

## 'Key regulators of the cell cycle': 2001 Nobel Prize for Physiology or Medicine

During the last three decades, significant progress has been made in our understanding of the regulatory control of step-wise progression of cell-division cycle, that involves alternation between chromosome segregation (anaphase separation of chromosomes) and chromosome duplication (DNA synthesis). The importance of this work for human health care has been recognized by the award of the centenary Nobel Prize for Medicine or Physiology for the year 2001 to three scientists [Timothy (Tim) Hunt, FRS and Sir Paul Nurse, FRS of The Imperial Cancer Research Fund, London and Leland (Lee) Hartwell of the Fred Hutchinson Cancer Research Center, Seattle, USA]. Paul Nurse and Lee Hartwell were also among the seven recipients of the 1998 Albert Lasker Medical Research Award, which is considered as an indicator of a future Nobel Prize for Physiology or Medicine. This year's Nobel Prize-winning discoveries are particularly important in understanding how disturbances within a cell at the sub-cellular and molecular level may lead to the development of cancer cells (cells with uncontrolled cell-division). An excellent and a fairly up-to-date account of the regulation of cell-division cycle is available in the third edition of the book *Molecular Biology of the Cell*, published in 1994 (ref. 1). A brief summary of molecular basis of the regulation of cell-division cycle is also available in the author's book *Cytology, Genetics and Evolution*<sup>2</sup>, written for undergraduate students and a relatively more detailed account is available in the author's other two textbooks, *Genetics*<sup>3</sup> and *Cell and Molecular Biology*<sup>4</sup>, both written for honours and postgraduate students. Several reviews, some of them written by this year's Nobel Prize winners, are also available on the subject<sup>5-10</sup>.

Among the above three Nobel Laureates, Hartwell was responsible for the discovery of cell-division-cycle genes (designated *CDC* genes) in budding yeast (*Saccharomyces cerevisiae*)<sup>11-17</sup>, Nurse was responsible for the discovery of cell-division-cycle genes (designated *cdc* genes) in fission yeast (*Schizosac-*

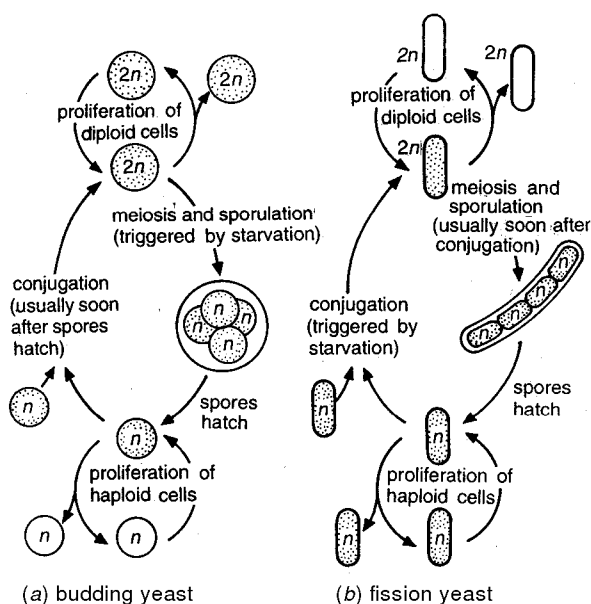
*charomyces pombe*)<sup>18-20</sup> and Hunt was responsible for the discovery of cyclins in sea urchin, frog and mammals<sup>21-23</sup>. The differences in the life cycles of the two yeasts used by Hartwell and Nurse for their studies are shown in Figure 1 and some of the cell-division-cycle genes encoding cyclin-dependent kinases (Cdks), and the cyclins discovered in the two yeasts are listed in Tables 1 and 2. Some of the genes for Cdk-molecules and cyclins can function as oncogenes and/or collaborate with the products of tumour-suppressor genes (e.g. p53 and Rb) during the cell cycle.

Hartwell also introduced the concept of 'checkpoints', a valuable aid to understanding the cell cycle<sup>24,25</sup>. It was also shown by Nurse that CDK drives the cell through the cell cycle, by reversible phosphorylation of a number of proteins (including Cdks themselves) that are involved in the regulation of cell cycle. Hunt also showed that cyclins bind to the Cdk molecules forming Cdk-cyclin complexes (CDKs), thereby not only regulating the Cdk activity, but also facilitating the selection of proteins

to be phosphorylated<sup>23</sup>. The discovery of cyclins, which was first made using sea urchin, *Arbacia*, as a model system, was the result of Hunt's finding that this protein was degraded periodically in the cell cycle, a feature that is used in the general control mechanism of the cell cycle<sup>21,22</sup>. Hunt later discovered cyclins in other organisms and also found that the cyclins were conserved during evolution. (Throughout this article, the symbol Cdk refers to a cyclin-dependent kinase and CDK refers to a Cdk-cyclin complex; symbols in italics refer to genes and the corresponding symbols in roman refer to proteins encoded by the corresponding genes.)

### Cell-division cycle, the central control system and the checkpoints

As we know, the cell-division cycle consists of the following phases: (i) mitosis (consisting of prophase, metaphase, anaphase and telophase); (ii) G1-phase (consisting of 'pre-start G1', 'start', and 'post start-G1' stages); (iii)



**Figure 1.** Life cycle of (a) budding yeast (*Saccharomyces cerevisiae*) and (b) fission yeast (*Schizosaccharomyces pombe*). Note that under supply of plentiful nutrients, budding yeast proliferates as diploid cells, while fission yeast proliferates as haploid cells. Some widely used strains of budding yeast also proliferate as haploid cells (redrawn and modified from ref. 1).

