Control of the cell cycle progression

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1. Introduction

Cell division is the most fundamental process for all living organisms. Progress of the cell cycle is subjected to certain conditions. In order to proliferate the cell must replicate all its DNA which must be followed by a round of mitosis, whereby a complete set of chromosomes gets into each daughter cell. The cell cycle is a set of steps that make possible the correct completion of these processes.

The cell cycle normally consists of four phases, of which the most important are the S phase when DNA replication occurs and the M phase when chromosomes are segregated into the daughter cells. In the majority of somatic cells S and M phases are separated by 'gap' phases: the G1 phase when the cell can grow and prepare for DNA replication, and the G2 phase when the cell can prepare for the next mitosis. There are several checkpoint controls that coordinate subsequent cell cycle events in space and time. They can brake the cell cycle in response to some irregularities in the progress of particular phases of the cycle. In this review I want to present a brief and general approach to this biochemical regulatory network controlling progress through the cell cycle in eucaryotes.

2. CDK family

It is well established now that a family of protein kinases termed cyclin — dependent kinases (CDKs) are key regulators of the cell cycle (1). The first discovered vertebrate CDK, p34cdc2 (CDK1) was shown to be a catalitic subunit of maturation promoting factor (MPF), the key component of mitotic regulatory mechanism (2,3).

The CDKs are serine/threonine kinases ranging from 30 to 40 kDa and closely related in sequence (4-7). In yeasts there are only few CDKs (CDC28

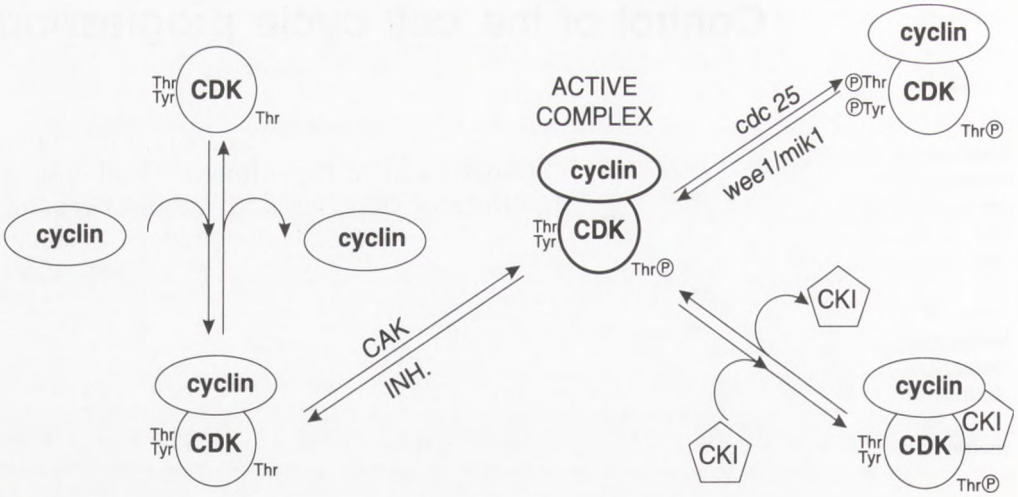

Fig.1. Regulation of CDK activity. Active complex is shown in the center: CDK is complexed with cyclin and phosphorylated at 'activatory' Thr residue. See text for details.

in *Saccharomyces cerevisiae* or CDC2 in *Schizosaccharomyces pombe*) while vertebrates' CDKs are a family of at least seven proteins. CDK are active only in complexes with a cyclin regulatory subunit. While CDKs are closely related, the cyclins are a diverse family. They are defined now as proteins that bind and activate CDKs, and whose levels oscilate during the cell cycle (1,8).

There are several mechanisms that regulate the activity of CDK/cyclin complexes (Fig. 1).

