

The Cell Cycle in the **Spotlight** of Cancer Research

The Nobel Prize in Physiology or Medicine 2001 was awarded to the American Leland (Lee) Hartwell and to Paul Nurse and Timothy (Tim) Hunt from Great Britain. These three scientists were honoured for their fundamental discoveries about the regulation of cell division. But the prize honoured not only three outstanding scientists, it also moved an important area of modern cell biology – research on the “cell cycle” – into the limelight. This research is devoted to the fundamental question of how biological cells multiply and in doing so pass on their genetic information – their “genome” – unchanged from one cell generation to the next.

The Nobel Committee presented the award to Hartwell, Nurse and Hunt for their contributions to cancer research. At first glance, this might appear more than a little surprising since the two geneticists Hartwell and Nurse studied the reproduction of yeast cells, while the biochemist Hunt worked mainly with sea-urchins and clams. Every baker and brewer is familiar with yeast, and many know about sea-urchins and clams, at least from their holidays, but what these organisms have to do with the development of cancer deserves a brief explanation. In fact, the latest chapter in cell cycle research illustrates once again that important discoveries in the field of

medicine are often made where they are perhaps least expected.

What yeast, sea-urchins, and human beings have in common with all other living creatures on this planet is that they are made up of cells. Although plant cells and the walls between them were made visible under a microscope as far back as the seventeenth century, it was only in the nineteenth century that researchers realised that animal tissues were also composed of cells. The discovery that all living creatures consist of cells is without doubt one of the most important scientific insights of all time. But even after the “cell theory” was formulated, the origin of cells was the subject of much conjecture and debate. Finally the recognition that cells arise by the binary division of pre-existing cells came to the fore – or as the famous pathologist Rudolf Virchow aptly formulated: “Omnis cellula e cellula.” Cell division is now thought of as a process which has been endlessly perpetuated ever since a first “original cell” came into being – indeed since the beginning of life on this planet.

The biological cell shows all the characteristics of life, in particular the ability to reproduce itself. The structure and function of each cell is imprinted in an inheritable substance, the famous “deoxyribonucleic acid” (or DNA). This inheritable substance, the so-called genome,

thus contains all the genetic information of a cell. Threaded around special proteins, the DNA lies in the interior of the cell nucleus in long and extremely thin threads. On these threads the genes of the respective organism are lined up, with each individual gene containing the necessary instructions for the production of a protein (or, in rarer cases, a ribonucleic acid). Thus, the genome

The term “cell cycle” describes the collection of all biochemical processes that take place during the division of a cell. To gain a deeper and more detailed understanding of this fundamental process of life on earth is initially a matter for basic research. However, the phenomenon of cell division is also of profound interest from the medical point of view, as

PROFESSOR ERICH A. NIGG, Director of the **MAX PLANCK INSTITUTE FOR BIOCHEMISTRY** in Martinsried, explains in the following report. For Nigg, a growing understanding of the cell cycle goes hand in hand with a growing hope for new approaches to cancer therapy.

can be compared to a blueprint for the production of all macro-molecules that are necessary for the construction and the activities of the organism.

Originating from a single cell, the fertilised ovum, an adult human being consists of approximately 10^{14} (one hundred thousand billion) cells. Even after growth is completed, cell divisions do not stop. Many cells in

the human body have a limited lifespan and must therefore be constantly replaced from a reservoir of stem cells. For example, red blood cells have a lifespan of only 120 days. Thus, in order to replace dying blood cells, the human body must produce about three million new cells every second. This production rate can even be increased if necessary (for instance after loss of blood).

How do the respective stem cells “know” when and how often they have to divide in order to keep a certain tissue or organ intact and functional? What happens in the interior of a cell when it prepares to divide? How, during each cell division, are all genes copied without fault and allocated correctly to the daughter cells? And what happens during tumour development? Why, in the case of cancer, do cell divisions continue unabated? And why are many tumour cells genetically unstable to the extent that the most-feared types of cancer display an ever more aggressive behaviour?

