Why Tibetans breathe easy

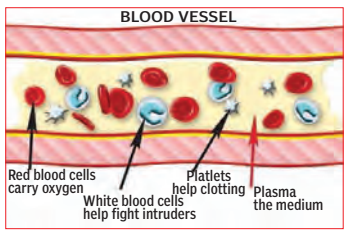
S ANANTHARAYANANAN REPORTS ON THE DICOVERY OF GENETIC BASES FOR THESE PEOPLE'S TOLERANCE TO HIGH ALTITUDES

The body has a well-oiled mechanism for getting oxygen to all parts to keep the processes going and, when oxygen supply is low, it has ways to adapt, to grab more of the scarce commodity. But the adaptation has its own cost and long spells can cause disease, even death. In this context, the way in which the Tibetan population thrives at altitudes with depleted oxygen raises questions that have not been fully answered.


Felipe Lorenzo, Josef Prchal and Tsewant Tashi.

The oxygen in the air, which we breathe into our lungs, reaches our body cells through *red blood corpuscles*, and when these are in a place where oxygen is rich, like in the lungs, they absorb oxygen and supply it at places where it is poor and needed, like at the site of body cells. It is, hence, important to have enough of this component in the blood and how much we have is measured by the levels of *haemoglobin*, the operative, iron-rich constituent of red blood corpuscles. To have 12-14 grams of haemoglobin per 100 cc of blood is considered okay and lower counts are usually treated with nutrition rich in iron to help create haemoglobin molecules.

But even with normal haemoglobin levels, the supply of oxygen to the cells can drop when the oxygen level in the air itself becomes low. The body then needs to adapt, and one way it reacts is to create more red blood corpuscles. But a danger of high levels of haemoglobin is that this makes the blood get sticky and difficult to move through the body, and this causes both low transport of oxygen as well as the mountain sickness that people feel when they move to high altitude places, where the oxygen supply in the air is low. There can also be other causes for oxygen levels to fall and haemoglobin to rise, and one of these is habitual smoking.



Cigarette smoke is highly depleted in oxygen and smokers' bodies also need to adapt by raising haemoglobin levels. Nutrition deficiency in smokers is often undetected because a blood test shows healthy haemoglobin counts, although this is only in reaction to the lungs being starved of oxygen, not an indication of vitality! But people in places of high altitude generally have higher haemoglobin levels and when plains people move to places like Tibet, where the altitude averages 14,000 feet, their bodies create so many red blood corpuscles that they fall sick and may even die. But for Tibetans who spend their lives at high altitudes, there seems to be an internal "brake" that keeps the level of red blood corpuscles and haemoglobin under control.

Josef T Prchal, from the University of Utah, with colleagues from the same and other institutes in the USA, Finland, China and India, report in the journal *Nature Genetics* that they have both worked out the genetic mechanism by which Tibetans are enabled to keep this form of adaptation under control and also the time frame during which Tibetans acquired this unique genetic trait.

The story starts with earlier work of Prchal's group, which announced in 2010 that there was a genetic basis for Tibetans' high altitude tolerance. And soon after, Felipe Lorenzo, also an author of the *Nature Genetics* paper, was able to identify the specific part of the Tibetan DNA where the adaptation had taken place. The current study has established that it is in a variation, a tiny variation, of a single gene called *EGLN1* that is responsible for a chain of genetically controlled biochemical events that help Tibetans keep haemoglobin growth in check, even while other genetic factors push for more red blood cells in response to a low-oxygen environment. And the genetic feature was clearly of great survival benefit, and very selective, as a majority of Tibetans have this variation, which is almost completely absent in closely related populations that live in lower altitudes.