**Table 1.** Some cell-division-cycle genes and their functions in the two yeasts

Gene		Gene product	Phenotype of loss-of function mutant
Budding yeast	Fission yeast		
<i>CDC2</i>	<i>pol3</i>	Catalytic subunit of DNA pol $\delta$	Arrest in S-phase
<i>CDC9</i>	<i>cdc17</i>	DNA ligase	Arrest in G2 with imperfectly replicated DNA
<i>CDC28</i>	<i>cdc2</i>	Serine/threonine protein kinase	Arrest at start
<i>SWI6</i>	<i>cdc10</i>	Gene regulatory protein required for transcription of G1 cyclins	Failure to enter S-phase
<i>CLN1,2,3</i>	?	G1 cyclins	Arrest at start
<i>CLN1,2,3,4</i>	<i>cdc13</i>	Mitotic cyclins	Arrest at G2
<i>WEE1</i>	<i>wee1</i>	Tyrosine protein kinase	Premature passage past mitotic entry (G <sub>2</sub> ) checkpoint, hence small size
<i>MIH1</i>	<i>cdc25</i>	Tyrosine protein phosphatase	Arrest at mitotic entry (G <sub>2</sub> ) checkpoint
<i>RAD9</i>	?	Protein of unknown function	Failure to delay mitosis with damaged DNA
<i>DIS2 S1</i>	<i>dis2</i>	Protein of phosphatase I	Arrest in mitosis

**Table 2.** Cdks and their corresponding cyclins in budding yeast (*S. cerevisiae*)

Cdk	Cyclin	Cdk–cyclin function
CDC28	CLN1, CLN2, CLN3	START
	CLB5, CLB6	DNA replication
PHO85	PCL1	Needed for START in the absence of CLN1 and CLN2
	CLG1, PCL5, PCL9	Unknown
	PHO80	Regulates transcription factor PHO4p
	PCL6, PCL17	Unknown
	PCL8, PCL10	Glycogen synthase kinase
KIN28	CCL1	Transcription (CTD kinase)
SRB10	SRB11	Transcription (CTD kinase)
CTK1	CTK2	Transcription (CTD kinase)

S-phase (involving DNA synthesis step); and (iv) G<sub>2</sub>-phase (pre-mitotic and post-DNA synthesis resting phase); this G<sub>2</sub>-phase is absent in budding yeast (*S. cerevisiae*), but present in fission yeast (*S. pombe*) (Figure 2). As mentioned earlier, the success of a mitotic cell-division actually depends upon faithful alternation of chromosome segregation (the M-phase) and chromosome duplication (the S-phase). With the help of pioneering and singular discoveries of this year's Nobel Prize winners, it was shown that while the cell has its own machinery for the processes that are essential for completion of different phases of cell-division, there is also a central control system (independent of the machinery used for different processes involved in cell-division cycle) that is responsible for the regulation of the onset of these different phases in an orderly and regulated manner (Figure 3). This control system, for instance, ensures that the cell is not driven into mitosis before DNA synthesis is completed or damaged DNA is repaired, and

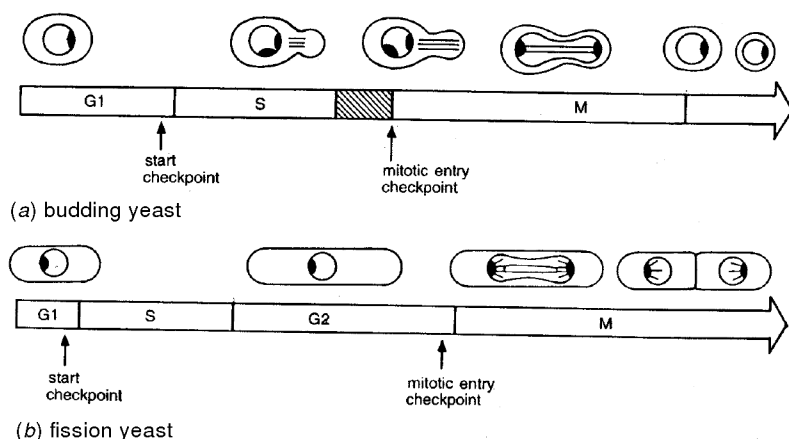
it is not driven into anaphase before all chromosomes are aligned on the equatorial plate and kinetochores of all chromosomes are attached to the spindle. The Nobel Prize-winning work involved discovery, isolation and characterization of a large number of genes and the corresponding important proteins involved in the regulation of this central control system that operates during the progress of the cell-division cycle.

The central control system, as above, involves the use of a surveillance mechanism that detects mistakes if any, in a particular phase of the cell-division cycle, and then induces inhibition of the corresponding key cell-cycle transition like G<sub>2</sub>-M and G<sub>1</sub>-S transitions (Figures 2 and 3). The Cdk and cyclins involved in G<sub>2</sub>/M and G<sub>1</sub>/S transitions in the two yeasts and also in the mammalian cells are listed in Table 3. These transitions have been described as checkpoints, suggesting the involvement of a position (border or transition) and a process (scrutiny) analogous to the road-blocks, where travellers are

stopped and scrutinized<sup>24–27</sup>. Only after orderly completion of the step preceding a transition, the inhibition is removed and the cell is allowed to enter the next phase of the cell-division cycle.

