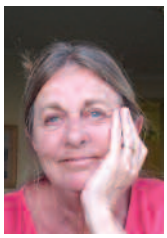

Recent Developments in Science and Medicine

Marilyn Monk

Co-operating sperm swim faster

Sperm have evolved clever strategies in their race to fertilise an egg. In some rodent species, sperm from one male can recognise each other and form trains by hooking their heads together. The 'sperm train' of tens of cells swims faster towards the egg than the individual sperm.

Fisher and Hoekstra (Harvard University, Cambridge, Massachusetts) compared train-making behaviour of sperm cells in two species of the deer mouse (*Peromyscus maniculatus* and *P. polionotus*). Sperm from each species, labelled with different coloured dyes, teamed up with sperm of their own species when mixed in a petri dish.

This feat of recognition of sperm of own kind was also seen between brother males in the promiscuous *P. maniculatus* species, where females mate with a number of males consecutively. In this species, sperm from different males (brothers) mixed together in a dish, recognise each other if they have come from the same male. The level of discrimination between littermates is the same as that between species.

In the more monogamous species *P. polionotus*, sperm have not evolved this ability to compete between brother males as they are unlikely to be in competition for the egg. So in this case mixed sperm trains are formed.

Most people think of sperm as independent single cells although, in reality, sperm are highly differentiated and it is not so surprising that co-operative behaviours may be selected by evolution. However, only one sperm can fertilise an egg so the supporting sperm in the trains sacrifice their chances to fertilise in order to help a brother sperm win the race to the egg. The extra sperm in the train also help to bore through the egg membranes.

Reference

Fisher, HS & Hoekstra, *HE (2010)* 'Competition drives cooperation among closely related sperm of deer mice.' *Nature 463:801-3.*

The human genome is 10 years old

It is 10 years since the private company, Celera (then at Rockville, Maryland), and the publicly funded international company, the Human Genome Project, announced the completion of their first draft sequences of the human genome at a televised press conference attended by Bill Clinton and Tony Blair. This extraordinary technical feat heralded a future of molecular medicine to prevent, treat and cure all disease. But, as is often the case with hype associated with every new breakthrough in science, we are yet to see the promised advances in medicine. Progress is slow in the translation of basic research to clinical application

Many other large scale scientific endeavours followed the publication of the human sequence, viz., the mapping of common variants in the human sequence, the identification of every functional gene in a genome and, with the increased efficiency and lower costs of sequencing, the complete genome sequences of many other animals and plants. One can envisage a future when every individual will carry his genome DNA base sequence on his personal computer. However, despite the huge deluge of data generated by high-throughput technologies, meaningful biological insights are rare. Rather, a greater complexity than previously envisaged is revealed The particular genes we inherit are just one part of the story – the hardware. It is now becoming clear that the programming of gene function by our interaction with internal and external environment (epigenetics) is more important in determining who we are and our susceptibility to disease.

Reference

Erika Check Hayden *(2010)* 'Human genome at ten: Life is complicated.' *Nature 464, 664-667*

What your genes do

Now that we can identify each and every one of our genes, their sequence and variations from individual to individual, we want to know the function of each of these genes. A remarkable paper published by Neuman and colleagues (European Molecular Biology Laboratory, Heidelberg, Germany) sets out to systematically disable each of the 21,000 protein coding genes, one by one, in human cells and record the resulting cellular behaviour under the microscope. After the silencing of each specific gene, the chromosomes of the cells were labelled with fluorescent dye, studied by time lapse imaging for two days, followed by computational image processing of the huge amount of data generated (19 million cell divisions). This allowed identification of hundreds of human genes involved in diverse biological functions such as cell division, chromosome alignment and segregation, and cell migration and survival. Scientists around the world are contacting the lead author, Jan Ellenberg, requesting the 'movie' associated with a defect in their favourite gene.

