Alberts • Johnson • Lewis • Raff • Roberts • Walter

# *Molecular Biology of the Cell*

**Fifth Edition**

## Chapter 25

The Adaptive Immune System

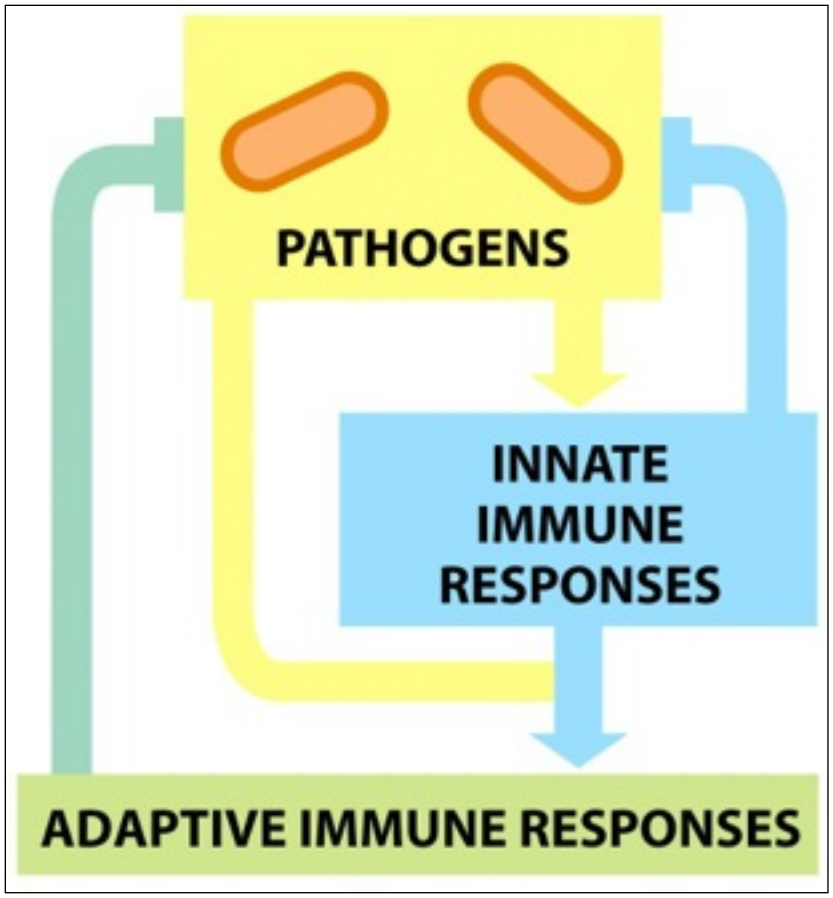



Figure 25-1 *Molecular Biology of the Cell* (© Garland Science 2008)

Omurgasız canlılar; koruyucu engeller, toksik moleküller, daha büyük hücreleri yok edip sindiren fagositik hücreler gibi korunma mekanizmaları geliştirmişlerdir.

Omurgalılarda doğuştan bağışıksal yanıtları ilk savunma hattı olarak kullanırlar, bunun yanında uyarlanır bağışıklık sistemi çok daha karmaşık bir sistemdir ve her ikisi birlikte çalışarak patojenleri ortadan kaldırır.

Uyarlanır bağışıklık sistemi, patojene özgüdür ve uzun süreli koruma sağlarlar. Yıkıcı sonuçları olduğu için, konağa ait olmayan yabancı moleküllere karşı uyarılmaları önemlidir. Yabancı olanı tanıma ve kendinden olmayanı ayırt etme en temel özelliğidir (otoimmünite).

Vücuda giren birçok molekül zararsızdır ve bunlara karşı tepki geliştirmek gereksizdir. Ancak saman nezlesi, astım gibi alerjik durumlar buna örnektir.

Konağa antijen geldiğinde, o moleküle özgü yanıt oluşur. bir aminoasit farklılığı veya optik izomerlere de farklı yanıt geliştirecek kapasitededir.

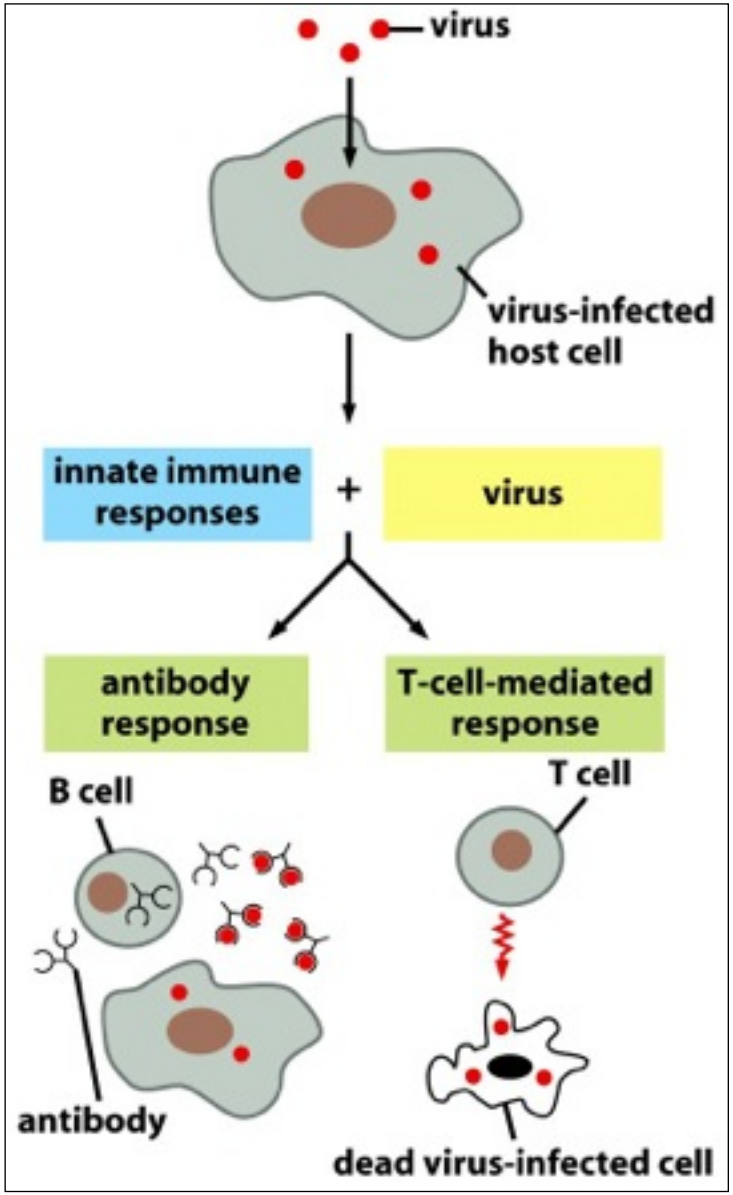
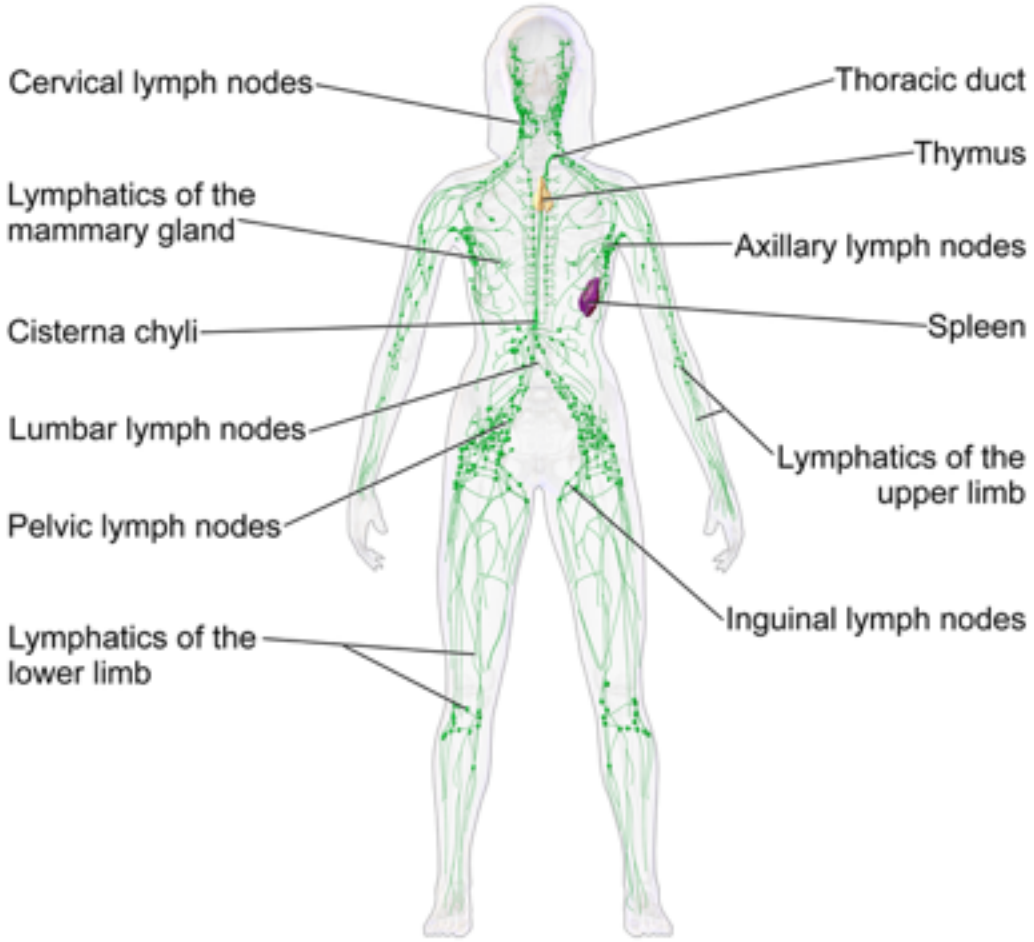





Figure 25-2 *Molecular Biology of the Cell* (© Garland Science 2008)




B ve T hüc. Lenfoid organlarda bulunur.
Primer lenfoid organlar: Timüs ve kemik iliği
Sekonder lenfoid organlar: Bademcik, dalak, peyer plakları, apandis, lenf nodları.

B hücreleri immünglobulin üretiminden sorumludur, bu antikorlar antijenlere spesifik olarak bağlanırlar ve onları etkisizleştirirler ve diğer yandan fagosite edilmelerini sağlar.

T hücreleri ise konak hücrelerin yüzeyinde sunulmuş olan yabancı antijene doğrudan harekete geçer.

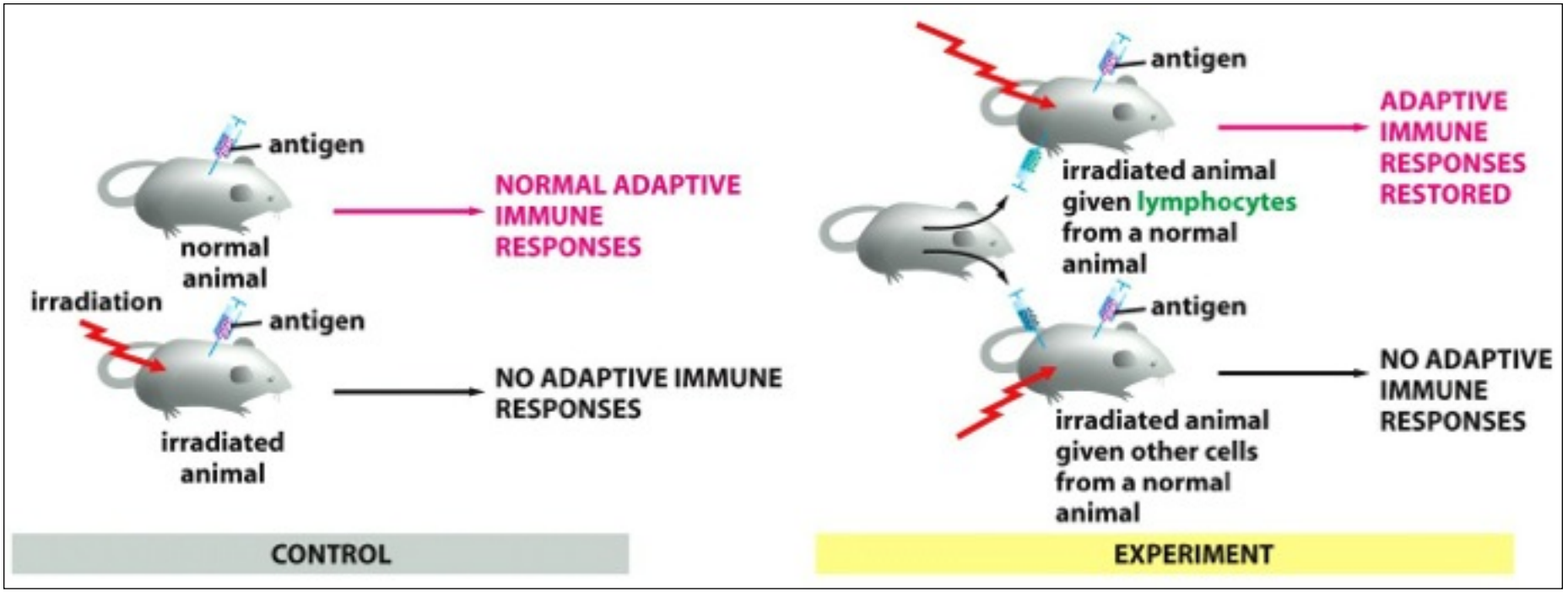
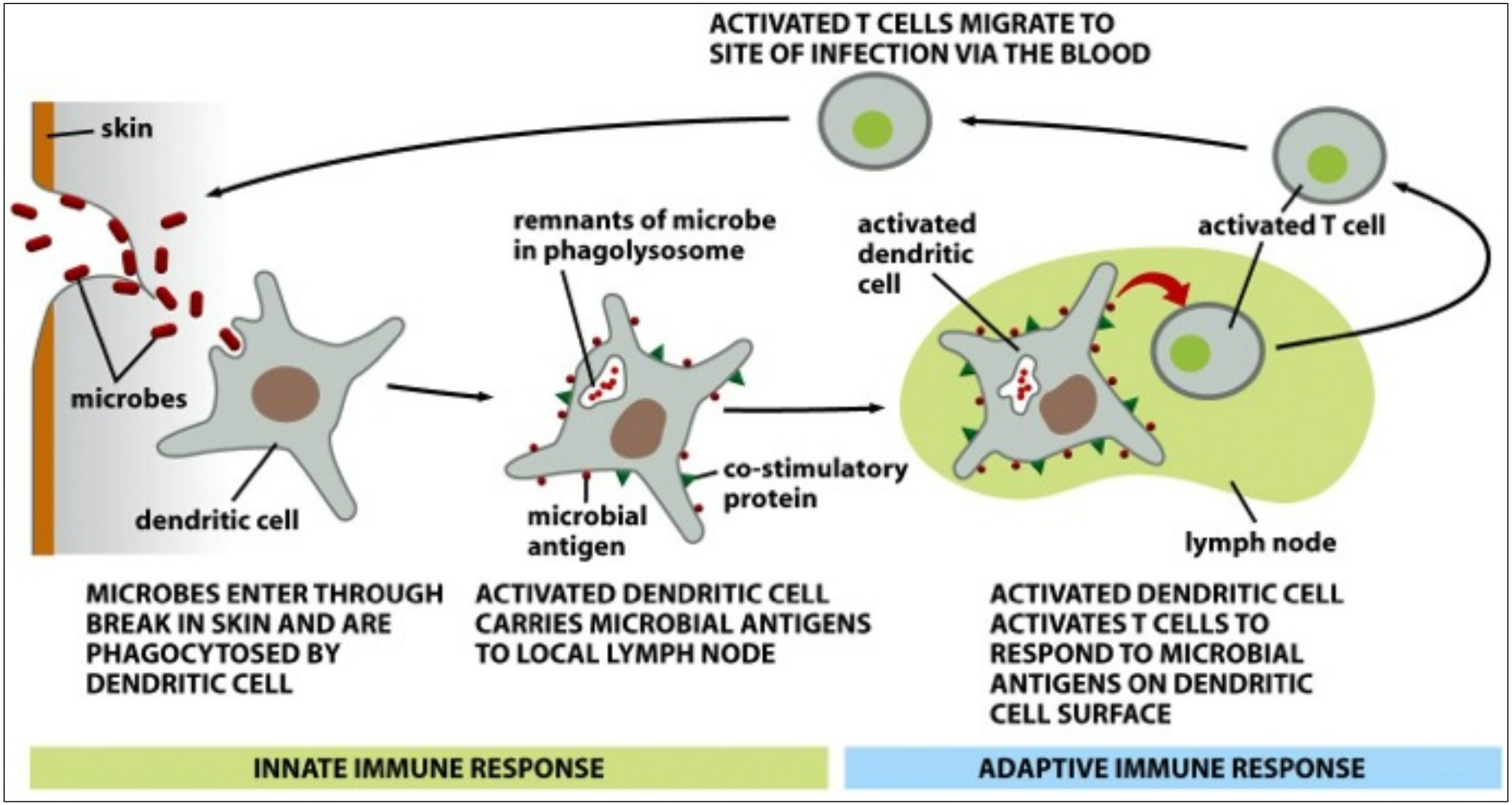
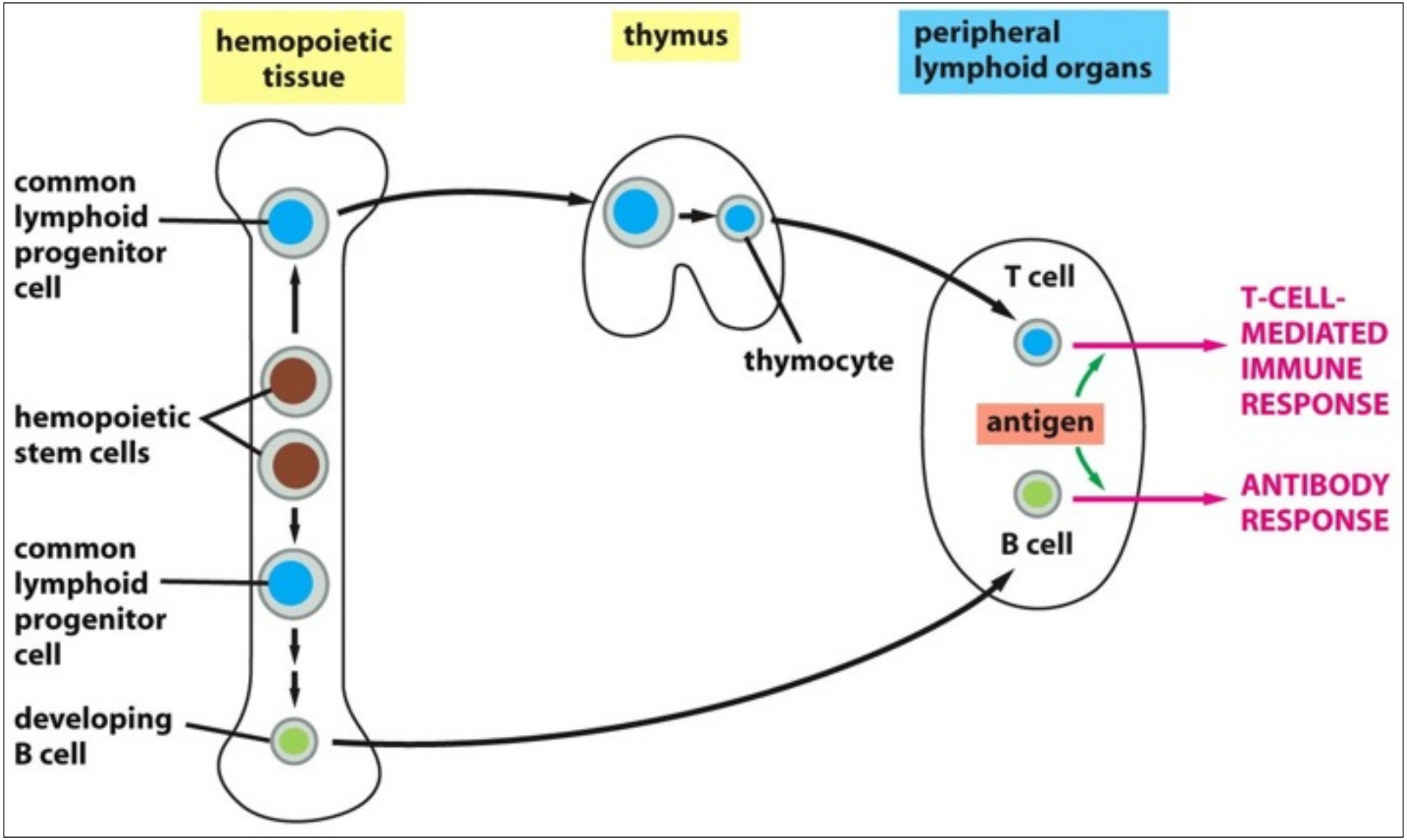


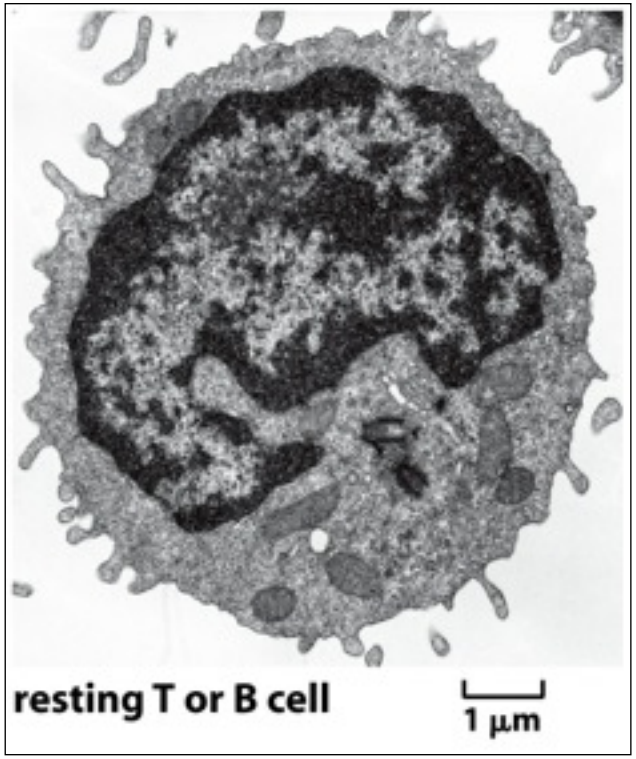

Figure 25-4 *Molecular Biology of the Cell* (© Garland Science 2008)



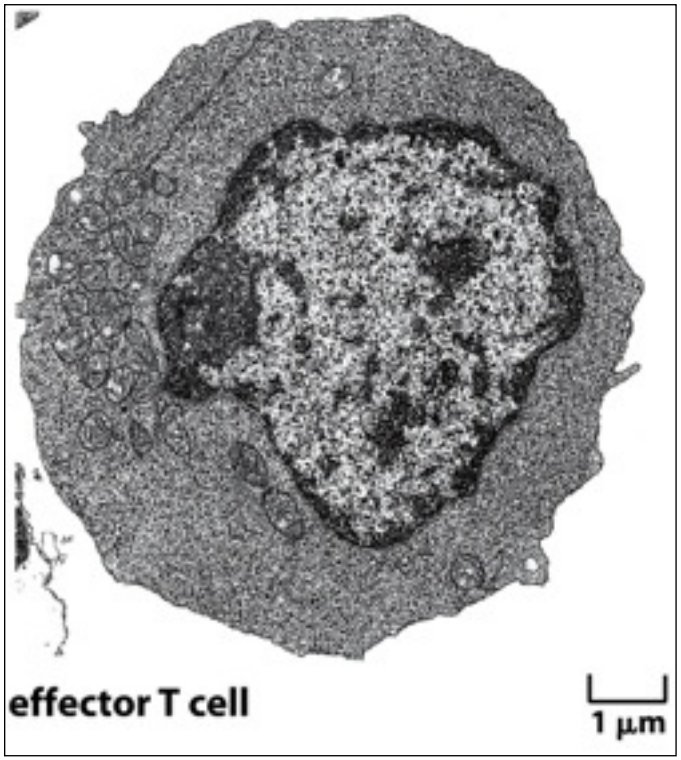

Dentirik hücre (Makrofaj, nötrofil)

Figure 25-5 *Molecular Biology of the Cell* (© Garland Science 2008)


hemopoietic tissue
thymus
peripheral lymphoid organs
common lymphoid progenitor cell
hemopoietic stem cells
common lymphoid progenitor cell
developing B cell
thymocyte
T cell
antigen
B cell
T-CELL-MEDIATED IMMUNE RESPONSE
ANTIBODY RESPONSE








Antijenle uyarılıp farklılaşmayan T ve B hüc. ayırt edilemez, B hüc. ER fazla bulunur.
Sitotoksik T hüc. enfekte hüc yok ederken
T helper'lar sitokinler salgılayarak Makrofaj, B Hüc., Sito. T hüc. farklılaşmasına yardım ederler.

Figure 25-7a *Molecular Biology of the Cell* (© Garland Science 2008)

# Klonal seçilim

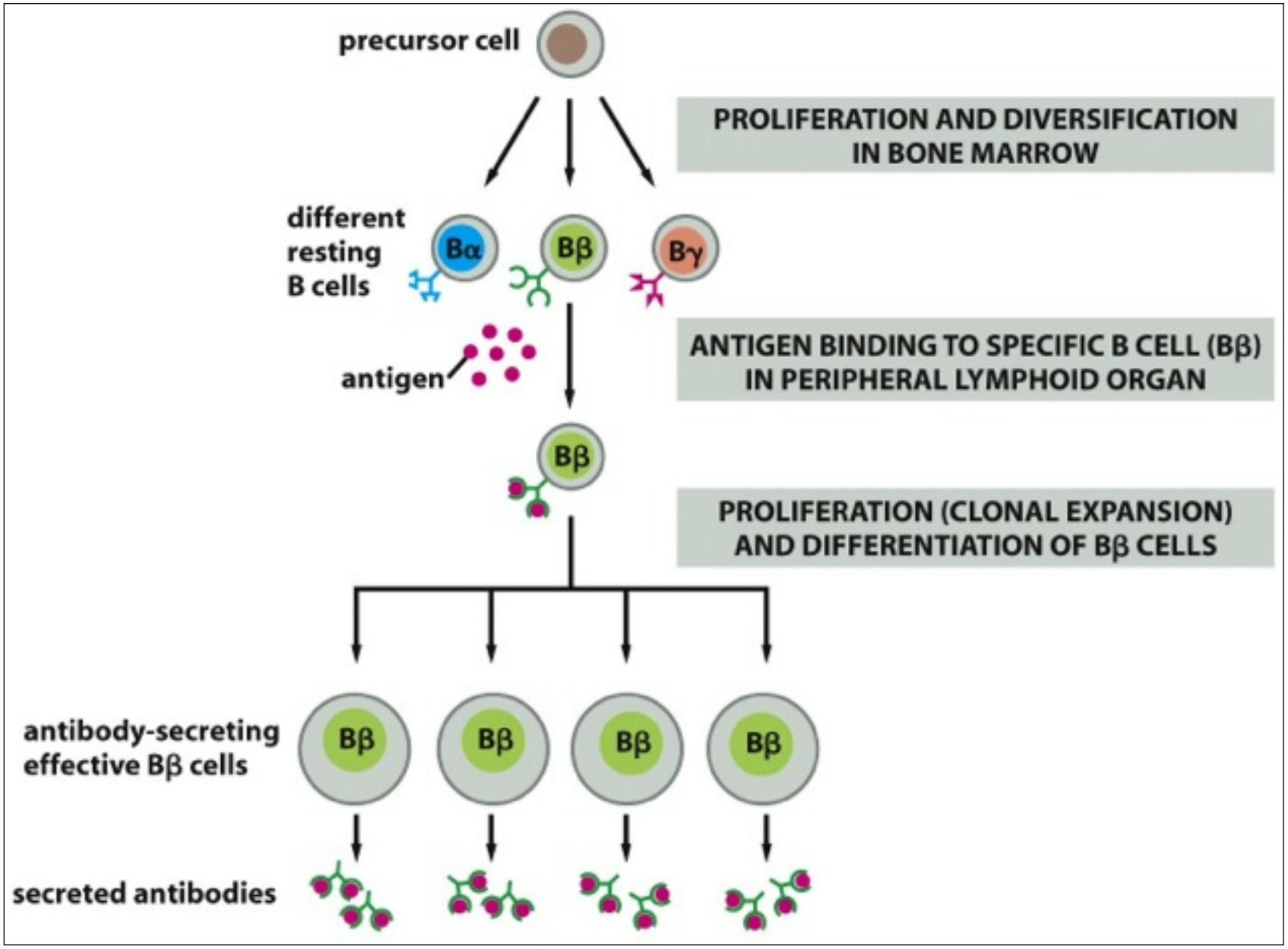
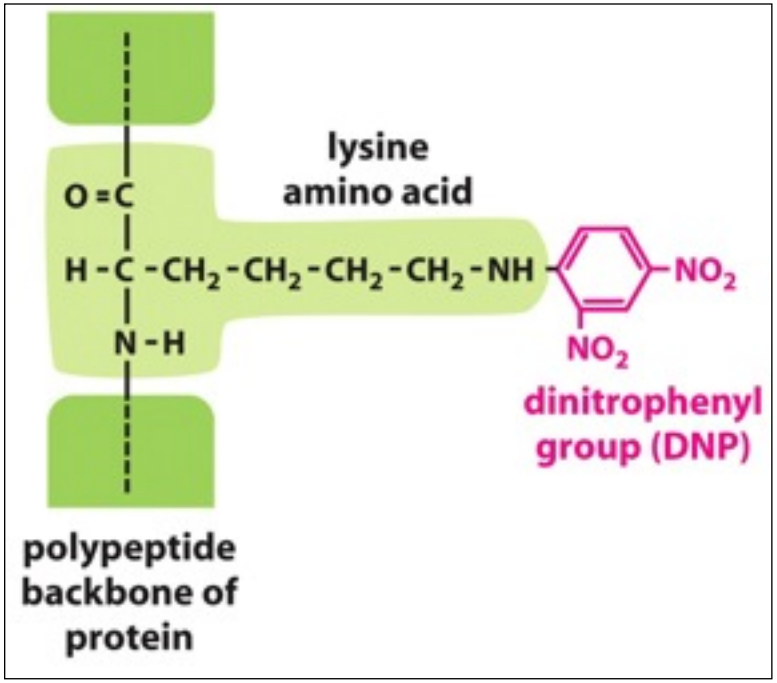



Figure 25-8 *Molecular Biology of the Cell* (© Garland Science 2008)




Antijenin antikora bağlandığı bölgeye Antijenin determinant yada epitop denir. Kuvvetli epitoplara immünodominant bölge denir.

Örneğin lizin köklerinin DNP grubuna bile birden çok hücre uyabilir, yüzlerce farklı anti-DNP antikoru oluşması muhtemeldir.

Bu tür yanıtlar poliklonal olarak adlandırılır. Sadece birkaç klon etkinleşmişse oligoklonal, tekbir klon oluşmuşsa monoklonal denir.

