CONTROL OF CELL CYCLE

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Introduction:

Extensive investigations carried out during the last two decades of the 20th century have shown that a centralized cell cycle control system regulates the orderly progress of events during the cell cycle.

The cell cycle control system makes use of a set of interacting proteins (enzymes) that induce and coordinate downstream process involved in the cell cycle. In this control system, there are checkpoints, where brakes and feedback signals can operate. The brakes can stop the cycle at checkpoints and feedback signals can delay progress of the control system itself, so that it will not be able to trigger the next event before the previous one is completed.

The environment also acts on the control system at $G_1 - S$ or at $G_2 - M$ transition.

Regulatory Activities of the Cell Cycle:

The presence of different regulators at different stages of the cell cycle have been determined successfully through cell fusion studies between cells at different cell cycle stages. Such a cell fusion makes a hybrid cell containing heterokaryons, i.e., two different nuclei in a common cytoplasm. Cell fusion can be induced through the use of chemical agents or inactivated Sendi virus.

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The various combinations of cell fusion experiments and their results are as below:

(a) S phase cell x G_1 phase cell

(i) When an S phase cell is fused with a cell in G_1, it reveals that both the nuclei in the heterokaryon replicate their DNA. This suggests that the cytoplasm of the S phase cell contains an activator or regulator of DNA replication. This is called S phase activator.

(ii) The nature of S phase activator is unknown. It could be a regulator whose activation is decided when cells in G_1 are ready to enter a cycle of replication.

(b) S phase cell x G_2 phase cell

(i) When a cell in S phase is fused with a G_2 cell, the S phase nucleus continues to replicate its DNA but G_2 nucleus does not replicate. This suggests that DNA that has replicated once becomes recalcitrant to the effects of S phase activator.

(ii) It means that S phase activator fails to induce the replication of DNA of the G_2 cell wherein DNA replication has already been completed once.

(iii) But in this fusion experiment S phase nucleus enters M phase sooner than it would have in its former cytoplasm, but the G_2 cell does not enter mitosis. This can be explained that some regulators in the S-phase cell — possibly the S phase activator itself inhibits the start of mitosis.

(c) M phase cell x G_1 or G_2 Cell

(i) When a cell in mitotic phase (M phase) is fused with a cell at either G_1 or G_2 stage of interphase, it brings about

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the interphase nucleus to enter a pseudo mitosis which is characterized by premature chromosome condensation in the interphase nuclei. This suggests that a mitotic phase inducer is present in dividing cells. The existence of inducer can be proved by the fact that the fusion between G_1 and G_2 cells do not induce replication or mitosis in either nucleus of the heterokaryon.

(d) S phase cell x M phase cell

(i) When S phase nuclei are fused with mitotic cells (M phase cell), a more complex pattern is found in which the S phase chromosomes show a fragmented or pulverized configuration.

(ii) Blocking of DNA replication with inhibitors (e.g., hydroxy urea) prevents somatic cells from processing through S phase into G_2 and M phase.

Thus completion of DNA replication is a prerequisite for cell division.

Enzymes involved in the Control of Cell cycle:

(i) It has been established through a number of studies on yeast, fruitfly, frog and mammals that eukaryotic cell cycle is governed by two major kinds of proteins (enzymes):

(a) Cyclin dependent kinases (Cdks) and (b) Cyclins

(ii) Cdk (kinase subunit) associates with cyclin (regulatory subunit) to form a Cdk - cyclin complex (CDK). This is described

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as cell cycle's engine.

(iii) A mere association of cyclin and Cdk is not sufficient to confer kinase activity to Cdk, since its activity is controlled firstly, through a programme of activating and inhibitory phosphorylation events, and secondly, through the association with different classes of regulatory molecules including cyclins and inhibitors.

(iv) Both Cdk and cyclin have one or more amino acid residues (threonine/tryosine), which can be phosphorylated and dephosphorylated (reversible phosphorylation).

(v) Binding of cyclin subunit also modulates substrate specificity of the kinase.

— A number of Cdks are now known, eg., Cdk1, Cdk2, Cdk3, Cdk4, Cdk5 and Cdk6.

— Likewise, three types of cyclins are known: mitotic cyclins (cyclin B), S-phase cyclins (cyclin A) and G_1 cyclins (cyclin C, D, E and F in vertebrates).

