

**DNA**



**RNA**



**PROTEIN**



**FUNCTION**

**Protein synthesis**



**Protein degradation**



**AMINO ACIDS**

# THE DYNAMIC STATE OF BODY CONSTITUENTS

BY

RUDOLF SCHOENHEIMER, M.D.

*Late Associate Professor of Biological Chemistry,  
Columbia University*

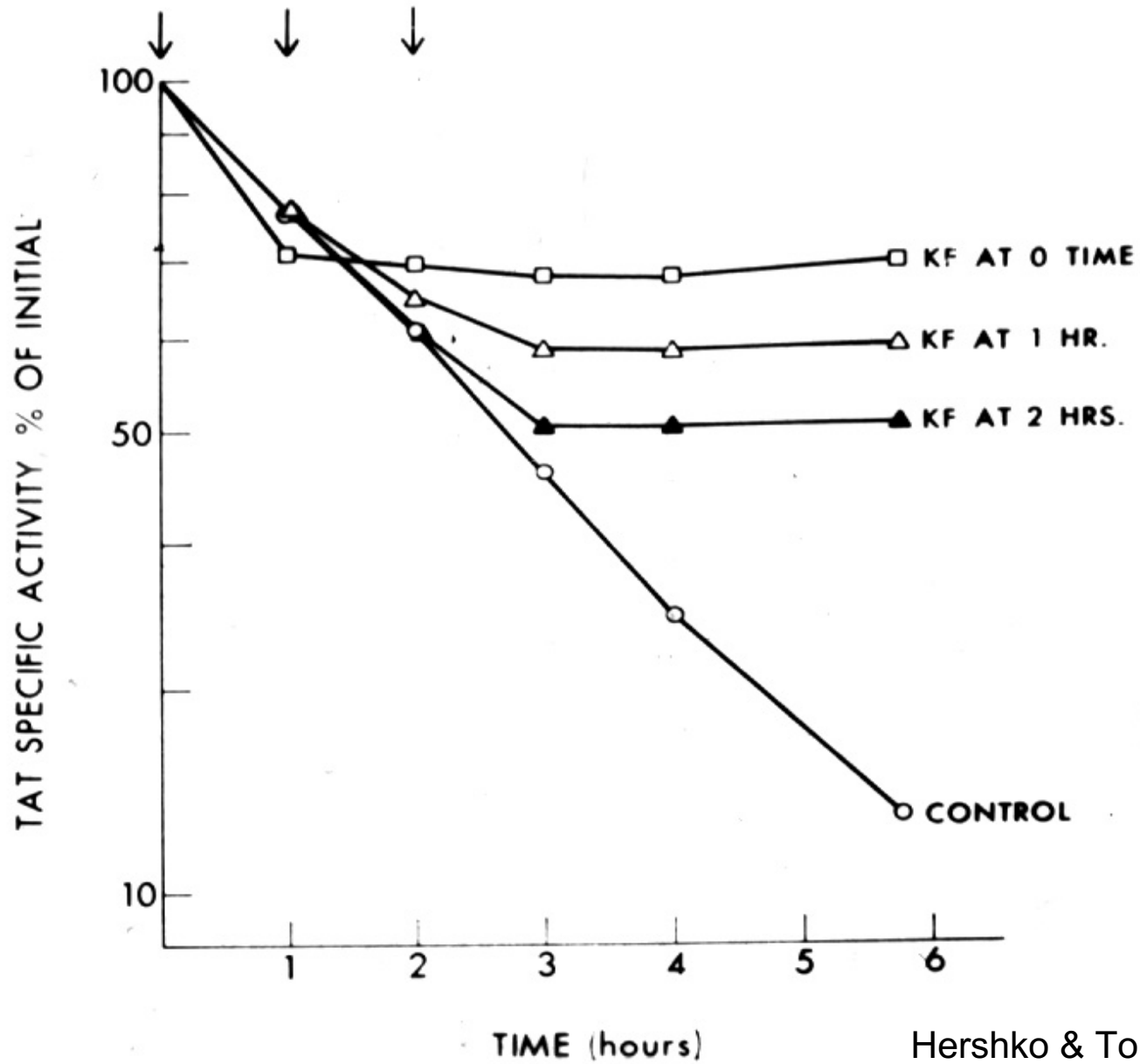


CAMBRIDGE, MASSACHUSETTS  
HARVARD UNIVERSITY PRESS

1942

## **Some properties of intracellular protein degradation (1970).**

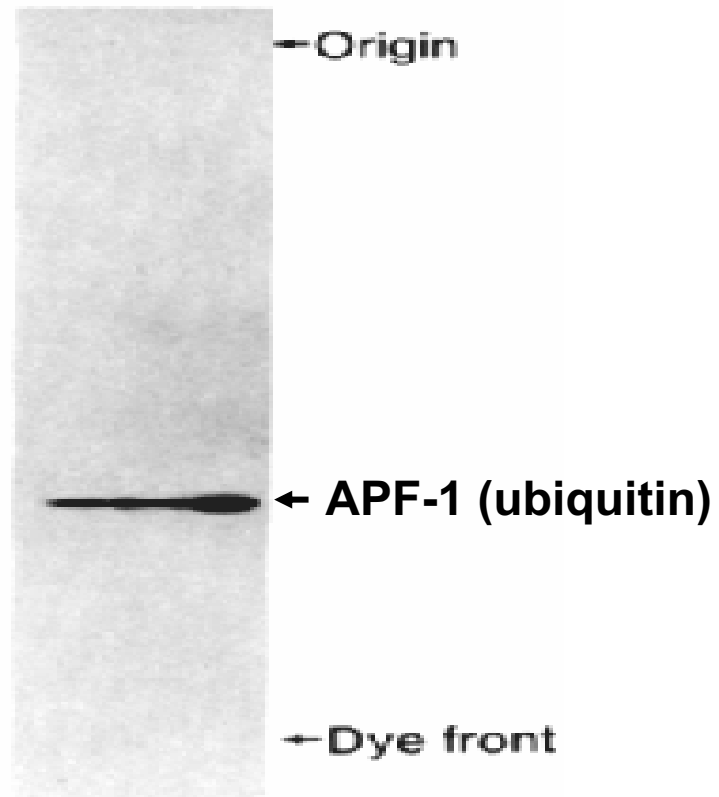
- **Abnormal proteins are rapidly eliminated.**
- **Normal proteins are selectively degraded at widely different rates.**
- **Levels of specific proteins in animal cells can be regulated by changes in rates of synthesis or rates of degradation (Schimke, 1970).**



Hershko & Tomkins JBC 1971

TABLE 1: Resolution of the ATP-Dependent Cell-Free Proteolytic System Into Complementing Activities

