Quicker fix for snakebite

A team of researchers has created a mixture that can be administered orally

S ANANTHANARAYANAN

If the number of persons who succumb to malaria is a cause for worldwide concern, those that succumb to snakebites, which is a fourth of that number, should be of concern too.

Managing snakebite, however, has not received the proportionate attention of the global health community, says a paper in the journal, *Nature Communications*, while proposing an alternate preparation that could be more effective, easier to administer and more readily available. Laura-Oana Albulescu, Chunfang Xie, Stuart Ainsworth, Jaffer Alsolaiss, Edouard Crittenden, Charlotte A Dawson, Rowan Softley, Keirah E Bartlett, Robert A Harrison, Jeroen Kool and Nicholas R Casewell, from the Liverpool School of Tropical Medicine, Vrije Universiteit, Amsterdam and Centre for Analytical Sciences, Amsterdam describe a combination of just two preparations, which can be orally administered, and is effective against the venom of most of the medically-important vipers of Africa, South Asia and Central America.

In the contest between health workers and the community of snakes, of saving or immobilising victims of snakebite, snakes have the advantage of millions of years of evolution of highly effective venoms, and instruments of delivery. Snakes administer their cocktails of chemically complex venoms through perfectly adapted needle-like fangs, and the venom quickly spreads across the victim's body through the bloodstream. For centuries, humans had no inkling of how the venom acted and the only recourse was tourniquets and amputation.

It was after the late 1800s that scientists observed that it was possible for people to get immunity to snake or insect bites if they trained with low doses of the same poison that they feared. The notion that the body generates an antidote was followed through and methods were found to culture the antibodies against important venoms by injecting the venoms into the bodies of animals. The process was successful and there are now several farms, or labs, all over the world, that produce doses of antivenin, as the substance is called, against a variety of snakes, spiders, and so on.

As each antivenin is almost solely effective against the venom of a small group of species, the appropriate antivenin needs to be near at hand, to be administered fairly soon and it often needs refrigeration to stay effective. And again, as the antivenin is produced in the body of an animal, there are often reactions when used in humans. Hence, both for administration, by injection, and then to deal with possible reactions, there is a need for trained personnel. These features limit the value of the line of treatment. However, is almost the only recourse in case of a poisonous snakebite. And antivenin does save thousands of lives each year.

Snake venom is now understood to consist of proteins and enzymes, or substances that promote or retard body processes. Venom has evolved to contain those agents that lead to tissue damage, or that affect the nervous system -- leading to paralysis, or that affect the clotting of the blood, either by creating clots or by preventing clotting. Although the discovery of the constituents of the substances the immune system of the animal produces is daunting, we now have the possibility of analysing what snake or other venom consists of and devising synthetic agents to neutralise the active portion of the venom.

One approach, the paper says, has been the use of "small molecule" inhibitors, as an alternative to the products of the immune system. The "small molecule", which is what most of the drugs that we use consist of, are units that act by attaching to cells or other molecules, to block or facilitate the cell action. While acting in a way not different from the enzymes in snake venoms, the advantage with small molecules is that they can be administered orally, unlike large molecule drugs, which need to be administered intravenously.

The authors of the paper in *Nature Communications* note that the viper family of snakes, which consists of hundreds of varieties, including the rattlesnake, the adders, pit vipers, bush vipers, the Russel's viper, the saw scaled viper, is responsible for the majority of snake poisoning incidents over the Americas, Africa and Asia. While treatment of snakebite needs to take care of several classes of toxins, across species, it is found that there are three specific kinds that account for more than 60 per cent of the toxins found. These three, which are substances that cause the breakdown of proteins, are found to be the main cause of (a) destruction of tissue, (b) decay of cell membrane, with leakage of fluids and (c) breakdown of the clotting mechanism, leading to haemorrhage.