A note from the University of Utah also describes the human relations part of the research effort, in getting sufficient numbers of Tibetans to volunteer blood samples. "It took several trips to Asia, meeting with Chinese officials and representatives of exiled Tibetans in India to get the necessary permission to recruit subjects for the study. But he (Prchal) quickly learned


In the high mountains of the Tibetan Plateau, average elevation 14,800 feet.

that official documents would not be enough. Wary of foreigners, the Tibetans refused to participate," the note says. Even the Dalai Lama was approached. "The Dalai Lama felt that a better understanding of the adaptation would be helpful not only to the Tibetan community but also to humanity at large," Prchal says. And the list of authors of the research paper includes native Tibetan Tsewang Tashi, MD and clinical fellow at the Huntsman Cancer Institute, the University of Utah.

Age of adaptation

The way this protective genetic feature arose in Tibetans is by evolutionary selection, of a chance error during DNA replication. When living cells reproduce, they create an extra copy of the DNA molecule, which contains all the genetic information, so that the new cell can have its own DNA. As the DNA molecule is billions of units long, this is a complex process and there are generally some errors during the replication.

But all such errors are not significant, because DNA has a built-in redundancy by which the most common errors leave its function unchanged. If the errors are serious, the new cell may not survive, or its progeny may not be successful and the strain with this error would die out. But if the error proved to be an advantage, progeny with the error may do well and proliferate.

In the case of Tibetans, too, a chance error like this conferred the capacity to live on at high altitudes and this proved a survival advantage. Progeny that had the advantage then prospered and soon most of the population had the advantage, too.

Now the way to estimate when this change in DNA first began is by looking at the other, non-consequential, small genetics changes, which continue in the progeny of individuals who have the change, but these changes do not dominate or spread as they do not confer a survival advantage. Now, these changes show certain relationships, or association with one another, which decay over generations. It is this rate of decay, in the near environment of the genetic change of interest, that leads, by statistical analysis, to how many generations ago the change of interest may have happened.

Prchal and his group considered generations to arise every 25 years, and worked it out that the genetic trait that helps Tibetans arose 8,000 years ago.

The Dalai Lama was quite right that the analysis, assisted by the cooperation of Tibetan subjects, has progressed our understanding of the science of genetics. The study has also shown us a case of very rapid consolidation of a genetic variation, and invites further studies on the movement of people or the rise of population in Tibet, to validate this way of working things out or to find refinements.

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BETWEEN GENERATIONS

IT BECOMES CONCEPTUALLY EASIER TO IMAGINE A SYSTEM OF RNA MOLECULES ACTING BOTH AS CATALYSTS AND AS REPLICATING SYSTEMS CAPABLE OF TRANFERRING INFORMATION, SAYS **TAPAN KUMAR MAITRA**

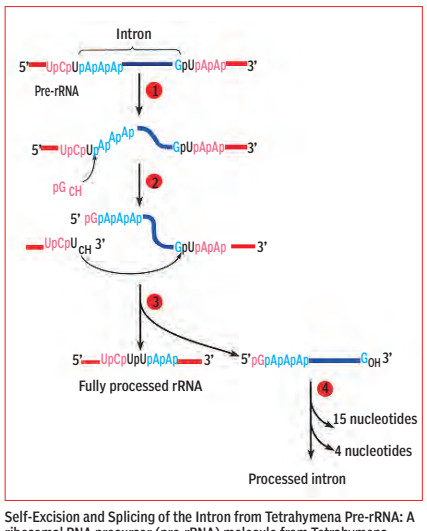
Prior to the early 1980s, it was thought that all enzymes were proteins and this was regarded as one of the fundamental truths of cellular biology — found in every textbook. Cell biologists became convinced that all enzymes were proteins because every enzyme isolated in the 55 years following James Sumner's purification of urease in 1926 turned out to be a protein. But biology is full of surprises and we now know that the statement needs to be revised to include RNA catalysts called ribozymes.

