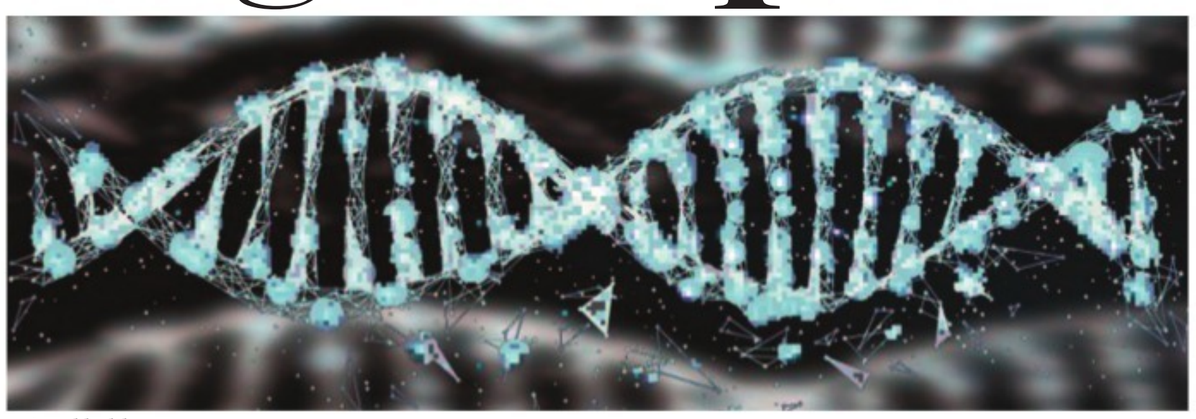
Splitting and pairing up

Breaking the rule of two is found to make genetics go berserk



S ANANTHANARAYANAN

The DNA in cells of living things carries the information that determines what animal or plant the cell belongs to. When a cell divides, the DNA splits in two. Each half then rebuilds the missing half to become two DNA. Each daughter cell then gets the same DNA and looks exactly like the mother cell. When things go wrong during division, the daughter cells may not know how to divide, or they may not know how to stop dividing. Both conditions cause disease, the second is usually cancer.

Kan Yaguchi, Takahiro Yamamoto, Ryo Matsui, Yuki Tsukada, Atsuko Shibanuma, Keiko Kamimura, Toshiaki Koda, and Ryota Uehara, from Hokkaido University and Nagoya University, in Japan, report in the *Journal of Cell Biology*, that they have unravelled a scheme of the components of the cell, which prescribes the number, two, as central to ensuring stable cell division. "Incompatible bio-processes, which have different scaling properties, may underlie the instability of body cells in mammals", the researchers conclude.

This process where the separate halves of a cell that has split in two rebuild the original DNA is possible because DNA consists of a pair of complementary halves, like two pieces of a jigsaw puzzle. If the two pieces are separated, fresh pieces that fit the shape of the separate pieces can be built. We would then have two sets of paired pieces where we had started with one.

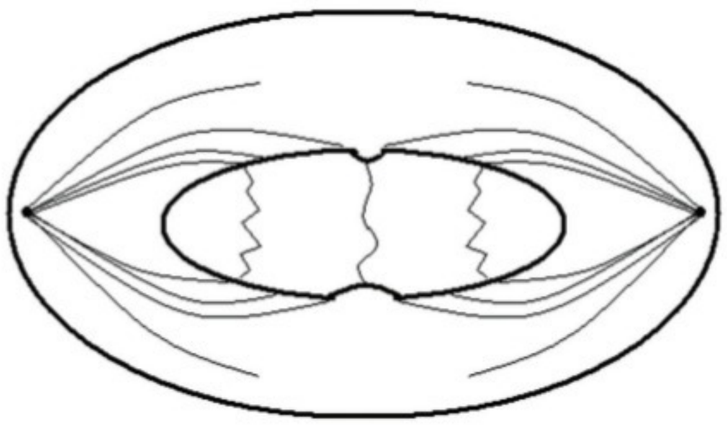
The DNA molecule is a pair of long threads, each with a series of side chains, called bases, and each of these bases has one of just four basic forms. As the two threads are side by side, the bases of one thread connect to the bases of the other thread and the shape of the DNA molecules is like a twisted ladder.

