

DNA



RNA



PROTEIN



FUNCTION

Protein synthesis



Protein degradation



AMINO ACIDS

THE DYNAMIC STATE OF BODY CONSTITUENTS

BY

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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).**

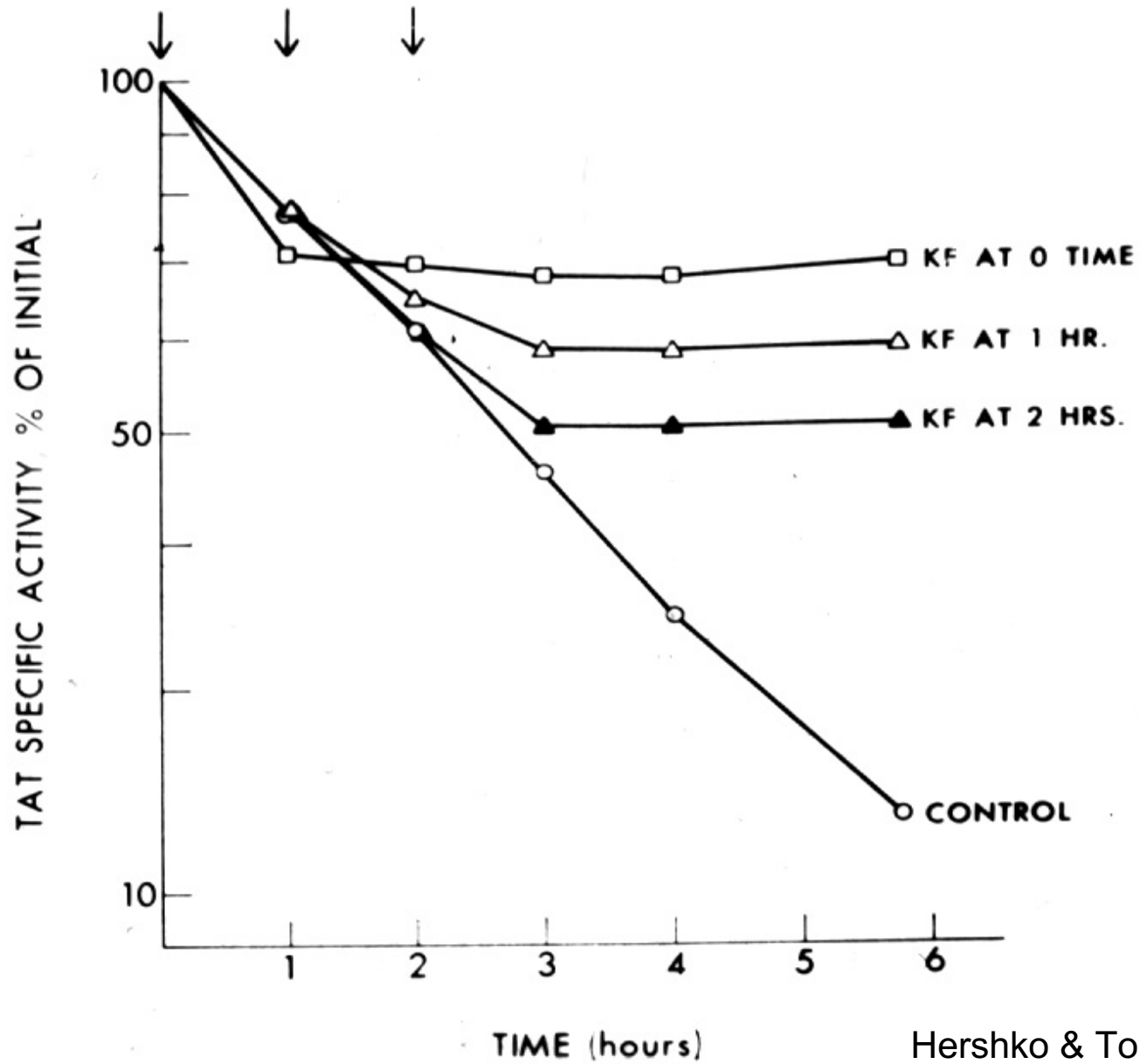
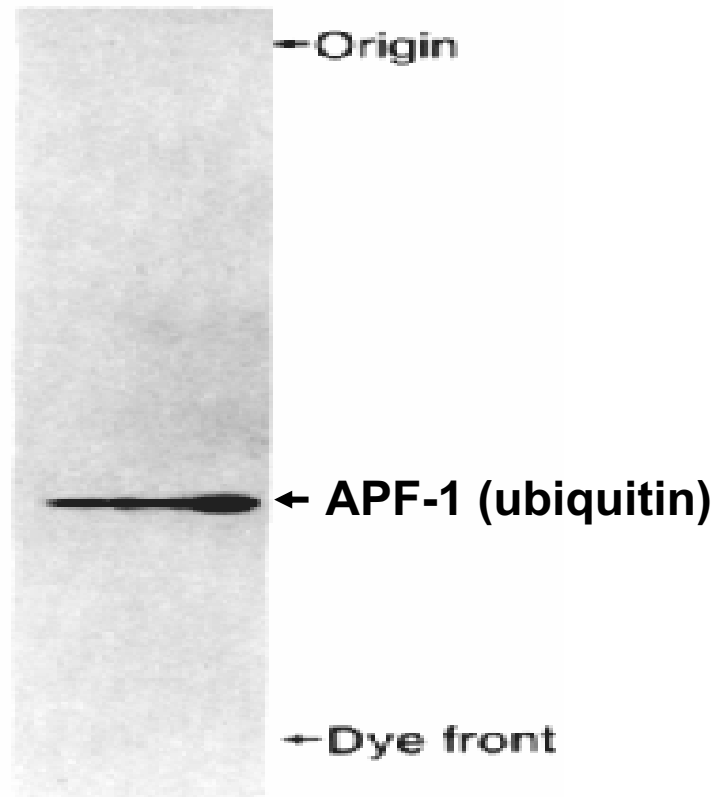


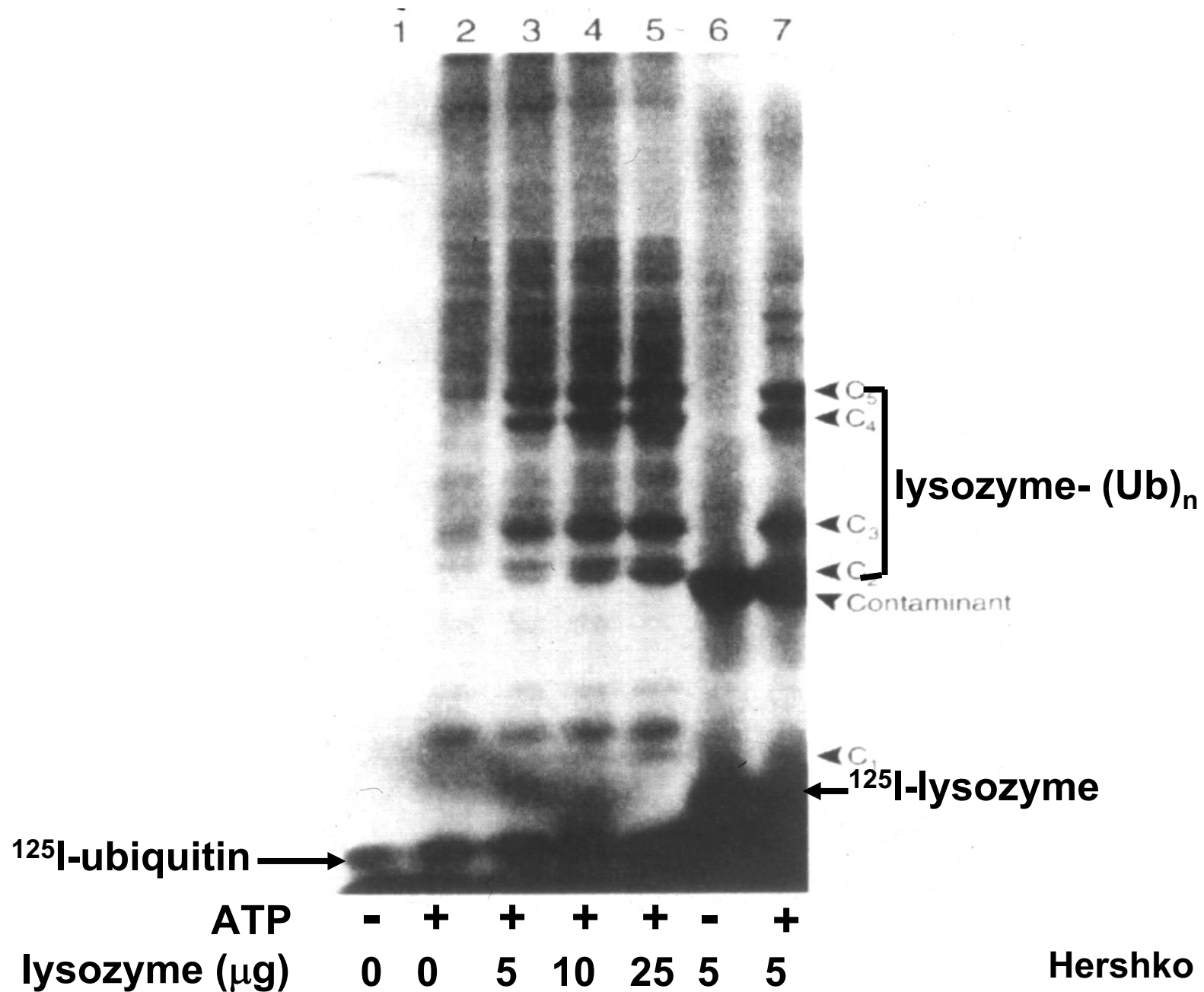
TABLE 1: Resolution of the ATP-Dependent Cell-Free Proteolytic System Into Complementing Activities

