

## Cell multiplication

### Peering in and peering out: regulation of and by the cell cycle

#### Editorial overview

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#### Abbreviations

**Cdk** cyclin-dependent kinase  
**CKI** Cdk inhibitor

#### Backdrop

The identification of mitosis-promoting factor (MPF) as the same molecule as p34<sup>cdc2</sup> marked a turning point in the molecular analysis of the eukaryotic cell cycle. During the first ten years following this watershed discovery research on the cell cycle focused primarily on identifying the components of the basic cell cycle machinery and determining how their activities were linked together to generate a regulatory circuit capable of controlling the cell cycle. This effort has been remarkably successful. There now exists a large catalog of proteins that control various aspects of cell cycle progression, and we have a basic understanding of how certain aspects of the cell cycle are organized. One example of this progress is that it is now clear that DNA replication is restricted so that it occurs once per cell cycle, during S phase, because subcomplexes of the large protein superstructure that assembles at origins of replication can load onto the origin only when cyclin/Cdk (cyclin-dependent kinase) activity is low. Once a complete superstructure is assembled, it then requires a high level cyclin/Cdk activity to promote the initiation of DNA replication. Thus, as cyclin/Cdk activity escalates in late G<sub>1</sub> phase, competent origins assembled in the previous cell cycle or in early G<sub>1</sub> are fired. No new active origins can be specified until cyclin/Cdk activity returns to a basal state, thereby allowing the construction of a new replication-promoting superstructure at the origin. Thus, consecutive ‘firings’ of a replication origin require that Cdks oscillate between states of low and high activity.

With a catalog of cell cycle regulatory proteins and a crude map for their logical organization in hand, research on the cell cycle has, over the past few years, been turning in two different directions. First, there is an increasing effort to understand the multiple processes that the cell cycle program controls, and to understand how correct temporal regulation of these processes is achieved; much remains to be learned in this area. For example, although many of the

proteins that mediate the copying of the chromosomes during S phase have been described, it is still not known in molecular detail how the activation of S phase Cdks triggers the firing of replication origins at the beginning of S phase. Second, we are steadily gaining a more finely textured view of how various signaling pathways, including those that sense both intracellular and extracellular signals, impinge on the basic cell cycle machine. This section of *Current Opinion in Cell Biology* focuses primarily on the downstream events that are controlled by the cell cycle machinery (in particular those that occur at the end of the cell cycle: mitosis and cytokinesis) and the signaling pathways that regulate cell division.

#### Processes controlled by the cell cycle

Reduced to its simplest form, the cell cycle is comprised of two events: replication of chromosomes during S phase, and segregation of the replicated chromosomes during M phase. Chromosome replication and segregation are the two most fundamental processes of cells, hence the primary job of the cell cycle is to ensure that these occur in the proper order and with high fidelity. This section does not review mechanisms and regulation of DNA replication; these topics were recently reviewed in this series [1].

The review by Zachariae (pp 708–716) reports on the impressive progress that has recently been made in understanding how the initiation of chromosome segregation is triggered at the metaphase/anaphase boundary. This fundamental problem has fascinated cell biologists for well over a century. A clear model for this visually obvious, yet mechanistically elusive, process has emerged during the past two years. A protein known as cohesin holds replicated sister chromatids together. Cohesin’s ability to link sisters together is abruptly terminated at the entrance to anaphase by separin, which inactivates cohesin by cleaving it. Separin is normally held at bay by its inhibitor securin. At the metaphase/anaphase transition, the anaphase-promoting-complex/cyclosome (APC/C) ubiquitin ligase is activated and specifies the destruction of securin, which brings about the activation of separin and the separation of sister chromatids.

In addition to reviewing the securin–separin–cohesin circuit, Zachariae also describes two other important recent advances in our understanding of mitosis. Of all the transitions that control progression through the cell division program, the exit from mitosis has provided perhaps the greatest resistance to the elaboration of a specific molecular model. All of that has changed in the past year with the

realization that the protein phosphatase Cdc14 plays a key role in mobilizing two mitotic Cdk inactivation pathways, and that the activity of Cdc14 is abruptly switched on in late anaphase by a novel mechanism that involves its release from a storage depot within the nucleolus. A second key advance discussed by Zachariae concerns the spindle checkpoint, which monitors that status of the mitotic spindle and prevents progression through mitosis if the function of the mitotic spindle is compromised. Intriguingly, this checkpoint is comprised of two distinct pathways that control different aspects of the mitotic program. The 'classic' Mad2-dependent pathway restrains activation of the anaphase trigger, APC/C<sup>Cdc20</sup>, whereas the recently uncovered Bub2-dependent pathway regulates the activity of proteins that function as part of the mitotic exit network (MEN) that somehow participates in the mobilization of Cdc14 activity.