The secret of rebuilding the whole from halves is in the way the bases connect. The bases are called C, G, A and T and the rule is that C pairs with G and A pairs with T. Thus, if a part of the series of one thread is A, C, G, G, T, for instance, the complementary series has to be T, G, C, C, A.

Just specifying the order of bases of one thread decides the order of the bases in the other thread. This is the secret — when the threads separate, they contain the information for constructing a copy of the partner they have lost and can rapidly build themselves another one, to be whole again.

This much about the cell and genetics has been worked out and we now know a great deal about the actual order of the bases in a large part of the DNA of many species. We know how segments of the series are the templates for the production of different proteins, which decide the identity of the cell and then the organism to which the cells belong. We know of errors in the DNA, which cause genetic or inherited diseases, and we even know how to snip, splice and repair the DNA. But what we do not really know is what makes the cell decide to divide and the mechanism that coordinates the dividing process.

The paper in the *Journal of Cell Biology* describes how much we do understand of the process of cell division and then their studies that have uncovered features that may help understand the development of cancers, and perhaps develop strategies to prevent cancers from spreading. Specifically, they find that that stable



cell division in animals is linked to cells having bits of DNA, called chromosomes, derived from either parent, in pairs, as opposed to single chromosomes or chromosomes in three or four copies.

In a cell that is not on the point of dividing, the whole DNA lies compact and coiled up, associated with agents that give the DNA structure and determine what part of the DNA will be active, or "expressed", to create particular proteins. When the cell gets ready to divide, however, the DNA breaks up into pieces, and these are the chromosomes.

In humans, there are 46 chromosomes, organised into 23 matched pairs. The chromosomes of each pair are identical in structure, with one chromosome having come from one parent and the other from the other parent. During division, the two branches in the bit of DNA in each chromosome come apart and each half uses its sequence information to regenerate a whole chromosome. The result is that there are two sets of the cell's genetic information available for two new, daughter cells.

This detail of the multiplication of the DNA apart, an important part of cell division is what draws the two halves apart for the cell to split into two.

For this, cells have structures called centrosomes on opposite sides of the cell, which throw out "tubules" that guide chromosomes and bring about cell division. We can see that along with the replication of pairs of chromosomes, there is also doubling of the number of centronomes, for a pair of normal, new cells. A pair of centronomes matches the two chromosomes in each of the 23 pairs of chromosomes in the cell and there is stable cell division.

There are also stages in the growth of cells when their chromosomes are not in pairs but single. Such organisation of chromosomes usually switch to the paired, or diploid state and in the single or haploid state, normal cell division is not possible. And then there are cells where chromosomes are organised in threes, and again, there is mismatch with centronomes. The sensitivity of normal cell division with respect to the organisation of the chromosomes is hence a matter of interest.

The researchers in Hokkaido and Nagoya studied this question by watching the speed of cell division of collections of human cells that were in the paired chromosome, diploid state and cells in the single chromosome, haploid state. A first result was that haploid cells were slow to divide, a good number died in the process of division and that large numbers underwent transformation to the diploid state, over time.

Further analysis revealed that there was reduction in the number of centronomes and associated structures in haploid cells. It was found that the haploid state was a major contributor to the chain of changes that led to defects in cell division. Along with the loss of centronomes it was seen that in haploid cells even the pace of doubling of the number or centronomes was slowed down, so that it could not keep pace with the duplication of DNA.

A further discovery was that when the level of pairing of chromosomes was increased from two to three and four, there was an increase in the pace of duplication of centronomes, this time outpacing the pace of duplication of DNA. Similarly, some other factors that affect centronome population were found to depend on the organisation of chromosomes.

While the findings are in keeping with the diploid state, where the processes involved in cell division are sycnchronised, the work is an addition to the knowledge about what makes the proliferation of cells go out of control, the main cell dysfunction in the case of cancer. The work is doubly relevant because it is found that cancer cells are usually in a non-diploid state.

