

# **Grundlagen der Immunologie**

*11-12. Vorlesung*

## **Erster Schritt der spezifischen Immunantwort:**

**T-Zell-Aktivierung, Signaltransduktionswege**

**T-Zell-Polarisierung, Lymphozyten Rezirkulation, Homing**

# Hauptstadien der adaptiven Immunantwort

**Antigenerkennung**



**Aktivierung, Differenzierung**



**Effektorfunktionen**

# Die entzündliche und spezifische Immunantwort ist örtlich und zeitlich getrennt

2.

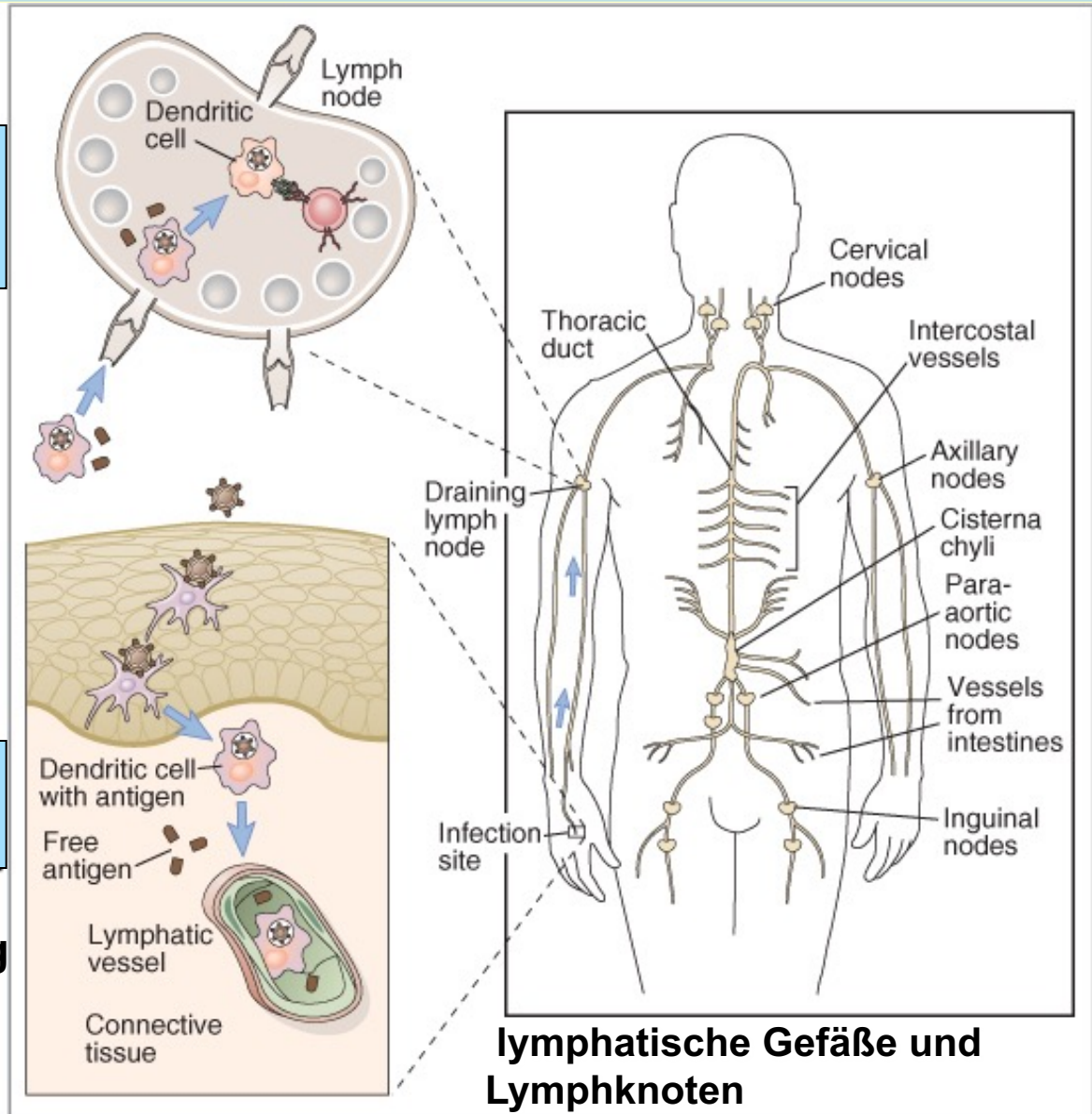
Antigen-  
presentation und  
T-Zell-  
aktivierung



1.

