Immune response to human embryonic stem cells in mice suggests human therapy may face challenge

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Human embryonic stem cells trigger an immune response in mice, researchers from the Stanford University School of Medicine report. The finding suggests that the effectiveness of human therapies derived from the cells could be limited unless ways are found to dampen the rejection response.

The researchers found the immune response in mice could be mitigated by the use of common antirejection medications. Overall, the work indicated that, contrary to previous suggestions, the immune system is not blind to the presence of foreign embryonic stem cells.

"It's getting harder and harder to believe that these cells are immunoprivileged," said Joseph Wu, MD, PhD, assistant professor of cardiovascular medicine and of radiology. "In fact, the rejection of these cells confirms our suspicions that they do cause an immune response."

Embryonic stem cells form all cells in an embryo. Many researchers have suggested that these cells may receive a kind of "free pass" from the normally vigilant immune system in order to allow the growth of a fetus that contains both maternal and paternal genetic material. Such an immunological exemption could alleviate many concerns about using cells for therapy that don't exactly match the recipient's immune system - such as existing embryonic stem cell lines that are not directly derived from the recipient.

"We all want to know what's going to happen if you transplant these stem cells into a person," said Mark Davis, MD, PhD, the Burt and Marion Avery Family Professor and professor of microbiology and immunology. But because unmodified embryonic stem cells can cause cancer, the researchers transplanted the cells into mice rather than people.

Davis, who is also an investigator for the Howard Hughes Medical Institute, is a co-author of the paper, which will be published Aug. 18 in the online early edition of the *Proceedings of the National Academy of Sciences.* Wu is the senior author of the research.

Wu, Davis and their colleagues injected human embryonic stem cells into the leg muscles of mice with either normal or compromised immune systems. They followed the fate of the transplanted cells with a novel molecular imaging technique that can visualize whole, living animals. Previous studies of this type relied on microscopic examination of tissue samples from sacrificed animals, but this new approach allows researchers to watch the life or death of cells in real time.

Although the cells died within about seven to 10 days in mice with functioning immune systems, they survived and proliferated in the immunocompromised mice. Repeated injections of cells into the immune-normal mice led to more rapid cell death, indicating that the immune system was becoming more efficient at recognizing and rejecting the cells.

"The data is quite convincing," said Wu. "Based on these results, we believe that transplanting these cells into humans would also cause an immune response."

It's not known what triggers the immune system to attack the embryonic stem cells, but the scientists believe it may be a protein that begins to appear on the surface of the cells as they differentiate into more-

specialized tissues. Once the immune system has been primed to recognize the foreign molecules, it responds even more quickly to repeated invasion.

"That's the beauty of this kind of noninvasive imaging system," said Wu. "It allows us to assess the response of one animal to a variety of conditions and gives us much more valuable information."

Because the aggressive reaction of the immune system somewhat mimics the way the body reacts to transplanted organs, the researchers wondered if common antirejection medications would increase cell survival. They found that a combination of two compounds - tacrolimus and sirolimus - allowed the cells to survive for up to 28 days in the mice with normal immune systems.

Wu and his colleagues will continue to investigate whether different combinations can more effectively mitigate the immune response in mice. They also plan to conduct similar experiments in a mouse model that more closely approximates what would happen in humans.

"A lot of research efforts are devoted to the basic science of stem cells," said Davis. "This work is focused on the immediate practicalities of actually using these cells therapeutically."

Source: Stanford University Medical Center