

the case in the glancing collision.

The third and, in our view, most striking result compares the transport of baryon number with that of electric charge. Quarks carry electric charge, but baryon junctions do not, so the ratio of baryon number to charge arriving at mid-rapidity offers a direct clue as to the identity of the carrier. To investigate this, the STAR collaboration performed two sets of collision experiments between two beams of either ruthenium-96 or zirconium-96 isotopes. These isotopes have the same total number of protons and neutrons altogether and therefore roughly the same mass, but different numbers of protons and therefore different charges. If valence quarks carry the baryon number, the electrical charge and baryon number should be transported together in a one-to-one ratio in all the collisions. Instead, in most head-on collisions, STAR measured a ratio nearly twice that of the valence-quark prediction.

Taken together, these three measurements converge on a picture in which an electrically neutral object, something that is influenced by the strong force but not electromagnetism, is the main vehicle for baryon-number transport. The baryon junction is currently the only candidate that accommodates all the observations.

The implications of this result reach beyond a technicality in QCD bookkeeping. If baryon number is bound to baryon junctions rather than to quarks, it alters how theorists should model the early Universe, when baryons emerged from a high-energy plasma of quarks and gluons. It could also aid the understanding of the structure of 'exotic' multi-quark particles, as well as hypothetical states made entirely from gluons that have yet to be observed. Because baryon number is an emergent property of the strong interaction, the finding that it defies simple quark-level explanation could point to unknown properties of QCD.

Further tests are needed, and future experiments are well-placed to provide them. The Electron-Ion Collider, under construction at Brookhaven National Laboratory, will probe the spatial distribution of baryon number inside protons and neutrons with unprecedented resolution, while ongoing programmes at the Large Hadron Collider at CERN, Europe's particle-physics laboratory near Geneva, Switzerland, and the Thomas Jefferson National Accelerator Facility in Newport News, Virginia, offer other perspectives. For now, we think that the STAR result marks a turning point. After 50 years of work, it seems that one of the proton's most fundamental properties resides not in its quarks, but in the gluonic web that binds them together.

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Developmental biology

DNA-editing 'pencils' used in human embryos

Sherif Khodeer & Vincent Pasque

A genome-rewriting approach known as adenine base editing offers a precise way to investigate gene function in early human embryos. **See p.1281 & p.1289**

Writing in *Nature*, Bower *et al.*¹ (page 1281) and Jerabek *et al.*² (page 1289) describe how they have used a precision genome-editing tool, known as base editing, in human embryos to reveal how a key gene contributes to early development, and how embryos respond to specific DNA changes. The work sharpens scientists' view of this developmental stage while inevitably reactivating debates about heritable DNA editing.

Much of what we know about early mammalian development comes from studies of mouse embryos, but human embryos do not always follow the same rules. Direct studies in human embryos are therefore essential for reproductive medicine and for understanding genetic diseases. Many inherited conditions can be traced back to a change of a single DNA base, making precision-editing tools especially valuable for investigating how such mutations can affect development^{3,4}. To study these changes in human embryos, scientists need genome-editing tools that can modify DNA precisely and with minimal unintended damage^{5,6}.

Conventional CRISPR-Cas9 editing works like molecular scissors, cutting both strands of a DNA double helix at a precise location. The goal is either to inactivate the gene at that location or to introduce a specific DNA change with the help of a repair template (a short piece of DNA carrying the intended sequence, which the cell can copy during the repair process). In human embryos, however, this repair is often unreliable, sometimes causing large DNA losses, structural chromosome damage or mosaicism – in which a mixture of cells have different editing outcomes⁷. This limits scientists' ability to interpret experimental results.

In base editing, by contrast, an enzyme that modifies DNA (such as a deaminase) is fused

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to a Cas9 'nickase' enzyme, allowing one DNA base to be converted into another without causing a double-strand break – acting more like a pencil than scissors⁸. By avoiding a large break, base editing offers a way to interrogate gene function while reducing the risk of unintended genomic damage. Bower and colleagues¹ now use base editing to uncover the role of a gene called *NANOG* in early human embryos. Jerabek *et al.*² assess the efficiency and genomic safety of base editing *PCSK9* – a gene involved in cholesterol metabolism and linked to heart-disease risk.

Bower *et al.*¹ first validated their strategy in human embryonic stem cells, using a base editor that targets adenine bases to disrupt *NANOG*. The edited stem cells lost the molecular signatures of pluripotency (the ability to self-renew and to generate nearly all cell types of the body) and could no longer maintain themselves as stem cells. Therefore, the authors determined that *NANOG* is required to preserve human pluripotency.

The team then applied the same strategy to human embryos. Disrupting *NANOG* did not prevent the formation of the early hollow ball of cells known as the blastocyst, but it did reduce the quality of the blastocyst's inner cell mass. Single-cell gene-expression analysis showed that the loss of *NANOG* diverted cells so that they formed cells belonging to layers in the blastocyst called the primitive endoderm and trophoctoderm. There was less expression of genes that are characteristic of the epiblast – the cell layer in a blastocyst that gives rise to the embryo (Fig. 1a). The persistence of primitive endoderm cells in human embryos lacking *NANOG* is in contrast to the loss of these cells in mouse embryos with mutant *Nanog*^{9–11}. These findings suggest that *NANOG* is essential for