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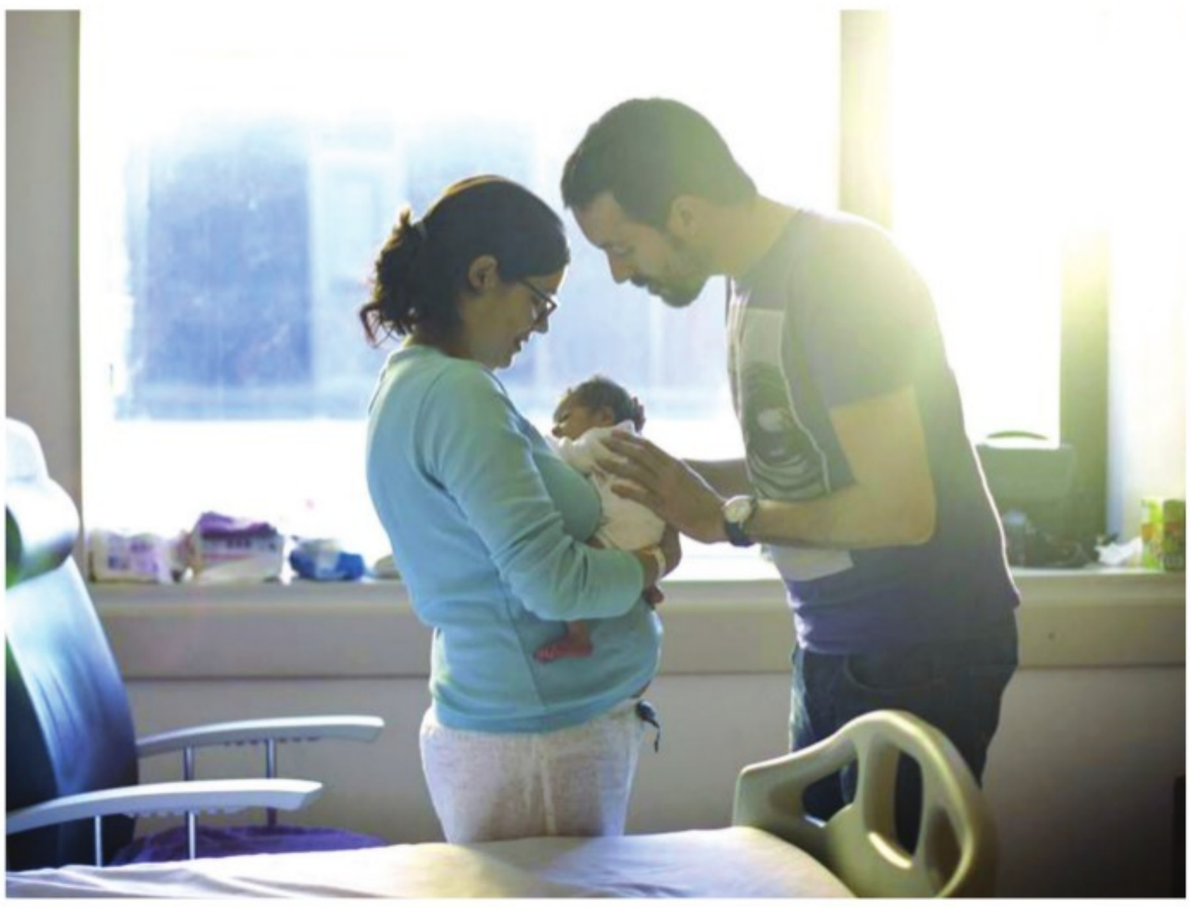
Lifeline in the womb

If a new treatment works, it could open the door to curing a variety of hereditary disorders before birth



DENISE GRADY

In the three months before she was born, Elianna Constantino received five blood transfusions and a bone-marrow transplant. All were given with a needle passed through her mother's abdomen and uterus, into the vein in her umbilical cord.

Elianna, born 1 February with a robust cry and a cap of gleaming black hair, has a genetic disease that usually kills a foetus before birth. The condition, alpha thalassaemia major, leaves red blood cells unable to carry oxygen around the body, causing severe anaemia, heart failure and brain damage.

The transfusions in the womb kept her alive, but only treated her illness. The bone-marrow transplant has the potential to cure it. Whether it will succeed is still too soon to tell.

Elianna and her mother, Nichelle Obar, were the first patients in an experiment that pushes the limits of foetal therapy, a field already known for its daring approach. If the treatment works, it could open the door to using bone-marrow transplants before birth to cure not just Elianna's blood disease but also sickle cell anaemia, haemophilia and other hereditary disorders, some so severe that the prenatal diagnosis may lead parents to end the pregnancy.