The first evidence came in 1981 when Thomas Cech and colleagues at the University of Colorado discovered an apparent exception to the "all enzymes are proteins" rule. They were studying the splicing of an internal segment from a specific ribosomal RNA precursor (pre-rRNA) in *Tetrahymena thermophila*, a single-called eukaryote. Many eukaryotic RNA molecules require the removal of one or more internal segments called *introns* before they become functional in the cell. The removal process involves the excision of the intron and a splicing together of the two pieces of the original molecule at the excision site. In the course of their work, the researchers made the remarkable observation that the process apparently proceeded without the presence of proteins!

Describing their attempt to study intron excision in vitro, Cech later wrote, "It turned out that some of the small molecules — notably magnesium ion and any of several forms of the nucleotide guanosine — were required for the reaction to proceed. To our great surprise, however, the nuclear extract containing the enzymes was not. We were forced to conclude either that the enzymatic activity came from a protein bound so tightly to the RNA that we were unable to strip it off or that the RNA was catalysing its own splicing. Given the deeply rooted nature of the idea that all biological catalysts are proteins, the hypothesis of catalysis by RNA was not easy to accept."

One might argue that the rRNA molecule fails to satisfy the definition of a catalyst, which requires that the catalyst itself is not altered in the reaction process. However, another RNA-based catalyst discovered two years later in the laboratory of Sidney Altman at Yale University overcomes this objection. The enzyme, called *ribonudease P*, cleaves transfer RNA precursors (pre-tRNAs) to yield functional RNA molecules. (In this case, a terminal segment of the RNA molecule is removed rather than an intron as for pre-rRNA processing.)

It had been known for some time that ribonudease P consisted of a protein component and an RNA component, and it was generally assumed that the active site was on the protein component. By isolating the components and studying them separately, however, Altman and colleagues showed unequivocally that the isolated protein component was completely inactive, whereas the isolated RNA component was capable of catalysing the specific cleavage of tRNA precursors on its own and was not itself altered in the process. Further, the RNA-catalysed reaction followed Michaelis-Menten kinetics, further evidence that the RNA component was acting like a true enzyme. (The protein component enhances activity but is not required for either substrate binding or cleavage.)



Self-Excision and Splicing of the Intron from Tetrahymena Pre-rRNA: A ribosomal RNA precursor (pre-rRNA) molecule from Tetrahymena contains an intron that is capable of catalysing its own excision from the pre-rRNA molecule. The excision and splicing process occurs in four steps. The pre-rRNA molecule forms a loop at the intron region. The intron loop is attacked by a hydroxyl group of a free guanosine nucleotide, pG, that functions as a cofactor. The pre-rRNA molecule is cleaved at the 5' end of the intron segment, with the addition of G to the intron. The uridine at the 3' end of the other rRNA fragment then attacks the 3' end of the intron, releasing the intron and splicing the two rRNA pieces together to form the fully processed rRNA. The intron then undergoes further autocatalytic cleavage to remove 19 more nucleotides by cleaving first a 15-nucleotide segment and then a four-nucleotide piece.

The significance of these findings was recognised by the Nobel Prize that Cech and Altman shared in 1989 for their discovery of ribozymes. Since these initial discoveries, additional examples of ribozymes have been reported. Of special significance is the active site for a crucial step in protein synthesis as it occurs on ribosomes. Ribosomes can be thought of as very large enzymes because they catalyse the formation of the peptide bonds that add successive amino acids to a growing polypeptide chain. More specifically, the large ribosomal subunit is the site of the peptidyl transferase activity that catalyses peptide bond formation.

It had long been assumed that the active site for peptidyl transferase was located on one of the protein molecules of the large sub-unit. However, a series of studies by Harry Noller and colleagues at the University of California, Santa Cruz, pointed toward one of the rRNA molecules instead. That work led them to the demonstration, published in 1992, that despite the removal of at least 95 per cent of the protein from the large ribosomal subunit of a particular bacterium, the rRNA retained 80 per cent of the peptidyl transferase of the intact sub-unit.