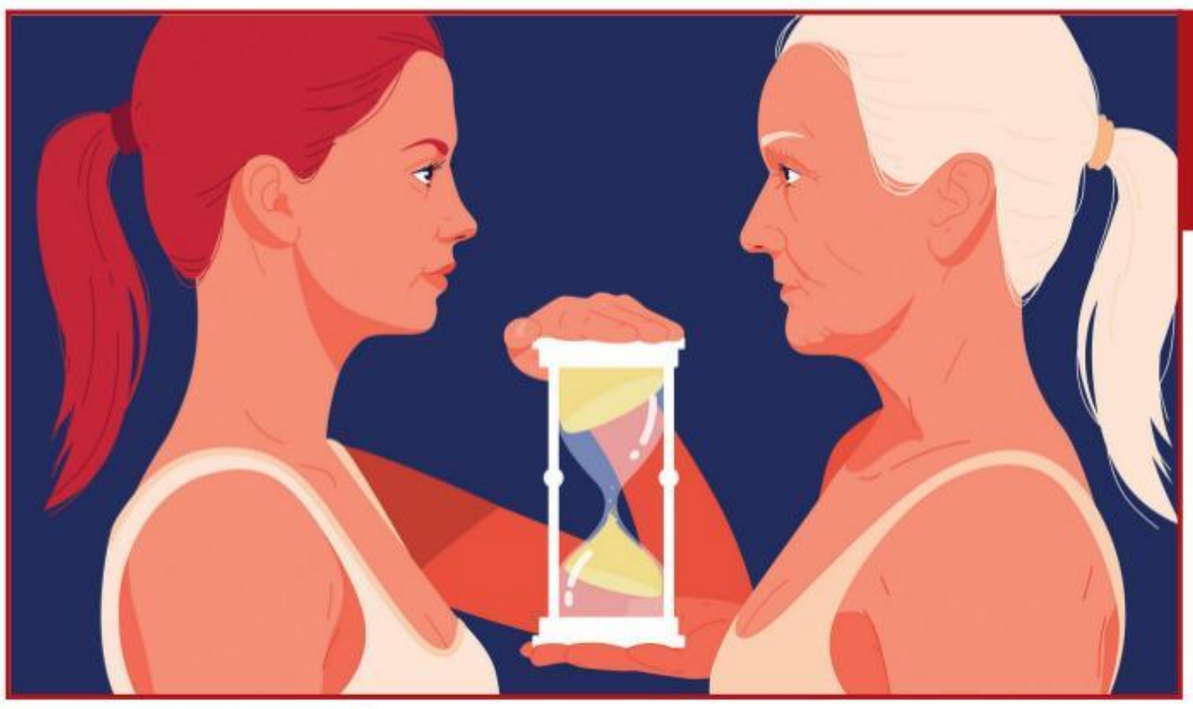
The authors draw attention to a known preparation, *varespladib*, which inhibits the action of enzymes that break up proteins, and was considered for the treatment of a cardiac disease. While this application did not progress, *varespladib* showed promise as antivenin, as it could block the action of a category of components of the venom and another group, which includes the cobra. In addition, the authors say, there were other substances in use to inhibit other groups of enzymes, which also proved effective against venom-induced haemorrhage and tissue death. They also cite a licensed oral medicine, used to treat cases of poisoning by heavy metals (mercury, arsenic), which worked against the venom of the saw-scaled viper.

The authors hence proposed that a selection of such small molecule specifics could be combined, to act as "broad spectrum" treatment and take care of the venom of several species of snakes. And in this effort, "to rationally select and preclinically validate a therapeutic small molecule mixture capable of neutralising distinct pathogenic toxins found in the venoms of geographically diverse, medically important, hemotoxic (toxic to blood) vipers," the authors, say, they have succeeded.

They prepared a mixture of just two small molecule substances. One is *marimastat*, which was tried out for its ability to suppress the action of some enzymes, in the immune system for instance. The other is *varespladib*, which we have spoken of. The paper describes how this combination, administered to experimental mice, a fixed time after controlled doses of different venoms were administered, showed that the combination was successful in overcoming the main viper venoms that are encountered.

About a year ago, a group from the University of California, writing in the journal of the American Chemical Society, described a nanoparticle-based "long molecule", which was easier to handle and had similar "broad spectrum" application. The present, small molecule solution, however, has the great advantage that it can be administered orally, or need not be injected. The concept that has been demonstrated could hence lead to an antivenin dose that a person could carry with her when she ventures into the wild. If she should be bitten, she could just swallow a first-aid dose which would keep her well till she reached medical attention!