2.1. Role of cyclins

Cyclins are the primary regulators of CDK activity. Binding the cyclin is necessary for activation of CDK and it is obvious that removing this regulatory subunit from CDK/cyclin complex inactivates kinase. Cyclins can also modulate substrate specifity of CDK/cyclin complexes (9). In yeasts, single kinase interacts with different cyclin subunits depending on the stage of the cell cycle (10,11). In higher eucaryotes CDK/cyclin interactions are more complex, as there are several CDKs and they can make active complexes with stage-specific subset of cyclins (8,12,13). Cyclin function is controlled by changes in cyclin protein levels. These oscillations are produced both by regulation of the transcription, and by the specific degradation of cyclin protein (12,14-16). As the CDKs are absolutely dependent on binding a cyclin for their activity, oscillations in cyclin levels at different stages of the cell cycle can obviously regulate the activity of corresponding CDKs.

2.2. Role of phosphorylation

Complete CDK activation requires also phosphorylation at a conserved threonine residue (Thr161 in CDC2, Thr160 in CDK2) (17). This Thr161/160 residue in CDC2/CDK2 is phosphorylated by CAK (CDK — Activating Kinase). Lately it has been found that CAK is a complex of CDK — related p40MO15 catalytic subunit and cyclin regulatory subunit. (7,18,19). There is a evidence that CAK activation may require phosphorylation at Thr 170 or 176 (20). MO15 has been counted among the CDKs family as a CDK7. A protein phosphatase of the type 2A can dephosphorylate CDC2 at Thr161/160 residue (21). This phosphatase is called Inhibitor (INH) and has been proposed to be the antagonist of CAK activity.

Phosphorylation of specific residues in CDKs can activate but also inhibit the activity of CDK/cyclin complexes. There are two well known sites in CDC2 and CDK2 kinases — Tyr15 and Thr14, placed in ATP binding site (22,23). Phosphorylation at these sites can inhibit the activity of CDK/cyclin complex despite the phosphorylation of activatory Thr161/160 residue. Phosphorylation of Tyr/Thr inhibitory residues is due to the activity of Wee1 protein kinase (24,25), though there is some evidence that other kinases can play a role in this process (8,12). The activity of Wee1 is negatively regulated by Nim 1 kinase (26). Tyr15 and Thr14 are both dephosphorylated by a CDC25 phosphatase, whose activity is cell cycle — dependent (27,28).

2.3. Role of inhibitors

Recently, several proteins have been identified as the CDK inhibitors (CKIs). Among CKIs identified in vertebrates one can find p21, p27, p15 and p16. P21 can inhibit the activity of CDC2, CDK2 and CDK4 and it can also interact with DNA polymerase subunit, inhibiting DNA replication (36). P27 is structurally related to p21 and it preferentially inhibits CDK2/cyclin E complexes (29). P15 and p16 are closely related and they inhibit CDK6 and CDK4 (1,30,31).

3. Control of the cell cycle

Some external signals the control entry into the cell cycle or exit from it toward terminal differentiation. If the cells enter cell cycle they must ensure they finish DNA replication and repair, and chromosome segregation. There are multiple checkpoint controls assuring that this occurs in the correct order. They respond to signals generated within the cell and can detect the failure of complete DNA replication, repair or spindle assembly. Checkpoint mechanisms may cause the cell cycle arrest to allow the cell to finish all events that should occur in subsequent phases of the cell cycle (Fig. 2). In this part of the review I want to give a brief introduction into the regulation of the cell cycle progression.