The reproduction of cells demands the exact coordination and precise execution of a large number of biochemical processes. In order to divide, a cell must grow and prepare proteins, lipids, carbohydrates, and other building blocks for the replication of cellular structures. Most importantly, it must produce a faultless copy of its entire genome. Then, during the actual process of cell division, the replicated genome has to be

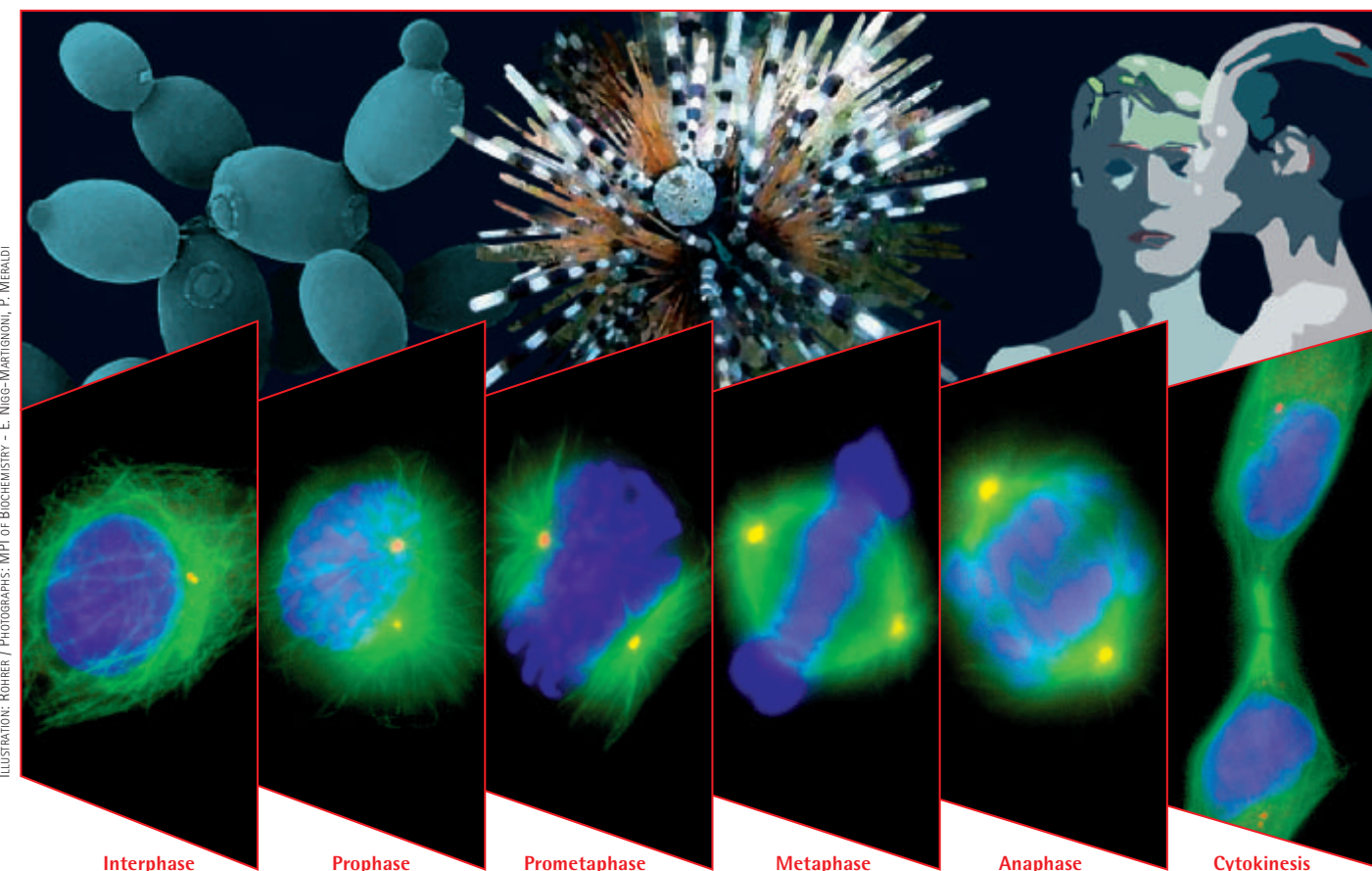
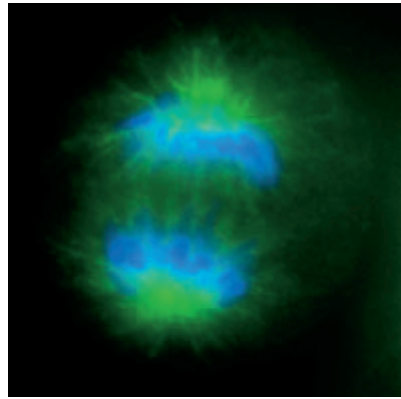


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All living organisms – be they yeast, sea-urchins, or human beings – are made up of cells which multiply by dividing. The images in the foreground, taken by fluorescence microscopy, show the division of a human cell (i.e. the different stages of mitosis). The chromosomes (DNA, blue) are distributed between the two newly emerging cells by means of a dynamic scaffolding framework (spindle apparatus) consisting of thread-like structures (microtubules, green) and two small organelles (the centrosomes, yellow).