### Cyclin-dependent kinases and cyclins (cell cycle's engine)

Due to the seminal work of this year's three Nobel Laureates, which was supplemented and pursued by many other workers around the world, it is now known that the cell-division cycle in majority of eukaryotes is controlled by two major types of proteins: (i) cyclin-dependent kinases (Cdks) and (ii) cyclins (so called because their abundance varies during the cell cycle). These two classes of proteins have been shown to be conserved through evolution<sup>28</sup>. A beginning of the study of regulation of cell-division cycle was actually made, when in the year 1970–71, Y. Masui at the University of Toronto first identified in frog's eggs, a protein that was described as a maturation promoting factor (MPF), which is now also called M-phase promoting factor (MPF, active during the M-phase) as against S-phase promoting factor (SPF, active during the S-phase). Almost at the same time (early 1970s), Hartwell identified a number of cell-division cycle genes called *CDC* genes (including *CDC28* that was also called 'start' gene by Hartwell) in *S. cerevisiae*<sup>11–17</sup>, and Nurse identified a number of *cdc* genes (including *cdc2*) in *S. pombe*<sup>18–20</sup>. The cell-division-cycle genes, *CDC28* and *cdc2* were later found to be analogous to each other, both coding for the MPF



**Figure 2.** Comparison of the cell cycle of (a) budding yeast and (b) fission yeast. Note the absence of G2-phase in budding yeast. Unlike higher eukaryotes, the nuclear envelope does not break in either case (redrawn and modified from ref. 1).

**Table 3.** Cdks and cyclins involved in G2/M and G1/S transitions of cell cycle of yeast and the mammal

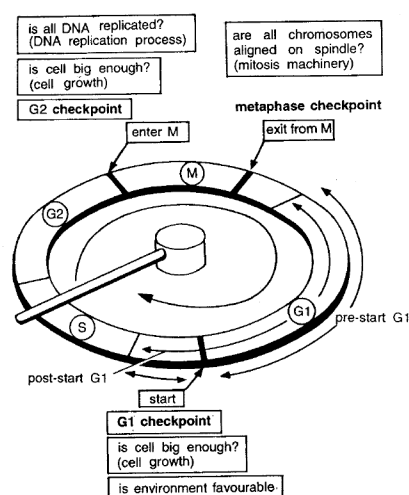
	G2/M-phase		G1/S-phase	
	Cdk	Cyclin	Cdk	Cyclin
<i>S. pombe</i> (fission yeast)	cdc2 (Cdk1)	cdc13 (A-like)	cdc2 (Cdk1)	cig1, cig2
<i>S. cerevisiae</i> (budding yeast)	CDC28 (Cdk1)	CLB1-4 (B like)	CDC28 (Cdk1)	CLN1-3
Mammal/frog	Cdc 2 (Cdk1)	A, B1, B2	Cdk2 (p33), Cdk4, Cdk6	A, D1, D2, D3, E

of *CDC/cdc* genes in both yeasts were later shown to encode Cdks (Cdk1–Cdk7). Of these, Cdk1 (identified by Nurse in 1987) corresponds to MPF in sea urchin and frog, to CDC28 in budding yeast and to *cdc2* (also described as p34<sup>cdc2</sup>) in fission yeast (Figure 4). In animal systems, more than one Cdk is involved, including Cdk1 and Cdk2 in animals and Cdk1, Cdk2, Cdk3, Cdk4 and Cdk6 in mammals. These Cdks can be classified into three groups (M-phase Cdks, S-phase Cdks and G1-phase Cdks). Similarly, the following three major types of cyclins are known (although ten different cyclins have been isolated from human cells and as many as more than 20 cyclins have been identified in yeasts): (i) mitotic cyclins, found during M-phase are called cyclin B (*cdc13* in fission yeast and CLB1–6 in budding yeast); (ii) S-phase cyclins, found during S-phase are called cyclin A; and (iii) G1-cyclins, found during G1-phase are called cyclins C, D, E and F in vertebrates (called *cig1* and *cig2* in fission yeast; CLN1, CLN2 and CLN3 in budding yeast).

Both in budding yeast and fission yeast, S- and M-phases are induced by a solitary Cdk1 which is associated with different B-type cyclins one at a time and giving rise to MPF specific for M-phase, and SPF specific for S-phase. In animal cells, however, at least two different Cdk proteins are needed, one for each of the two major checkpoints, called G1 and G2 checkpoints. Cdk2 complexed with S-phase cyclins (E or A types) induces S-phase, which follows G1 checkpoint and Cdk1 complexed with M-phase cyclins (A and B types) induces M-phase, which follows G2 checkpoint. In mammals, there are additional kinases like Cdk4 and Cdk6 that are specialized for some other transitions, e.g. transition from G0 (G zero) to G1 (Figure 6).