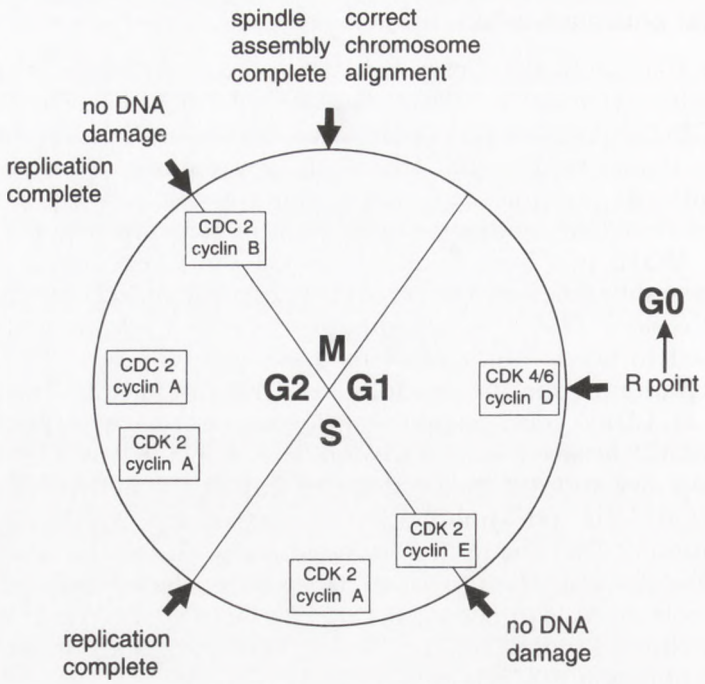

Fig. 2. Cell cycle checkpoint controls and the main cell cycle regulators — schematic view.

3.1. G1/G0 transition at the START/Restriction point and G1 phase progression

G1 phase comes after mitosis. It is the time for a cell to grow and prepare for DNA replication before the next mitosis. It is also the time for the decision whether a cell is to divide or to enter the quiescent state (G0) which is the first step for cell to differentiate. This decision occurs about mid — G1 and is known as a START in yeasts or Restriction point in mammalian cells (32,33). Progression through this checkpoint is highly dependent on the presence of extracellular growth factors, mitogen antagonists, differentiation inducers or inhibitors. In mammalian cells, progression through the G1 phase is monitored by a CDKs complexed with D- and E-types of cyclins. D-type cyclins are key regulators of G1 progression and they bind to CDK4 and CDK6. Their protein level is regulated by the rate of transcription, depending on the presence of growth factors (34). Destruction of D-type cyclins after mitogens removal results in the failure to enter the S phase. D-type cyclins synthesis begins during G0/G1 transition, but associated CDK activity occurs late in G1 and increases as the cell approaches the G1/S point (12,35). Unlike the D-type cyclins, cyclin E is synthesized periodically in late G1 and it binds to CDK2. The CDK2/cyclin E complex reaches its

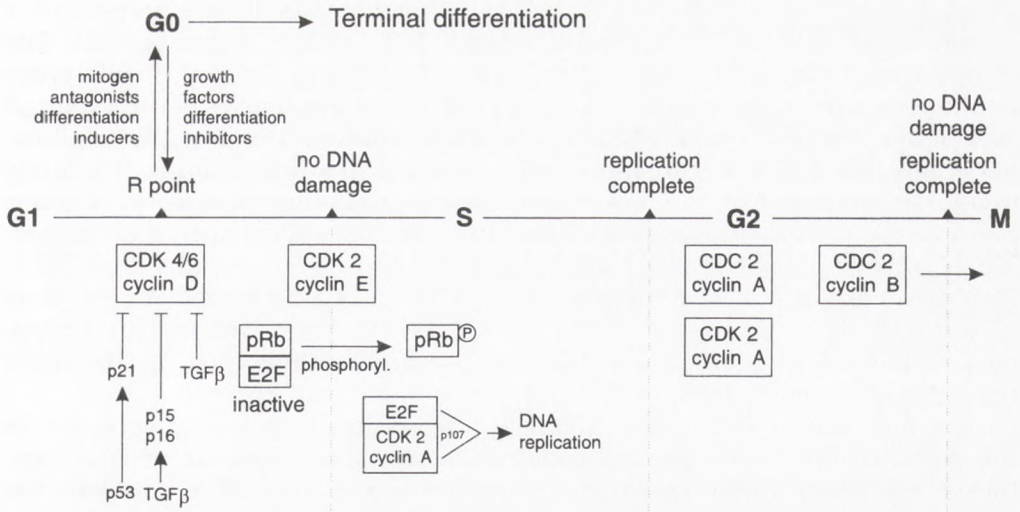

Fig. 3. Schematic view of the controls monitoring G1 to G2 phase progression.

maximum activity at G1/S transition and is probably essential for cells to enter the S phase.

