Award lectures

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THE CELL CYCLE, CHECKPOINTS, AND CANCER

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Studies carried out initially in yeast and marine invertebrate and amphibian eggs, have identified the cyclin dependent kinases (CDKs) as key elements in controlling the cell cycle. In the fission yeast a single CDK $p34^{cdc2}$ encoded by *cdc2* is required to initiate both S-phase and mitosis, the major events common to all eukaryotic cell cycles. This protein kinase is regulated by several mechanisms, including the availability of B-cyclin to form an active complex with $p34^{cdc2}$, an inhibitory tyrosine phosphorylation in the active site of the enzyme, and the action of a specific protein inhibitor. These mechanisms ensure that the $p34^{cdc2}$ protein kinase activity is precisely regulated during the cell cycle. Low level activity in G1 is required to bring about S-phase and during G2 to prevent a further round S-phase. Activation to high level in G2 initiates mitosis, and a failure to complete S-phase prevents this activation. Thus $p34^{cdc2}$ controls the onset of S-phase and mitosis and ensures they occur in the correct order during the cell cycle.

The human *CDC2* gene was isolated by its ability to substitute for the *cdc2* gene in fission yeast. It controls the onset of mitosis in human cells indicating that the basic elements of cell cycle control are likely to be conserved in all eukaryotes. Other related CDKs have also been identified in human cells which act in G1, both in mid-G1 and at the onset of S-phase in late G1. These CDKs and their associated regulatory molecules play important roles in controlling cell cycle progression, and so have provided a new set of potential targets for restraining uncontrolled proliferation during malignancy.

The CDKs are also important in the checkpoint controls which prevent initiation of S-phase and mitosis if earlier events of the cell cycle have not been properly completed. For example, premature $p34^{cdc2}$ activation can lead to mitosis without S-phase and inhibition of $p34^{cdc2}$ can lead to S-phase without mitosis. Defects of this sort lead to genomic instability with obvious significance for tumour progression. Understanding these controls may also provide new strategies for treating cancer. Quiescent cells do not have potentially activatable CDKs required for mitosis and so would be resistant to treatments which could activate these protein kinases. Malignant cells which are unable to become properly quiescent could respond to such treatments by a premature entry into mitosis which would be lethal, selectively killing malignant cells.

These studies provide a useful example of how work with simple organisms such as yeast and starfish can illuminate fundamental problems in human cells which may ultimately be of practical importance for improving clinical practice.

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DOES PROGRESS TRANSLATE INTO OUTCOME?

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There is now ample evidence that there are wide divergences in the outcome of treatment of cancer in different countries, regions and hospitals.

This would suggest that available knowledge and know-how is not always applied to its full extent and the available numbers would indicate that important progress in overall outcome for the global population could be made, if state of the art treatment would be asked and given at the right time.

The analysis of the reasons of such differences complex. After treatment efficacy of a new biological or technological development has been proven in clinical research, a complex process is required for a novelty to reach the whole patient population. Even major improvements have been shown to take up to 10 years to be applied and, as in cancer most progresses have been achieved in small steps, their diffusion can be expected to be even slower.

Three main steps can be assessed: a treatment has to be available, needs prescription at the right time and has to be given in the correct form.

The availability is dependent on decisions by the structures governing the health care system and these are influenced by political and financial arguments. The adequate prescription pattern is dependent from training and educational aspects, as well from the public as from the general practitioner, the non oncological specialist and the oncologist. The rapidly expanding body of knowledge has created very specific requirements for continued medical education and structural support for diffusion of information. Finally, the correct execution of a treatment, monitored by quality control, is an aspect which has only in the very recent years been identified in its full importance. This is linked with the fact that the complexity of cancer treatment has been rapidly increasing with the involvement of growing numbers of people and the implementation of more sophisticated treatment schedules.

The whole of these elements are covered in the process of "quality assurance", which is the responsibility of all bodies involved. The importance of the different aspects of this process can be illustrated with a number of specific examples.