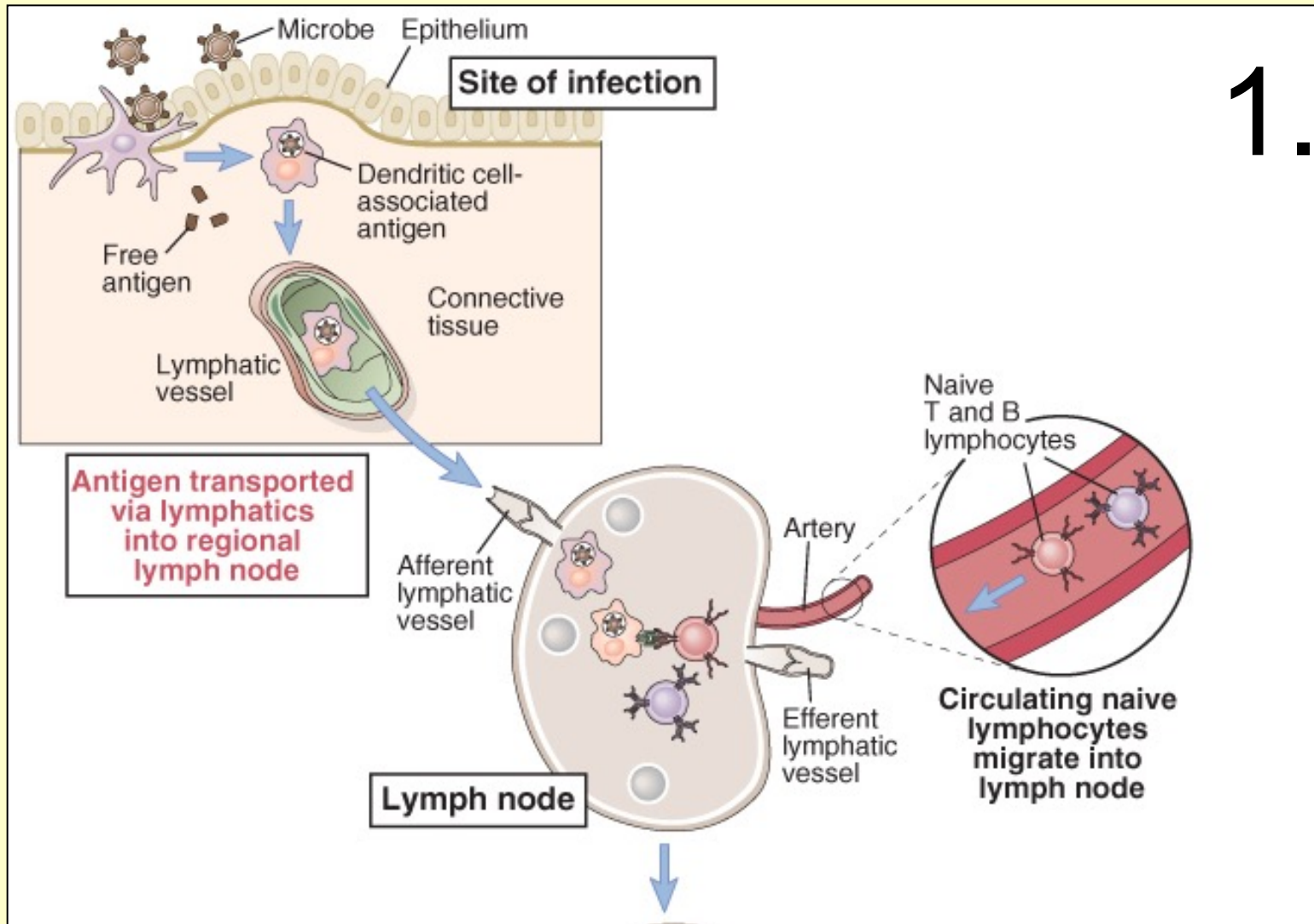
Antigen-  
aufnahme und  
Transport

Entzündung



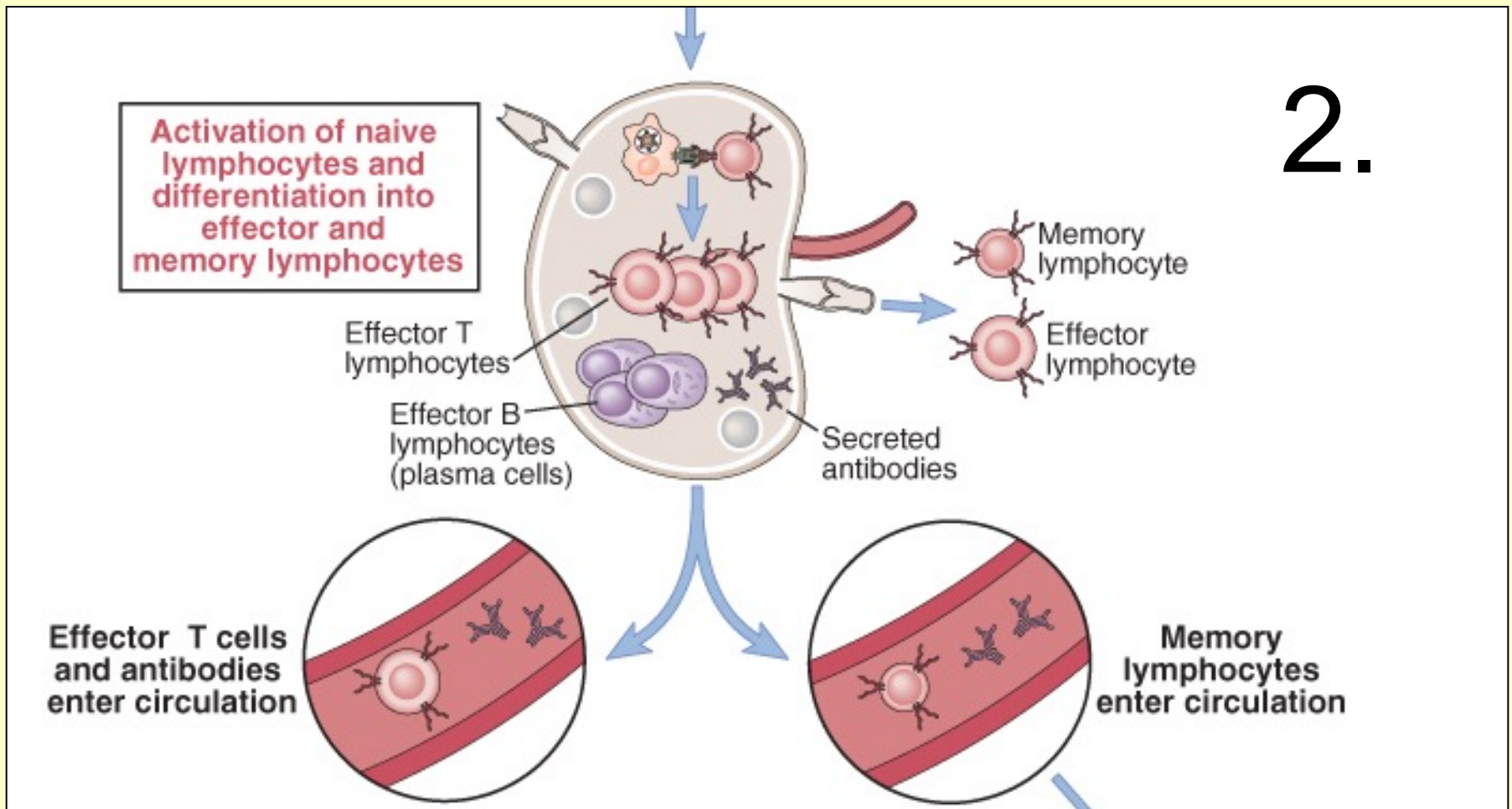
# Hauptschritte der Immunantwort

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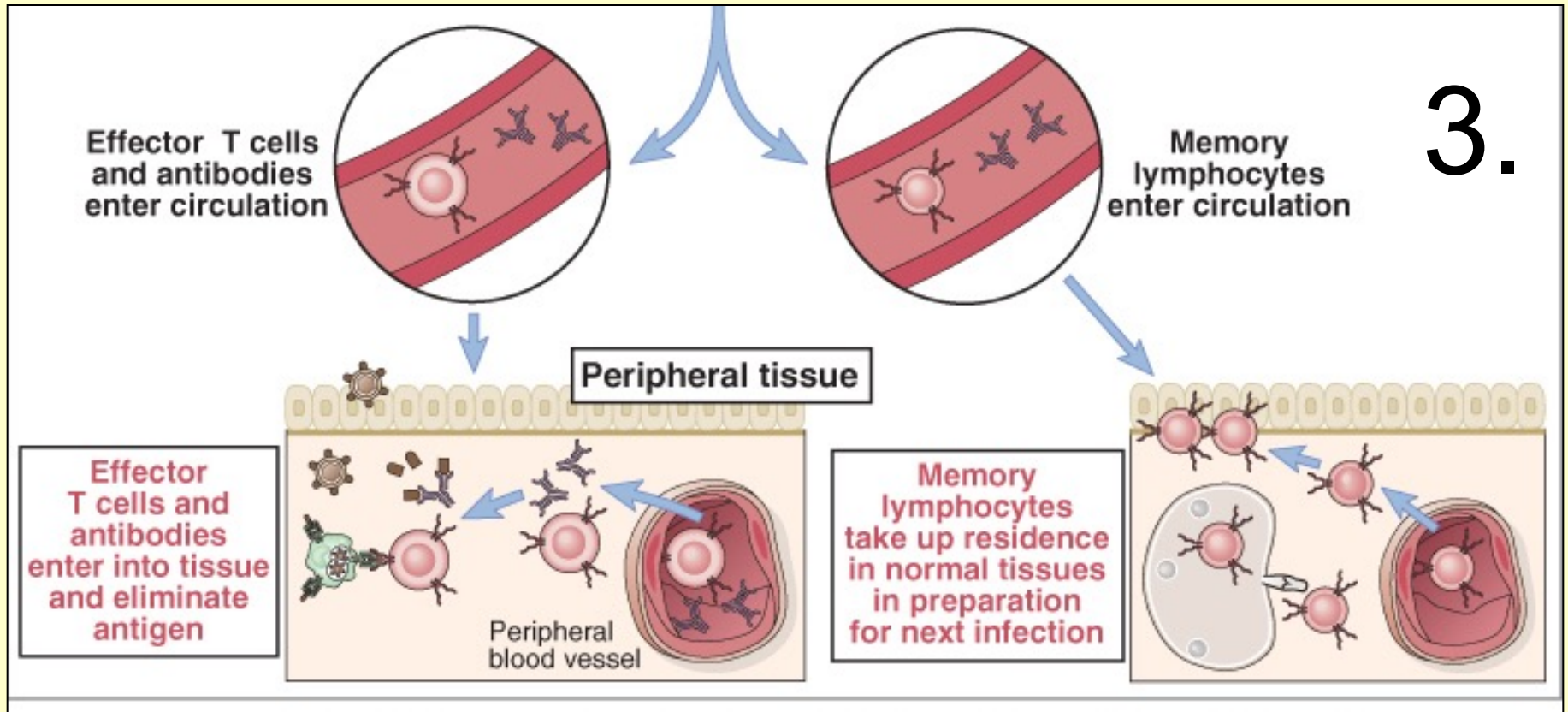


# Hauptschritte der Immunantwort

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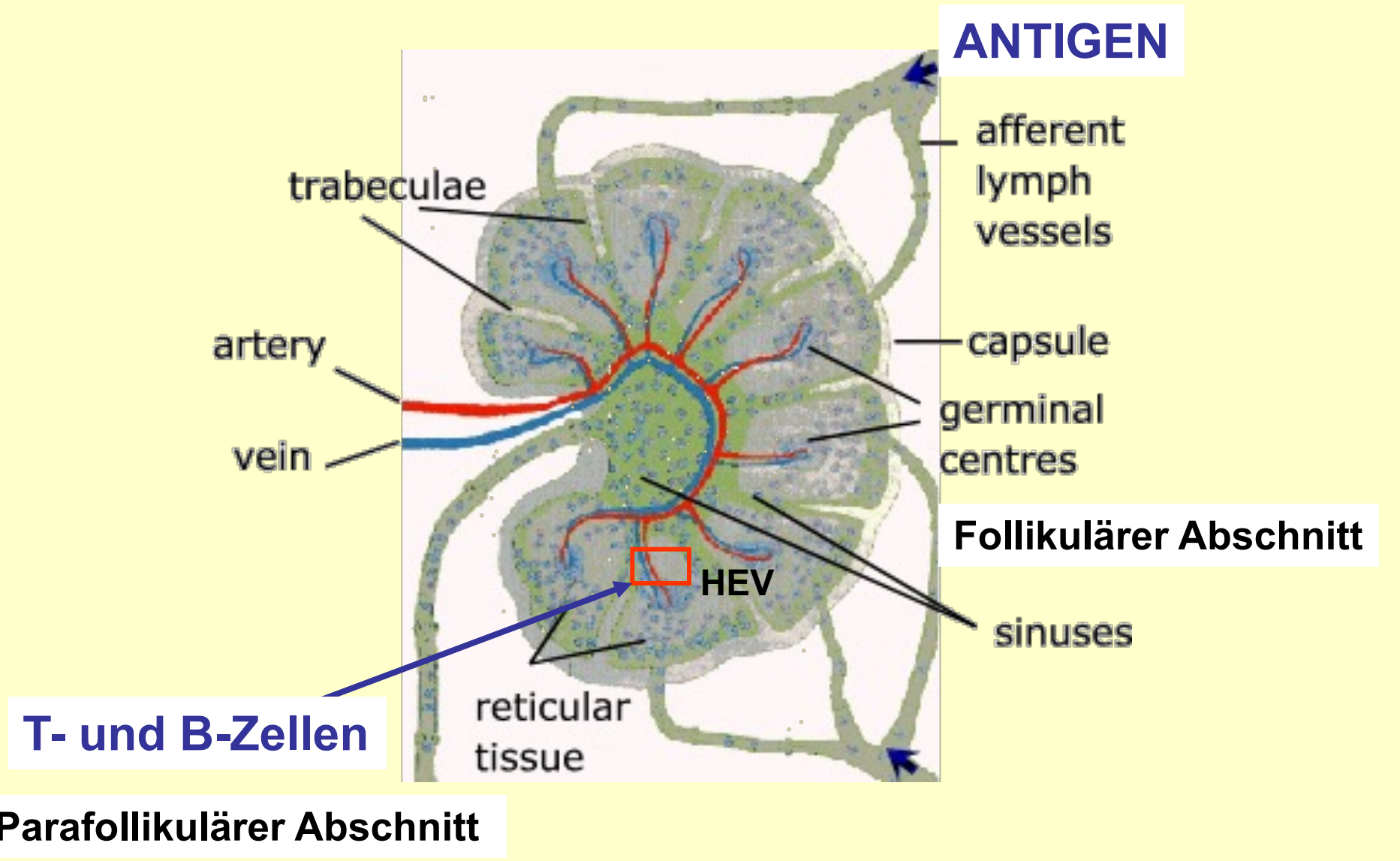


# Hauptschritte der Immunantwort



**Naive T-Zellen treffen sich während ihrer  
Wanderung durch die peripheren Lymphorgane mit  
Antigenen**

**Wie kann das Antigen in die sekundären  
lymphatischen Organe gelangen?**





# Antigentransport in die sekundären lymphatischen Organe / Gewebe

## Dendritische Zelle – **prozessiertes Antigen**

1. Peripherie – Antigenaufnahme + Prozessierung
2. Wanderung in die T-Zell-Zone der sekundären lymphatischen Organe / Gewebe (afferente Lymphgefäße)
3. Antigenpräsentierung auf MHC-II für T-Zelle in den sekundären lymphatischen Organen / Geweben (Lymphknoten, Milz)

**Natives Antigen** - gelangt mit Lymphe in die umliegenden Lymphknoten  
- mit Blut in die Milz

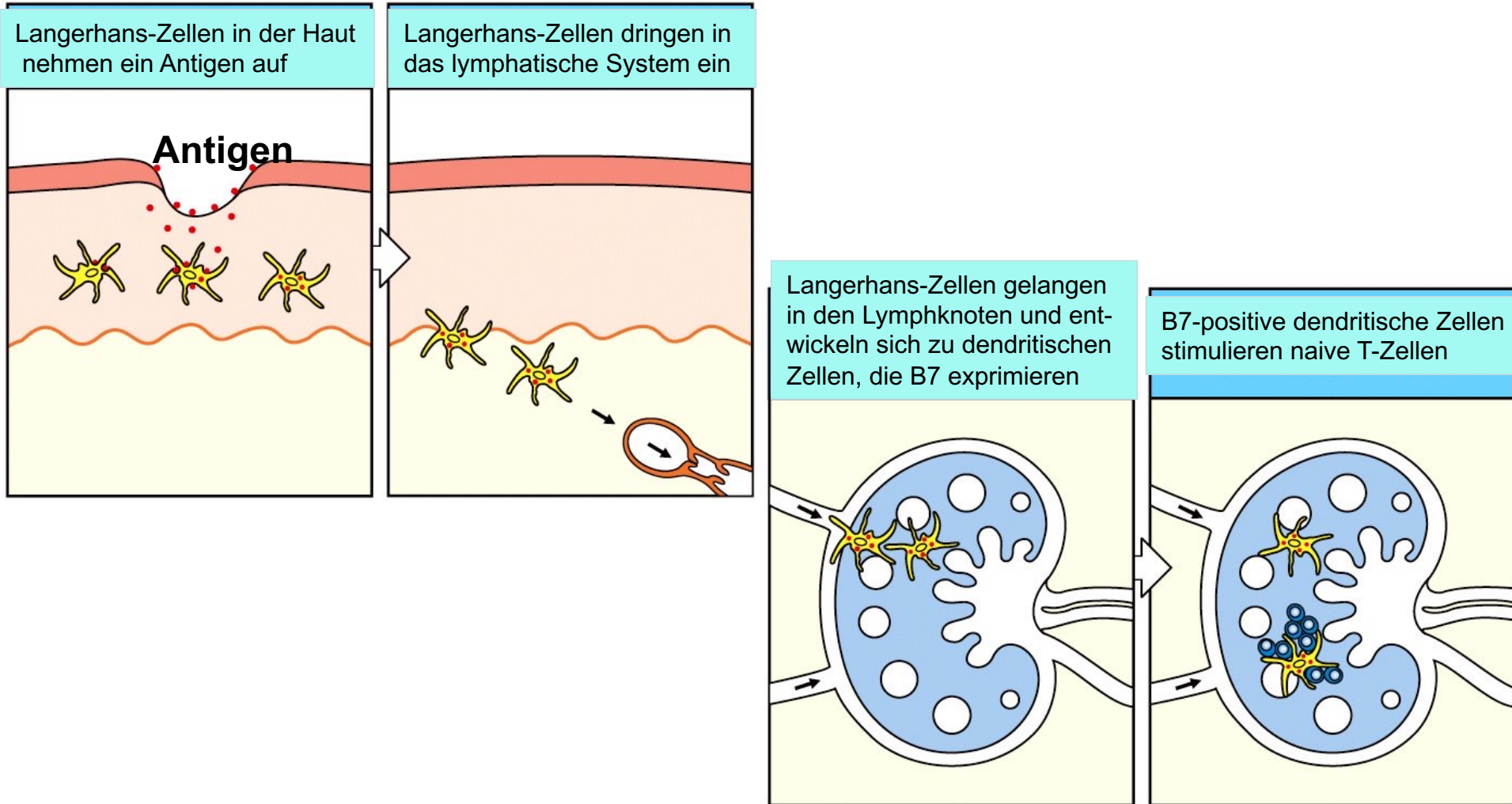
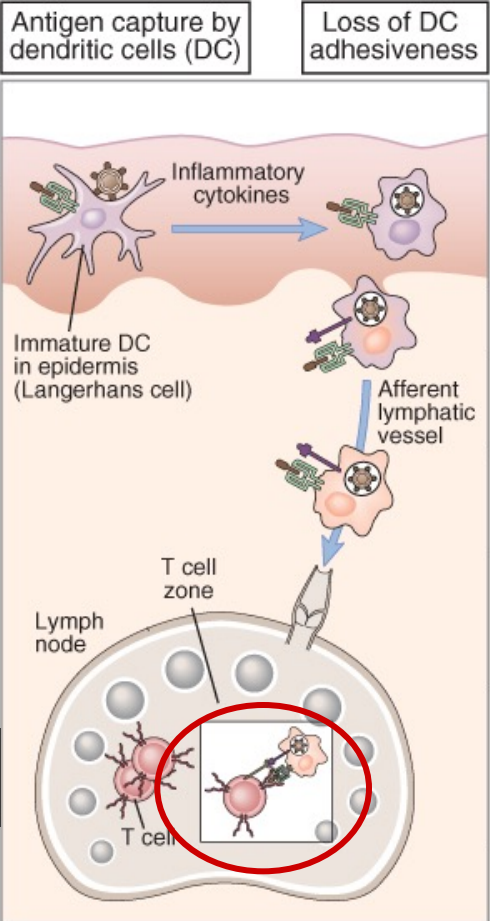


