The Cell Cycle

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The Cell Cycle

Video for the cell cycle

Regulation of the Cell Cycle

Certain genetically controlled factors played a key role in regulating the cell cycle (mutants of the budding yeast Saccharomyces cerevisiae that had defects at specific stages of the cell cycle).

Checkpoints: in the cell cycle that sense the completion of one event before allowing the cell to proceed to the next event.

Regulation of the Cell Cycle

CDC genes

(mutation produced defects in cell cycle progression.)

cdc28: Controls entry into mitosis, Cdc28 is replaced by Cdc2

Evolutionary point:

1) Maturation promoting factor (MPF): Frog (Induced immature oocytes to undergo mitotic division)

2) MPF is conserved in oocytes of distantly related species such as starfish.

3) MPF was found to be a protein complex containing a factor identical to the cdc2 gene product of S. pombe.

4) It was also later shown that a homologous human gene could substitute for a defective cdc2 gene in S.Pombe.

Regulation of the Cell Cycle

CDC2 Functions:

Protein kinase activity that phosphorylated histone H1 and that oscillated in activity with cell cycle phase.

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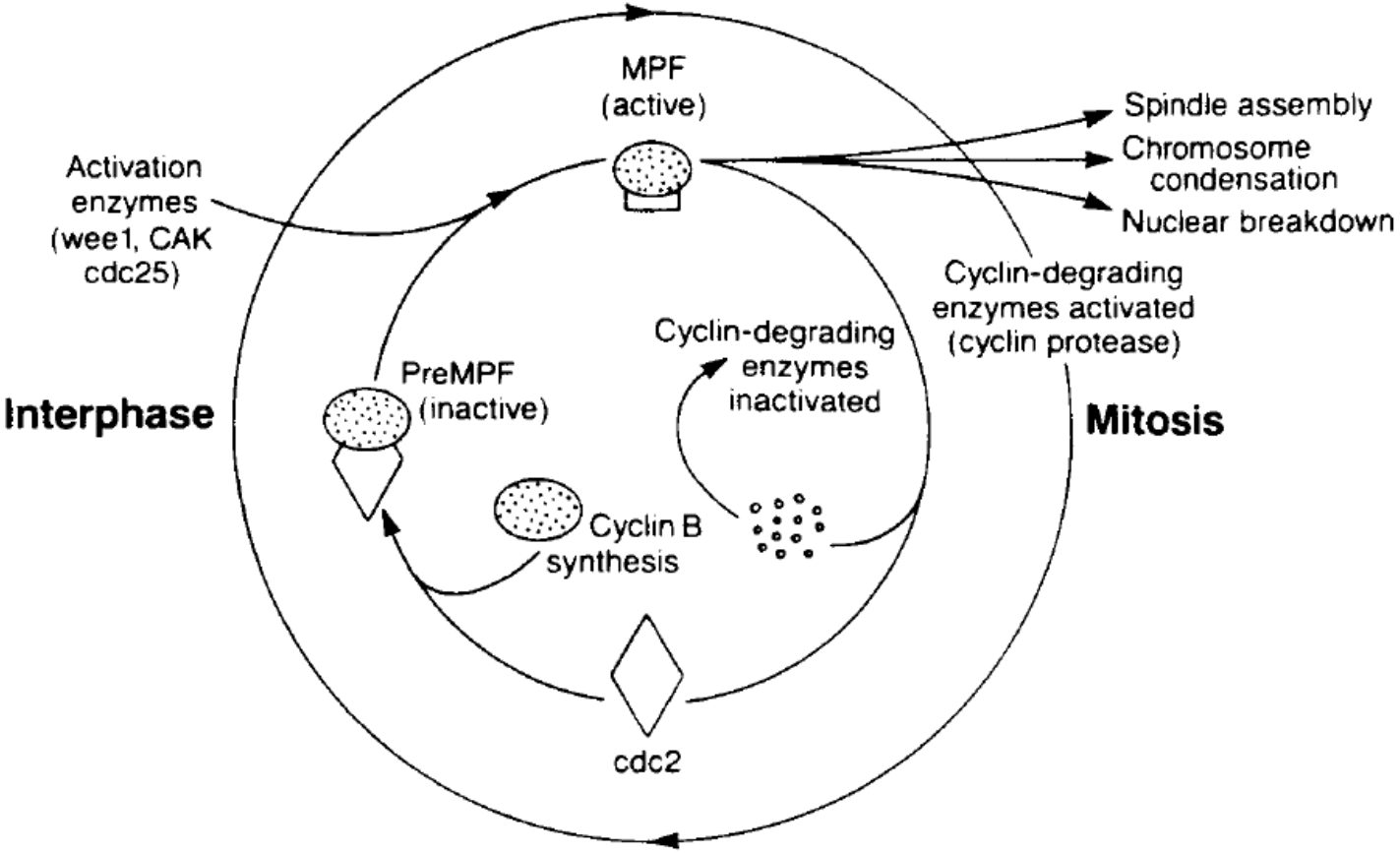
Regulation of the Cell Cycle



