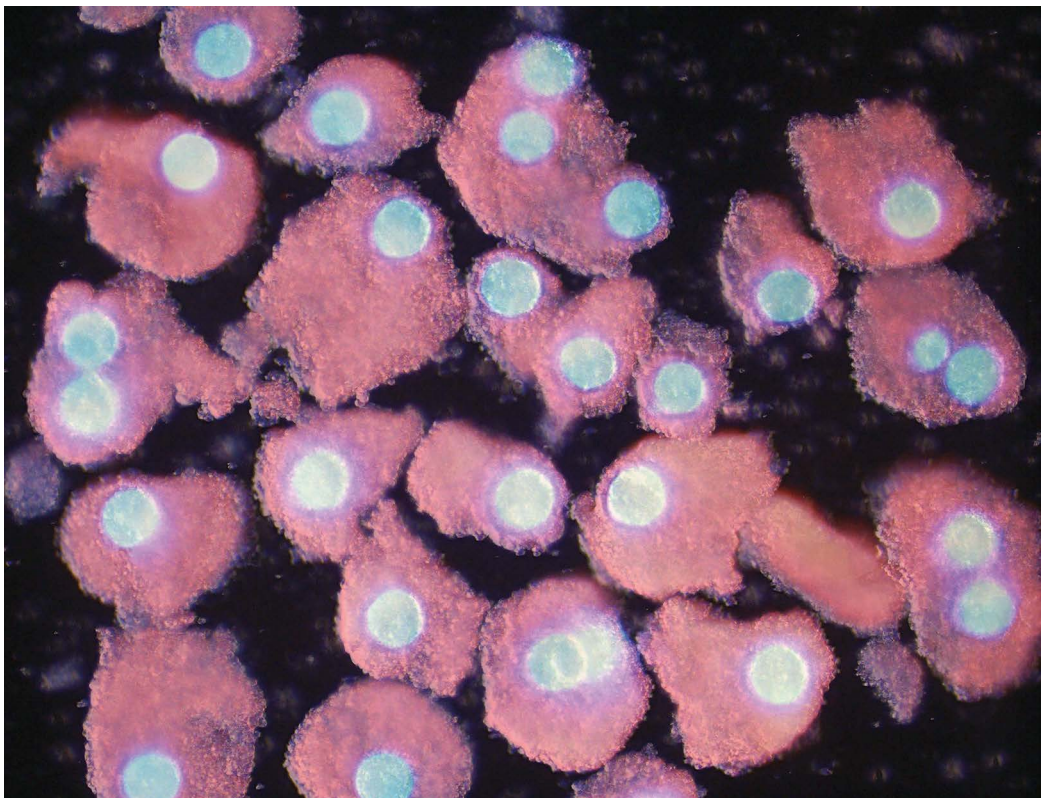
Research round-up

Highlights from stem-cell research. By Anthony King



T. YOSHINO *ET AL. SCIENCE* **373**, EABE0237 (2021)

Follicle structures, including oocytes, have been reconstructed from mouse pluripotent stem cells.

Gametes generated from scratch

A group of researchers from Japan has for the first time produced mouse egg cells in a test tube using only stem cells — an advance that could enable the development of treatments for infertility.

The team, led by Katsuhiko Hayashi at Kyushu University, had previously generated eggs from stem cells in 2016, but the process involved culturing the cells alongside ovarian tissue taken from a mouse embryo. Now, the team has managed to create the egg-supporting ovarian tissue from stem cells as well.

Eggs mature in specialized ovarian niches, which offer the right environment and signals for growth. To generate eggs from stem cells, biologists previously either moved stem cells back into a live animal or placed them into embryonic ovarian tissue in culture. Instead, Hayashi's group used signalling molecules to coax embryonic stem cells into differentiating into the ovarian cell types that support egg maturation. When mixed with germ-like cells cultured from mouse embryonic cells, an ovarian organoid developed. These generated functional mouse eggs that could be fertilized in a dish, forming mouse embryos.

This work opens the door to investigating how eggs and ovarian tissue interact — defects in which can cause infertility — without the need for experimental animals. In addition, it might enable researchers to create implantable eggs from the skin cells of a person or animal, to treat infertility or resurrect extinct or endangered animal species (see page S18).

Science **373**, eabe0237 (2021)

Dead cells deliver therapeutic benefit

Many stem-cell therapies that are already available all over the world rely on an uncertain mechanism of action. It is often assumed that they work as an emergency patch, proliferating and replacing injured tissue, but evidence for this is lacking. The findings of researchers at the University of Cincinnati in Ohio suggest that in some cases cells might instead make a difference by stimulating a beneficial immune response at the site of injury.

The study, led by Jeffery Molkentin, gave mice with cardiac injury an infusion of adult stem cells taken either from the heart or the bone marrow. In both cases, the damaged rodent hearts improved after the stem cells were delivered to the organ, but without directly making new heart muscle. Injected cells were not seen to differentiate into cardiac muscle or endothelial cells, and had cleared two weeks after injection.

The mice instead got a boost from an immune response that summoned a battalion of macrophages, a type of white blood cell that engulfs dying cells and debris or anything suspiciously foreign. The macrophages gathered at the site of injection after three days, remained there after seven days, and had mainly withdrawn by two weeks. When the researchers treated mice with a high dosage of an immunosuppressant called cyclosporine A, the recuperating effects of the cell injection were erased.