Figure 8-15 Immunobiology, 6/e. (© Garland Science 2005)

# Rolle der dendritischen Zellen

**Antigen-sammlung**



**Antigen-präsentation**

- Migration of DC
- Maturation of migrating DC
- Mature dendritic cell presenting antigen to naive T cell

**Reifung:**

MHC-II  
B7  
ICAM  
IL-12



FcR  
MannoseR  
TLR



**Antigenpräsentierung (APC)**

	Immature dendritic cell	Mature dendritic cell
--	-------------------------	-----------------------

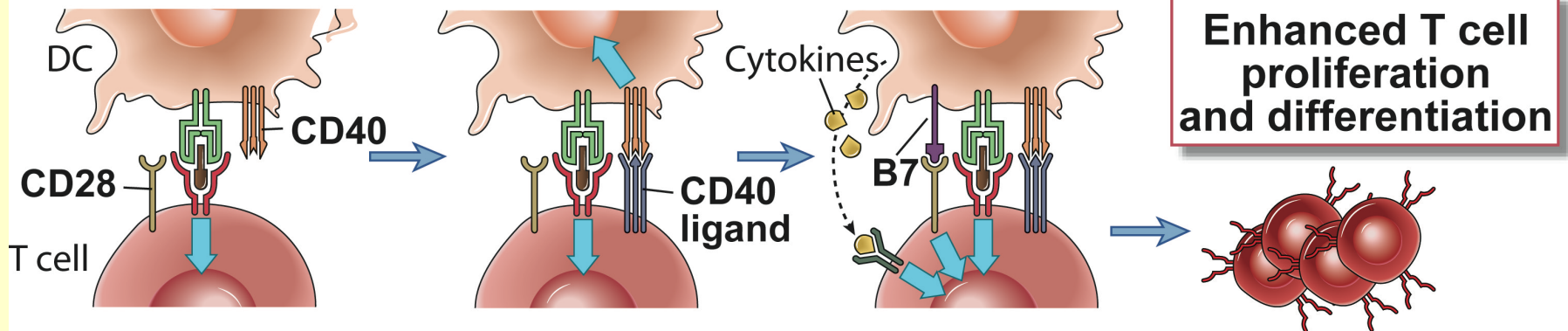
Principal function	Antigen capture	Antigen presentation to T cells
Expression of Fc receptors, mannose receptors	++	-
Expression of molecules involved in T cell activation: B7, ICAM-1, IL-12	- or low	++
Class II MHC molecules		
Half-life on surface	~10 hr	>100 hr
Number of surface molecules	~10 <sup>6</sup>	~7 x 10 <sup>6</sup>

# Die Wechselwirkung zwischen Helfer-T-Zellen und APC induziert die Expression der Korezeptoren: CD40L auf T-Lymphozyten, B7 auf APC

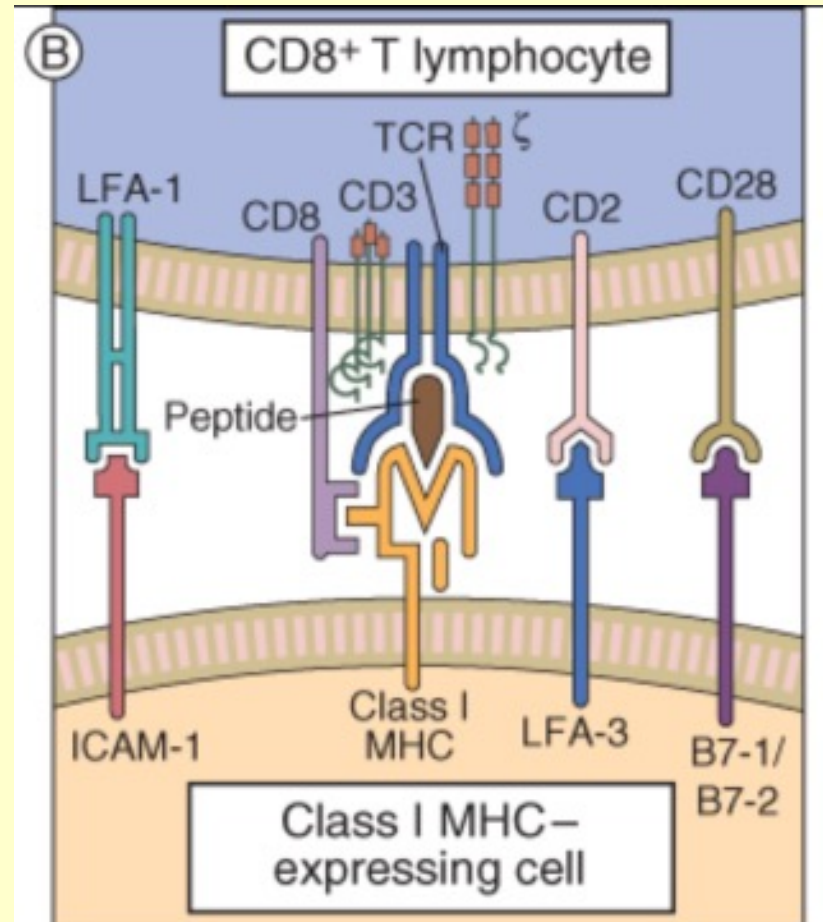
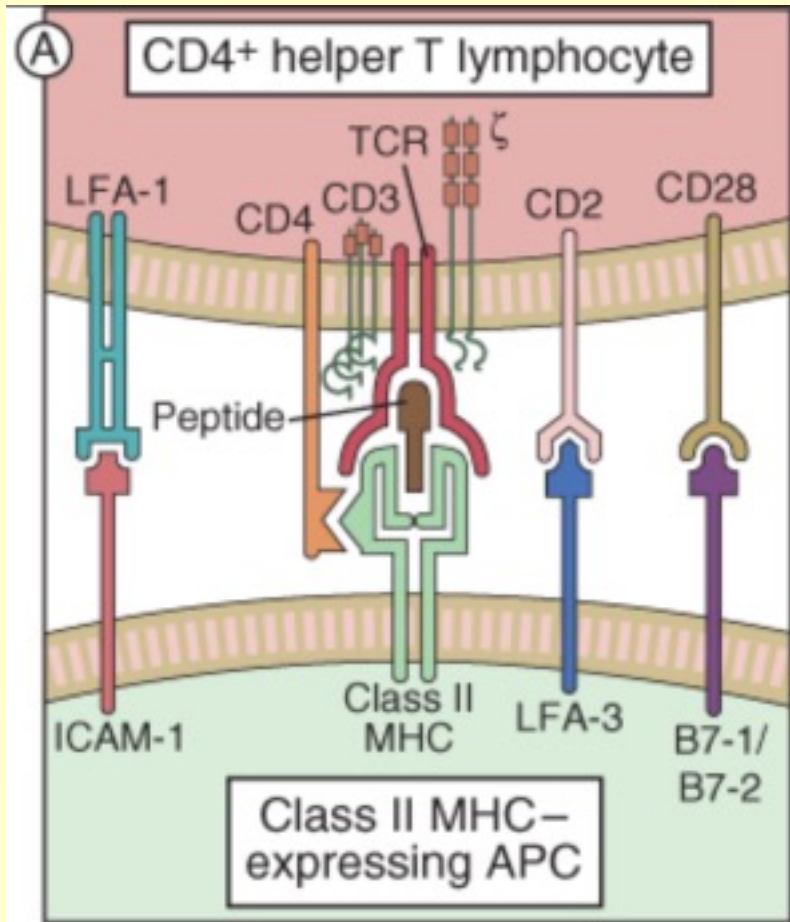
T cells recognize antigen (with or without B7 costimulators), causing expression of CD40L on T cells