### *Cdks and cyclins in budding yeast and fission yeast*

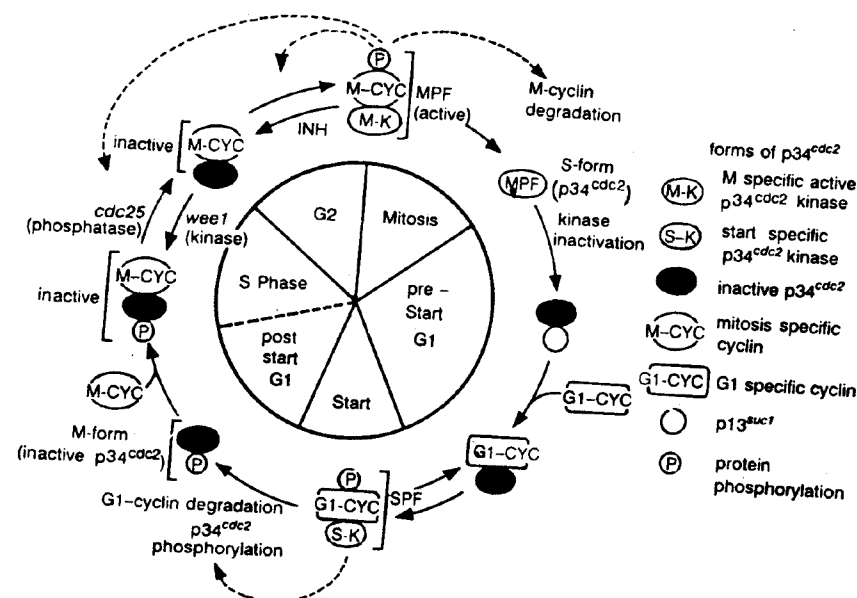
The Cdks and cyclins of the two yeasts involved in G2/M and G1/S transitions are listed in Table 1, but only those for fission yeast will be briefly described here. In fission yeast, a single Cdk (Cdk1) encoded by *cdc2* (its corresponding gene in budding yeast is *CDC28*) and three cyclins encoded by



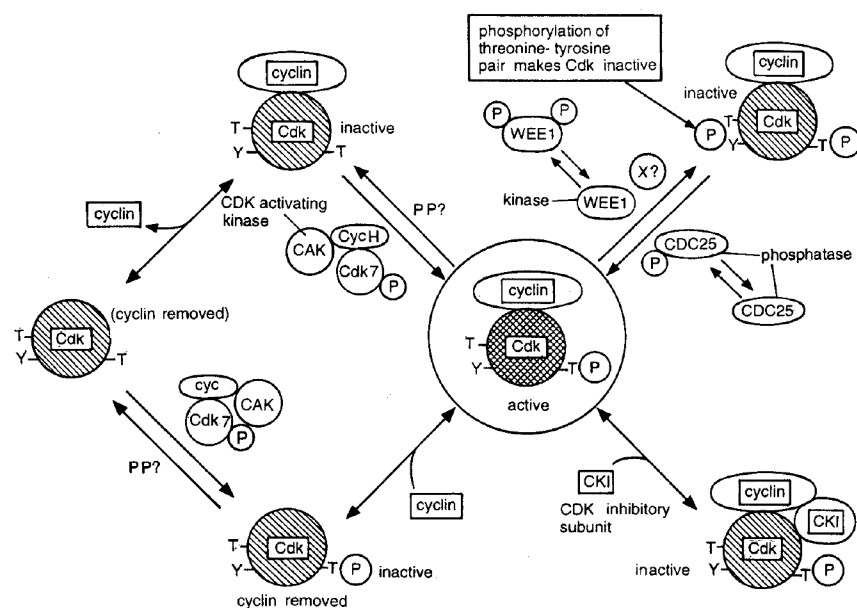
**Figure 3.** Checkpoint and input of regulatory information of the cell-cycle control system. Prominent checkpoints are highlighted, but other checkpoints are also found as discussed in the text (redrawn and modified from ref. 1).

isolated the human analogue of *CDC28/cdc2*, which became known as Cdk1 (cyclin-dependent kinase 1). Cyclins were later discovered for the first time in the sea urchin, *Arbacia*, by Hunt. Subsequently, it was shown that a CDK associates with a specific cyclin to form a Cdk–cyclin complex (CDK), which has been described as the cell cycle's engine, in view of its pre-eminent role in regulation of cell-division cycle. The Cdk subunit of this CDK complex is inactive as a protein kinase without the cyclin subunit, which confers basal kinase activity on Cdk (Figure 4). Nurse also observed that activation and inactivation of Cdk are dependent on reversible phosphorylation<sup>22</sup>. The crystal structures of human cyclin A and Cdk–cyclin A complex were also published in the year 1995 (refs 29 and 30). It was shown that both Cdk and cyclin have one or more amino acid residues (threonine or tyrosine), which can be phosphorylated and dephosphorylated (reversible phosphorylation) at different stages of the cell-division cycle (Figure 5). A number

(now known to be the proteins, *CDC28* or *cdc2*) that was identified earlier by Masui in Toronto. In 1987, Nurse also



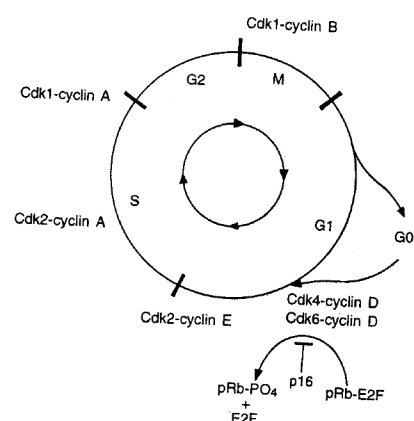
**Figure 4.** Model of the cycle of *cdc2* gene product ( $p34^{cdc2}$ ) during the cell cycle in fission yeast. Note that  $p34^{cdc2}$  molecule lacks kinase activity during most of the cell cycle, but becomes active as MPF at mitosis and SPF at start as a result of association with M cyclins and G1 cyclins, respectively. Active forms can also stimulate their own activation and/or inactivation ( $\rightarrow$ ). (redrawn and modified from ref. 43).