Figure 25-9 *Molecular Biology of the Cell* (© Garland Science 2008)

## *Bağışıksal Bellek*

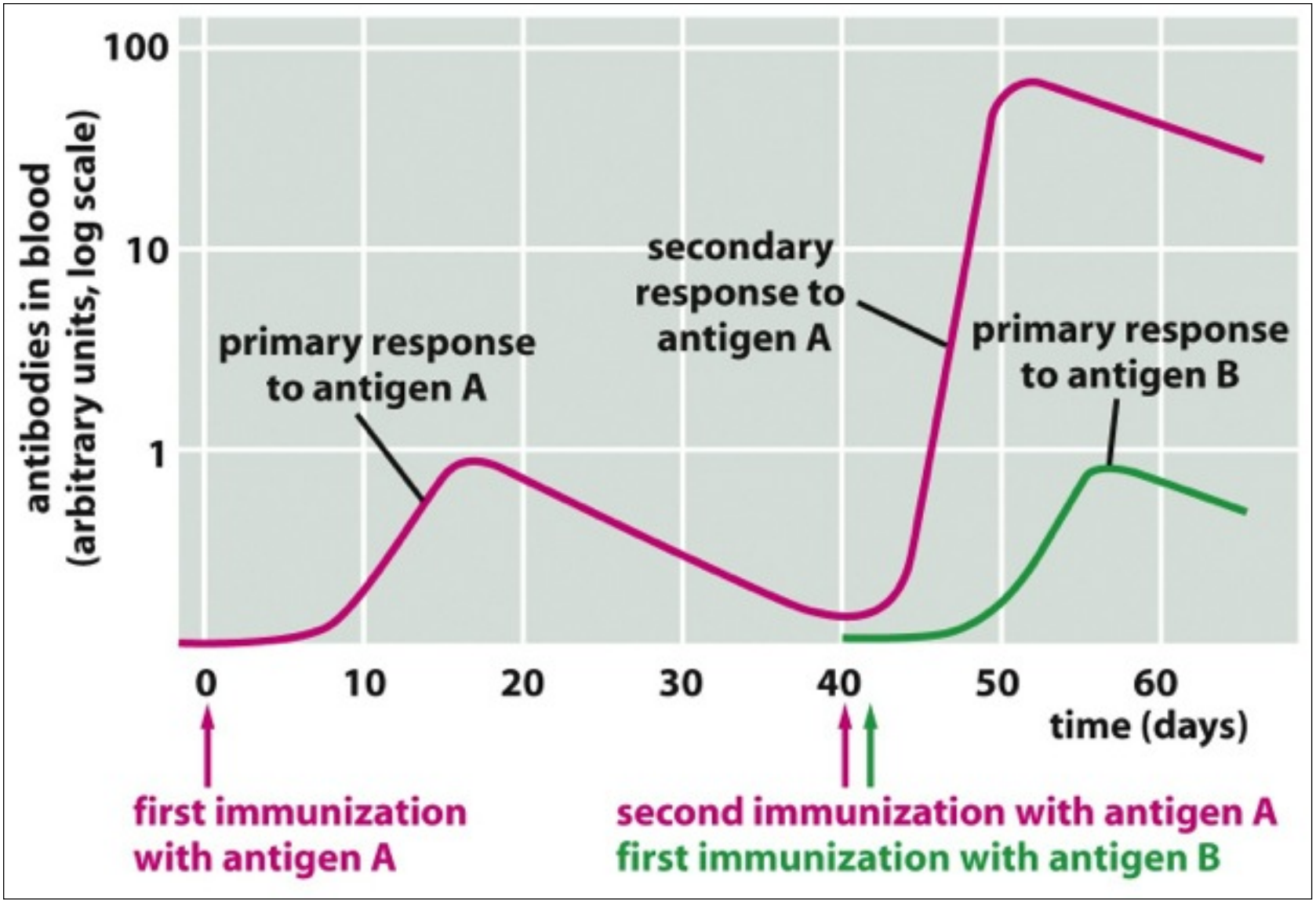
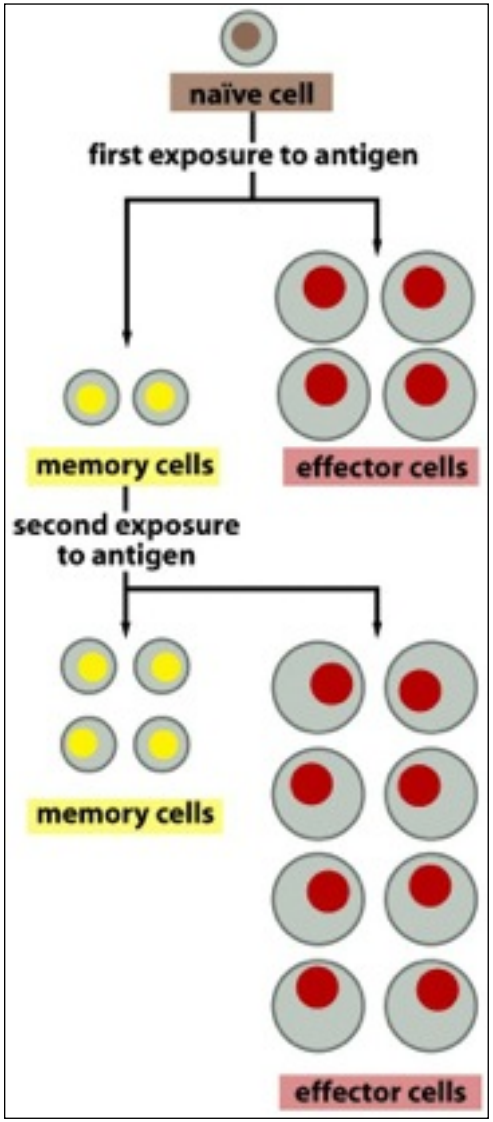



Figure 25-10 *Molecular Biology of the Cell* (© Garland Science 2008)

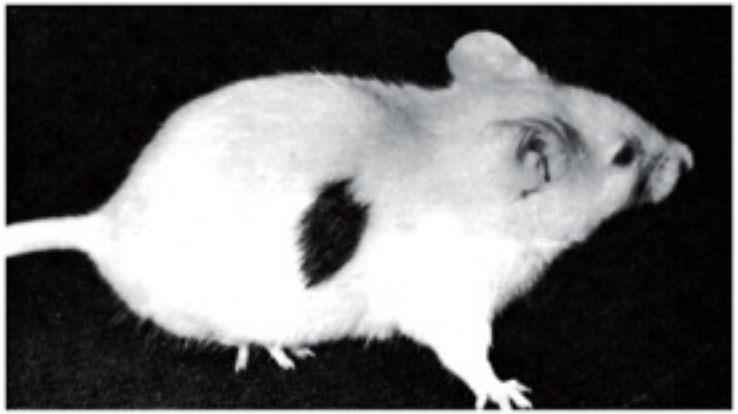
## Klonal Genleşme




Bellek hücreleri ilk cevaptan itibaren farklılaşmaya başlar.

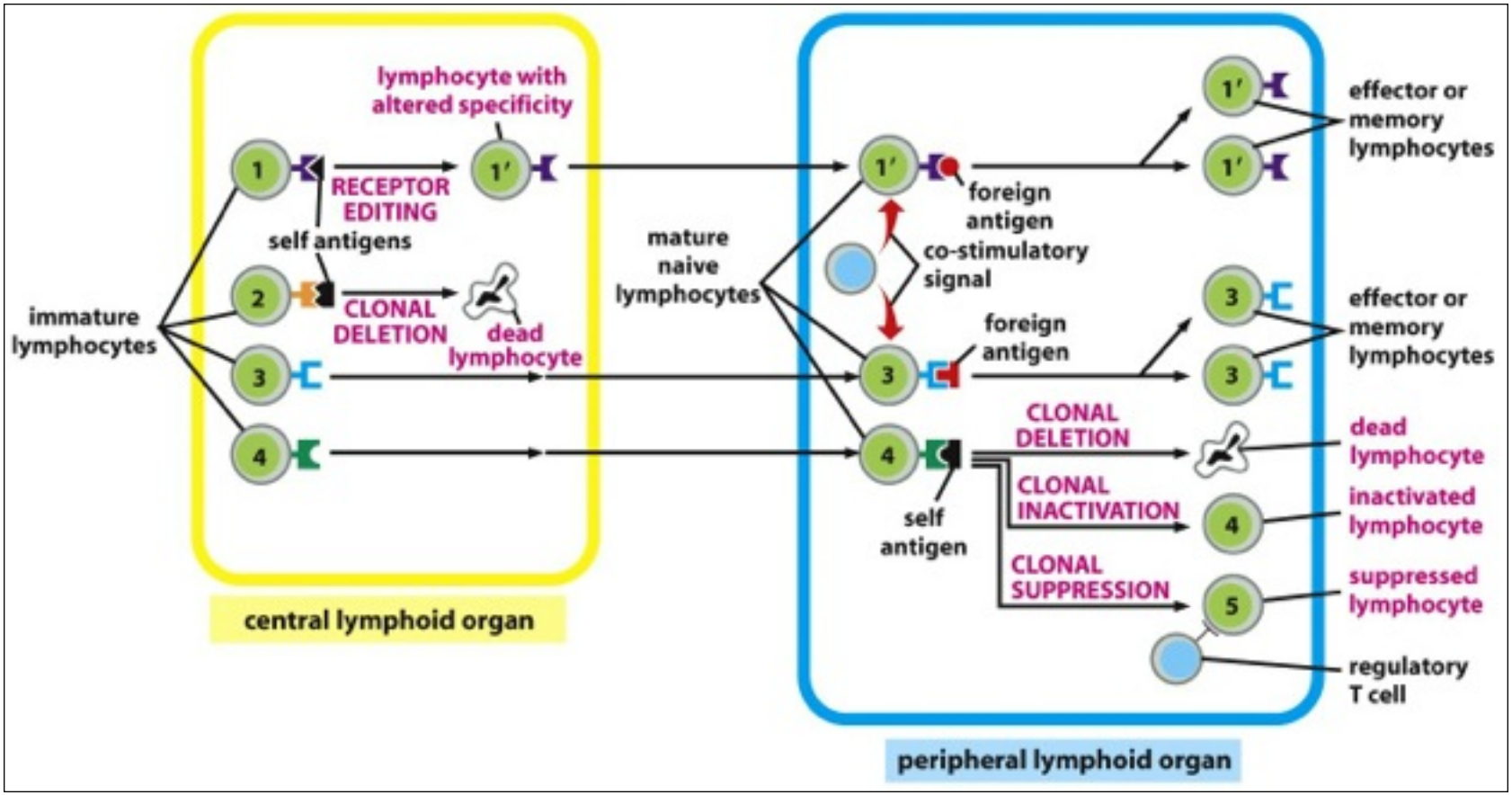
Figure 25-11 *Molecular Biology of the Cell* (© Garland Science 2008)

**Nerdeyse sınırsız sayıda moleküle karsı immün yanıt gelişirken, Konak'ta kendi moleküllerine karşı yanıt gelişmez?**



Balb/C'ye doğumdan sonra nakledilen C57Bl/6 deri parçasına edinilmiş bağışıksal tolerans geliştirilebilir.

Figure 25-18 *Molecular Biology of the Cell* (© Garland Science 2008)




Kendine karşı tolerans geliştirme: Klon delesyonu, Klon duyarsızlaştırılması, reseptör düzeltme, Özel bir T hüc. ile “kendi” ile tepkimeye giren lenfositleri baskılama işlemlerini içerir.
Kendi antijeni ile karşılaşıldığında etkinleşmek yerine neden toleransa yol açar?

İmmün yanıt oluşabilmesi için bir eşuyarıcı sinyal oluşması gerekir. antijen sunan bir hücrenin T helper’larla etkileşmesi ve bunun B hüc. uyarması gereklidir. Yine de karşılaştığı zaman, eşuyarı olmaksızın, antijen lenfositi etkisizleştirme yada öldürme eğilimindedir.
Myasthenia Gravis hastalığında tolerans kalkar ve asetilkolin reseptörlerine B ve T hücreleri saldırırlar.
Toleransın nasıl ortadan kalktığı bilinmemektedir.

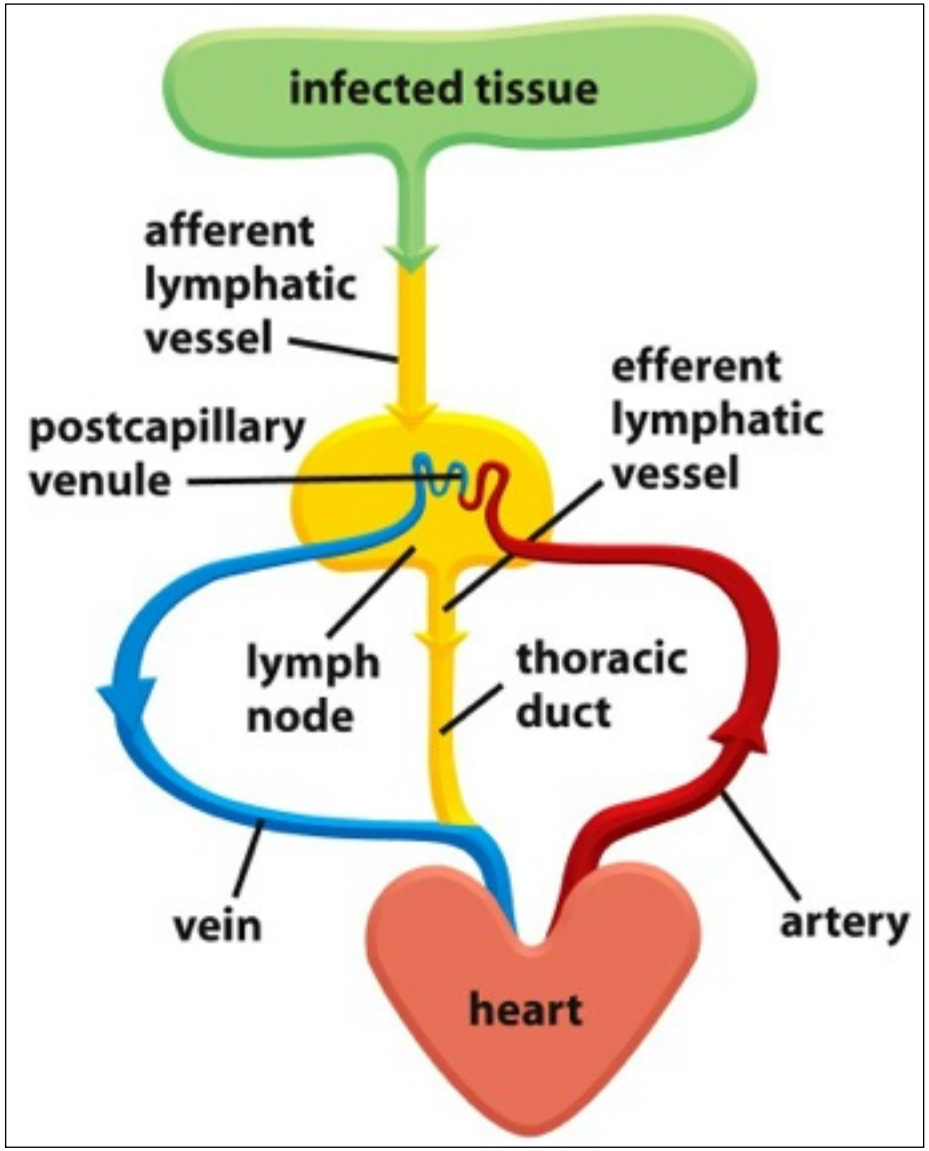



Figure 25-14 *Molecular Biology of the Cell* (© Garland Science 2008)

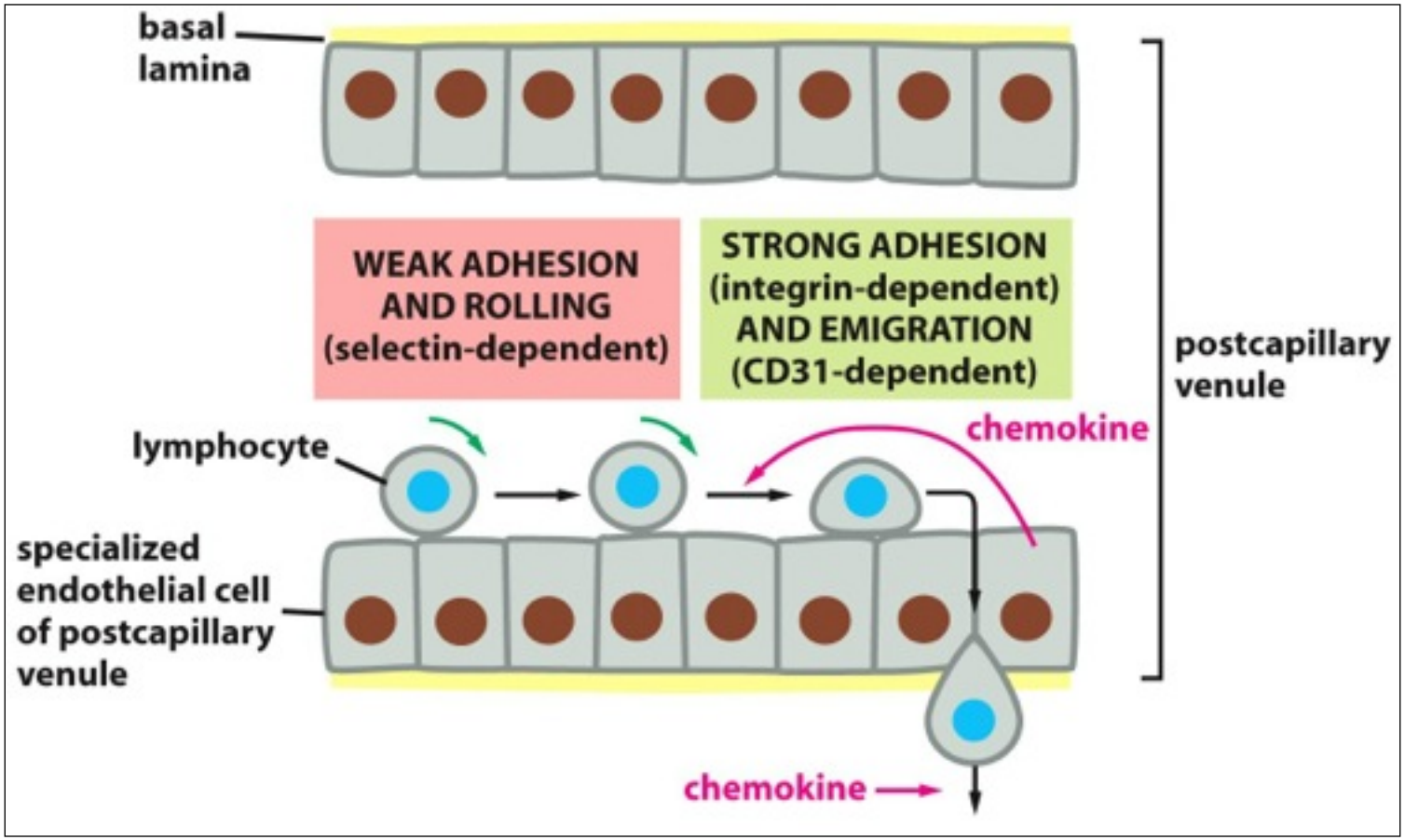



Figure 25-15 *Molecular Biology of the Cell* (© Garland Science 2008)

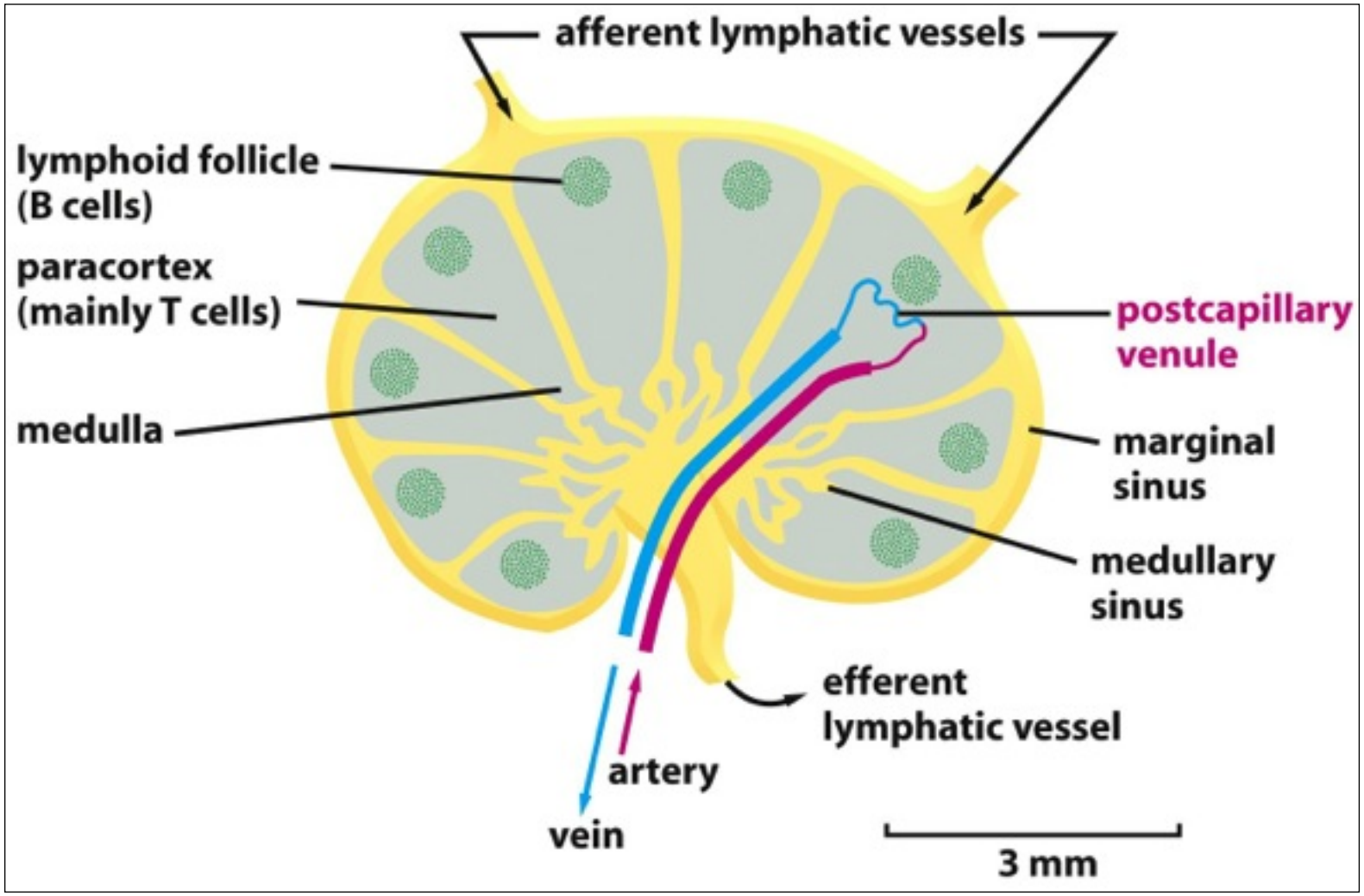
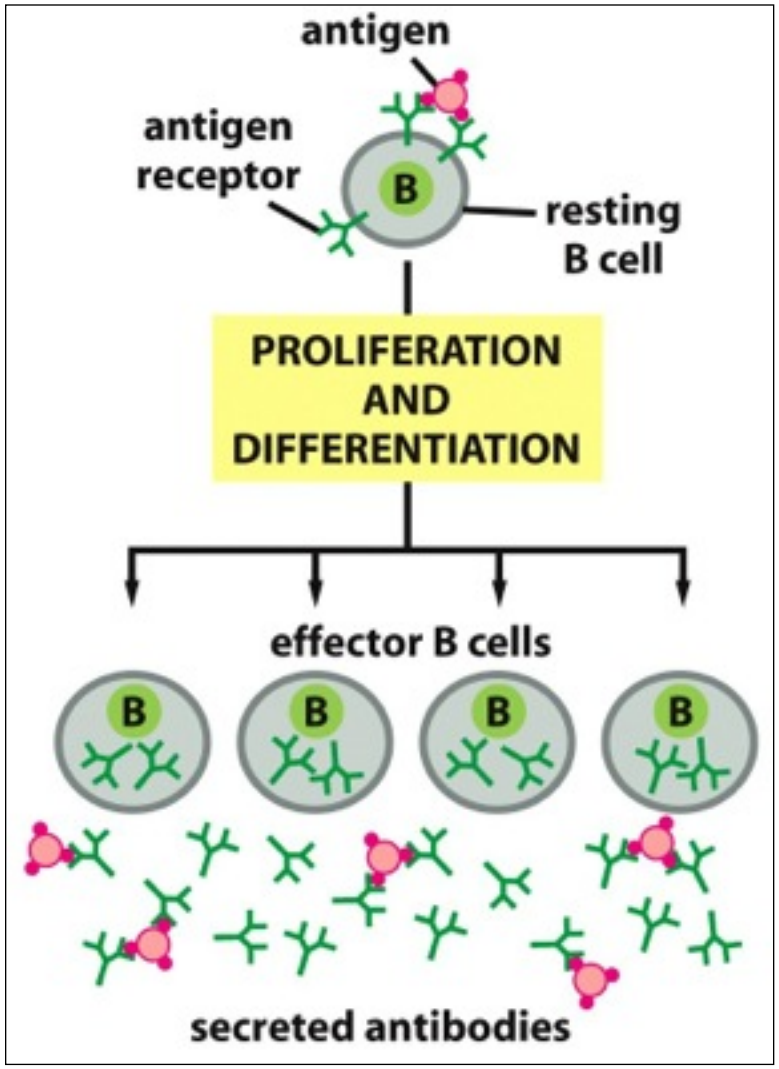
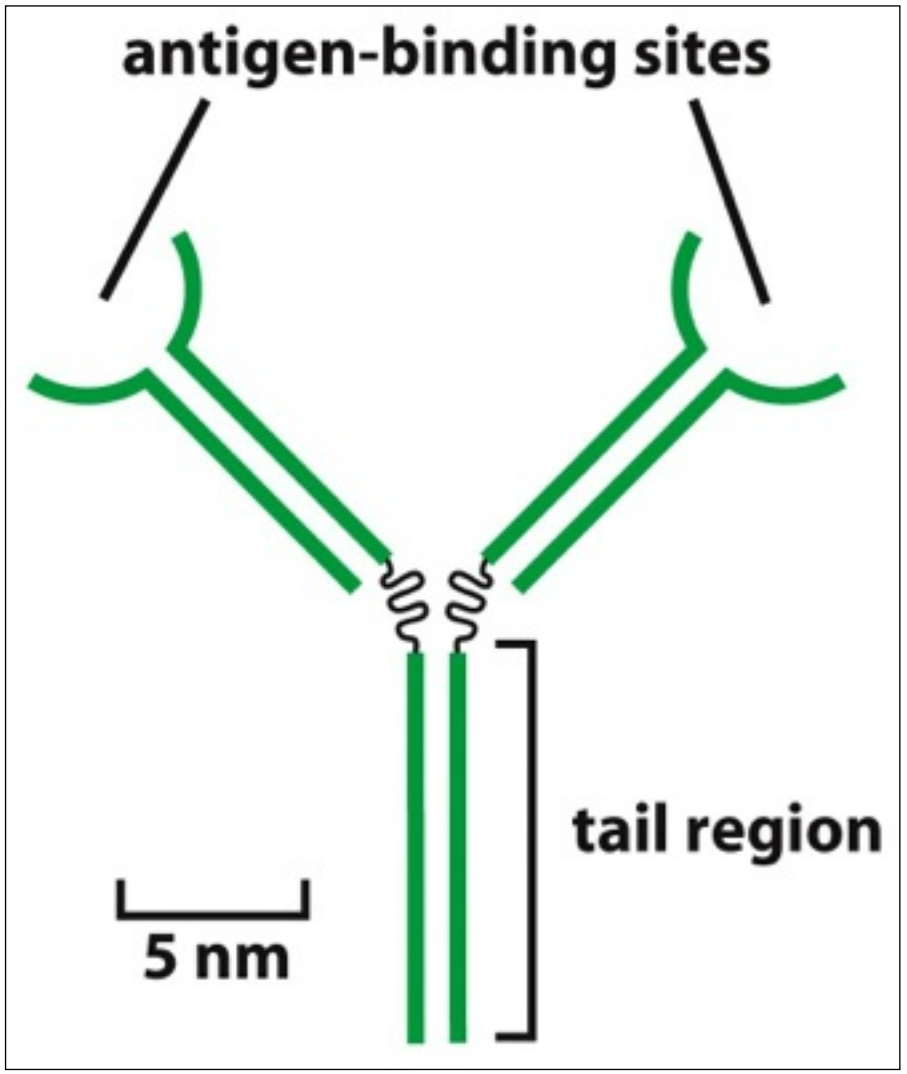



Figure 25-16 *Molecular Biology of the Cell* (© Garland Science 2008)




Antikorlar yalnızca B hüc tarafından yapılır. Plazma prot. %20'sini oluştururlar. İlk salgılanan IgG'ler salgılanmaz yüzeyde kalır ve yaklaşık $10^5$ IgG bulunur bir hücre yüzeyinde. Farklılaştıklarında saniyede 2000 molekül IgG salgılayabilirler.

