

Embryonic Stem Cells

Some people are uncomfortable allowing the use of embryonic stem cells, because of their potential to grow into human life. While scientists say other cells are less controversial -- adult stem cells and skin cells, for instance -- those cells also lack some of the properties of embryonic cells, and are less useful in research.

The advantage of adult stem cells is largely that they are from adults, and we know what they are comprised of, said Dr. Mohammed El Majdoubi, PhD, an assistant professor at Dominican.

In addition, "adult stem cell research has never been excluded from federal funding," said Dr. Renee Reijo Pera, professor and director of the Center for Human Embryonic Stem Cell Research and Education within the Stanford Institute for Stem Cell Biology and Regenerative Medicine in the Department of Obstetrics and Gynecology at Stanford University School of Medicine.

Dr. Warren Hoeffler, PhD, the founder of Xgene Corporation, a company commercializing discoveries in tissue engineering, agreed, with a caveat. "I see a lot of potential for adult stem cells, but embryonic stem cells, because they are more durable, are very appealing," he said. "Adult stem cells are difficult to isolate. They lose their 'stem-ness' in passing from one Petri dish to another. They lose a lot of their stem cell ability."

Those were among the many disadvantages Dominican's Majdoubi cited. "We have difficulty in growing them or isolating them," Majdoubi said. "They have limited longevity. We cannot make a lot of cells out of them. They have questionable quality due to age, toxins, and diseases."

Neurons can live in the body for 80 years or more, but they stop dividing, said Dr. Xianmim Zeng, PhD, assistant professor at the Buck Institute for Age Research. "This is called senescence, or aging."

A cell from an infant, on the other hand, will divide 50 times, she said. "Human embryonic stem cells can self-renew indefinitely," Zeng said. "They can bypass senescence."

Embryonic stem cells have many more advantages to researchers, Majdoubi said. They're easy to grow in cell culture, they can be maintained for a long time, and they have the potential to be useful in clinical medicine for a wide array of diseases.

Since they can be grown in a dish, Majdoubi said scientists hope that the nerve cells, heart cells, liver cells, blood cells they are making in the lab can be used some day in a variety of transplantations.

Scientists have some indications those cells might be used in humans battling diabetes, Parkinson's, spinal cord disease, or stroke. "Imagine injecting pancreatic cells into a patient to replace the pancreatic cells that were lost or damaged in a disease of Type I Diabetes," he said.

But to achieve such dreams, scientists like Majdoubi first want to dispel some of the misperceptions.

“Stem cells themselves cannot make humans. They cannot implant themselves. They can only create other cells,” he said. “The myth of making human clones from embryos from a hospital is just that, a myth.”

There can be several sources of embryonic stem cells, he said. Most common are the embryos from *in vitro* fertilization. In that process, sperm from a man is used to fertilize an egg from a woman, and because of the uncertainty involved, couples usually choose to fertilize more than one, but not transplant more than one or two, Majdoubi said.

“There are always embryos left over from the IVF procedure,” he said. “Four hundred thousand are frozen in hospitals around the country. When their use is over, they’re discarded.”

“Because this procedure involves destruction of embryos, there are groups opposed to it,” he said.

Doctors in Wisconsin have developed a new procedure that shows promise in using skin cells as a substitute for stem cells. But those are still far from perfect, Majdoubi said. “In order to reprogram skin cells, we have to introduce viruses, and we still don’t know very well how to control viruses in the body” he said. “There’s still a long way to go to use this approach.”

Other workarounds include Somatic Cell Nuclear Transfer, but that procedure – used in cloning Dolly the sheep – is highly controversial. “Therapeutic cloning – cloning for the purpose of making cells – involves an egg from which the pronucleus has been removed and replaced with an adult nucleus,” Majdoubi said. “What you have in the end is a little embryo that does not involve sex. That embryo can make stem cells custom-made for a patient who gave that nucleus.”

Reijo Pera, from Stanford, gave a dramatic account of the early life of embryonic stem cells, one that unflinchingly cast their journey in human terms.