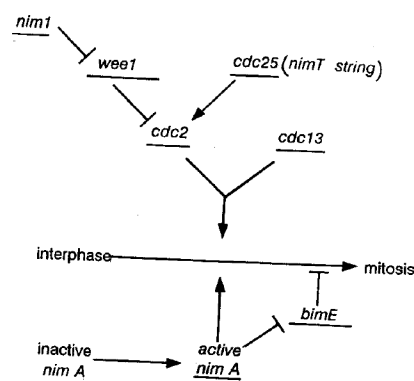
**Figure 5.** Different stimulatory and inhibitory steps ( $\rightarrow$ ) involving reversible phosphorylation of Cdk-cyclin (CDK) complexes (redrawn and modified from ref. 44).

*cdc13*, *cig1* and *cig2* are now known to control cell-cycle progression (in budding yeast as many as 22 cyclins are known; nine of them involved in activation of CDC28). At the time of onset of mitosis (G2/M transition), cyclin *cdc13*, which is also called cyclin A (and to a

minor extent also *cig1* protein) activates Cdk1 or *cdc2* protein (also described as  $p34^{cdc2}$ , in view of its molecular weight being 34 kDa); later after completion of mitosis, degradation of *cdc13* leads to inactivation of *cdc2* (Figure 4). Although *cig1* might make a minor contri-



**Figure 6.** Outline of cell cycle in a mammalian cell showing the role of a number of Cdks (A, B, D, E) in the form of Cdk-cyclin complex, which facilitates passage through different phases of the cell cycle (from ref. 4, with permission).



**Figure 7.** Model for induction of mitosis in fission yeast. Gene products are shown as stimulating ( $\rightarrow$ ) or inhibiting ( $\leftarrow$ ) the activity of other gene products. The *cdc2* and *cdc13* gene products are shown acting in concert to induce mitosis (redrawn and modified from ref. 45).

bution to activation of *cdc2*, it is not essential for onset of mitosis.

The coordinated activity of genes *cdc2* (encoding Cdk1) and *cdc13* (encoding cyclin A) is regulated by two additional genes, which act antagonistically to control and regulate the entry of cell into mitosis. The gene *cdc25* stimulates, and the gene *wee1* inhibits entry into mitosis through their effect on  $p34^{cdc2}$  (product of gene *cdc2*). Another gene *nim1* exercises a negative control on *wee1* (Figure 7). Both *wee1* and *nim1* encode kinases for phosphorylation and *cdc25* encodes for a phosphatase for dephosphorylation of a tyrosine residue (tyr-15) of  $p34^{cdc2}$  (see later for reversible phosphorylation).

Therefore, these genes act by reversible phosphorylation during the cell cycle. The molecular events that regulate cell-division cycle of fission yeast are depicted diagrammatically in Figure 4.

### *Cdks and cyclins in mammalian cells*

In contrast to yeasts, where a single Cdk is known to control the cell-cycle progression, in mammalian cells, at least two and under special situations (e.g. cell growth) more than two Cdks are used. Cdk1 (*cdc2* protein) complexed with cyclin B is used for passage through mitosis or M-phase and Cdk2 complexed with cyclin A is needed to activate the DNA replication machinery. Cdk4 and Cdk6 complexed with cyclin D are involved in cell growth (particularly after exit from a quiescent or G0-phase; Figure 4). The activation of Cdk1–cyclin B complex also needs phosphatase *cdc25* in late G2, to bring about dephosphorylation needed for activation of Cdk1. Further, the Cdk2–cyclin A complex needs to be phosphorylated at threonine-160, for full activation.

There are other non-cyclin proteins that play a major role in cell-cycle regulation in the mammalian cells. For instance, p53 (product of a tumour-suppression gene) is a strong activator of transcription and responds to DNA damage or to conditions unfavourable for DNA replication. Actually, p53 activates a number of genes, including the gene *p21* encoding a Cdk–cyclin inhibitor, thus arresting the progression of cell cycle and giving time for repair of DNA damage (Figure 8).

### *Cdk activators (Cak) and inhibitors (CKI)*

It is obvious from the above discussion that tyrosine and threonine kinase activities are vital for the progression of cell-division cycle. Activators and inhibitors of kinase activity are also available within the cell, to regulate the activity of Cdks. A protein responsible for activating threonine phosphorylation in Cdk1 is called Cdk-activating kinase (Cak), which is itself a Cdk and has been identified in higher organisms. Cak is actually Cdk7 or MO15 (Cdk7 is

a Ddk, Dbf4-dependent kinase; see later), which associates with cyclin H to bring about threonine phosphorylation. This Cak is also a component of transcription factor, TFIIF, which brings about phosphorylation of C-terminal repeat domain (CTD) of the larger subunit of RNA polymerase II (RNAPII), so that Cdk7–cyclinH complex has been shown to have a role, both in cell-division progression and transcription initiation.