CD40L binds to CD40 on DC; leads to DC expression of B7; secretion of cytokines

Activated DCs stimulate T cell proliferation and differentiation



# Akzessorische Korezeptoren bilden die immunologische Synapse



# Die Immunologische Synapse

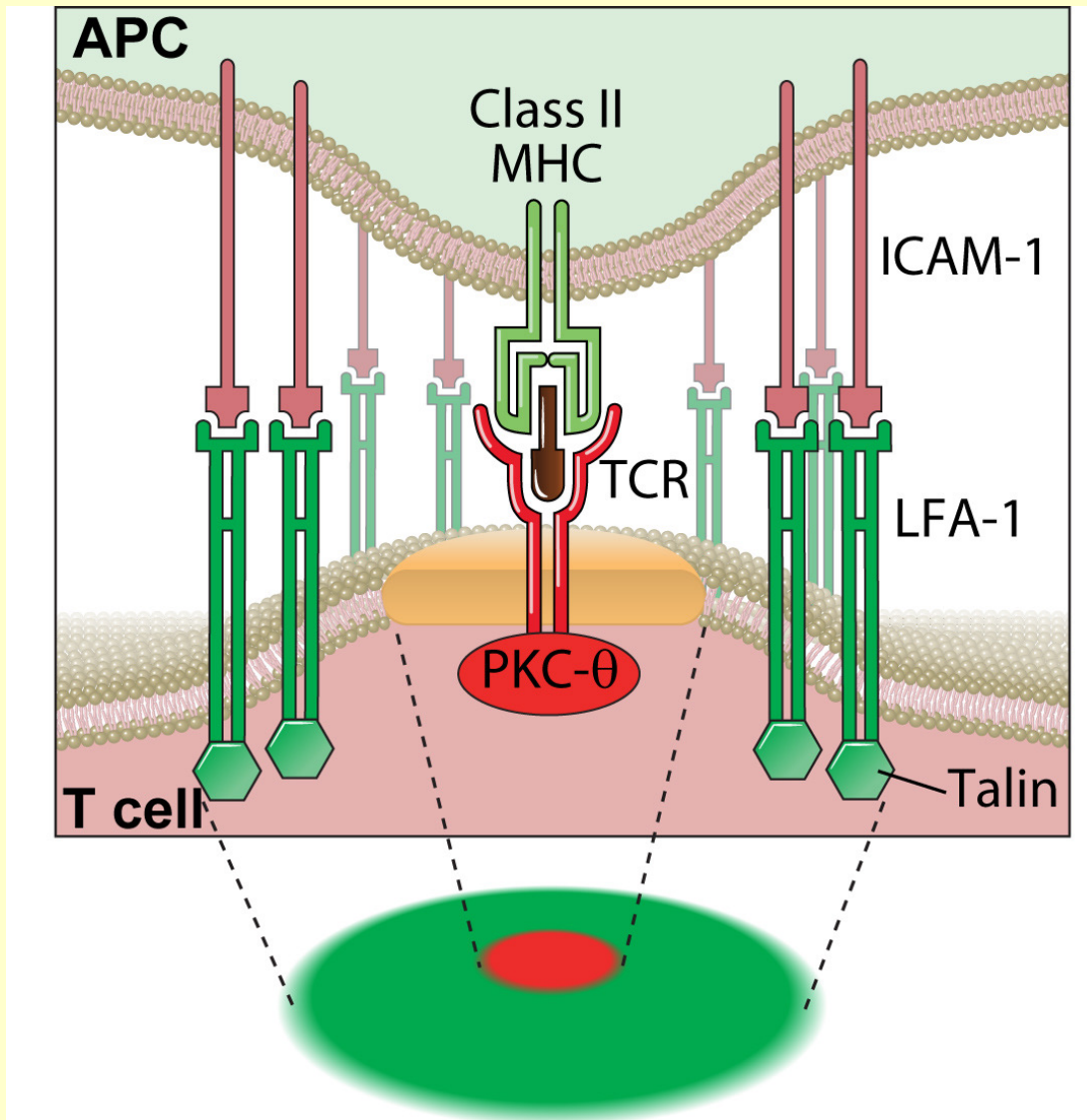
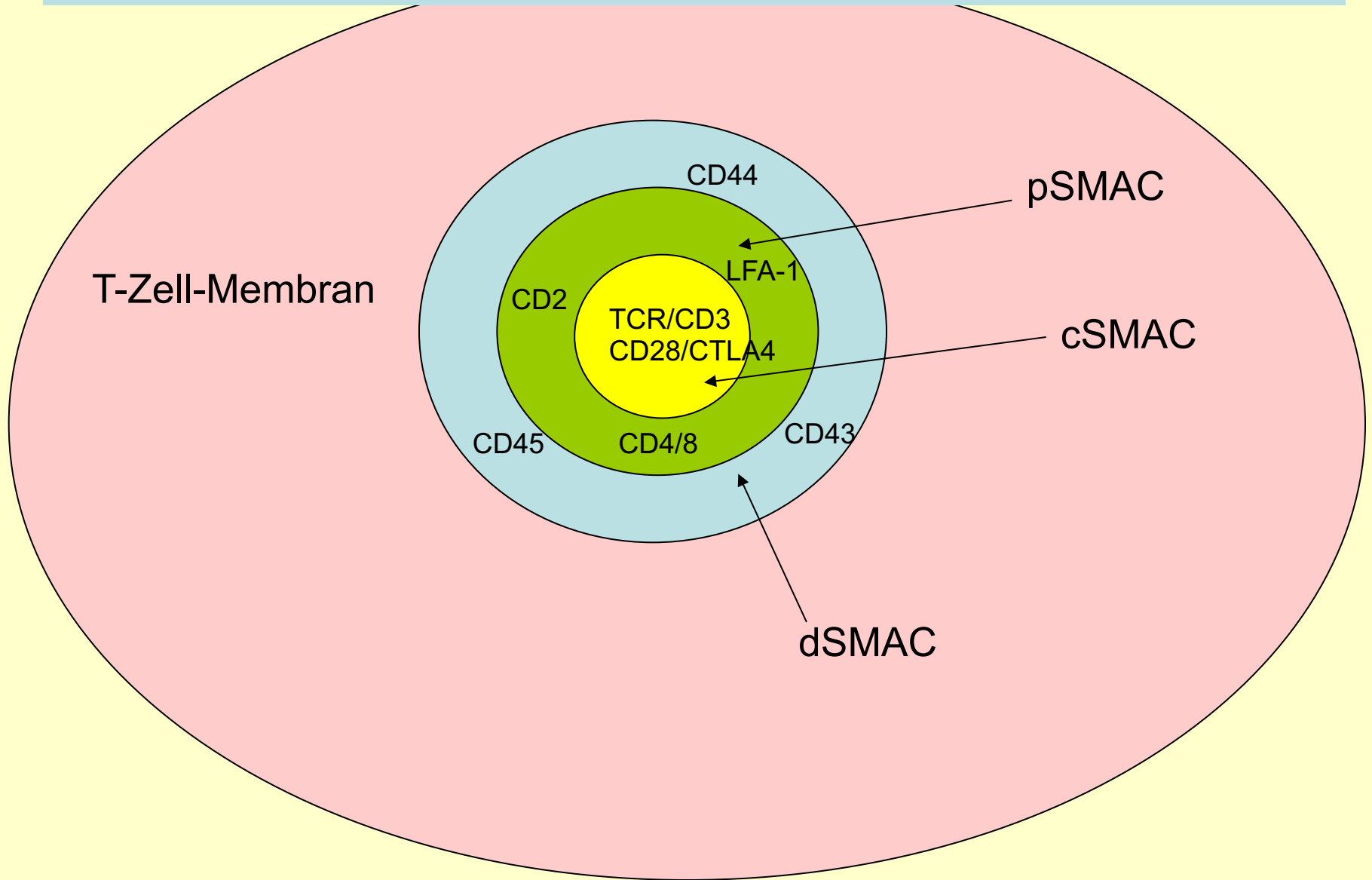


Fig. 7-13B

# SMAC: Central Supramolecular Activation Complex



# Für die T-Zell-Aktivierung werden zwei Signale gebraucht:

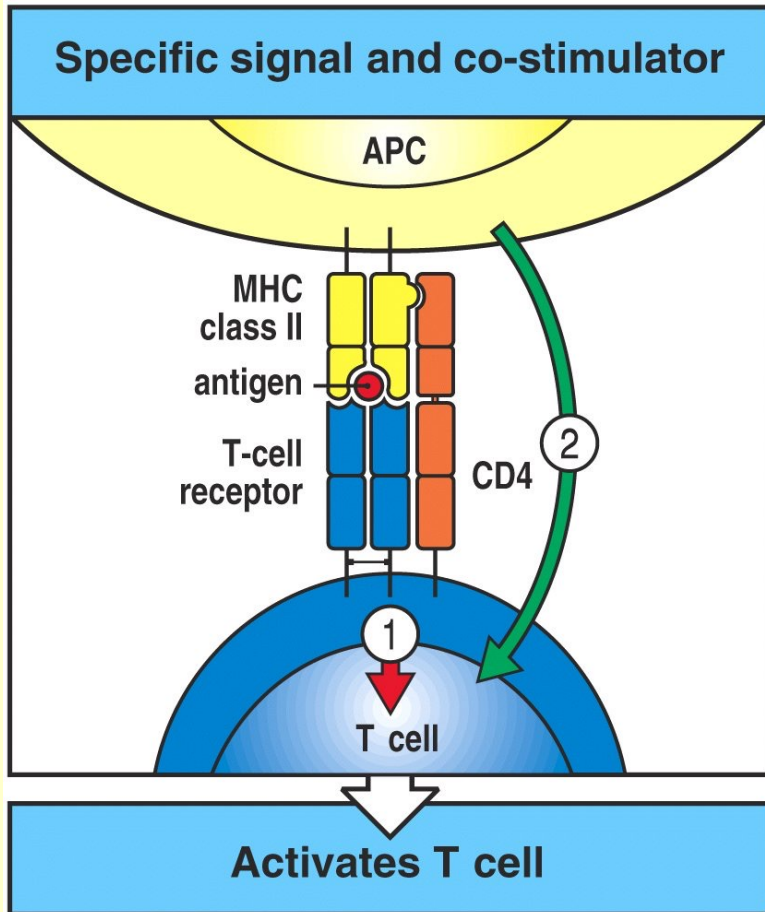


Figure 8-10 Immunobiology, 6/e. (© Garland Science 2005)

1. **Signal:** vom TcR-CD3-Komplex  
**Antigen-spezifisch**
2. **Signal:** **Ko-Stimulierungs**signal  
durch CD28 - B7-Wechselwirkung