| Enzyme fraction | Degradation of [³ 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 |



Protein (μg) 1.5 3 7

PNAS 1980



Hershko *et al.*, PNAS 1980

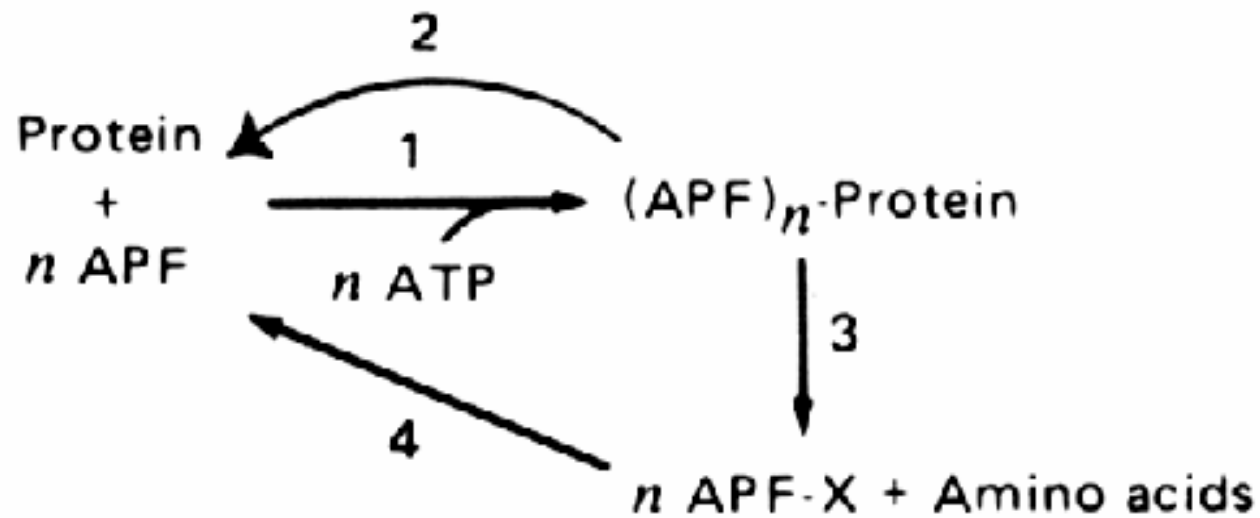
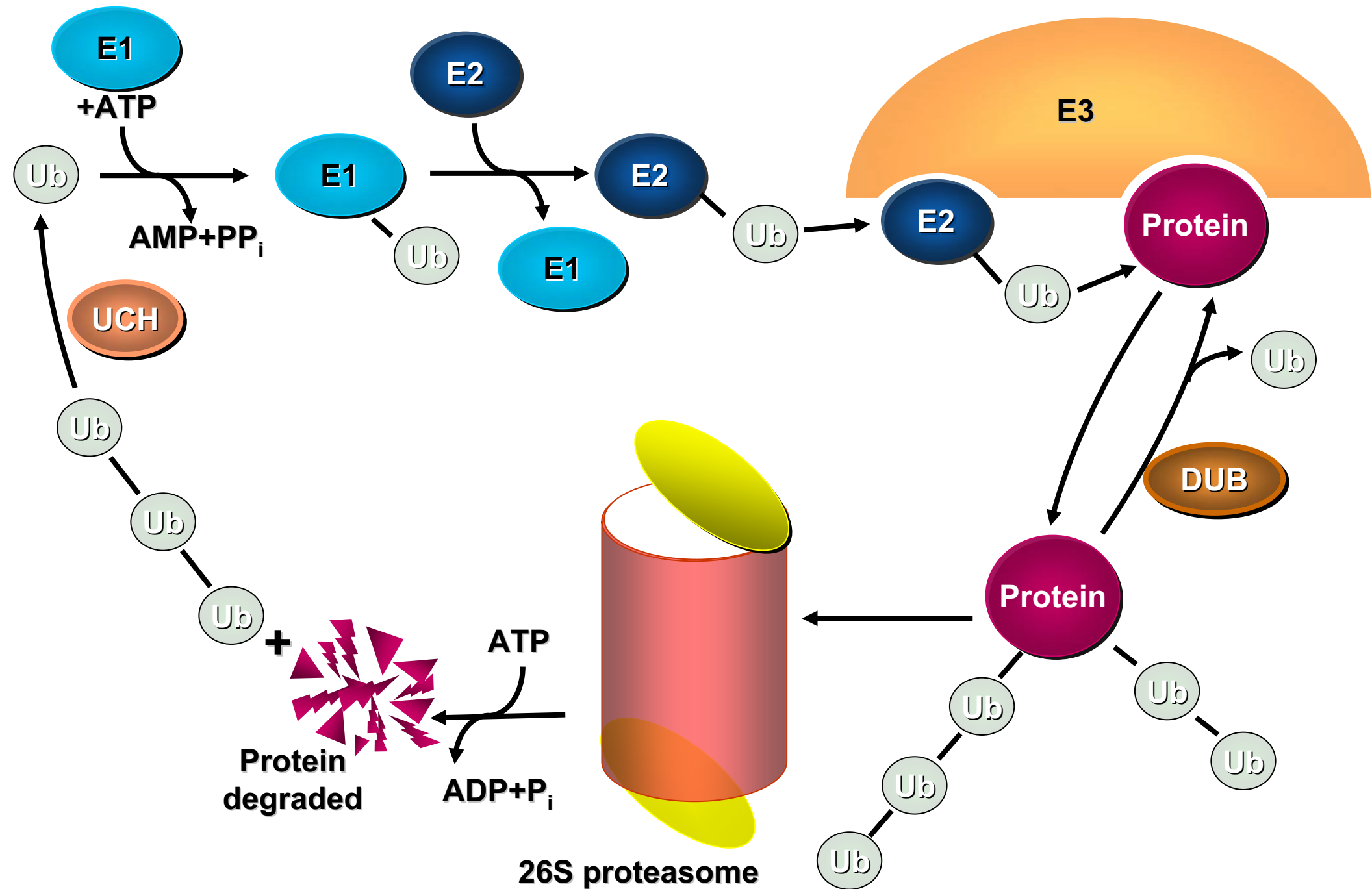


FIG. 6. Proposed sequence of events in ATP-dependent protein breakdown. See the text. 1, APF-1-protein amide synthetase (acting



