

JUNE 21, 2007

Discovery in Fish May Aid Human Blood Cell Transplants

The discovery that zebrafish produce natural chemicals that enhance production of blood-forming stem cells may translate rapidly into new treatments to increase the success of bone marrow or cord blood transplants in humans.

The research team, which was led by Leonard Zon, a Howard Hughes Medical Institute researcher at Children's Hospital in Boston, published its findings in the June 21, 2007, issue of the journal *Nature*. Trista North, a postdoctoral fellow in Zon's laboratory, was lead author.

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- Leonard I. Zon

In their experiments, the researchers were searching for compounds that would increase the production of blood-forming, or hematopoietic, stem cells (HSCs). Zon said that such compounds could be clinically important in enhancing success of bone marrow and cord blood transplantation. One of the aims of bone marrow transplantation is to restore the immune systems of patients whose blood cells have been depleted by cancer therapy.

"In earlier work, we developed staining methods that marked HSCs in the developing zebrafish embryo," said Zon. "Since we can produce and test thousands of zebrafish embryos at a time, we have a very quick and efficient model for large-scale testing. So, Trista and I came up with the idea of conducting a mass screening of chemicals from a library to see whether we could find any that increased the quantity of stem cells."

The researchers screened a library of 2,275 chemicals, about a third of which are already FDA-approved, said Zon. They began by placing fish embryos in the tiny wells of a culture dish. Once the embryos were in place, the researchers added one of the chemicals, stained the embryos for stem cells, and observed whether the chemical enhanced or decreased stem cell production.

The scientists identified 35 compounds that increased HSC production and 47 that decreased it. The result of the screening also yielded an important discovery about the regulatory mechanism for stem cells, said Zon.

“When we looked at the list of chemicals that affected stem cells, what was staring us in the face was that many acted on the prostaglandin regulatory pathway,” said Zon. “This prompted us to explore this pathway in more depth.” Prostaglandins are fatty hormone-like chemicals known to regulate a wide array of body processes.

Further exploration revealed that the prostaglandin E2 (PGE2) in the zebrafish played a central role in regulating HSC formation. When they administered a long-acting version of PGE2 to fish embryos, they saw a considerable enhancement of stem cell production.

In additional studies with both adult zebrafish and mice, they found that the long-acting PGE2 greatly enhanced HSC production. Conversely, inhibiting PGE2 diminished HSC production. In particular, when they transplanted both PGE2-treated and untreated stem cells into mice, the treated cells far outperformed the untreated cells in their ability to proliferate.

The researchers also found that decreasing expression of two regulators of PGE2—cox 1 and cox 2—also decreased stem cell production. This finding is important for human bone marrow recipients, because pain medications such as aspirin and ibuprofen are cox inhibitors, said Zon.

While the HSC-enhancing drugs they identified could find use in aiding marrow transplantation, they will likely be especially important in cord blood transplantation, said Zon. In this treatment, stem cells from umbilical cord blood are transplanted to restore the immune system in immune-compromised patients.

“Cord blood has a limited number of stem cells in it, enough so that the blood from a single cord is sufficient for a small child. However, when it is transplanted into an adult, there is a 40 percent chance that the patient won't engraft, because there aren't enough stem cells in the sample,” said Zon. “When adult patients are given two cords from unrelated donors, this chance of failure is reduced, but there may be immunological problems from interaction between the two sources.

“Using drugs that enhance PGE2 to amplify the number of stem cells in a cord sample could enable use of only one cord in such patients,” said Zon. “And it may even help patients who don't engraft.” Zon said he and his colleagues plan to begin clinical trials of such HSC-enhancement using the long-acting version of PGE2.