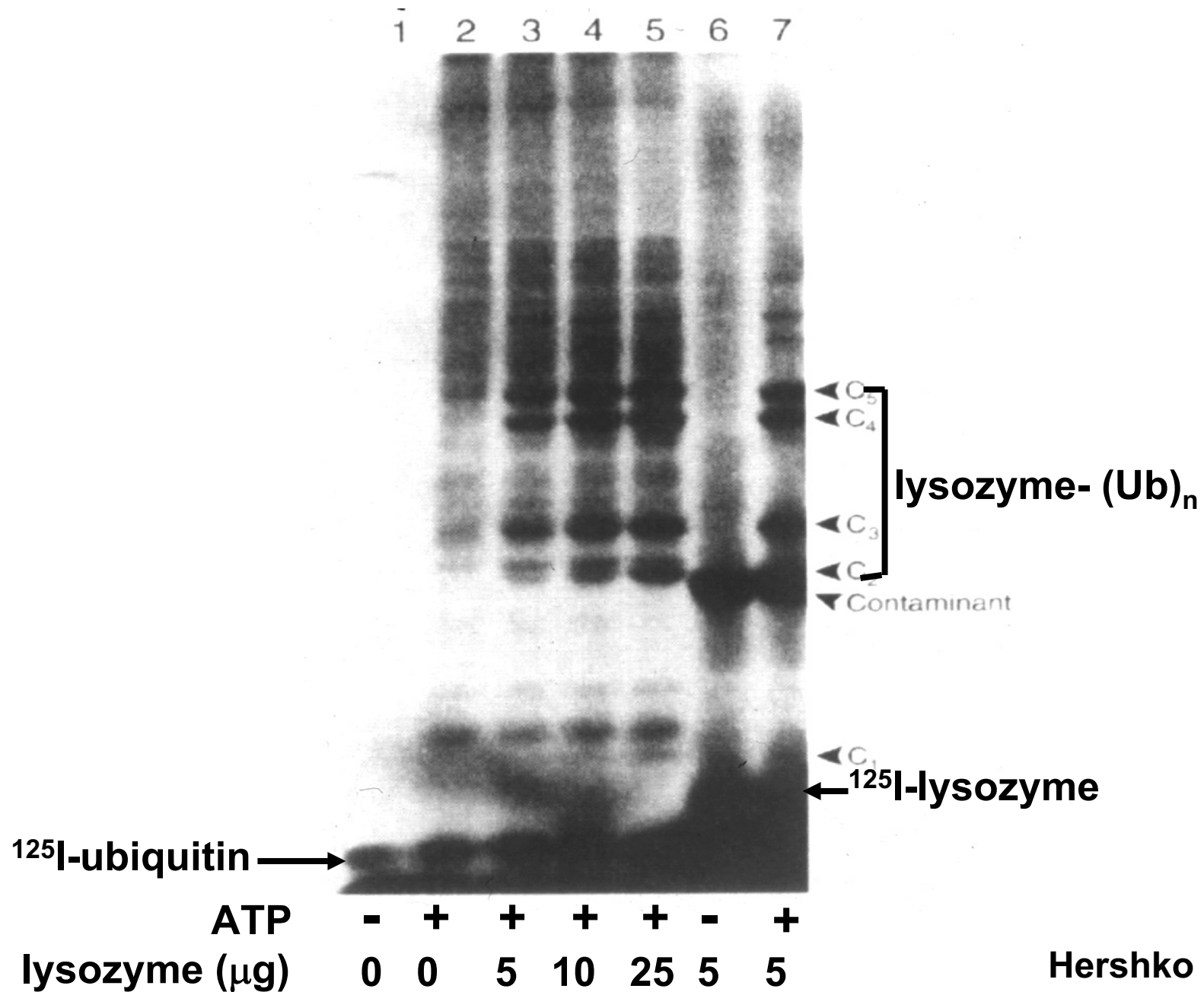
Enzyme fraction	Degradation of [ <sup>3</sup> H]globin percent/h	
	-ATP	+ATP
lysate	1.5	10.0
fraction I	0	0
fraction II	1.5	2.7
fraction I and fraction II	1.6	10.6



a b c

Protein ( $\mu\text{g}$ ) 1.5 3 7

*PNAS* 1980



Hershko *et al.*, PNAS 1980

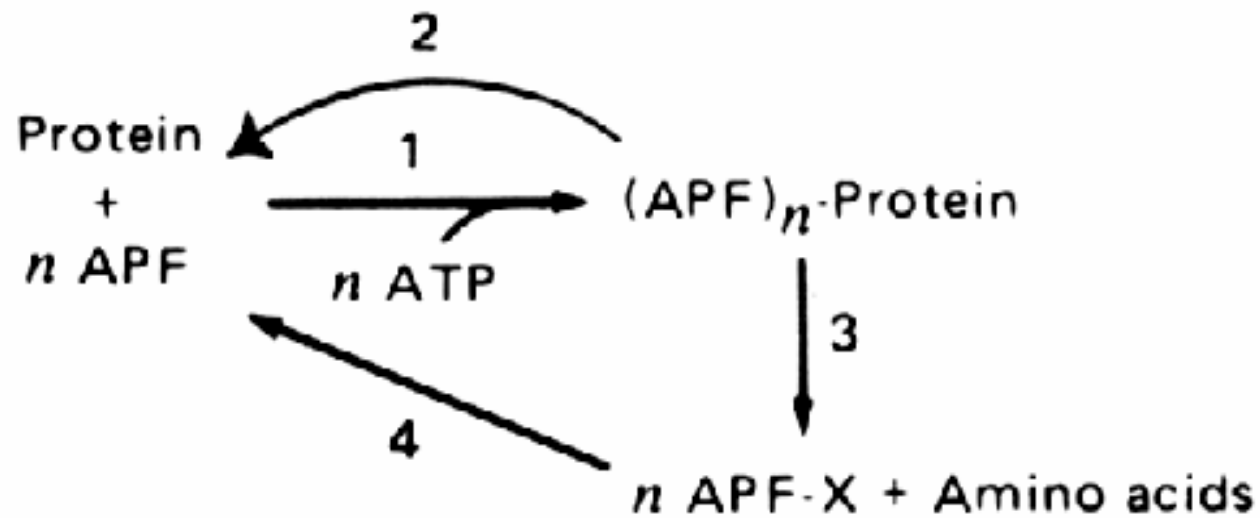
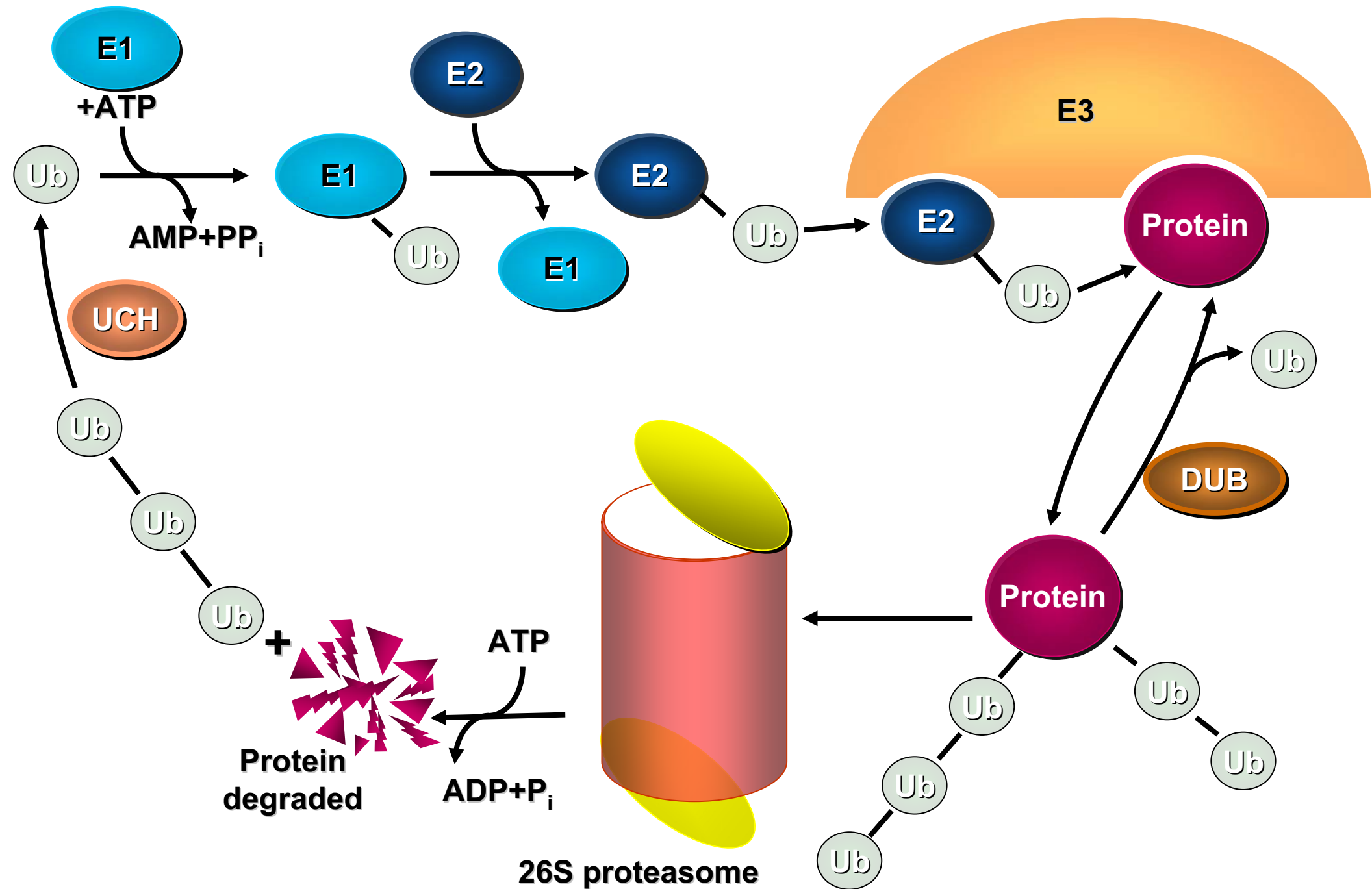
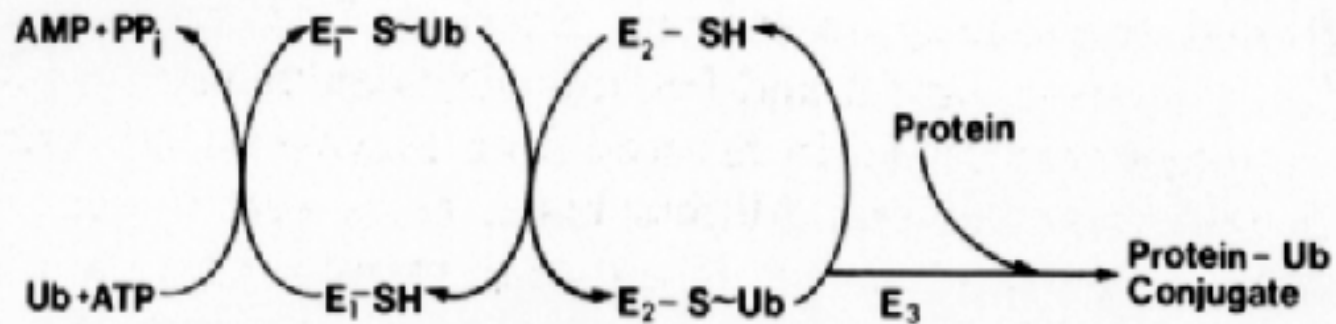