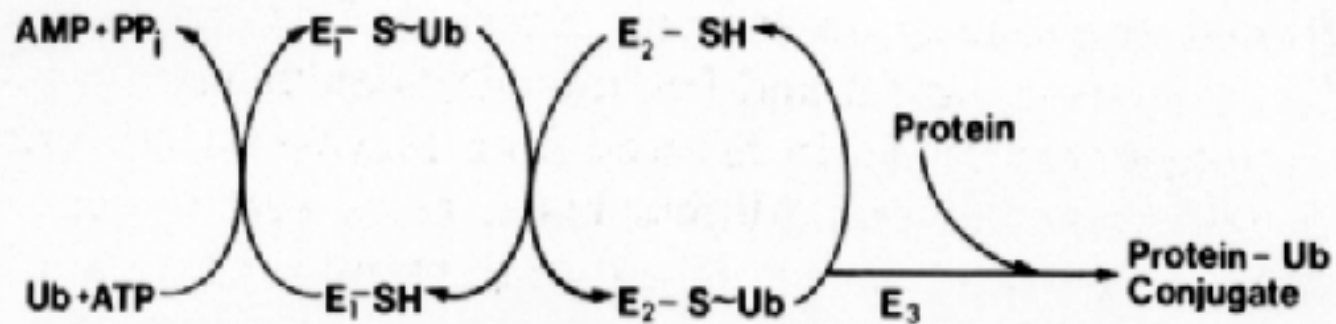
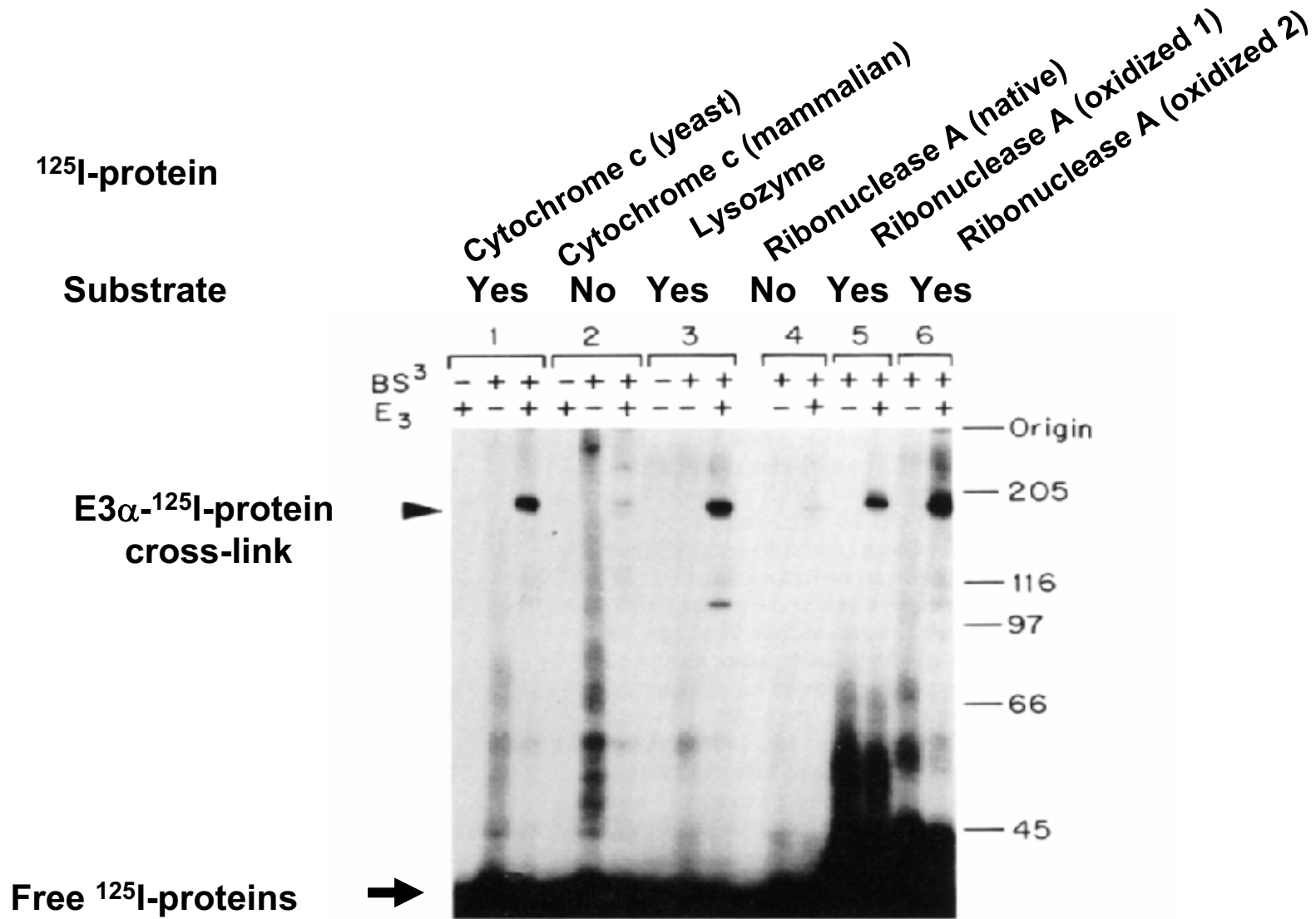
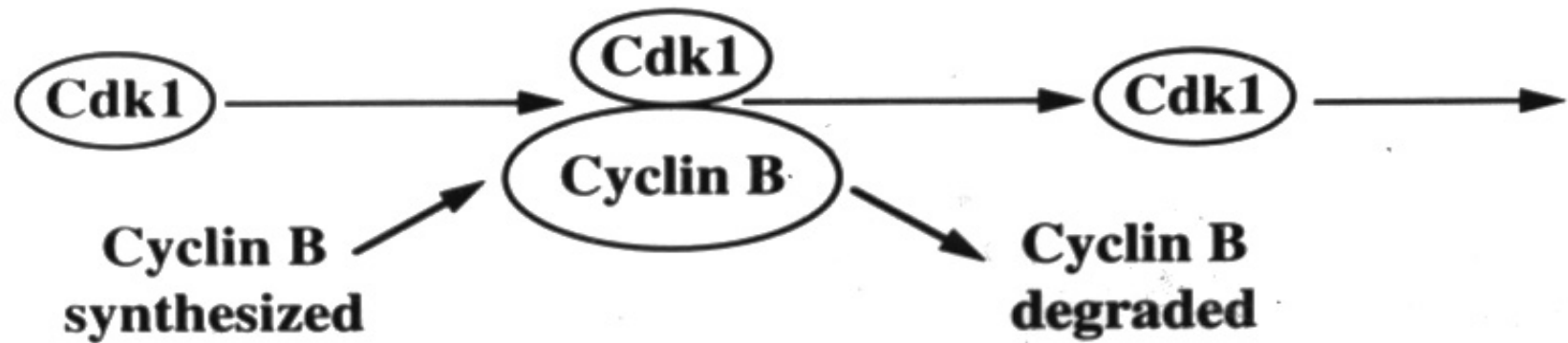
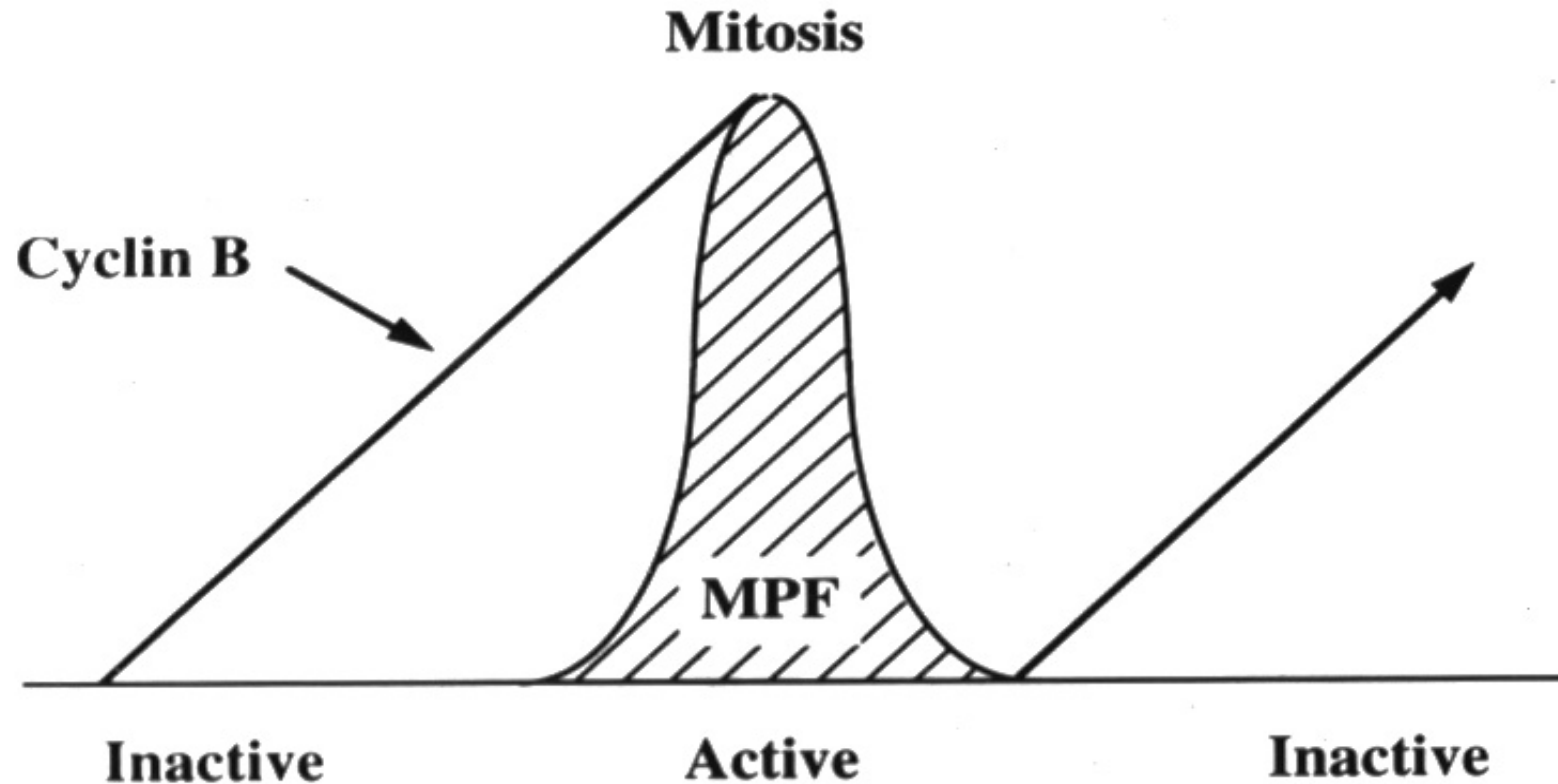