Regulation of the Cell Cycle

Activation and inactivation of CDC2

Wee 1, a tyrosine kinase that phosphorylates a specific tyrosine on CDC2, tyrosine 15, leading to inactivation of CDC2. CDC2 is re-activated by a phosphatase, called CDC25 in S. pombe, which removes the phosphate at tyrosine 15.

A second phosphorylation step, phosphorylation of threonine 167, is required for activation of CDC2 kinase activity. Thus, the phosphorylation state of CDC2 is important for its regulation.

CDC2-like kinases are key cell cycle regulators in all cell types examined, making it the mother of all cell cycle kinases.

Regulation of the Cell Cycle

Cyclin-Dependent Protein Kinases

- Crucial regulators of the timing and coordination of eukaryotic cell cycle events. They transiently activated in specific cell cycle phases.

G1 cyclins encoded by the CLN genes interact with, and are necessary for the activation of, the CDC2 kinase (also called p34cdc2), driving the cell cycle through a regulatory point called START and committing cells to enter S phase.

- The CDKs work by forming active heterodimeric complexes following binding to cyclins, CDK2, 4, and 6, and possibly CDK3 cooperate to push cells through G1 into S phase. CDK4 and CDK6 form complexes with cyclins D1, D2, and D3, and these complexes are involved in completion of G1.

CyclinD–dependent kinases accumulate in response to mitogenic signals,

Regulation of the Cell Cycle

CDK Inhibitors:

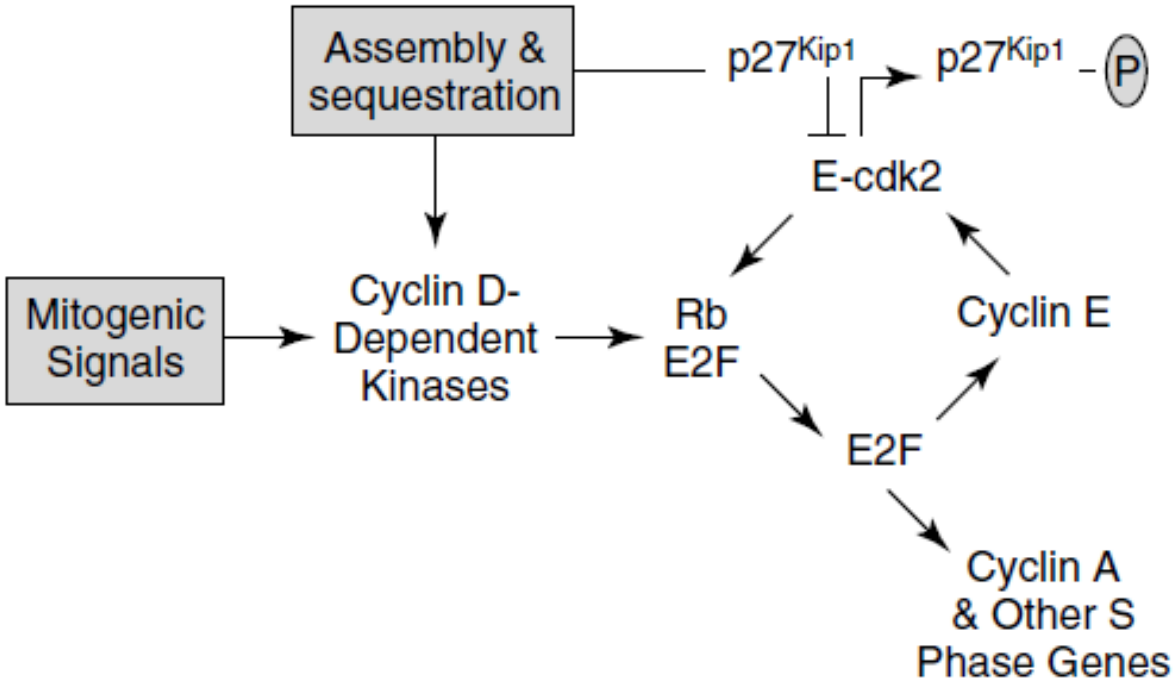
Cip/Kip (p21cip1, p27kip1, and p57kip2)
Inhibit CDK2. -