Figure 25-17 *Molecular Biology of the Cell* (© Garland Science 2008)

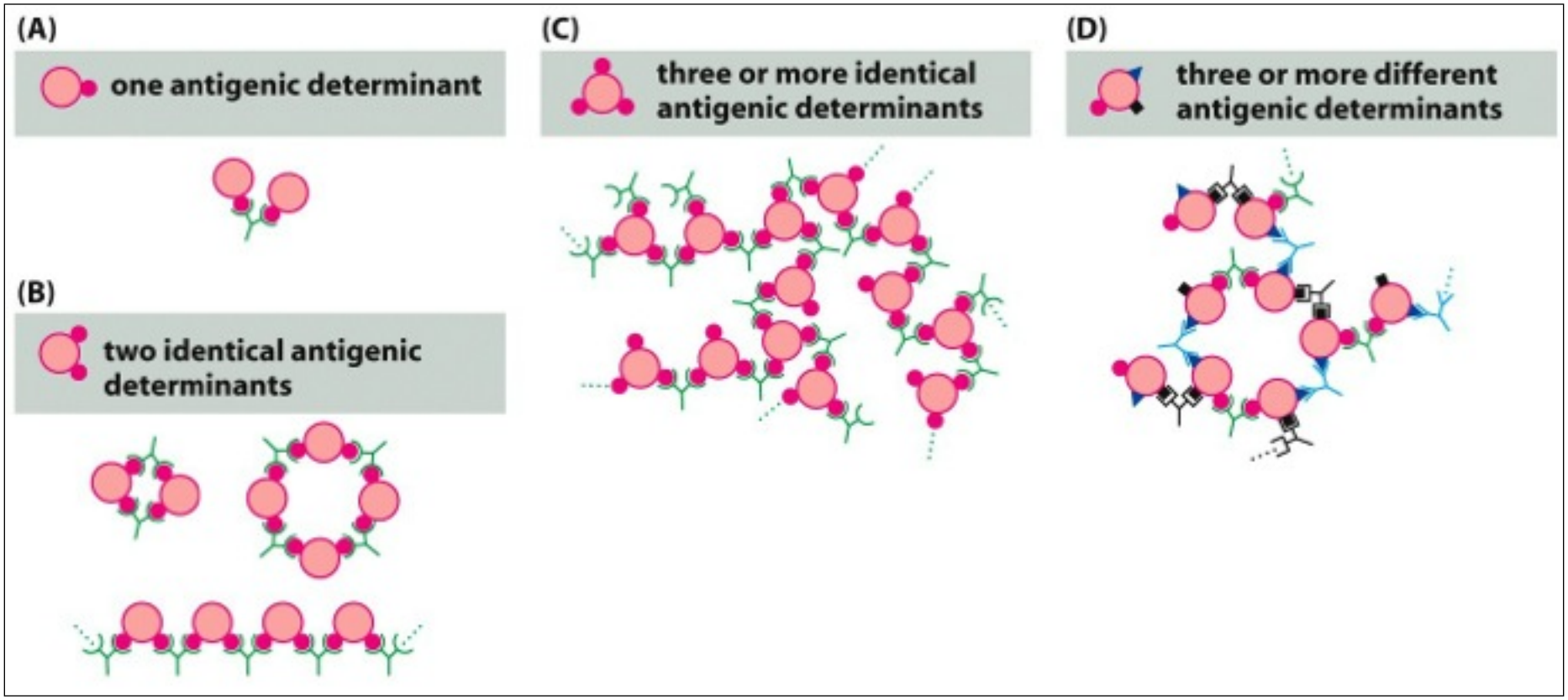
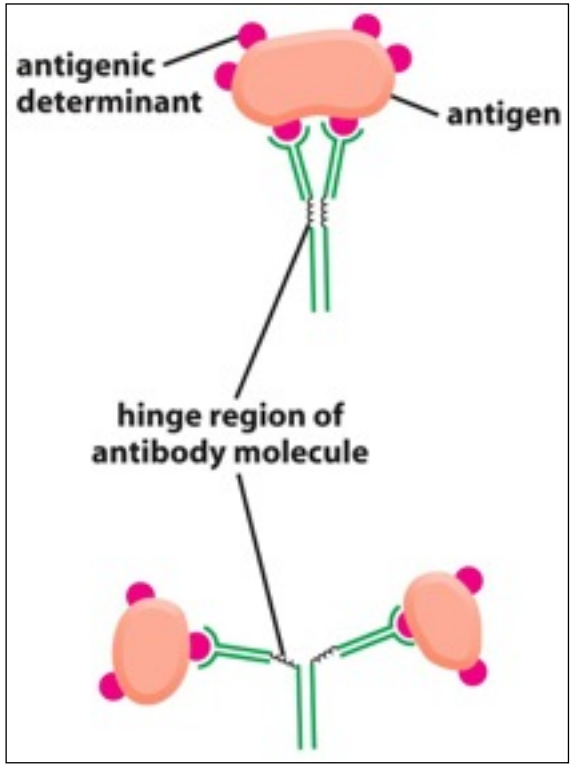
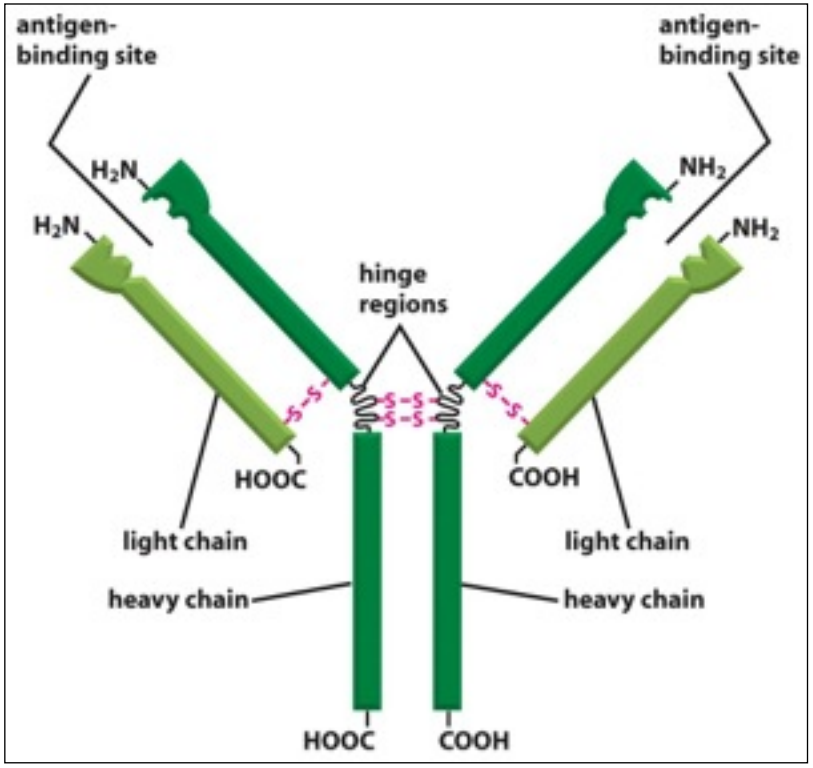



Figure 25-19 *Molecular Biology of the Cell* (© Garland Science 2008)




Hafif zincir 220 aa ve Ağır zincir 440 aa. Her iki yarı aynı antijene bağlanmadan sorumludur.
IgA, IgD, IgE, IgG, and IgM

heavy chain—a, d, e, g, m,

α, δ, ε, γ, μ

Figure 25-20 *Molecular Biology of the Cell* (© Garland Science 2008)

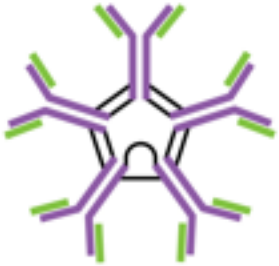
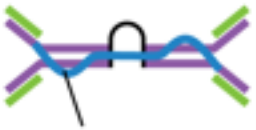
| The Five Immunoglobulin (Ig) Classes | | | | | |
|---|---|---|---|---|---|
| | IgM pentamer | IgG monomer | Secretory IgA dimer | IgE monomer | IgD monomer |
| |  |  |   |  |  |
| Heavy chains | μ | γ | α | ε | δ |
| Number of antigen binding sites | 10 | 2 | 4 | 2 | 2 |
| Molecular weight (Daltons) | 900,000 | 150,000 | 385,000 | 200,000 | 180,000 |
| Percentage of total antibody in serum | 6% | 80% | 13% | 0.002% | 1% |
| Crosses placenta | no | yes | no | no | no |
| Fixes complement | yes | yes | no | no | no |
| Fc binds to | | phagocytes | | mast cells and basophils | |
| Function | Main antibody of primary responses, best at fixing complement; the monomer form of IgM serves as the B cell receptor | Main blood antibody of secondary responses, neutralizes toxins, opsonization | Secreted into mucus, tears, saliva, colostrum | Antibody of allergy and antiparasitic activity | B cell receptor |

Figure 25-21 *Molecular Biology of the Cell* (© Garland Science 2008)

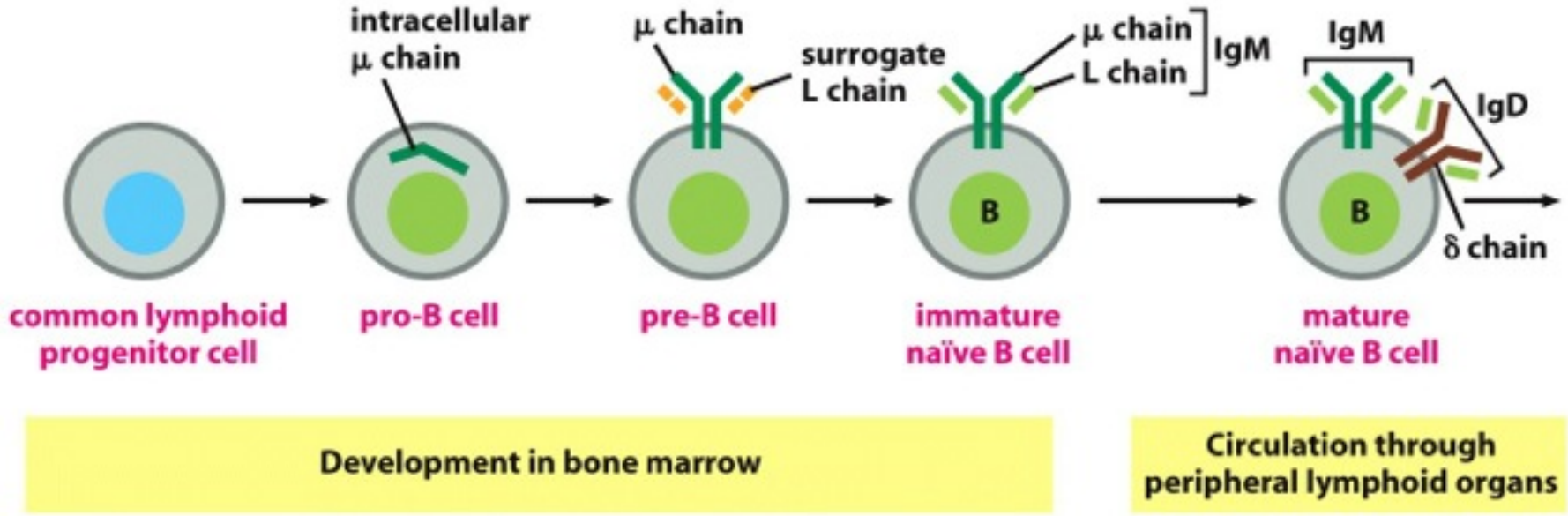



Figure 25-22 *Molecular Biology of the Cell* (© Garland Science 2008)

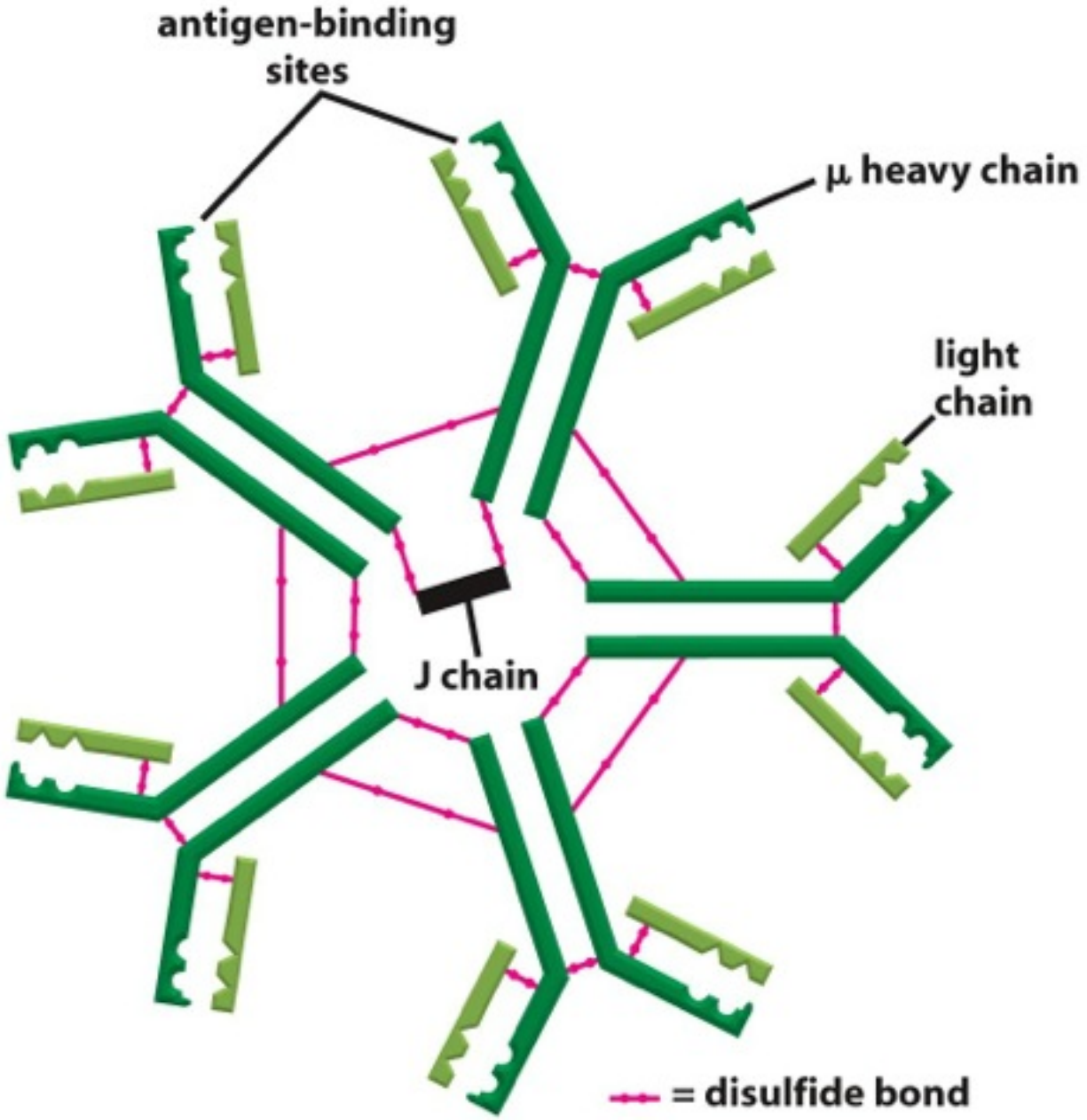
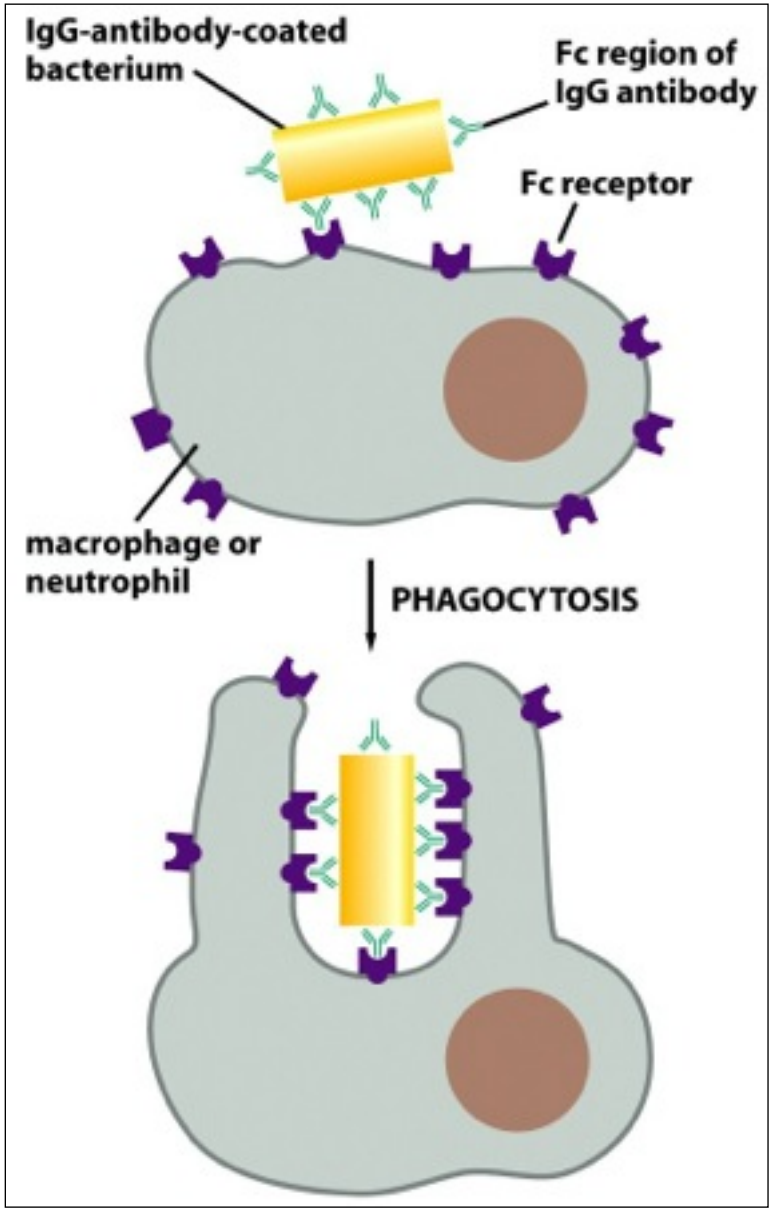



Figure 25-23 *Molecular Biology of the Cell* (© Garland Science 2008)



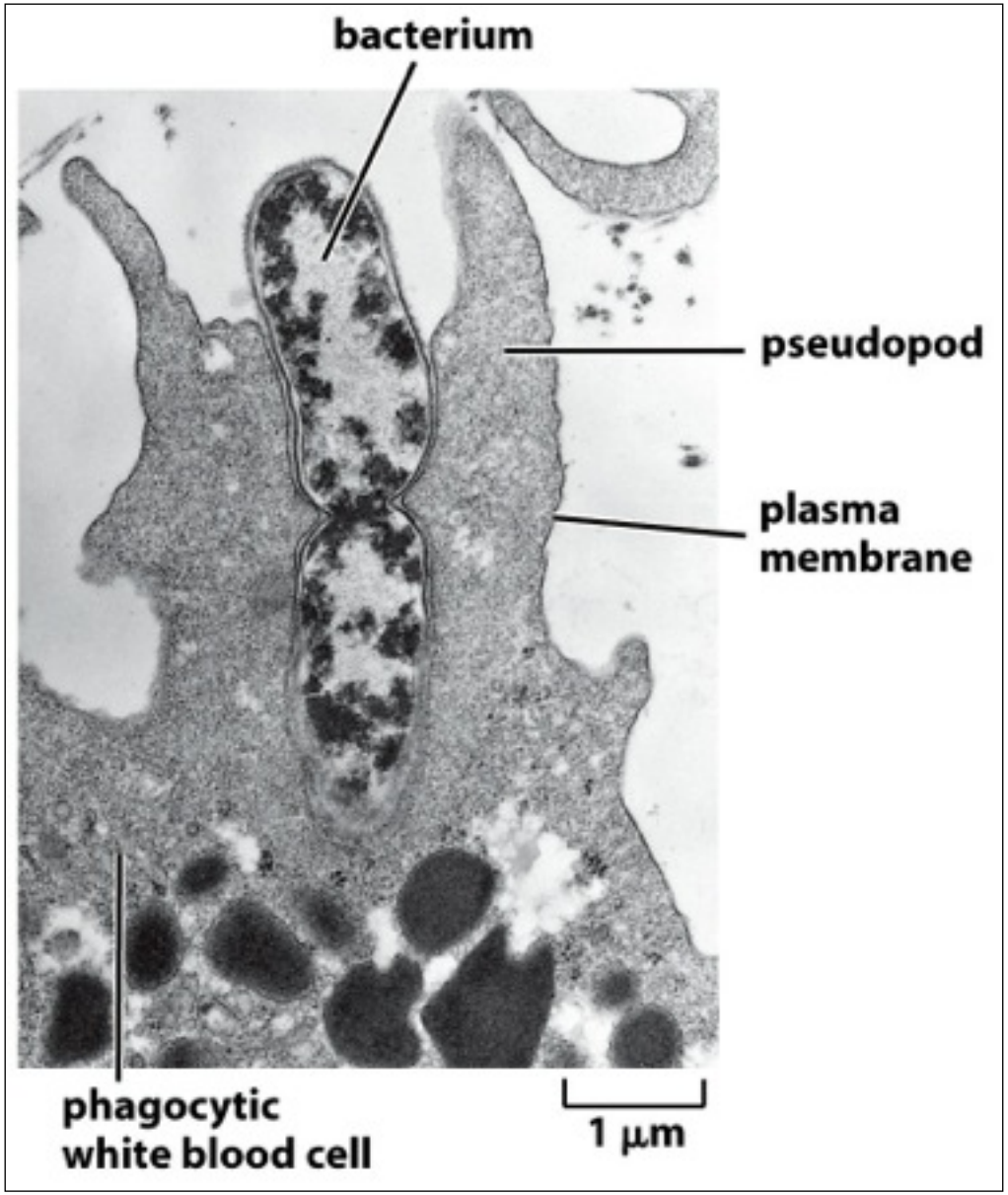




Figure 25-24a *Molecular Biology of the Cell* (© Garland Science 2008)

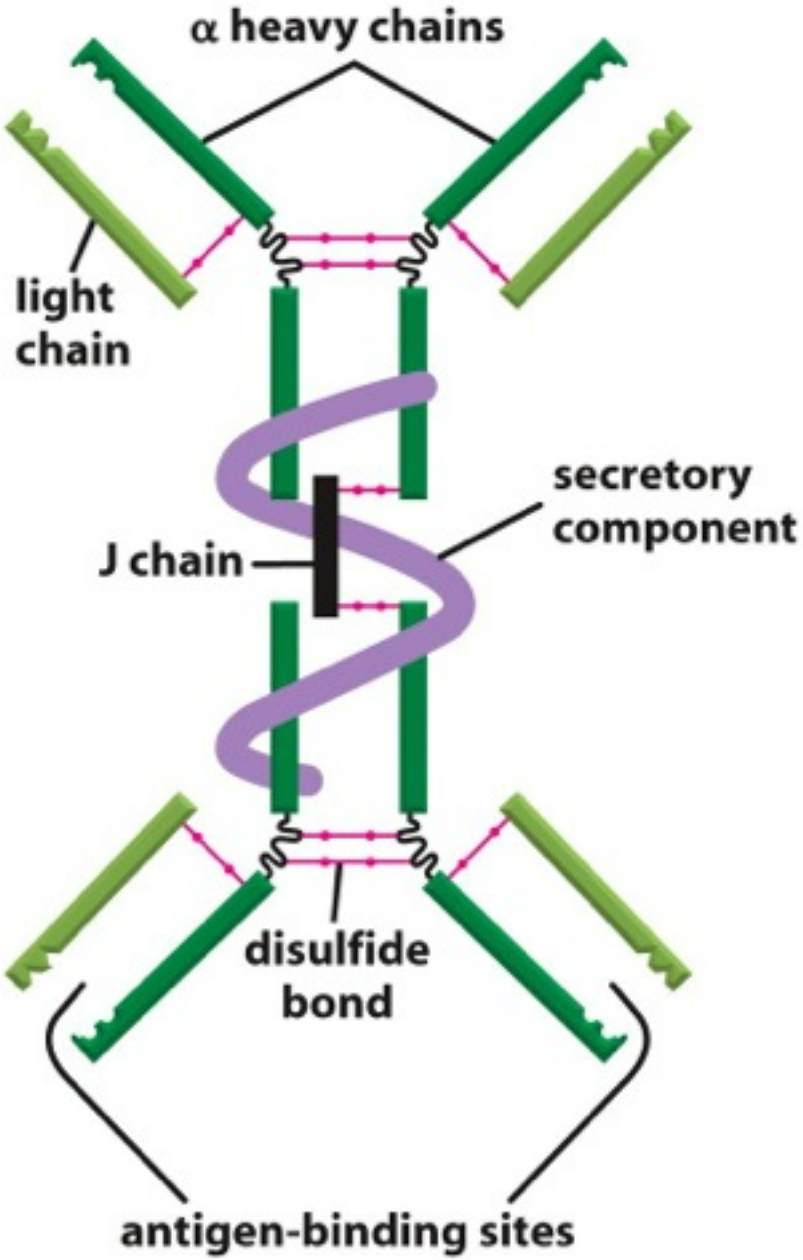



Figure 25-25 *Molecular Biology of the Cell* (© Garland Science 2008)

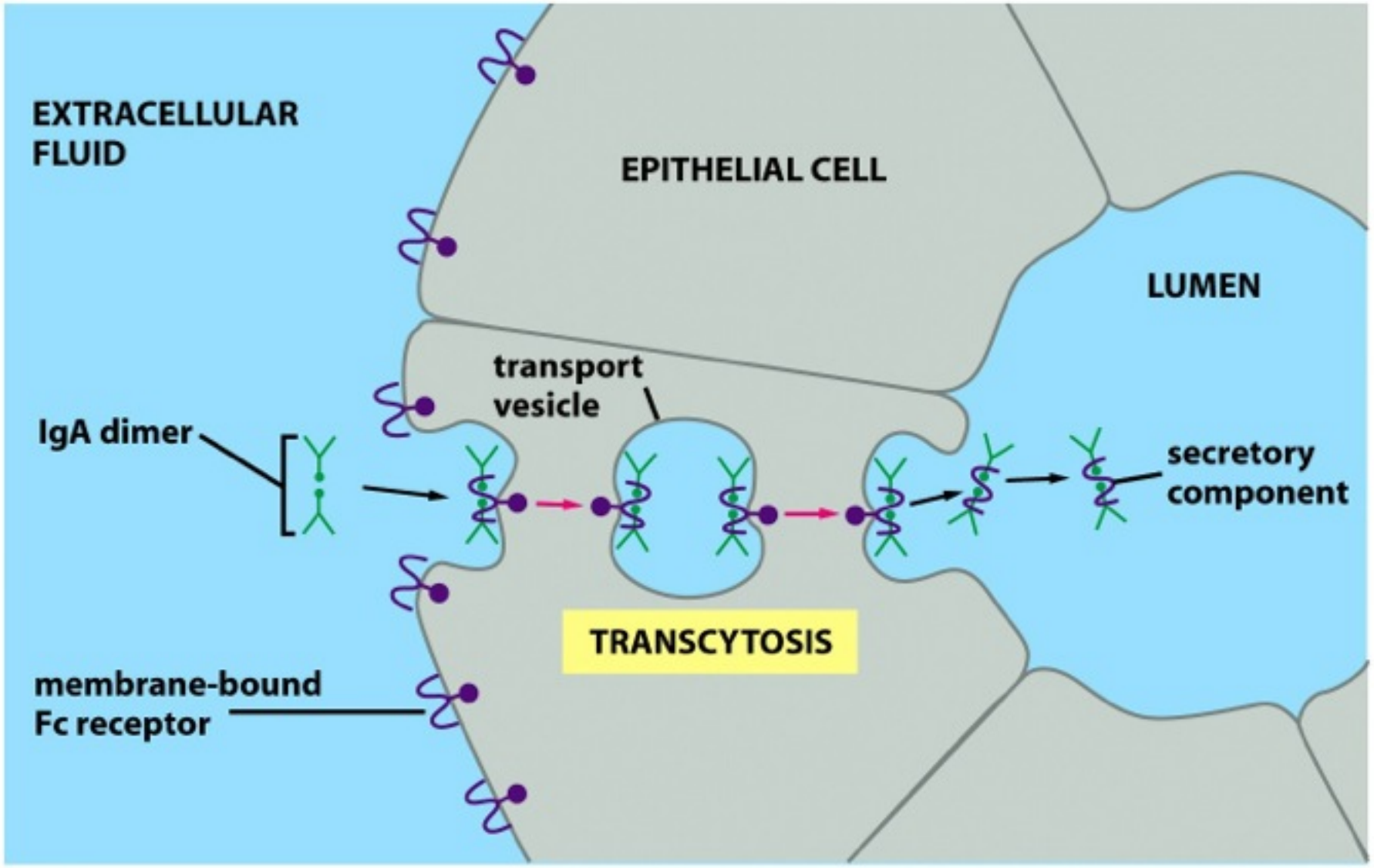



Figure 25-26 *Molecular Biology of the Cell* (© Garland Science 2008)

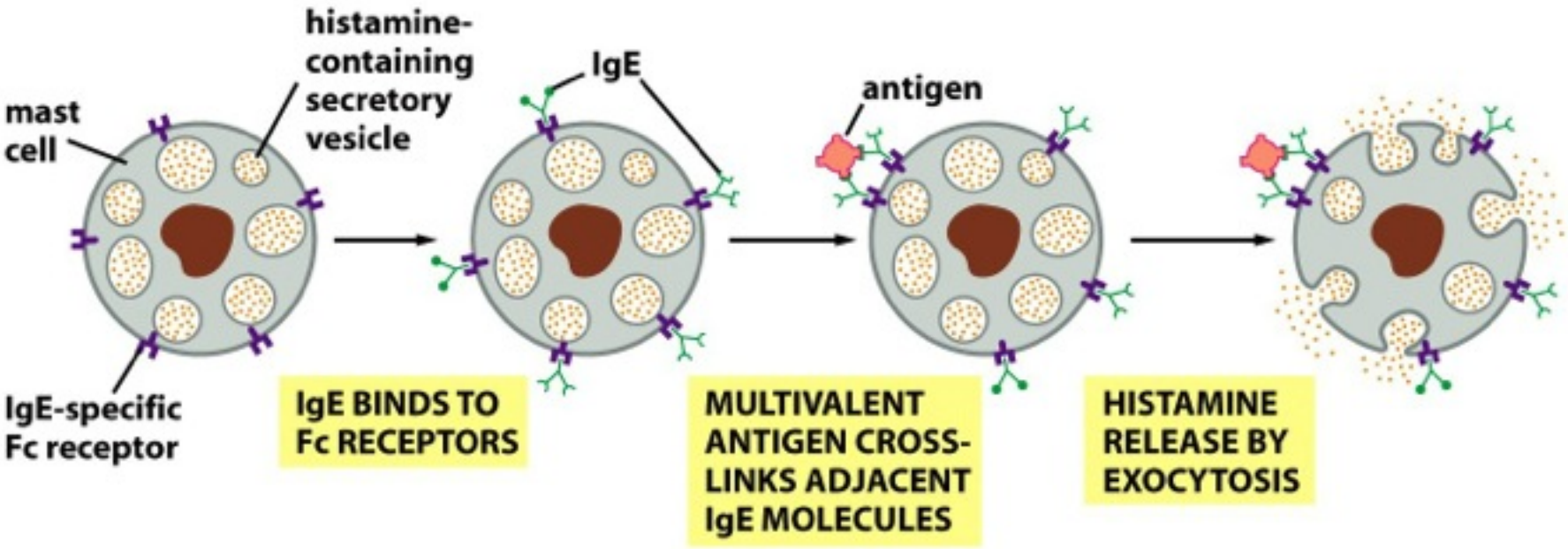
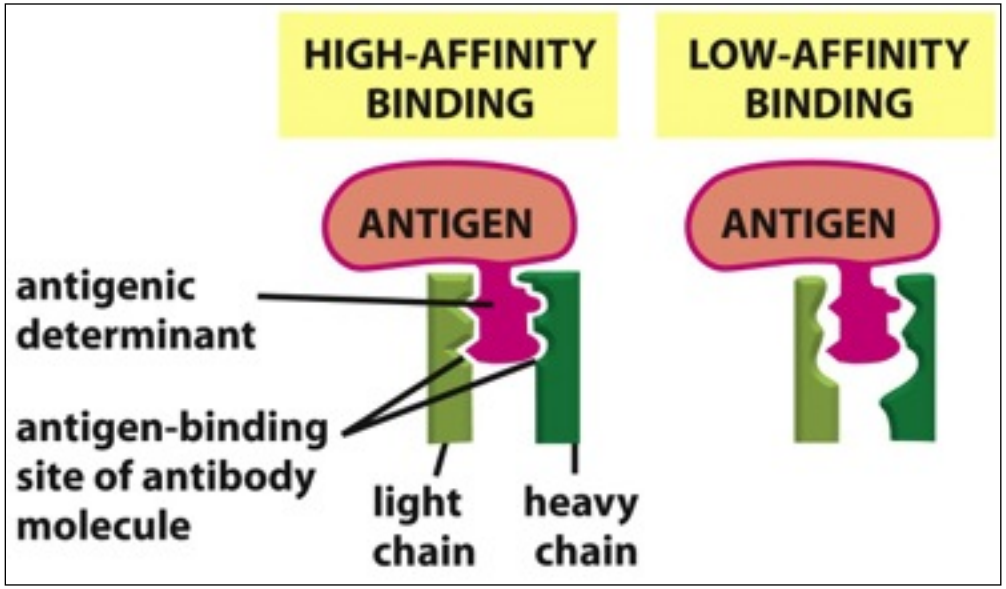



Figure 25-27 *Molecular Biology of the Cell* (© Garland Science 2008)

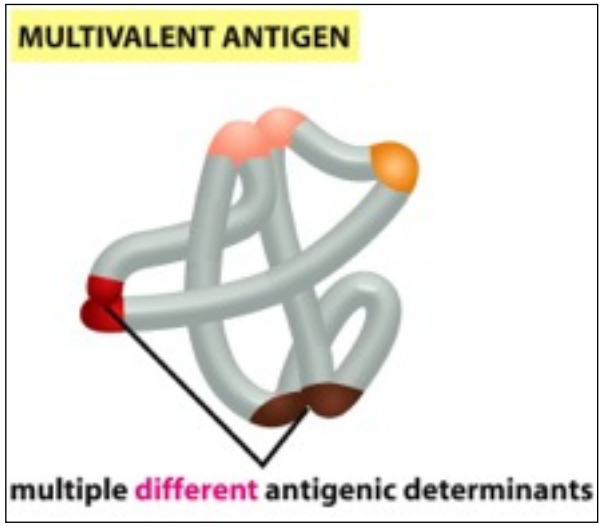
**Table 25–1 Properties of the Major Classes of Antibodies in Humans**

| PROPERTIES | CLASS OF ANTIBODY | | | | |
|---|---|---|---|---|---|
| | IgM | IgD | IgG | IgA | IgE |
| Heavy chains | μ | δ | γ | α | ε |
| Light chains | κ or λ | κ or λ | κ or λ | κ or λ | κ or λ |
| Number of four-chain units | 5 | 1 | 1 | 1 or 2 | 1 |
| Percentage of total Ig in blood | 10 | <1 | 75 | 15 | <1 |
| Activates complement | ++++ | – | ++ | – | – |
| Crosses placenta | – | – | + | – | – |
| Binds to macrophages and neutrophils | – | – | + | – | – |
| Binds to mast cells and basophils | – | – | – | – | + |

Table 25-1 *Molecular Biology of the Cell* (© Garland Science 2008)




Antijen-Antikor bağlantısı nispeten zayıf kovalent olmayan güçlerle bağlıdır. Hidrogen bağları, hidrofobik ve van der Waalsbağları ve iyonik etkileşimlerle kurulur.