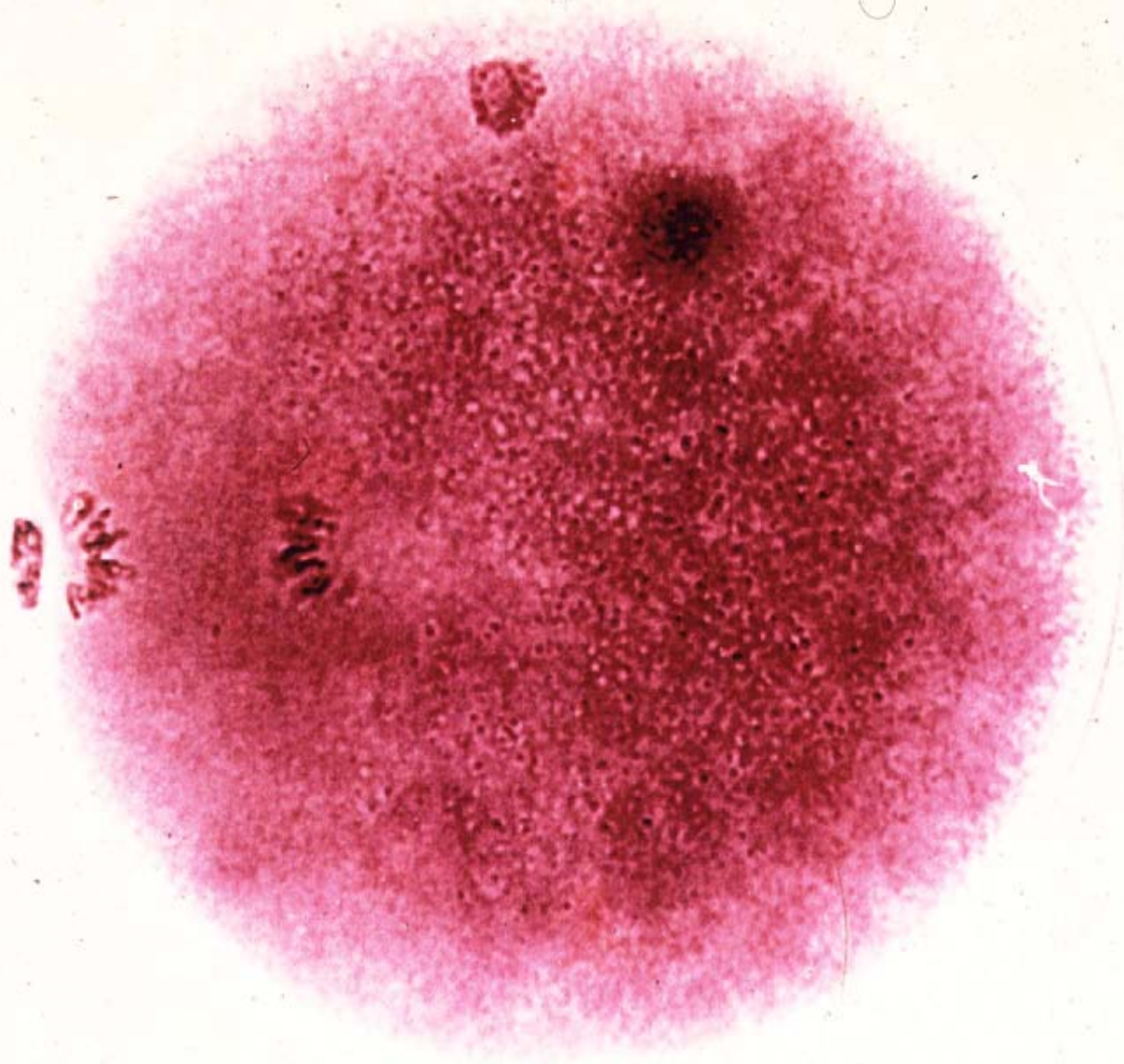
FIG. 7. Proposed sequence of events in the ubiquitin-protein ligase system. See the text. *Ub*, ubiquitin.