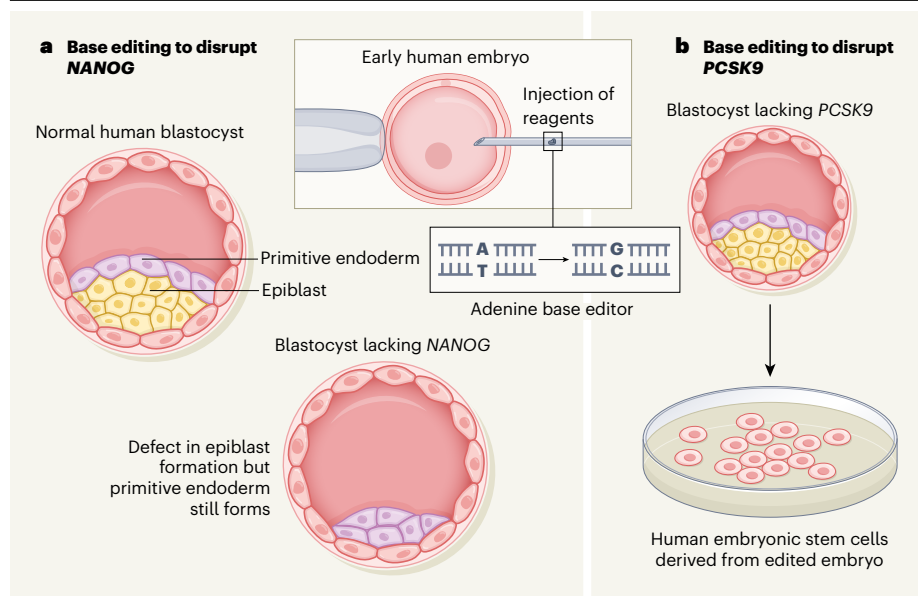


Figure 1 | Precision genome editing in human embryos. **a**, Genome-editing tools called adenine base editors make precise changes to DNA, causing an adenine (A) base to be altered to a guanine (G). The reagents can be delivered when sperm is injected into a human egg cell to fertilize it. Bower *et al.*¹ used base editing to disrupt a gene called *NANOG* and examine its role in early human development. Compared with control blastocysts (embryos at five to six days of development), *NANOG*-deficient blastocysts showed defective formation of the epiblast (the tissue that will form the fetus), but cells resembling primitive endoderm (which forms supportive extra-embryonic tissue) were retained. Therefore, *NANOG* is required for human epiblast formation, but compensatory mechanisms seem to enable primitive endoderm to form, unlike in mice⁹. **b**, Jerabek *et al.*² used base editing to disrupt *PCSK9*, a gene linked to heart-disease risk, to test whether this approach could generate a clinically relevant 'loss-of-function' edit in human embryos. The embryos developed into blastocysts, from which the authors derived *PCSK9*-deficient embryonic stem cells.

human epiblast formation, but primitive endoderm differentiation might be supported by backup molecular mechanisms that are unique to humans. Further analyses revealed minimal off-target genome editing, and no obvious large-scale chromosomal abnormalities.

Jerabek *et al.*² focused on how human embryos respond to DNA lesions introduced by base editing, looking at the genes *PCSK9*, *HBB1* and *HBB2* specifically (Fig. 1b). For *PCSK9*, the authors designed an editing event that reproduces the effect of known mutations associated with reduced heart-disease risk¹². For *HBB1* and *HBB2*, they introduced a natural variation that leads to the production of fetal haemoglobin (a fetal form of the oxygen-carrying protein in red blood cells) in adulthood, which can lessen the severity of blood disorders such as sickle-cell disease. They found that delivering an adenine base editor as a protein directly into fertilized eggs produced consistent editing, did not interfere with blastocyst development and enabled the generation of stem-cell lines carrying the intended edit on both gene copies. Compared with conventional CRISPR–Cas9 editing of the same gene, adenine base editing led to fewer unintended changes.

Together, these studies mark an important shift in human embryo editing. Adenine base editors offer a gentler and more precise way to interrogate gene function than does

conventional CRISPR–Cas9 cutting. Excitingly, they make it possible to ask biological and developmental questions that were previously difficult to approach, such as which genes are truly required for the normal development of human embryos, how human development differs from that of other animals and how early embryos respond to targeted DNA changes. Answering these questions might help to improve infertility treatments, assisted reproduction and regenerative medicine.

Both studies highlight the importance of the delivery approach. When the base editor was delivered as a messenger RNA rather than a protein complex, many embryos arrested in early development. Even with protein-based delivery, a few embryos showed chromosomal abnormalities or unintended edits elsewhere in the genome, and several showed mosaicism, highlighting limitations in the new approach. Both groups argue against premature clinical translation – underlining that base-editing tools must be carefully tested and optimized before any clinical application can be considered¹³.

Both studies will inevitably reignite the controversial topic of editing germline DNA, a process that could cause changes to be inherited by future generations. The use of CRISPR–Cas9 editing in human embryos, which led to the birth of two children in 2018, provoked widespread condemnation and legal sanctions^{14,15}. The work by Bower and colleagues

and Jerabek *et al.* shows that base editing can reduce some of the genomic damage associated with double-strand breaks, but it also exposes fresh risks, including off-target effects and mosaicism. Despite the progress made, genome editing in embryos that will reach full term, and will therefore carry edits in the germ line, remains unethical and should not be done under any circumstances.

Realizing the promise of base editing in human embryos will require much more precision than has been demonstrated here, as well as improved delivery into embryos. But technical progress alone will not be enough. International scientific and ethics organizations have stressed that important safety and efficacy conditions would need to be met to use the technique. But even if embryo editing becomes safer, any potential future use will require broad oversight from scientists, ethicists, regulators, people providing or receiving health care, and wider society. Heritable genome editing also raises profound ethical, moral and social questions that science alone cannot answer¹⁶. Its implementation, including for commercial purposes, should be forbidden unless the scientific, ethical and safety concerns can be resolved.

For now, base editing in human embryos is best understood not as a route to clinical use, but as a tool for judicious basic research. With careful application and used within the proper ethical framework, DNA-editing 'pencils' offer a powerful way to study the first days of human life, one DNA letter at a time.

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