Further, the activity was destroyed by treatment with ribonudease, an enzyme that degrades RNA, but was not affected by proteinase K, an enzyme that degrades protein (and that was, in fact, one of the agents used to remove the protein from the sub-unit). Thus, the peptidyl transferase activity responsible for a crucial step in ribosomal protein synthesis is now known to be a ribozyme.

The discovery of ribozymes has markedly changed the way we think about the origin of life on earth. For many years, scientists had speculated that the first catalytic macromolecules must have been amino acid polymers resembling proteins. But this concept immediately ran into difficulty because there was no obvious way for a primitive protein to carry information or to replicate itself, which are two primary attributes of life. However, if the first catalysts were RNA rather than protein molecules, it becomes conceptually easier to imagine a system of RNA molecules acting both as catalysts and as replicating systems capable of transferring information between generations.

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'Growing' living organs

IT'S A DEVELOPMENT THAT COULD ONE DAY BE USED TO PROVIDE REPLACEMENTS FOR PEOPLE WITH WEAKENED IMMUNE SYSTEMS, SAYS **STEVE CONNOR**

Scientists have created the first functional organ in a living animal from reprogrammed cells. The thymus organ, a vital immune-system "nerve centre" near the heart, was initially grown in a laboratory from connective-tissue cells and then transplanted into laboratory mice, where it continued to grow and develop into a fully functional organ, they said.

This is believed to be the first time scientists have strung several technologies together to produce a working organ from stem cells that has been transferred into a living animal. It could lead to the transplant of "made-to-order" organs grown from a patient's own skin cells, though such a breakthrough could take another 10 years and tons of money for research.

However, Paolo De Coppi, an expert on regenerative medicine at the Institute of Child Health at Great Ormond Street Hospital in London, suggested an earlier time frame was possible. "Engineering of relatively simple organs has already been adopted for a small number of patients and it is possible that within the next five years more complex organs will be engineered for patients using specialised cells derived from stem cells in a similar way as outlined in this (study)," he said.

Professor Clare Blackburn of the Medical Research Council Centre for Regenerative Medicine at Edinburgh University said, "We've managed to produce an artificial cell type which, when transplanted, can form a fully organised and functional organ. This is an important step towards the goal of generating a clinically useful artificial thymus in the lab."

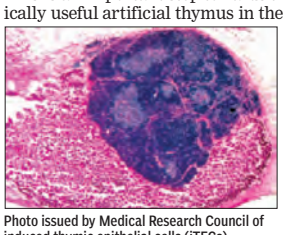
Photo issued by Medical Research Council of induced thymic epithelial cells (iTECs) transplanted on to a mouse kidney to form an organised and functional mini-thymus (kidney cells in pink; thymus cells dark blue). Reprogrammed cells created in a laboratory have been used to build a complete and functional organ in a living animal for the first time.

The thymus is a vital part of the immune system because it produces T-cells, which constantly guard the body against invading microbes, viruses and even rogue cancer cells. People who lack a healthy thymus can be treated with infusions of immune cells or a transplant operation but there is a lack of donors and there are problems with matching tissue types. Being able to create thymus organs from a patient's own cells would overcome the problem of organ rejection and supply, the researchers said.

"The ability to grow replacement organs from cells in the lab is one of the 'holy grails' in regenerative medicine. But the size and complexity of lab-grown organs has so far been limited," Professor Blackburn added.

Rob Buckle, head of regenerative medicine at the Medical Research Council, said, "Growing 'replacement parts' for damaged tissue could remove the need to transplant whole organs from one person to another, which has many drawbacks, not least a critical lack of donors."

The thymus organs created by the scientists were able to produce T-cells, a type of white blood cell, in the laboratory and displayed the hallmarks of a fully developed and functional organ.

The scientists started out by taking mouse fibroblasts and inducing them with a "transcription factor" that stimulated their development into thymic epithelial cells. After mixing these cells with other thymus cells in the laboratory, rudimentary thymus organs began to develop. These were then transplanted on to the kidneys of living mice.

