13·11·87

The clockwork that drives everything under the sun

All life shares a simple ancestor. Roger Highfield, Science Editor, explains

ALMOST all living things are descended from a common ancestor that existed hundreds of millions of years ago. This heritage has been revealed with the discovery that the clockwork that drives human growth is the same clockwork that rules a humble organism such as yeast.

Some of the most dazzling adventures in genetics this decade have led us to understand how the cells in living things grow and develop. They have involved detective work of the most elegant kind, as shown in the journal Nature this month, which reports how scientists in Britain, France and America have uncovered the clock's innermost mechanisms.

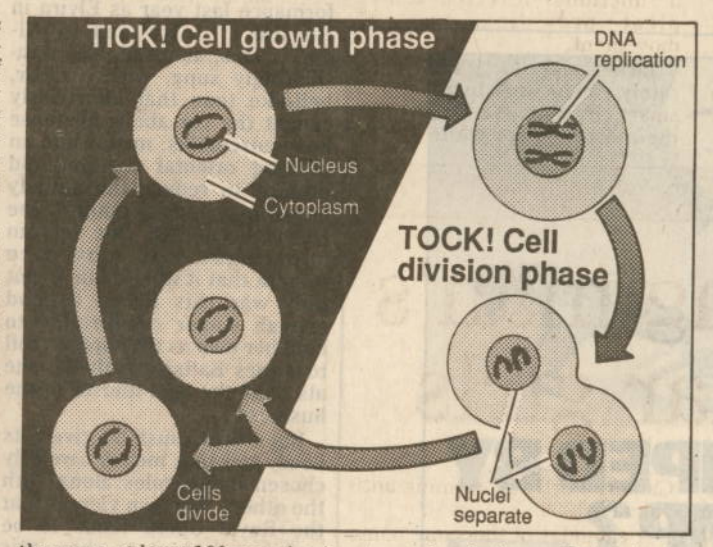
All life is made of living cells. Understanding the mechanism by which the 10 million million cells in our bodies divide and multiply underpins our understanding of all processes of growth, development and ageing, and of what happens when they go wrong.

Like the tick-tock of a clock, cells oscillate: during the "tick" the cell grows while division is prevented. During the "tock", growth halts while the cell divides. It seems that nature's timepieces controlling cell division have the same mechanism.

"Whether we make a nose or an ear depends largely on regulated cell proliferation. When this regulation goes wrong, this results in disorganised cell reproduction, which can lead to cancer," said Prof Paul Nurse of the Imperial Cancer Research Fund's Cell Cycle Group. The group is based at the Microbiology Unit at Oxford University, where the work reported in Nature was performed.

Two basic approaches to understanding the mechanism of the cell clock have been used. One relies on studying the clock's design, which is held in human genes, the blueprints for hereditary characteristics. The second is concerned with studying the clock components that the genes are responsible for — proteins — in work on the eggs of a range of creatures, from frogs to starfish.

The genetic work has focused on yeast, a simple organism. Prof Nurse started his work in Edinburgh by studying mutant yeasts in which the clock was disabled and cell division did not occur. So far, nearly 100 genes needed for cell division have been discovered through such research. Since each is responsible for making a protein, there are at least 100 proteins in the cell clock mechanism.



The next stage was to find which proteins were important. Prof Nurse knew that if he found a gene that could boost cell division, it would be responsible for an important control protein.

He explained this by analogy with the clock. "We all know that cogs are essential to the works of a clock but you do not control a clock by taking out a cog." It is easy to slow down or stop a clock by such drastic action. But an adjustment to a controlling component that makes the clock speed up reveals components that are crucial for controlling speed.

In the same way, the control genes the group wanted to find made the yeast divide faster than it could increase in size, leading to a smaller cells. The hunt was on for what the workers in Edinburgh dubbed "Wee" mutants.

Four genes were found that produced Wee mutants. The most interesting was caused by defects in a gene called Cell Division Cycle 2 (or CDC2), which was found to be the blueprint for a molecule that belonged to a large group of proteins called protein kinases. These proteins can influence other enzymes in the cell by donating phosphate. The effect on the enzymes is to distort their structure, which can, in effect, turn them on or turn them off.

The activity of the CDC2 protein is seen to rise just before cell division, and appears to act by rushing around preparing other enzymes for the act. In the latest work at Oxford, Prof Nurse and Dr Kathleen Gould show that the protein itself is turned on before cell division by a similar method.

Other major advances in dismantling the cell clock have come from comparing the genetics of cell division with the parallel efforts to find the factors that push an immature egg taken from a frog to divide. It is analogous to taking a defective watch and finding which component makes it work normally.

Last year Dr Jim Maller's group from Denver, Colorado, found a protein capable of this feat. When Prof Nurse learnt that they were purifying this protein he suggested they compare their mystery factor with the CDC2 protein discovered in their studies.

"It turned out to be the same. We were enormously excited. Dr Chris Norbury, who performed the crucial experiment in Oxford, really did shout 'Eureka!'" Prof Nurse said. A protein which pushed immature starfish to divide and which was found by Dr Marcel Dorée's group working in Montpellier, in the South of France, also turned out to be CDC2.

Another experiment carried out by Dr Melanie Lee in the Oxford group showed that the clock component was not limited to frogs, starfish and yeasts but also worked in humans. "We reasoned that if it was truly universal we would find proteins similar to CDC2 in all organisms," Prof Nurse said.

They took a yeast that was unable to divide because it lacked the all-important CDC2 protein and added human genetic material. Amazingly, one enabled the yeasts to reproduce as normal, showing it produced a human version of CDC2.

Subsequent analysis has shown that the human version is almost identical to that of the yeast. During evolution, yeasts and our ancestors parted company one billion years ago.

Research is turning up other proteins that play a role in the cell clock. One is cyclin, discovered by Dr Tim Hunt and coworkers at Cambridge University, and another is made by a gene called CDC25.

Understanding the cell clock gives insights into ageing. While cells taken from a human foetus will go through 50 cycles of division before they die, scientists have found that cells from an 80-year-old grind to a halt after only 30 cycles.

This work will also be of fundamental use in cancer research. Prof Nurse speculated that finding new ways to turn the cell clock on and off within cancer cells may one day make it possible to retard the spread of a tumour until the optimum treatment is found.

Focusing on bacteria

THE FIRST picture of a genetic switch that controls the way bacteria become resistant to antibiotics has been taken, with the help of a nuclear reactor.

Using a beam of nuclear radiation, scientists were able to make an image of a bacterium's "switch" in action. The switch is a clump of proteins, measuring 11 millionths of a millimetre in length, that sticks to the bacterium's genetic material to affect the way it is used.

New insights into the development of resistant strains of bacteria, an increasing problem in hospitals, will emerge from the work being carried out at the world's leading research reactor, the Institut Laue Langevin in Grenoble, France, said Dr Roland May, one of the team.

"We believe this technique will become one of the most important tools for the study of such complex structures, which determine basic life processes," Dr May said.

The Institut, where scientists study the molecular structure of materials, has a £28 million budget, a third of which comes from our Science and Engineering Research Council. A Briton, Prof Peter Day, has recently been appointed as its director.

RH