

Cells I

Cell Cycle and Proliferation

Overview

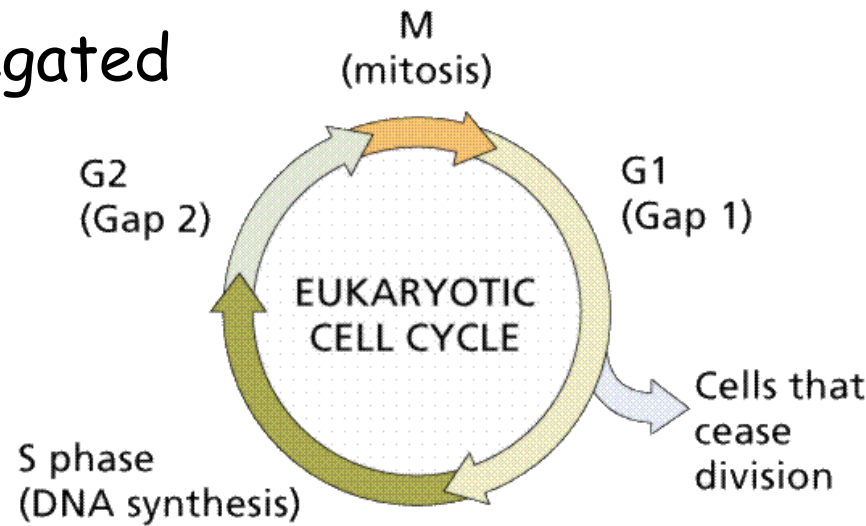
- Importance of cell cycle to IMCB
- Biology of cell cycle
- Molecular Pathways of cell cycle
- Modeling of the cell cycle
- Manipulating proliferation with growth factors
- Relationship of proliferation vs. apoptosis

Cell cycle

- Controls proliferation of cells in mitosis
- We like to augment proliferation in
 - Stem cell expansion
 - Wound healing
 - Seeding of regenerative scaffolds (e.g., bone)
- We like to halt proliferation in
 - cancer

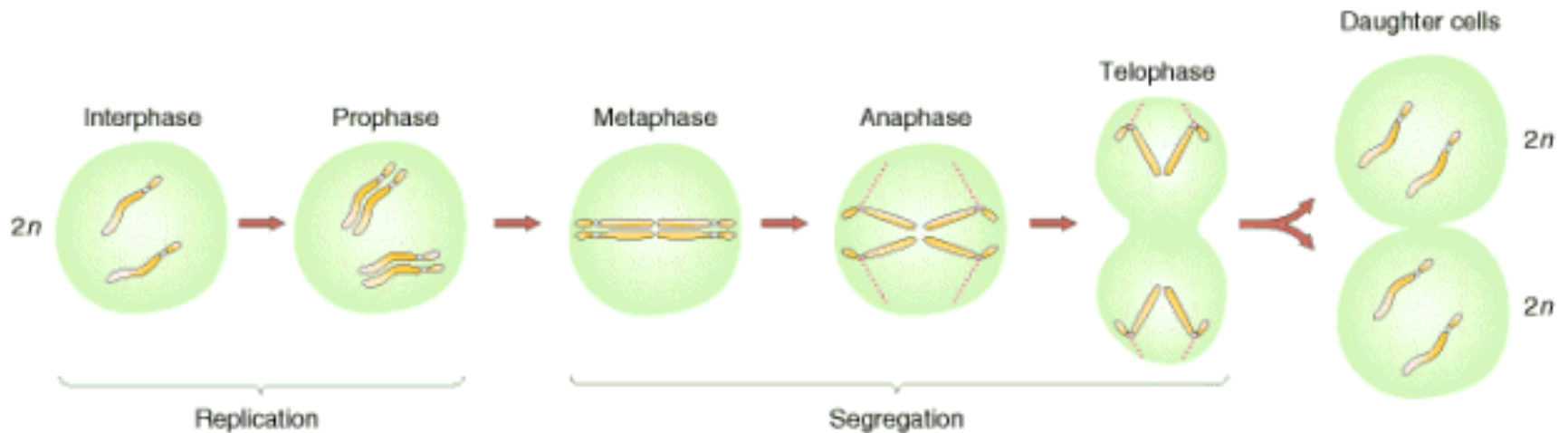
Phases of cell cycle

- Gap1 (G1): commitment to DNA replication, synthesis of replicative enzymes
- Synthesis (S): replication of genome
- Gap2 (G2): preparations for mitosis - chromosomal condensation, synthesis of mitotic factors
- Mitosis (M): chromosomes segregated into daughter cells