FIG. 6. Proposed sequence of events in ATP-dependent protein breakdown. See the text. 1, APF-1-protein amide synthetase (acting

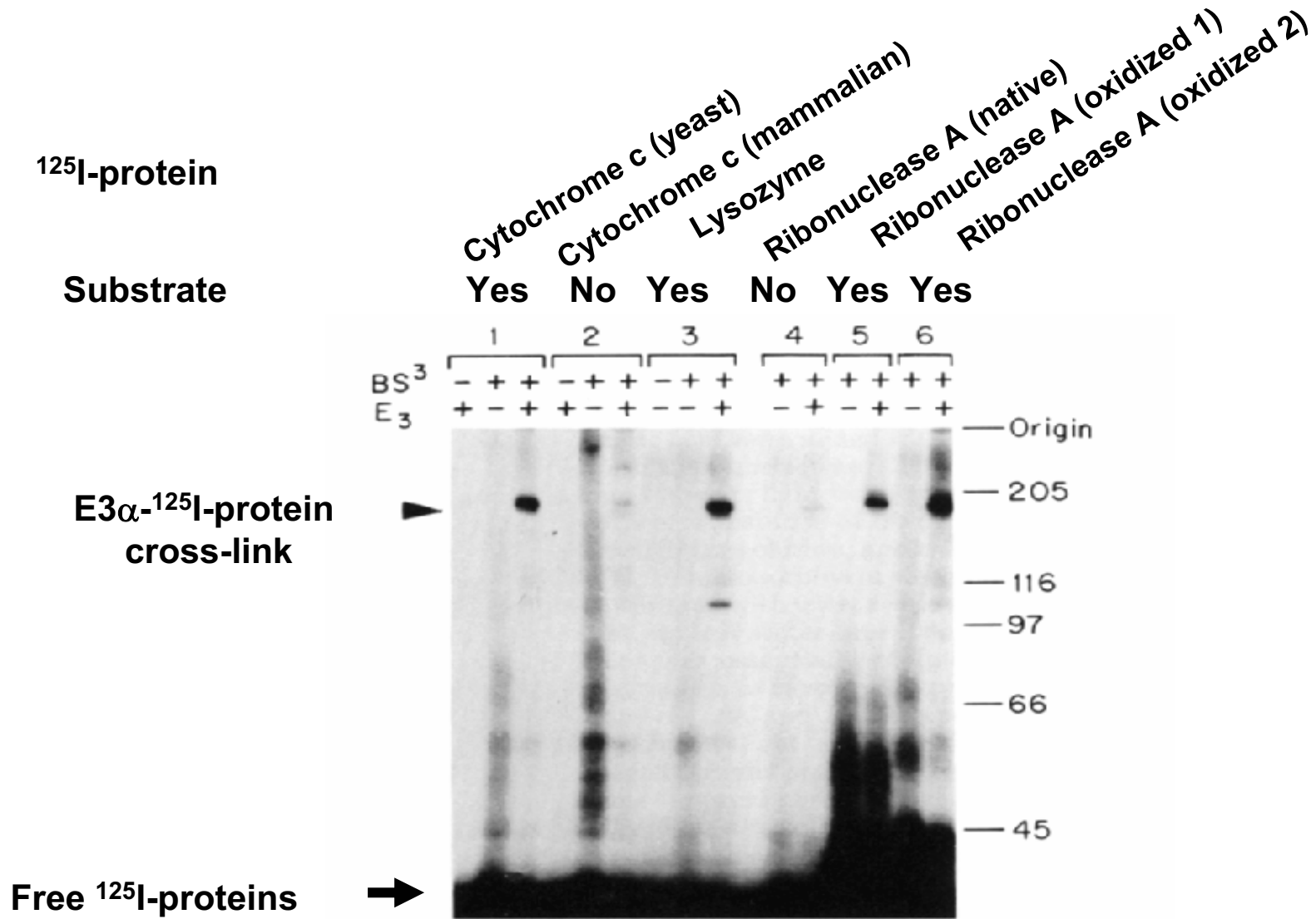


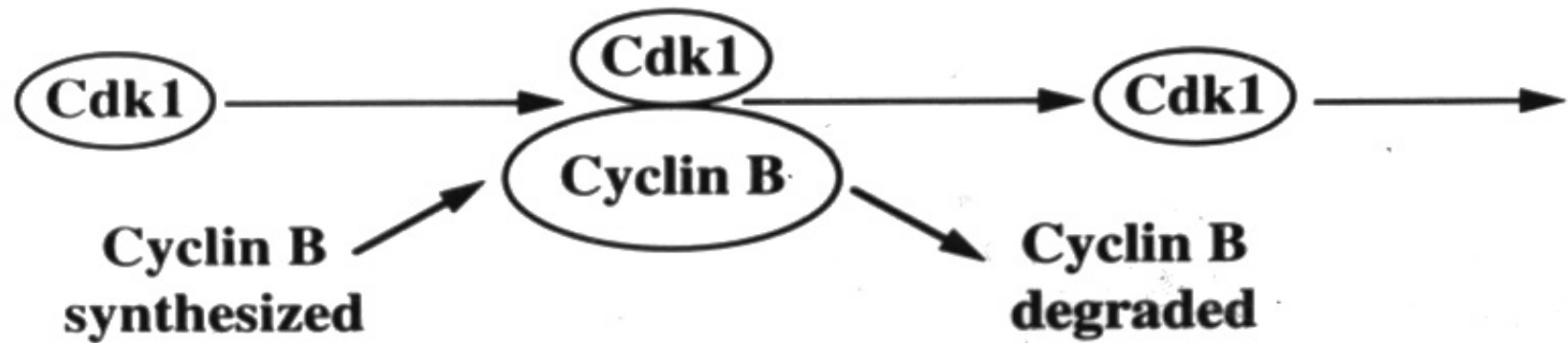
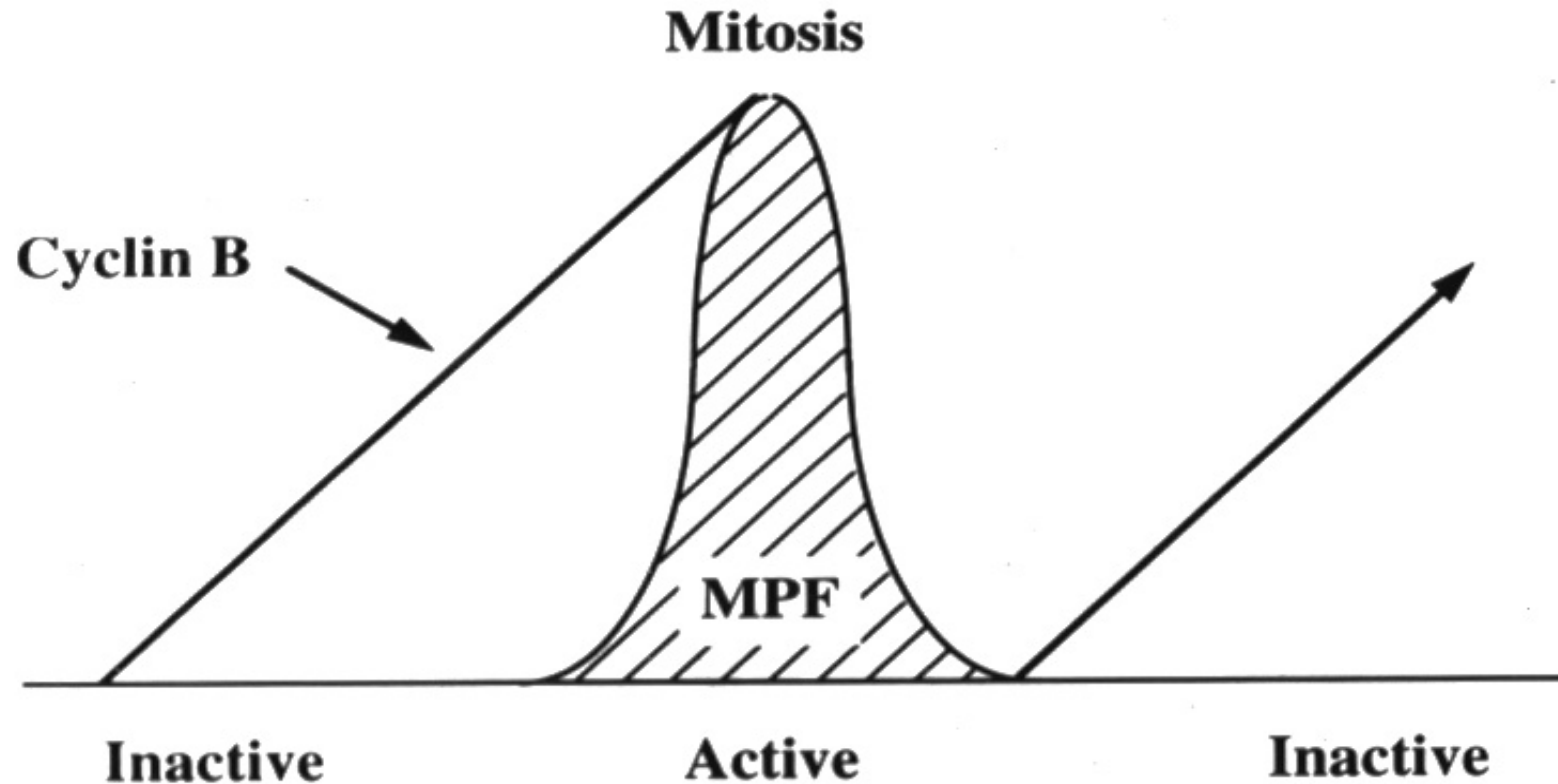




