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The Nobel Prize for Physiology or Medicine 2001

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Tim Hunt FRS and Sir Paul Nurse FRS of The Imperial Cancer Research Fund, London, and Leland Hartwell of the Fred Hutchinson Cancer Research Center, Seattle, USA were today (8 October 2001) awarded the 100th Nobel Prize for Physiology or Medicine for their work identifying the key regulatory molecules of the cell-cycle.

In a sequence of experiments with the yeast *Saccharomyces cerevisiae* in 1970-71, Leland Hartwell identified a number of mutations in the genes that control the cell-cycle. Hartwell decided to study yeast cells because they are simpler and easier to manipulate than human cells. At the time, Hartwell recalls, this was "a fairly risky assumption". He identified over one hundred such genes and labelled them cell division control (CDC) genes. Further work led to the identification of the *CDC28* gene that controls the process by which cells progress through the G1 phase of the cell-cycle. This gene was consequently called 'start', and it controls a crucial point at which cell proliferation is integrated with extra- and intra-cellular signals.

In other studies, Hartwell examined the impact of irradiation on the yeast cells, making another important discovery along the way. He found that cells in which the DNA had been damaged by radiation underwent cell-cycle arrest. This allowed time for the cell to repair the damage before undergoing replication, a concept that he defined as checkpoint and which was subsequently found to ensure the correct order of the different cell-cycle phases. He also showed that early events in the cell-cycle prevented the initiation of events downstream in the pathway. Mutations in checkpoint genes enable late events to occur even if DNA damage hasn't been repaired, a mechanism implicated in the development of many cancers.

At about the same time, Sir Paul Nurse began to use the genetic approach to cell-cycle research on another yeast, *Schizosaccharomyces pombe*. He discovered the gene *cdc2* and initially showed that is was responsible for the transition from G2 phase of the cell-cycle to mitosis. Further work showed that *cdc2* was homologous to the 'start' gene identified by Hartwell, and in 1987 Nurse isolated the human homologue, which became known as CDK1 (cyclin-dependent kinase 1). He then went on to show that CDK activation is dependent on reversible phosphorylation.

"Naturally I am thrilled to win the Nobel Prize, particularly as the prize celebrates its centenary this year, but this is a team effort and it's important to realize that this achievement was made possible by the efforts of the many researchers I've worked with over the years", said Nurse.

Tim Hunt's discovery of a class of proteins named the cyclins added a further layer of sophistication to the cell-cycle. The cyclins - so-called because their levels vary during the cell-cycle - bind to CDK molecules and by controlling CDK phosphorylation regulate CDK activity. The first cyclin was discovered in the sea urchin *Arbacia,* and so far around ten distinct cyclins have been isolated from humans. They are highly conserved through evolution and the periodic protein degradation characteristic of the cyclins is an important control mechanism in many cell-cycle pathways.

Hunt said: "I am over the moon to win this award, which is a tribute to the work of my whole team at Imperial Cancer Research Fund. Both mine and Paul's research has opened up a new chapter in cancer

research and it's fantastic that this has been recognized in this way. The knowledge we have gained about how cancer cells work should lead to exciting new therapies for cancer patients in the future."

The work undertaken by Hartwell, Hunt and Nurse has shown that a combination of constant numbers of CDK molecules and fluctuating levels of cyclins enables the complex process of the cell-cycle to proceed efficiently. Furthermore, perturbations of these finely balanced systems have serious implications for human health. Mutation in cell-cycle genes can lead to the chromosomal instability that develops in cancer cells, and the gene products of CDKs and cyclins can interact with the products of tumor suppressor genes such as p53.

The discovery that elevated levels of CDK molecules and cyclins are present in certain forms of tumor could open new avenues of research in the field of tumor diagnostics, and clinical trails currently in progress using CDK inhibitors could allow new approaches to cancer therapy.

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