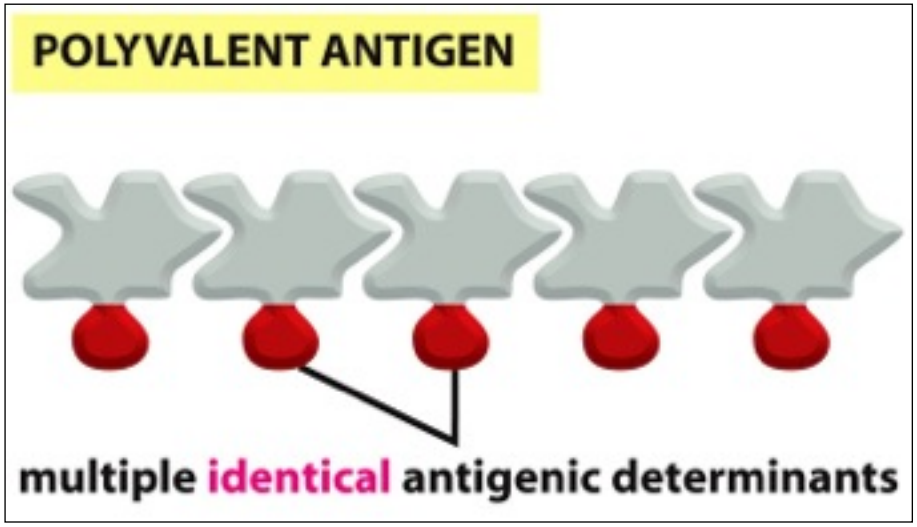




Figure 25-28 *Molecular Biology of the Cell* (© Garland Science 2008)

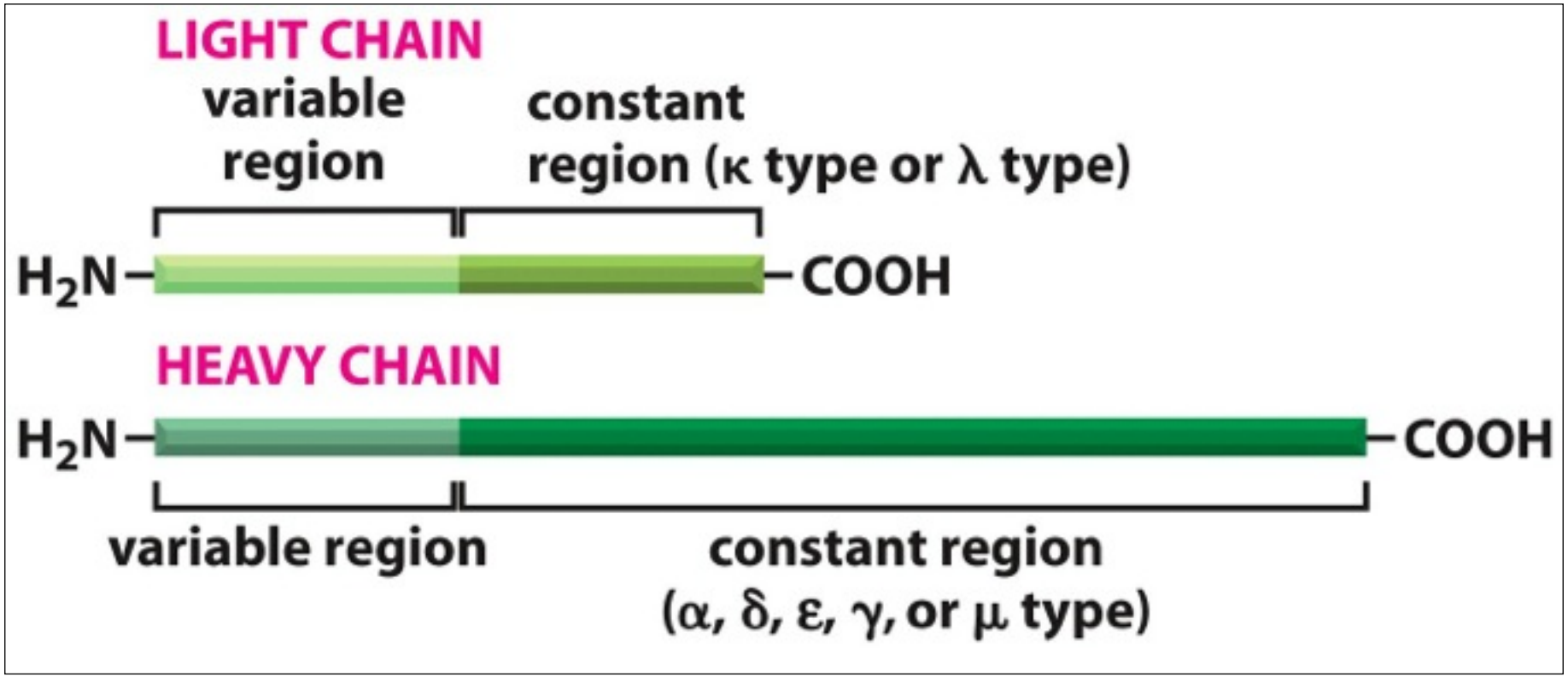
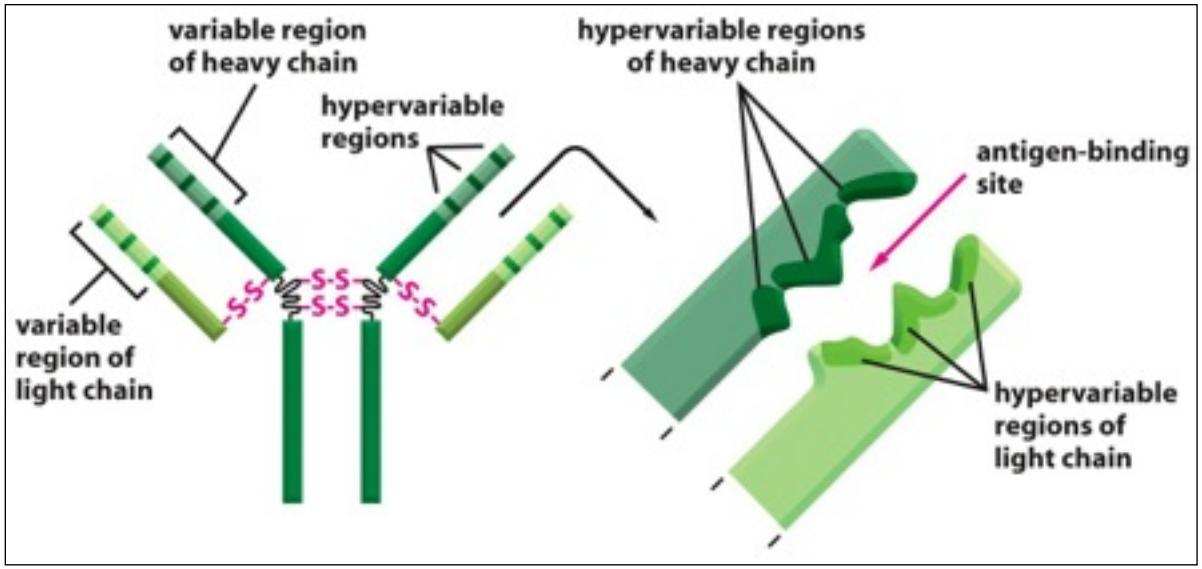



Figure 25-30 *Molecular Biology of the Cell* (© Garland Science 2008)



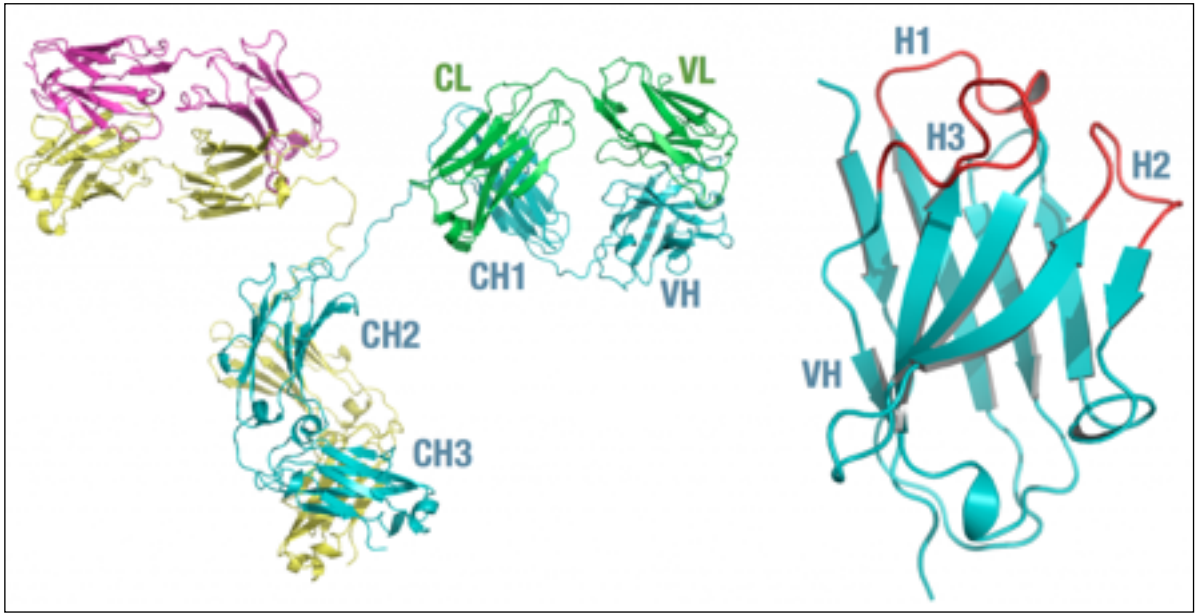
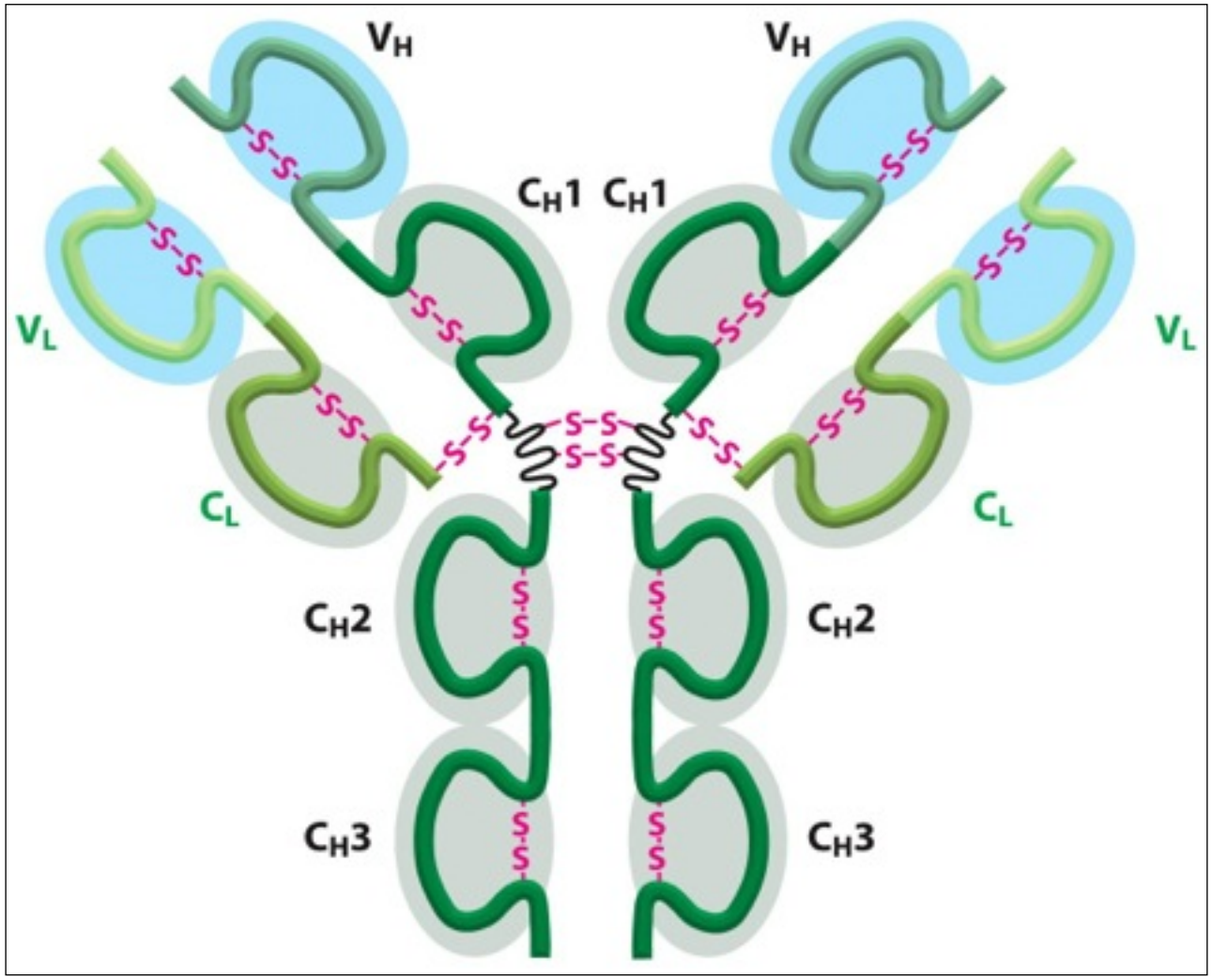
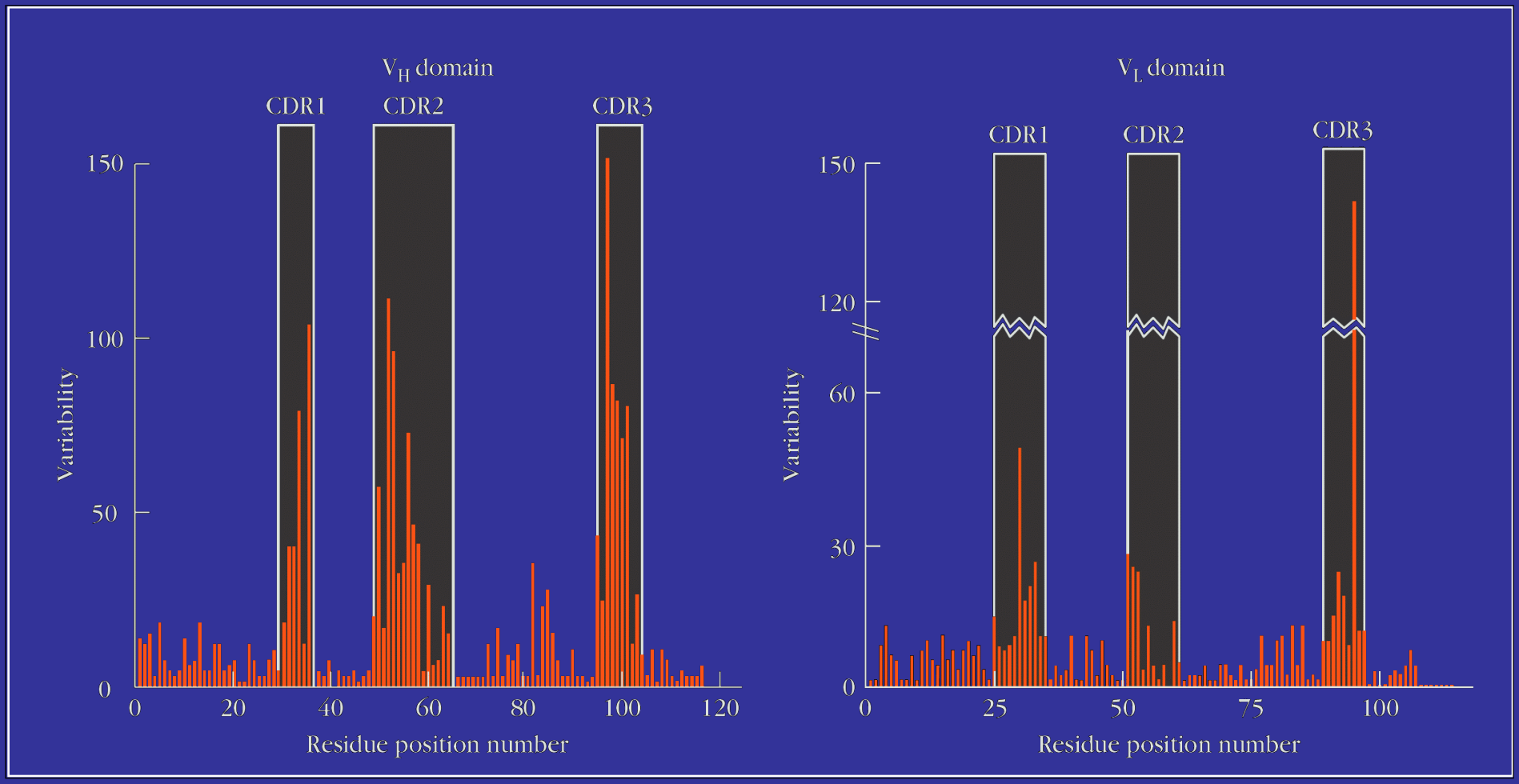
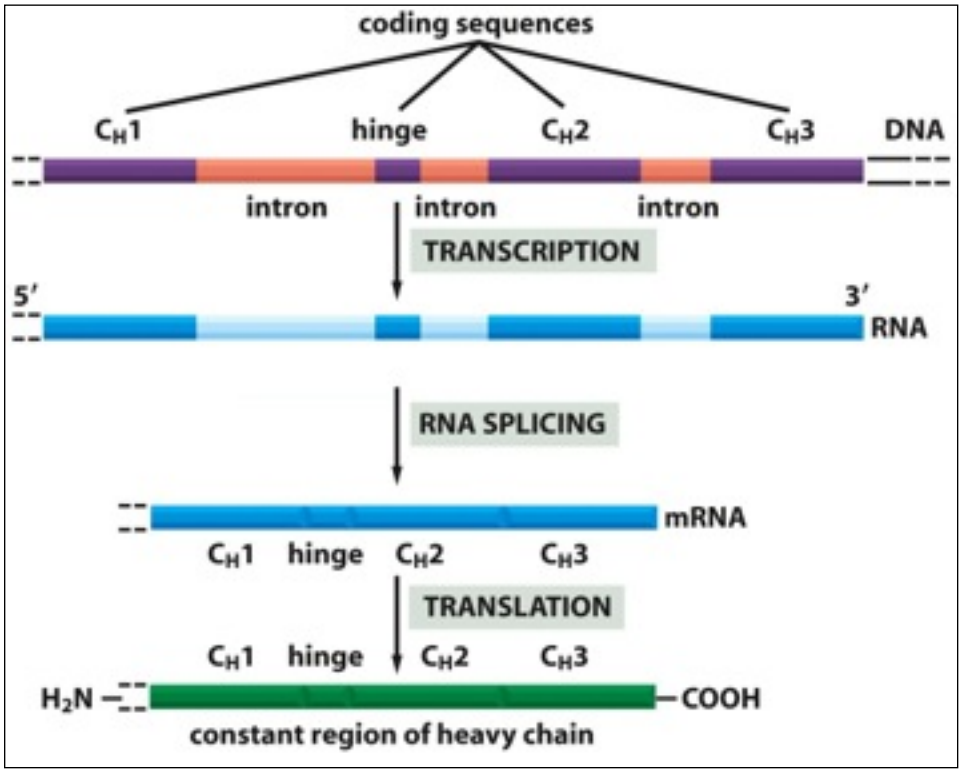




Figure 25-31 *Molecular Biology of the Cell* (© Garland Science 2008)

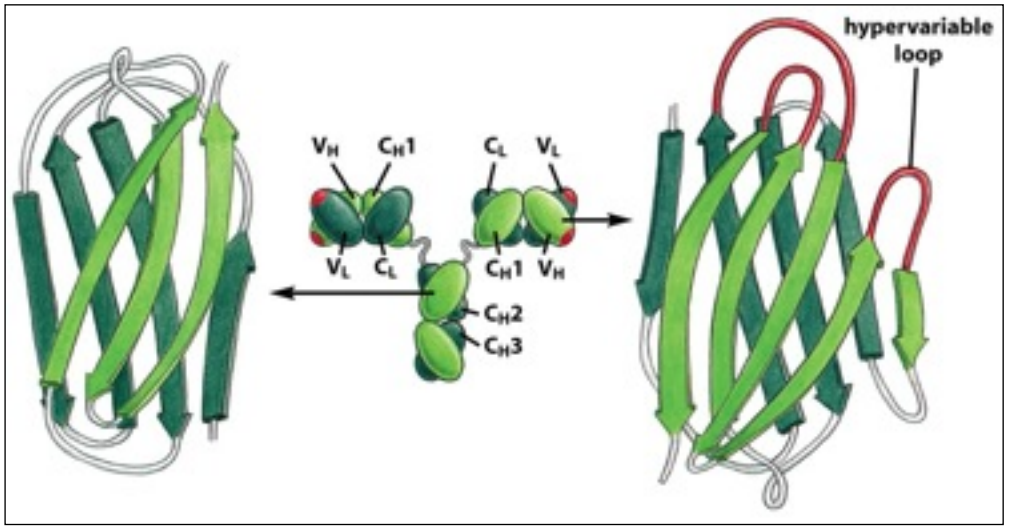

VH
VH
CH1 CH1
VL
VL
CL
CL
CH2
CH2
CH3
CH3


$V_H$ domain
CDR1
CDR2
CDR3
150
100
50
0
Variability
0
20
40
60
80
100
120
Residue position number
$V_L$ domain
CDR1
CDR2
CDR3
150
120
60
30
0
Variability
0
25
50
75
100
Residue position number




Alanlar arasındaki benzerlik, antikor zincirlerinin tek bir işlevsel genden, ikilenme ile evrimleştiğini düşündürtmektedir.

Figure 25-33 *Molecular Biology of the Cell* (© Garland Science 2008)



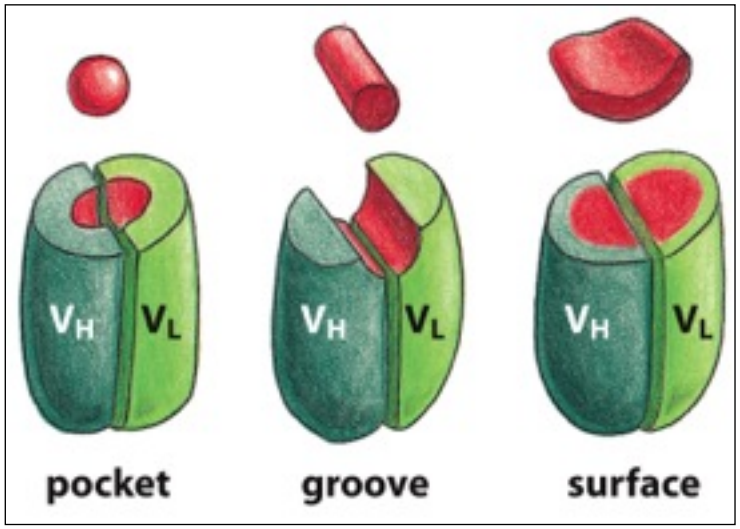




Figure 25-34 *Molecular Biology of the Cell* (© Garland Science 2008)

Milyarlarca farklı antikor molekülünü üretebilen genetik mekanizmalar nelerdir?

