Pig-Human Chimeric Embryos First Step to Organ Formation

Ricki Lewis, PhD | January 27, 2017

Researchers have created chimeric early embryos that combine human cells with pig or cattle cells, taking the first steps toward growing human organs in species more like us than rodents, according to a report in *Cell* .

In a technique called interspecies blastocyst complementation, pluripotent stem cells (PSCs) from one species are introduced into blastocysts of another species for which gene editing has resulted in an organ not developing. The donor cells then form the organ, filling the niche that the obliterated gene vacated in the "organogenesis disabled hosts." The technique has enabled rat pancreases to form in mice, rescuing the smaller rodents from diabetes and enabling some of them to live a normal lifespan.

Jun Wu, PhD, from the Salk Institute for Biological Studies, and colleagues repeated the rodent experiment and expanded the repertoire of rat-in-mouse cell types and tissues to heart and eye. They then showed that rat cells introduced into pig blastocysts did *not* form chimeras, presumably because of the great evolutionary distance separating the species.

The next step toward applying the technology to the human organ shortage problem was to create chimeras using human pluripotent stem cells (hPSCs) and a host species more like ourselves in anatomy, physiology, and organ size than rodents. "To start filling this void, we tested different types of hPSCs for their chimeric contribution potential in two ungulate species, pigs and cattle," the researchers wrote.

They derived human induced pluripotent stem cells (hiPSCs) from human foreskin fibroblasts. The cells formed teratomas (demonstrating ability to differentiate) and were labeled with fluorescent markers for tracking integration into the inner cell mass of pig or cattle blastocysts.

"First Step"

The experiments cultured the stem cells in four types of media that affect the degree of pluripotency. Overall, the human cells, from "naïve" to "primed" (less pluripotent), integrated efficiently into both cattle and pig blastocysts and survived.

Because preimplantation success does not predict postimplantation survival, the researchers undertook a second set of experiments that ran longer in development. They introduced naïve hiPSCs and hiPSCs at an intermediate stage between naïve and primed into pig blastocysts only, because pigs have more offspring at a time than cattle and have organs more similar in size to those of humans.

The researchers injected 3-10 hiPSCs into each of 2181 pig blastocysts, of which 2075 were transferred to sows, with 41 animals receiving 30 to 50 embryos each. From the 18 sows that became pregnant, from day 21 to 28, the researchers harvested 186 embryos. An artificially inseminated sow harbored 17 control embryos.

The fluorescence signal indicated that 67 of the 186 embryos included human cells, but 50 of the embryos were small and underdeveloped, whereas only 37 of 119 embryos without the label were in this state, suggesting that introduction of the human cells might have disrupted development of the pig embryos.

Immunohistochemistry analysis confirmed the fluorescent signal and identified human cell types representing different lineages in the chimeric embryos. However, efficiency of chimera formation was

very low.

The researchers concluded that "naïve hiPSCs injected into pig blastocysts inefficiently contribute to chimera formation, and are only rarely detected in postimplantation pig embryos." Slightly more efficient were hiPSCs at the intermediate developmental state. The investigators also noted that chimera formation was less likely between pigs and humans than between rats and mice, which is consistent with the greater evolutionary distance.

Whether the degree of chimerism demonstrated is sufficient to make human-pig blastocyst complementation feasible, as it is between mice and rats, "remains to be demonstrated," the researchers concluded, calling the findings "a first step towards realizing the potential of interspecies blastocyst complementation with hPSCs."

If the technology can mature, it could provide a platform to observe human embryogenesis in health and disease and to test drugs, with addressing the human organ shortage a long-term goal, they added.

The researchers have disclosed no relevant financial relationships.

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