Chromosomal replication and segregation

Mitosis

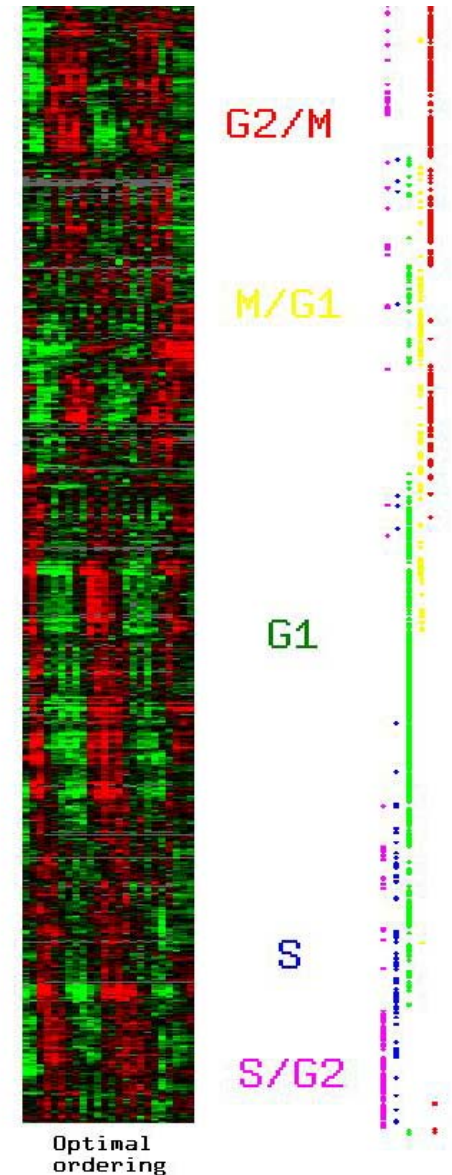


Length of Cell Cycle

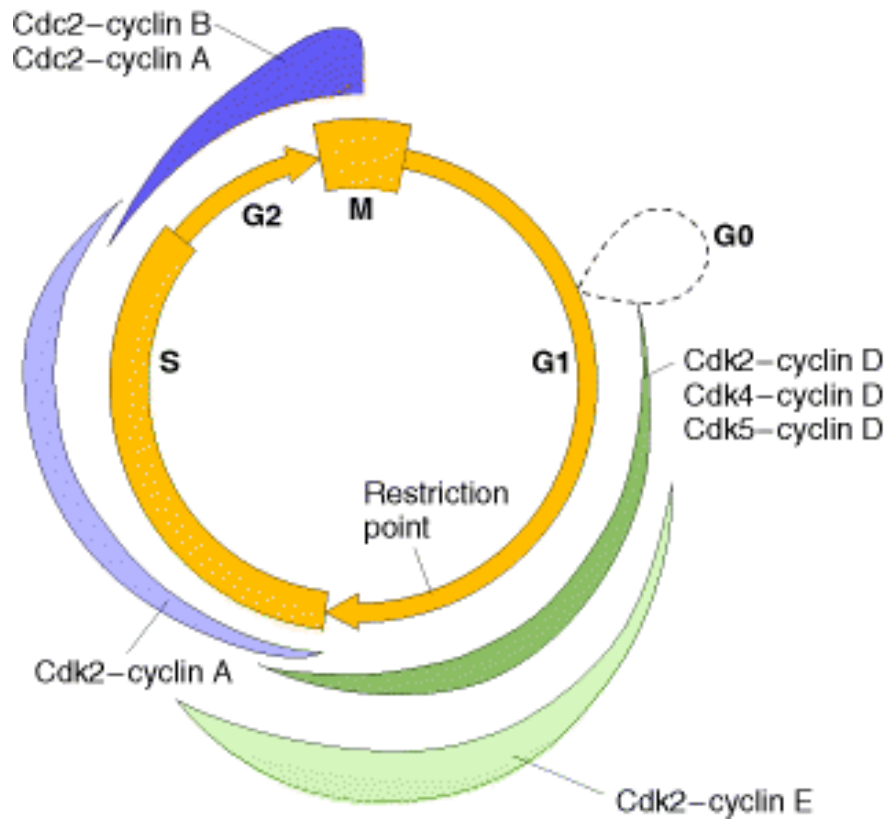
<u>Organism</u>	<u>M</u>	<u>G1</u>	<u>S</u>	<u>G2</u>	<u>Total</u>
Human (h)	1	8	10	5	~24
Plant (h)	1	8	12	8	~29
Yeast (min)	20	25	40	35	~120

Gene Expression in Cell Cycle

- Coordinated expression of distinct sets of genes at each phase of cell cycle
- Implies control elements