As the cell undergoes G1 phase to prepare for DNA replication, the mechanism controlling the G1 progression is thought to be responsive to DNA damage present in the cell. P21 is a universal CDK inhibitor, whose expression is regulated by the tumor suppressor factor, p53 (36). DNA damage increases the level of p53 in the cell, resulting in the increase of p21 synthesis (37,38). P21 may directly block DNA replication by interacting with PCNA (proliferating-cell nuclear antigen), an essential DNA replication protein. However, P21 does not block DNA damage responsive repair, mediated by PCNA (39). This ability of p21 does not allow the cell to pass G1/S transition until the DNA damage is repaired. If the damage is too severe to be repaired, the cells undergo apoptosis, which is also connected with the presence of p53 in the cell (38,40). Transforming growth factor β (TGFβ also blocks cells in late G1 phase. This growth inhibitor can act directly by inhibiting the expression of CDK4, or indirectly by promoting the expression of CKIs, p15 and p16 (41). TGFβ blocks the cell cycle prior to the phosphorylation of retinoblastoma protein (pRb) which is necessary for the entry into S phase (38,42) (Fig. 3).

3.2. G1/S transition and S phase progression

In mammalian cells the activity of three CDK/cyclin complexes is required for the cell to pass G1/S boundary: CDK4/cyclin D, CDK6/cyclin D and CDK2/cyclin E. CDK2/cyclin E reaches its maximum activity at G1/S tran-

sition. Lately, it has been shown that TGFβ mediated cell cycle arrest in G1 is correlated with CDK2/cyclin E activity (43), which suggests that this complex may play a role in the initiation of S phase. Once the cells enter S phase, cyclin E is degraded and CDK2 forms complexes with cyclin A (38). CDK4/cyclin D and CDK6/cyclin D complexes are thought to phosphorylate pRb at G1/S transition. In its hypophosphorylated form pRb binds to and suppresses E2F, a transcription factor promoting expression of genes required for DNA synthesis (44). This situation takes place during G1 phase. When pRb is phosphorylated at G1/S transition, it dissociates from E2F. E2F then can form a new complex with p107 and CDK2/cyclin A (45), thus allowing the DNA synthesis replication (33,44,71). The CDK2/cyclin A complex remains active throughout the S phase and is thought to be the main regulator of S phase progression (Fig. 3).

The mechanism controlling S phase progression is probably sensitive to the presence of some transcriptional regulators or components of DNA synthesis machinery. Disappearance of these complexes or factors could be the first signal for the cell to enter G2 phase (46). The mechanism monitoring S phase is also sensitive to DNA damage; if there is any DNA damaged in the cell, S phase can be prolonged or even arrested until DNA damage is repaired.

3.3. S/G2 transition and G2 phase progression

When the DNA replication is completed, cells enter G2 phase, which is the time to prepare for division. The mechanism monitoring S/G2 transition is responsive to signals showing that DNA synthesis is completed and that there is no DNA damage in the cell. Passage through the S/G2 checkpoint is connected with changes of CDK/cyclin complexes. The CDK2/cyclin A activity does not disappear as the cells enter G2 phase, but cyclin A also binds to another CDK, CDC2. During the G2 progression, CDC2/cyclin A complex is gradually replaced by CDC2/cyclin B complex (Fig. 3). This complex remains inactive however, until the cells are ready to enter mitosis. The main regulators of G2 phase are CDK2/cyclin A and CDC2/cyclin A complexes, which play an important role in reorganizing cells for their mitotic stage. The presence of these complexes may be also a part of the mechanism monitoring completion of DNA synthesis (12,14,47).

