Cell multiplication

Editorial overview

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The award of this year's Nobel prize in physiology or medicine to Paul Nurse, Lee Hartwell and Tim Hunt marks a key point in cell cycle research. Starting with the discovery of the cyclin proteins, followed by the isolation of the first cell-cycle and checkpoint mutants, many of the fundamental mechanisms by which cells ensure ordered replication and division have been elucidated. In addition, much has been learned about the regulatory circuits that cells use to regulate entry into, and exit from, the cell cycle in response to external signals such as hormones and growth factors. Finally, the elucidation of whole genome sequences has shown us that we now know the entire set of genes encoding the key players in cell cycle regulation, such as cyclins or cyclin-dependent kinases, in many of the model organisms used. The reviews in this section of *Current Opinion in Cell Biology* highlight how far the field has progressed, and at the same time focus on some of the central open questions that are currently being addressed.

In mammalian cells, phosphorylation of the retinoblastoma protein has emerged as a central event that dictates the irreversible commitment of cells to another round of cell proliferation. Signals from the cell surface control transcription of the D-type cyclins (which comprise part of the kinase that phosphorylates the retinoblastoma protein) through Ras- and Myc-dependent signalling pathways. In parallel, the growth of cells (i.e. increase in cell mass) is strictly controlled by external signals. Both processes are tightly linked; cells in an organism each have a characteristic size that is not identical between different cell types; similarly, replication is only initiated when cells have reached a certain cell size. Although it is thus clear that cell growth is tightly coupled to proliferation, the mechanisms that link both processes are far from clear and may differ between different organisms. This issue is discussed by Nicolas Tapon, Kenneth Moberg and Iswar Hariharan (pp 731–737) in the opening review of this issue.

Cell proliferation is not only controlled by external factors but also critically depends on the integrity of cellular DNA; thus genomic DNA is under constant surveillance by checkpoint mechanisms. These mechanisms, operating in the G2 phase of the cycle, have been under intense scrutiny for some time, but the arrest of mammalian cells early in the cycle had been ascribed solely to p53 and its homologues. Now, Jiri Bartek and Jiri Lukas (pp 738–747) summarise recent advances, demonstrating that this view is too simple and review the mechanisms that allow a very rapid arrest, rather than the relatively slow transcriptional response that is controlled by p53.

Even when growth factors are present and no obvious damage is inflicted upon cellular DNA, cell proliferation does not always proceed. Often, this is due to inherent genetic control mechanisms, which control the lifespan of cells both in culture and also in the intact organisms; such mechanisms are collectively termed 'senescence'. Yet as María Blasco and Manuel Serrano (pp 748–753) show in their review, senescence in different cells reflects very different genetic mechanisms. In some cells, these are indeed clockwork mechanisms operating at the telomeres at chromosome ends. In other cells, particularly primary rodent cells, senescence largely reflects cellular responses to the stressful environment in culture. Perhaps most surprisingly, the analysis of these mechanisms has yielded information about genes involved in human tumours, suggesting that both intrinsic timing mechanisms and appropriate responses to cellular stress are critical for maintaining genomic integrity.

Frank Uhlmann's review (pp 754–761) shifts the focus to events closer to the end of the cell cycle, describing the molecular machinery which controls the ordered distribution of sister chromatids to the newly emerging daughter cells in mitosis. Findings from a number of different organisms have converged to show how the regulated proteolysis of a group of proteins, termed cohesins, at the onset of anaphase ensures that chromatins are held together until all chromosomes are properly aligned — a process defined as the spindle assembly checkpoint.

The checkpoint defines one striking example of how cell cycle events can be controlled by spatial clues within a cell, using information transmitted from the microtubular network to control the cell cycle machinery. A second example is provided by Gislene Pereira and Elmar Schiebel (pp 762–769) in their discussion of the mitotic exit network and its control by the spindle pole body in yeast. The critical proteins that regulate exit from mitosis by controlling the localisation of the Cdc14 phosphatase are localised at specific structures in the nuclear envelope. This spatial restriction ensures that exit from mitosis and cytokinesis only takes place when one spindle pole body has entered the emerging bud and is thus critical for the correct distribution of chromosomes to the two daughter cells.

Brian Lee and Angelika Amon (pp 770–777) discuss how modifications of the mitotic machinery generate meiotic cell divisions such that in the first division, homologous chromosomes are segregated to opposite poles; segregation of sister chromatids only takes place in a second cell division cycle that follows without an intervening round of DNA replication.

From the collection of reviews, it becomes very clear that not only deregulated cell cycle progression, but also failure of checkpoint events throughout the cell cycle can generate genomic instability, thereby leading to the accumulation of further mutations and eventually contributing to the development of cancer. Obviously, the identification of critical components of both processes should enable their genetic manipulation in the mouse and thus enable the generation of appropriate models of human cancer. However, this strategy has not been universally successful and many cancer-prone phenotypes in the mouse do not accurately reflect human diseases occurring in the same organ, or carrying similar mutations. Byron Hann and Allan Balmain (pp 778–784) summarise recent progress in modelling human cancer in mouse models using novel conditional and site-specific techniques. They point to possible strategies that will turn our increasing understanding of cellular proliferation into new treatments of cancer patients.