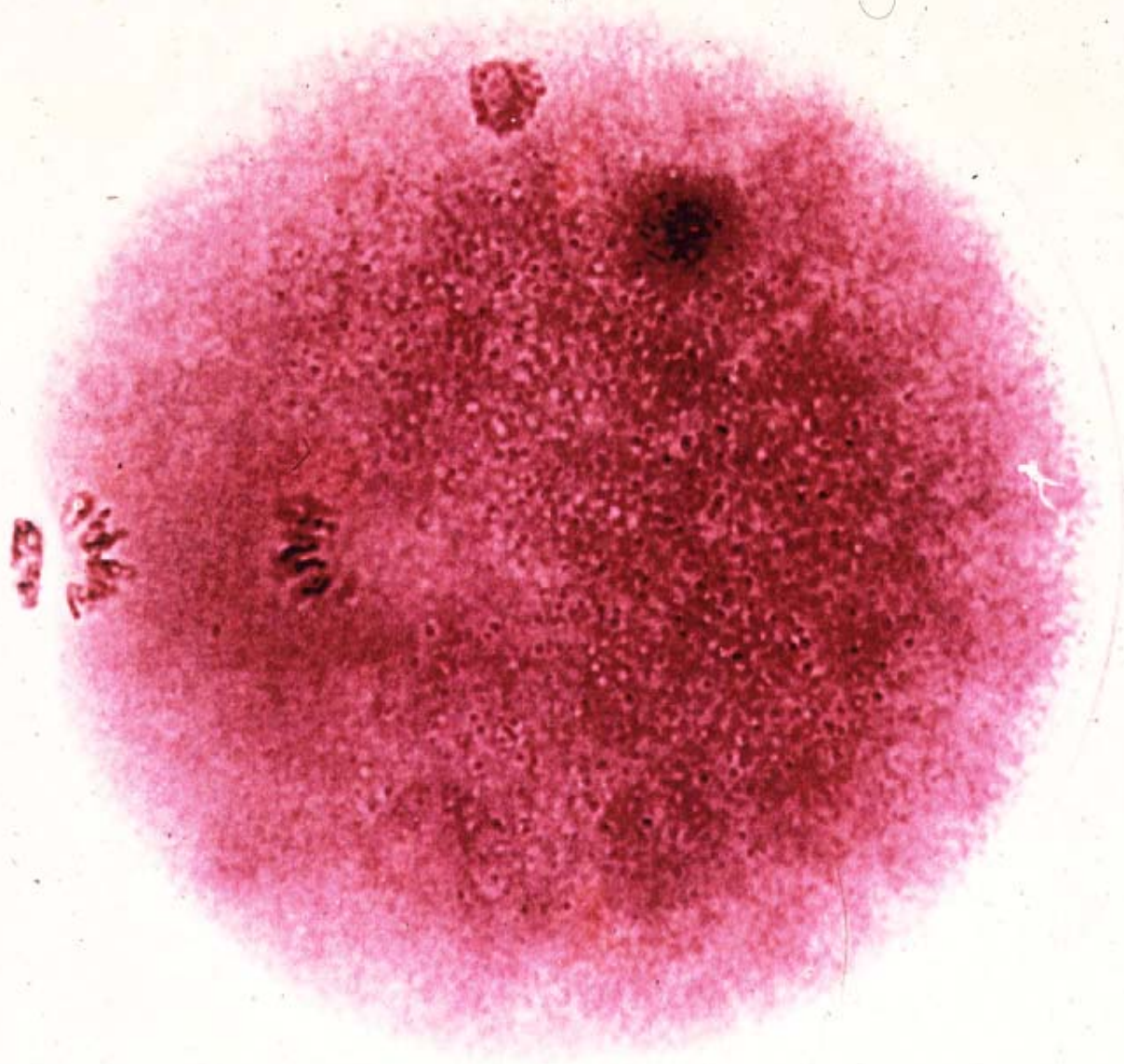
**FIG. 7. Proposed sequence of events in the ubiquitin-protein ligase system. See the text. *Ub*, ubiquitin.**