The writer can be contacted at response@simplescience.in



SLOWING DOWN AGING

New research holds promise that tissues could be maintained and ultimately, regenerated

MAHARSHI KRISHNA DEB

While pluripotent cells of mammalian embryos (commonly referred to as embryonic stem cells) differentiate to give rise to all the cell types that constitute our body, the discovery of the ability to convert differentiated cells back into their embryonic pluripotent state through the generation of induced pluripotent stem (iPS) cells, by Kazutoshi Takahashi and Shinya Yamanaka in 2006, has brought about a paradigm shift in our understanding of the biological system. Moreover, this discovery allows generation of patient-specific iPS cells (by converting an abnormal cell into an iPS cell) from which normal cells or organs can be created and thus offers the opportunity to implant such patient-specific cells or organs back to the patient and thereby, bypass the disadvantage of rejection owing to compatibility.

However, one of the biggest hurdles to using these revolutionary cells for regenerating any cell type is that the process of cellular reprogramming is highly inefficient. Most studies indicate the role of overlapping pathways in the induction of tumorigenesis and pluripotency, which has thereby led to the development of a perception that iPS cells may harbour tumorigenic potential. Therefore, although the appeal of application of iPS cells in regenerative medicine is highly revered, such strategies to generate a high number of these iPS cells can offset their therapeutic benefit.

To rip the regenerative advantage that iPS cells can offer, we set out in a quest to identify an oncogene whose inactivation may improve the efficiency of cellular reprogramming. We conducted a loss-of-function screen by deploying an RNA interference approach of silencing gene expression. We targeted 1,000 putative cancer-related genes (genes that are activated upon cancer formation) upon generation of iPS from differentiated cells. This screen identified *Tnfaip2*, which is a potential oncogene as the roadblock in generation of iPS cells. Intriguingly, while various tumour suppressors have thus far been known to be impediments to cellular reprogramming, emerging evidence indicates the involvement of *Tnfaip2* in promoting cell invasion and migration in almost all types of cancers. Thus, ours is one of the first studies to report an oncogene whose depletion can generate an enhanced number of pluripotent cells from differentiated cells.

We then decided to investigate the possible role of *Tnfaip2* in an *in vivo* model in which organ homeostasis (continuous supply of new cells of an organ whose cells are worn out with time) and regeneration (ability to make new organs) are maintained by pluripotent cells. The immortal flatworm of planarian species *Schmidtea mediterranea* was the ideal choice to study the biology of pluripotent cells in tissue maintenance and regeneration *in vivo*. Unlike mammals, planarians maintain a life-long reservoir of a pluripotent population commonly termed as cNeoblast (wherein "c" refers to the clonogenic capacity of the cells to revive the entire pluripotent population in lethally irradiated planarians when transplanted as a single cell). Planarians rely on these pluripotent populations to meet their homeostatic and regenerative demands and thus, as such, their immortality is attributed to the omnipresent existence of those omnipotent cells.

Phylogenetic analysis indicated that planarians express a *Tnfaip2* homolog called exoc3. Hence, we decided to check the implication of suppressing the expression of this gene in planarians. Strikingly, although the depletion of exoc3 similarly increased the number of pluripotent cells, these planarians exhibited severe deformations of various tissues and organs owing to impaired differentiation of their pluripotent cells. Together, the data indicated planarian homolog of *Tnfaip2* is required to maintain tissue homeostatic and regenerative potential in planarians.

To gain mechanistic insight about the role of *Tnfaip2* in stem cell differentiation, we analysed the protein profile of mammalian pluripotent cells devoid of *Tnfaip2* gene. This analysis revealed *Tnfaip2* affects lipid metabolism since repression of *Tnfaip2* resulted in the loss of architectural intermediate filament protein Vimentin (VIM) which is required for the formation of Lipid Droplets (LDs) that are central hubs for lipid metabolism. Besides Vim, we also detected the loss of another factor involved in lipid metabolism, carnitine palmitoyltransferase (CPT1A). CPT1A facilitates transfer of fatty acid from cytoplasm to mitochondria where these fatty acids are subsequently metabolised by undergoing beta-oxidation for production of energy in the form of ATP. Interestingly, lipid profile of both exoc3 and *Tnfaip2* lacking pluripotent cells of planarians and mammals showed significant deficiency of fatty acids.

To test whether external supply of fatty acid could rescue differentiation defects of planarian and mammalian pluripotent cells depleted of exoc3 and *Tnfaip2* respectively, we supplemented the cells with fatty acids. Strikingly, this external supply of fatty acids was found to restore differentiation in both and thus led to the revival of organ homeostasis and regeneration.