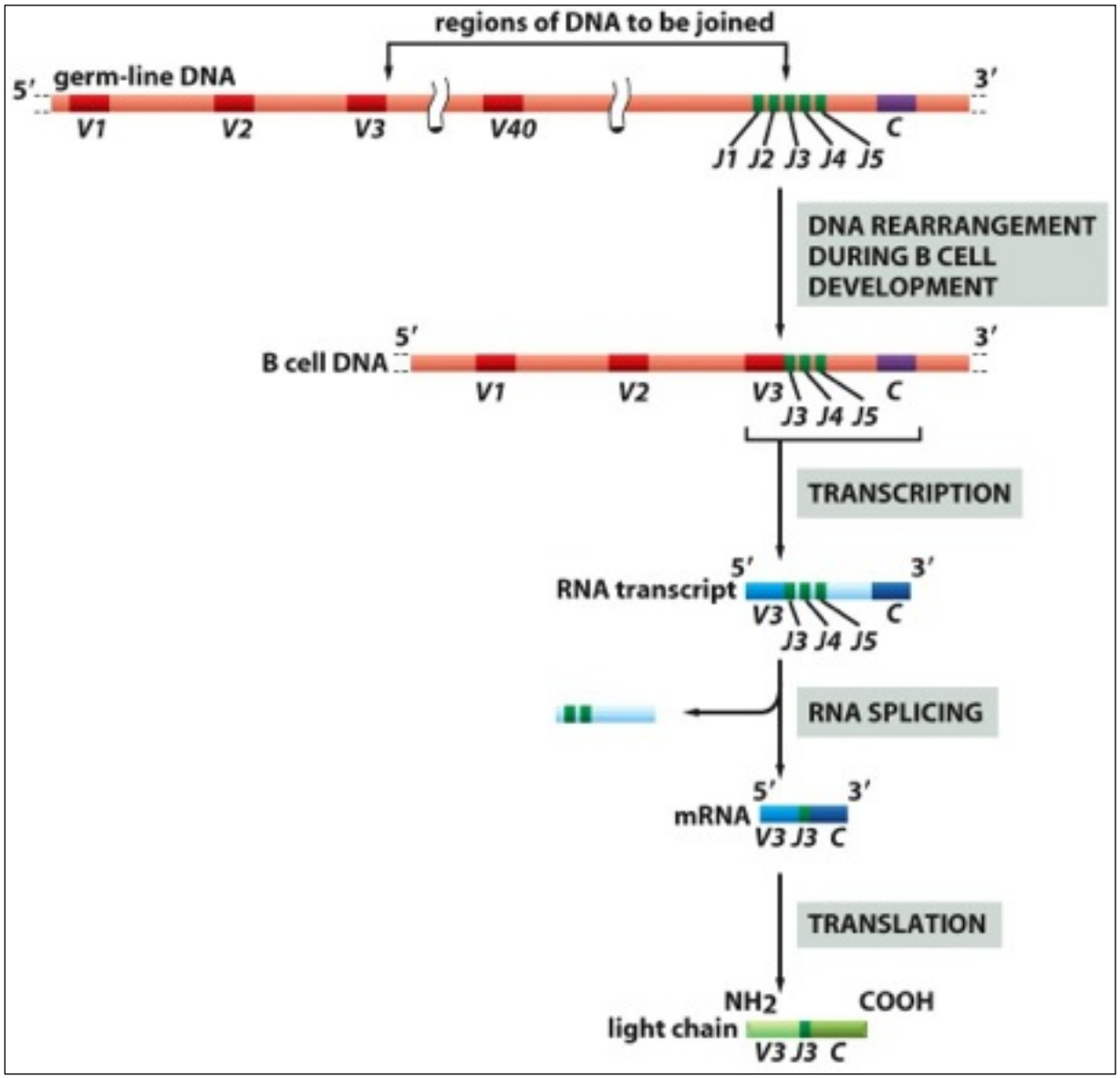
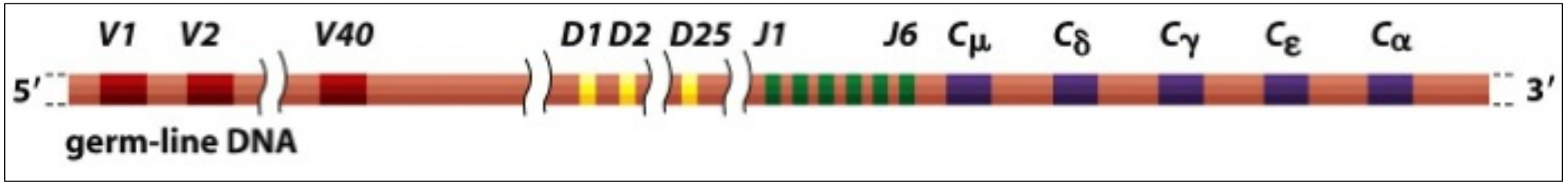
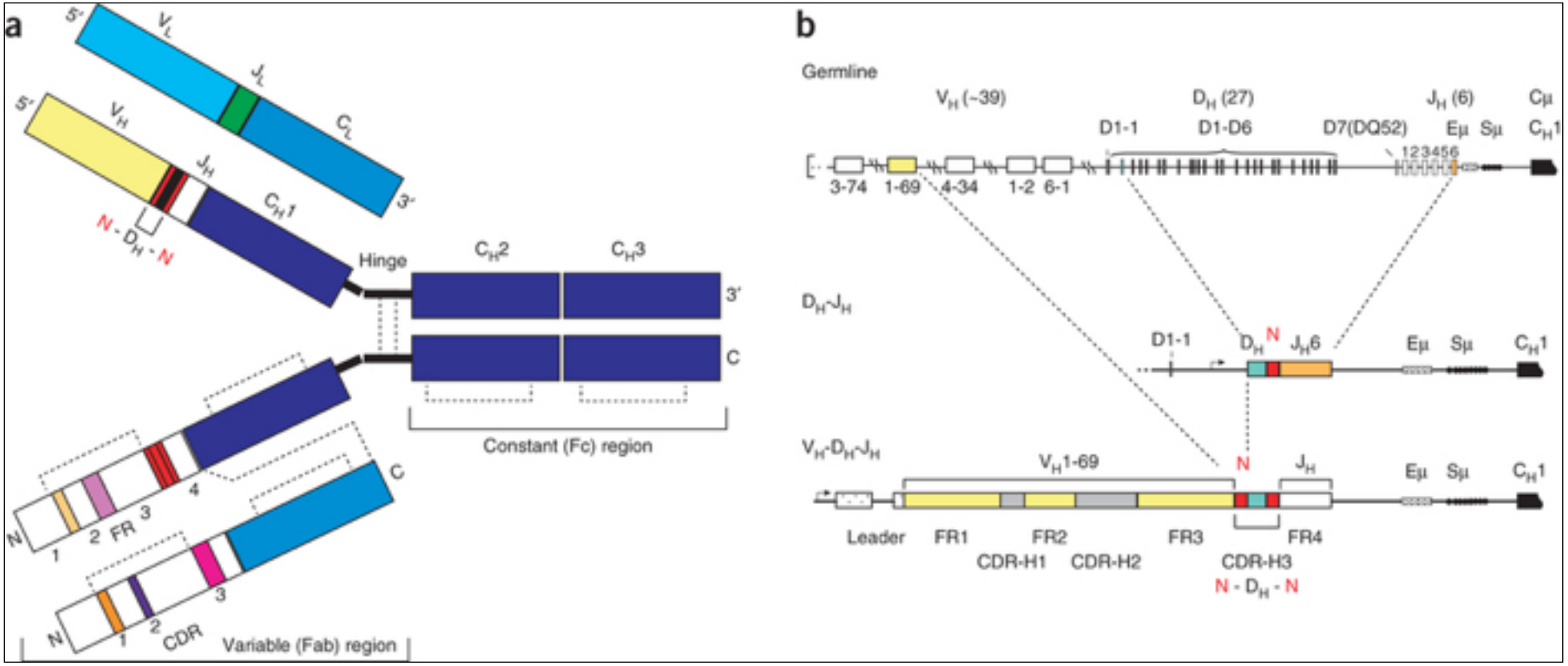
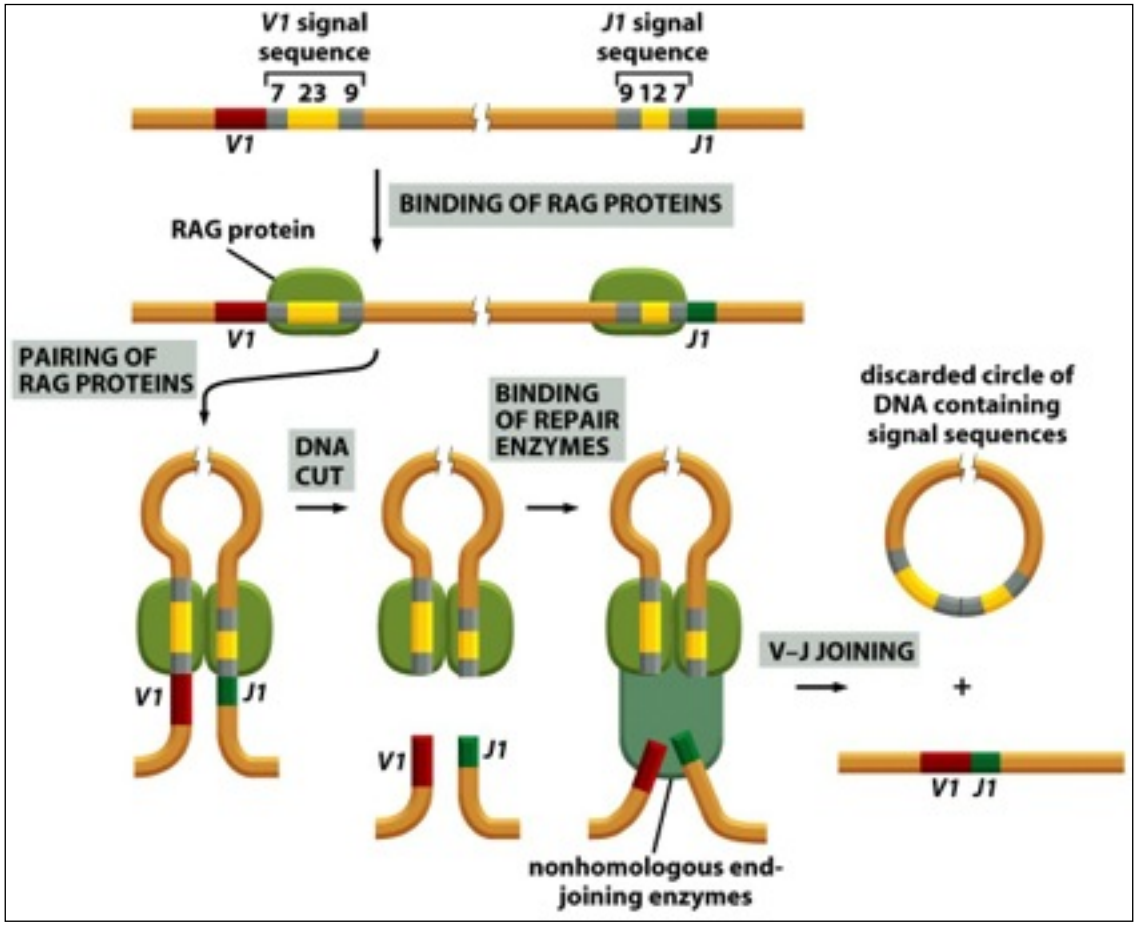
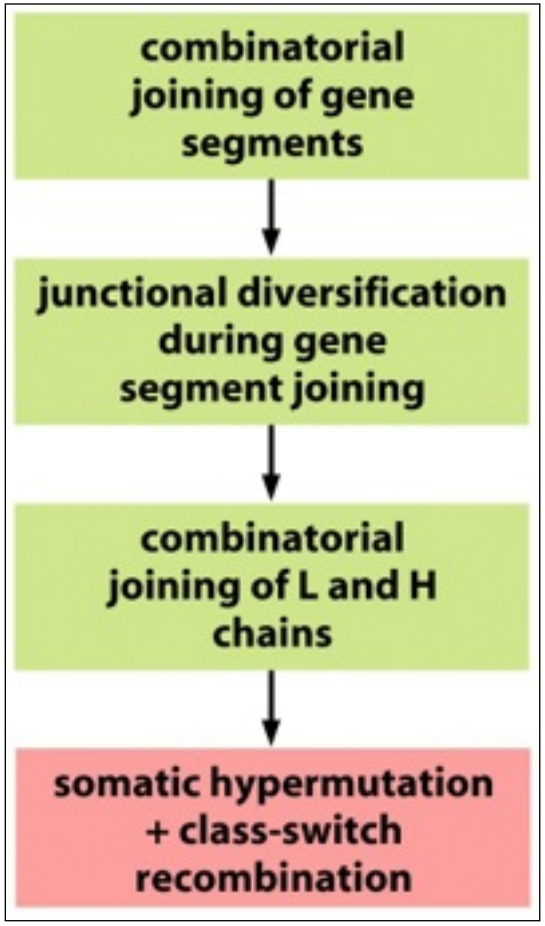



Figure 25-36 *Molecular Biology of the Cell* (© Garland Science 2008)


V1
V2
V40
D1 D2
D25
J1
J6
Cμ
Cδ
Cγ
Cε
Cα
5′
3′
germ-line DNA


a
5′
VL
JL
CL
3′
VH
JH
CH1
N - DH - N
Hinge
CH2
CH3
3′
C
Constant (Fc) region
FR
CDR
Variable (Fab) region
b
Germline
VH (~39)
DH (27)
JH (6)
Cμ
D1-1
D1-D6
D7(DQ52)
Eμ
Sμ
CH1
3-74
1-69
4-34
1-2
6-1
DH-JH
JH6
VH-DH-JH
VH1-69
Leader
FR1
FR2
FR3
FR4
CDR-H1
CDR-H2
CDR-H3
N - DH - N




Eklenti çeşitliiği RAG1 ve RAG2 ile sağlanır. TCR'larda da aynı mekanizma kullanılır. Olası nükleotid kayıp ve kazançları **eklenti çeşitliliği** olarak adlandırılır. Özellikle CDR3'ün çeşitliliğini çok artırır.

Antijene bağlandıktan sonra RAG'lar tekrar aktive olur ve matürasyon devam eder, buna **reseptör düzeltme** adı verilir.
Her V bölgesi oluşumunda bir nükleotidlik mutasyon oluşumu normaldir, diğer genlere göre bu değer bir milyon kat fazladır. Buna **somatik hipermutasyon** adı verilir.
toplamda Afinite maturasyonu denir.

**Allelik drop-out**

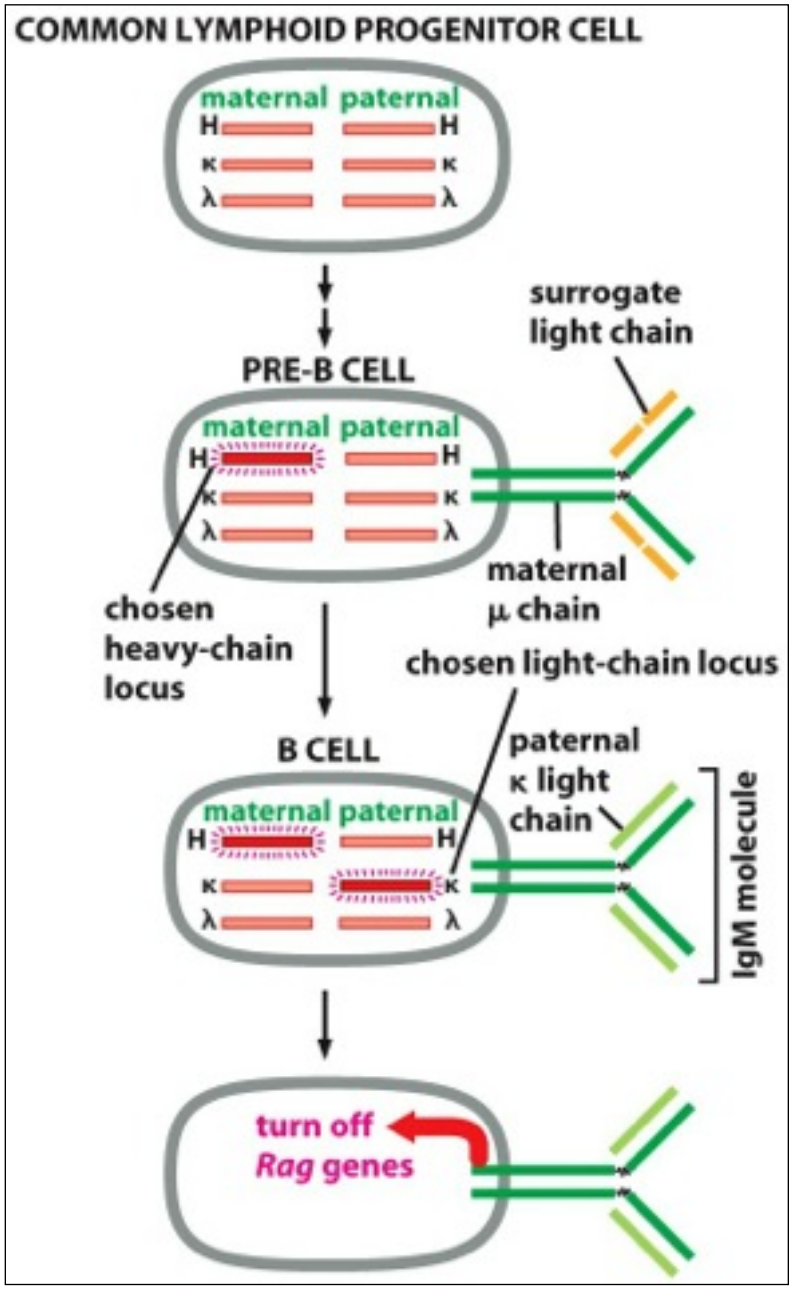



Figure 25-39 *Molecular Biology of the Cell* (© Garland Science 2008)

## Sınıf Değişim Rekombinasyonu

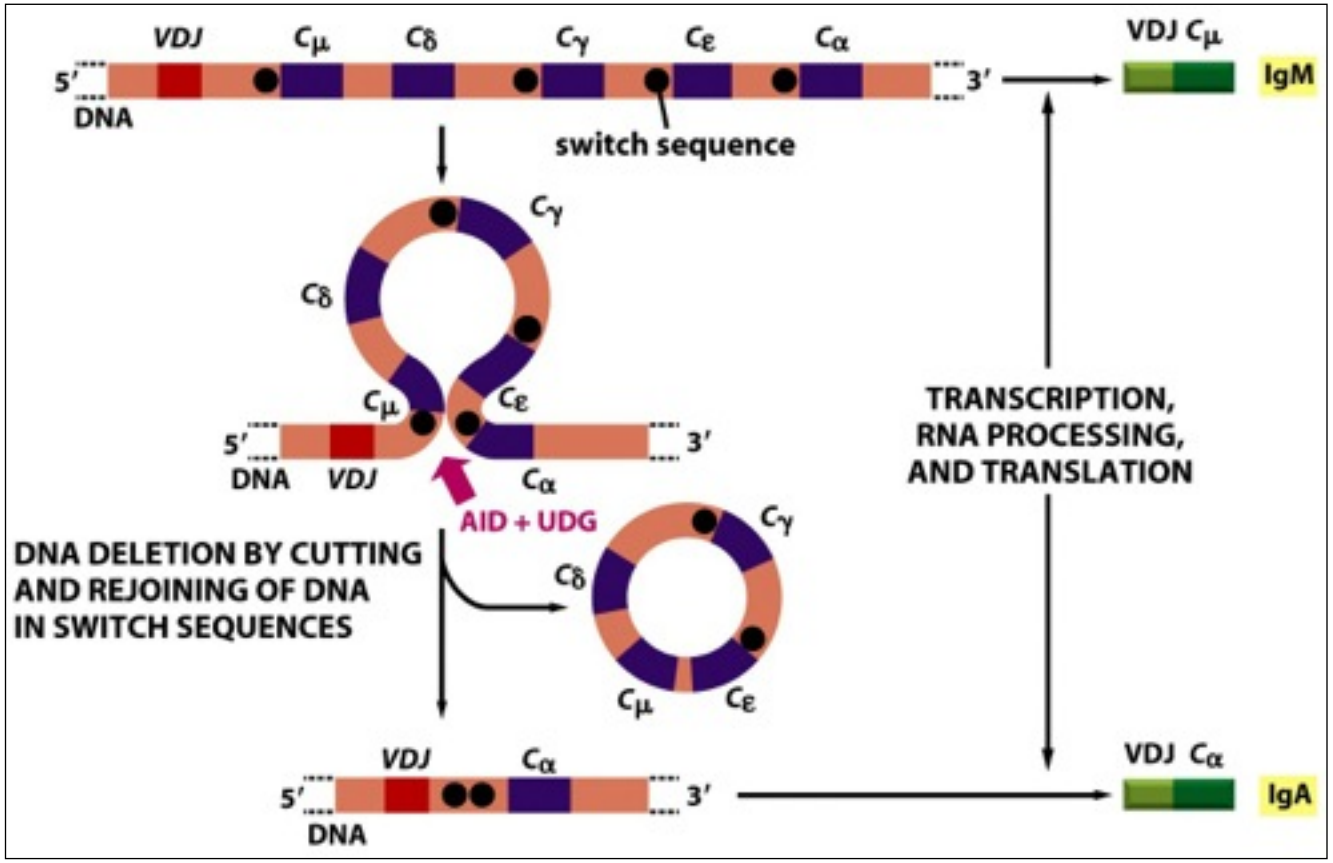
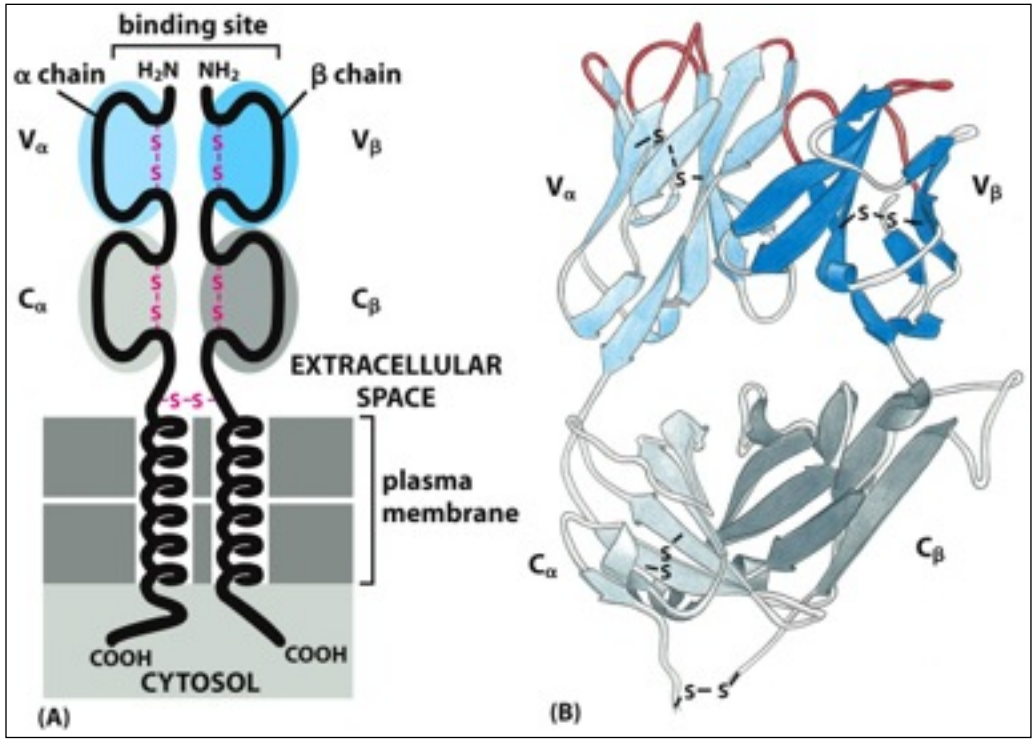



Figure 25-41 *Molecular Biology of the Cell* (© Garland Science 2008)

Figure 25-42 *Molecular Biology of the Cell* (© Garland Science 2008)




T hüc. B hüc. uyarılmasından sorumlu olmalarının yanında patojenlerin ortadan kaldırılmasından da sorumludur.
antijen sunan hücreler, antijene ait peptid parçalarını MHC'ler sayesinde sunar.
T hüc. ikincil lenfoid dokuda yada göç ettiği enfeksiyon odağında kısa mesafede etkilidir.

T hüc. reseptörleri, sadece membran bağlıdır ve salgılanmazlar. hem helper'larda ve sitotoksik T hüc. bulunur, Ig'lerin tek koluna benzer bir yapıdadır.

B hüc. antikor çeşitliliğini sağlamakta kullanılan sistemler aynıdır, aynı V(D)J rekombinaz kullanılır, ancak somatik hipermutasyon görülmez.
T Hüc. uyarılmaları Antijen sunan hücrelerce gerçekleştirilir, bunlar dentritik hücreler, makrofajlar ve B hücreleridir. Olgunlaşmamış dentritik hücreleri deri, bağırsak, solunum yollarına yakın olarak bulunurlar ve karşılaştıkları patojenleri ve toksinleri en yakın lenfoid organa götürürler.

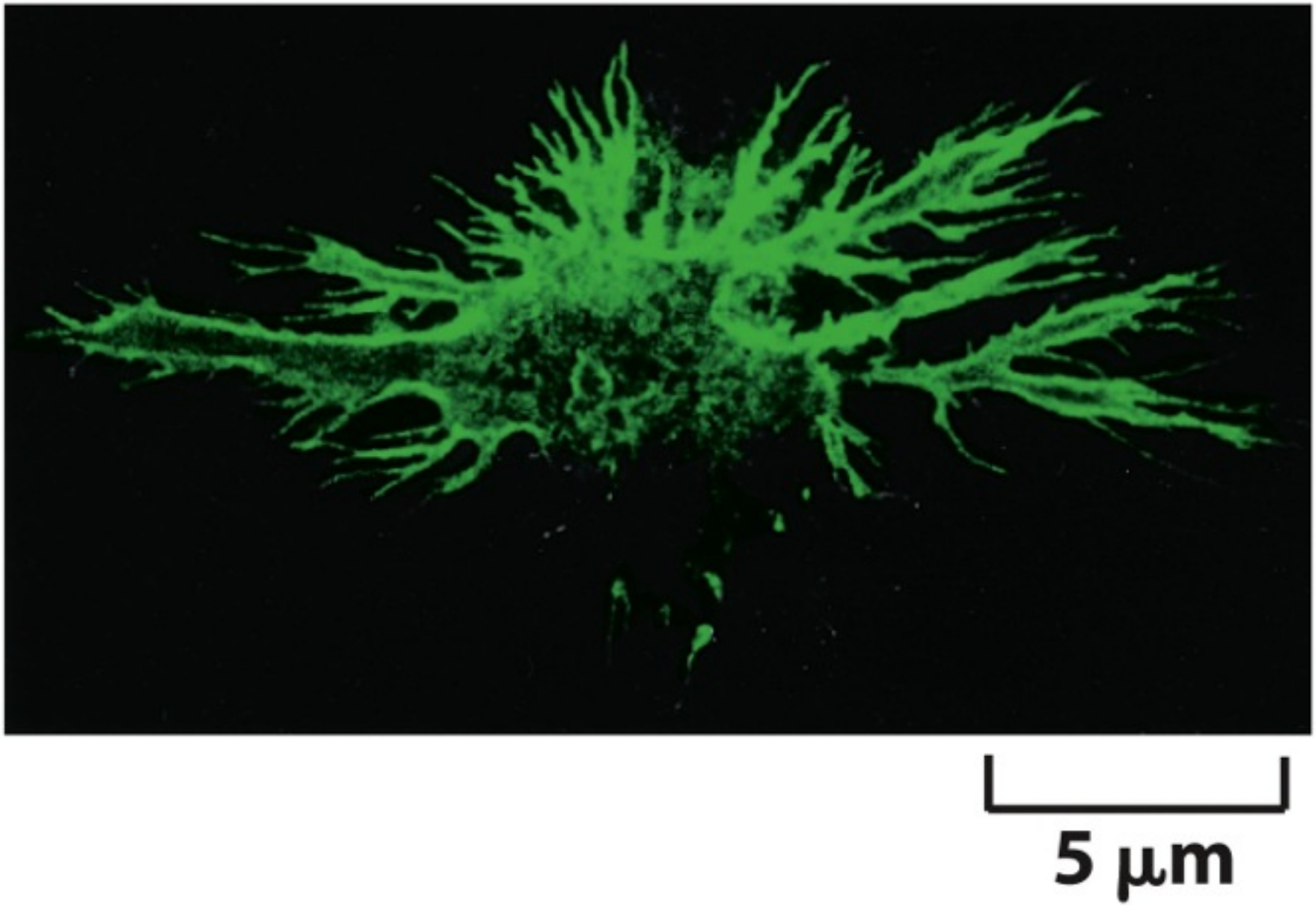
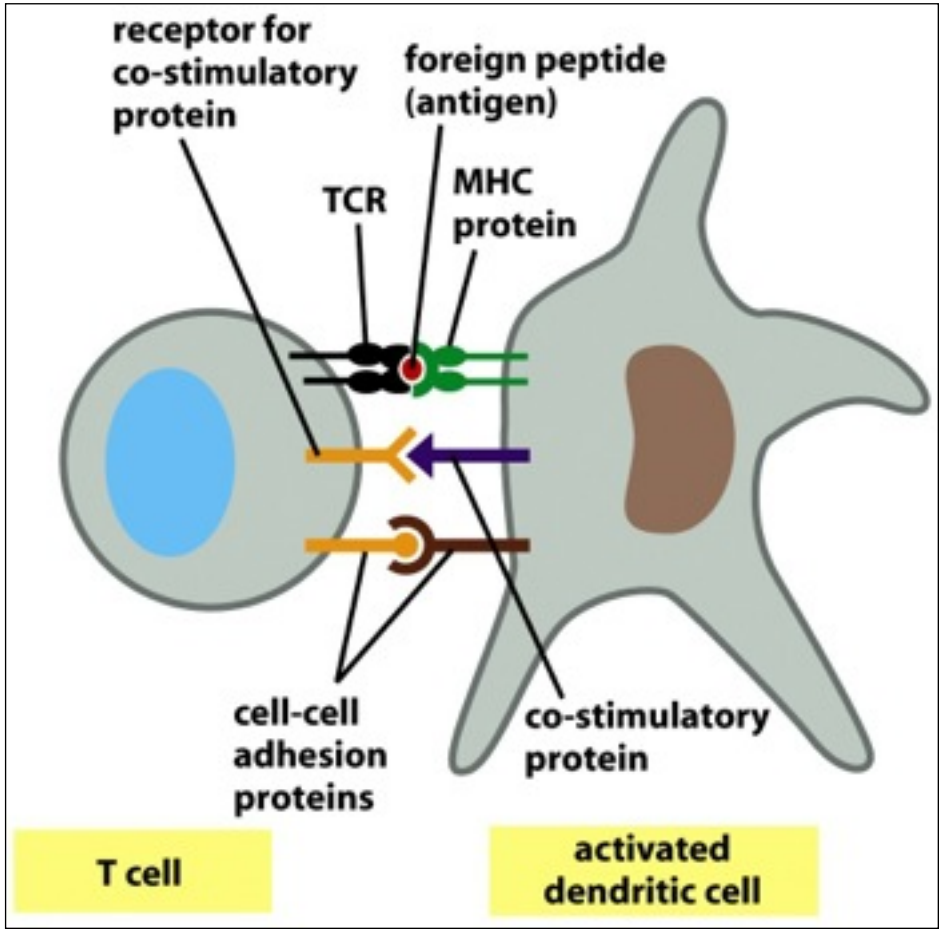



Figure 25-44 *Molecular Biology of the Cell* (© Garland Science 2008)




Antijen sunan hücreler
1) yabancı antijenleri T hüc. reseptörüne sunan MHC prot.
2) T hüc. yüzeyinde kendilerine uyan reseptörlere bağlanan eş-uyarıcı proteinler.
3) hücre-hücre yapışmasını sağlayan moleküller.