(vi) In animal cells, at least two different Cdk proteins are needed one for each of the two major checkpoints (G_1 and G_2).

— S phase is induced by Cdk2 complexed with S phase cyclins (E or A types), and M phase is induced by Cdk1 complexed with M phase cyclins (A and B types).

— In mammals there are additional kinases that are specialized for different transitions.

(Figs. ↓ below)

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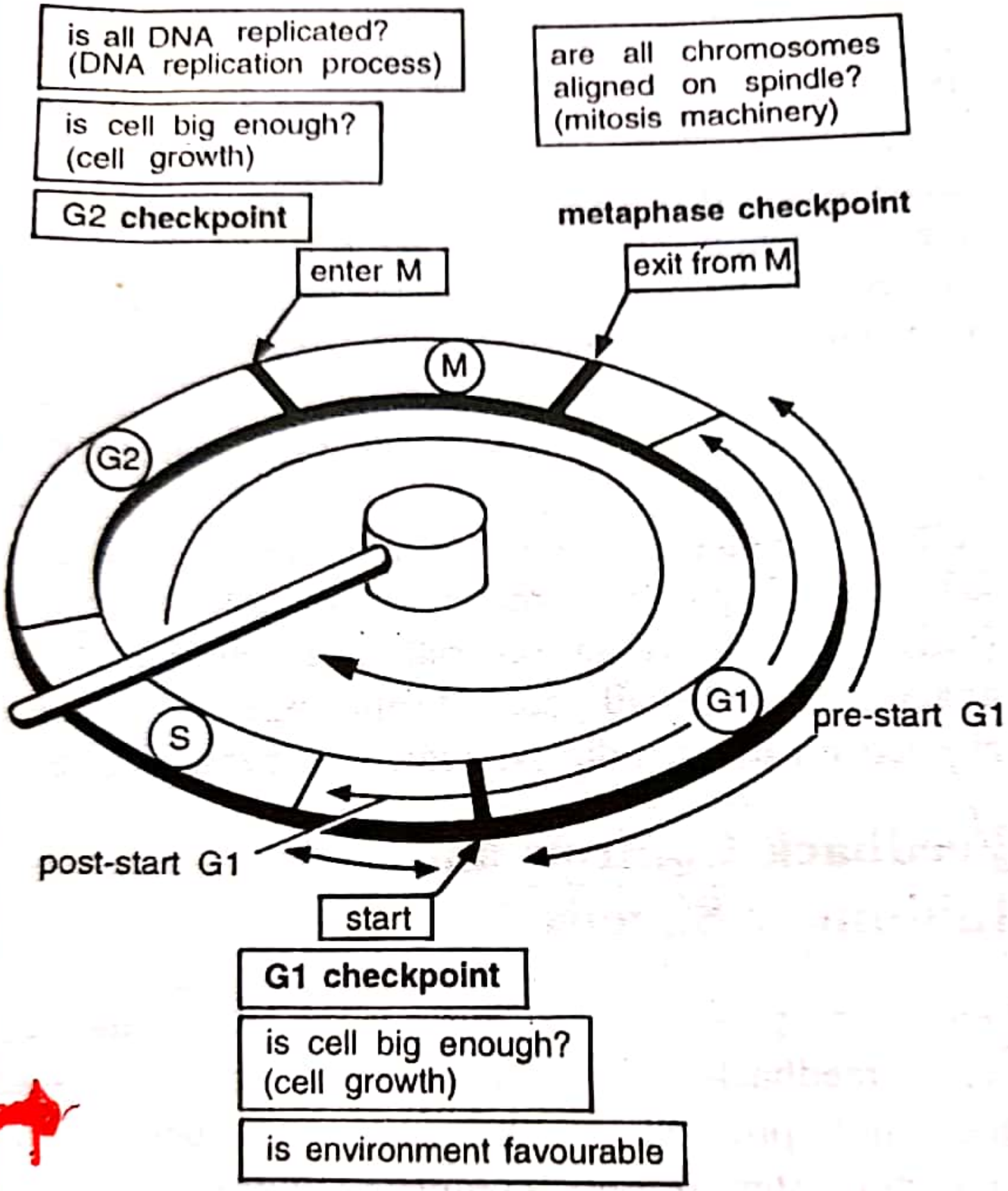

Fig. 18.6. Checkpoint and inputs of regulatory information of the cell cycle control systeln; the prominent checkpoints are highligsted, but other checkpoints are also found as discussed in the text. (redrawn from Alberts *et al.*, '*Moleclar Biology of the Cell*', 1994).

