MOLECULAR BASIS OF ONCOGENESIS

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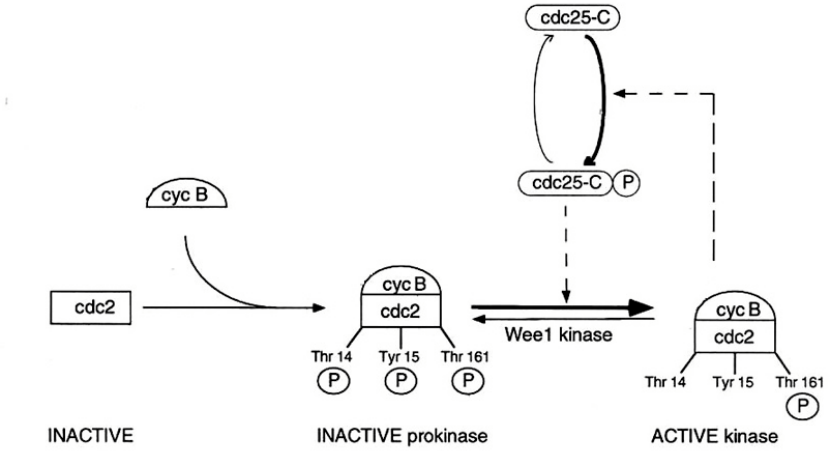
Activation of cdk1 (=cdc2) by phosphorylation/dephosphorylation



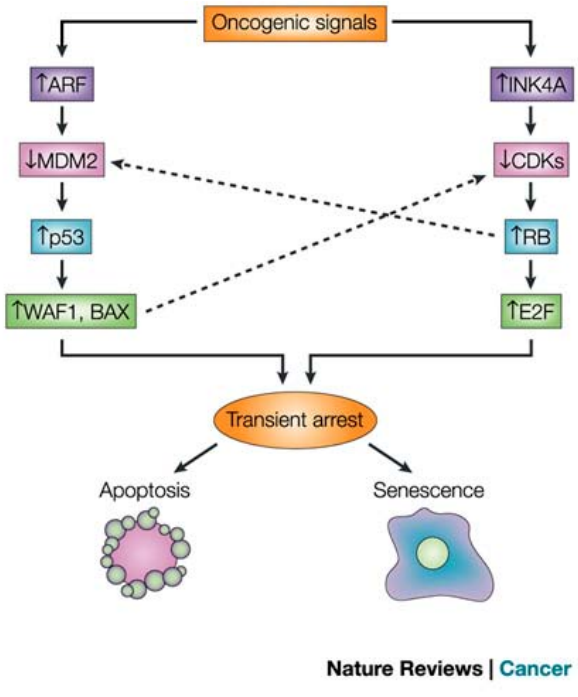
Cell processes which result also in cell cycle effects.

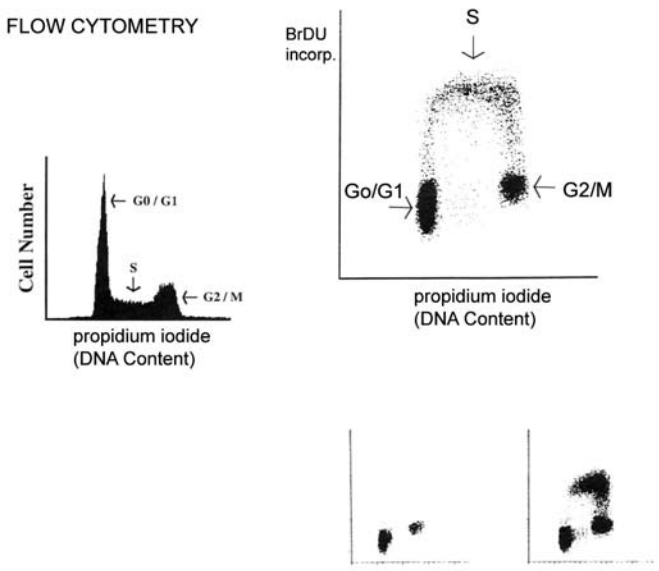
Differentiation.
Differentiated cells are usually in the G0 phase of the cell cycle.
Terminal differentiation (nerves, muscles) normally does not allow
the re-entry into the cell cycle. Differentiated cells have specific differentiated phenotype which includes morphology and expression of cell type-specific markers.

Senescence.
Replicative senescence results in exit from the cell cycle into G0.
Again, normally, senescent cells are unable to re-enter the cell cycle.
Senescent cells have also specific morphology and express senescent specific markers.

Cell cycle checkpoints.

Non-physiological state:
Cell cycle control, mostly in G1, is deregulated in cancer cells.
Also, checkpoints are deregulated in cancer cells.





Oncogenes

(activated forms of protooncogenes)

Protooncogenes are cellular genes the functions of which are required by normal cells.

X

Supressor genes (= antioncogenes)

Supppressor genes are inactivated in tumor cells

Mechanisms of activation of cellular oncogenes:

Point mutations (H-ras, K-ras, N-ras)

Enhanced expression
- increased (deregulated) transcription
- gene amplification
- chromosomal translocation (myc 8q24) > IgH (14q32)
  (cellular gene is transcribed from a strong promoter after translocation)

Translocation creating a new fusion protein with aberant function
Abl (9q34)+Bcr(22q11) > Abl-Bcr fusion (Philadelphia chr.)