INK4 targets the CDK4 and CDK6 kinases, sequester them into binary CDKINK4 complexes, and liberate bound Cip/Kip proteins. This indirectly inhibits cyclin E–CDK and promotes cell cycle arrest.

The INK4- directed arrest of the cell cycle in G1 keeps Rb in a hypophosphorylated state and represses the expression of S-phase genes.

Regulation of the Cell Cycle

Four INK4 proteins have been identified: p16INK4a, p15INK4b, p18INK4c, and p19INK4d.



Regulation of the Cell Cycle

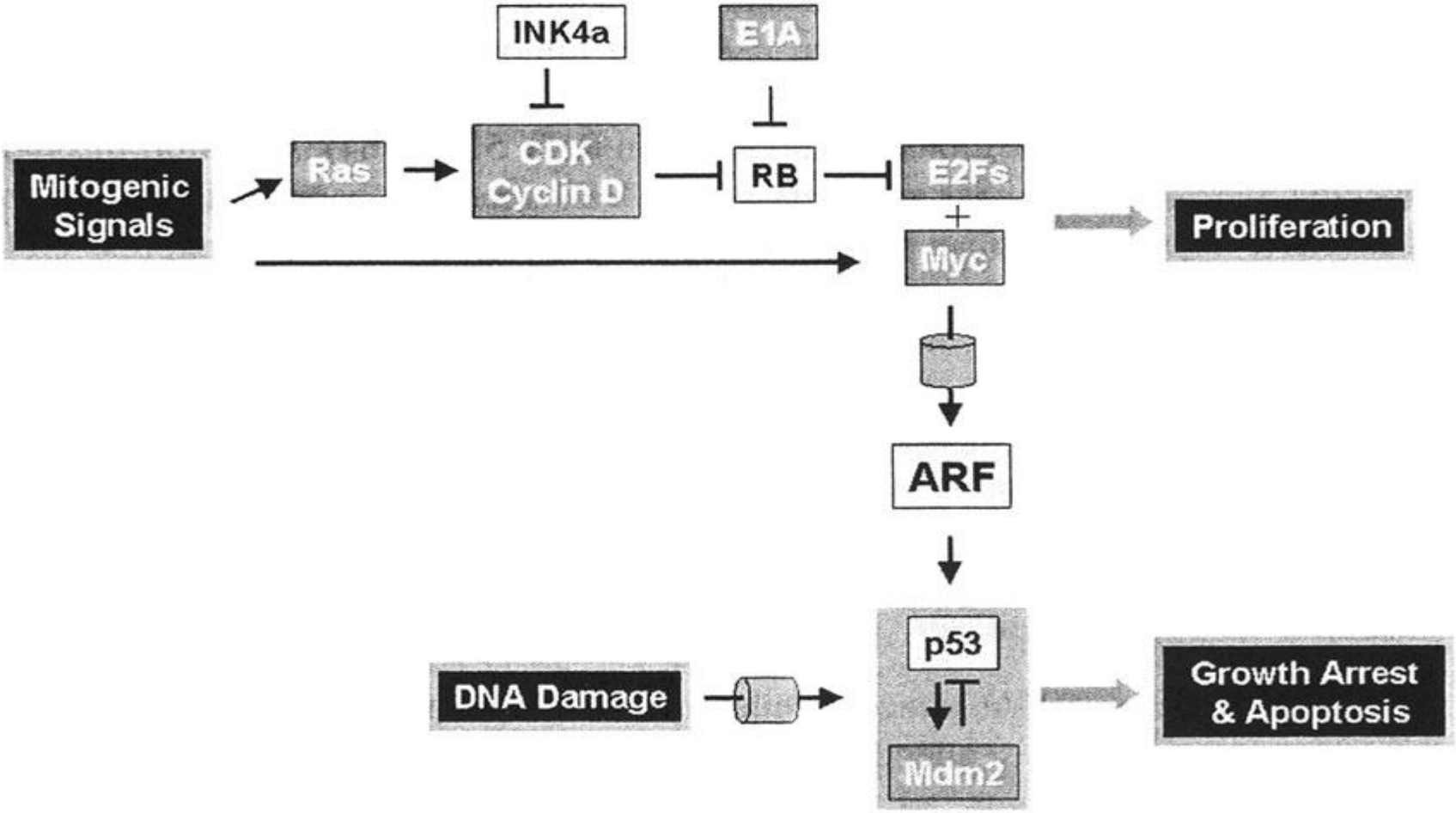
Roles of Cell Cycle regulators in cancer