Once sister chromatids have been separated from each other and the mitotic Cdk has been shut off, the next task is to partition the segregated chromosomes into two distinct cells via cytokinesis. Hales *et al.* (pp 717–725) provide an excellent summary of the proteins involved in cytokinesis, the mechanism by which cytokinesis proceeds, and how cytokinesis is timed to occur at the appropriate stage of the cell division program. Recent work in fission yeast suggests that a conserved set of proteins, which includes the small GTPase Spg1 and the protein kinase Cdc7, specify the timely activation of cytokinesis at the end of mitosis. A particularly interesting aspect of the review by Hales *et al.* is that it draws together cytokinesis in plant and animal cells into a common mechanistic framework. Prior studies on cytokinesis in animal cells have emphasized the contraction of the actomyosin ring in the cleavage furrow, whereas studies in plants have emphasized localized secretion and the role of a microtubular structure known as the phragmoplast. Hales *et al.* discuss evidence that both cleavage furrow ingression and localized secretion operate in parallel, and argue that cytokinetic processes in plant and animal cells are fundamentally similar. Special attention is drawn to two interesting molecules — the effector molecule IQGAP and cdc15/PSTPIP — that may play a crucial and highly conserved role in co-ordinating actomyosin ring contraction and localized secretion.

Any discussion of the mechanisms of cell division would not be complete without a consideration of prokaryotes. After all, prokaryotes number  $5 \times 10^{30}$  and harbor about 50% of the fixed carbon on earth [2]. Although much is known about how chromosomes are replicated in *Escherichia coli*, little is known about how the replicated chromosomes are segregated to opposite ends of the cell, and how the cell subsequently divides in two. In both of these areas, however, considerable progress is now being made, and is described by Jensen and Shapiro (pp 726–731). One key advance has been the application of green fluorescent protein technology to the study of the dynamics of individual chromosomal loci in living cells. A

second key advance has been the realization that some of the proteins employed by bacteria to package their chromosomes (structural maintenance of chromosomes [SMC]-like proteins) have homologs in eukaryotic cells, and structures such as the centromere that were thought to be unique to eukaryotic cells appear to have functional counterparts in the prokaryotic chromosome. Thus, detailed analysis of chromosome packaging and segregation in simpler prokaryotic organisms may shed light on how these processes occur in more complex eukaryotic cells.

### Pathways that control the cell cycle

Layered on top of the basic oscillations of the cell cycle are regulatory mechanisms that allow cells to respond to their environments, and to ensure that conditions are appropriate for cell cycle progression. A central question in this area is the linkage between the signal transduction pathways downstream of growth factor receptors and the triggering of cell cycle entry and progression. The review by Marshall (pp 732–736) summarizes recent work in mammalian cells that indicates that multiple signaling pathways, involving (among others) Ras, other small GTPases and PI3-kinase, can act to induce the expression of G<sub>1</sub> cyclins and stimulate the degradation of the Cdk inhibitor (CKI) p27. The dual role of CKI as both inhibitor and assembly factor for G<sub>1</sub> cyclin/Cdk is also discussed by Marshall (see also [3]). These studies suggest that the commitment to cell cycle entry and progression follows from an integration of multiple inputs from diverse pathways, which allows for a high degree of regulation and fidelity of the process.

A related subject that has received considerable attention in recent years is the mechanisms by which cells monitor their contacts with the extracellular matrix and with other cells in the process of cell growth and division. Aplin, Howe and Juliano (pp 737–744) provide a comprehensive review of this important topic, in which they describe several mechanisms by which cell adhesion molecules can elicit signals and co-operate with other signaling pathways to ensure that cells are in appropriate contexts for cell cycle entry and progression. Here again, members of the small GTPase family are critical to the story, through the activation of various signal transduction cascades, as well as their involvement in the regulation of the actin cytoskeleton. The authors briefly review the role of integrins in cell cycle control (see also [4]) and discuss at length the issue of cell–cell interactions in regulating cell cycle activity. Aplin, Howe and Juliano (like Marshall) conclude that cross-talk and functional interaction among multiple pathways allow for the appropriate cellular response. Physical association of signaling complexes with the cytoskeleton contributes significantly to signal integration.

The subjects discussed above concern the issue of integrating signaling pathways with the cell cycle machinery to determine whether or not cells will initiate the cell division cycle. Over the past several years it has become clear that perturbations of this process can lead to an irreversible cellular

response, namely the induction of apoptosis. Gou and Hay (pp 745–752) review recent progress in this emerging area, including the regulatory pathways that link oncogenic activation (e.g. myc expression and loss of pRb function) to the induction of p53-dependent cell death. They also discuss possible roles for core cell cycle components Cdks and CKIs as regulators of apoptosis, which might constitute one mechanism by which proper execution of the cell cycle is monitored toward this end. Another mechanism is suggested by the association of survivin, a member of the IAP family of caspase (cell death protease) inhibitors, with spindle microtubules. These observations raise the interesting possibility that caspases may be activated (and properly regulated) in the course of the normal cell cycle.

### Conclusions

From the starting point of the increasingly vivid image of the basic cell cycle machinery, this section of *Current Opinion in Cell Biology* looks inward towards the co-ordination of critical cellular processes in cell division with the

cell cycle, and outward toward the regulation of the cell cycle by extrinsic factors. From this series of reviews, it is clear that these fields are moving forward at an impressive pace, and we look forward to the development of an integrated view of this essential process.

We would like to thank all of the authors who gave generously of their time to assemble interesting reviews that provide us with an excellent snapshot of their fields of expertise.

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