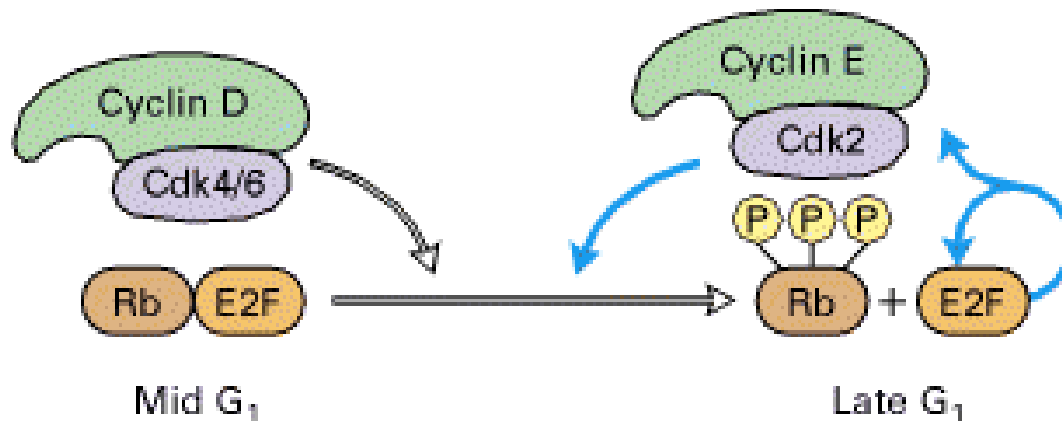


Cyclins and cyclin-dependent kinases



Restriction Point

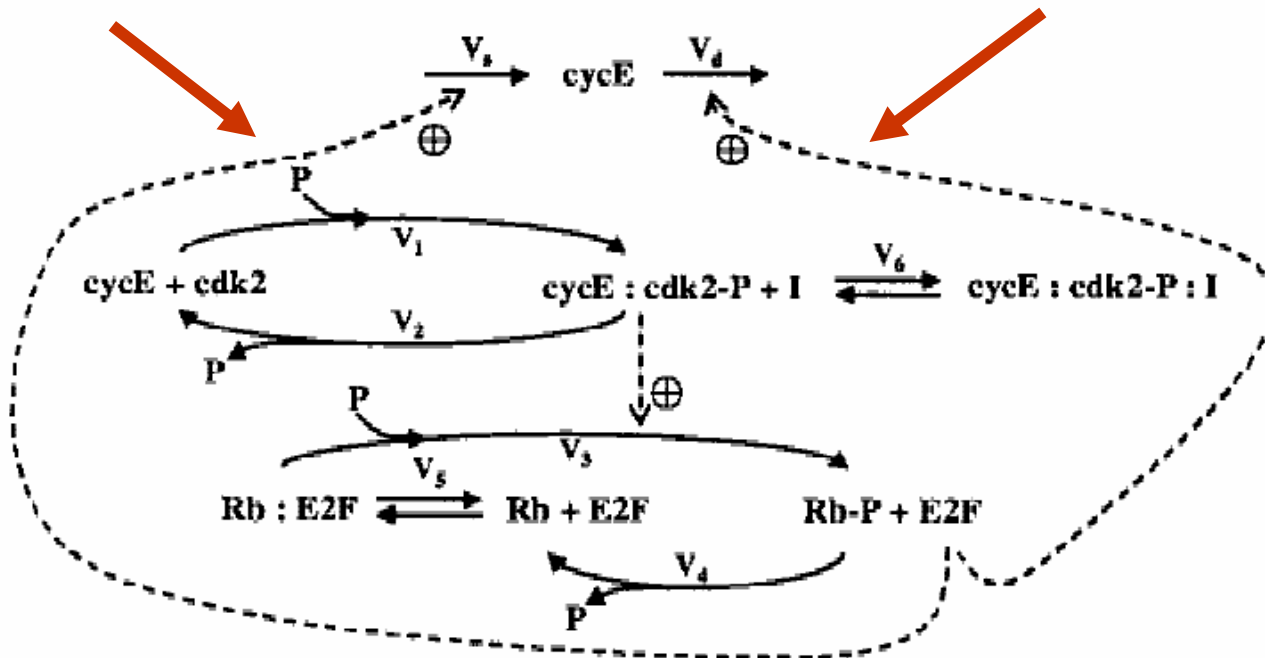
- A key element: activation of the transcription factor E2F.
 - Promotes synthesis of dNTP and DNA
 - Inhibited by Rb protein
 - E2F is autoregulatory (positive)



Modeling the G1-S transition

Positive feedback

Negative feedback



$$\frac{dC}{dt} = V_s - V_1 + V_2 - V_d$$

$$\frac{dK}{dt} = V_2 - V_1$$

$$\frac{dK_P}{dt} = V_1 - V_2 + V_{6,r} - V_{6,f}$$

$$\frac{dK_{P,I}}{dt} = V_{6,f} - V_{6,r}$$

$$\frac{dR_P}{dt} = V_3 - V_4$$

$$\frac{dR}{dt} = V_4 - V_3 + V_{5,r} - V_{5,f}$$

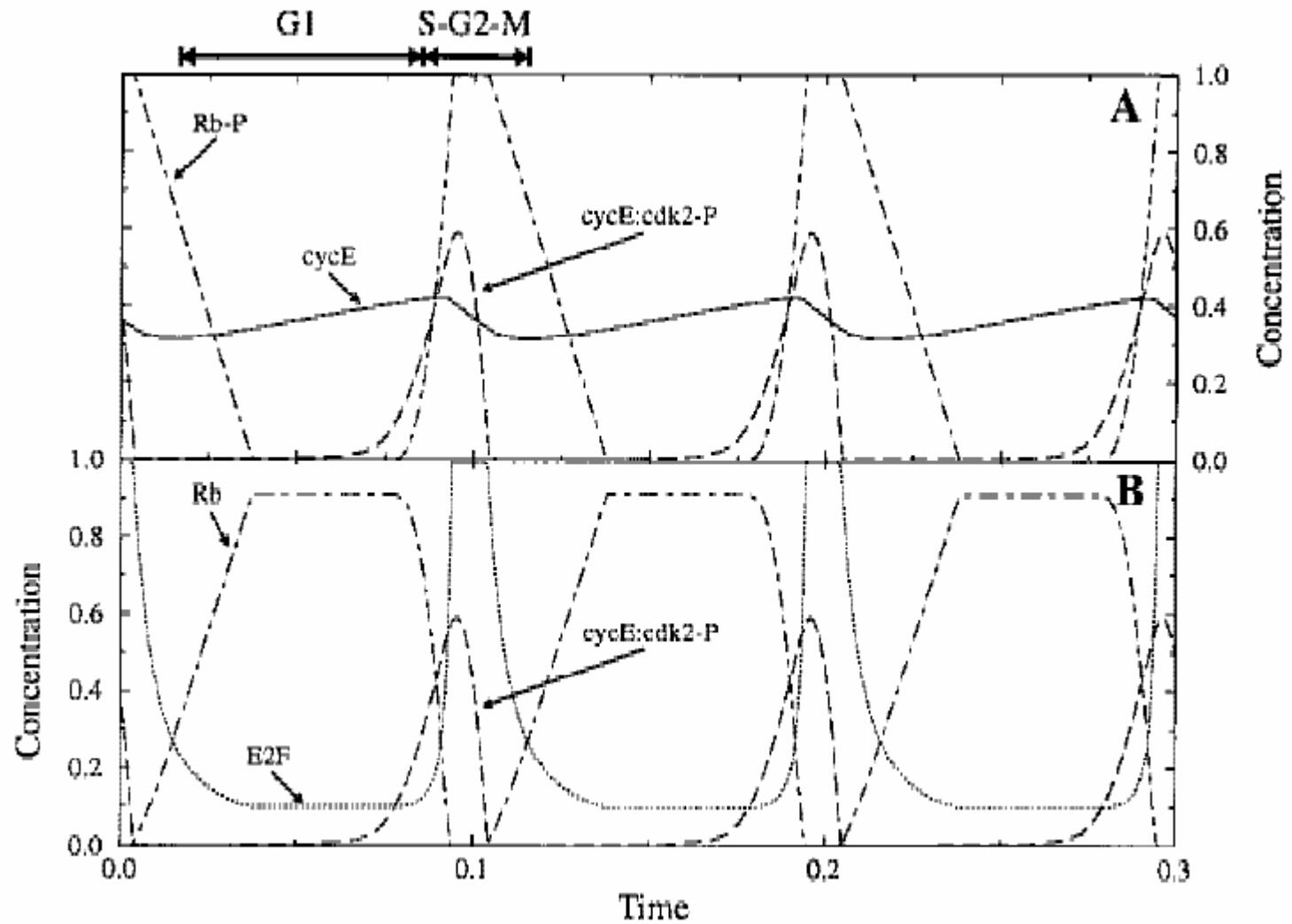
$$\frac{dR_E}{dt} = V_{5,f} - V_{5,r} - V_3$$