Impaired degradation of protein (some cyclins)

Non-cellular oncogenes from DNA tumor viruses

Mechanisms of inactivation of tumor suppressors:

Point mutations: retinoblastoma (Rb) protein, p53 protein

Deletions (loss of a locus on the chromosome)
(many different losses of locuses are associated with almost all cancer cells)

Decreased expression
- decreased transcription caused by promoter methylation

Increase protein degradation (p53 x mdm2)

Two important suppressor pathways: Rb and p53.
At least one pathway is almost invariantly impaired in cancer cells
Other tumor suppressors: p16(INK4a)-Rb pathway, and p14(ARF)-p53 pathway

Mutations in suppressor genes can be inherited – cancer syndromes)

Cancer "syndromes"

Gene	Locus	Somatic mutations in tumors
Rb	13q14	Retinoblastoma,osteosarcoma, SCLC,
p53	17p13	Syndrome Li-Fraumeni
NF1,2	17q11; 22q12	Neurofibromatosis type 1,2
p16	9p21	"Familiar" melanoma
WT1	11p13	Wilms tu.

Cellular processes disrupted in cancer cells.

(Cellular processes which result also in cell cycle effects)

Differentiation.
Differentiated cells are usually in the G0 phase of the cell cycle.
Terminal differentiation (nerves, muscles) normally does not allow
the re-entry into the cell cycle. Differentiated cells have specific differentiated phenotype which includes morphology and expression of cell type-specific markers. **Differentiation program is often impaired in cancer cells.**

Senescence.
Replicative senescence results in exit from the cell cycle into G0.
Again, normally, senescent cells are unable to re-enter the cell cycle.
Senescent cells have also specific morphology and express senescent specific markers. **Cancer cells are unable to senesce (cancer cells are always immortal).**

Apoptosis.
Apoptosis (programmmed cell death) occurs after the activation of pro-apoptotic genes or inhibition of anti-apoptotic genes and in most instances it is initiated in G1. **The execution of apoptosis is impaired in cancer cells.**

Cell cycle checkpoints.
Non-physiological state:
Cell cycle control, mostly in **G1**, is **deregulated in cancer cells**.
Also, other cell cycle checkpoints are deregulated in cancer cells.

Cell cycle checkpoints deregulated in cancer

Normally, checkpoints enable cells to halt the cell cycle and repair damaged DNA or complete spindle assembly at mitosis:

- restriction point in late G1 (after this point, the cell is committed to enter the S-phase)

- DNA replication checkpoint (this checkpoint ensures that mitosis occurs only after DNA has replicated completely - DNA replicates once and only once during a single cell cycle). Endoreduplication (re-replication of DNA without mitosis) may occur in cancer cells.

- spindle assembly checkpoint (ensures proper segregation of chromosomes during mitosis (at the metaphase to anaphase transition). Chromosomal aberations in cancer cells.

- DNA damage checkpoint(s) (cell cycle can be arrested in G1, S , or G2). Inability to arrest (and repair DNA) after DNA damage may lead to the accumulation of mutations.

Cell transformation:

Normal cell >>>> malignant cell

Stepwise accumulation of several mutations (deletions) in oncogenes and suppressor genes

Escape from senescence (activation of telomerase)

Immortalization (cancer cells are always immortal)

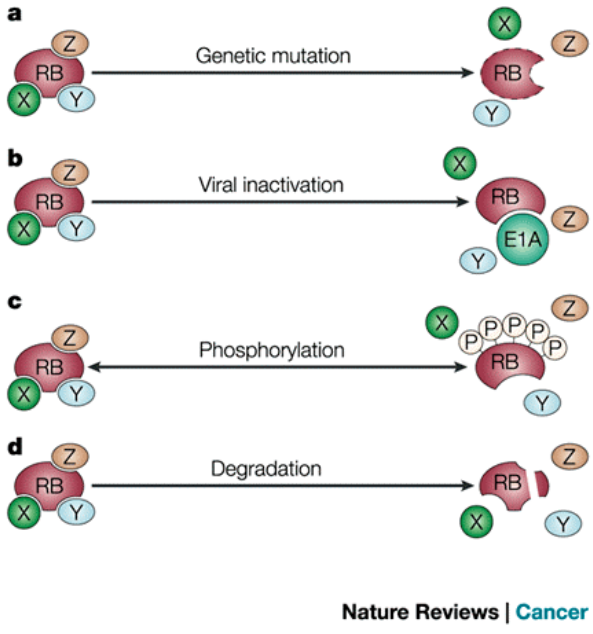
Mouse cells are much more easily transformed – activation of one oncogene and inactivation of one suppressor egene is usually sufficient. Mouse cells can be easily immortalized.

Normal human cells are very difficult to transform in vitro.

Oncogenic DNA viruses

Virus:	Oncoprotein:	Genome size (kb):
SV-40 virus	large T Ag	5
Polyomavirus	middle T (large T)	5
Adenoviruses (Ad12)	E1a (E1b)	35
Papilomaviruses (HPV16)	E7, E6	8

Hepatitis B viruses
Herpesviruses, Epstein-Barr virus
Poxviruses



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