- INKA4a loss of function occurs in a variety of cancers including pancreatic and small cell lung Carcinomas (Tumour suppressor gene).

- The INK4a gene encodes another tumor suppressor protein called ARF (p14ARF). ARF and p53 act in the same pathway to insure growth arrest and apoptosis in response to abnormal mitogenic signals such as myc-induced carcinogenesis

Regulation of the Cell Cycle

Roles of Cell Cycle regulators in cancer



Regulation of the Cell Cycle

Cyclins

Cyclin A and B.

Cyclin A is first detected near the G1/S transition
Cyclin B is first synthesized during S phase and accumulates in complexes with p34cdc2 as cells approach the G2-to-M transition. Cyclin B is then abruptly degraded during mitosis.

Cyclin C levels change only slightly during the cell cycle but peak in early G1.
Cyclin E peaks at the G1–S transition, suggesting that it controls entry into S.

Regulation of the Cell Cycle

Cyclins

Cyclin D:

Cyclin D (D1, 2, and 3).

Cyclin D levels are growth factor dependent in

mammalian cells: when resting cells are stimulated by growth factors, D-type cyclin levels rise earlier than cyclin E levels, implying that they act earlier in G1 than E cyclins.

Cyclin D levels drop rapidly when growth factors are remove

from the medium of cultured cells.

Regulation of the Cell Cycle

Cell Cycle Checkpoints

G1–S checkpoint:

Phosphorylation of the Rb protein by cyclin D–dependent kinase releases Rb from the transcriptional regulator E2F and activates E2F function.

p53 gene: p53's essential roles is to arrest cells in G1 after genotoxic damage, to allow for DNA repair prior to DNA replication and cell division

G2–M checkpoints

P53 gene to guarantee a damage free genome before proceeding to the mitosis.

Regulation of the Cell Cycle

Cell Cycle Checkpoints

Mitotic spindle checkpoint

bub (budding uninhibited by benomyl) and **mad** (mitotic arrest deficient).

There are three bub genes and three mad genes involved in the formation of this checkpoint complex. A protein kinase called **Mps1** also functions in this checkpoint.

Mutant alleles of the human bub1 gene have been observed in colorectal tumor displaying aneuploidy.