In another approach, Eric Davidson and colleagues (Division of Biology, CALTECH, Pasadena, USA) systematically ablate, one by one, the regulatory genes (transcription factors) that control the development and shaping up of the body of the sea urchin. The effects on the body structure and on the expression of other genes defines how networks of genes function in concert to progress development. Common principles in gene regulatory networks and function may be extrapolated to other organisms, from fruit flies to humans. Davidson sees the advent of the human genome sequence influencing scientists to work in systems of increasing complexity rather than with one single gene. Working with simple model animals like the sea urchin enables more freedom to manipulate and experiment in order to unravel and simplify complex regulatory systems of development. And working with the bigger picture to uncover the common rules sometimes allows a clearer view than the more reductionist approach looking at the component parts

References

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Oliveri P, Tu Q, Davidson EH *(2008).* 'Global regulatory logic for specification of an embryonic cell lineage.' *Proc Natl Acad Sci U S A.105:5955-62*

Patents on breast cancer genes judged invalid

The awarding of patents for specific genes and gene sequences has been a controversial issue for several decades. Nevertheless, courts in the US and in Europe have upheld these patents so far. Mutations in the genes *BRCA1* and *BRCA2* are associated with an increased risk of developing breast and ovarian cancer. Following the discovery of these genes, the diagnostic tests for inherited susceptibility were patented by a number of companies. Myriad Genetics in Salt Lake City, for example, charges $3000 per test. In March 2010, in a US district court, a judge ruled these patents invalid (see report by Meredith Wadman in Nature 39 March 2010). This decision obviously has major implications for the biotechnology industry.

The plaintiffs - individual physicians, patients and American societies and associations - claimed that the patents restrict scientific research and medical care and that the genes are products of nature and thus not patentable. The judge ruled on the latter argument - that the purification of a natural product like a gene does not render it patentable. How this will affect other companies and their technologies and gene based patents remains to be seen. Genetic testing is currently expanding beyond testing for mutations in one or two genes to assays on many genes and indeed to whole genome sequencing. And if a ruling can be based on what is a product of nature, one wonders whether so-called synthetic life forms will be exempt from this ruling. Myriad will appeal the patent.

Learning and memory

Memory formation results from the modification of synapses and neuronal circuits (plasticity) in the brain. Plasticity, and behavioral memory, are favoured by coordinated action potential timing across populations of neurons giving rise to oscillations of different frequencies (recorded in local field potentials). Scientists at the California Institute of Technology, Pasadena, California, measured the activity of single neurons along with the local field potential in humans engaged in a memory task. Subjects with electrodes implanted in the hippocampus and amygdala were shown 100 images followed by another set of 100 images half of which were new. For each image in the memory session, the participants had to indicate whether they had seen it before and how confident they were about their response. It was found that successful memory formation was associated with coordinated timing of the spike of individual hippocampal and amygdala neuronal activity with the local theta oscillation - neurons fired in response to an image close to either the peak or the trough of the oscillation. The strength of this phase-locking predicts the strength of the memory being formed.

Reference

Rutishauser U, Ross IB, Mamelak AN, Schuman EM. *(2010)* 'Human memory strength is predicted by theta-frequency phase-locking of single neurons.' *Nature. 464:903-907.*

Stem cells and the Vatican

Stem cells are pluripotent cells capable of generating a range of differentiated cells and/or tissues. Their discovery has opened the new field of regenerative medicine – transplantation of stem cells and/or their derivative cells into the body for the treatment of injury or disease. The archetypal stem cell is the embryonic stem cell (totipotent) which has the capacity to make all cells of the body including the germ cells - eggs and sperm. However, the production of embryonic stem cells requires the destruction of a human embryo, albeit at a very early stage when the embryo can exist outside the body and consists of only 100 to 200 cells.