$$\frac{dE}{dt} = V_3 - V_{5,r} + V_{5,f}$$

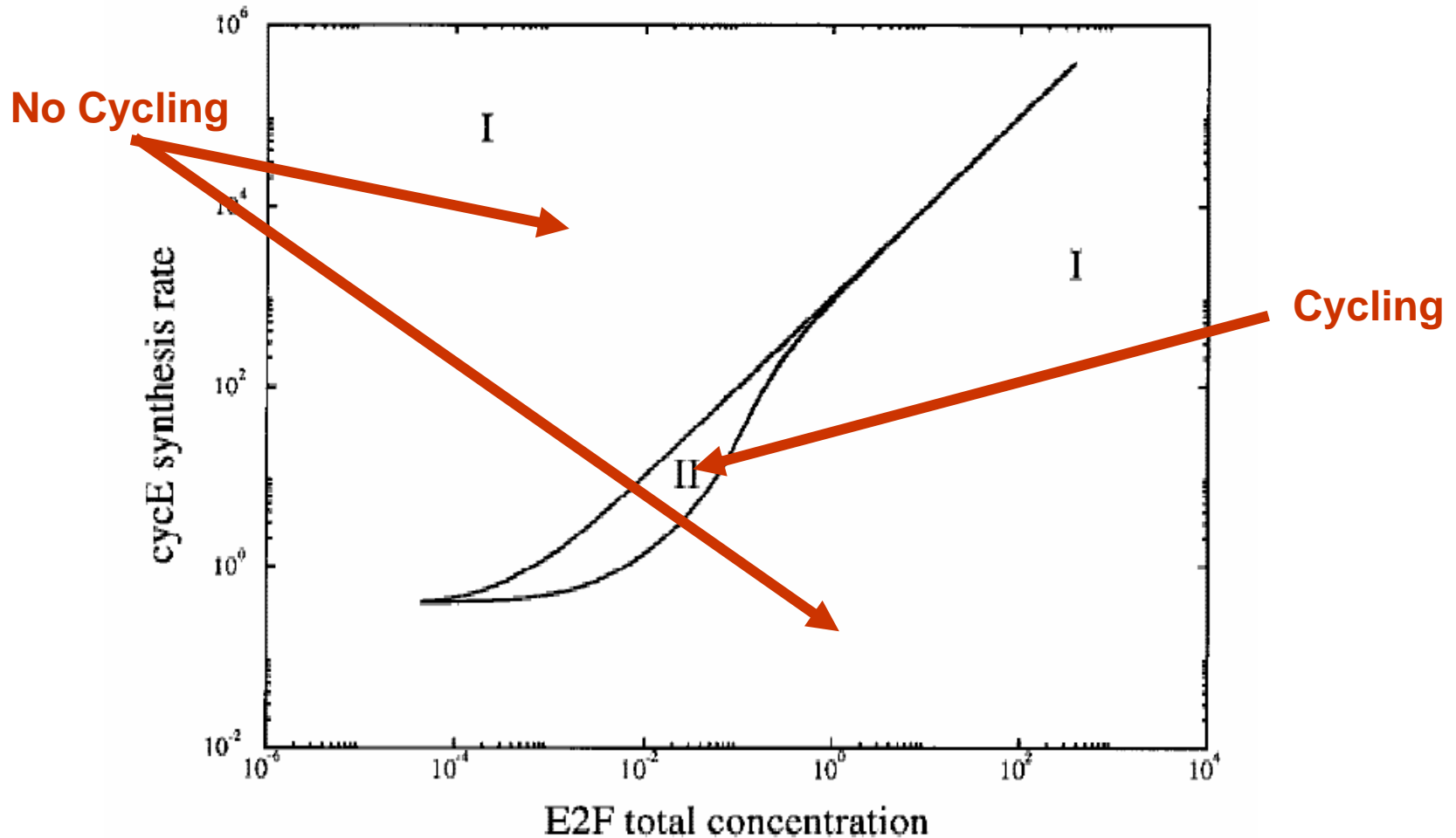
$$\frac{dI}{dt} = V_{6,r} - V_{6,f}$$

Does this model result in cyclic behavior?

