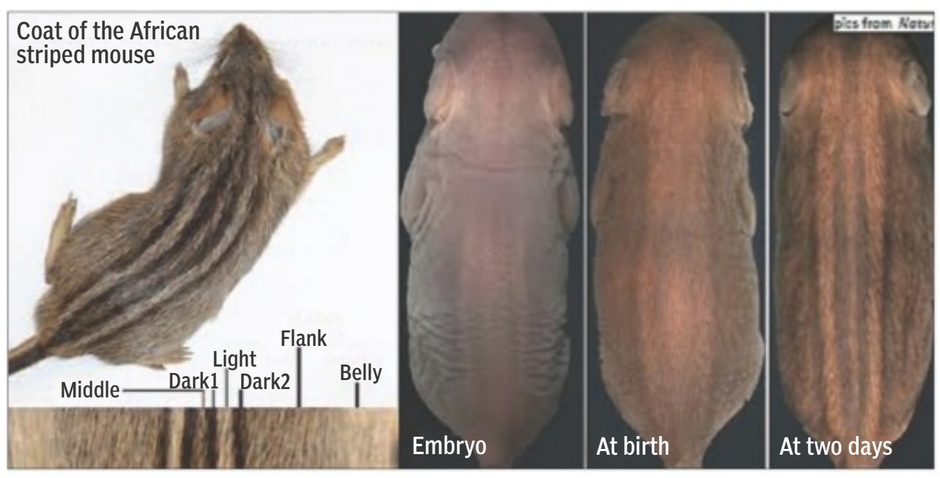
How the squirrel got its stripes

UNDERSTANDING WHAT GIVES RISE TO THE PATTERNS ON THE COATS OF RODENTS HAS MOVED A STEP CLOSER, WRITES **S ANANTHANARAYANAN**



Indian epics and folklore say squirrels participated when Lord Rama's built a bridge across the sea to Lanka, by carrying pebbles. In appreciation, Lord Rama stroked them on the back, hence the stripes they have carried since then. Evolutionary biologists, however, have sought an answer more in terms of the cellular, developmental and molecular processes that lead to the periodic appearance of hair pigmentation, even if it were Lord Rama who set those processes off, to start with.

Ricardo Mallarino, Corneliu Henegar, Mercedes Mirasierra, Marie Manceau, Carsten Schradin, Mario Vallejo, Slobodan Beronja, Gregory S Barsh and Hopi E Hoekstra from institutes in Harvard, Massachusetts, Stanford, Seattle, Madrid, Paris, Strasbourg and Johannesburg report in the journal *Nature* that they have identified the agent that causes differences in the action of pigment-creating cells, and hence the variations in the colouring of animal hair. This is a finding that could help understand how individual, visible forms of organisms evolve, the study says.

The genes that give rise to cells that produce melanin, a complex chained molecule that gives skin and hair its colour, and the mechanisms that regulate the balance between dark and light pigmentation, are part of existing knowledge through research based on animals, like laboratory mice. How these processes contribute to the array of pigment patterns seen in wild animals, however, is not understood, the study says. The researchers, hence, took up the naturally occurring coat pattern of the African striped mouse to gain insight into the processes that bring about stripes, "a striking and characteristic pattern that has evolved independently" in a large number of animals, the study says.

While the melanocytes, or the cells that produce melanin, are present in many parts of the skin tissue, it is the presence of agents that allow the transport of specific parts of the genetic code to pigment-creating centres that get the cells to become active. The study discovers that it is a protein called Alx3 that plays the role of regulator by suppressing the action of Mitf, another protein that is implicated in pigment production by melanocytes. The researchers examined traces of these regulators, which are called transcription agents because they allow parts of the DNA to be copied as templates for the assembly of proteins in the tissue of different parts of the animal body and where fur of different shades arose, and also at different times, starting from the early embryonic stages of growth till adulthood.

A remarkable thing about the striped patterns that arise in animals is that similar patterns are seen in species that seem to have evolved along different genealogical lines. The last common ancestor of the mouse and the chipmunk, for instance, the paper says, dates back 70 million years, or the time of the dinosaurs. While the African striped mouse has one light coloured stripe sandwiched between two darker lines on either side of its spine, the chipmunk and the squirrel display similar but distinct patterns. Analysis of the proteins present in skin biopsies revealed that the colour distribution arose in the animals through similar pathways, of expression of the Alx3 gene and the Alx3 transcription agent, which regulate the rate of pigment production and also the ASIP and Edn3 genes, which bring about changes in the pigments produced.