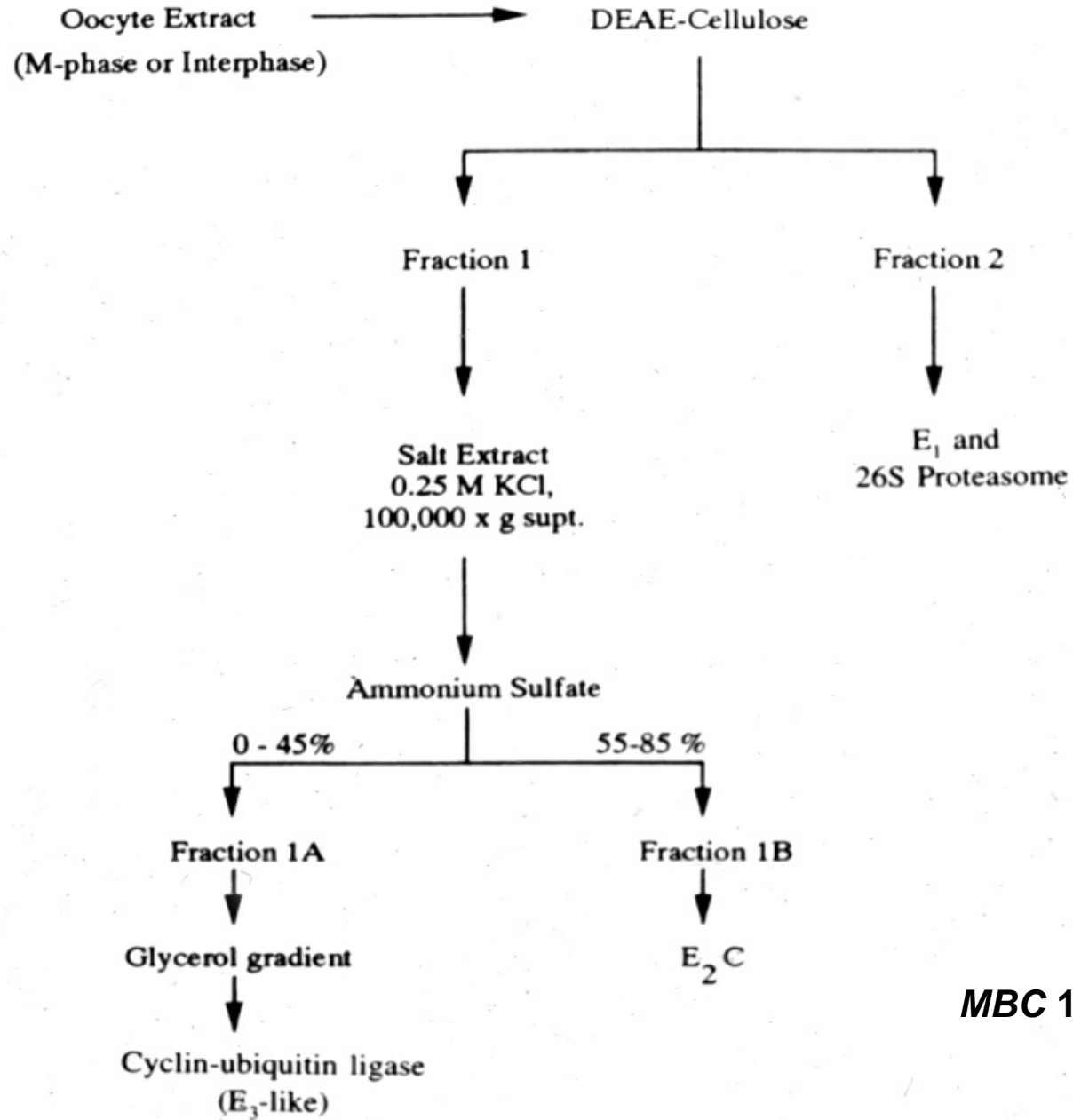
# DETECTION OF E3-SUBSTRATE BINDING BY CHEMICAL CROSS-LINKING



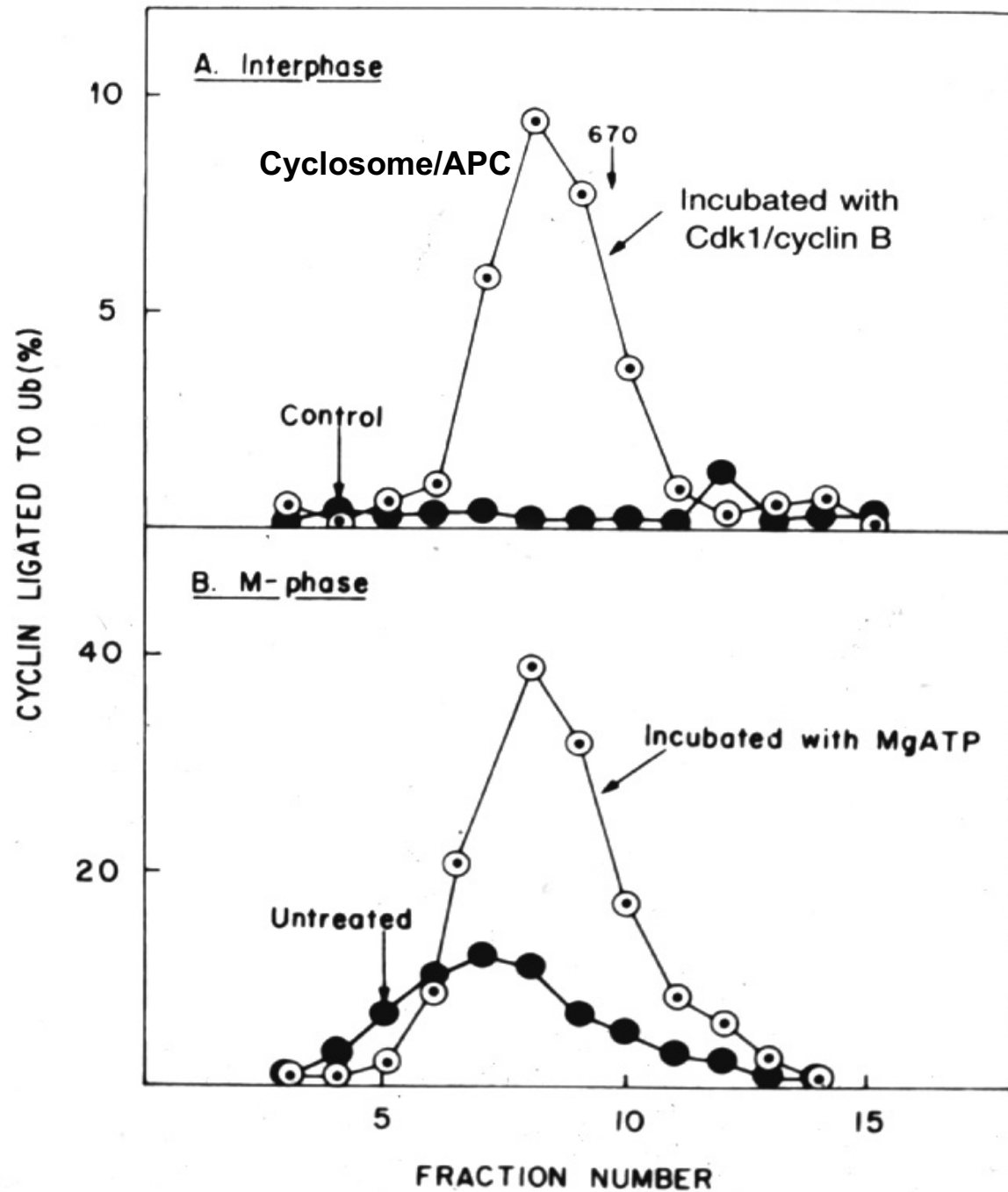