Yes, It Can

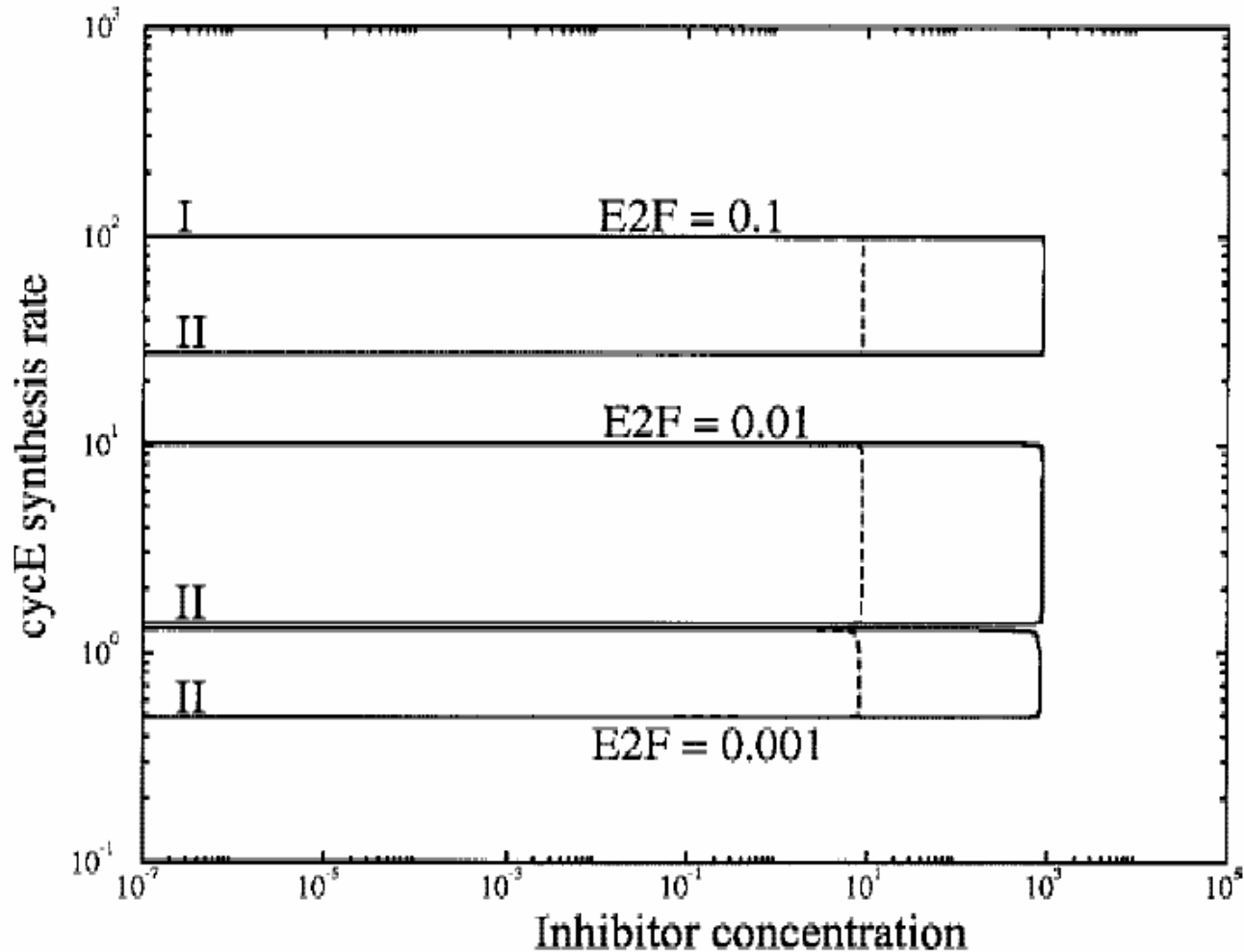


Cycling only for Select Parameter Values



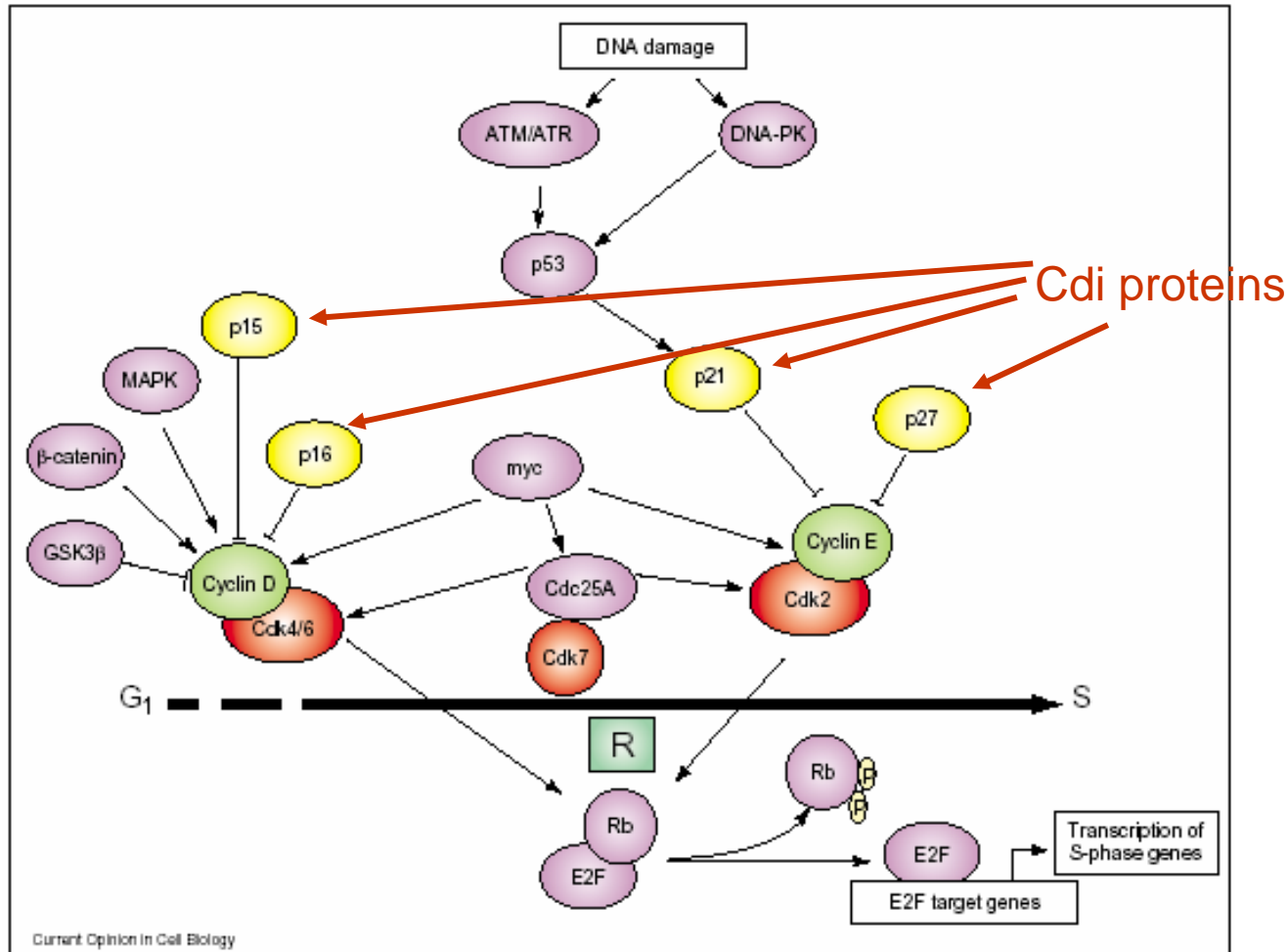