The outcome of this work would be essential to attenuate aging which is the biggest risk factor for most human diseases like cardiovascular diseases, cancer, diabetes, sarcopenia, rheumatoid arthritis, macular degeneration, cataract, osteoporosis besides several neurodegenerative diseases like Alzheimer's, Parkinson's and schizophrenia as well as predisposition to various viral diseases like influenza and Covid-19. The risk factors for these diseases increase exponentially with age owing to reduction in the number of functional stem cell pools that leads to deterioration in tissue homeostasis. It would be interesting to identify *Tnfaip2* to increase the stem cell population in aged cells, while decline of the effect of the drug would allow the stem cells to differentiate for restoration of organ homeostasis to ameliorate hallmarks of aging like tissue atrophy which would result in alleviation of aging-associated diseases. Although aging is inevitable, such therapeutic interventions can offer options to extend one's healthy lifespan.

The work has been published in the journal, *EMBO Reports* on 10 December this year.

The writer is a former researcher of Stanford University and is currently the principal investigator in the laboratory of germline and chromosome biology at Adamas University, Kolkata

PLUS POINTS

Hibernating humans?

Early humans could have hibernated to survive harsh winters like some modern animals do, researchers have suggested.

Scientists came to this conclusion after examining fossilised human remains found in a cave burial chamber known as Sima de los Huesos – or the "Pit of Bones" – at the Atapuerca archaeological site near Burgos in northern Spain. Using microscopes and CT scanning, the academics discovered that the bones, which are roughly 430,000 years old, had lesions and other bone damage like those seen in animals that hibernate. By slowing their metabolism, it is thought that early human species could have slept for months to weather freezing winters, a time when food supplies would have been extremely scarce.

The researchers – Juan-Luis Arsuaga, who heads the Atapuerca Foundation, and Antonis Bartsiokas, of Democritus University of Thrace in Greece – acknowledge that the "notion that humans can undergo a hypometabolic state analogous to hibernation may sound like science fiction". However, in a paper published in the December issue of the journal *L'Anthropologie*, they point out that "primitive mammals and primates" like bush babies and lorises hibernate, which suggests that "the genetic basis and physiology for such a hypometabolism could be preserved in many mammalian species, including humans".

Speaking to *The Guardian*, Patrick Randolph-Quinney, a forensic anthropologist at Northumbria University, Newcastle, said, "It is a very interesting argument and it will certainly stimulate debate. However, there are other explanations for the variations seen in the bones found in Sima and these must be addressed fully before we can come to any realistic conclusions. That has not been done yet, I believe."

The Sima de los Huesos site has been excavated annually since 1983 and 5,500 human skeletal remains have been unearthed there to date, according to the Atapuerca Foundation website. The bones, which are believed to have been thrown to the bottom of the cave shaft deliberately, have yielded many clues about early human evolution in Europe.

–THE INDEPENDENT

Telescope in China opens

Nestled among the mountains in Southwest China, the world's largest radio telescope signals Beijing's ambitions as a global centre for scientific research.

The Five-hundred-metre Aperture Spherical Telescope (Fast) – the only significant instrument of its kind after the collapse of another telescope in Puerto Rico this month – is about to open its doors for foreign astronomers to use, hoping to attract the world's top scientific talent.

Wang Qiming, chief inspector of Fast's operations and development centre, told AFP during a rare visit by the foreign press last week that he had visited Arecibo in Puerto Rico. "We drew a lot of inspiration from its structure, which we gradually improved to build our telescope." The Chinese installation in Pingtang, Guizhou province, is up to three times more sensitive than the US-owned one, and is surrounded by a five km "radio silence" zone where mobile phones and computers are not allowed. Work on the Fast began in 2011 and it started full operations in January this year, working mainly to capture the radio signals emitted by celestial bodies, in particular pulsars – rapidly rotating dead stars. The 500m giant satellite dish is easily the world's largest – covering the area of 30 football pitches – and cost 1.1 billion yuan to build, as well as displacing thousands of villagers to make room for it.

China has been rapidly boosting its scientific credentials to become less reliant on foreign technology. In the last two decades, it has built the largest high-speed train network in the world, finalised its Beidou geolocation system – a competitor of the American Global Positioning System – and is now in the process of bringing lunar samples back to Earth.

The data being collected by Fast should allow for a better understanding of the origins of the universe – and aid in the search for alien life.

–THE STRAITS TIMES/ANN