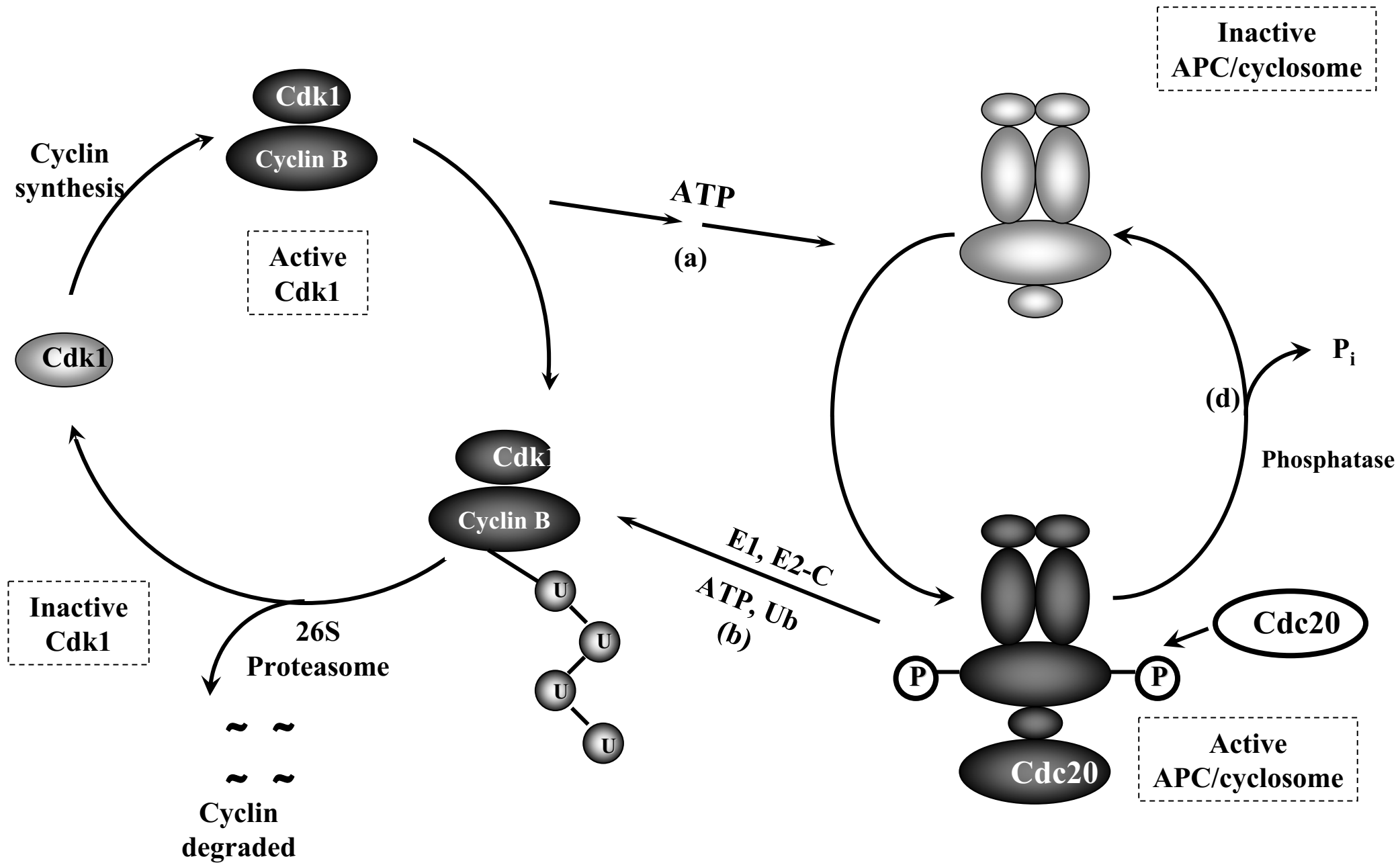


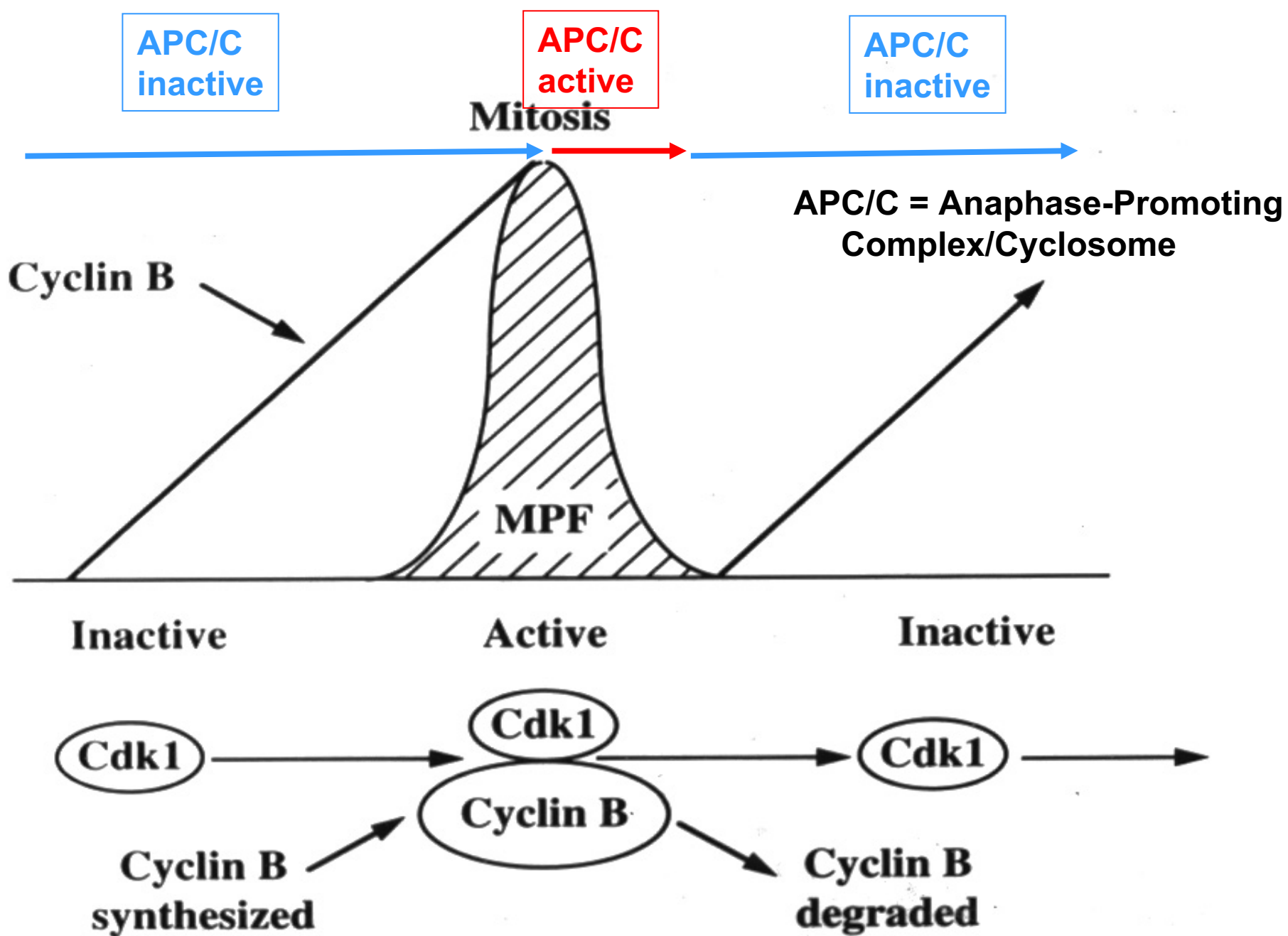


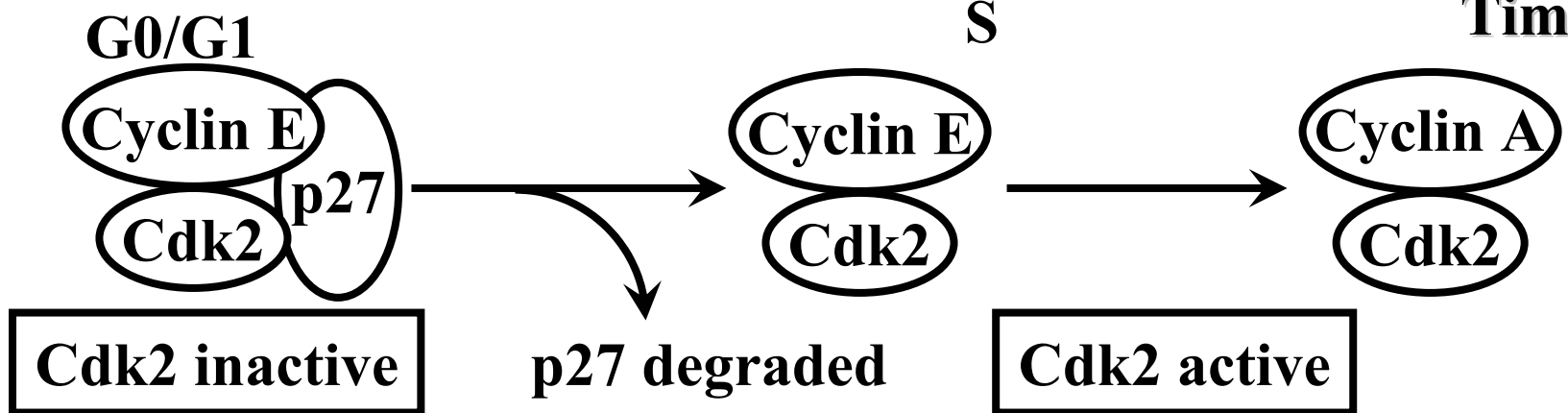
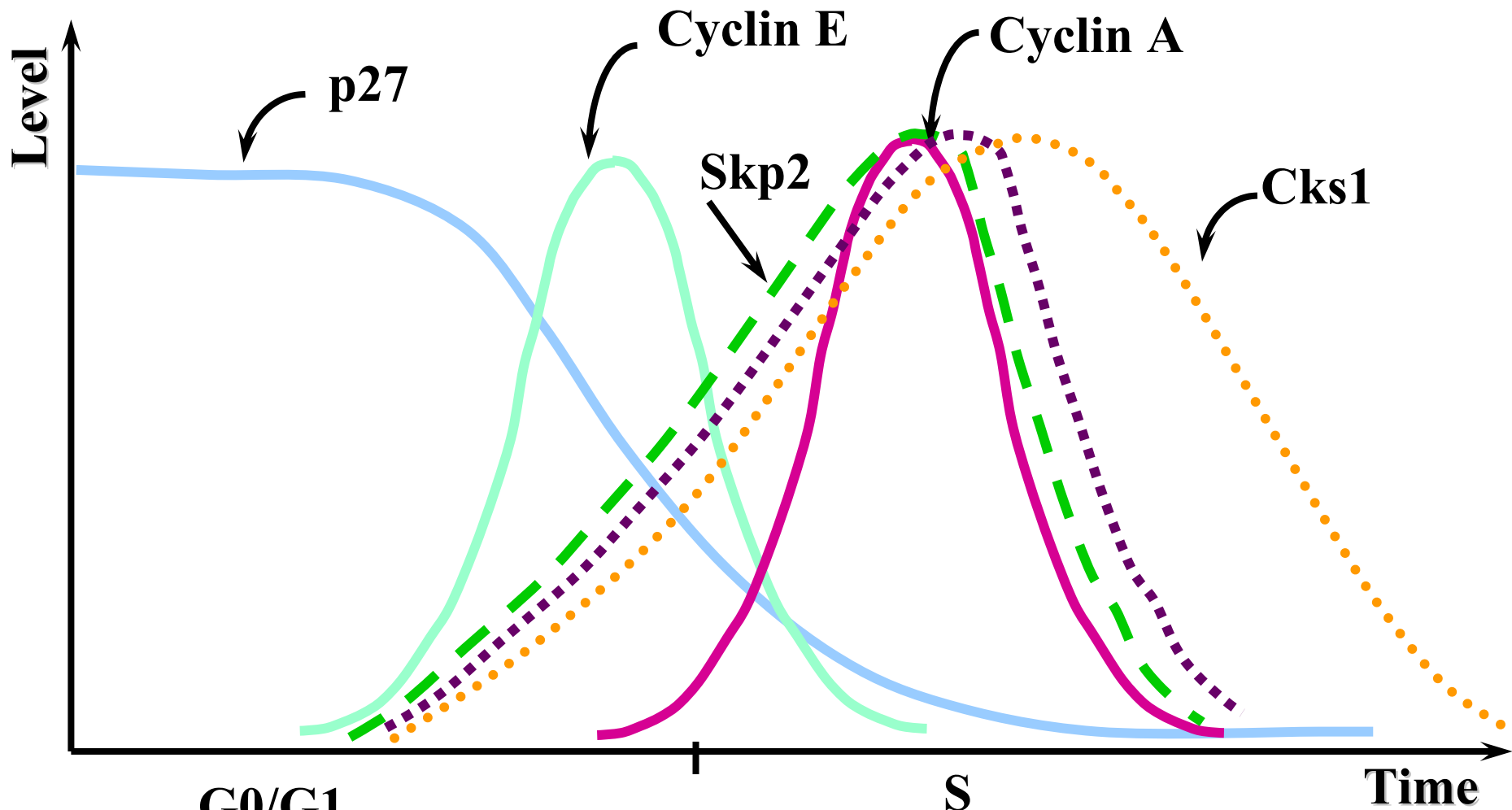
**MBC 1995**