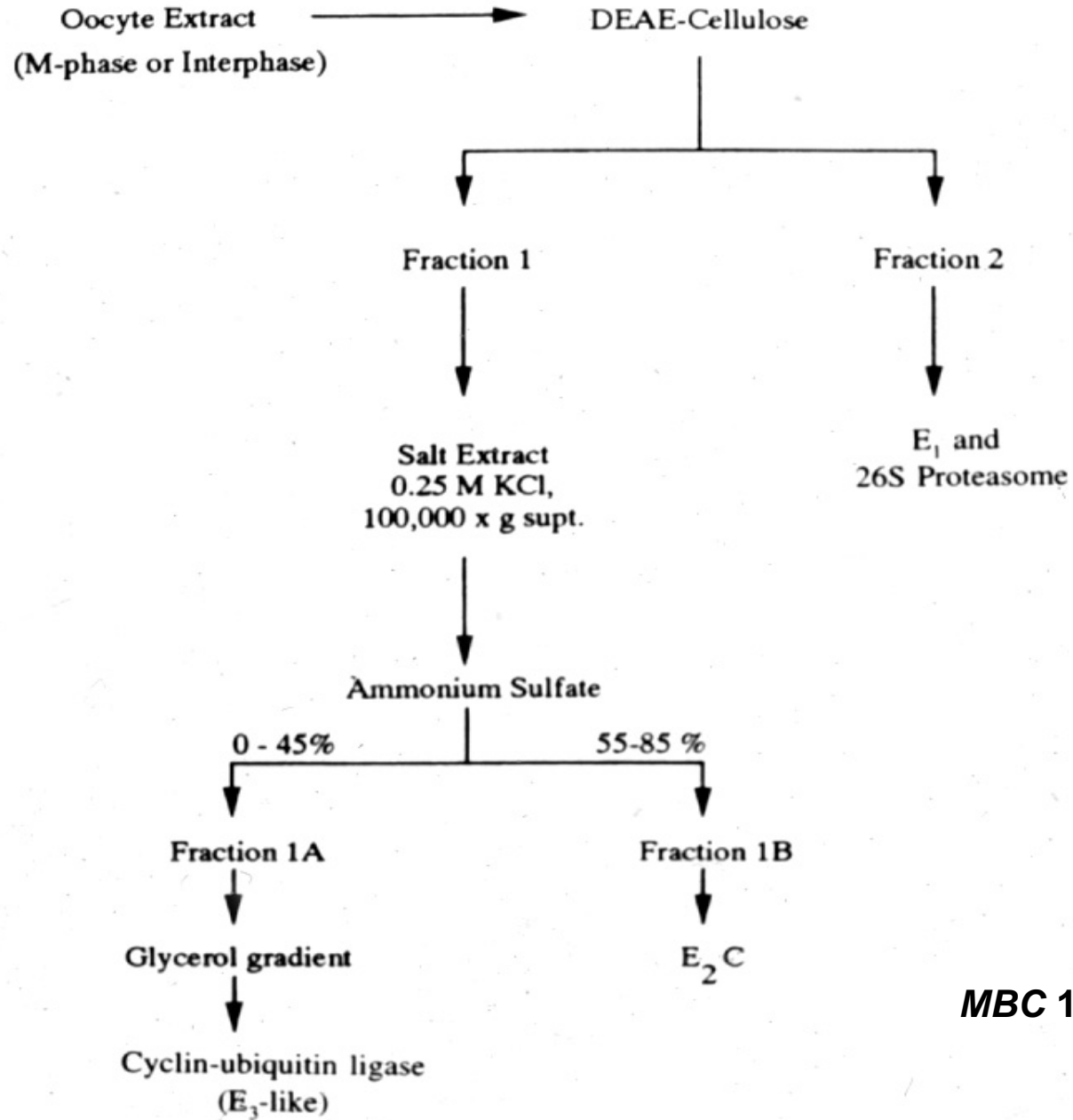
DETECTION OF E3-SUBSTRATE BINDING BY CHEMICAL CROSS-LINKING



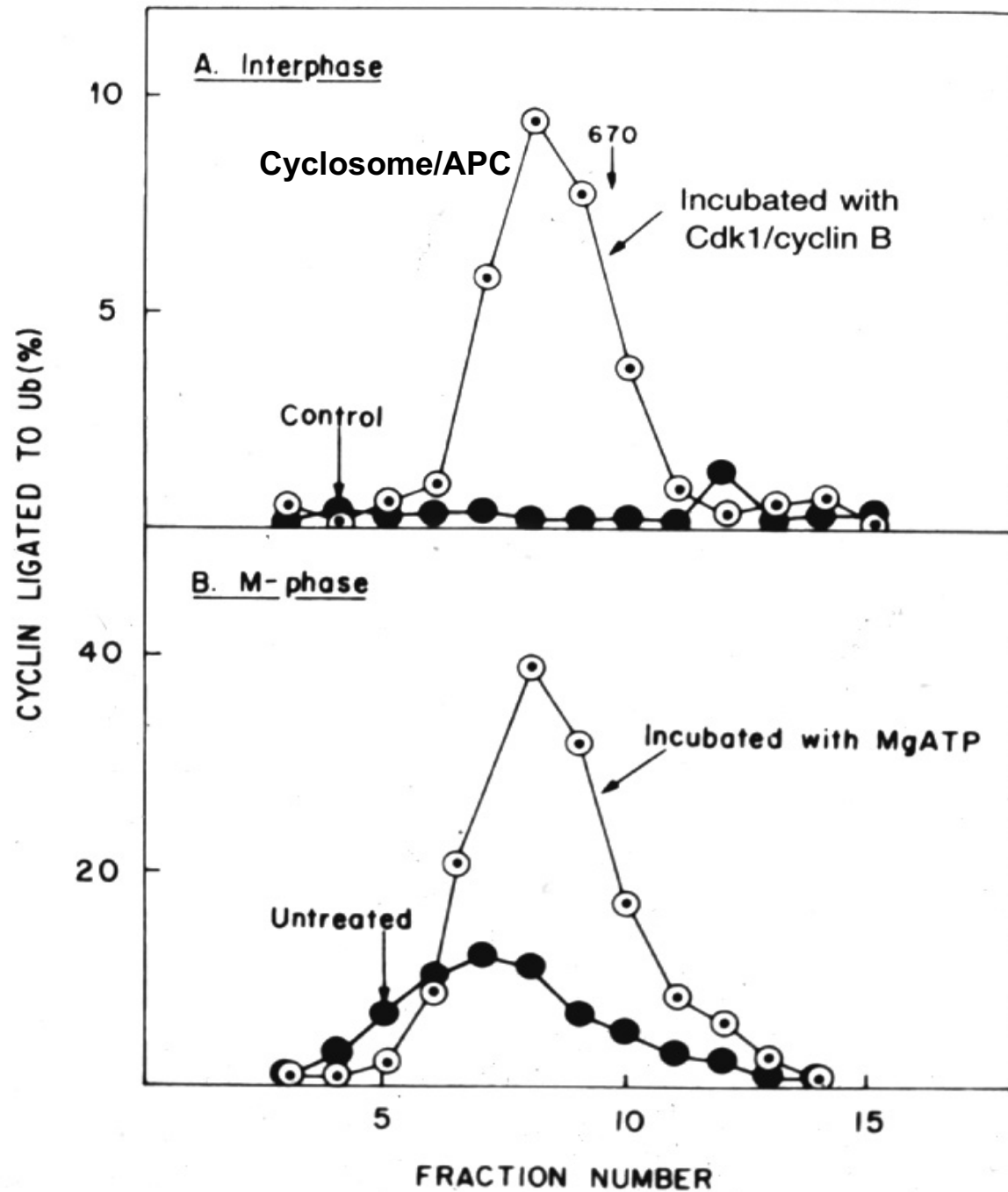