Bone marrow is considered a potential cure because it teems with stem cells, which can create replacements for cells that are missing or defective as a result of genetic flaws. "This line of work moves the field of foetal surgery, which currently consists of big operations for anatomic disorders, in a new direction of molecular and cellular therapies given non-invasively," says Dr Tippi MacKenzie, a paediatric and foetal surgeon who is leading the study at the UCSF Benioff Children's Hospital in San Francisco, US.

Obar, 40, and her husband Chris Constantino, 37, are healthy but learned during her first pregnancy that they are thalassaemia carriers. There are several forms of the disease, and worldwide about 100,000 children a year are born with severe cases. Millions of people are carriers, most commonly those from Asia, the Mediterranean, Africa or West Asia.

Carriers are generally healthy but when two have children together, the children are at risk of being born with the disease. Obar's ancestry is Filipino and Puerto Rican; her husband's is Filipino. They live in Kilauea, on the Hawaiian island of Kauai.

Their first child, Gabriel, now three, is healthy. But each child they conceive has a one in four chance of being affected, and during Obar's second pregnancy, her doctors were on the lookout for the disease.

They found it. An ultrasound at 18 weeks showed that Elianna's heart was twice the size it should have been, and fluid was accumulating around her lungs and other organs. Blood flow through her brain was abnormally rapid, a sign of severe anaemia.

Everything pointed towards alpha thalassaemia major — the most severe form of the disease. Obar's doctor and genetic counsellor warned her and her husband that their daughter might not survive. "Her heart was working so hard," Obar says, with tears in her eyes. By this point in pregnancy, the second trimester, an affected foetus has little or no working haemoglobin, the molecule that carries oxygen to cells all over the body. Tissues are suffocating and the heart struggles to compensate.

Some medical references describe the illness as "incompatible with life" and most foetuses die in the womb from heart failure. The pregnancy may end in miscarriage, and parents may not know why. Many do not know they are carriers.

Sometimes, as the foetus weakens, a phenomenon called mirror syndrome occurs — the mother also becomes ill, with severe high blood pressure and other problems that can kill her unless the pregnancy is ended.

Infants with untreated alpha thalassaemia major who somehow survive until birth almost always have severe brain damage from lack of oxygen. Transfusions into the umbilical cord during pregnancy can save the foetus and may prevent brain damage. The child will then require transfusions every three or four weeks for life; the procedures cost about $50,000 a year and pose their own risks, especially a dangerous buildup of iron.

Many obstetricians do not even tell patients about transfusions, MacKenzie says. "Everyone now is told to abort," says Dr Elliott Vichinsky, one of MacKenzie's research partners and the founder of the Northern California Comprehensive Thalassaemia Centre at the UCSF Benioff Children's Hospital Oakland. "We understand families should make that decision if that's right for them. We're just saying they should be given the information that there are other options."

MacKenzie and Vichinsky say they did not try to discourage parents who preferred abortion. But some parents would rather avoid it. "These are not unwanted pregnancies," MacKenzie says. "We're as pro-choice as you get. These are wanted pregnancies for whom therapy could be offered. And you can have a choice to terminate or you can have a choice to have therapy, but the bottom line is you have to be given those choices. And we recognise that's a very personal choice but we as doctors need to be providing you with those choices."

Obar's genetic counsellor mentioned termination — but also transfusions. She and her husband chose transfusions.

The counsellor also described MacKenzie's study. The chance that the transplant might help their daughter appealed to them, though they understood that it was an experiment and that there were no guarantees. At this early stage in the research, the primary aim of the study was to find out whether the treatment was safe.

The general goal of foetal therapy is to act early enough to minimise or even prevent lasting harm from severe problems that start in the womb. With a bone-marrow transplant, the added advantage of giving it before birth is that the foetal immune system is not yet fully developed, so it is unlikely to reject the transplant.

In contrast, when transplants are given after birth, the child first needs an arduous course of chemotherapy to wipe out the immune system and prevent rejection. That treatment itself can be fatal — the death rate is about seven per cent, mostly from infection.

Bone-marrow transplants in foetuses, sometimes using the father as a donor, were first tried in the 1990s. Some worked, but most failed, and doctors mostly abandoned the procedure, MacKenzie says. But research continued in animals, and a key finding emerged — the mother, not the foetus, was rejecting transplants that came from fathers or other donors.

A possible solution became evident. "Everybody has a perfect donor when they're a foetus, and that's the mom," MacKenzie says.