More recently it has been shown that differentiated cells of the body (somatic cells) may be reprogrammed to generate totipotent stem cells – either by the transplantation of the cell nucleus (containing the DNA genome) into an egg, or by the introduction into the cell of four genes whose products direct reprogramming. The latter stem cell is called an IPS cell (Induced Pluripotent Stem cell) but whatever its mode of derivation, or what it is called, it is in essence an embryonic stem cell capable of generating a new individual (as shown in the mouse).

The Vatican, strictly against the generation of therapeutic stem cells from a human embryo, and also the experimental generation of similar cells, has announced its intention to finance research (two million Euros) into the use of adult stem cells for therapeutic purposes. Adult stem cells, unlike embryonic stem cells, are restricted in their potential to generate cells of just the one tissue. The research project will be carried out at the University of Maryland's School of Medicine in the US into the use of intestinal adult stem cells to treat disease.

Hubble Space Telescope is 20 years old

In April 1990, the space shuttle Discovery launched the Hubble Space Telescope into orbit 575 kilometers from Earth. Hubble, named after American astronomer Edwin Hubble, has now been orbiting Earth for 20 years, sending back images in the visible, near-infrared and ultraviolet parts of the spectrum. (For some beautiful images see website below.)

Katharine Sanderson writes in Nature in April 2010 on Hubble's troubled beginnings and history. The National Academy of Sciences first recommended the building of a space telescope in 1962 and the idea was carried forward by Bob O'Dell (now at Vanderbilt University, Nashville, Tennessee). The telescope survived through many unexpected problems to be solved – such as blurring mirror or solar wind shaking - and underwent many servicing missions performed by astronauts delivered by the shuttle. Hubble today is 60 times more powerful than it was in 1990.

In its 20 years Hubble has proved the existence of dark energy and dark matter, informed us on the life and death of supernova, and provided many beautiful pictures as evidenced in the link below. Robert Kirshner (Harvard University, Boston) studying supernovae (explosions of dying stars) with Hubble provided the evidence that the expansion of our universe is accelerating – not contracting as previously thought. And today many eager scientists compete to get on to the Hubble Space Telescope. Hubble will still be there for the next few years but after that it might be replaced by the James Webb Space Telescope, set to launch in 2014.

Reference

See http://www.nature.com/news/specials/hubble/slideshow.html

Psychological disorder in mice linked to defect in immune system

In 2002, Greer and Capecchi published that a timed deficiency in a single gene called *Hoxb8*, a gene normally associated with establishment of body plan in development, caused mice to exhibit excessive and compulsive grooming behaviour resulting

in loss of hair and skin wounds. The mouse behaviour is thought to be a model for obsessive compulsive disorder in the human but this is yet to be verified. It was generally assumed that abnormal behaviour resulted from some impairment of neurological function. More recently, Capecchi and colleagues (Howard Hughes Medical Institute, University of Utah School of Medicine, Salt Lake City, USA) have taken their research further and shown that the *Hoxb8* mutation results in a deficiency in microglia cells in the brain. These microglia cells originate in the bone marrow and migrate to the brain where they are responsible for immune surveillance, protecting the brain from infection and mopping up debris. Significantly, transplantation of wild type bone marrow having a good copy of the gene rescues the mutant mice from their pathological phenotype. Conversely, some of the normal mice that received bone marrow transplants from *Hoxb8* mutant mice began to groom compulsively and developed bare patches. Immunological dysfunctions have been previously linked to psychiatric disorders, but the causative relationships have been unclear. This study is unique in that it establishes a causal link although it is not clear how a dysfunction in the immune system causes defective neural circuits in psychiatric disorders.

References

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Greer, J. M. & Capecchi, M. R. *(2002).* 'Hoxb8 is required for normal grooming behavior in mice.' *Neuron 33:23-34.*

The crop circle evolves

Crop circles are becoming more and more intricate and beautiful (see report by Richard Taylor, Professor of physics, psychology and art, Department of Physics, University of Oregon, Eugene, Oregon, USA, in Nature June, 2010). In the first scientific publication on crop circles (Nature 22, 290–291; 1880) John Capron speculated that the 'circular spots' were induced by cyclonic winds. But crop circles have been bewildering the British since the 1600s, and today the crop-circle phenomenon has spread to Europe, Russia, North America, Japan and India. The complexity of the designs — many of which have a mathematical basis — has escalated in the past two decades, reflecting a serious and science-literate artistic movement.