There are also a number of Cdk inhibitors described as cyclin-dependent kinase inhibitors or CKIs (e.g. Sic1, Far1, Rum1, p15, p16, p18, p19, p21, p27, p57) which respond to signals induced by growth inhibitors like TGF- $\beta$ . For instance, p21 is a universal Cdk inhibitor and binds with Cdk2, Cdk4 and Cdk6, suggesting that it inhibits progression through all stages of G1/S.

### *Reversible phosphorylation of CDKs and Caks*

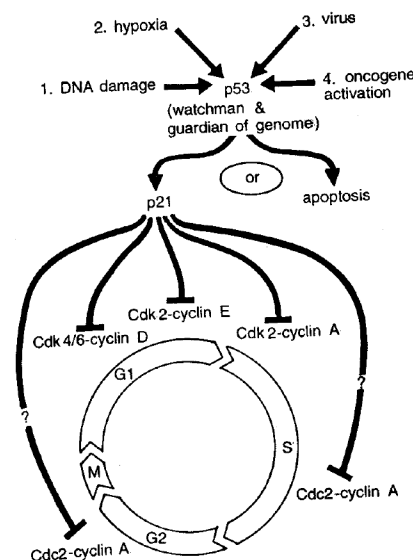
During the cell-division cycle, activation of CDKs (Cdk–cyclin complexes) is regulated by reversible phosphorylation due to kinase and phosphatase activities of certain proteins (Figure 5). For instance in fission yeast, activities of gene *cdc2* encoding Cdk1 and gene *cdc13* encoding a cyclin are regulated

by three other genes, two genes (*nim1* and *wee1*) encoding kinases and one gene (*cdc25*) encoding a phosphatase. Cdk phosphorylation at tyr-15 (with the help of Cak that is called Cdk7) renders it inactive, while phosphorylation at thr-167 and concomitant dephosphorylation (due to *cdc25*) at tyr-15 renders it active, which leads to induction of mitosis. In the next cell-division cycle, dephosphorylation of thr-167 and phosphorylation at tyr-15 of Cdk1 (p34<sup>cdc2</sup>) is similarly needed for G1/S transition for entry into S-phase (Figures 4 and 5). Similar reversible phosphorylation occurs in budding yeast and mammalian cells also, and is often also associated with protein (cyclin) degradation for successful and orderly execution of the cell-division cycle (see later).

### **DNA damage and DNA replication checkpoints in the S-phase of cell cycle**

During the cell-division cycle there is a G2/M checkpoint, so that cells with damaged or incompletely replicated DNA do not enter mitosis due to cell-cycle arrest at G2/M transition. Consequently, DNA damage and DNA replication checkpoint mutant cells (described as *cut*<sup>−</sup> mutants) do not wait for completion of DNA repair/replication and enter mitosis with damaged DNA or incompletely replicated DNA. In a number of recent studies, Hartwell examined the impact of irradiation on the yeast cells, and found that cells in which the DNA had been damaged by radiation underwent cell-cycle arrest, permitting time for the cell to repair the damage before undergoing replication<sup>31–33</sup>. This was described as DNA damage checkpoint and requires a number of genes, including *RAD9*, *RAD17*, *RAD24*, *MEC3*, *MEC1*, *RAD53*, *DUN1*, *PDS1*, *SFP1* in budding yeast and *rad3*, *rad9*, *rad17*, *rad26*, *hus1*, *wee1* and *chk1* in fission yeast<sup>34–36</sup>. Mutations in the checkpoint genes enable late events to occur even if the DNA damage has not been repaired, a mechanism implicated in the development of many cancers.

It has also been recognized that perhaps DNA damage and unreplicated DNA might have separate checkpoints during the cell cycle and that DNA replication checkpoint is independent of



**Figure 8.** Model showing the roles of p53 and p21 in regulating the different phases of cell cycle in a mammalian cell (from ref. 4, with permission).