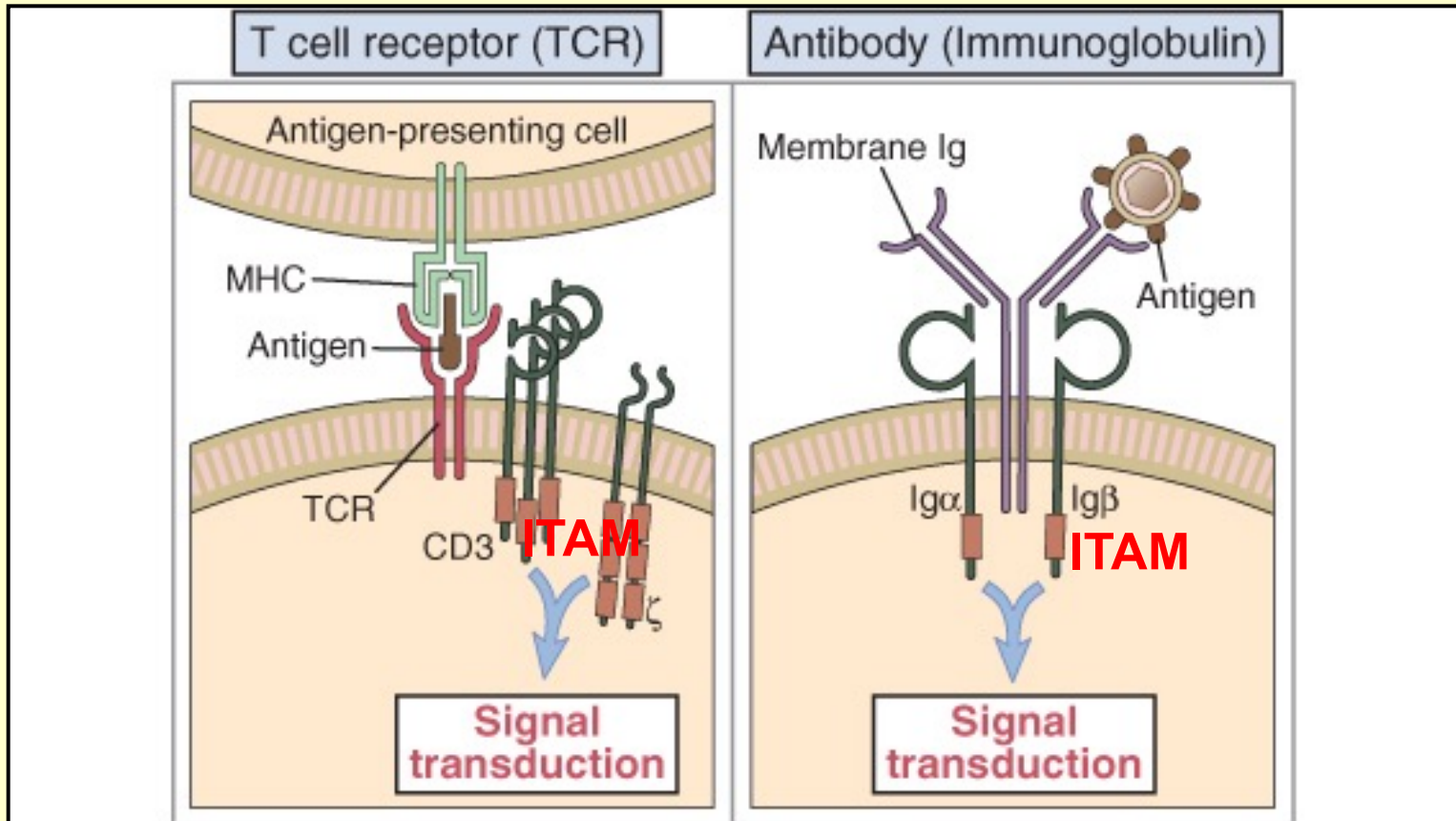
nicht Antigen-spezifisch

T-Zell-Aktivierung  
und Proliferation

Effektor- und  
Gedächtnis-T-Zellen



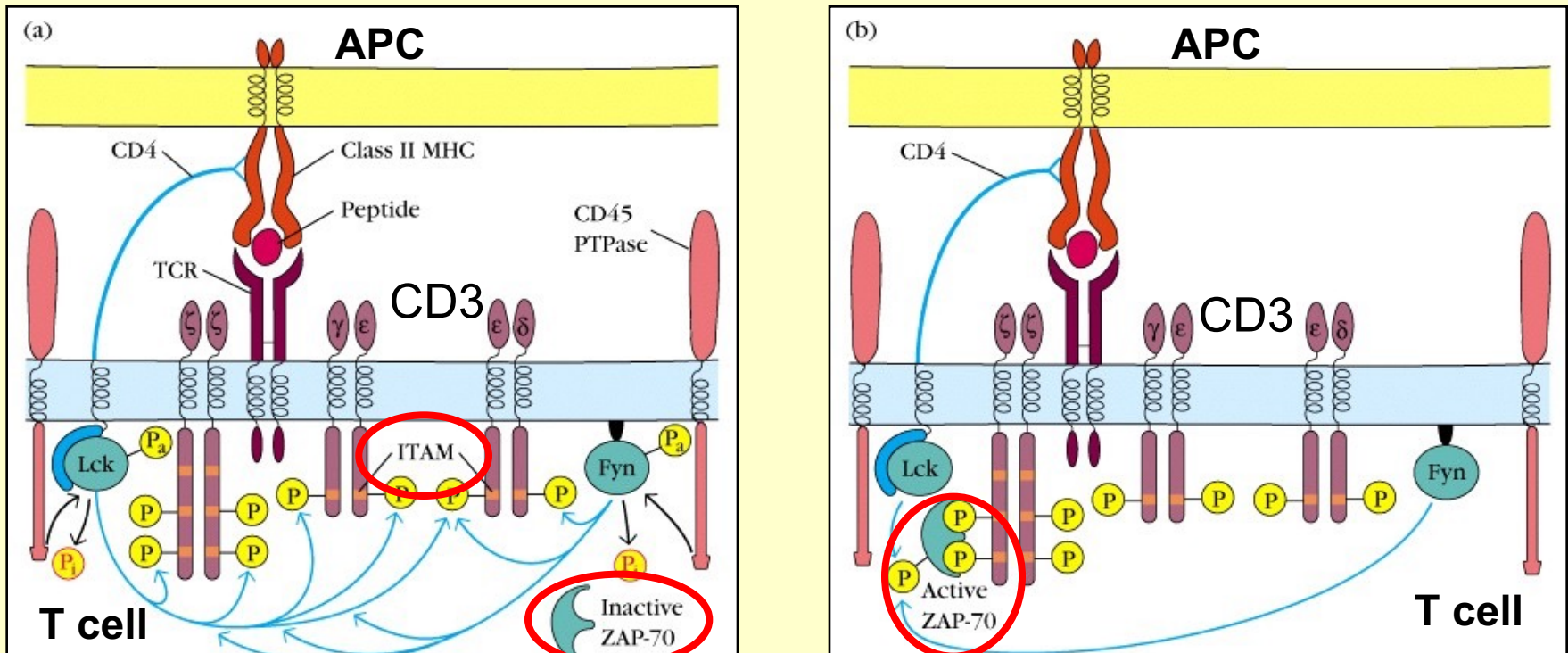
# Die Antigen-Erkennung und Signaltransduktion werden durch verschiedene Polypeptidketten koordiniert (zusätzliche Moleküle)



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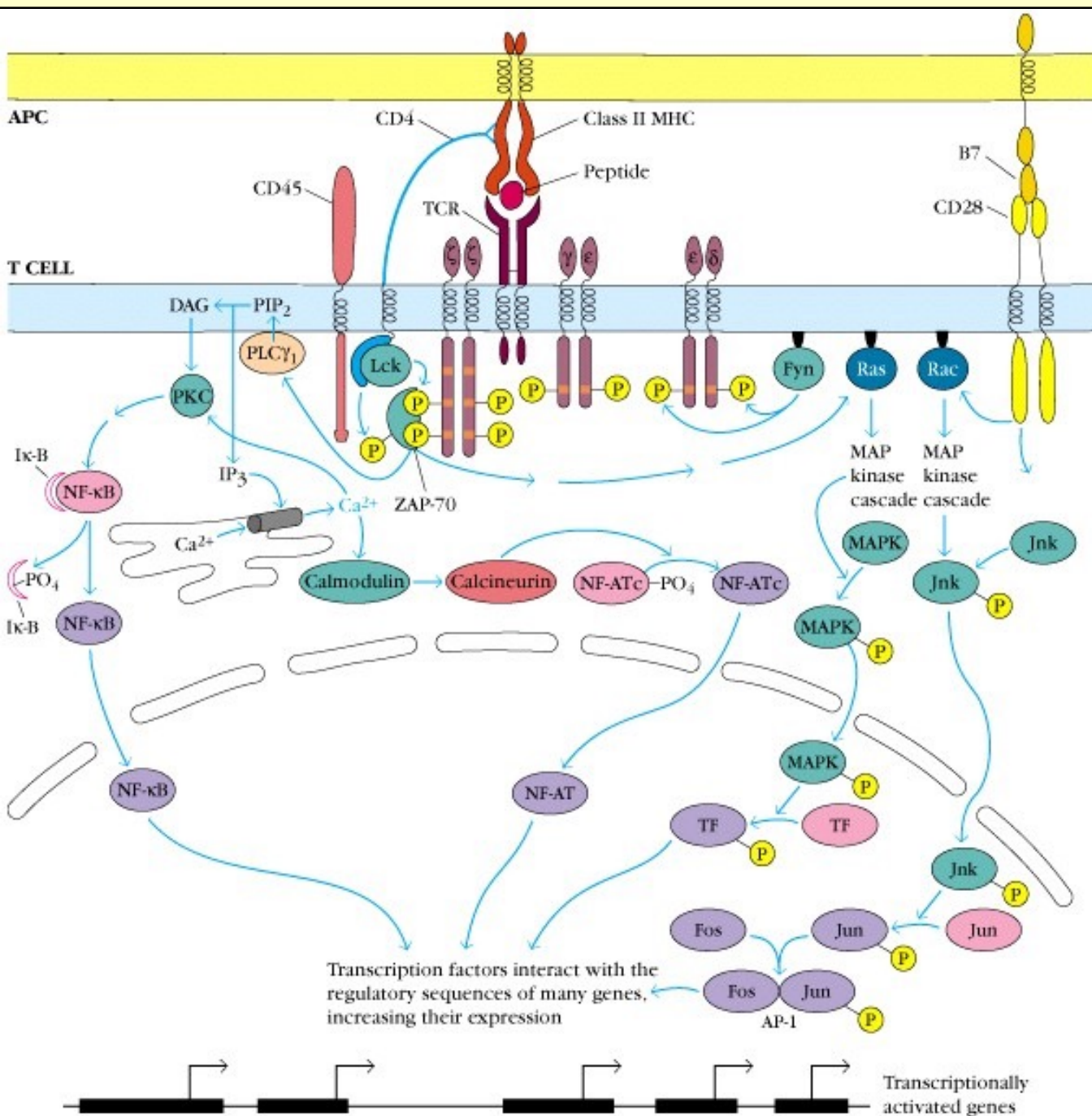
**ITAM: Immunorezeptor Tyrosin reich Aktivierung Motiven**

# Beginn der Signaltransduktion im T-Zelle

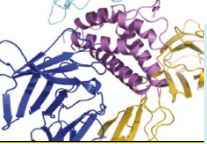


**ITAM: immunoreceptor tyrosine-based activating motif**

1. Querverbindung des TcR ergibt die nähere Assoziation von Korezeptoren (CD4, CD3, CD45) zu TcR
2. Protein-Tyrosinekinase (PTK) Lck- und Fyn-Aktivierung: CD45 Phosphatase entfernt ein hemmendes Phosphat (Pi)
3. Fyn und Lck phosphoryliert ITAMs von CD3-Komplex
4. Andockstellen für ZAP-70 PTK auch phosphoryliert wird und das Signal wird weitergeschickt



1. Antigenerkennung
2. PTK-Aktivierung
3. Ca<sup>2+</sup> Signal
4. Protein-Phosphorylierung
5. Translokation von Transkriptionsfaktoren
6. Genaktivierung