3.4. G2/M transition and mitosis progression

The control of mitosis is one of the most conserved features of the cell cycle (Fig. 4). At this phase the primary CDK/cyclin complex is CDC2/cyclin B, well known as a maturation promoting factor (MPF) (2,3). During G2 phase progression, cyclin B accumulates above a threshold level defined as the point after which new cyclin synthesis is not required. In the same time CDC2 is phosphorylated at Thr161. Cyclin B binds to CDC2, but because of the 'inhibitory' phosphorylation of CDC2 at Tyr15/Thr14 residues, the complex remains inactive. Wee1 or the related Mik1 are the protein kinases

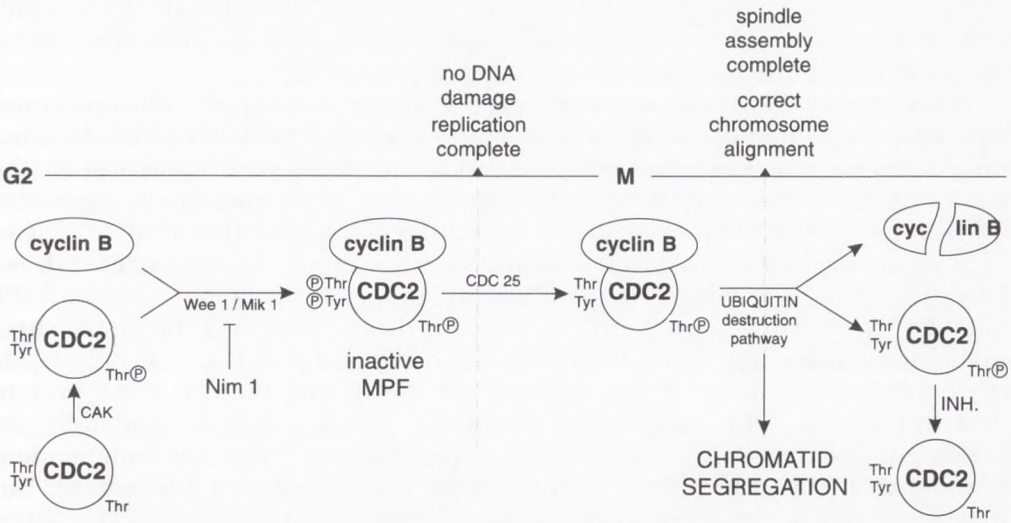

Fig. 4. Schematic view of the regulation of G2/M phase transition and mitosis progression.

which phosphorylate the 'inhibitory' sites in CDC2 (25). Nim1 kinase can phosphorylate and inhibit Wee1/Mik1, although there is some evidence that CDC2 and/or other kinases may play the same role as Nim1 (48-50). It is very important for the cell to have DNA duplicated before division, as the G2/M checkpoint controls are very sensitive to DNA synthesis and repair completion signals. Wee1/Mik1 is one of the key components of the mechanism monitoring G2/M transition. During the time Wee1/Mik1 is active, CDC2/cyclin B remains as an inactive complex, pre-MPF. The CDC25 phosphatase activates MPF by dephosphorylation of Tyr15/Thr14, allowing the cells to enter mitosis. However, if the DNA replication or repair is incomplete, Wee1/Mik1 activity remains high in the cell and CDC25 activation is impossible (25,51). There is also evidence that the exit from G2 phase is dependent not only on DNA damage repair, but also on the activity of topoisomerase II. This enzyme removes the catenations formed between sister chromatids during replication and it is needed for chromosome condensation (72).

Once activated, MPF initiates a cascade of events preparing the cells to undergo division. It can phosphorylate a lot of proteins, like nuclear lamins, H1 histones, microtubule associated proteins (MAP), proteins composing microtubule organisation center (MTOC) and many of protein kinases. MPF activity directly or indirectly causes nuclear envelope breakdown, chromosome condensation, mitotic spindle assembly and reorganization of the whole microtubule network from interphase into mitotic state (12,51-56). There is an internal mitotic checkpoint which controls the spindle assembly process. If the spindle is not formed correctly, cells remain arrested in M phase.

There has been shown that this mitotic checkpoint also monitors the completion alignment during metaphase. Single unattached chromosomes present in cells inhibit the transition into anaphase (73).