She started her slide show on “day zero.”

“Here’s an egg that’s been retrieved from a woman,” she said. “It’s 100 microns in size. It’s smaller than the point of a pin. It’s a single nucleus containing the mother’s DNA. This is the maternal pronucleus.

“This can be put in a dish with a sperm,” she said. “The sperm will find the egg. The sperm has the male DNA – the male pronucleus.

“What’s interesting about the first day of human life? It seems like not much has happened,” she said. In reality, “this is one of the most eventful days you can imagine. As these two pronuclei migrate towards each other, it’s like a movie where you see two people running across a field toward each other. It’s the same thing. Here you have a male and a female, and they meet and they fuse.”

As they do that, Reijo Pera said, they’re being reprogrammed. “What has to happen on the first day of life is, we have to have a complete reprogramming of the egg and the sperm nucleus. Erase the hard drive.”

“The DNA is erased, but a couple of marks are left to track where it came from.”

And then the egg starts dividing. It doesn’t grow, it just cleaves. “On day two,” Reijo Pera said, “it becomes two cells. On day three, it’s four cells early, and later on, there’s eight. This is incredibly slow growth. It’s incredible that on day three there are just eight cells.”

This activity takes place in what Reijo Pera called “a sea of transcriptional silence.” Her slides looked like photos of craters on the moon, but the little circles were actually cells dividing.

“What’s interesting on day three is, suddenly the embryo turns on its own genome,” she said. “The embryo starts relaying messages. That cell is truly an embryonic cell. We call it the oocyte, or egg-to-embryo transition. It has to become an embryo in order to survive and go on to develop.”

There are many mysteries of human development, Reijo Pera said. “Why does human embryonic genome activation occur on day three? It’s like a clock. It’s very mysterious.”

“It’s things like these decisions at a cell-based level that we failed to learn much about in human biology,” she said.

That process takes only 12 hours in mice, and does not have nearly the “transcriptional silence” evident in human embryo development. “Humans are special this way,” Reijo Pera said.

And yet it’s a fragile time. “A lot of errors can occur here,” she said. The loss of embryos derived from *in vitro* fertilization exceeds 75 percent. There’s an incredible rate of miscarriage in *in vitro* fertilization clinics. There are failures to get pregnant, and the first three days expose us to birth defects. It shows how much we don’t understand about this process.”

On day four, the embryo is making its own genetic material. On day five, the outer layer attaches the embryo to the uterus. The inner layer – from which embryonic stem cell lines are derived – begins to give rise to the fetus.

On day six, the blastocyst – which becomes the embryo -- has hatched. “It’s worked up some pressure and the cells spill out,” she said. “It wants to get closer to the tissues of the mother. Here, there’s a question of how you can have a foreign object invade the body of the female. It’s not quite the same, but there’s no rejection.”

This begins a dramatic period, with the formation of different structures like the hypoblast, the epiblast, and the yolk sac. That period is known as gastrulation, and it involves cells moving, caving in on each other, and transforming themselves.

“The hardest thing you’re ever going to do in your life is gastrulation,” Reijo Pera said. “The worst is over, that’s the way I look at it.”

As the cells move, some will become the ectoderm, or the outer surface of our body. Others will be the mesoderm – the heart, the muscles. And those on top will be the endoderm – the gut and the pancreas.

Although Reijo Pera spelled everything out on a daily basis, she said much remains unknown about those first days. “The rules have obviously been written because we exist,” she said. “We have beating hearts and beautiful skin, yet we don’t know the rules.”

“We need to understand how a cell makes a decision,” she said. “Today we really do have the opportunity not only to isolate embryonic stem cells, but also to understand our beginnings. Those are the decisions that make us uniquely human. We start out with a program that’s uniquely human.

“We need to pursue these studies in understanding our development. We need to understand and embrace the beauty of the programs that make us who we are and dictate

how we develop,” she said. “Two cells come together, a sperm and an egg, and the rest is history.”

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