# Mechanismus der T-Zell Stimulation mit CD28

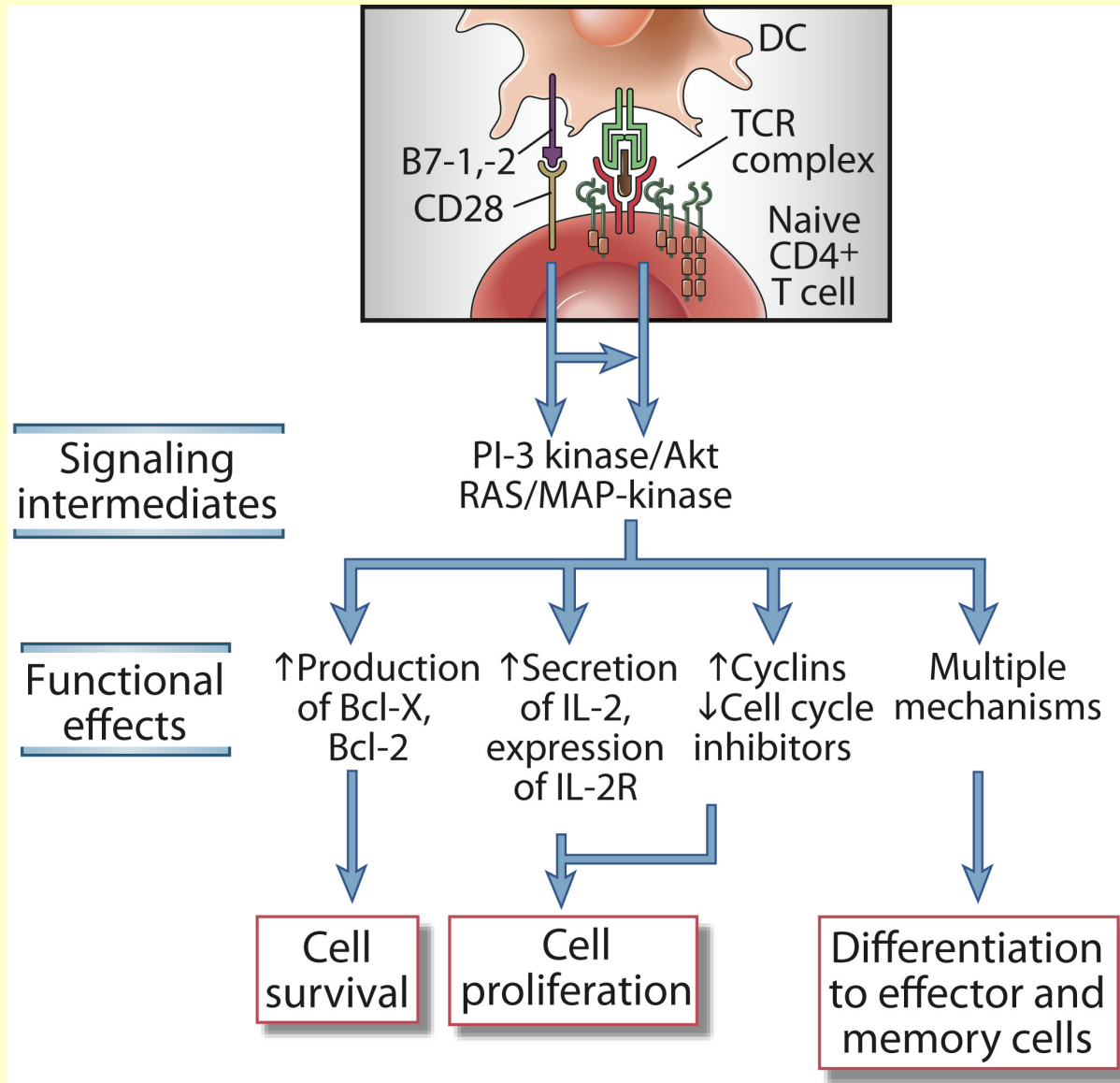


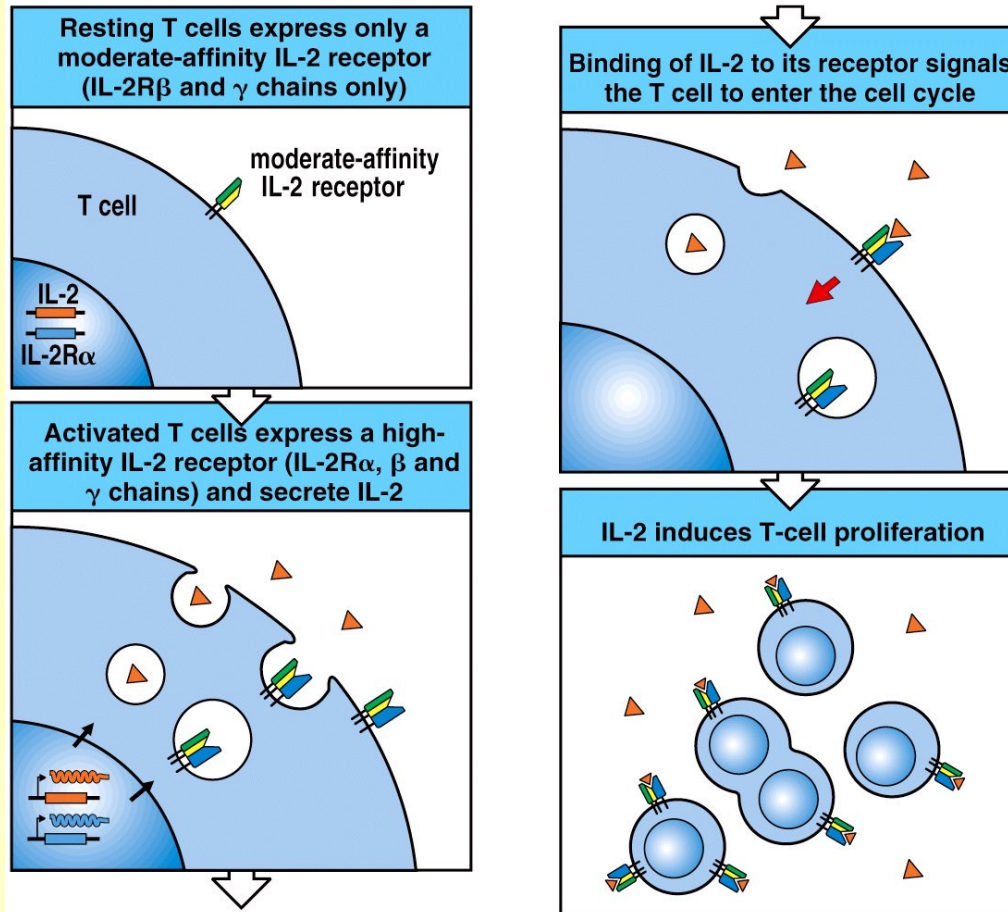
Fig. 9-4

# Zeitlicher Verlauf von Genexpression der aktivierten Th-Zellen

## FOLLOWING INTERACTION WITH ANTIGEN

Gene product	Function	Time mRNA expression begins	Location	Ratio of activated to nonactivated cells
<b>Sofortige</b>				
c-Fos	Protooncogene; nuclear-binding protein	15 min	Nucleus	> 100
c-Jun	Cellular oncogene; transcription factor	15–20 min	Nucleus	?
NF-AT	Transcription factor	20 min	Nucleus	50
c-Myc	Cellular oncogene	30 min	Nucleus	20
NF-κB	Transcription factor	30 min	Nucleus	> 10
<b>Frühe</b>				
IFN-γ	Cytokine	30 min	Secreted	> 100
IL-2	Cytokine	45 min	Secreted	> 1000
Insulin receptor	Hormone receptor	1 h	Cell membrane	3
IL-3	Cytokine	1–2 h	Secreted	> 100
TGF-β	Cytokine	<2 h	Secreted	> 10
IL-2 receptor (p55)	Cytokine receptor	2 h	Cell membrane	> 50
TNF-β	Cytokine	1–3 h	Secreted	> 100
Cyclin	Cell-cycle protein	4–6 h	Cytoplasmic	> 10
IL-4	Cytokine	<6 h	Secreted	> 100
IL-5	Cytokine	<6 h	Secreted	> 100
IL-6	Cytokine	<6 h	Secreted	> 100
c-Myb	Protooncogene	16 h	Nucleus	100
GM-CSF	Cytokine	20 h	Secreted	?
<b>Späte</b>				
HLA-DR	Class II MHC molecule	3–5 days	Cell membrane	10
VLA-4	Adhesion molecule	4 days	Cell membrane	> 100
VLA-1, VLA-2, VLA-3, VLA-5	Adhesion molecules	7–14 days	Cell membrane	> 100, ?, ?, ?

# Funktionelle Folge von Th-Zell-Aktivierung 1.: IL-2-induzierte Proliferation – CD25 (IL2R $\alpha$ )

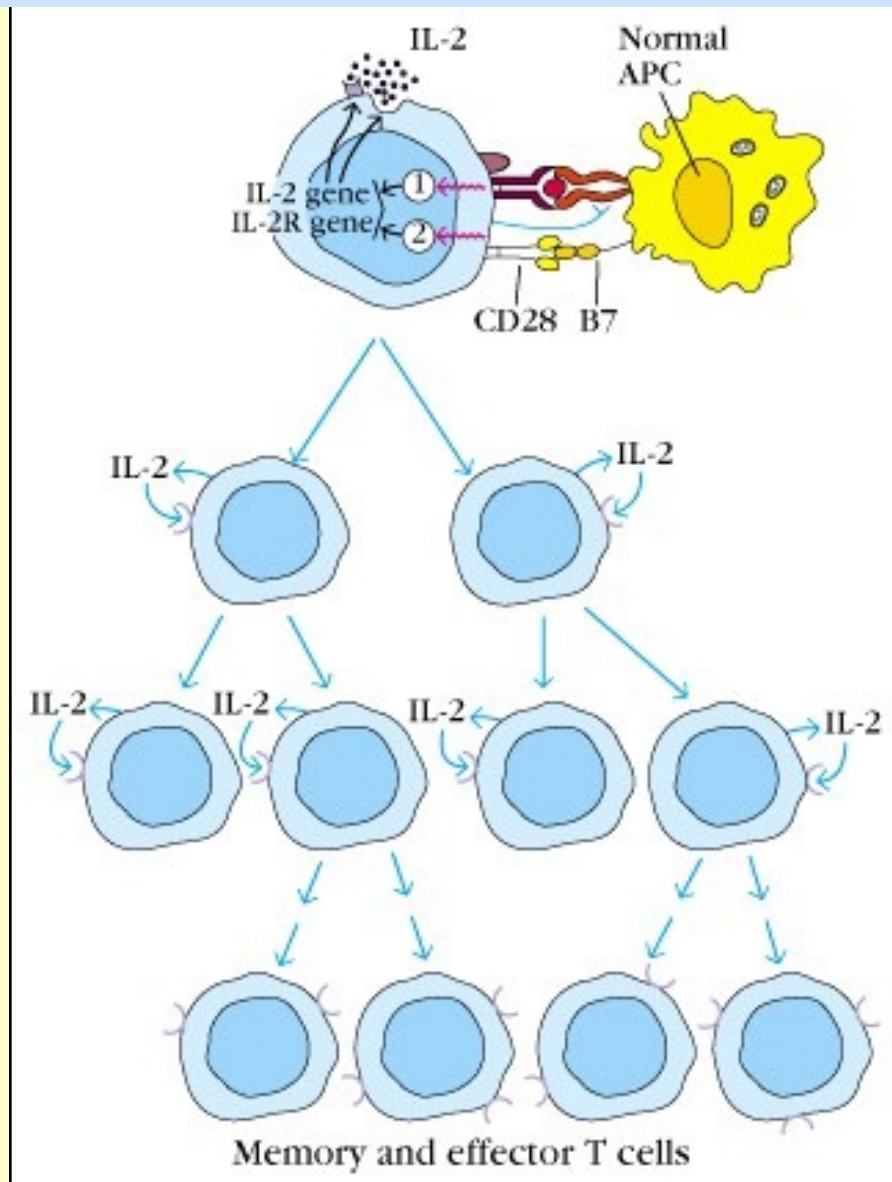


	Intermediate affinity IL-2R	High affinity IL-2R	Low affinity IL-2R
Subunit composition:	IL-2R $\beta$ IL-2R $\gamma$	IL-2R $\alpha$ IL-2R $\beta$ IL-2R $\gamma$	IL-2R $\alpha$
Affinity constant ( $K_d$ ):	$10^7 M$	$10^{11} M$	$10^8 M$
Dissociation constant ( $K_d$ ):	$10^{-9} M$	$10^{-11} M$	$10^{-8} M$
Cells expressed by:	<b>NK-Zelle, ruhende T-Zelle</b>	<b>aktivierte T-Zelle und B-Zelle</b>	