In a final test, injecting debris from dead bone marrow cells into injured mouse hearts also boosted cardiac function through recruitment of macrophages. The results indicate that an acute inflammatory response might underpin the benefits seen after many cell therapies.

Nature **577**, 405–409 (2020)

Cells cry tears in a dish

Tears are crucial to lubricating and protecting the eye, and dysfunction of the glands that produce them, such as in Sjögren's syndrome, can be debilitating. In severe cases, it can even lead to loss of sight. Yet, it is difficult to study tear-producing lacrimal glands because they are positioned above the eyeball, and as a result their biology is poorly understood.

But help might be on the way. Miniature versions of the mouse and human lacrimal glands have been grown in a dish by a team of researchers led by Hans Clevers at the Hubrecht Institute in Utrecht, the Netherlands, who then made the tiny glands cry.

Clevers's team started with gland tissue that contained adult stem cells and cultured them in a 3D environment. The culture medium activated the stem cells, which proliferated until they resembled miniature versions of the real glands. The team then showed that a cocktail of chemicals including noradrenaline, a neurotransmitter that passes messages between nerve cells and glands, could induce the organoids to swell with tears.

An atlas of cells based on their gene expression was drawn up from lacrimal gland tissue and the organoids, to compare the two and identify the cell types in the organoid. Additionally, the researchers showed that deletion of the regulatory gene *Pax6* in the organoids prevented full development of tear glands, suggesting that this gene plays a crucial part.

It might eventually be possible for such organoids to be created from a person's own cells and transplanted into their eyes, to keep their eyes moist in cases where they cannot produce tears.

Cell Stem Cell **28**, 1221–1232 (2021)

Self-organizing heart model

A 3D model of the early human heart, built from pluripotent stem cells, could provide a window onto congenital heart defects. A team led by Sasha Mendjan at the Austrian Academy of Sciences in Vienna, showed that stem cells can be directed to organize into a cavity structure typical of the human heart in the third and fourth weeks of development.

Malformations of the heart are by far the most common birth defect, affecting about 1–2% of live births, yet how or why they develop is not fully understood. Several self-organizing tissue models, known as organoids, have been created from stem cells for the purposes of research, such as for the kidneys and liver. However, attempts to model the developing human heart have proved challenging.

Researchers have mostly focused on building tissue around a scaffold to recreate the heart's chambered structure. Mendjan's team members, however, did not use a scaffold. Instead, they coaxed human pluripotent stem cells to form a heart organoid, also known as a cardioid, by adding six signalling factors at specific doses and times. This recapitulated the heart as it appears during development from around day 15 to day 30. Furthermore, injury to the cardioid resulted in the formation of a matrix that is a hallmark of natural heart regeneration and disease.

The self-organizing nature of the cardioids allows researchers to better probe early heart development and investigate how young heart organoids respond also to toxins, viruses and drugs.

Cell **184**, 3299–3317 (2021)

Cultured cells mutate faster

Human stem cells in culture accumulate mutations at a much faster rate than when they are inside the body, according to a team led by Edwin Cuppen at the University Medical Center Utrecht in the Netherlands.

As human pluripotent stem-cell lines divide in culture, they evolve, and genetic variants with a growth advantage can begin to dominate. If selected for in stem-cell trials, these mutants could place people in harm's way. Mutations previously identified in human embryonic stem-cell lines involved tumour suppressor genes, which are common in human cancers.

Cuppen and colleagues investigated the mutation rate of human pluripotent stem cells, as well as adult tissue stem cells that live in the intestine and liver. They cultured single stem cells for several months and then counted the mutations that arose in these cells during this period. Compared with their previous estimate of the mutation rate of adult stem cells *in vivo*, the rate at which the cultured cells accumulated mutations was almost 40 times greater.

The researchers propose that oxidative stress was to blame for the higher mutation rate of cells in a dish, and that optimizing culture conditions to reduce oxygen tension in cultured cells could bring mutation rates more in line with what happens in our bodies and suppress the emergence of rogue variants. This might allow stem cells to be cultured for longer periods to generate the large cell banks needed for many clinical trials.

Nature Commun. **11**, 2493 (2020)

A fresh blend of pluripotency

A new state of pluripotency, identified by a group of researchers mainly in the Netherlands, could change conventional understanding of the trajectory of stem-cell development.

Pluripotent stem cells are usually considered to be either naive or primed. Cells that exist in the early embryo, before implantation in the womb, have an immature state of naive pluripotency; after implantation, they mature into primed pluripotent cells and can then differentiate into all cell types of the embryo.

Derk ten Berge at Erasmus University Medical Center in Rotterdam, the Netherlands, and his colleagues, have found evidence of an intermediate stage of pluripotency in mice. This transient state — called rosette-stage pluripotency — formed during implantation and lasted a few hours, before the cells abruptly became primed.

The team suggests that the rosette phase might act as a kind of checkpoint, at which the correct architecture needs to be in place to move forwards. It is already known that, early in development, abnormal cells might need to self-destruct or cease growing, to be replaced by healthy cells. The rosette stage might allow such problems to be fixed before the embryo implants and primed cells proliferate into more specialized tissue.

An equivalent rosette stage in human embryos is yet to be confirmed — a challenge, given that it might require the study of human embryos within hours of implantation.

Nature Cell Biol. **22**, 534–545 (2020)

online

For the latest research published by *Nature* visit: http://go.nature.com/2xyawlx