Figure 25-45 *Molecular Biology of the Cell* (© Garland Science 2008)

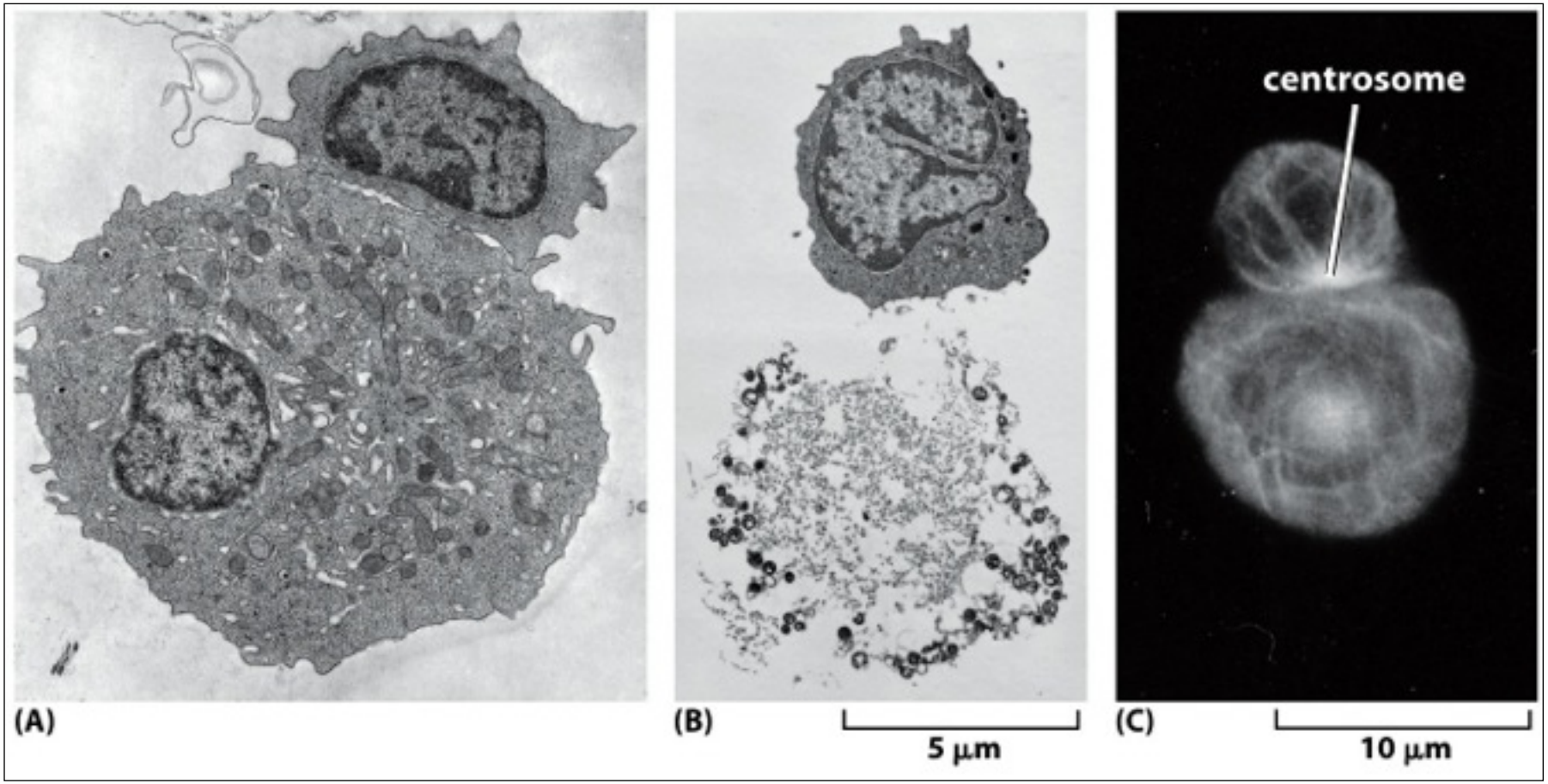
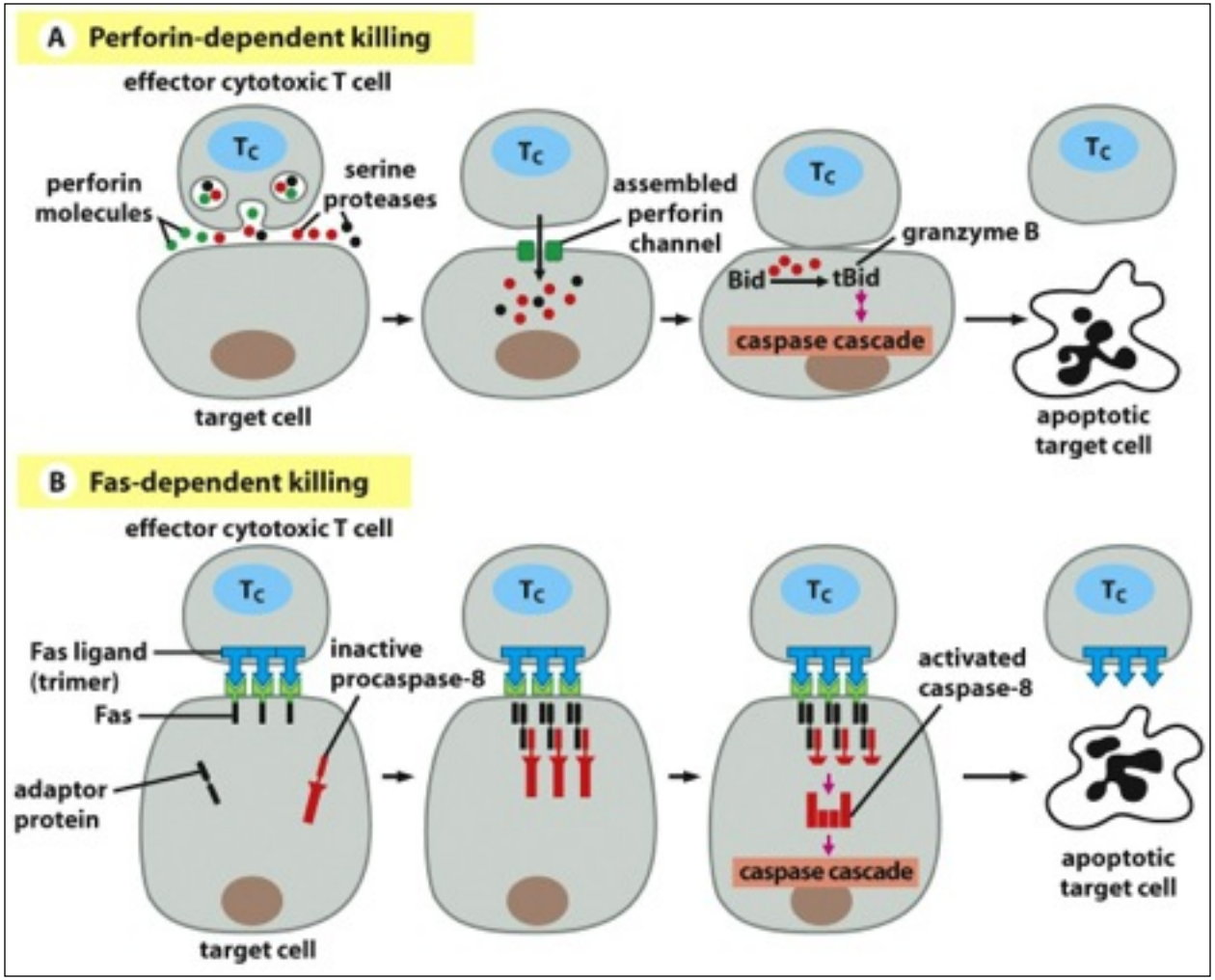
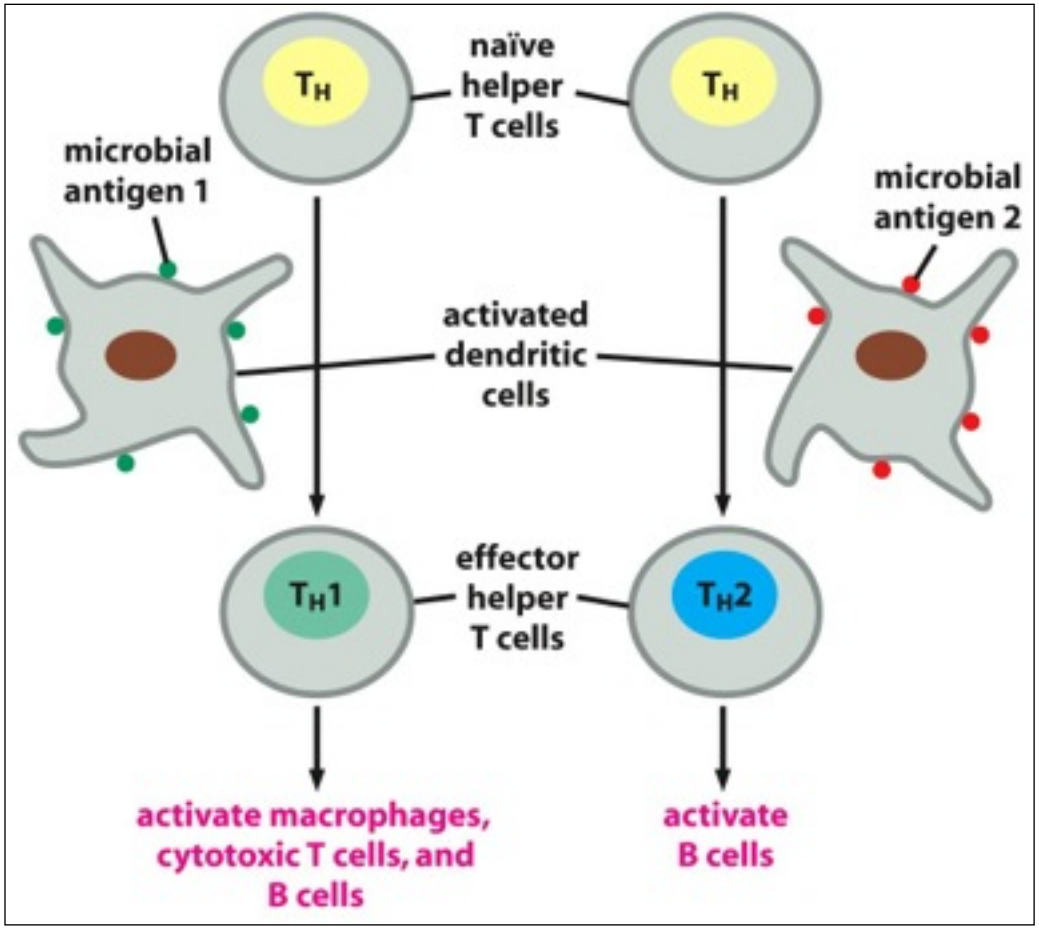
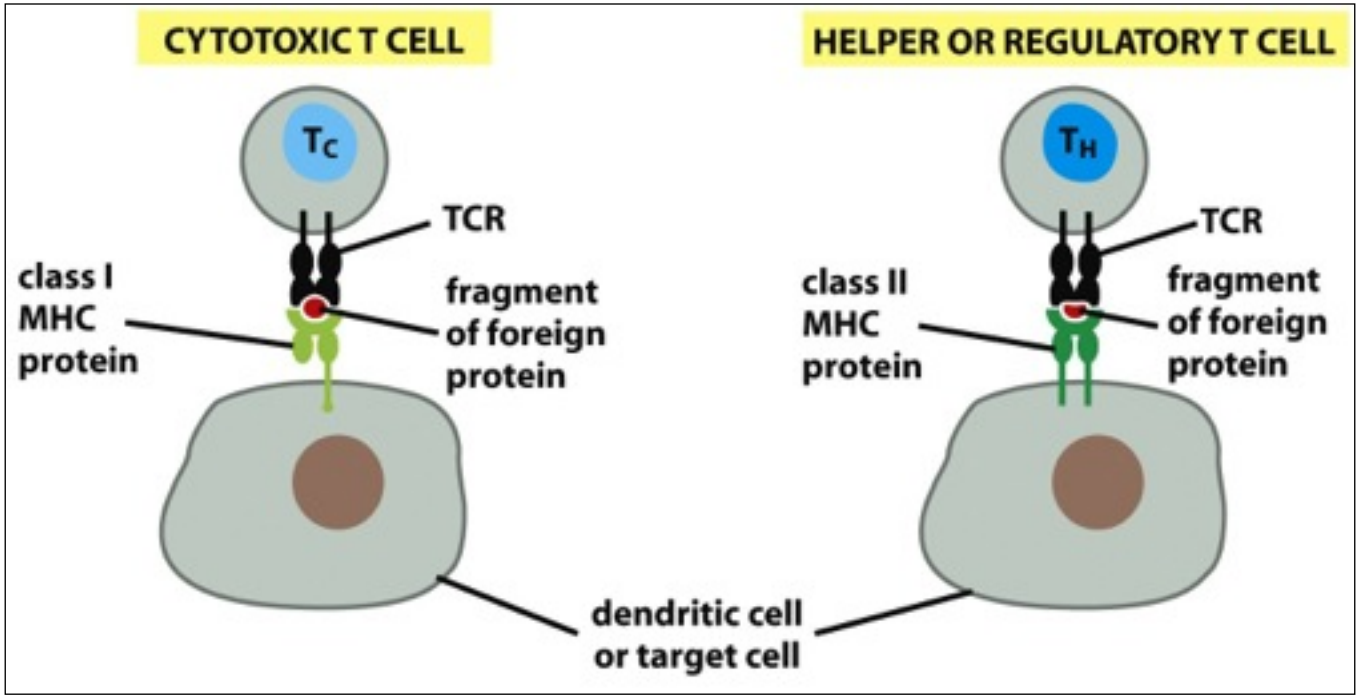



Figure 25-46 *Molecular Biology of the Cell* (© Garland Science 2008)


A Perforin-dependent killing
effector cytotoxic T cell
Tc
perforin molecules
serine proteases
assembled perforin channel
granzyme B
Bid
tBid
caspase cascade
target cell
apoptotic target cell
B Fas-dependent killing
effector cytotoxic T cell
Fas ligand (trimer)
Fas
inactive procaspase-8
adaptor protein
activated caspase-8
caspase cascade
target cell
apoptotic target cell


$T_H$
naïve
helper
T cells
$T_H$
microbial
antigen 1
microbial
antigen 2
activated
dendritic
cells
$T_H1$
effector
helper
T cells
$T_H2$
activate macrophages,
cytotoxic T cells, and
B cells
activate
B cells




MHC (doku uyumluluk molekülleri) ilk kez transplantasyon tepkilerinde belirlenmiştir.

Figure 25-49 *Molecular Biology of the Cell* (© Garland Science 2008)

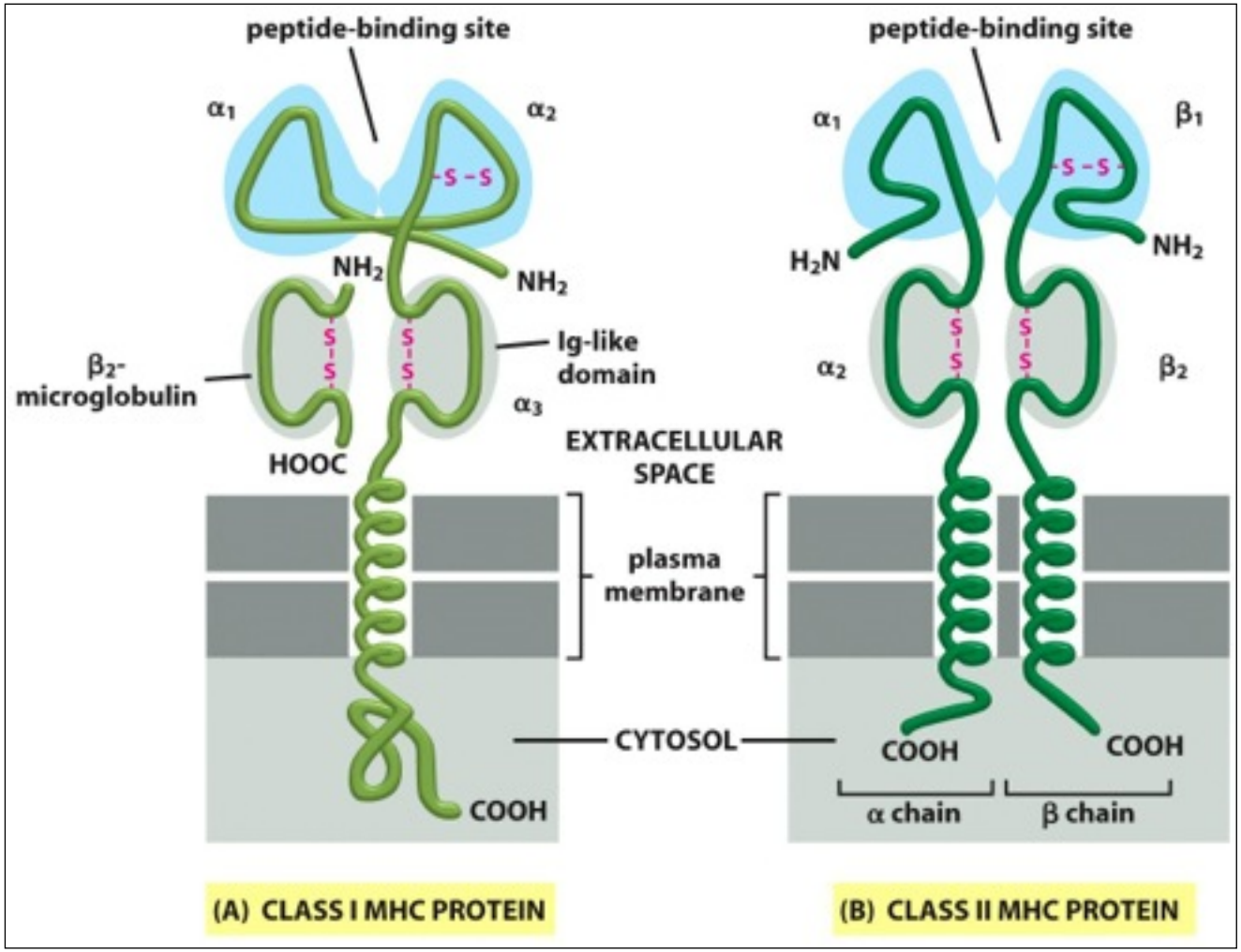



Figure 25-50 *Molecular Biology of the Cell* (© Garland Science 2008)

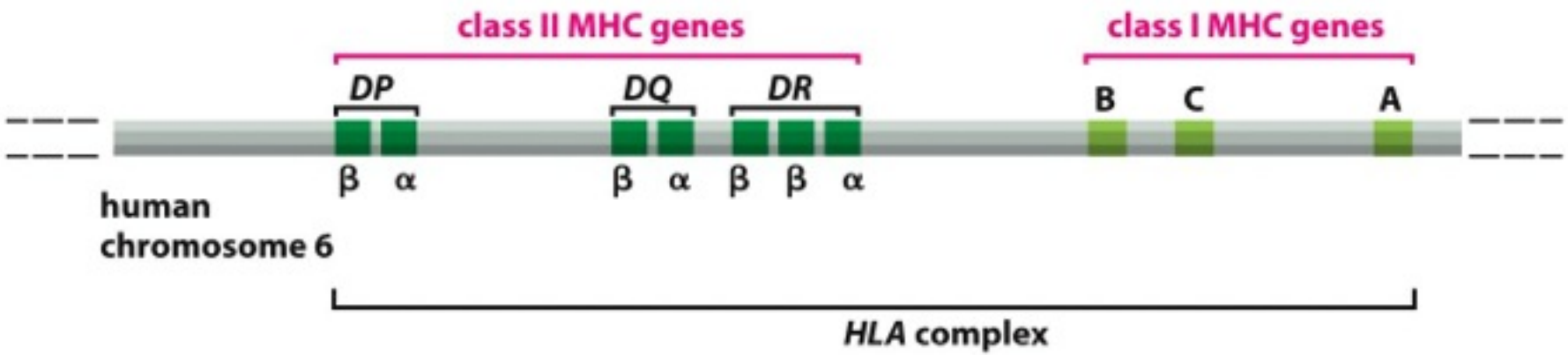



Figure 25-51 *Molecular Biology of the Cell* (© Garland Science 2008)

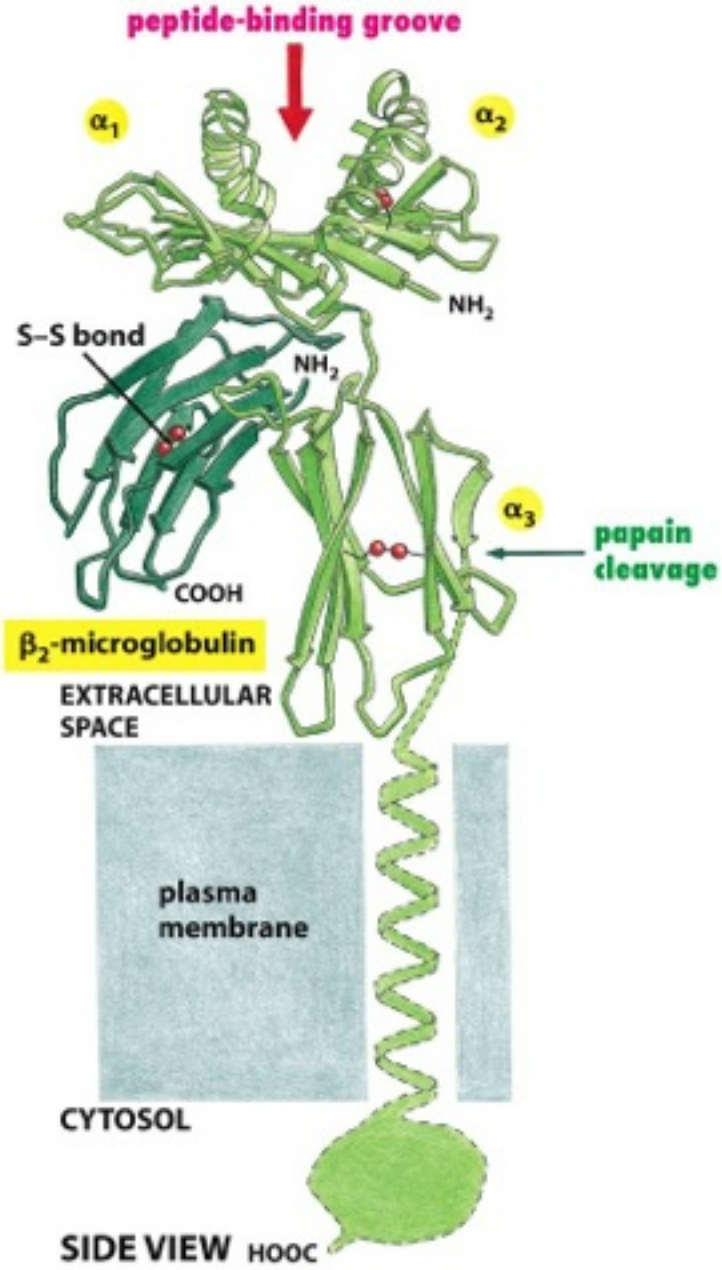



Figure 25-52a *Molecular Biology of the Cell* (© Garland Science 2008)

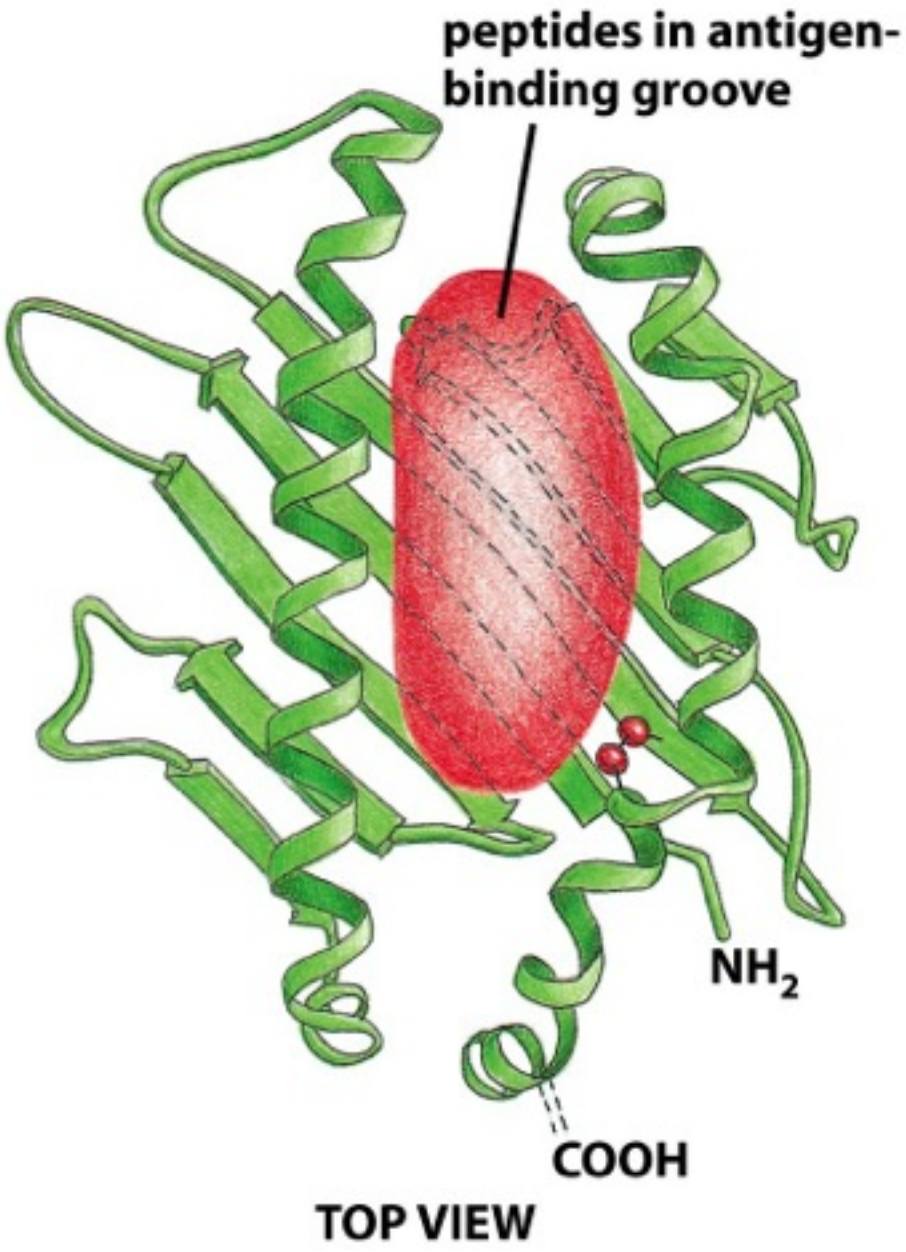
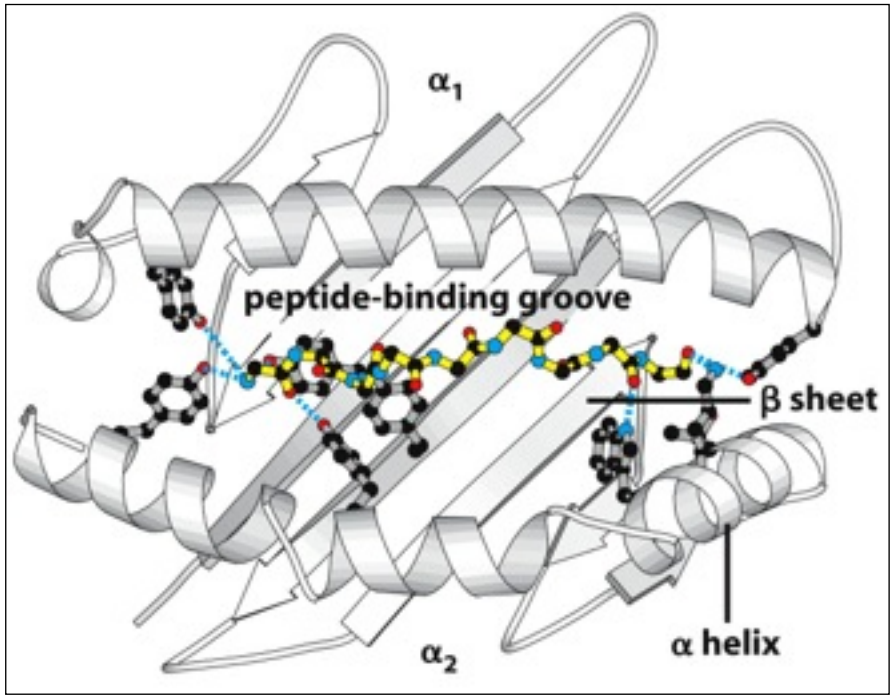



Figure 25-52b *Molecular Biology of the Cell* (© Garland Science 2008)



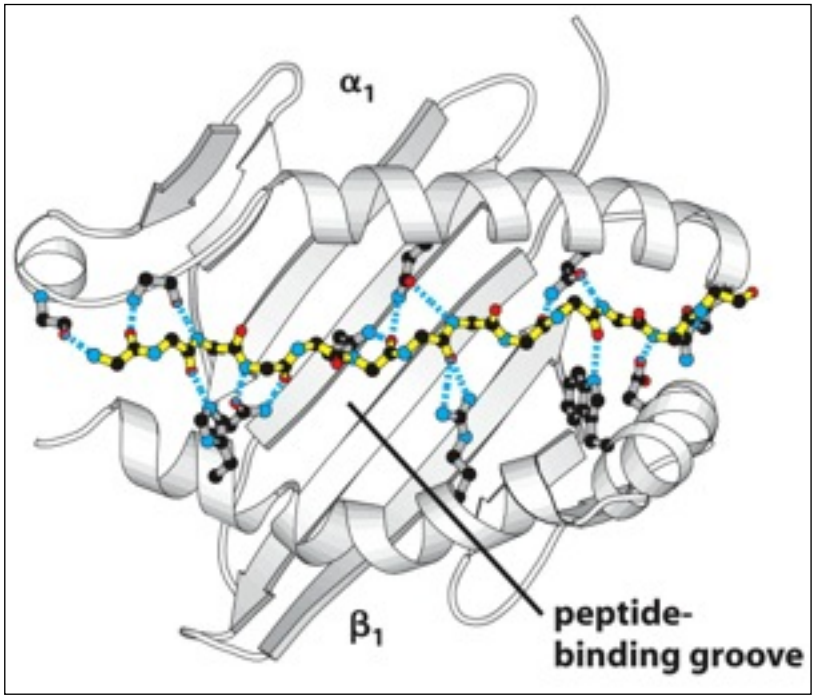




Figure 25-53 *Molecular Biology of the Cell* (© Garland Science 2008)

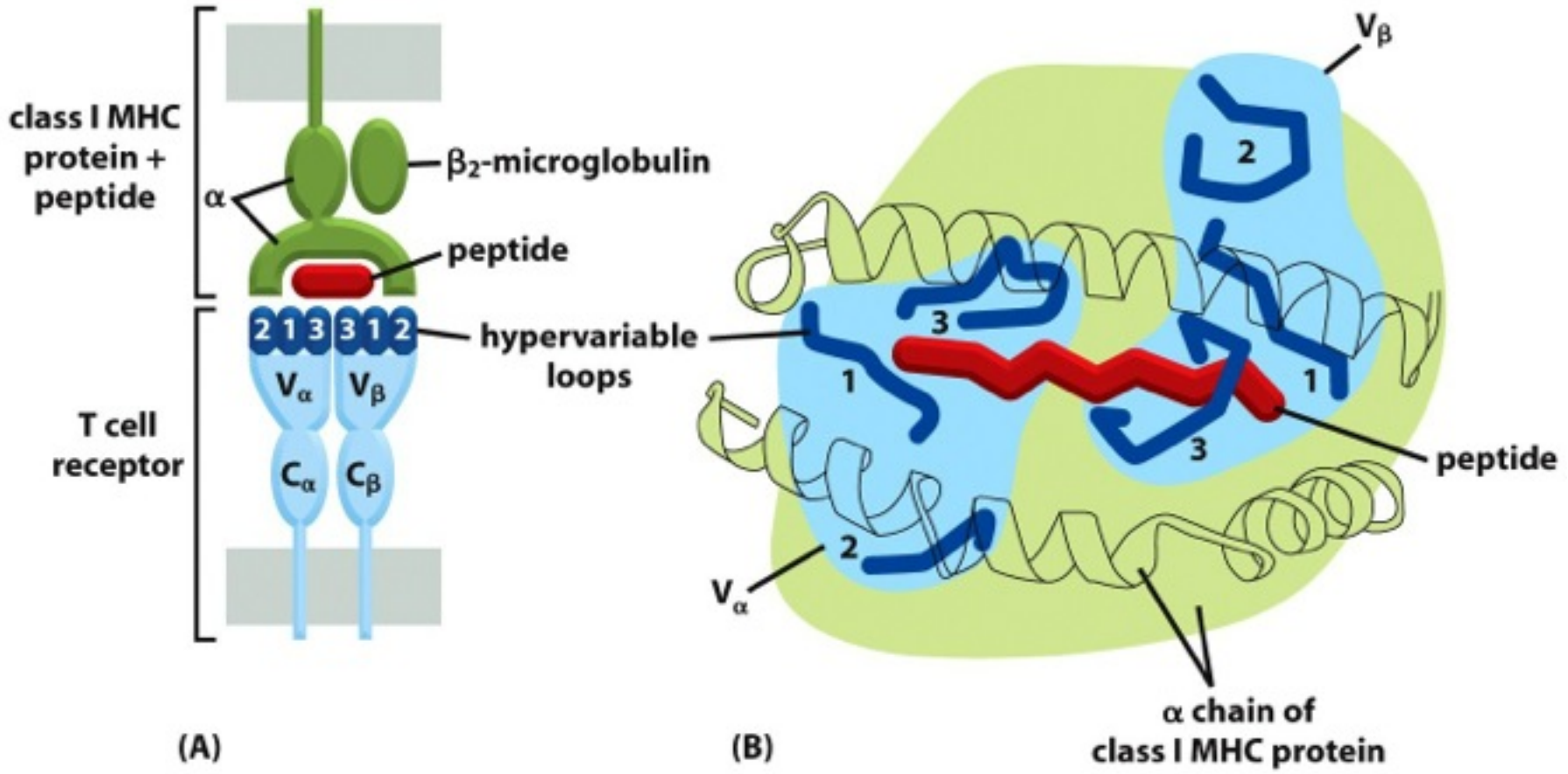



Figure 25-55 *Molecular Biology of the Cell* (© Garland Science 2008)

**Table 25–2 Properties of Human Class I and Class II MHC Proteins**

| | CLASS I | CLASS II |
|---|---|---|
| Genetic loci | *HLA-A, HLA-B, HLA-C* | *DP, DQ, DR* |
| Chain structure | $\alpha$ chain + $\beta_2$-microglobulin | $\alpha$ chain + $\beta$ chain |
| Cell distribution | most nucleated cells | dendritic cells, B cells, macrophages, thymus epithelial cells, some others |
| Presents antigen to | cytotoxic T cells | helper T cells, regulatory T cells |
| Source of peptide fragments | mainly proteins made in cytoplasm | mainly endocytosed plasma membrane and extracellular proteins |
| Polymorphic domains | $\alpha_1 + \alpha_2$ | $\alpha_1 + \beta_1$ |
| Recognition by co-receptor | CD8 | CD4 |