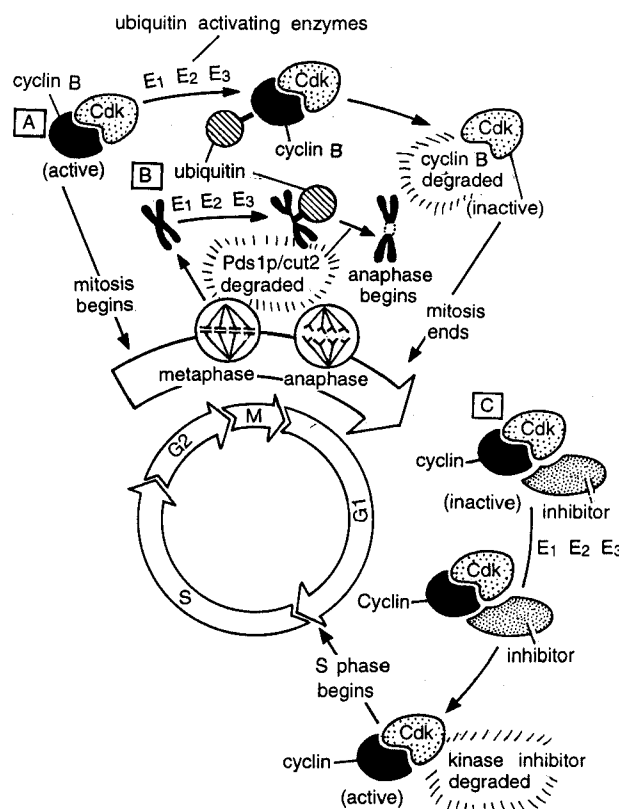
DNA damage checkpoint. DNA replication during S-phase of cell cycle actually involves nucleation of MCM proteins (MCM1–MCM7) to the chromatin, which is facilitated by the protein CDC6/cdc18 and the origin recognition complex (ORC) assembled at the site of initiation of DNA replication. The nucleation of MCM proteins provides a licence for the initiation of DNA replication (licensing concept) and with the help of other key regulators of the cell cycle (e.g. CDC28–CLB in budding yeast and *cdc2–cdc13* in fission yeast), these proteins also ensure that during one cycle of cell-division, the DNA replication occurs only once. Although DNA replication checkpoint is not as well-understood as the DNA damage checkpoint, some genes for this checkpoint have been identified, which include genes encoding for the proteins CDC6 and MCM2–7 and the components of ORC in fission yeast and those encoding for *sum3*, *chk1* and the two 14–3–3 proteins (*rad24*, *rad25*) in budding yeast. It has also been shown that the assembly of pre-replicative complex (pre-RC) and initiation of DNA replication are regulated independent of each other<sup>37</sup>. Earlier Nurse had also identified another protein gene, *rum1*, encoding protein *rum1*, such that an overexpression of *rum1* leads to multiple rounds of replication and the absence of *rum1* leads to two successive mitoses, without intervening pre-start G1-phase<sup>38</sup>.

### Protein degradation (proteolysis) and regulation of cell-division cycle

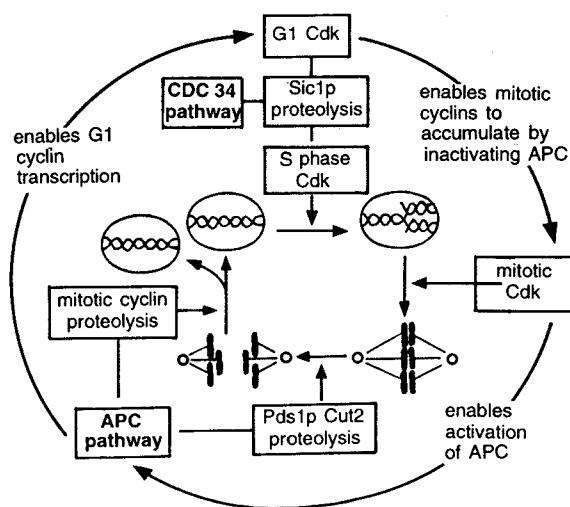
In the initial period of cell-cycle research, it was felt that it is the synthesis of a number of cell-cycle proteins, including Cdks, cyclins and some other proteins, which is responsible for the regulation of the cell cycle. However, later it was shown that the periodic protein degradation is also a characteristic feature of most cyclins and some other proteins involved in the regulation of cell-division cycle, so that protein degradation is also now known to play an important role in regulation of several cell-cycle pathways<sup>39,40</sup> (Figures 9 and 10). This proteolysis is facilitated by the protein ubiquitin (activated by three enzymes E1, E2 and E3; E2 is encoded

by *CDC34*), which forms a 26S proteasome with the target proteins to be degraded. The following proteins are degraded at three different checkpoints: (i) cyclins (M-cyclins degraded at the end of mitosis and G1-cyclins degraded during post start-G1), (ii) Cdk inhibitors like *Sic1p* in yeast and *p27* in humans, degraded for initiation of S-

phase, and (iii) PDS1p in budding yeast and *cut2* in fission yeast (these proteins are cohesins and keep the sister chromatids of chromosomes together), degraded for crossing metaphase–anaphase transition (promoted by cyclosome or anaphase promoting complex (APC)). It has also been shown that in mutants where the above essential pro-



**Figure 9.** Ubiquitination of cell-cycle proteins with the help of three enzymes (E<sub>1</sub>, E<sub>2</sub>, E<sub>3</sub>), as a pre-requisite for degradation (from ref. 4, with permission).



**Figure 10.** Two proteolytic pathways (CDC34 pathway and APC pathway) which regulate progression of cell cycle through interaction with CDKs (from ref. 4, with permission).

teolysis fails to occur, uncontrolled cell-division and cancer may occur. Therefore proteolysis in the cell cycle has opened a new area of research, which will provide a means for developing additional therapies for cancer patients in the future.

### Cell-division cycle and cancer

It is now fairly well established that disturbances in finely balanced systems regulating the cell cycle may lead to chromosomal instability that develops in cancer cells. In fact, some of the genes encoding components of the key regulators of the cell cycle have already been shown to be oncogenes and some others are also known to be oncogene candidates<sup>41</sup>. Further, the products of some of the Cdk and cyclin genes can interact with the products of tumour-suppressor genes such as p53, which in its mutant form is responsible for more than 50% of human cancers. Intrinsic defects in the key regulators of cell-division cycle may also cause cancer. For instance, cyclin D1 (shown to be product of an oncogene) is overexpressed in most breast cancers, and mice designed to lack D1 have recently been shown to be completely resistant to breast cancers induced due to *neu* and *ras* oncogenes<sup>42</sup>. Similarly, cyclin E, cyclin A and Cdk4 were found to be overexpressed in cancer cell lines. Loss of activity of some genes encoding cell-cycle inhibitors like p53 (described as the 'guardian of the genome' or 'watchman') and *Rb* (retinoblastoma) may also lead to cancer. All these and other similar cell cycle genes will be the targets for cancer therapy in future. Therefore the discovery of the key regulators of the cell-cycle has opened new avenues of research in the field of tumour diagnostics and cancer therapy.