After the cytoskeleton is reorganized and the condensed chromosomes aligned on the metaphase plate, the cell is prepared to divide. The destruction of cyclin B is necessary for the exit from mitosis and progress to the next cell cycle. It is well established that cyclin B is specifically degraded by ubiquitin-dependent proteolysis and there is a evidence that MPF can activate this cyclin degradation system (57-59). Recent studies suggest, however, that sister chromatid separation at anaphase does not require MPF inactivation. Furthermore, both the cyclin B destruction and the sister chromatid separation depend on the activation of ubiquitin-dependent proteolytic system. The last process may depend on the destruction of some protein that binds sister chromatid together (60,61). Thus anaphase and MPF inactivation are mediated by the same mechanism, but are independent events. MPF inactivation is not required for the transition to anaphase, but it is necessary for the cell to complete cytokinesis and return to the interphase state (62).

4. Checkpoint controls in meiosis

In mammals, oocytes are blocked prior the M phase of meiosis until they reach proper size. This arrest may be regulated by some cell — size checkpoint inhibitory system (63). There is an opposite hypothesis, however, suggesting that the time for the initiation of growth rather than cell size may determine meiotic progression (64). It has been shown before that in oocytes undergoing meiotic maturation checkpoint monitoring DNA damage and replication is absent or attenuated. However, there is a checkpoint present during meiosis, which controls the chromatid separation and exit from metaphase I. It is possible that these checkpoint controls can recognize some early metaphase molecules and delay meiotic progression if these molecules are present in the oocyte (63).

5. Checkpoint controls in embryonic cell cycles

Early embryonic cells have fewer checkpoints than somatic cells (63). It is well known that inhibition of DNA synthesis blocks entry into mitosis in somatic cells. In *Xenopus* embryos such inhibition does not block the cell cycle progression up to the mid-blastula stage (65). Embryonic cells also do not react to the presence of damaged DNA, as they do in *Rana pipiens*, *Xenopus* and bovines (66,67). Also, the spindle checkpoint during the M phase does not exist in some types of embryonic cells. The early cell cycles of echinoderm embryos are delayed but not blocked by microtubule inhibitors (68). In *Xenopus* embryos during the first 12 cleavages, the cell cycle

is not blocked by microtubule depolymerization, though at mid-blastula stage spindle checkpoint appears in all cells (69,70). In contrast, mouse embryos seem to possess all the checkpoints from the first mitotic cell cycle. In my opinion, that situation may be correlated with the character of the cell cycles which occur during the early development. Simple embryonic cell cycles (such as the early *Xenopus* cleavages, for example) consist only of the S and M phase and they are to multiply cells in the developing embryo. Supposedly, this is why there is only few checkpoint controls during these cleavages. When the simple 'multiplying' cell cycles switch to the more complex somatic cell cycles (consisting of four phases instead of two), the checkpoint controls obviously appear, which may be the first sign of developmental determination.

Abbreviations

Abbreviations used in current text have been shown alphabetically:
CAK-CDK — activating kinase
CDK — cyclin dependent kinase
CKI — CDK inhibitor
INH — inhibitor
MAP — microtubule associated proteins
MPF — maturation promoting factor
MTOC — microtubule organization center
PC NA — proliferating-cell nuclear antigen
TGFβ — transforming growth factor β