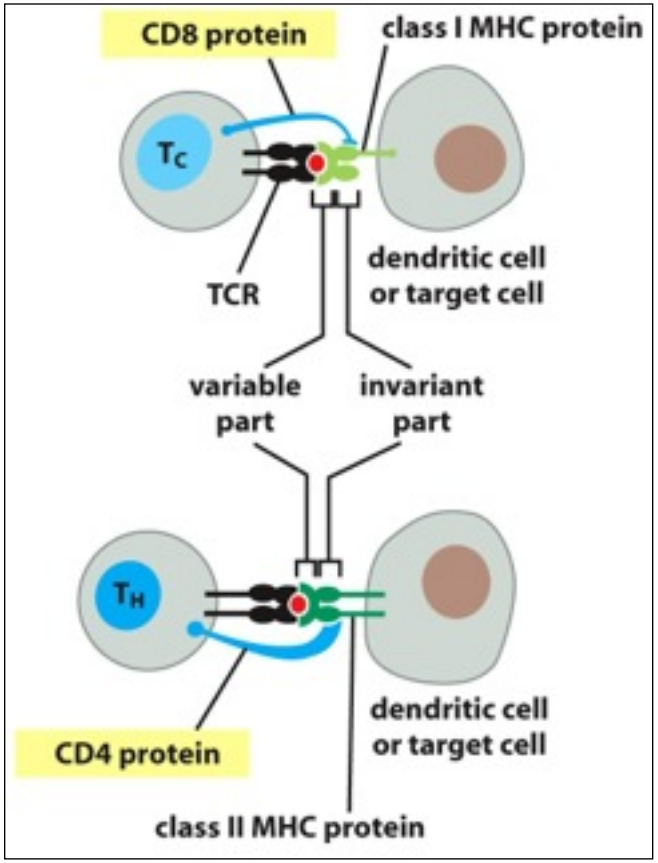



Figure 25-56 *Molecular Biology of the Cell* (© Garland Science 2008)

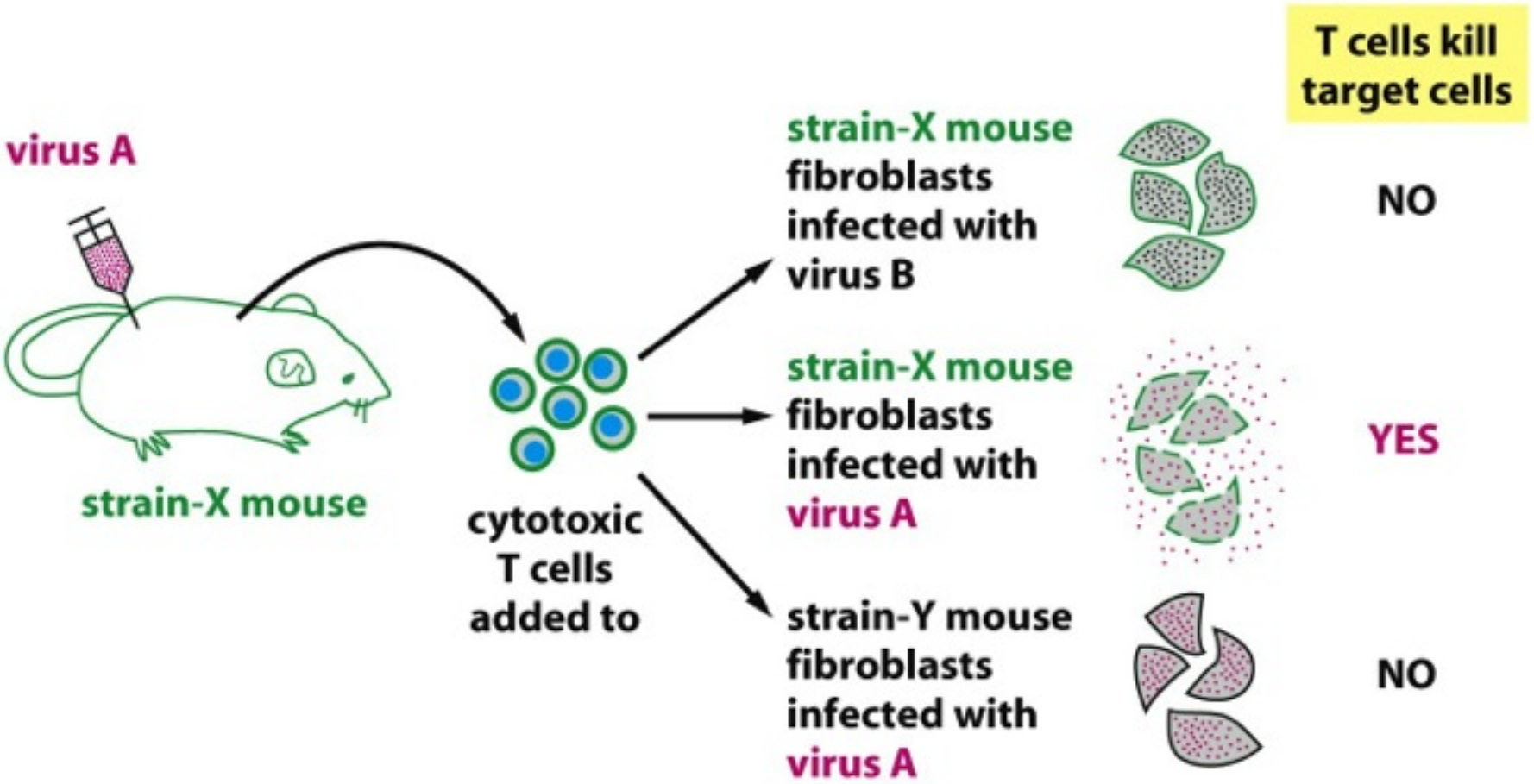



Figure 25-57 *Molecular Biology of the Cell* (© Garland Science 2008)

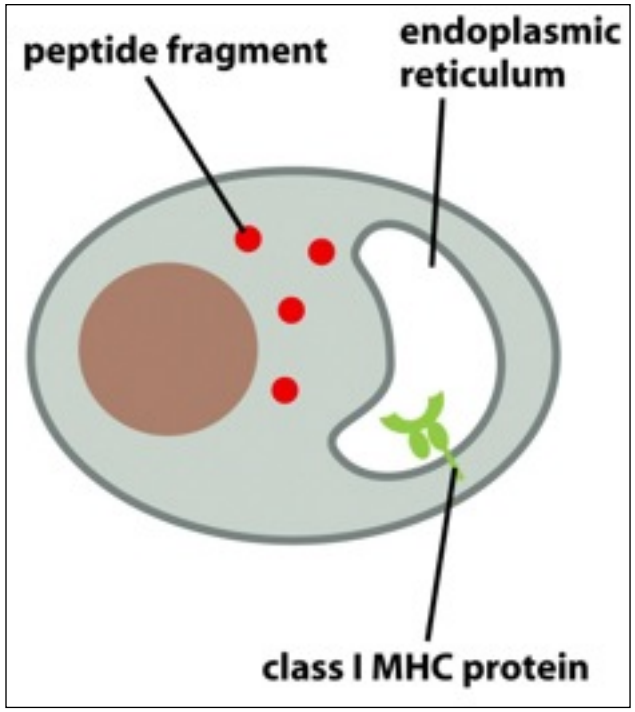



Figure 25-58 *Molecular Biology of the Cell* (© Garland Science 2008)

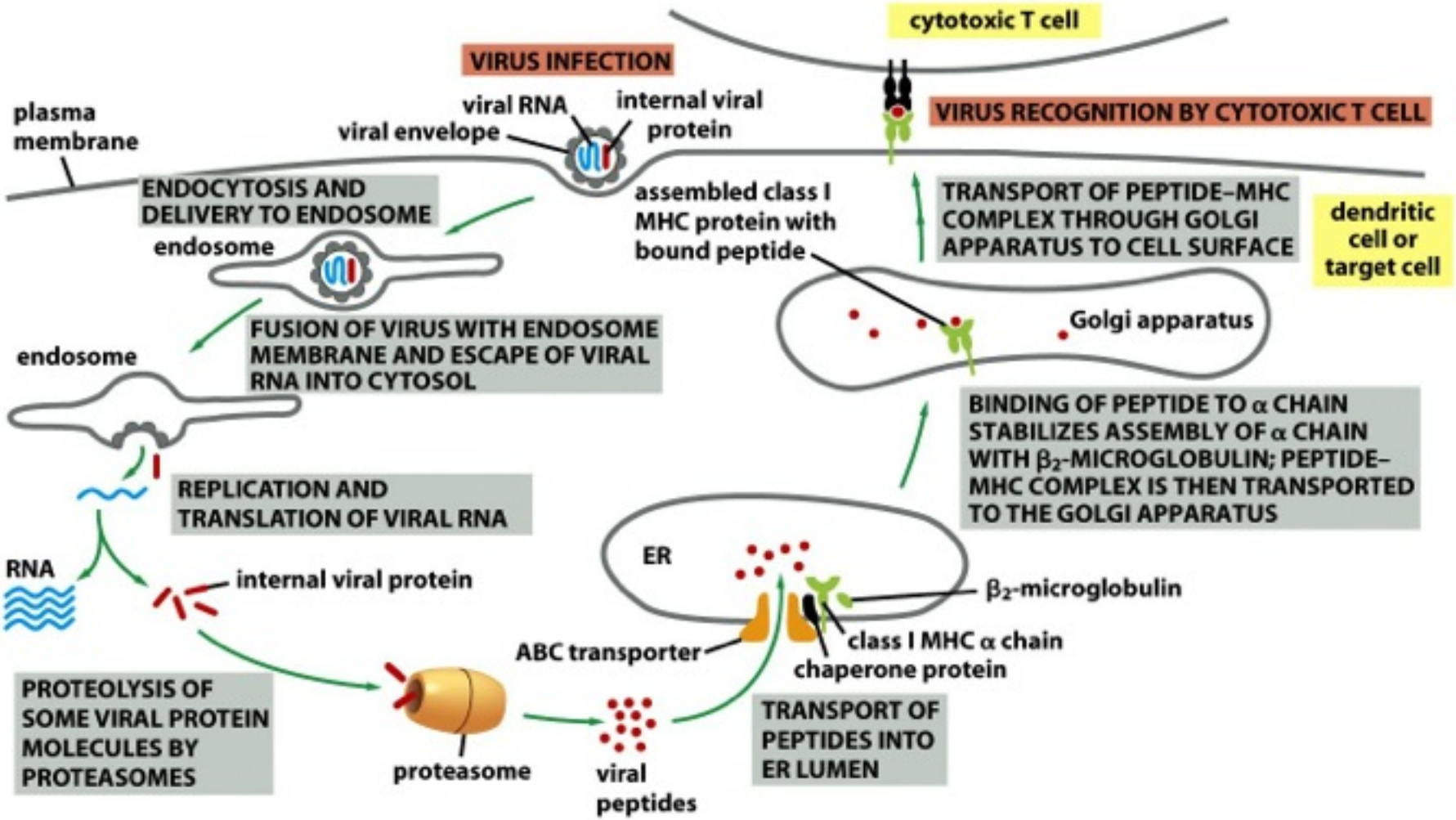



Figure 25-59 *Molecular Biology of the Cell* (© Garland Science 2008)

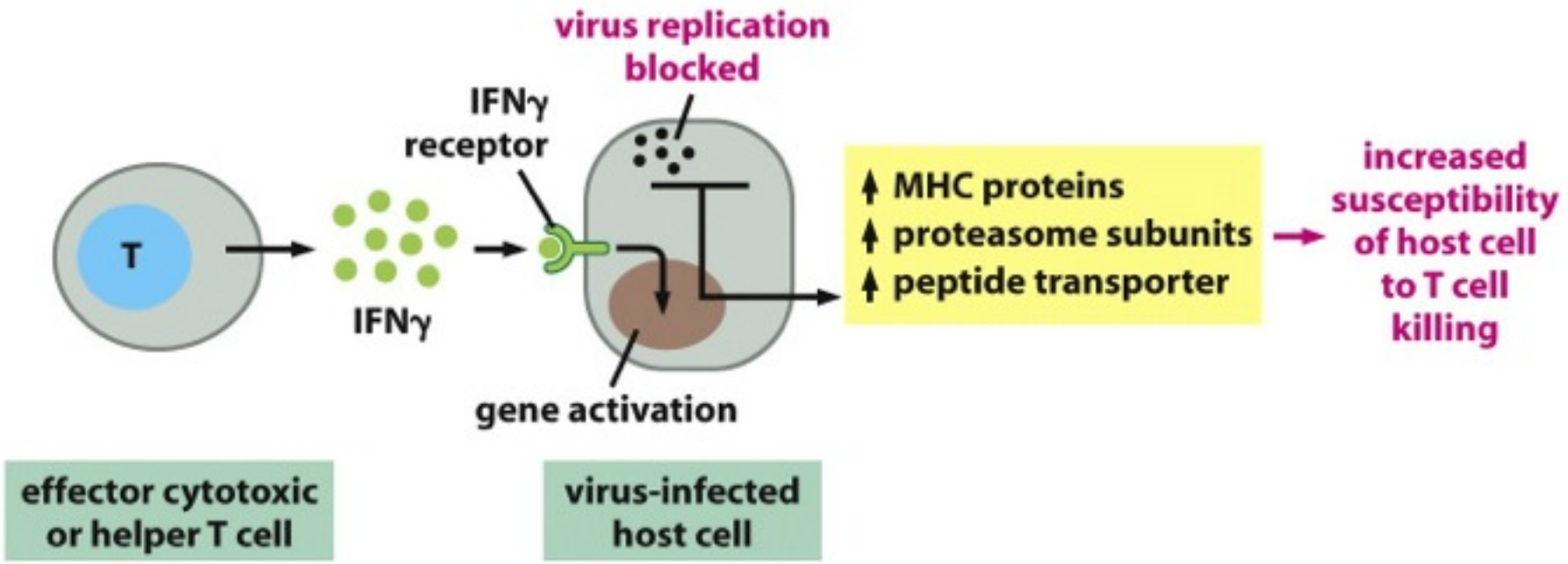



Figure 25-60 *Molecular Biology of the Cell* (© Garland Science 2008)

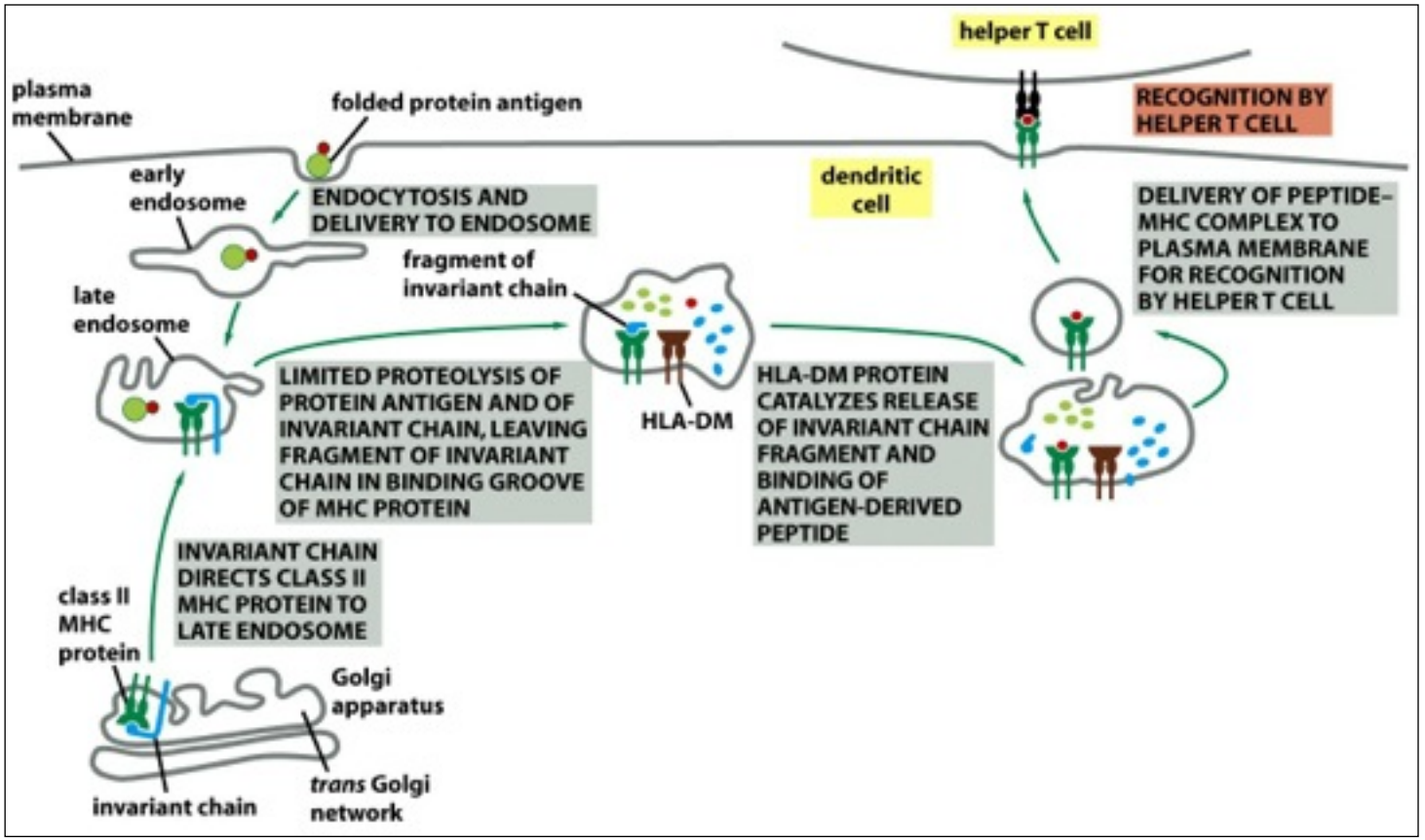
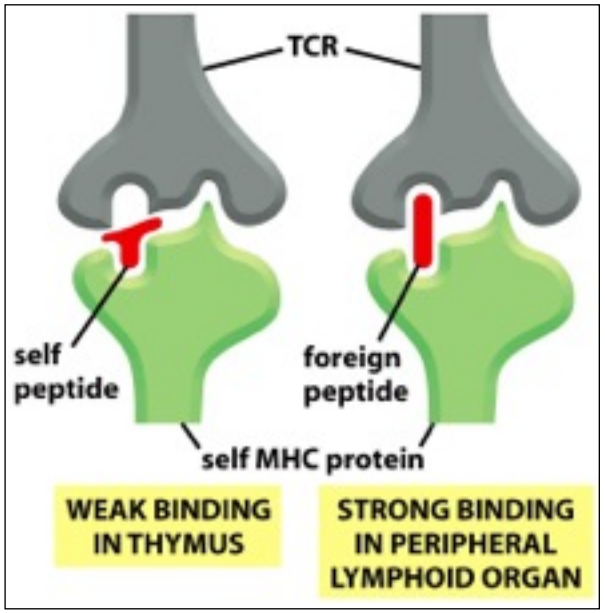



Figure 25-61 *Molecular Biology of the Cell* (© Garland Science 2008)



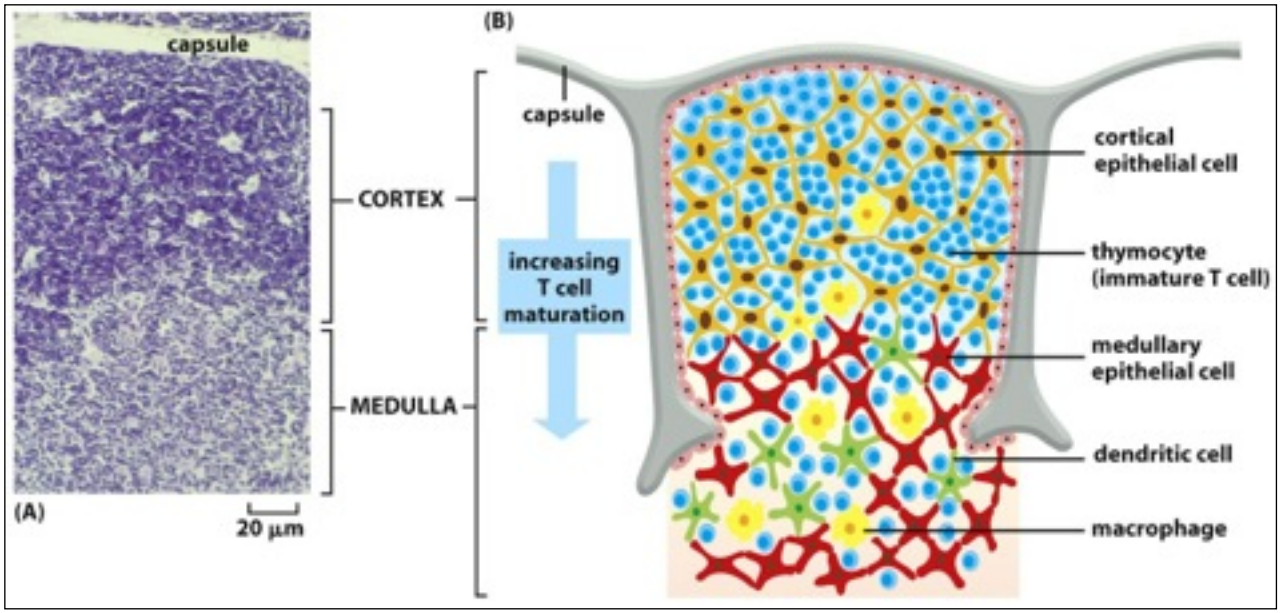




Figure 25-62 *Molecular Biology of the Cell* (© Garland Science 2008)

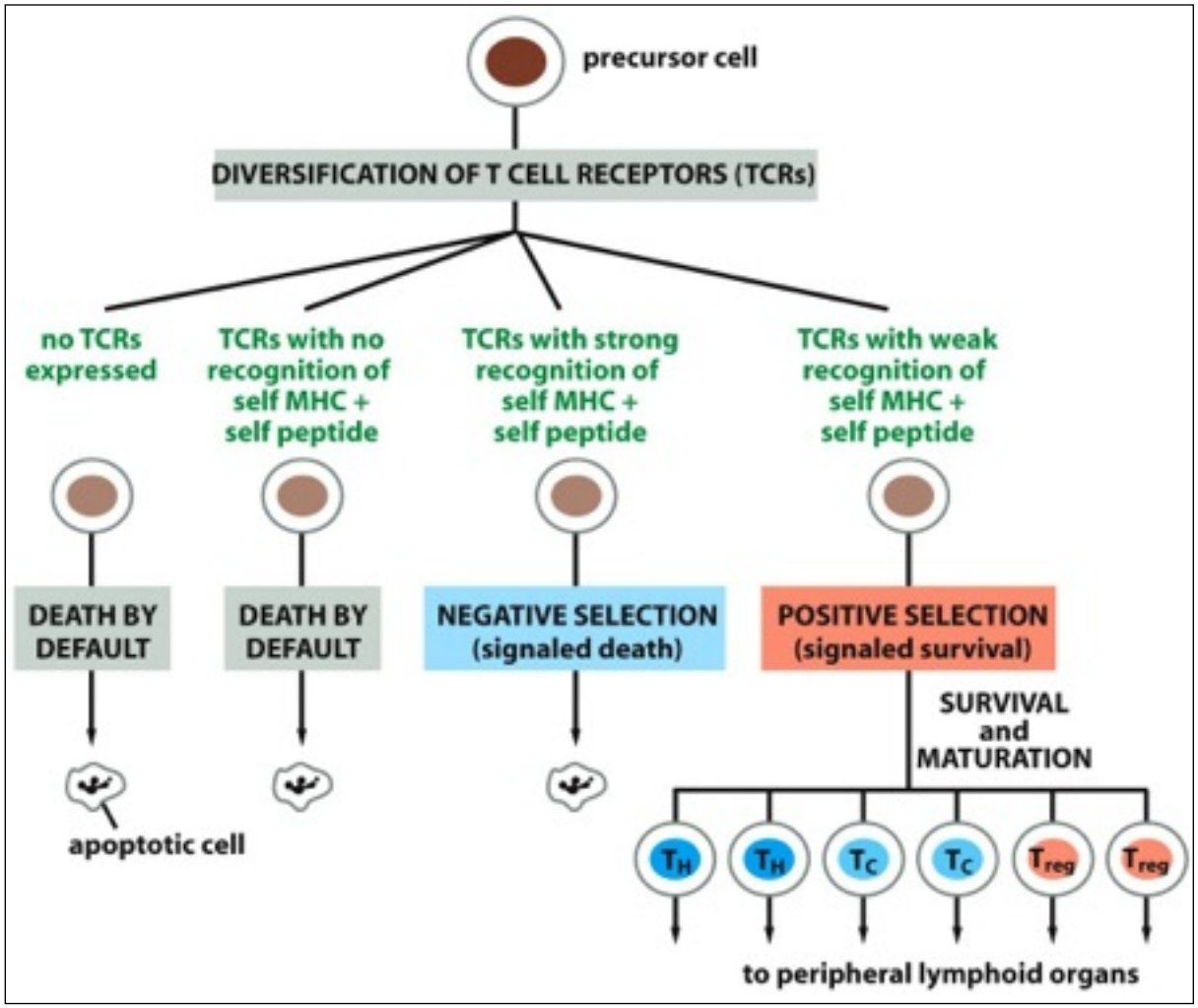



Figure 25-64 *Molecular Biology of the Cell* (© Garland Science 2008)

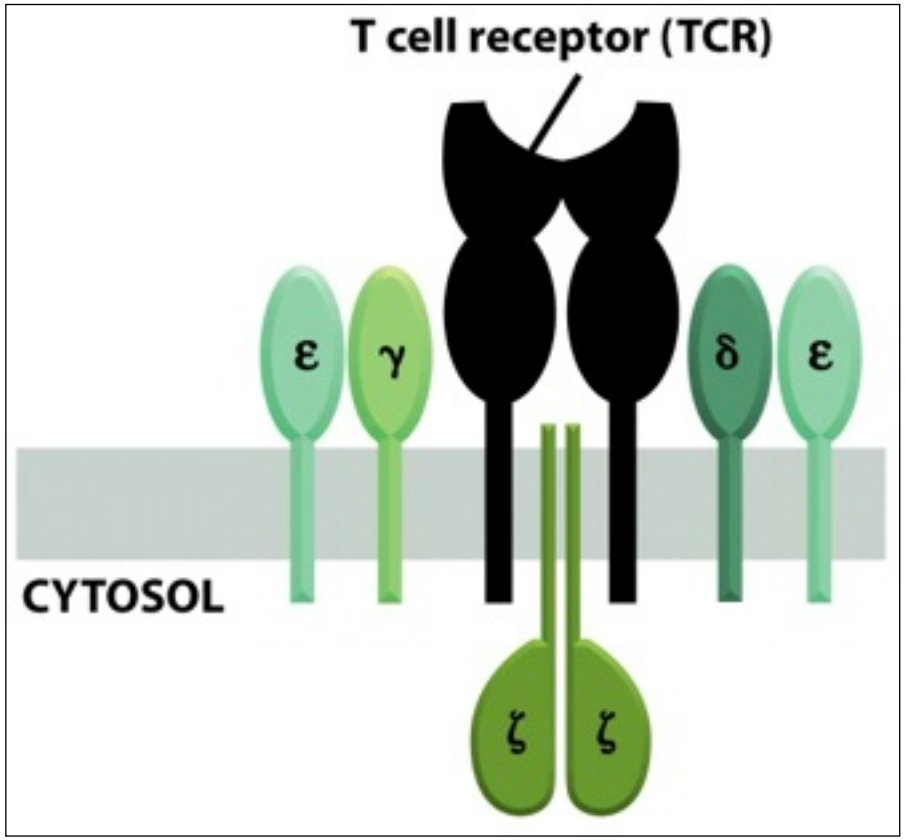



Figure 25-65 *Molecular Biology of the Cell* (© Garland Science 2008)

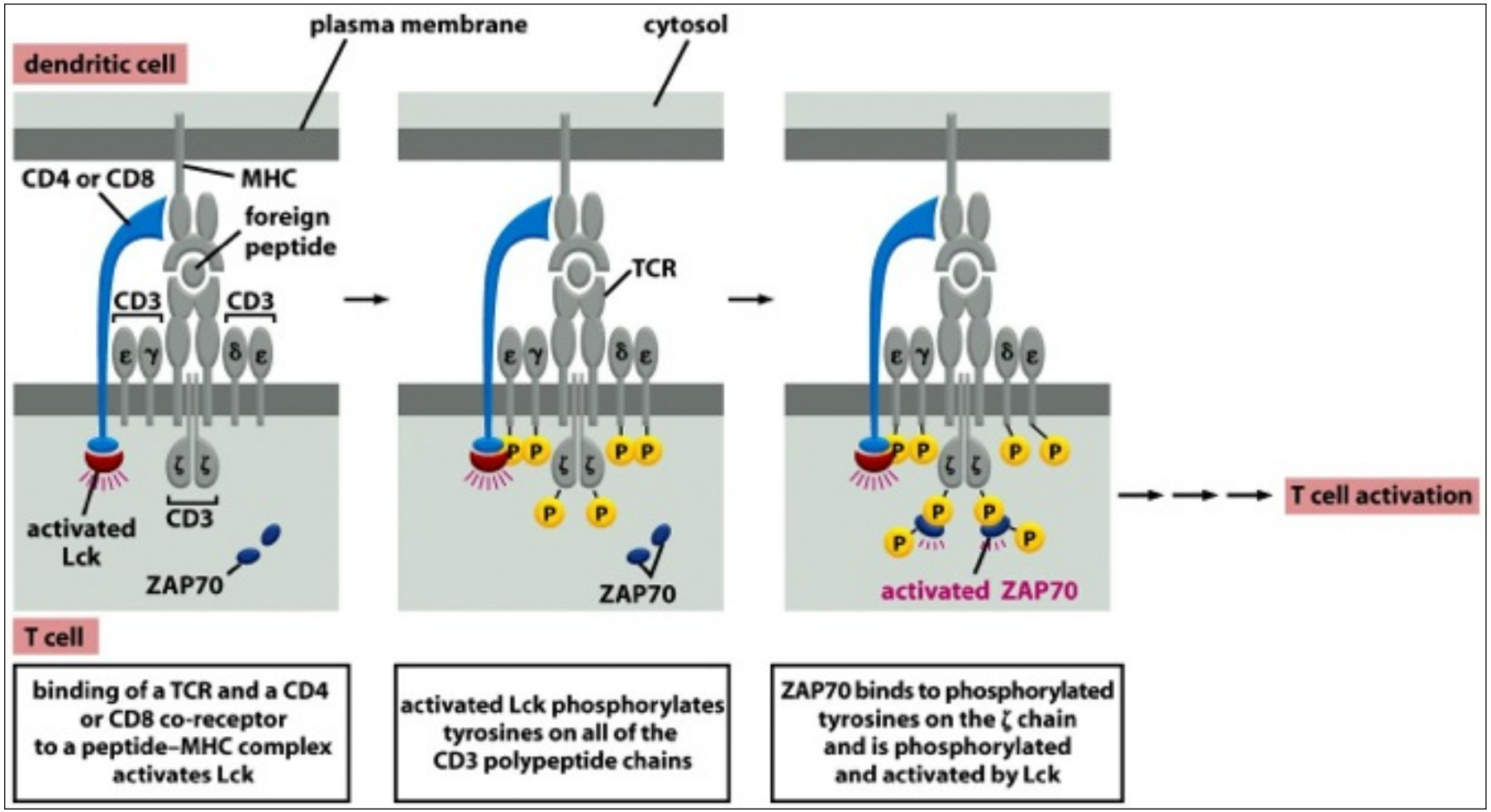



Figure 25-66 *Molecular Biology of the Cell* (© Garland Science 2008)

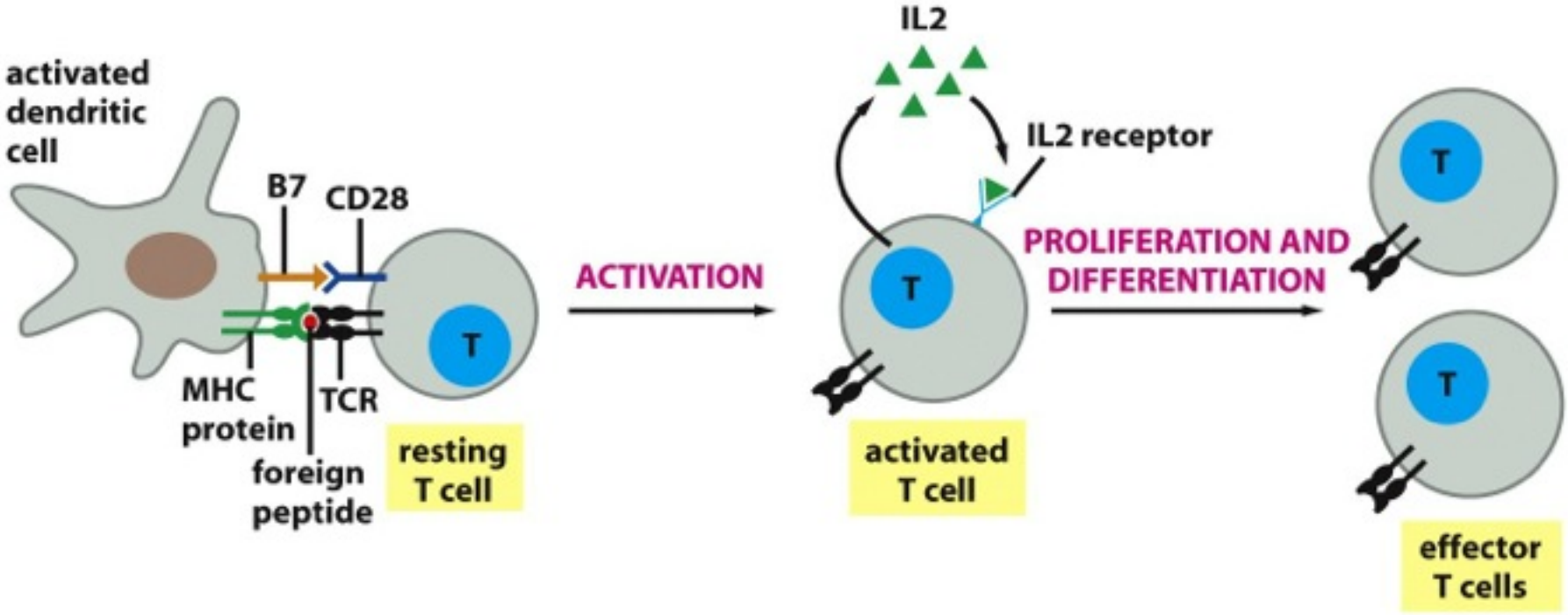



Figure 25-67 *Molecular Biology of the Cell* (© Garland Science 2008)

**Table 25–3 Some Accessory Proteins on the Surface of T Cells**

| PROTEIN* | SUPERFAMILY | EXPRESSED ON | LIGAND ON TARGET CELL | FUNCTIONS |
|---|---|---|---|---|
| CD3 complex | Ig (except for ζ) | all T cells | — | helps transduce signal when antigen–MHC complexes bind to TCRs; helps transport TCRs to cell surface |
| CD4 | Ig | helper T cells, regulatory T cells | class II MHC | promotes adhesion to dendritic cells and target cells; signals T cell |
| CD8 | Ig | cytotoxic T cells | class I MHC | promotes adhesion to dendritic cells and infected target cells; signals T cell |
| CD28 | Ig | most T cells | B7 proteins (CD80 and CD86) | helps activate T cells |
| CTLA4 | Ig | activated T cells | B7 proteins (CD80 and CD86) | inhibits T cell activation |
| CD40 ligand | Fas ligand family | effector helper T cells | CD40 | co-stimulatory protein that helps activate macrophages, B cells, and dendritic cells |

*CD stands for cluster of differentiation, as each of the CD proteins was originally defined as a blood cell "differentiation antigen" recognized by multiple monoclonal antibodies. Their identification depended on large-scale collaborative studies in which hundreds of such antibodies, generated in many laboratories, were compared and found to consist of relatively few groups (or "clusters"), each recognizing a single cell-surface protein. Since these initial studies, however, more than 240 CD proteins have been identified.