Implication: overexpression of E2F or cyclin E could lead to arrest, not growth

Effect of Inhibitor

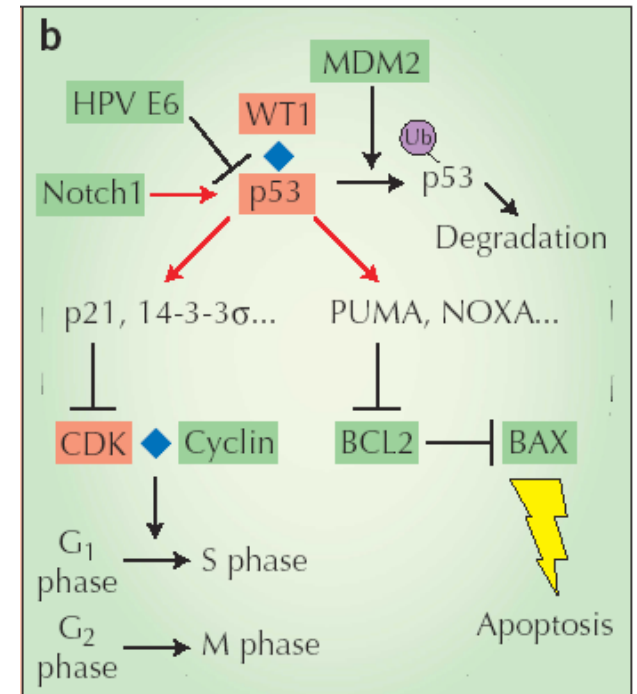
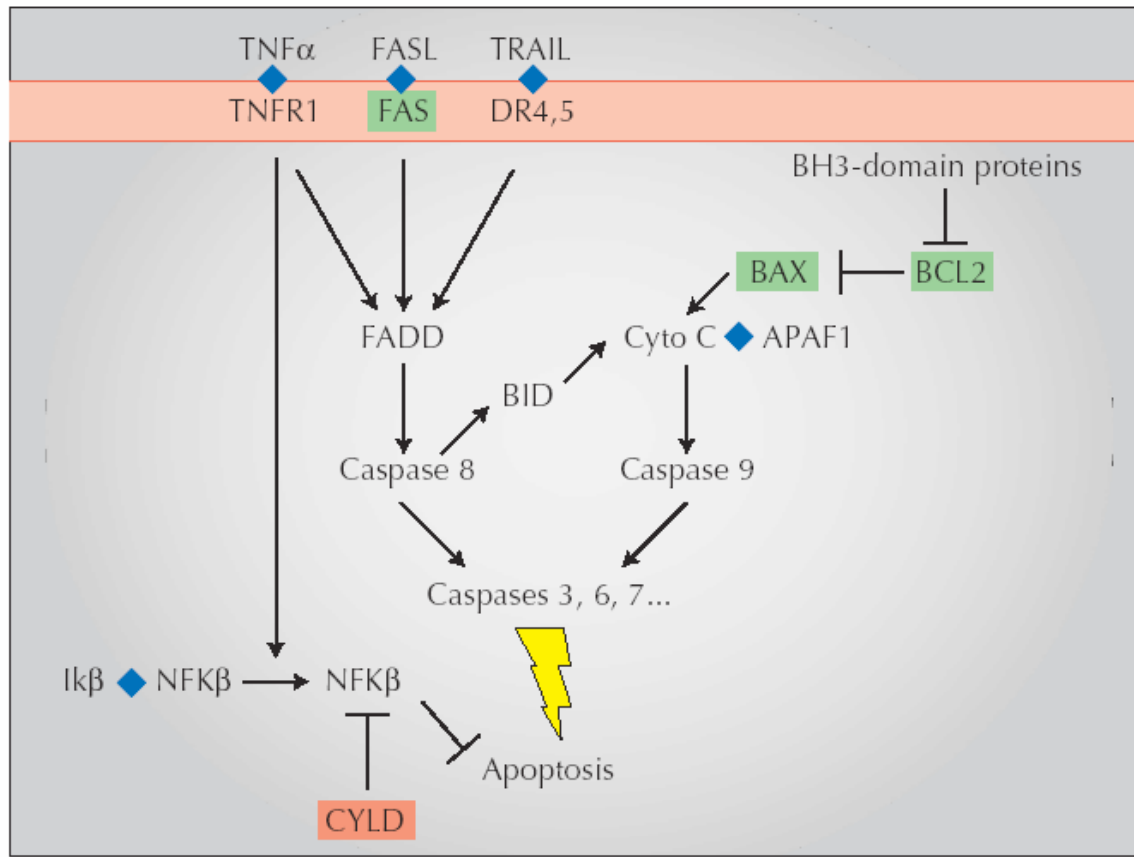