Literature

1. Nigg E., (1995), BioEssays, 17, 6, 471-480.
2. Masui Y., Markert C. L., (1971), J. Exp. Zool., 2, 129-146.
3. Gauthier J., Norbury C., Lohka M., Nurse P., Maller J., (1988), Cell, 54, 433-439.
4. Lohka M. J., Hayes M. K., Maller J. L., (1988), Proc. Natl. Acad. Sci. USA, 85, 3009-3013.
5. Meyerson M., Enders G. H., Wu C. L., Su L. K., Gorka C., Nelson C., Harlow E., Tsai L. H., (1992), EMBO J., 11, 2909-2917.
6. Gabrielli B. G., Roy L. M., Gautier J., Philippe M., Maller J. L., (1992), J. Biol. Chem., 267, 3, 1969-1975.
7. Poon R. Y. C., Yamashita K., Adaczewski J., Hunt T., Shuttleworth J., (1993), EMBO J., 12, 3123-3132.
8. Morgan D. O., (1995), Nature, 374, 131-134.
9. Peeper D. S., et al., (1993), EMBO J., 13, 3772-3781.
10. Nasmyth K., (1993), Curr. Opin. Cell Biol., 5, 166-179.
11. Amon A., Tyers M., Futher B., Nasmyth K., (1993), Cell, 74, 993-1007.
12. Pines J., (1994), Cell Biol., 5, 399-408.
13. Sherr C. J., (1993), Cell, 73, 1059-1065.
14. Pines J., Hunter T., (1990), Nature, 346, 760-763.
15. Hunt T., Luca F. C., Ruderman J. V., (1992), J. Cell Biol., 116, 707-724.
16. Murray A., (1995), Cell, 81, 149-152.
17. Lorca T., Lebbe J.-C., Devault A., Fesquet D., Capony J.-P., Cavadore J.-P., Bouffant F., Doree M., (1992), EMBO J., 11, 2381-2390.
18. Fisher R. P., Morgan D. O., (1994), Cell, 78, 713-724.

19. Makela T. P., Tassan J. P., Nigg E., Frutiger S., Huges G. J., Weinberg R. A., (1994), Nature, 371, 254-257.
20. Poon R. Y. C., Yamashita K., Howell M., Ershler M. A., Belyavsky A., Hunt T., (1994), J. Cell Sci., 107, 2789-2799.
21. Krek W., Nigg E. A., (1991), EMBO J., 10, 3331-3341.
22. Norbury C., Blow J., Nurse P., (1991), EMBO J., 10, 3321-3329.
23. de Bondt H. L., Rosenblatt J., Jancarik J., Jones H. D., Morgan D. O., Kim S.-H., (1993), Nature, 363, 595-602.
24. Featherstone C., Russel P., (1991), Nature, 349, 808-811.
25. Lundgren K., Walworth N., Booher R., Dembski M., Dirschner M., Beach D., (1991), Cell, 64, 1111-1122.
26. Wu L., Russel P., (1993), Nature, 363, 738-741.
27. Kumagai A., Dunphy W. G., (1991), Cell, 64, 903-914.
28. Dunphy W. G., (1994), Trends Cell Biol., 4, 202-207.
29. Toyoshima H., Hunter T., (1994), Cell, 78, 67-74.
30. Serrano M., Hannon G. J., Beach D., (1993), Nature, 366, 704-707.
31. Hannon G. J., Beach D., (1994), Nature, 371, 257-261.
32. Hartwell L., Weinert T., (1989), Science, 246, 629-634.
33. Pardee A., (1989), Science, 246, 603-608.
34. Matsushime H., Rousel M. F., Ashmun R. A., Sherr C. J., (1991), Cell, 65, 701-713.
35. Matsushime H., Quelle D. E., Shurtleff S. A., Shibuya M., Sherr C. J., Kato J.-Y., (1994), Mol. Cell Biol., 14, 2066-2076.
36. Xiong Y., Hannon G. J., Zhang H., Casso D., Kobayashi R., Beach D., (1993), Nature, 366, 701-704.
37. El-Deiry W. S., Tokino T., Velculescu V. E., Levy D. B., Parsons R., Trent J. M., Lin D., Mercer E., Kinzler K. W., Vogelstein B., (1993), Cell, 75, 817-825.
38. Hunter T., (1993), Cell, 75, 839-841.
39. LI R., Waga S., Hannon G. J., Beach D., Stillman B., (1994), Nature, 371, 534-537.
40. King K. L., Cidlowski J. A., (1995), J. Cell. Biochem., 58, 175-180.
41. Alexandrow M. G., Moses H. L., (1995), Cancer Res., 55, 1452-1457.
42. Laiho M., de Caprio J. A., Ludlow J. W., Livingston D. M., Massague J., (1990), Cell, 62, 175-185.
43. Polyak K., Kato J.-Y., Solomon M., Sherr C. J., Massague J., Roberts J. M., Koff A., (1994), Genes Dev., 8, 9-22.
44. Chellappan S., Hiebert S., Mudryj M., Horowitz J., Nevins J., (1991), Cell, 65, 1053-1061.
45. Mudryj M., Devoto S. H., Hiebert S. W., Hunter T., Pines J., Nevins J. R., (1991), Cell, 65(7), 1243-1253.
46. Nurse P., (1994), Cell, 79, 547-550.
47. Walker D. H., Maller J. L., (1991), Nature, 354, 314-317.
48. Coleman T. R., Tang Z., Dunphy W. G., (1993), Cell, 72, 919-929.
49. Wu L., Russel P., (1993), Nature, 363, 738-741.
50. Tang Z., Coleman T. R., Dunphy W. G., (1993), EMBO J., 12, 3427-3436.
51. Smythe C., Newport J. W., (1992), Cell, 68, 787-797.
52. Ward G. E., Kirschner M. W., (1990), Cell, 61, 561-577.
53. Arion D., Meijer L., Brizuela L., Beach D., (1988), Development, 112, 971-980.
54. Verde F., Labbe J.-C., Doree M., Karsenti E., (1990), Nature, 343, 233-238.
55. Gotoh Y., Nishida E., Matsuda S., Shiina N., Kosako H., Shiokawa K., Akiyama T., Ohta K., Sakai H., (1991), Nature, 349, 251-254.
56. de Pennart H., Houliston E., Maro B., (1988), Biol. Cell, 64, 375-378.
57. Glotzer M., Murray A. W., Kirschner M. W., (1991), Nature, 349, 132-138.
58. King R. W., Peters J.-M., Tugendreich S., Rolfe M., Hieter P., Kirschner M. W., (1995), Cell, 81, 279-288.
59. Sudakin V., Ganoth D., Dahan A., Heller H., Hershko J., Luca F. C., Rudermann J. V., Hershko A., (1995), Mol. Biol. Cell, 6, 185-198.