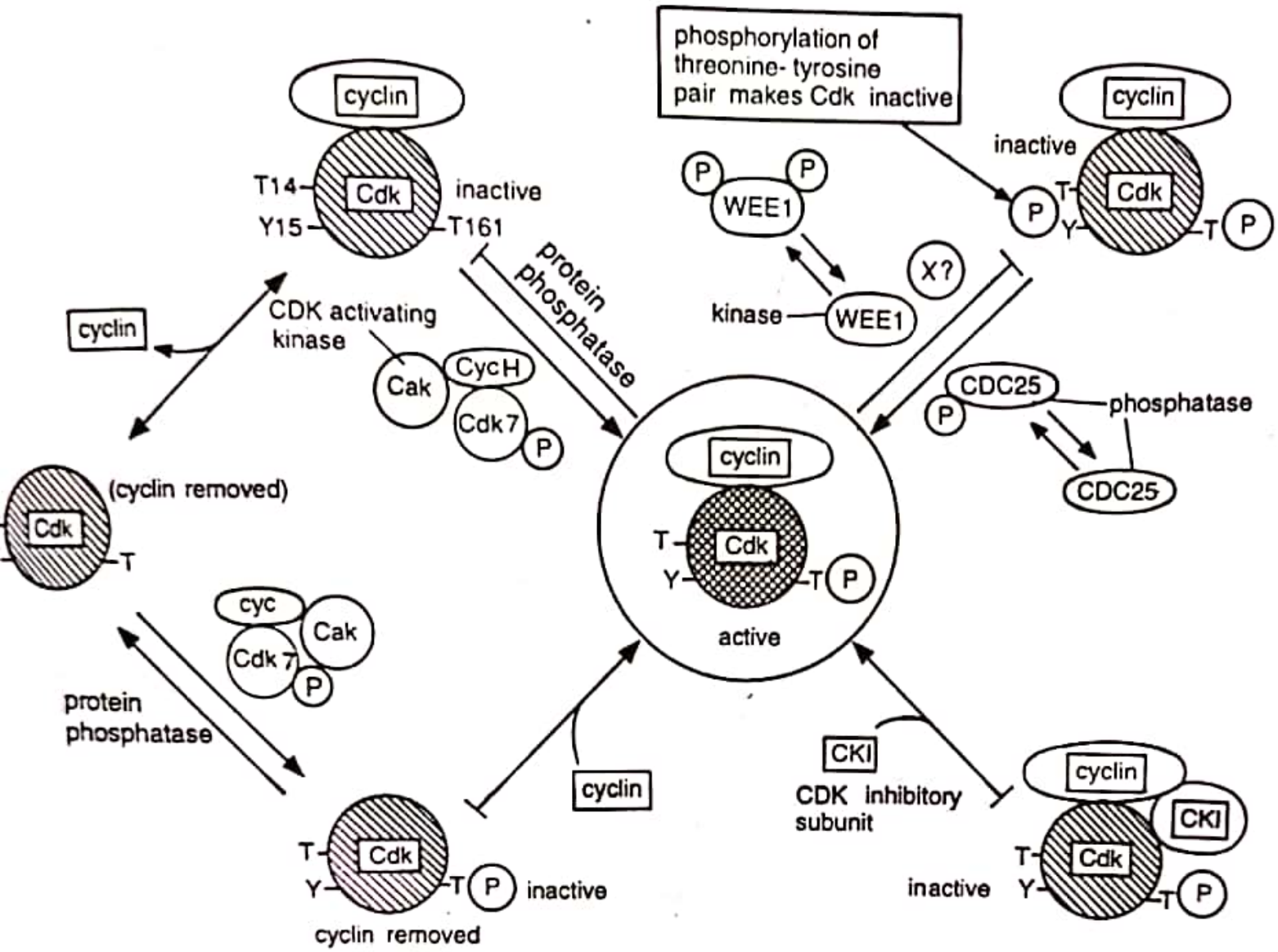

Fig. 18.7. Different stimulatory (→) and inhibitory (⊣) steps involving reversible phosphorylation of Cdk-cyclin (CDK) complexes.