Artists Douglas Bower and David Chorley began creating a series of circles in Hampshire's barley and wheat fields after reading old news reports about a pattern imprinted on Australian marshlands, supposedly by a UFO. After 10 years of secretly constructing circles, the two announced their hoax to the press in 1991.

The covert nature of the crop-circle movement fuels a cat and mouse game between artist and researcher. The artists create their designs during the night, leaving the scene free from evidence of their presence. Early artists used wooden planks, string and garden rollers, and bar stools to vault over regions of undisturbed crop. Today, increased technological expertise enables more complex patterns – the use of computers, laser pointers, satellite equipment and microwaves (crop stalks must be flattened rather than broken). Last summer, a 180-metre-long jellyfish arrived in a barley field in Oxfordshire, UK (microwave radiation, Global Positioning System receivers and lasers are suspected). Each season's designs are published in a catalogue and their artistic evolution is discussed by dedicated societies.

Free-riding surfing crocs

The widespread distribution of the estuarine crocodiles (*Crocodylus porosus*) throughout the oceanic islands of the South-east Pacific suggests these crocodiles travel over large distances in oceans spanning more than 10,000 square kilometres. Crocodiles are poor swimmers, so how did they manage this dispersal strategy? Craig Franklin and colleagues (School of Biological Sciences, University of Queensland, Brisbane, Australia) have shown that the crocodiles have evolved the behavioural strategy of surfing the water currents to facilitate their migration, Monitoring the crocodiles movement with acoustic telemetry they found that the animals only engaged on long distance travel when the current directions were favourable. Depth and temperature measurements from implanted transmitters showed that they remained at the water surface during travel but would dive to the river substratum or climb out on the river bank (thus increasing their temperature as they basked in the sun) if current flow direction became unfavourable. The crocodiles know when the current is flowing in the direction they want to travel. Correlations can be drawn between the migratory behaviour and cognitive abilities of crocodiles and birds. Previous studies have shown that both animals use magnetic cues to navigate.

References

Campbell HA, Watts ME, Sullivan S, Read MA, Choukroun S, Irwin SR, Franklin CE. *(2010)* 'Estuarine crocodiles ride surface currents to facilitate long-distance travel.' *J Anim Ecol. 7 Jun 2010.*

Acupuncture works for mice

Acupuncture is used worldwide to relieve pain. However, there have been problems in proving its efficacy in a number of clinical trials and in understanding in scientific terms its mode of action. Acupuncture is thus generally disregarded in mainstream medicine. Some would argue that acupuncture acts via a placebo response in the patient.

Now Maiken Nedergard and colleagues (Center for Translational Science, University of Rochester Medical Center, Rochester, New York) have a scientific explanation for the efficacy of acupuncture in mice. They showed that the neuromodulator molecule, adenosine, produced by injured tissue and known to have pain dulling properties, is released during acupuncture in mice. Pain was induced in the hind paw of the mouse, followed by acupuncture at a point below the 'knee' called the 'Zusanli' point. Following acupuncture the mouse was less sensitive to heat and touch. The pain relief required the adenosine receptor on the cells - if the receptor was blocked by the injection of an adenosine receptor antagonist the acupuncture was not effective. In addition, inhibition of enzymes involved in adenosine degradation, potentiated the acupuncture-elicited increase in adenosine, as well as its pain dulling effect. However, it was also noteworthy that acupuncture was not effective if applied to the rodents' pain-free left legs suggesting that there is no central mechanism. It is not clear how local release of adenosine could explain the effect of acupuncture against headaches. The work might account for only some of the treatment's supposed benefits.

References

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