### Conclusions

This year (2001) happens to be the centennial year of the Nobel Prize, and the Nobel Prize for Physiology or Medicine has been awarded to three scientists (Timothy Hunt, Paul Nurse and Leland Hartwell) for their pioneering work involving discovery of key regulators of the cell-division cycle. The key regulators that were discovered by these No-

bel Laureates include (i) cyclin-dependent kinases or Cdks, discovered by Hartwell in budding yeast and by Nurse in the fission yeast, and (ii) the cyclins (so called because their abundance varies during the cell cycle) discovered for the first time in a sea urchin and later in other organisms by Timothy Hunt. It was also shown by Hunt that cyclins bind to Cdks to form Cdk-cyclin complexes (which we abbreviate as CDKs), that regulate the different checkpoints during the cell cycle, a concept initially put forward by Hartwell. Different checkpoints and the genes regulating these checkpoints have been identified in the two yeasts and a number of other eukaryotes, including mammals. These genes regulate G2/M transition, metaphase/anaphase transition, G1/S transition, DNA damage and DNA replication checkpoints, etc. and do not allow the cell cycle to proceed to the next stage till the preceding stage is completed. For instance, due to these key regulators monitoring the cell-division cycle, the cell is not allowed to enter mitosis till the DNA replication is complete and/or any damaged DNA is fully repaired, and it is not allowed to enter anaphase till all the chromosomes are aligned at the equatorial plate and their kinetochores are attached to the spindle microtubules. Many of these cell-division cycle genes (*CDC* genes in budding yeast and *cdc* genes in fission yeast) encode kinases or phosphatases (also their activators or inhibitors) that are involved in reversible phosphorylation, essential for their specific functions. The products of some of these genes, particularly the cyclins or the Cdk activators or inhibitors, also need to undergo proteolysis after their functions are over, which is also essential for the orderly progression of the cell cycle. Mutations in these genes lead to derangements in the cell cycle, sometimes leading to uncontrolled cell-division causing cancer, so that several of these genes and their products are the potential targets for cancer therapy.

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## First Indian Honorary Fellow of the Institute of Information Scientists

Subbiah Arunachalam of the M. S. Swaminathan Research Foundation has been elected an Honorary Fellow of the Institute of Information Scientists, UK, the highest in the three categories of membership that this apex professional body of information scientists has. The only other Asian who is currently an Honorary Fellow is Liu Zhaodong, President of the Chinese Society of Scientific and Technical Information, Beijing.

## Stockholm Challenge Award for M. S. Swaminathan Research Foundation

The Information Village Project of the M. S. Swaminathan Research Foundation, has won this year's Stockholm Challenge Award in the Global Village category. The citation reads as follows:

‘The Information Village Research Project is an outstanding embodiment of the spirit of the Stockholm Challenge to promote inclusion through the use of information and communication technologies. Today, thanks to the Information Village Project, ten villages near

Pondicherry, India, are linked with computers, providing information on such aspects as health, crops, weather, and fishing conditions. These new technology tools are bridging the economic and social divide between the haves and have nots. They are empowering everyone with knowledge and opportunity by an inclusive use of local languages and a multimedia format that allows all to participate. Because of this project, some traditional barriers have fallen. For example, a temple that formerly excluded low-caste people now opens its doors to everyone, so they may use computers. This project is a wonderful example of the benefits of IT, and of the power of information and opportunity’.

## Prof Y. T. Thathachari Research Award for science – 2001: A report

The Bhramara Trust of Y. T. and Madhuri Thathachari, Mysore, set up in the year 1994, is dedicated to promote education, provide relief to the poor, medical aid to the sick, encourage research in science, Sanskrit studies and innovation in fine arts and in creative writing. In January 2001, the Board of Trustees decided to encourage pioneering research in science by instituting a national award in memory of Y. T. Thathachari. Thathachari worked at MIT, Stanford University and the University of California Medical Centre, San Francisco, USA. He was a visiting professor at the Indian Institute of Science (IISc), Bangalore, and the Indian

Institute of Technology (IIT), Chennai. His research field was wide and varied, encompassing crystallography, X-ray diffraction, electron microscopy, XAFS studies, Kirlian photography, new imaging techniques, medical information science and studies on language and information. This brilliant scientist, who was diagnosed for cancer in 1963, conquered it and lived for thirty years. He passed away in November 1993 at the age of sixty-three.

Y. T. Thathachari Research Award for Science is a biennial award. It is given to researchers from physical/chemical/mathematical science and life/agricultural science alternately. The

award carries a cash prize of rupees one lakh and a citation. The award money is given to the host institution to be used by the awardee for his/her research work. The award aims to encourage high quality research in the country by insisting that a major portion of the work should have been carried out in India.

The winners of the award for 2001 are S. V. Bhat from the Department of Physics, IISc, Bangalore, and R. S. Sirohi, IIT, Delhi.

S. V. Bhat is an experimental physicist making significant contributions in the field of nuclear magnetic resonance (NMR) and electron spin resonance. His