New stem cell line provides safe, prolific source for disease modeling and transplant studies

Researchers have generated a new type of human stem cell that can develop into numerous types of specialized cells, including functioning pancreatic beta cells that produce insulin. Called endodermal progenitor (EP) cells, the new cells show two important advantages over embryonic stem cells and induced pluripotent stem cells: they do not form tumors when transplanted into animals, and they can form functional pancreatic beta cells in the laboratory.
"Our cell line offers a powerful new tool for modeling how many human diseases develop," said study leader Paul J. Gadue, Ph.D., a stem cell biologist in the Center for Cellular and Molecular Therapeutics at The Children's Hospital of Philadelphia. "Additionally, pancreatic beta cells generated from EP cells display better functional ability in the laboratory than beta cells derived from other stem cell populations."

In addition to producing beta cells, the researchers also directed EP cells to develop into liver cells and intestinal cells—both of which normally develop from the endoderm tissue layer early in human development.

Gadue and colleagues are publishing their study Friday, April 6 in the journal Cell Stem Cell.

The researchers manipulated two types of human stem cells—embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs)—to become EP cells. Because both stem cell populations proliferate in great numbers and potentially generate all types of tissue, they offer enormous promise for scientists to precisely control cell development, both for the study of basic biology and for future cell-based treatments.

ESCs are derived from human embryos, typically unused embryos from fertility treatments that are donated for research purposes, while iPSCs are engineered from human somatic cells, such as skin cells or blood cells. Researchers have learned how to reprogram somatic cells to become pluripotent. Like ESCs, iPSCs are able to develop into many other types of human cells. However, when undifferentiated ESCs or iPSCs are transplanted in animal studies, they form teratomas, tumors containing many different cell types. Therefore, it has been critical that any cell type generated from ESCs or iPSCs and used for transplantation is stringently purified to exclude undifferentiated cells with tumor-forming potential.

In the current study, the researchers used signaling molecules called cytokines to steer ESCs and iPSCs into becoming EP cells, committed to developing into endoderm, one of the three tissue layers found in early human development. The EP cells have nearly unlimited potential for growth in the laboratory.

Both in cell cultures and when transplanted into animals, the study team showed

that EP cells can differentiate into multiple cell types, representing those found in the liver, pancreas and intestine. Importantly, undifferentiated EP cells did not form teratomas in the team's transplantation studies.

In cell culture, the researchers differentiated the EP cells into beta cells—insulin-expressing cells similar to those found in the pancreas. Those engineered beta cells passed an important test—when stimulated by glucose, they were able to release insulin, a function that is impaired or absent in patients with diabetes. While the cells achieved only 20 percent of normal function, this result is an improvement over that seen in similar cells derived directly from ESCs or iPSCs, which typically respond very poorly or not at all to glucose.

Gadue stressed that these promising early results are only the first steps in researching EP cells. Further work may focus on taking cells from individual patients with genetic forms of diabetes or liver disease to derive EP cell lines. The EP cell lines can then be used to model the development and progression of the patient's disease and discover new therapies for that particular disease.

Finally, although applying this science to cell therapy is years away from practical clinical use, EP cells may offer a powerful starting point for developing tissue replacement treatments, such as supplying beta cells for diabetes patients or hepatocytes (liver cells) for patients with liver disease. "While more work is needed to characterize EP cells, they may offer a potential source of safe, abundant cells for future diabetes treatments," said Gadue.

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