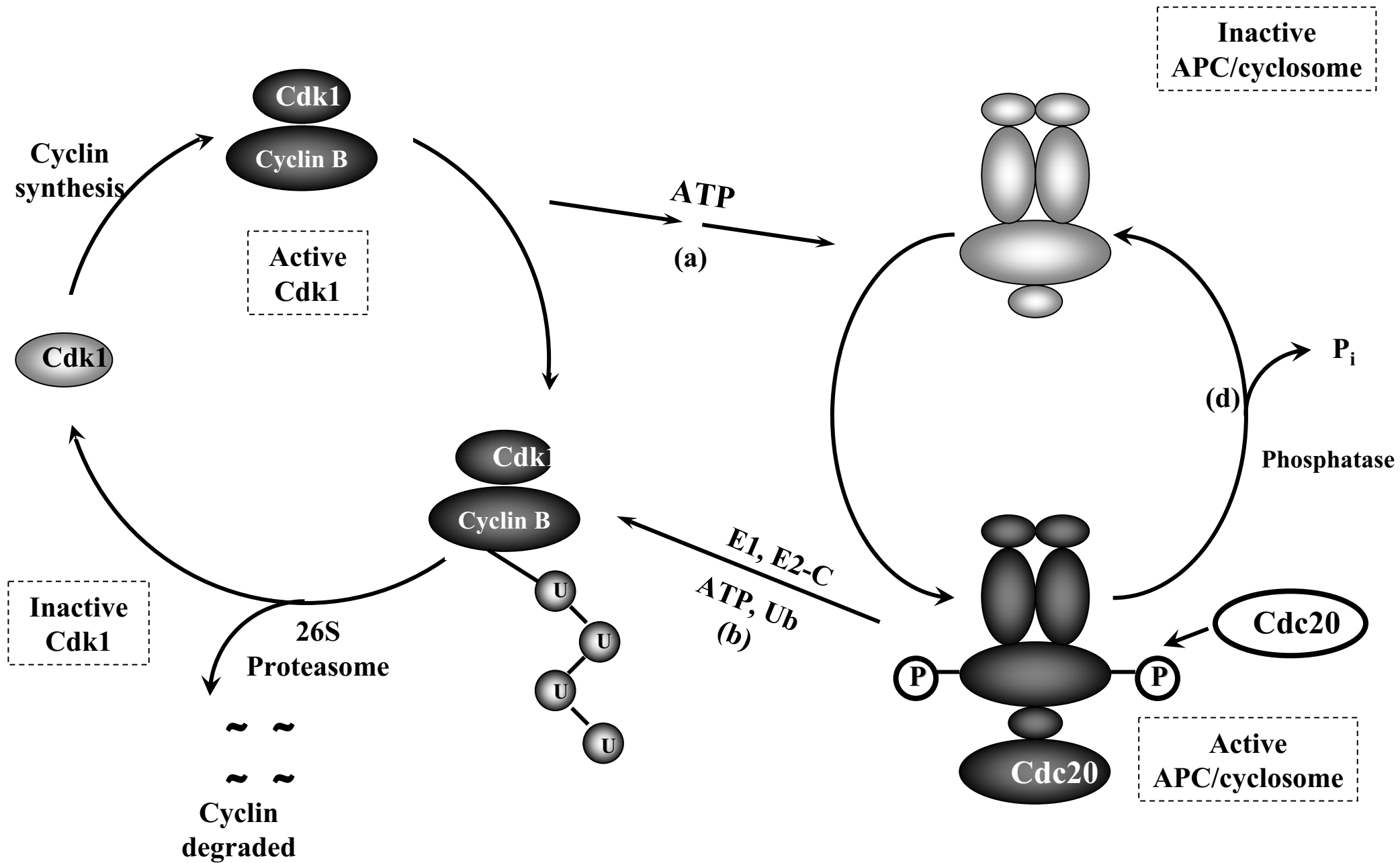


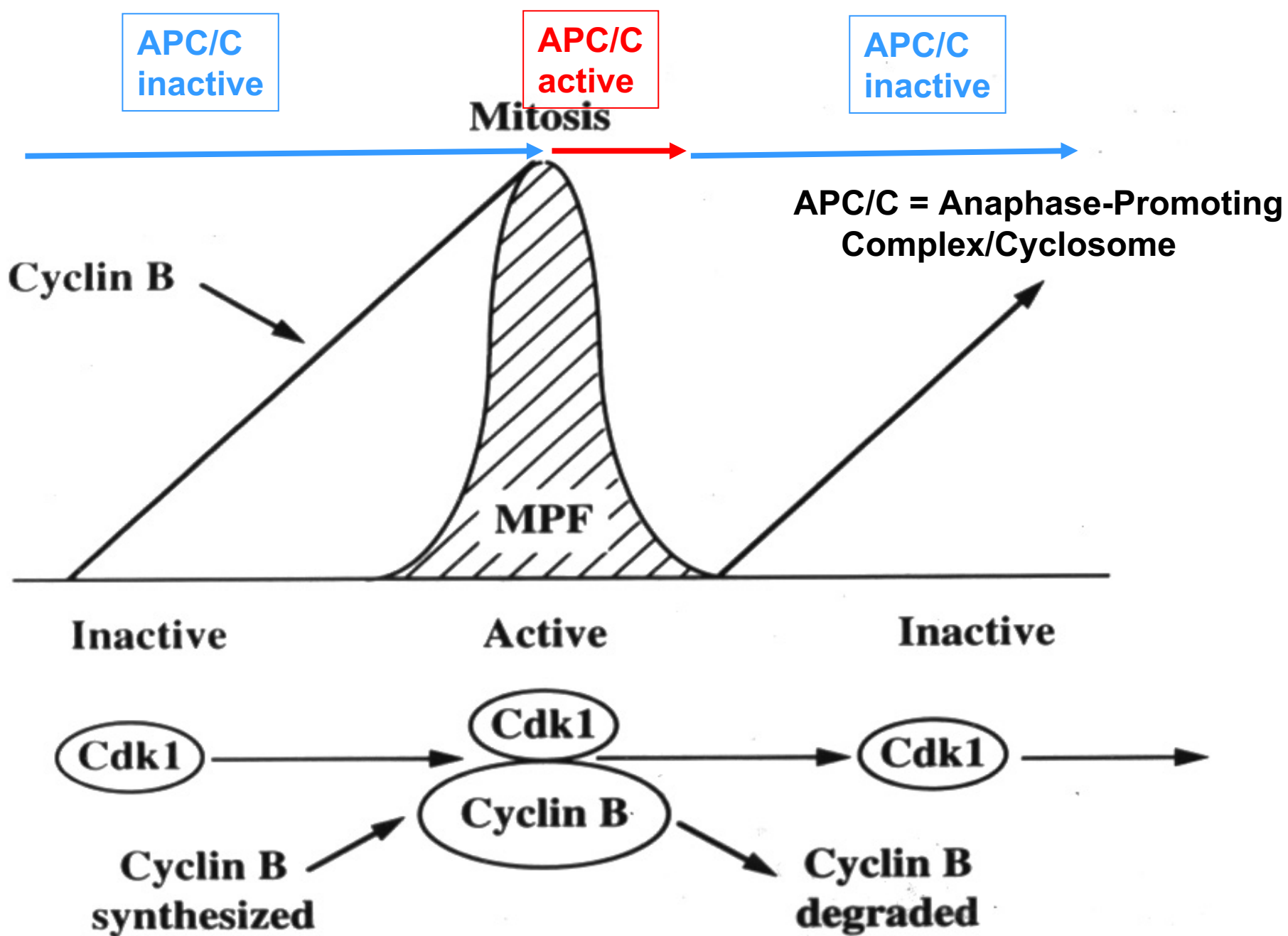




MBC 1995







APC/C
inactive

APC/C
active

APC/C
inactive

Cyclin B

MPF