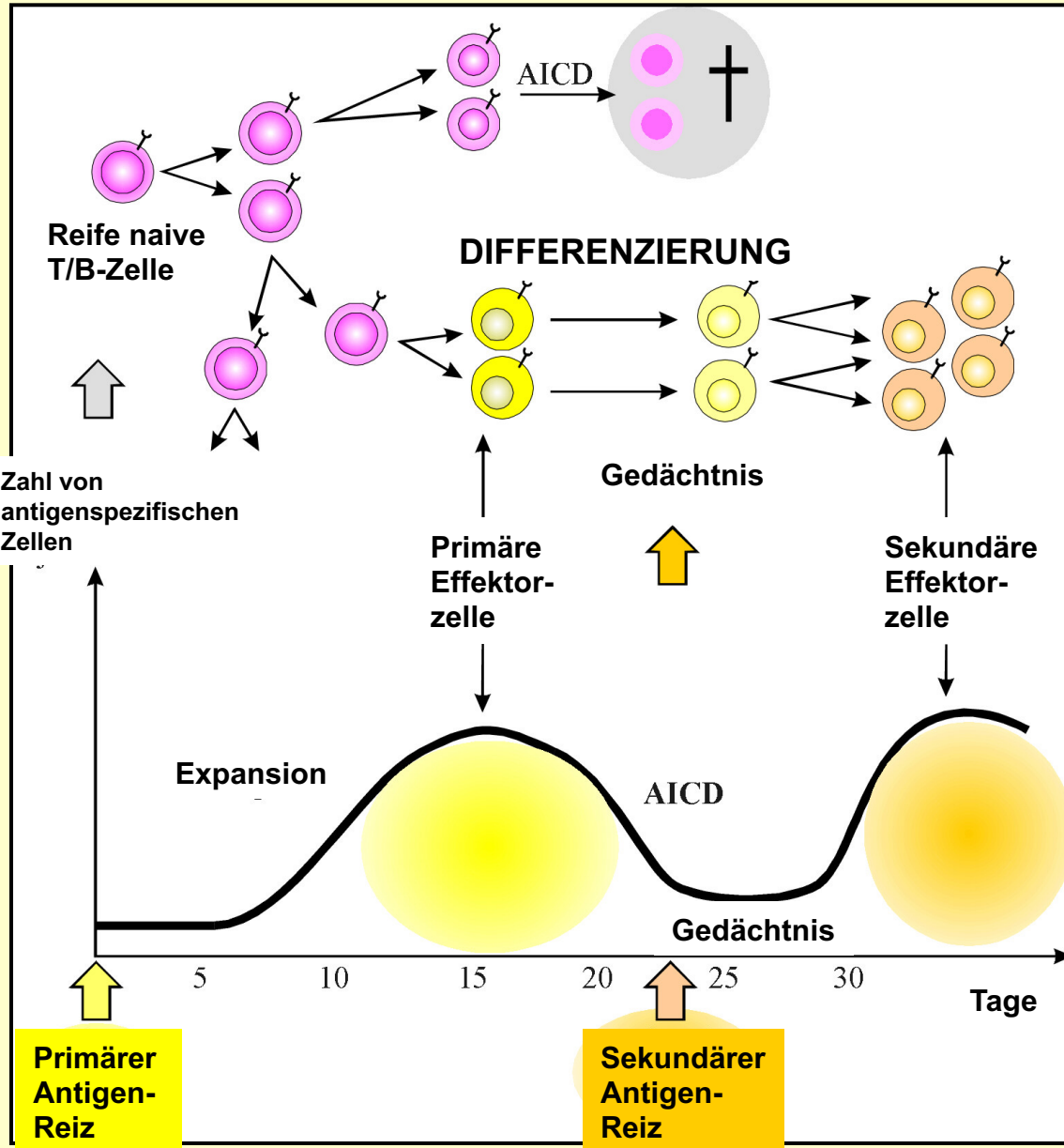
**IL-2: autokriner Wachstumsfaktor für aktivierte Lymphozyten**

Figure 8-20 Immunobiology, 6/e. (© Garland Science 2005)

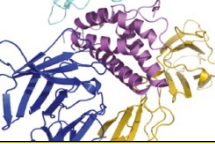
# Funktionelle Folge von Th-Zell-Aktivierung 1.: IL-2-induzierte Proliferation – CD25 (IL2R $\alpha$ )



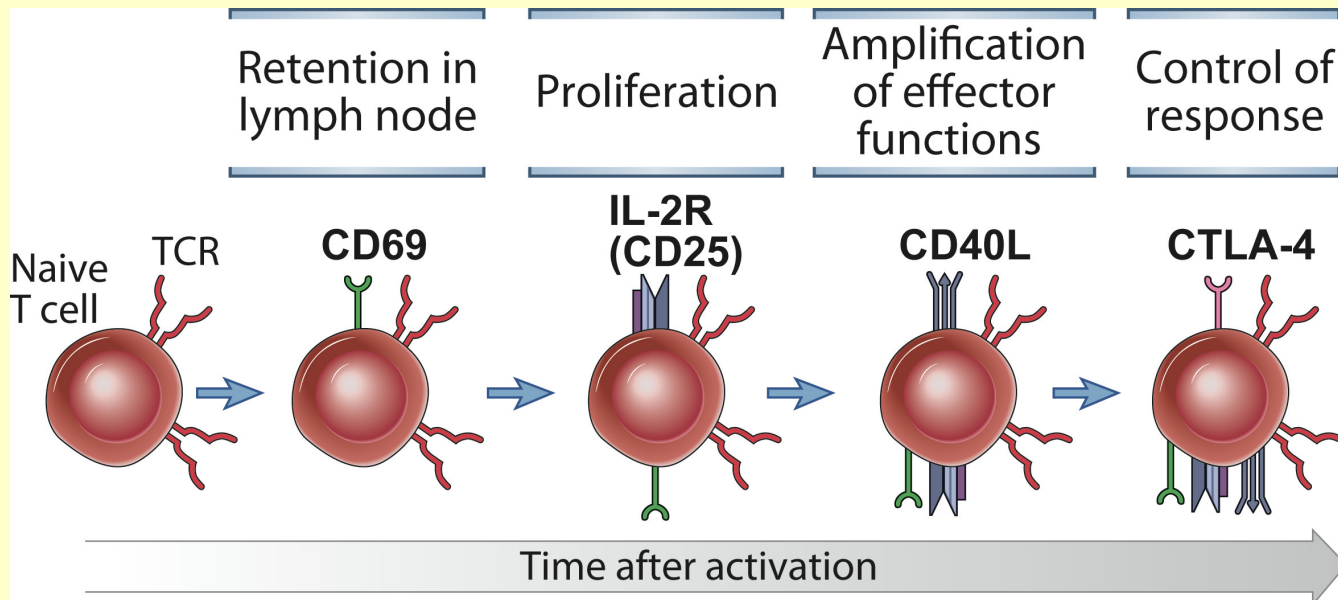
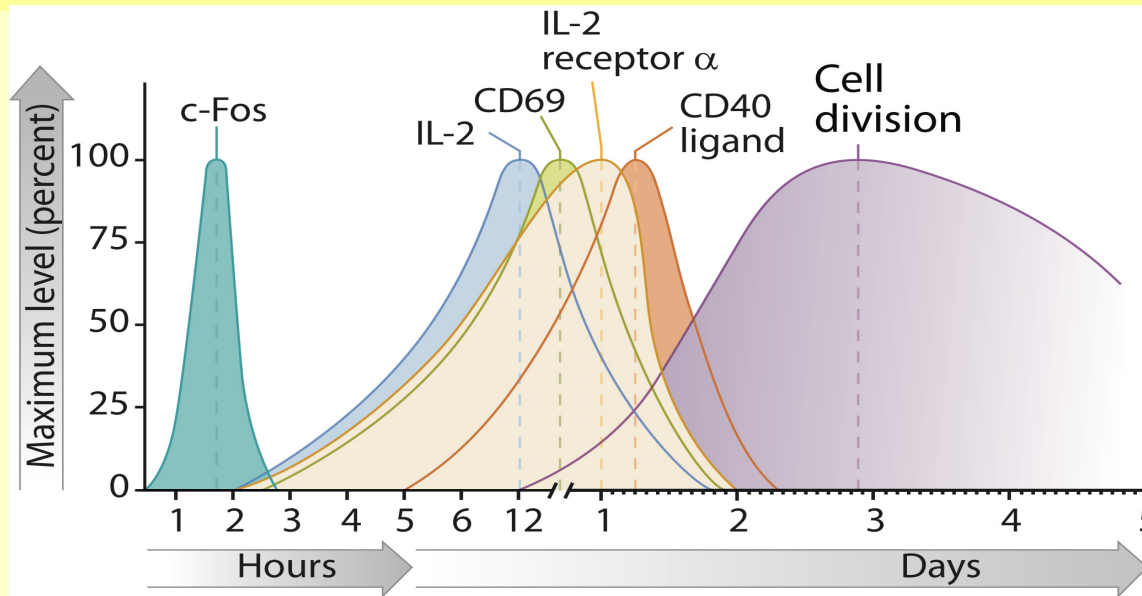
# Antigen-induzierte klonale Proliferation



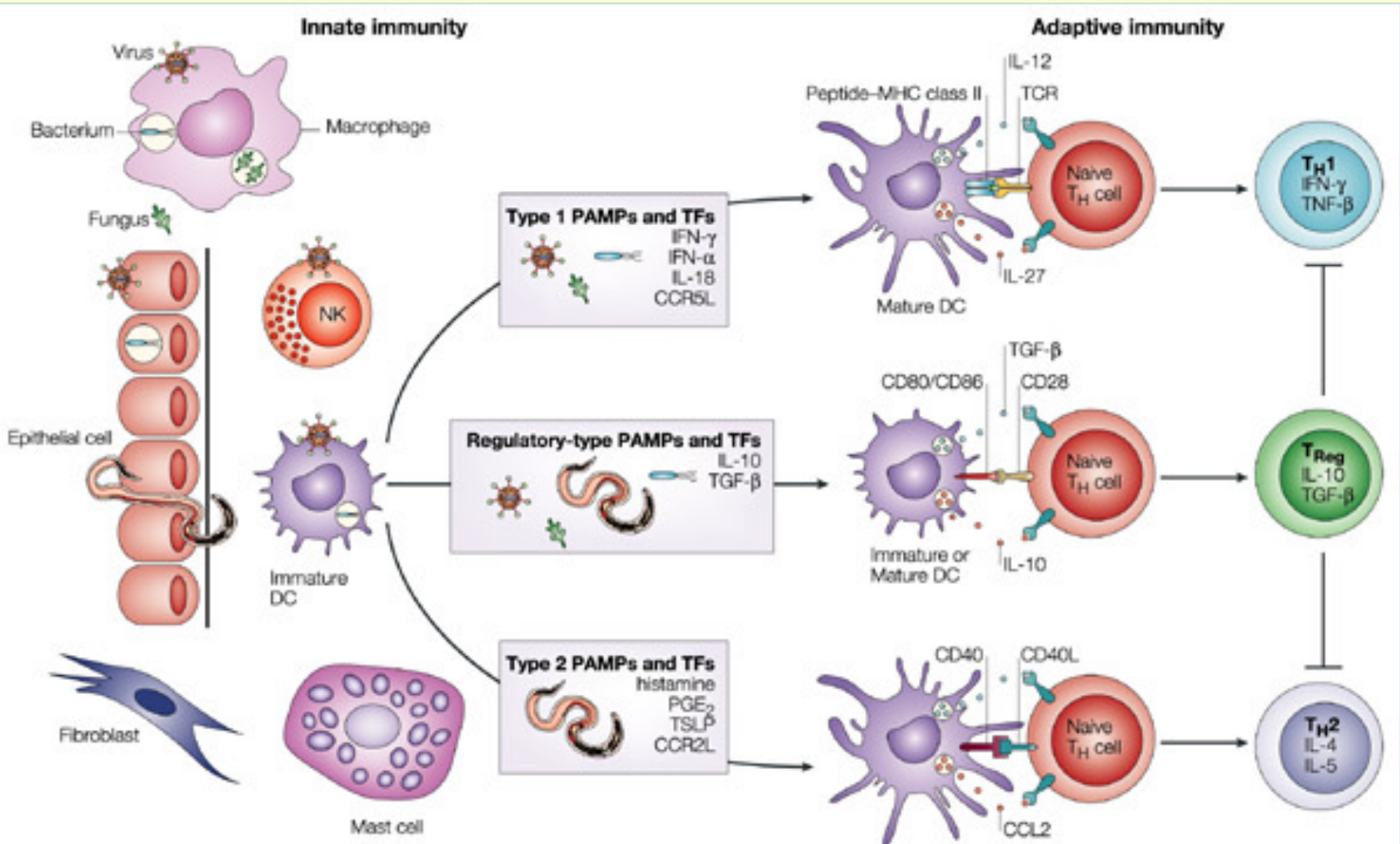




# Exprimierung Moleküle nach T-Zellaktivierung

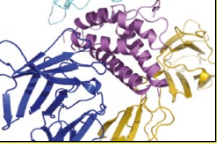


# Dendritische Zellen polarisieren das Immunantwort



**PAMP: Pathogen assoziierte molekulare Mustern**

TF: tissue Faktor (cytokine)