Genetically, the mother is not a complete match — half the foetal genes come from the father — but she's still the ideal donor before birth because during pregnancy the maternal and foetal immune systems are at peace. Mother and child tolerate one another — their cells do not fight. The truce ends at birth, or shortly before, when the infant's immune system starts to work.

In one sense, the experiment has already been a success — there have been no adverse effects to mother or baby, so the treatment seems safe.

"I'm thrilled that it was safe and it was feasible," MacKenzie says, adding it was also important "to get the message out that foetal transfusions for alpha thalassaemia are life-saving". She expects to perform transplants on a few more patients, see how they fare and then decide how to proceed.

So far for Elianna, in her first three months, there has been no obvious benefit from the transplant. Like all children with her blood disorder, she needs a transfusion every three weeks.

But tests have found some of her mother's stem cells in her blood. Whether they will start to help her is unknown. If they do not, her parents could eventually opt for a bone-marrow transplant to cure the disease and free her from a lifetime of transfusions.

Courtesy The New York Times
The independent

PLUS POINTS

Dolphin happiness

A team of scientists have attempted to measure "happiness" in dolphins for the first time.

Researchers in France assessed captivity from the perspective of the marine mammal and found that they were most happy when interacting with a human they had built a bond with. The study, published in the journal *Applied Animal Behaviour Science*, is part of a three-year project to measure the welfare of dolphins.

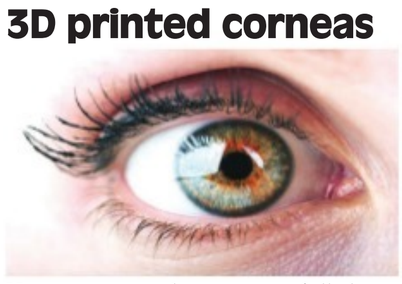
Lead researcher Isabella Clegg designed a number of experiments that looked at the posture of dolphins to determine what they were feeling. She tested dolphins when they were in sessions with a trainer, had toys in their pool and when they were left alone.

"We wanted to find out what activities in captivity they like most," she told the BBC. "We found a really interesting result — all dolphins look forward most to interacting with a familiar human."

When the dolphins saw a trainer they were familiar with they would spend more time at the edge of the pool and peer above the surface. "We've seen this same thing in other zoo animals and in farm animals," Clegg added. "Better human-animal bonds equal better welfare."

The independent

3D printed corneas



Human corneas have successfully been 3D printed for the first time by scientists at Newcastle University in England, *Xinhua* news agency reported.

By mixing stem cells from a healthy donor cornea with alginate, a gel derived from seaweed, and collagen, researchers managed to create a "bio-ink" solution that can be printed, *Xinhua* said last week. The bio-ink can be successfully expelled out of the printer in concentric circles in the shape of a cornea in less than 10 minutes, according to a paper published in Experimental Eye Research.

"Our unique bio-gel — a combination of alginate and collagen — keeps the stem cells alive while producing a material, which is stiff enough to hold its shape but soft enough to be squeezed out the nozzle of a 3D printer," said lead researcher Che Connon in a press release.

Connon's team also showed it was possible to create a cornea that matches a patient's unique specifications, Xinhua said. By taking the dimensions of the patient's actual cornea with scans, scientists can use the data to print a cornea that matches its size and shape.

The 3D printed corneas will now have to undergo further testing but it is hoped the technique could be in regular use within five years.

Professor Connon said the research could help with the worldwide shortage of corneas for transplants. Currently around 10 million people worldwide each year need surgery to prevent corneal blindness, and another five million already suffer total blindness from corneal scarring caused by burns, lacerations, abrasion or disease.

The straits times/ann

Startling study

Labour exploitation including forced labour is endemic at the base of global tea and cocoa supply chains, according to an international study published by researchers at the University of Sheffield last week.

Extensive on-the-ground research with the cocoa industry in Ghana and the tea industry in India revealed agricultural workers are paid severely low wages and routinely subjected to multiple forms of exploitation. The project involved in-depth interviews with more than 120 tea and cocoa workers, a survey of over 1,000 tea and cocoa workers from 22 tea plantations in India and 74 cocoa communities in Ghana, and over 100 interviews with business and government actors. The study also found that prominent ethical certification schemes are failing to create working environments that are free from exploitation and forced labour. It can be accessed at https://www.sheffield.ac.uk/research/forced-labour