APC/C = Anaphase-Promoting
Complex/Cyclosome

Inactive

Active

Inactive

Cdk1

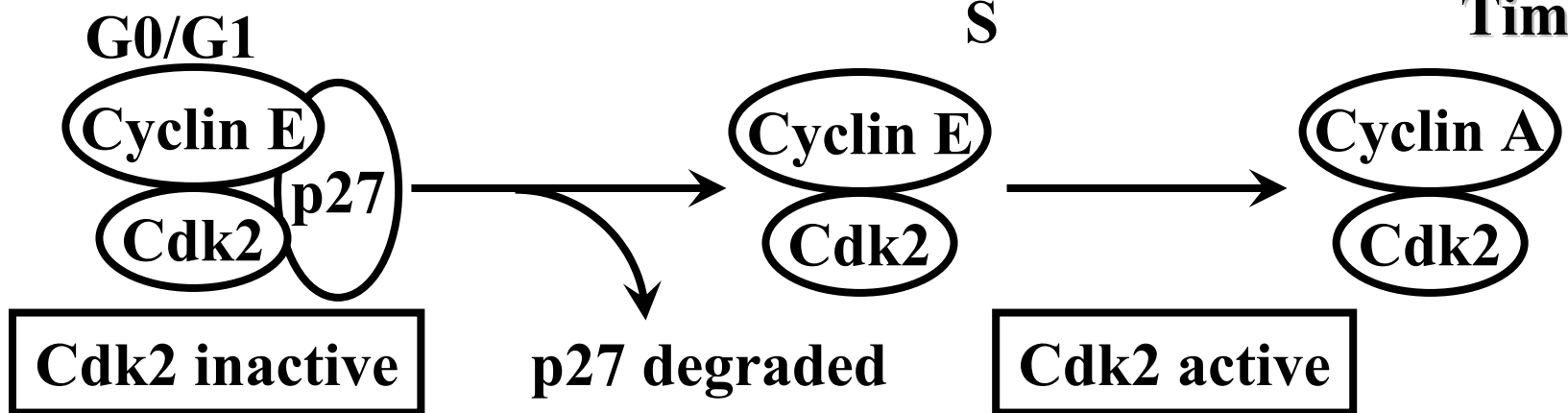
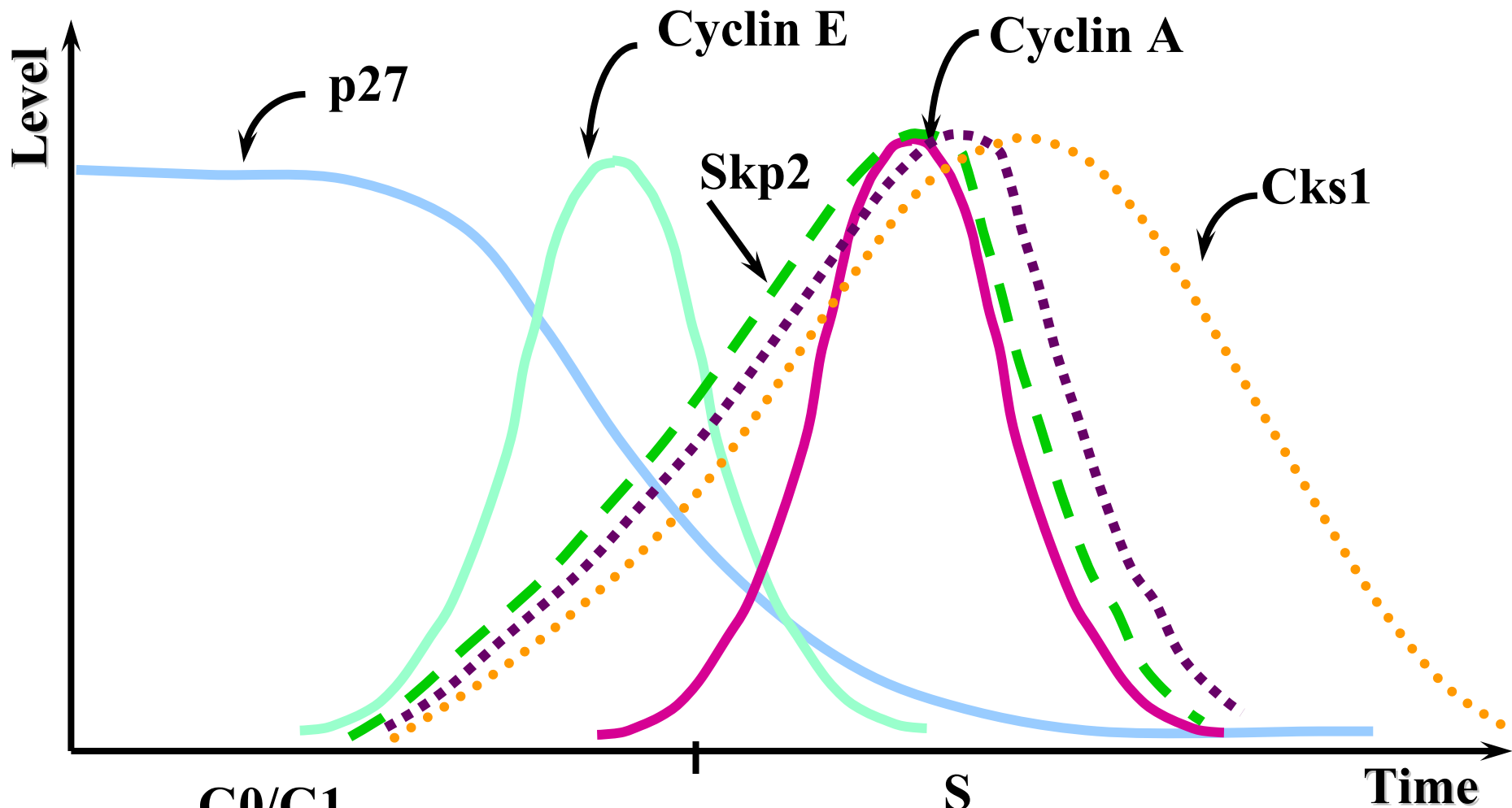
Cdk1