60. Holloway S. L., Glotzer M., King R. W., Murray A. W., (1993), Cell, 73, 1393-1402.
61. Irniger S., Piatti S., Michaelis C., Nasmyth K., (1995), Cell, 81, 269-277.
62. King R. W., Jackson P. K., Kirschner M. W., (1994), Cell, 79, 563-571.
63. Fulka Jr J., Bradshaw J., Moor R., (1994), Zygote, 2, 351-354.
64. Canipari R., Palombi F., Riminucci M., Mangia F., (1984), Dev. Biol., 102, 519-524.
65. Kimelman T., Kirschner M., Scherson T., (1987), Cell, 48, 399-407.
66. Briggs R., Green E. U., King T. J., (1951), J. Exp. Zool., 116, 455-499.
67. Gurdon J. B, (1960), Q. J. Microsc. Sci., 101, 299-311.
68. Sluder G., Miller F. J., Spanijan K., (1986), J. Exp. Zool., 159, 367-377.
69. Hara K., Tydeman P., Kirschner M., (1980), Proc. Natl. Acad. Sci. USA, 77, 462-466.
70. Clute P., Masui Y., (1992), Dev. Growth Diff., 34, 27-36.
71. Cao L., Faha B., Dembski M., Tsai Li-Huei, Harlow E., Dyson N., (1992), Nature, 355, 176-179.
72. Downes C. S., Clarke D. J., Mullinger A. M., Gimenez-Ablan J. F., Creighton A. M., Johnson R. T., (1994), Nature, 372, 467-470.
73. McKim K. S., Hawley R. S., (1995), Science, 270, 1595-1601.

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Summary

There is no doubt that CDK/cyclin complexes play a central role in the regulation of the cell cycle. Many other components of the cell division cycle regulatory network have been identified recently. There is still much to be learned, however, about how these components cooperate to form this perfectly working mechanism.

Many control points of the cell cycle regulatory mechanism are the same or similar across a wide range of eucaryotes. It is rather obvious that the cell division cycle is the most fundamental process for all living organisms. Still, there is no 'general' cell cycle. Individual regulatory mechanisms depend on the organism being studied and also on the developmental stage of cells within this organism.

Key words:
cell division, cell cycle, progression.

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