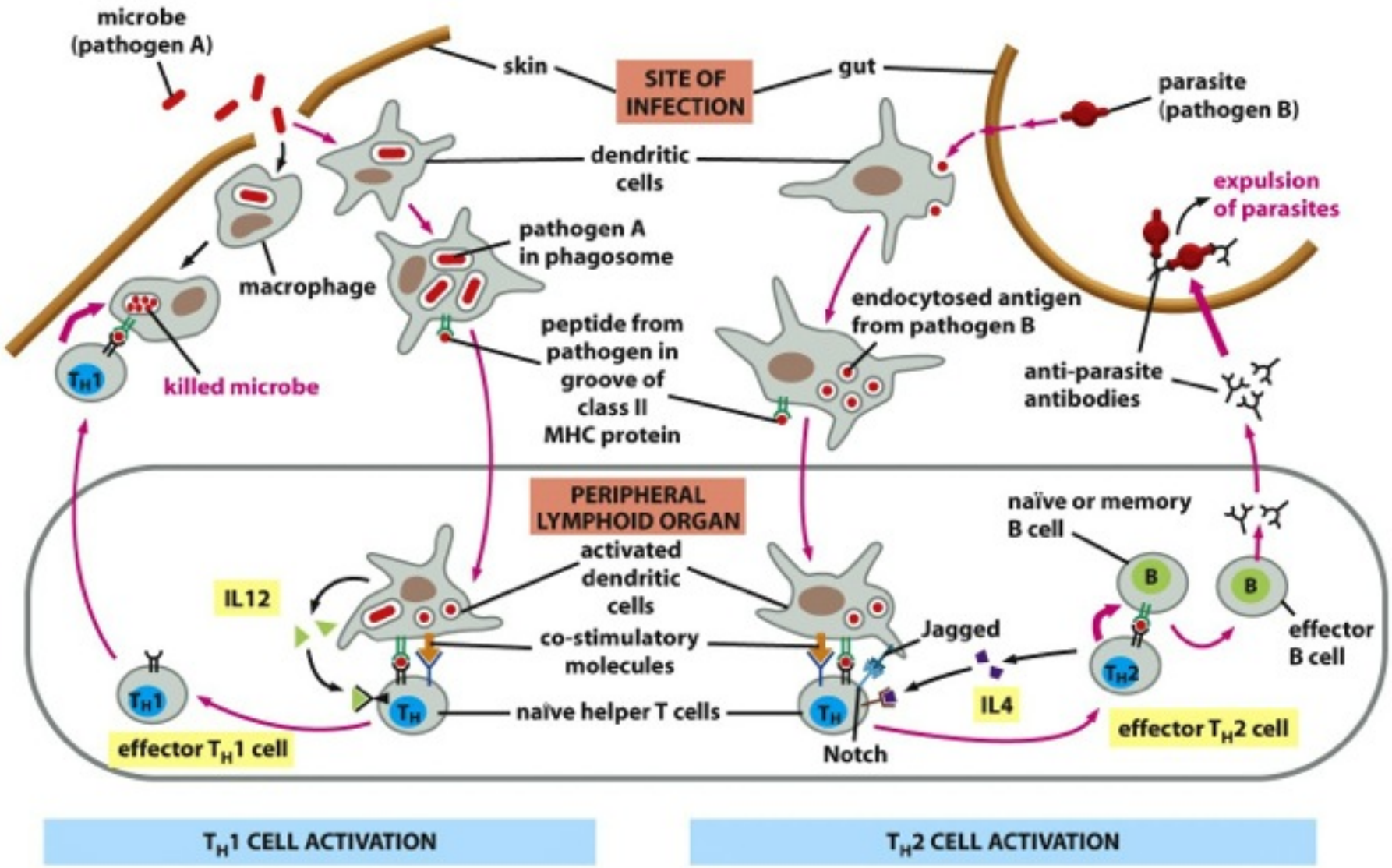



Figure 25-68 *Molecular Biology of the Cell* (© Garland Science 2008)

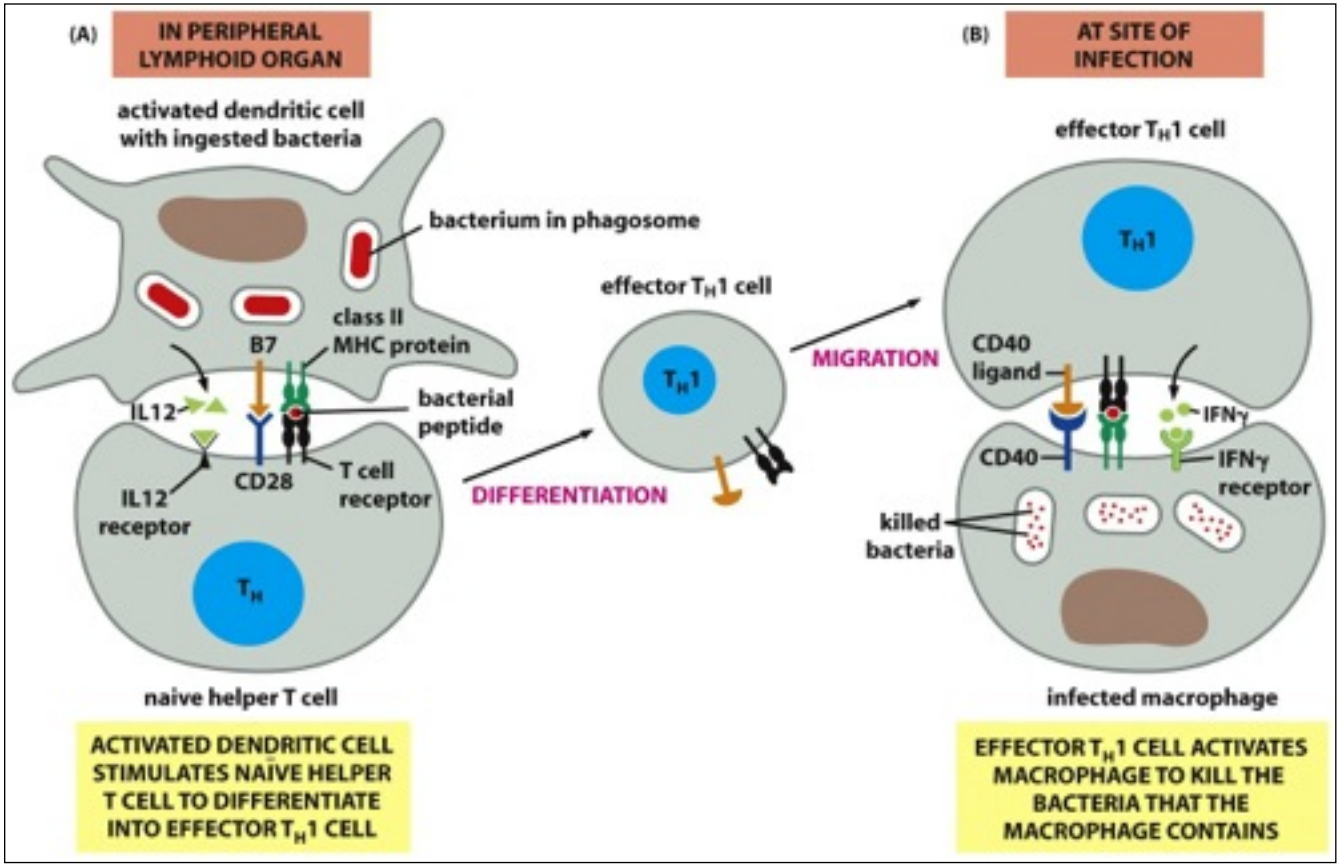



Figure 25-69 *Molecular Biology of the Cell* (© Garland Science 2008)

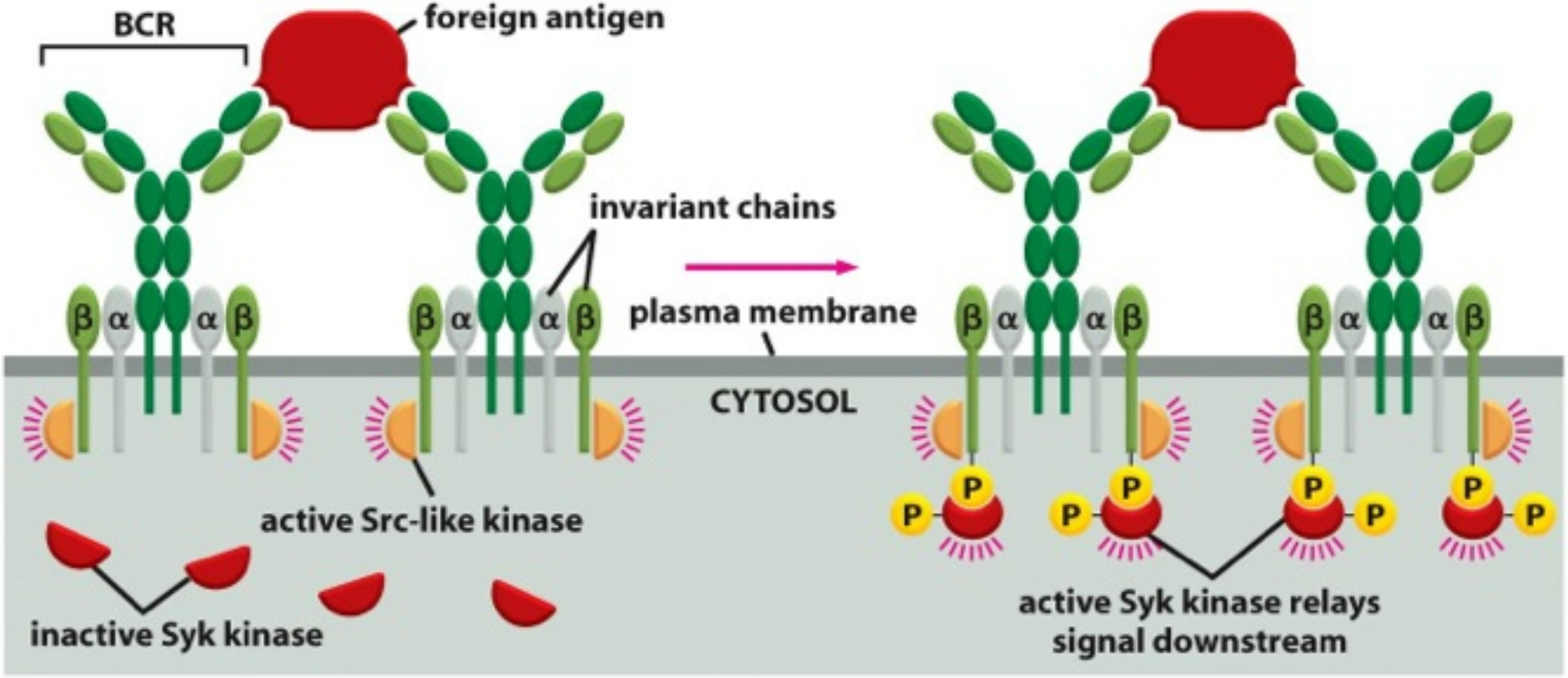



Figure 25-70 *Molecular Biology of the Cell* (© Garland Science 2008)

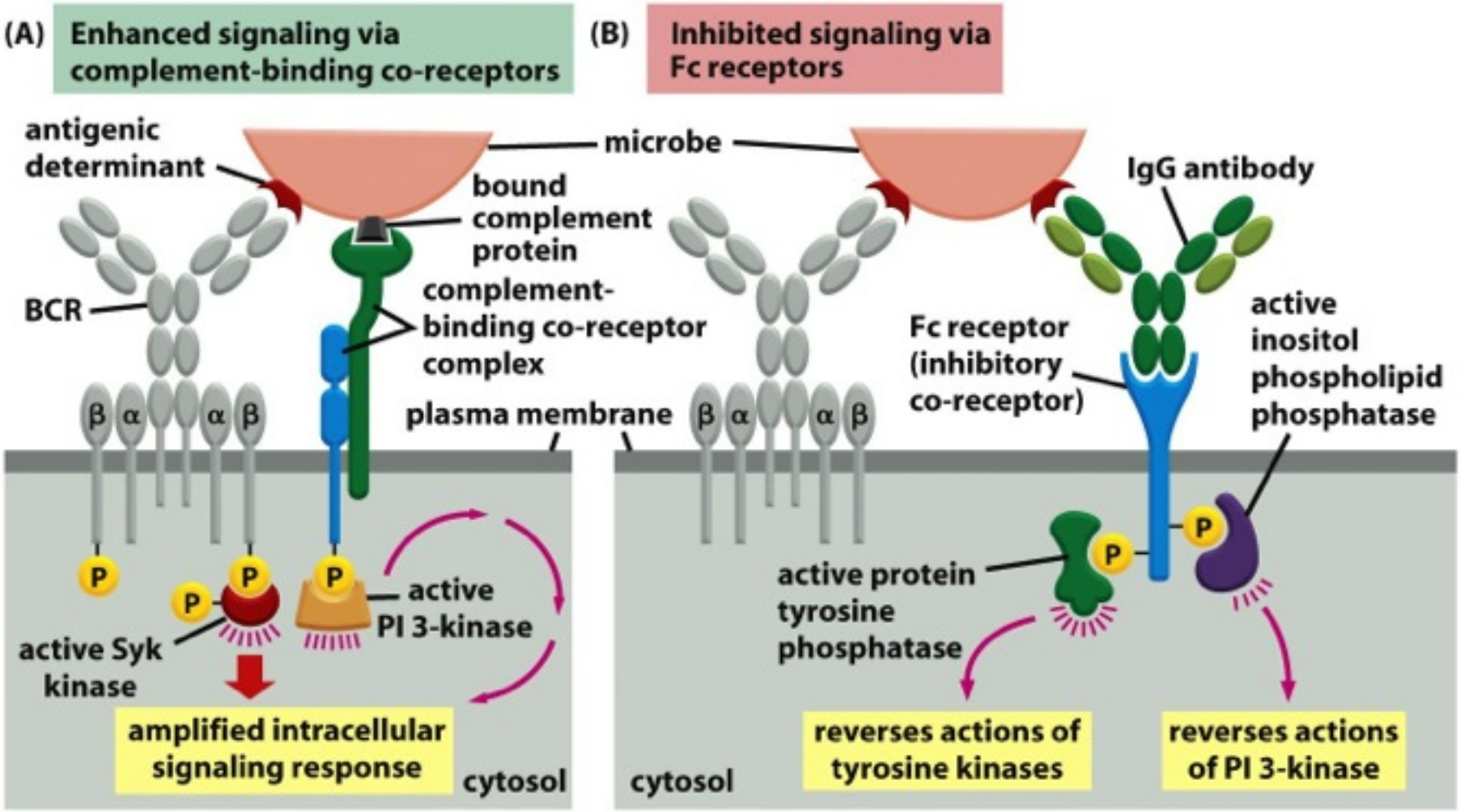



Figure 25-71 *Molecular Biology of the Cell* (© Garland Science 2008)

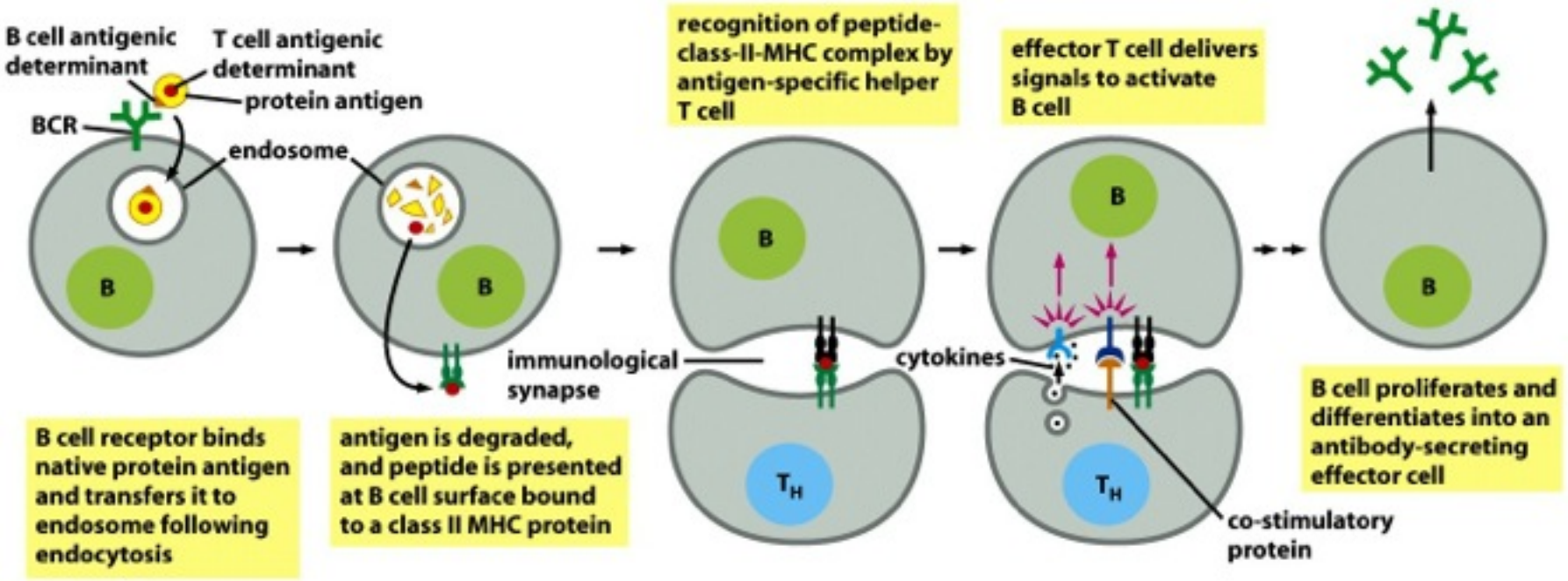



Figure 25-72 *Molecular Biology of the Cell* (© Garland Science 2008)

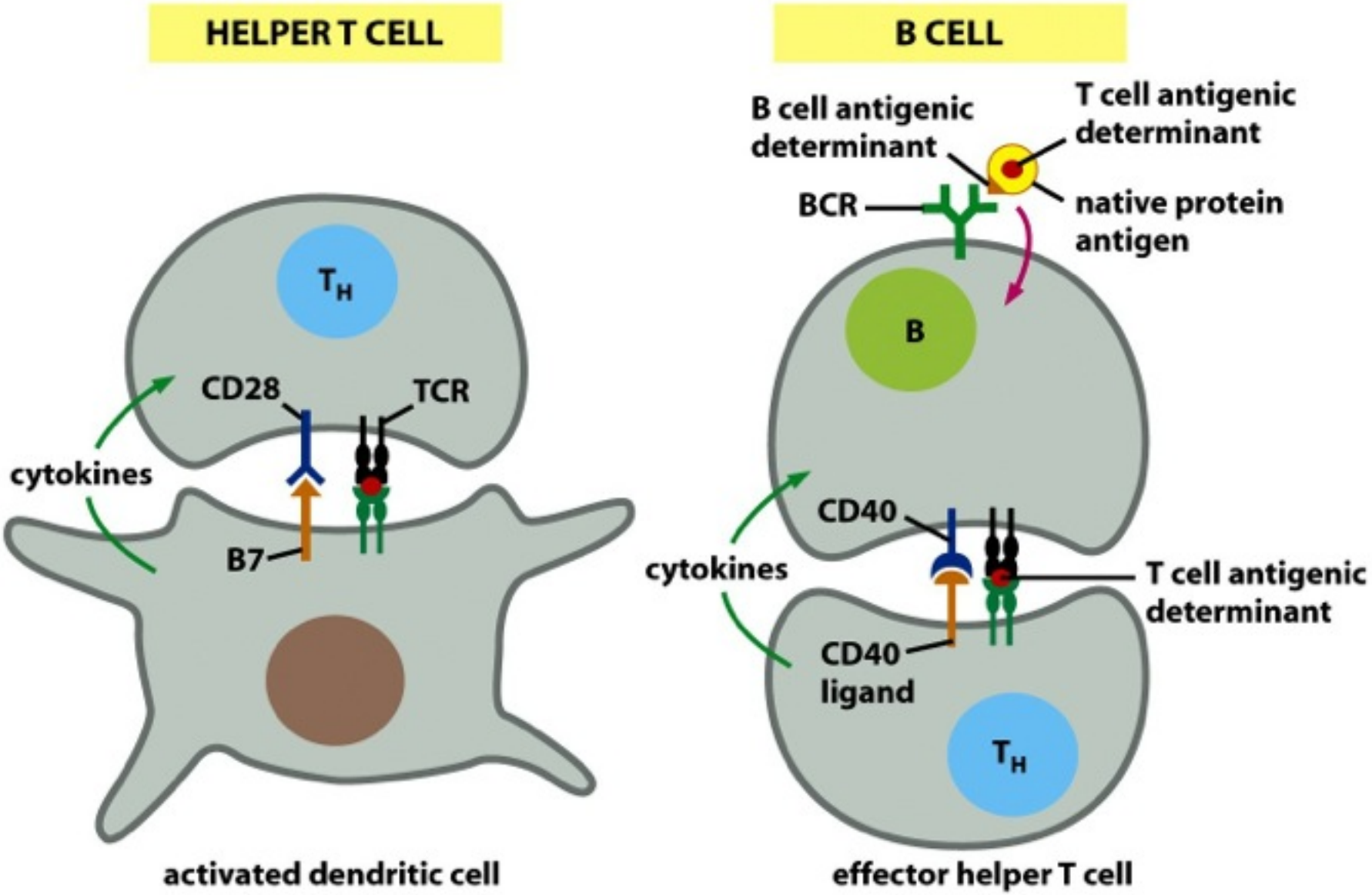
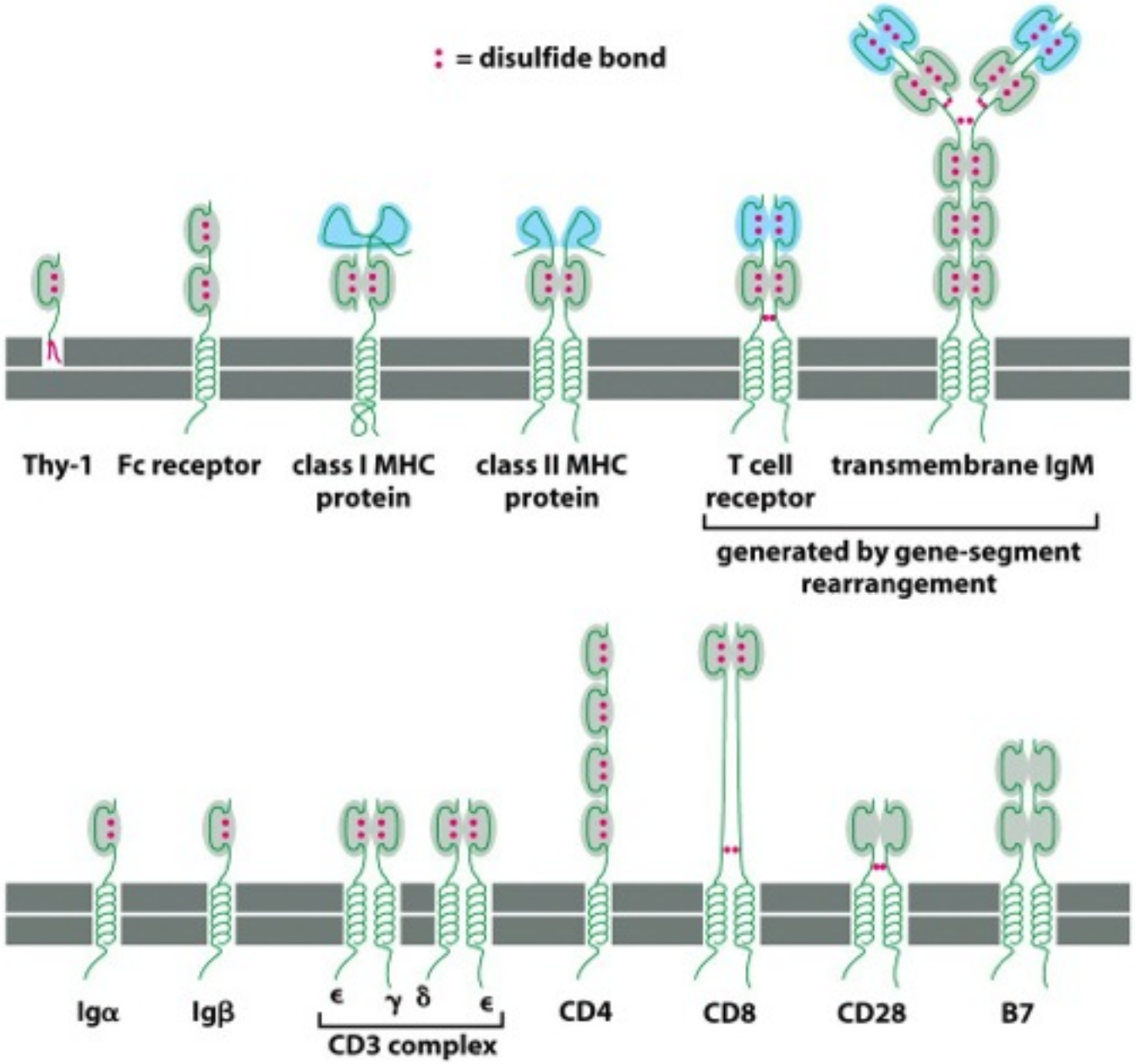



Figure 25-73 *Molecular Biology of the Cell* (© Garland Science 2008)

**Table 25–4 Properties of Some Cytokines**

| CYTOKINE | SOME SOURCES | SOME ACTIONS |
|---|---|---|
| IL2 | all helper T cells; some cytotoxic T cells | stimulates proliferation and differentiation of activated T cells; required for regulatory T cell development in thymus |
| IL4 | $T_H2$ cells, basophils, and mast cells | stimulates B cell proliferation, differentiation, and class switching to IgE and IgG1; promotes $T_H2$ and inhibits $T_H1$ cell development |
| IL7 | many non-T cells | promotes memory T cell survival |
| IL10 | $T_H2$ cells, macrophages, and dendritic cells | inhibits macrophages and $T_H1$ cell development |
| IL12 | B cells, macrophages, dendritic cells, and granulocytes | induces $T_H2$ cell development and inhibits $T_H1$ cell development |
| IL15 | many non-T cells | promotes memory T cell survival |
| IL17 | some effector helper T cells | stimulates inflammatory responses |
| IFNγ | $T_H1$ cells and cytotoxic T cells | activates macrophages; increases MHC expression in many cell types |
| TGFβ | regulatory T cells | suppresses effector T cell activity, dendritic cells, and macrophages |
| TNFα | $T_H1$ cells and macrophages | activates endothelial cells and macrophages |

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