Implication: cells arrested due to inhibitor cannot be overcome with cycE or E2F

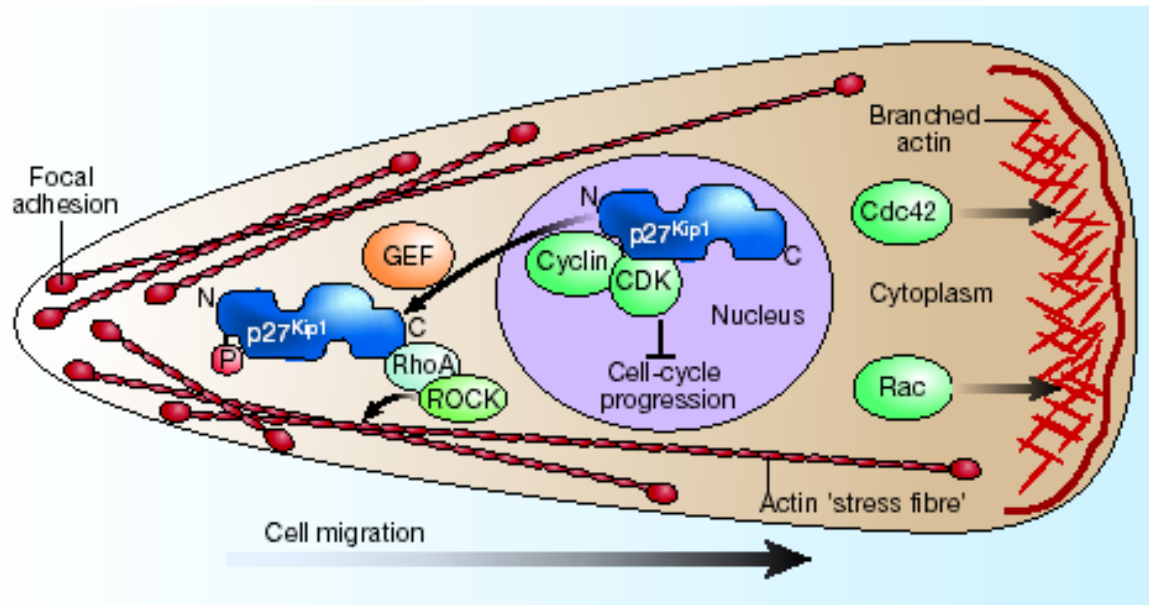
Cell Cycle Control by p53



p53 and Apoptosis



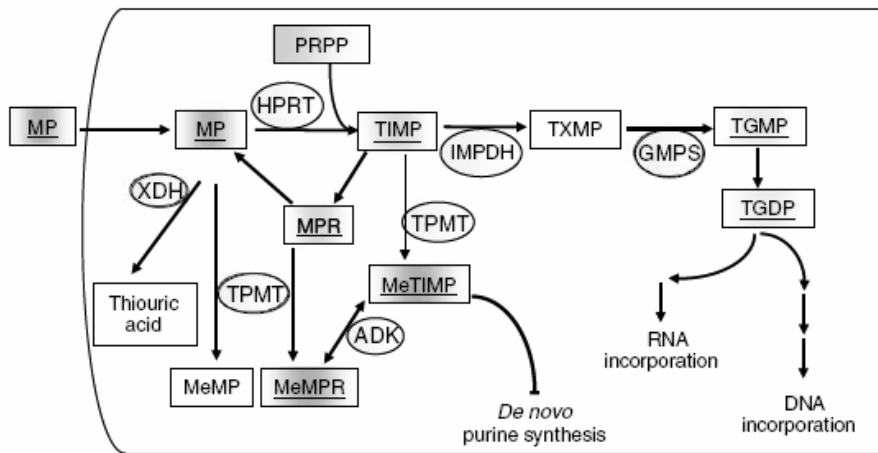
A Possible Connection between Tumor Proliferation and Invasiveness



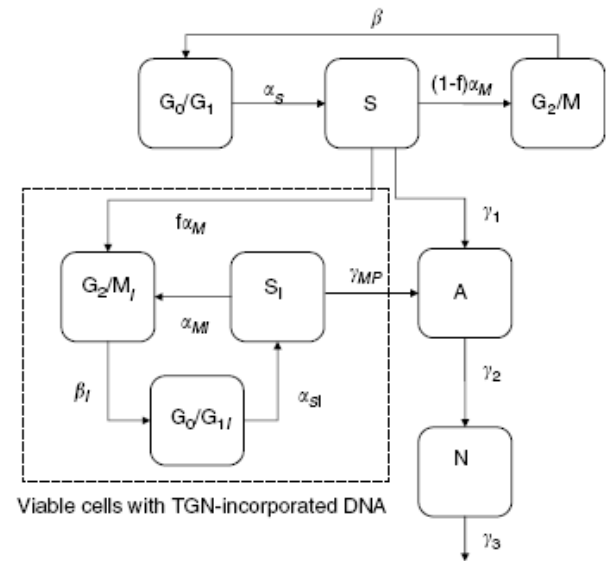
Implication: p27 inhibits both cell proliferation and migration

