive new livers. Otherwise, rejection quickly results and patients may die.

Sun and his colleagues gave the Lewis rats in their experiment the

equivalent of one-tenth the standard dose of tacrolimus. The goal was to have the new liver experience some mild rejection, but not enough to kill it. This "controlled rejection," Sun says, appears to create injury signals in the body that cry out for stem cells to come and repair the damage being done to the new liver. It also prevents the new liver from regenerating itself with cells from the donor because it is under immunologic attack, leaving an opening for the recipient's stem cells to jump in and play that role.

Sun and his colleagues used plerifaxor, a relatively new drug, known to free stem cells from the bone marrow and release them to circulate in the bloodstream. The drug is currently approved for patients about to undergo chemotherapy whose stem cells are harvested frozen and then returned to the body after cancer treatment.

Sun says that, in his experiment, many of these stem cells travel to the damaged liver to repopulate it with cells from the recipient, slowly taking over for the donor cells. Sun says the mechanism that brings the stem cells into the liver is becoming better understood, while the mechanisms by which stem cells become liver cells remain elusive. Equally interesting, Sun says, the stem cells also appear to modulate the immune response, increasing the number of regulatory T-cells and helping to reduce the chances of rejection.

"In our study, the risk of organ rejection is eventually eliminated because the liver is no longer a foreign object, but comprised of many of the recipient's own cells," Sun says. "Once the recipient's stem cells take over, the body sees the regenerated liver as its own and works to protect it, not attack it."

Within three months, Sun and his colleagues found that the majority of the liver cells in the transplanted organ belonged to the recipient, not the donor. When they used whole livers instead of partial livers, the process

took a year. This suggests that the transformation process is jumpstarted by using partial livers for transplant, because the organ already “needs” to regenerate itself to most effectively function, he says.

Sun cautions that clinical trials with human organ transplant patients might be years away, but only if further research in animals confirms the method’s safety and value. The technique might prove useful not only at the time of a new transplant, but even after years of immunosuppressant drug use.

Provided by Johns Hopkins University