Cdk1

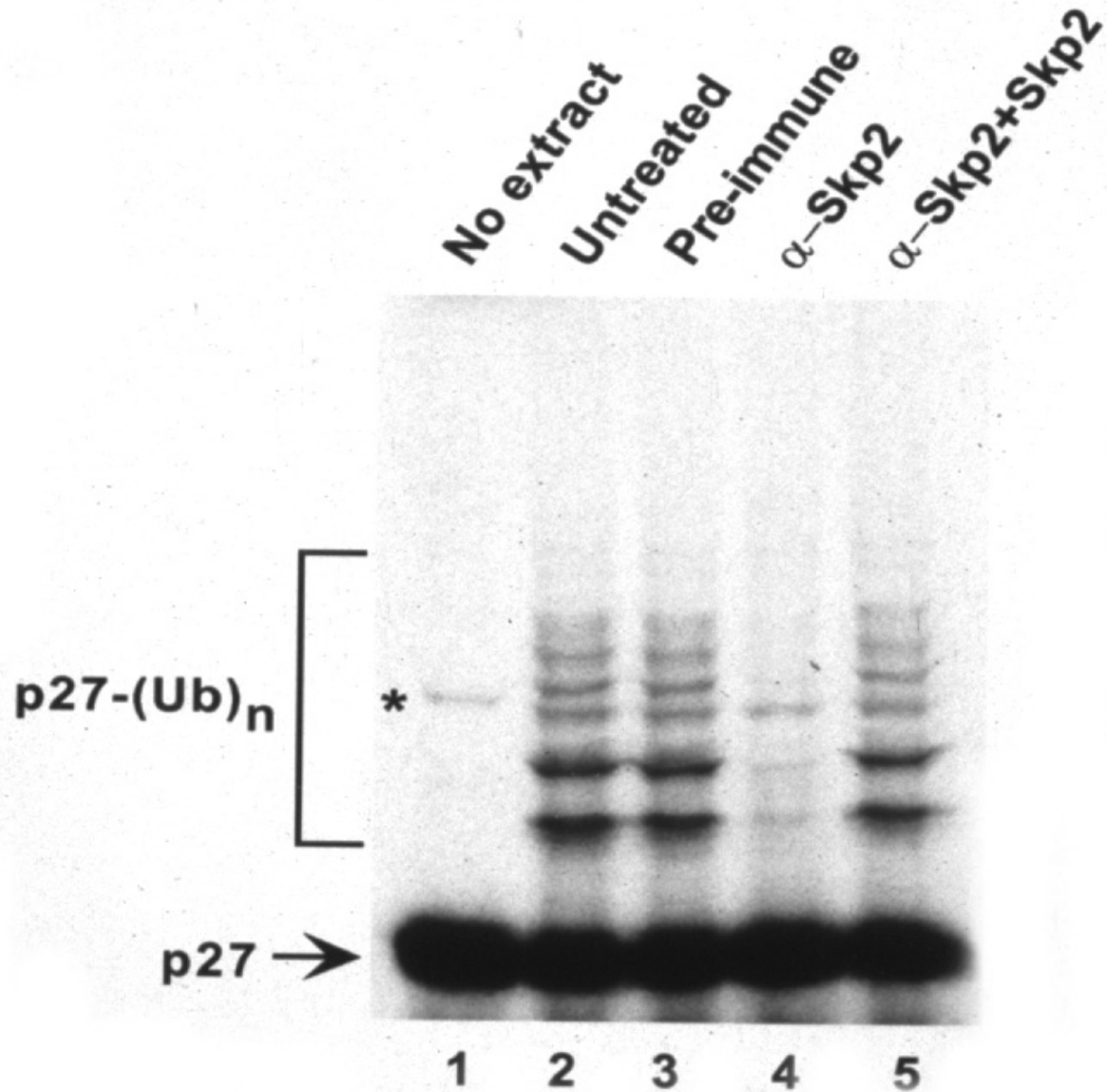
Cyclin B
synthesized

Cyclin B

Cyclin B
degraded

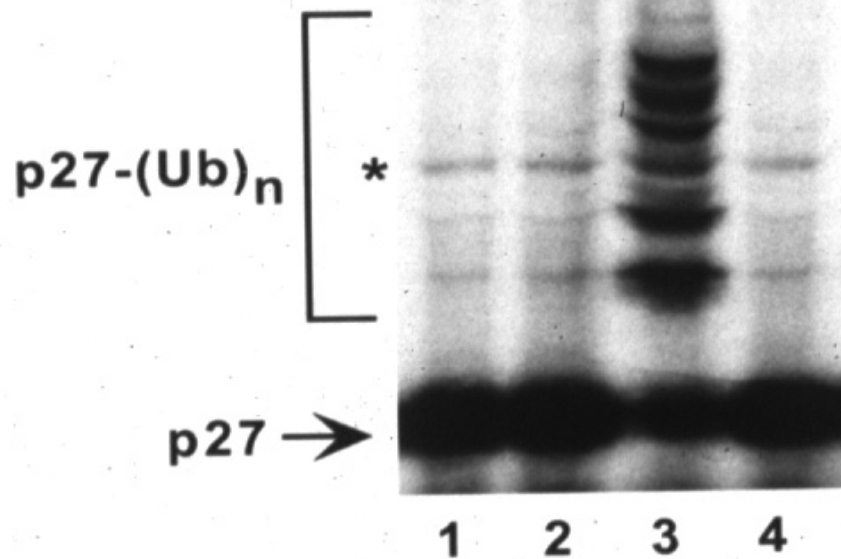


A



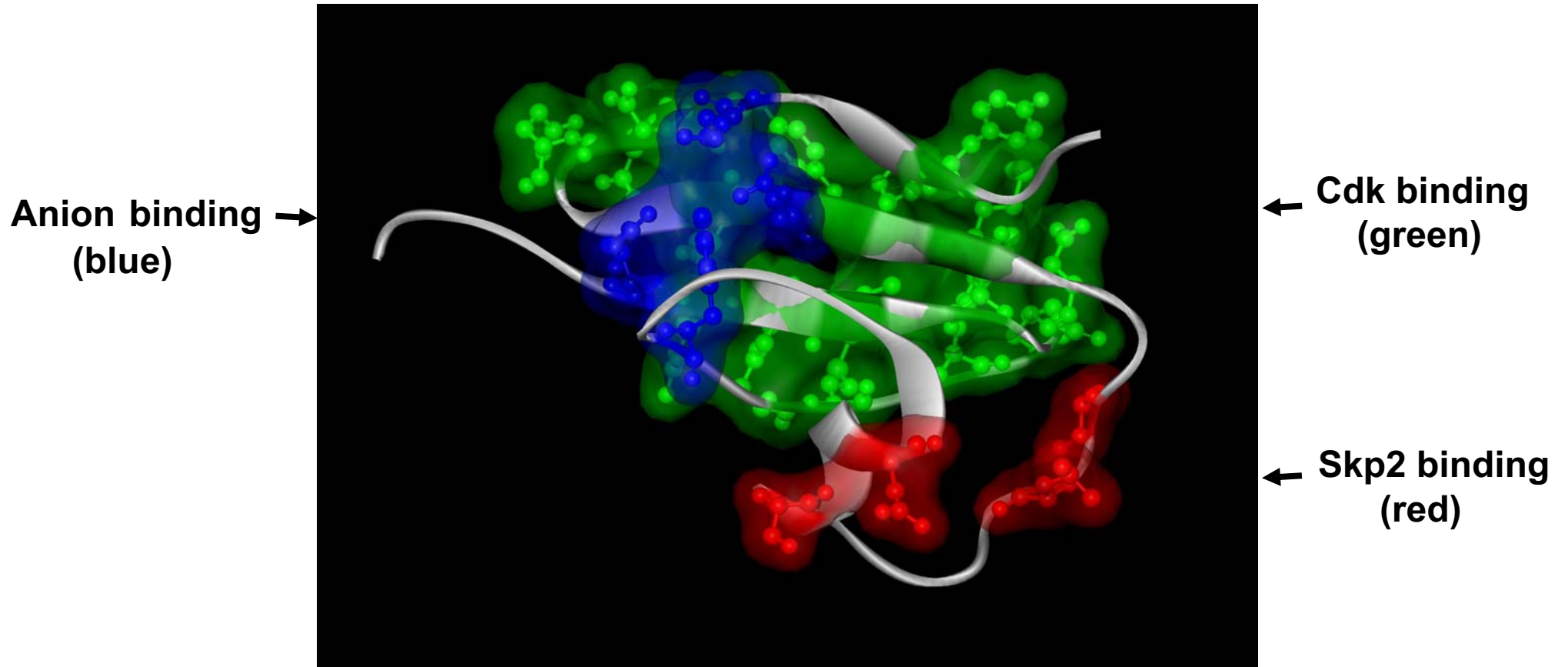
B

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



NCB 1999

The three binding sites of Cks1

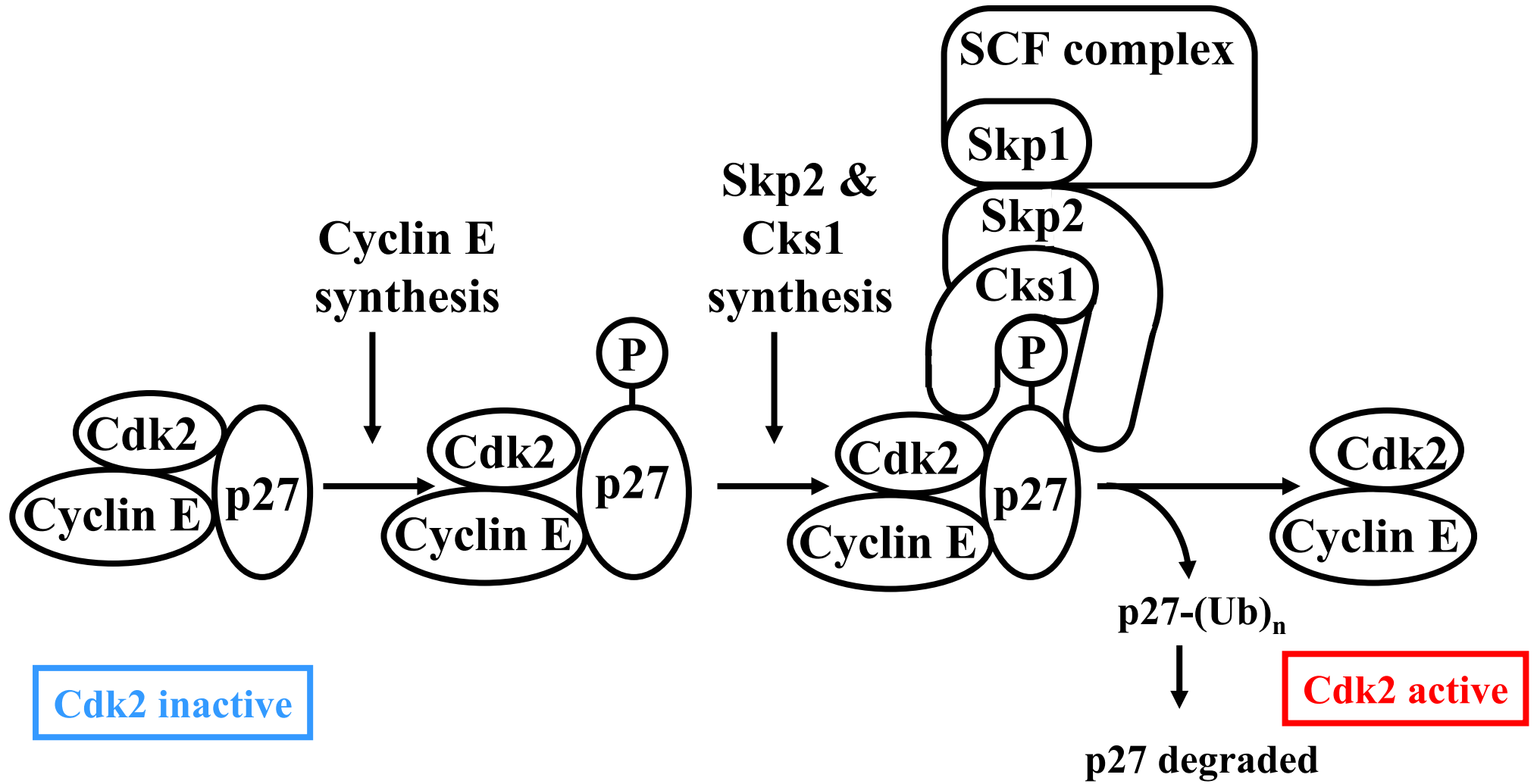


Anion binding
(blue)

Cdk binding
(green)

Skp2 binding
(red)

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 κ B transcriptional regulator |
| III | Positive or negative | Activation by stabilization | p53 tumor suppressor; β -catenin |

1900

2000

Microbe hunters



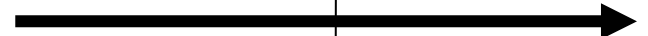
**Vitamin
hunters**



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