Cell Cycle Analysis of Chemotherapy

Mercaptopurine incorporation into nucleotides



Cell cycle modeling

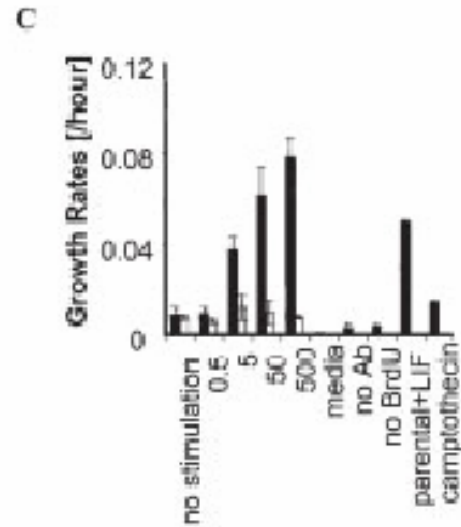


$$\begin{aligned} \text{Viable phase} & \left\{ \begin{array}{l} \text{Cells free of TGN incorporation} \left\{ \begin{array}{l} \frac{dG}{dt} = -\alpha_S G + 2\beta M \\ \frac{dS}{dt} = \alpha_S G - (\alpha_M + \gamma_1) S \\ \frac{dM}{dt} = (1-f)\alpha_M S - \beta M \end{array} \right. \\ \text{TGN incorporated cells} \left\{ \begin{array}{l} \frac{dM_I}{dt} = f\alpha_M S + \alpha_M S_I - \beta_I M_I \\ \frac{dG_I}{dt} = -\alpha_{SI} G_I + 2\beta_I M_I \\ \frac{dS_I}{dt} = \alpha_{SI} G_I - (\gamma_{MP} + \alpha_M) S_I \end{array} \right. \end{array} \right. \\ \text{Apoptotic phase} & \left[\frac{dA}{dt} = \gamma_1 S + \gamma_{MP} S_I - \gamma_2 A \right. \\ \text{Non-viable phase} & \left[\frac{dN}{dt} = \gamma_2 A - \gamma_3 N \right. \end{aligned}$$

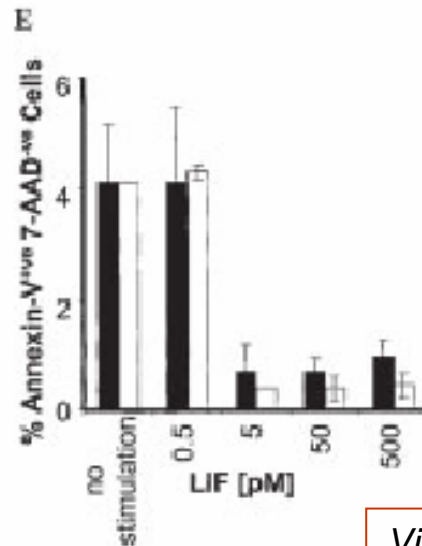
Growth factors: Wound Healing

Factor	Cell or Tissue of Origin	Selected Target Cells or Tissue	Selected Stimulatory (S) or Inhibitory (I) Actions	Clinical Trials
EGF	macrophages, monocytes	epithelium, endothelial cells	S: proliferation of keratinocytes, fibroblasts, and endothelial cells. S: keratinocyte migration.	venous ulcers
FGF	monocytes, macrophages, endothelial cells	endothelium, fibroblasts, keratinocytes	S: proliferation of endothelial cells, keratinocytes, and fibroblasts. S: chemotaxis, ECM	diabetic ulcers, venous ulcers, pressure ulcers
GM-CSF	macrophages, fibroblasts, endothelial cells	hematopoietic, inflammatory cells, neutrophils, fibroblasts	S: chemotaxis of endothelial cells, inflammatory cells S: keratinocyte proliferation, activation of neutrophils	venous and arterial ulcers
HGH	pituitary gland	hepatocytes, bone, fibroblasts	S: IGF-1 production	venous ulcers
IL-1	lymphocytes, macrophages, keratinocytes	monocytes, neutrophils, fibroblasts, keratinocytes	S: monocytes, neutrophils S: macrophage chemotaxis	pressure ulcers
PDGF	platelets, macrophages, neutrophils, smooth muscle cells	fibroblasts, smooth muscle cells	S: proliferation of smooth muscle cells and fibroblasts S: chemotaxis S: ECM, contraction	diabetic ulcers, pressure ulcers
TGF-β	platelets, bone, most cell types	fibroblasts, endothelial cells, keratinocytes, lymphocytes, monocytes	S: ECM, fibroblast activity S: chemotaxis I: proliferation of keratinocytes, endothelial cells	venous ulcers, pressure ulcers

LIF Promotes ES Cell Proliferation



Increased growth



Decreased apoptosis

Further Reading

- Biology of cell cycle
 - Molecular Biology of the Cell
 - Introduction to Genetic Analysis (Griffiths et al.)
- Growth factors and wound healing
 - Harding et al., BMJ, 324:160.
- Cell cycle genes as oncogenic targets
 - Senderowicz, Curr. Opin. Cell. Biol., 16:670 (2004)