The discovery by the group writing in *Nature* is an advance in understanding the specific mechanics of the development of colours in a large class of animals. Computer scientists-mathematician Alan Turing had developed a theory of how colour or form-yielding agents called morphogens could spread or diffuse at different speeds and interfere, like light waves, to clump together or negate each other and create bands or spots of different colours. Although without speaking of what the morphogens may be, Turing's theory of "reaction and diffusion" was able to explain the black and white patches on a breed of cows. The theory was carried forward by others and the stripes that appear on the back of the tiger are now understood as a pattern of pigmentation brought about by periodic waves of diffusion of chemicals in the animal's embryo.

There has also been some work to identify possible morphogens that lead to shapes, like ridges on the roof of the mouth of the common mouse, or the shape of some cacti. This approach is also used in modelling why some stripes are vertical while others may be horizontal, or even the reason for organs, like the fingers, to grow in particular directions. The current work, on the African striped mouse, however, is the first time that the very agent that results in colour distribution has been identified. The reason why the variation in colours is in the form of stripes, or even the different numbers of stripes, is yet to be understood, but the action of Alx3 has now been identified and tracked down to the early embryonic stage when the spinal cord is just forming.

An editorial in the journal *Nature* says that the genes that affect the colour of the skin also affect other things. At the embryonic stage, the tissue from which the spinal cord is formed also spreads out and leads to the formation of the hair and skin, the bones of the face, the nerves in the intestines, parts of the heart and the adrenal glands, crucial parts of the sense organs and many body structures that are unique to vertebrates, the editorial says. Unusual skin pigmentation is, thus, seen to signal other ailments.

Deficiency in Alx3 leads to the spinal cord or brain not forming correctly, a condition that can be moderated by doses of folic acid and deficiency of which, in human mothers, leads to spinal cord defects in babies, the editorial says. It is again mutations in the Alx3 gene that causes facial deformities and failure of the facial bones to knit properly. Understanding how the stripes come about on the backs of rodents is, hence, more than skin deep, the editorial says.

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UNDERSTANDING ANGIOGENESIS

BLOOD-FLOW PATTERNS AND ORGAN-SPECIFIC FACTORS DETERMINE WHERE CANCER CELLS METASTASISE, SAYS **TAPAN KUMAR MAITRA**

Once angiogenesis has been triggered at an initial tumour site, the stage is set for the cancer cells to spread throughout the body. This ability to spread is based on two distinct mechanisms: invasion and metastasis. Invasion refers to the direct migration and penetration of cancer cells into neighboring tissues, whereas metastasis involves the ability of cancer cells to enter the bloodstream (or other body fluids) and travel to distant sites where they form tumours — called *metastases* — that are not physically connected to the primary tumour.

The ability of a tumour to metastasise depends on a complex cascade of events, beginning with angiogenesis. The events following angiogenesis can be grouped into three main steps. First, cancer cells invade surrounding tissues and penetrate through the walls of lymphatic and blood vessels, thereby gaining access to the bloodstream. Second, the cancer cells are transported by the circulatory system throughout the body; and, third, cancer cells leave the bloodstream and enter particular organs where they establish new metastatic tumors. If cells from the initial tumour fail to complete any of these steps, or if any of the steps can be prevented, metastasis will not occur. It is, therefore, crucial to understand how the properties of cancer cells make these three steps possible.

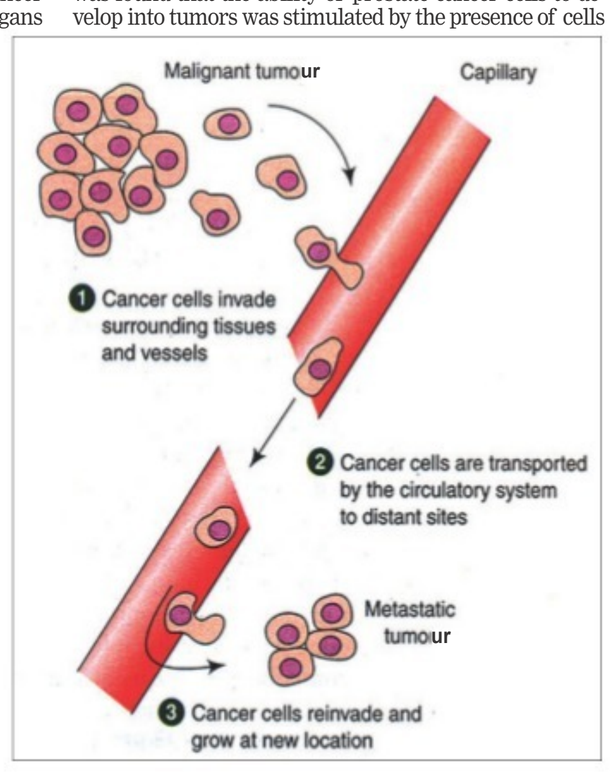
Some cancer cells circulating in the bloodstream eventually exit through the wall of a tiny vessel and invade another organ, where they form metastases that may be located far from the initial tumour. Although the bloodstream carries cancer cells throughout the body, metastases tend to develop preferentially at certain sites. One factor responsible for this specificity is related to blood-flow patterns. Based solely on size considerations, circulating cancer cells are most likely to become lodged in capillaries (tiny vessels with a diameter no larger than a single blood cell). After becoming lodged in capillaries, cancer cells penetrate the walls of these tiny vessels, enter the surrounding tissues and seed the development of new tumours.

