A functional immune system can be derived from embryonic stem cells, preliminary study finds

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A new study demonstrates for the first time that embryonic stem cells can be used to create functional immune system blood cells, a finding which is an important step in the utilization of embryonic stem cells as an alternative source of cells for bone marrow transplantation. This hopeful news for patients with severe blood and immune disorders, who need these transplants for treatment, was prepublished online in *Blood*, the official journal of the American Society of Hematology.

Embryonic stem cells (ESCs) are being intensely investigated as a renewable source of primitive cells theoretically able to regenerate all tissues and organs. The use of ESC-derived blood-forming cells may have an important advantage over traditional transplants that use bone marrow, umbilical cord blood, and peripheral blood from donors.

The antigens on the surface of donated cells must be compatible (determined by a method called HLA matching) with those of the patient to prevent rejection. The use of embryonic stem cells, which have low levels of these antigens and may therefore be less likely to provoke a defensive reaction by the patient's body, may allow patients who can't find suitable HLA-matched donors to receive transplants.

Previous studies have shown that mouse ESCs can be coaxed to form blood-forming hematopoietic cells by introducing a protein called HOXB4, known for its unique ability to greatly enhance cell

proliferation, into them. These cells could then be transplanted into mice whose own marrow had been destroyed by radiation, rescuing their marrow function and beginning to produce necessary blood cells. However, previous studies have not investigated whether ESC-derived bone marrow in these mice could regenerate normal immune function – in particular, if they could allow the mice to respond to viruses or vaccines. Because fetuses have no need for a functional immune system as they are protected from the environment while in the womb, it was unclear if ESC-derived marrow would recreate an immune system at all or just very slowly.

In this study, a team of scientists from Iowa, Taiwan, and Germany used HOXB4-containing ESCs to engraft the bone marrow and rescue mice that genetically lacked any immune system and had been irradiated to destroy their bone marrow. Only cells containing HOXB4 were able to engraft, rescue the mice, and produce blood cells long term. These engrafted cells were shown to be derived from the transplanted ESC-derived cells.

To determine if these transplants were able to rebuild the defunct immune system, the scientists injected the mice with LCMV, a common rodent virus, and watched for T-cell activity, a sign that the body was defending itself against the infection. Although the number of T cells generated by the new hematopoietic cells was low, they were able to respond effectively to the virus. In addition, the transplanted hematopoietic cells were also able to produce B cells and other defensive cells called antigen-presenting cells, which have a role in signaling T cells to action. They also tested the ability of the mice to respond to vaccination and demonstrated the induction of specific immune cells. Although the level of immune response was not what is seen in normal adult mice after exposure to the virus or vaccine, it was measurable and effective.

The study was also encouraging in that none of the 70 transplanted mice followed for more than 200 days developed any tumors – another concern when using ESCs for tissue regeneration.

“These results show, for the first time, that functional white blood cells, the key players in the body’s immune system, can be successfully derived from embryonic stem cells expressing HOXB4,” said lead study author Nicholas Zavazava, MD, PhD, Professor of Internal Medicine and Director of Transplant Research at the University of Iowa Hospitals and Clinics in Iowa City and Staff Physician at the Iowa City VA Medical Center. “Therefore, we’re hopeful that these exciting findings are the first step toward new, improved therapies for patients.”

Source: American Society of Hematology