Regulation of the Cell Cycle

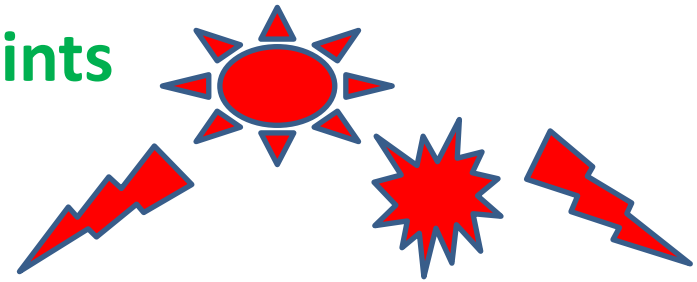
Cell Cycle Checkpoints

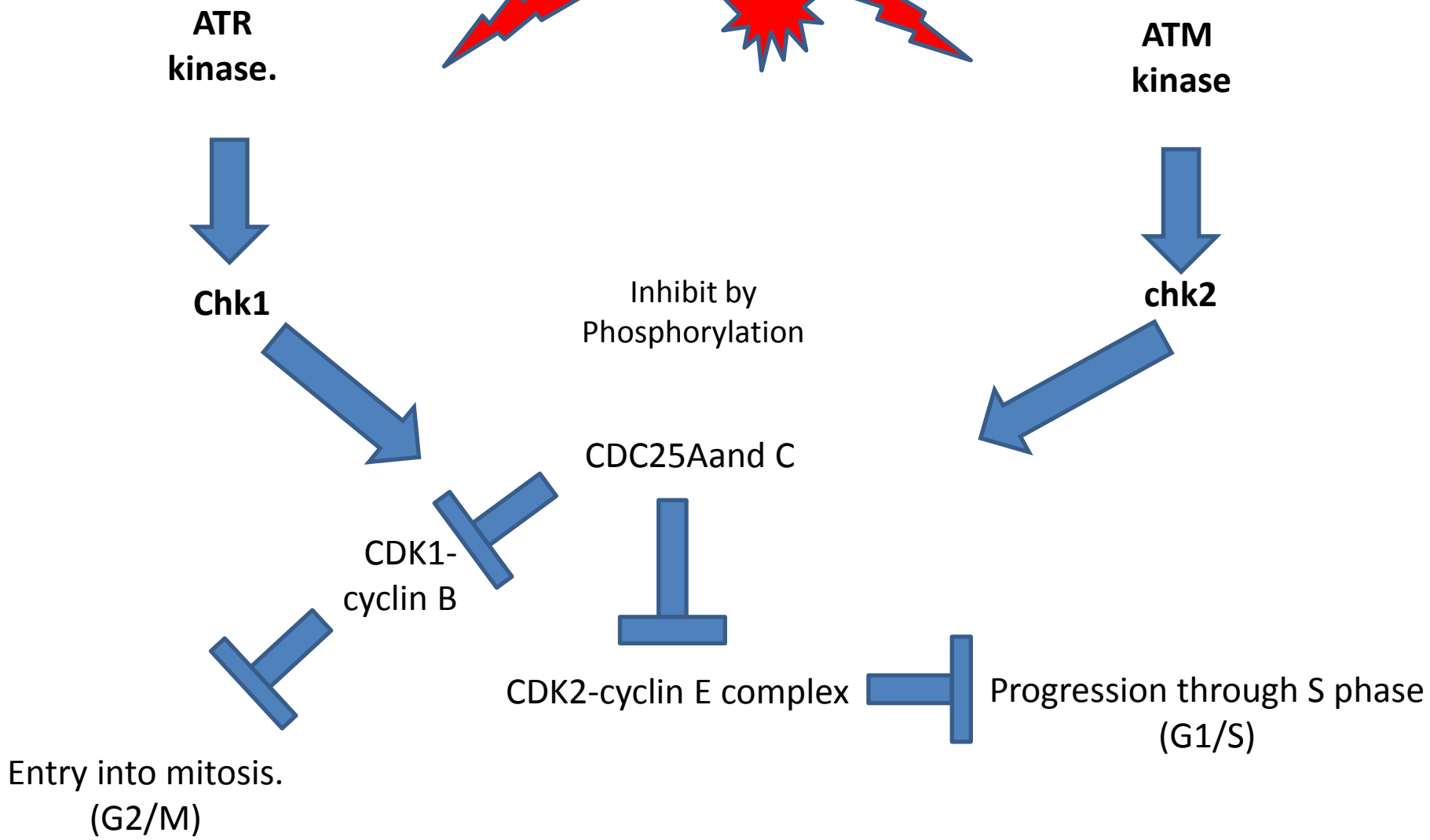
Chk1 and Chk2

Activated by DNA damage and initiate a number of cellular defense mechanisms that modulate DNA repair pathways and slow down the cell division cycle to allow time for repair.

Regulation of the Cell Cycle

Cell Cycle Checkpoints





Regulation of the Cell Cycle

Cell Cycle Regulatory Factors as Targets for Anticancer Agents

One approach is to inhibit cell cycle checkpoints in combination with DNA-damaging drugs or irradiation. ATM/ATR inhibitors such as caffeine or Chk1 inhibitors in combination with DNA-damaging drugs.

Another approach is to target the cyclin-dependent kinases directly.

Questions