For example, consider primary tumours originating in most organs. As the cancer cells enter the bloodstream, the first capillary bed they will encounter is in the lungs. As a result, the lungs are a relatively frequent site of metastasis for many kinds of cancer. However, blood-flow patterns do not always point to the lungs. For cancers arising in the stomach and colon, the cells entering the bloodstream are first carried to the liver, where the vessels break up into a bed of capillaries. As a result, the liver is a common site of metastasis for these cancers.

While blood-flow patterns are important, they do not always explain the observed distribution of metastases. As early as 1889, Stephen Paget proposed that circulating cancer cells had a special affinity for the environment provided by particular organs. Paget's idea is referred to as the "seed and soil" hypothesis based on the analogy that when a plant produces seeds, these are carried by the wind in all directions but only grow if they fall on congenial soil. According to this view, cancer cells are carried to a variety of organs by the bloodstream, but only a few sites provide an optimal growth environment for each cell type.

Supporting evidence has come from a systematic analysis of the sites to which cancers tend to metastasise. For roughly two-thirds of the human cancers examined, the rates of metastasis to various organs can be explained solely on the basis of blood-flow patterns. In the remaining cases, some cancers metastasise to particular organs less frequently than expected and others metastasise to particular organs more frequently than expected.

Why do cancer cells grow best at particular sites? The answer is thought to involve interactions between cancer cells and specific molecules present in the organs to which they are delivered. One example involves prostate cancer, which commonly metastasises to bone (a pattern that would not be predicted based on blood-flow patterns). The reason for this preference was uncovered by experiments in which prostate cancer cells were mixed with cells from various organs — including bone, lung, and kidney — and the cell mixtures were then injected into animals. It was found that the ability of prostate cancer cells to develop into tumors was stimulated by the presence of cells derived from bone, but not from lung or kidney.



Only a small fraction of the cells in a typical cancer successfully carry out all three steps involved in metastasis: (1) invasion into surrounding tissues and vessels; (2) transportation via the circulatory system; and (3) reinvasion and growth at a distant site.

Subsequent studies uncovered the explanation: Bone cells produce specific growth factors that stimulate the proliferation of prostate cancer cells. This is just one of several types of molecular interactions that can influence the ability of cancer cells to grow in particular organs.

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Grit & perseverance

FOR A WOMAN DETERMINED TO BUCK THE ODDS OF AGE DISCOURAGING CONCEPTION, A SILIGURI SET-UP MADE THE VITAL DIFFERENCE

Though 57-year-old Anamika Das (named changed to protect privacy) married late, at the age of 35 years, she longed to be a mother. For 10 years, this Siliguri woman battled thyroid problems coupled with hypertension, given the nature of her career, and, as though that weren't enough, over the past 22 years she also suffered from primary infertility. Having failed to conceive naturally, she began looking for assisted reproductive techniques and underwent several cycles of Intra-Uterine Insemination over a period of 20 years at different clinics in Kolkata. In 1998, she was diagnosed with having endometriosis and underwent laparoscopic cystectomy for removal of a huge ovarian cyst. In 2000, she underwent laparoscopic myomectomy for a uterine fibroid.

This was a situation that would have proved daunting for most of her gender, but Das fought on and for 12 years subjected herself to In-Vitro Fertilisation procedures at two Kolkata clinics, which added a huge financial burden to her already apparent distress. With no siblings or family members in Kolkata, she would have to stay at hotels and, then again, being a working woman she would have to take leave and the cost of to and fro travel often got her down. Her menstrual cycles having stopped over the past eight years lent despair to the many failed attempts she made to conceive.

Just when she was on the verge of throwing in the towel, so to speak, in January 2014 she came to know about Genome, the full-fledged state-of-the-art mother centre established in Siliguri the year earlier that helps childless couples achieve an addition to the family. And here is where Anamika Das' grit bore fruit in the face of impossibility, because advances in medical science and helping hands made her dream of decades come true when she was told, "You are pregnant."