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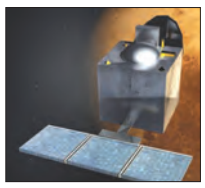
PLUS POINTS

India's Mars Orbiter

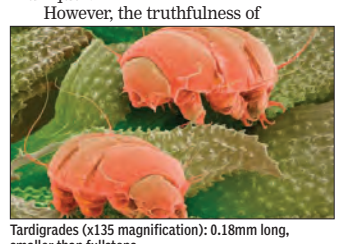

India's ambitious Mars Orbiter Mission is just nine million kilometres from the Red Planet, according to the Indian Space Research Organisation, and "189 million kilometres from the earth — 33 more days to Mars", it announced on its social networking site. Early this month, Isro scientists ruled out a Trajectory Correction Manoeuvre originally planned for August as the spacecraft was on track.

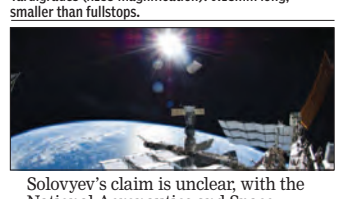
The ambitious Mars mission, under a Rs 450-crore project, was launched from Sriharikota in Andhra Pradesh on board the Polar Satellite Launch Vehicle on 5 November last year with the aim of reaching the Red Planet's atmosphere by 24 September. The project is expected to provide the scientific community better opportunities in planetary research.

Microbial life

A new report claims that Russian scientists have discovered traces of marine life living on the exterior of the International Space Station. Vladimir Solovyev, the official in charge of Russia's ISS segment, told news agency Itar-Tass that tiny plankton and microscopic organisms had been discovered on the spacecraft's exterior, describing the finds as "absolutely unique".

However, the truthfulness of


Tardigrades (x135 magnification): 0.18mm long, smaller than fullstops.


Solovyev's claim is unclear, with the National Aeronautics and Space Administration refusing to confirm the story. "As far as we're concerned, we haven't heard any official reports from our Roscosmos colleagues that they've found sea plankton," Nasa spokesperson Dan Huot told *Space.com*. He confirmed that Russian cosmonauts had been taking samples from the windows on their side of the ISS, but clarified that they'd only been looking for "residues that can build up on the visually sensitive elements… I don't know where all the sea plankton talk is coming from".

Although the reports from Itar-Tass have not been confirmed, the idea of life existing in the harsh environment of space (surviving cosmic radiation, freezing temperatures and zero gravity) is quite possible. A study in January 2013 found evidence of microbial life five to 10 miles above the surface of the planet, while a type of microscopic invertebrate known as a *tardigrade* has even survived the vaccum of space for 10 days, shrugging radiation exposure 100 times necessary to kill humans.

So while it's possible that some sort of terrestrial life has been hanging out on the side, it's not at all clear how – if the reports are confirmed – they got up there. It could be that they arrived via some contaminated space modules but Solovyev himself suggested that they might have come from "rising air currents, which settle on the surface of the station".

JAMES VINCENT/THE INDEPENDENT

Sony's next

Selfies have already taken over the world, so why not give in to all that glorious vanity? This seems to be


Sony's attitude, with the company rumoured to be releasing a perfume bottle-shaped selfie camera later this month. A teaser posted to their Chinese website shows that their next gadget will come with a massive, swivelling lens on the top that makes it look distinctly like a bottle of perfume.

Tech site Engadget says the odd look is meant to capitalise on the Chinese craze for buying smartphone cases that look like giant Chanel perfume bottles, with the top of the bottle providing an ideal place to stick a massive lens.

The device itself is expected to be Wi-Fi and NFC-enabled, according to leaks highlighted by *The Verge*, with a 19-megapixel sensor and optic image stabilisation allowing for some seriously professional looking self-portraits. Whatever happens, more will be known when Sony officially unveils the device.

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