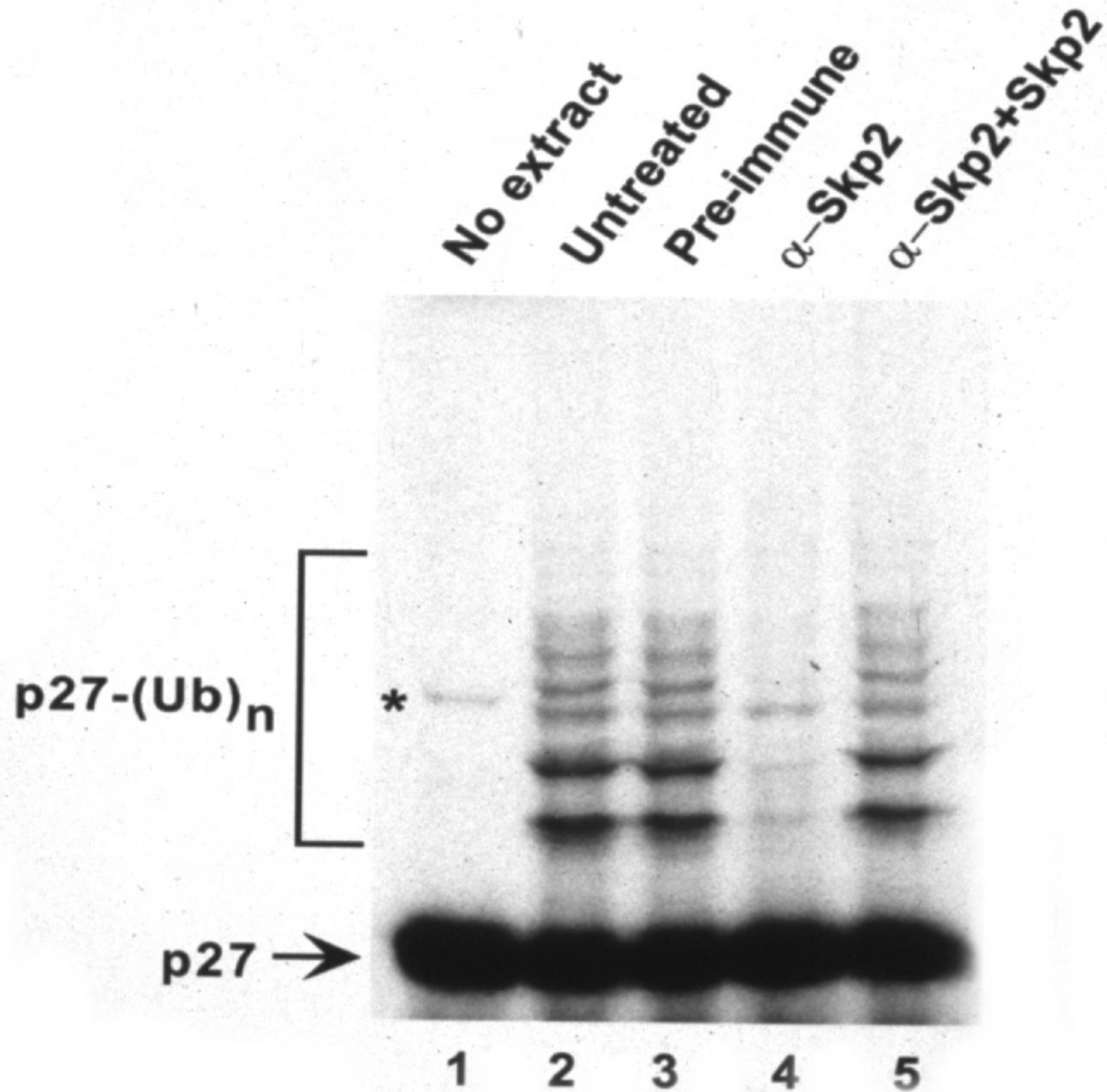








**A**

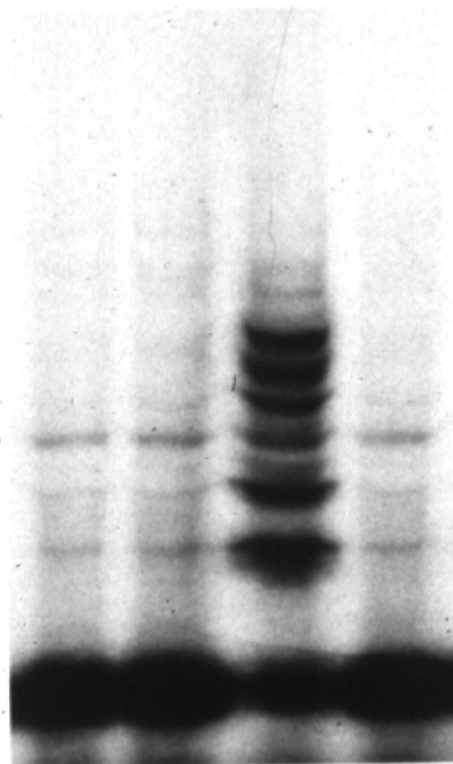


**B**

Skp1	-	+	-	-
Skp1/Skp2	-	-	+	-
Skp1/Cul1	-	-	-	+
Skp2-depl. ext.	+	+	+	+

p27-(Ub)<sub>n</sub> \*

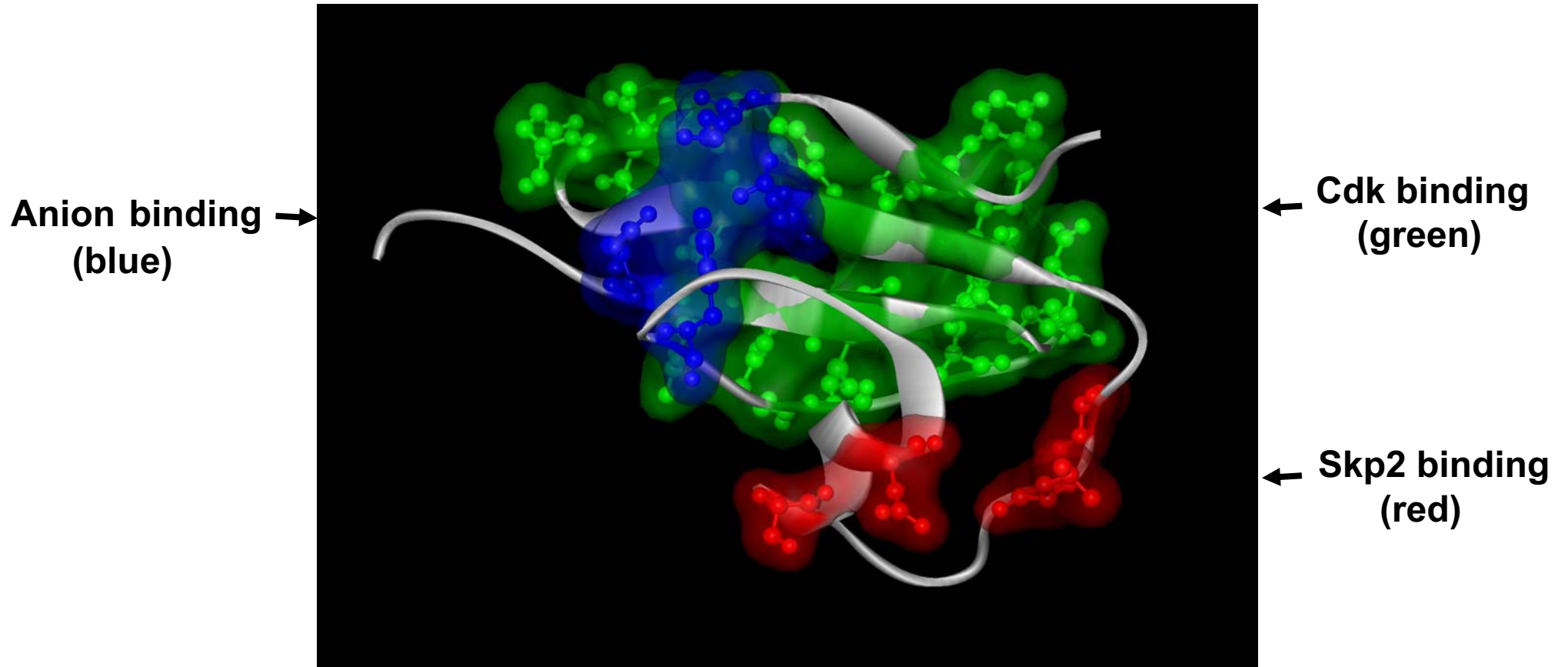
p27 →



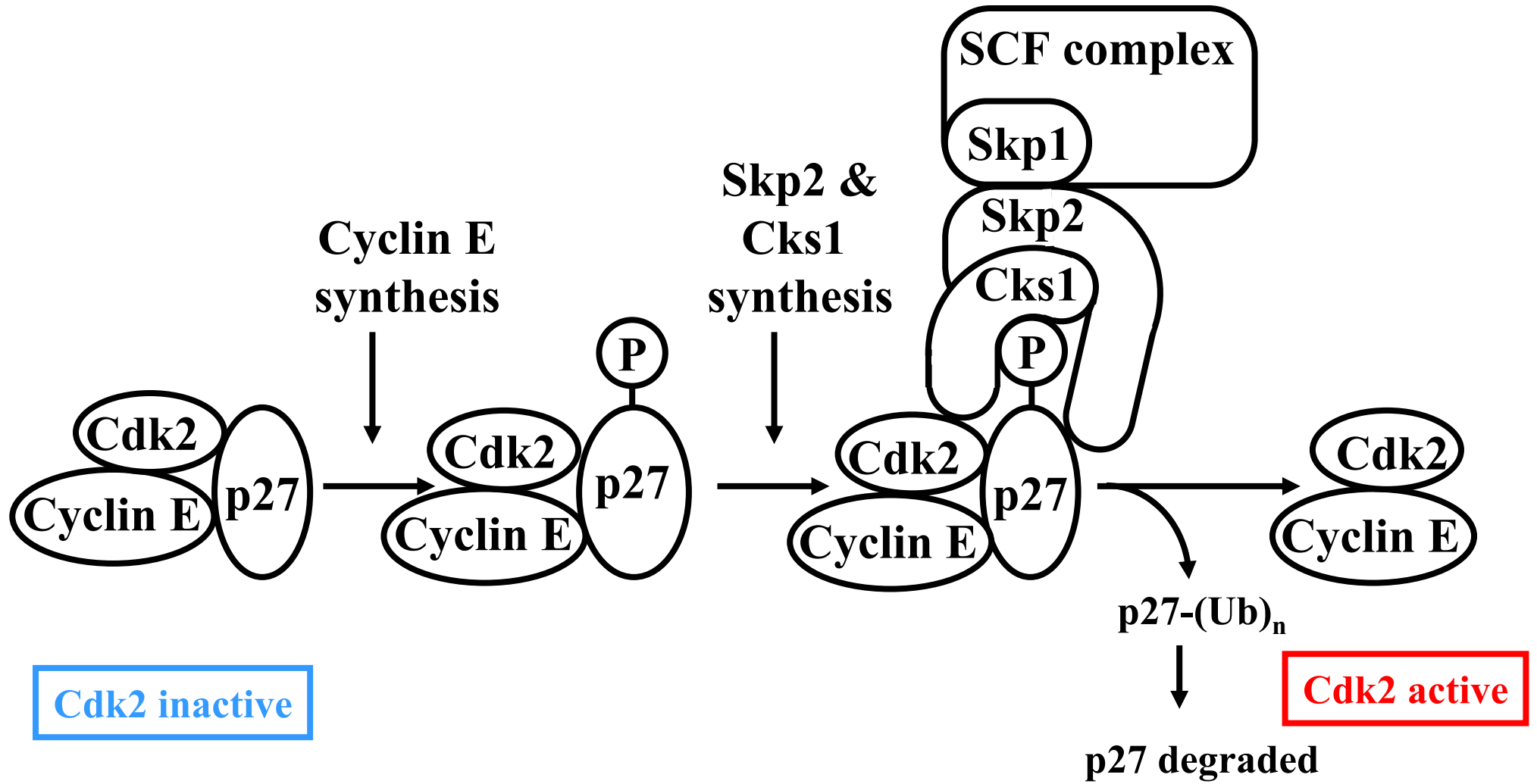
1 2 3 4

NCB 1999

## The three binding sites of Cks1



*JBC* 2002



## **Some roles of ubiquitin-mediated protein degradation.**

- **Control of cell division**
- **Signal transduction**
- **Regulation of gene expression**
- **Responses to inflammation**
- **Immune response**
- **Embryonic development**
- **Apoptosis**
- **Circadian clocks**



## Some regulatory proteins degraded by the ubiquitin system.

Type	Regulator	Role of degradation	Examples
I	Positive	Limitation of duration	Cyclins (G1, S, M-phase); transcription factors (myc, fos...)
II	Negative	Initiation of process	Cdk inhibitors Anaphase inhibitor I $\kappa$ B transcriptional regulator
III	Positive or negative	Activation by stabilization	p53 tumor suppressor; $\beta$ -catenin

**1900**

**2000**

**Microbe hunters**



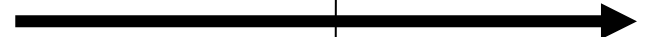
**Vitamin  
hunters**



**Enzyme hunters**



**Gene hunters**



**Arthur Kornberg : *For the Love of Enzymes* (1989)**

**Technion lab**  
**(1971-present)**

**Dvora Ganoth**  
**Hanna Heller**  
**Esther Eytan**  
**Sarah Elias**  
**Clara Segal**  
**Judith Hershko**

**Former graduate students**

**Aaron Ciechanover**  
**Yuval Reiss**  
**Valery Sudakin**  
**Shirly Lahav**  
**and many others...**

**Collaboration and help**

**Irwin A. Rose**  
**Leonard Cohen**  
**Joan Ruderman**  
**Michele Pagano**

**Present graduate students**

**Gil Bornstein**  
**Danielle Sitry-Shevah**  
**Yakir Moshe**