Thanks to its state-of-the art IVF technology, she has become one of North Bengal's oldest mothers to give birth to twins. Dr Prasenjit Roy, reproductive medical consultant at this facility where she underwent IVF, said, "Pregnancy for women above 50 has become possible in recent years due to advances in reproductive technology. She was counselled about the possibilities and risks of such a late pregnancy and the challenge for us was to prepare Anamika for the IVF cycle while controlling her thyroid problems and hypertension at the same time.

"Initially, she was in a bit of a dilemma concerning whether it was possible to have a baby after cessation of menstruation, and she was counselled about the possibility of risks of such a late pregnancy. After controlling her thyroid issue and changing her blood pressure medication, she was taken to our IVF cycle at Siliguri. She was prescribed medicines to start her periodic cycle and the process was continuously monitored. Our challenge was to prepare her for pregnancy and, at the same time, control her thyroid problem and hypertension."

Das underwent the IVF-ET in April 2014 at the Genome facility in Siliguri and delivered twins on 2 November the same year. Hers, then, is a story of courage in the assumed face of impossibility.

PLUS POINTS

Cure for aids?

Scientists have developed a drug they hope could lead to a cure for HIV and aids. Researchers in Israel have identified a protein they claim can reduce the virus in infected patients by 97 per cent in just eight days, according to the *Times of Israel*. The findings raise hopes for sufferers of a disease that killed more than a million people globally in 2015.

The HIV virus attacks a type of white blood cell known as a CD4, which is used by the body to fight off illnesses like flu. The virus uses the internal machinery of these cells to effectively take it over and make more and more copies of itself, destroying CD4s in the process. Once those cells in a sufferer fall below 200 per cubic millimetre of blood, they are considered to have progressed to aids.

The new drug was inserted into test tubes containing the blood of 10 aids patients by scientists at Hebrew University in Jerusalem. The active ingredient, called Gammora by researchers, caused several copies of the virus's DNA to enter an infected CD4 cell, instead of the usual one or two. That caused the damaged white blood cell to go into overdrive and self-destruct, leaving it unable to spread the virus any further.

Tests using Gammora will continue amid hopes it will soon be able to kill 100 per cent of infected HIV cells. It is currently treated with drugs taken daily that suppress the disease but there are no known cures.

Abraham Loyter, who helped develop the drug, told *Channel 2* in Israel, "With our approach we are destroying the cells, so there is no chance that the virus will awaken one day.

"Because there are no cells, there will be no cells that contain the virus."

TOM EMBURY-DENNIS/THE INDEPENDENT

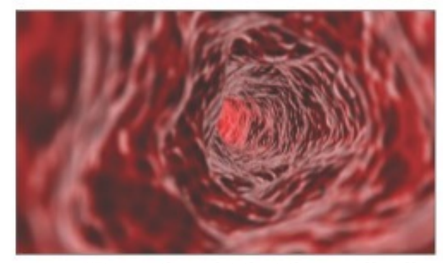
Cellular intelligence

Scientists at the University of Strathclyde are developing tiny devices that capture images of signals as they travel the innermost layer of the body's blood vessels — helping to revolutionise our understanding of vascular disease.

Researchers have received £1.4 million from Wellcome and the British Heart Foundation to develop imaging technology capable of visualising the endothelium — a thin layer of cells, which covers the inside of the body's entire cardiovascular system.

John McCarron, of the Strathclyde Institute of Pharmacy and Biomedical Sciences, is leading the research with Calum Wilson, John Girkin and Chris Saunter from Durham University.

McCarron said, "The endothelium is an exceptionally complex sensory system. Although the endothelium is just one cell thick, there are 10 trillion endothelial cells — 100 times more than there are neurons in the brain — in a continuous layer throughout the cardiovascular system. There are 2,000 cells per square millimetre.



"It was thought that these cells all operated in the same way. But we are now seeing each one has unique properties and senses its environment in a way that is slightly different from its neighbour. The cells pass their pieces of information around, so collectively there is a lot of information.

"They use this combined information to make decisions and solve problems as a collective. The behaviour provides a collective intelligence that is far beyond the capabilities of each cell and is like the intelligent behaviour — swarm intelligence — seen in colonies of ants or flocking birds. Problems in one part of the endothelium are sorted out without needing or affecting other regions.

"These techniques are already providing new understandings of how the endothelium network works normally and malfunctions in disease."

The study will look into changes brought about by hypertension and diabetes and aims to make the techniques available to laboratories across the world.