Fluorescence microscopic image of a normally dividing human cell. After degradation of the cyclins, chromosomes (blue) are drawn apart by microtubules (green).

distributed evenly between the two emerging daughter cells. For this purpose, the extremely long DNA threads of the genome are wrapped up into a compact form suitable for distribution. Through this process the genome becomes visible as so-called chromosomes, and the most impressive part of the cell cycle takes place, the phase known as “mitosis”: in a spatially and temporally coordinated process, the two complete sets of chromosomes are separated and distributed to the incipient daughter cells. Finally, the two daughter cells are separated by means of a cleavage process (cytokinesis). The term “cell cycle” embraces the entirety of all these events, from the growth of the cell through the replication of the genome and the distribution of the chromosomes during mitosis.

It is easy to comprehend that cell cycle progression should be subject to extensive monitoring. Even single-cell organisms such as yeast have an interest in adjusting their cell division behaviour to the availability of nutrients. In multi-cellular organisms these controls are even more important since the cell divisions within each organ must be subordinated to the requirements of the whole body. Every time a cell divides, the entire genome must in principle be transmitted in an unchanged form from one cell genera-

tion to the next. However, there are some important exceptions to this rule: in particular, the formation of germ cells – during the process known as meiosis – goes hand in hand with the halving of the number of chromosomes.

The reliability of genetic information is an indispensable prerequisite for the health of each living organism and the continued existence of each species. It is not surprising, therefore, that cell cycle progression is subject to a strict “quality control”. Individual cell cycle events must be exactly coordinated in time and space and this coordination is monitored through specialised biochemical monitoring systems, the so-called “checkpoints”. For example, the cell cycle is stopped as soon as a checkpoint has discovered damage to the DNA. In a similar way, mitosis is halted by means of a special checkpoint until all chromosomes are correctly attached to the division spindle. In higher organisms, specific monitoring systems are also able to invoke a programmed cell death (so-called apoptosis) in the case of irreversible damage, with the result that genetically-damaged daughter cells are prevented from arising.

MISTAKES HAPPEN – AND SOMETIMES THEY SHOULD

The degree of precision with which DNA synthesis and mitosis are carried out is truly amazing. Nevertheless, occasional errors are unavoidable. As a result of faulty DNA synthesis, mutations occur in the genome, so that the information content of individual genes changes. On the other hand, errors during the distribution of normal chromosomes lead to aneuploidy (lack or excess of chromosomes). From the medical point of view such changes in genetic characteristics of cells are just as important as they are undesirable,

because – in general – they lead to diseases. On the other hand it should not be overlooked that a certain minimal capacity for genetic information to change represents a basic prerequisite for evolution.

Epidemiological and molecular analyses have led to the recognition that cancer depends on the mutation (i.e. on changes in the information content) of certain key genes. These key genes are called oncogenes or tumour suppressor genes depending on whether their role in the development of tumours is linked to too much (in the case of oncogenes) or too little gene activity (in the case of tumour suppressor genes).

It should be emphasised, however, that these critical genes are only responsible for the development of diseases when problems arise with their regulation or function. In the healthy organism, the same genes are essential for carrying out important cell functions. In particular, many of these genes play a decisive role in promoting cell division whilst others carry out quality control (checkpoint) functions in the cell cycle. As a consequence of excessive oncogene activity it can happen that resting cells are continuously stimulated to divide. On the other hand, the loss of checkpoint functions in the cell cycle can cause increasing genetic instability. There are good reasons for assuming that it is the very capacity for constant genetic change which represents a decisive driving force behind the increasingly aggressive behaviour of certain cancer types. Moreover, it is highly probable that the explanation for the frequent appearance of therapy-resistant cells can be found in the capacity of tumour cells for genetic change.

It would be beyond the scope of this short article to discuss the individual biochemical processes that

take place during the cell cycle. However, it should be emphasised that the regulatory circuit underlying cell division is very similar in all animals and plants. Particularly in the past 10 to 15 years it has been recognised that certain “pacemakers” of the cell cycle have persisted during several hundred million years of evolution, remaining almost constant in both their structure and functionality. It was for the characterisation of these pacemakers that the three Nobel prize winners Hartwell, Nurse, and Hunt have been acclaimed. What they discovered were enzymes, so-called protein kinases, that are periodically switched on and off during the cell cycle. Through their activity these protein kinases control practically all important processes in the cell cycle, particularly the replication of DNA and the actual cell division (mitosis). Since all of them depend on special regulatory subunits, the so-called cyclins, they are known as “cyclin-dependent kinases” (or CDKs).

Protein kinases are enzymes which transfer phosphate molecules to proteins and thereby regulate their structure and/or activity. This phosphate transfer (or “phosphorylation”) acts on the molecular level like a switch by which biochemical activities can be turned on and off in quick succession. Today we know that hundreds of protein kinases are active in each cell. These control not only the cell cycle, but also metabolic processes, gene activities and the transfer of hormonal signals. The significance of protein kinases can hardly be over-estimated, and in 1992 the scientists who discovered the first protein kinases, Ed Krebs and Ed Fischer, were accordingly honoured with the Nobel Prize.

The discovery of CDKs, the cyclin-dependent protein kinases, opened the floodgates for cell cycle research.

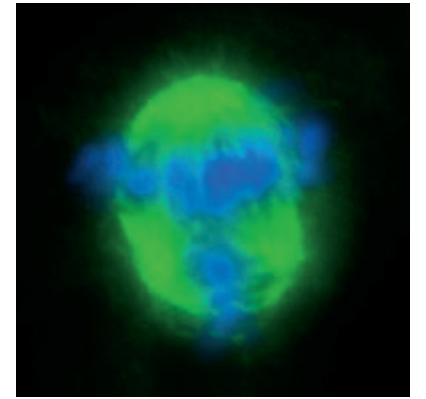
A few years after their discovery in yeast and invertebrate sea-animals, corresponding kinases were found to exist in human beings. In the meantime it has become known that structurally similar CDKs control the cell cycle in all eukaryotic organisms.

In normal cells, CDK activity is kept under control in many different ways. In particular, the availability of cyclin subunits is accurately regulated through both synthesis and degradation. Furthermore, the CDKs themselves are regulated through phosphorylation, and physiological inhibitors (CDK inhibitors) also play an important part in limiting CDK activity.

NEW APPROACHES TO CANCER THERAPY

Whilst the activities in CDKs are strictly regulated in normal cells, these regulatory mechanisms are disturbed in cancer cells. Thus, in many tumours certain CDK forms show significantly increased and prolonged activity. Depending on the type of tumour, this deregulated CDK activity may stem from the excessive production of cyclins or the loss of CDK-inhibitors.

The findings described above leave little doubt that the development of cancer is intimately linked to disturbances in the cell cycle. As a result, scientists around the world are working intensively in the hope of converting the knowledge gained from cell cycle research into clinical applications. For example, researchers in many pharmaceutical companies are searching for pharmacologically effective inhibitors for cell-cycle-regulatory protein kinases. Although it is important to bear in mind that the development of cancer is an extremely complex biological problem which cannot be reduced to loss of control over the cell cycle,



Fluorescence microscopic image of a human cell in which division is blocked through over-expression of a non-degradable cyclin mutant (chromosomes, blue; microtubules, green).

the latest advances in our understanding of cell cycle regulation raise legitimate hopes for new therapeutic approaches.

The field of cell cycle research is in its infancy and many fundamental questions are waiting to be answered. For example, we still know comparatively little about the regulation and monitoring of DNA synthesis, or the mechanisms that ensure correct distribution of all chromosomes during each cell division. For future therapeutic approaches to the treatment of cancer, the answers to these questions could be of greatest importance. If the genomic instability, which is so typical in tumour cells, can be linked to specific genetic differences between cancer cells and their normal neighbours, then these differences may well constitute the Achilles heel of the tumour. ●



Professor Erich A. Nigg, born in Switzerland in 1952, has been Director of the Max Planck Institute for Biochemistry in Martinsried since 1999. After gaining his doctorate at the ETH (Swiss Federal Institute of Technology) in Zurich in 1980, he went to the University of California in San Diego for two years. In 1988 he habilitated at the ETH in Zurich, specialising in Cell Biology. From 1987 to 1995 Nigg led a research team at the Swiss Institute for Experimental Cancer Research, and from 1995 to 1999 he was Professor of Molecular Biology at the University of Geneva. His research is focused on the regulation of cell division, the spindle assembly checkpoint, the centrosome cycle, as well as the mechanisms leading to the development of cancer.