# T-Zell-Polarisierung

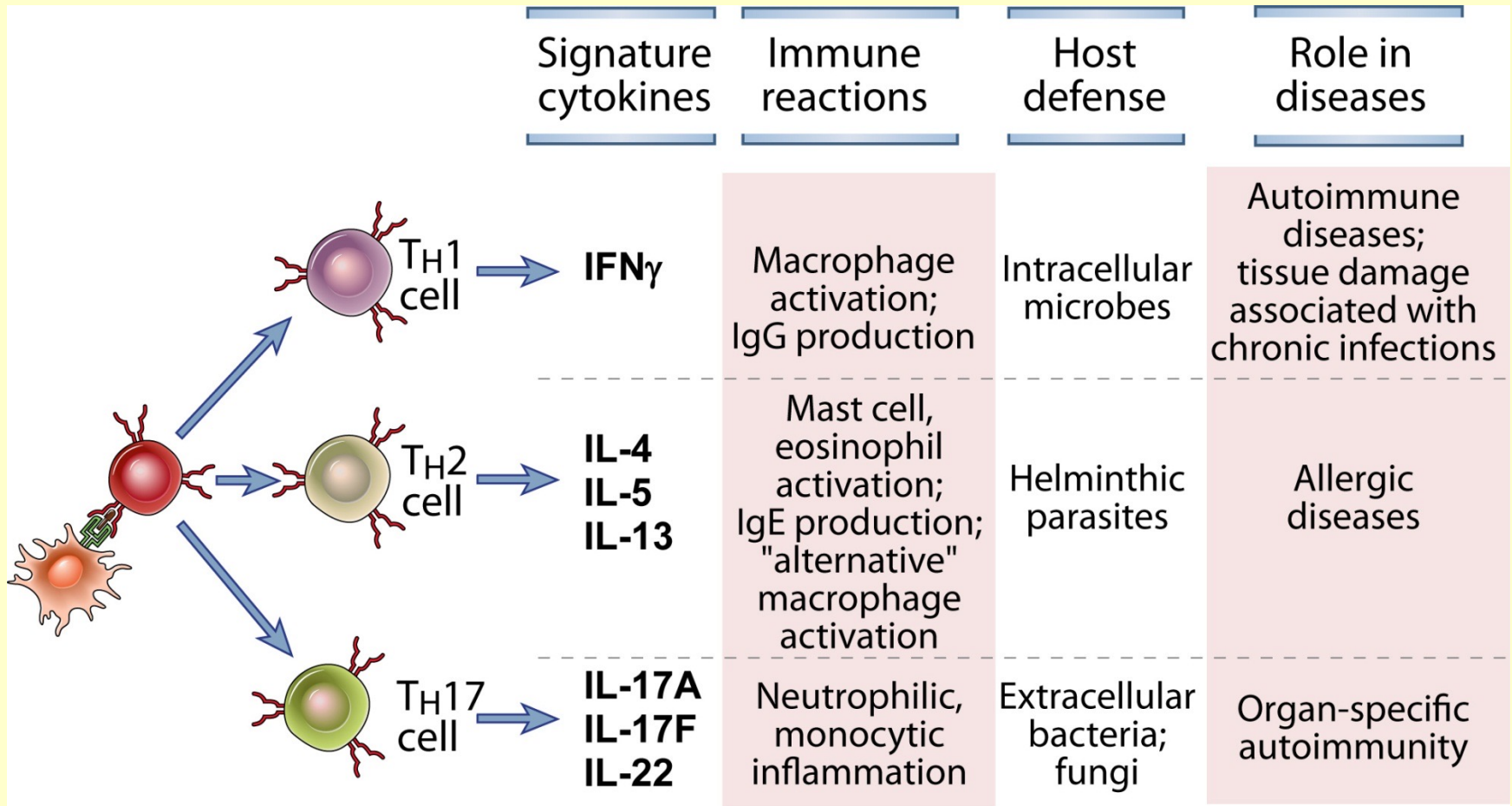
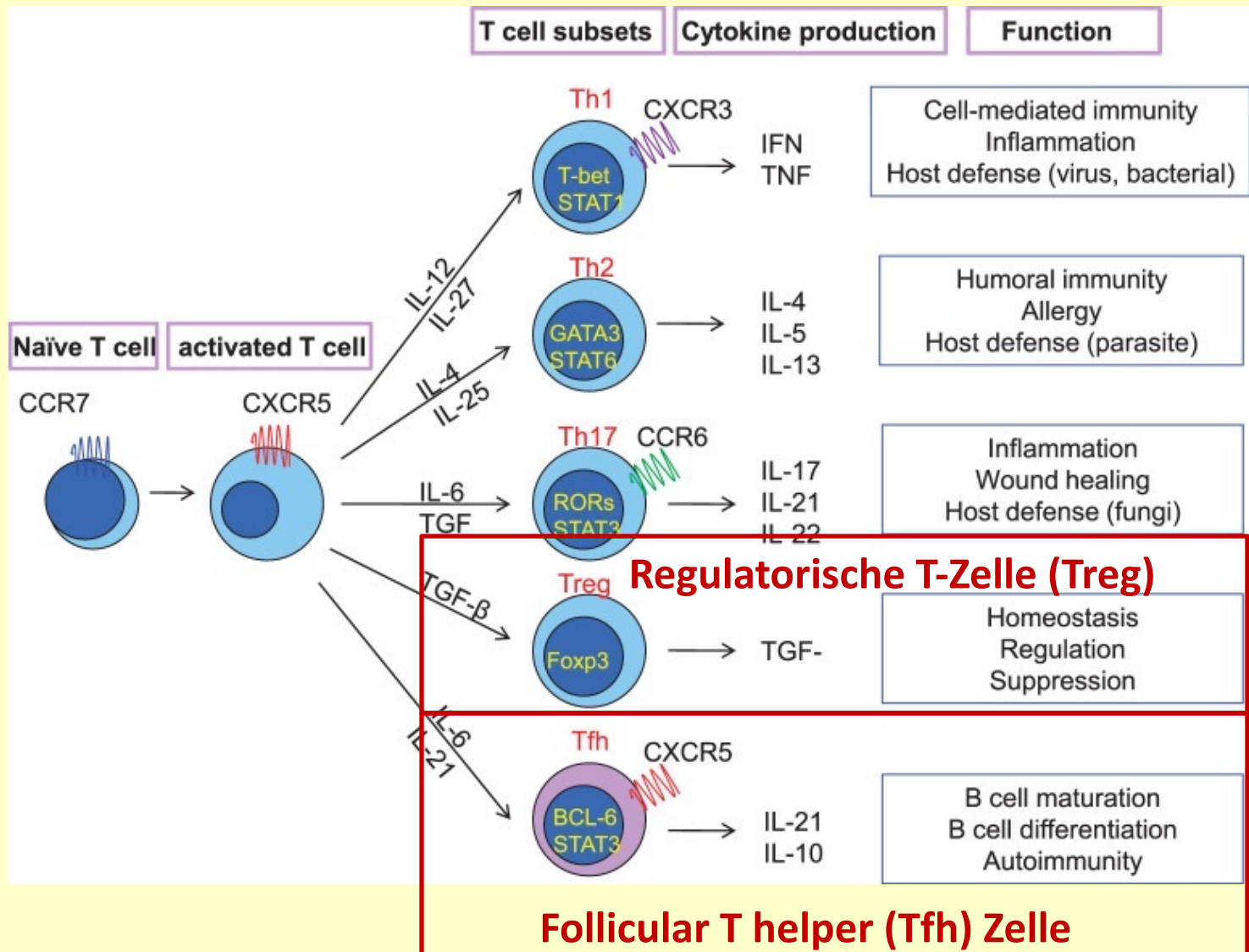
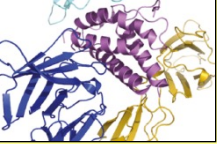


Fig. 9-13

# T-Zell-Polarisierung





# T<sub>H</sub>1-Zelle Differenzierung

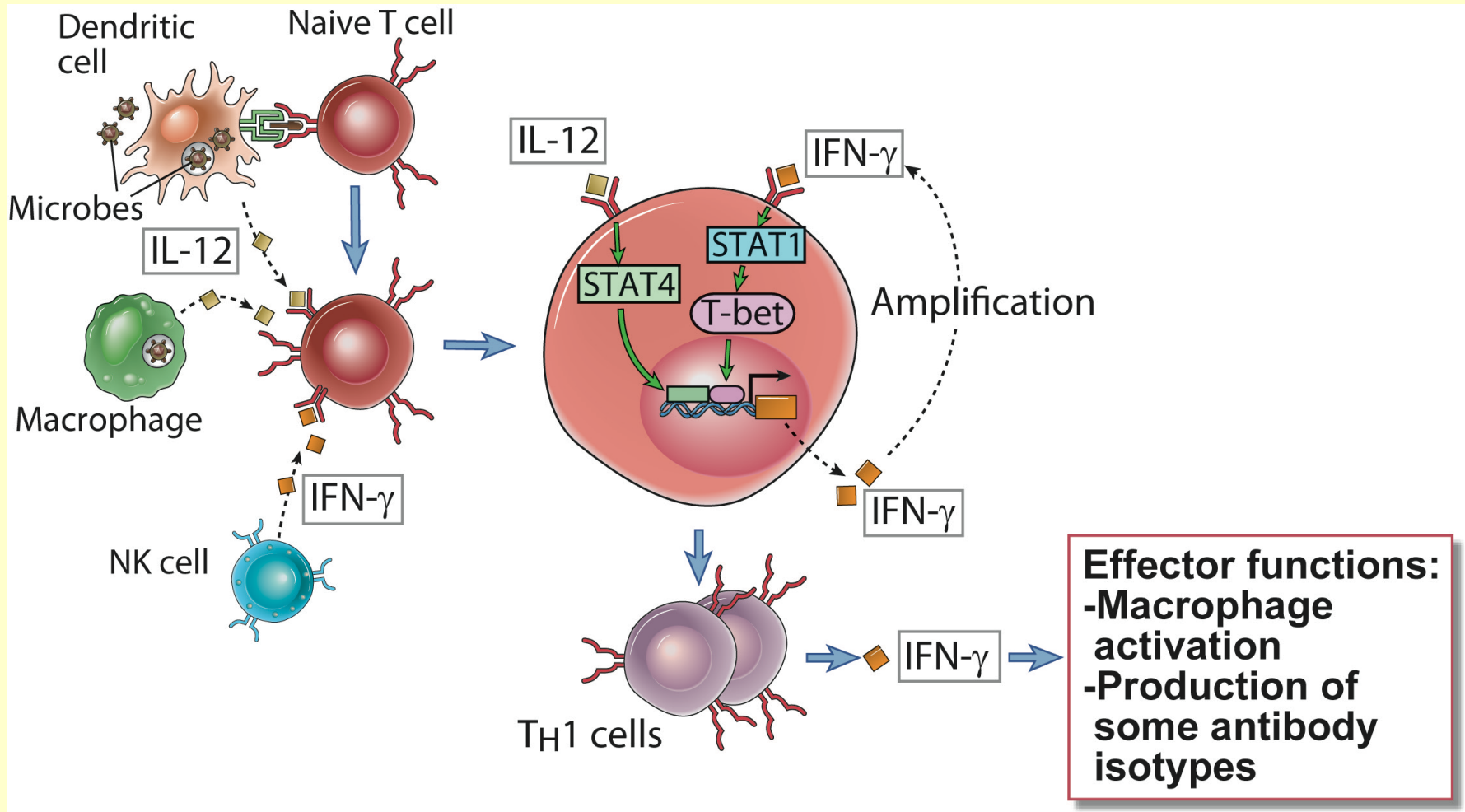
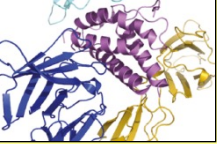


Fig. 9-15



# T<sub>H</sub>2-Zelle Differenzierung

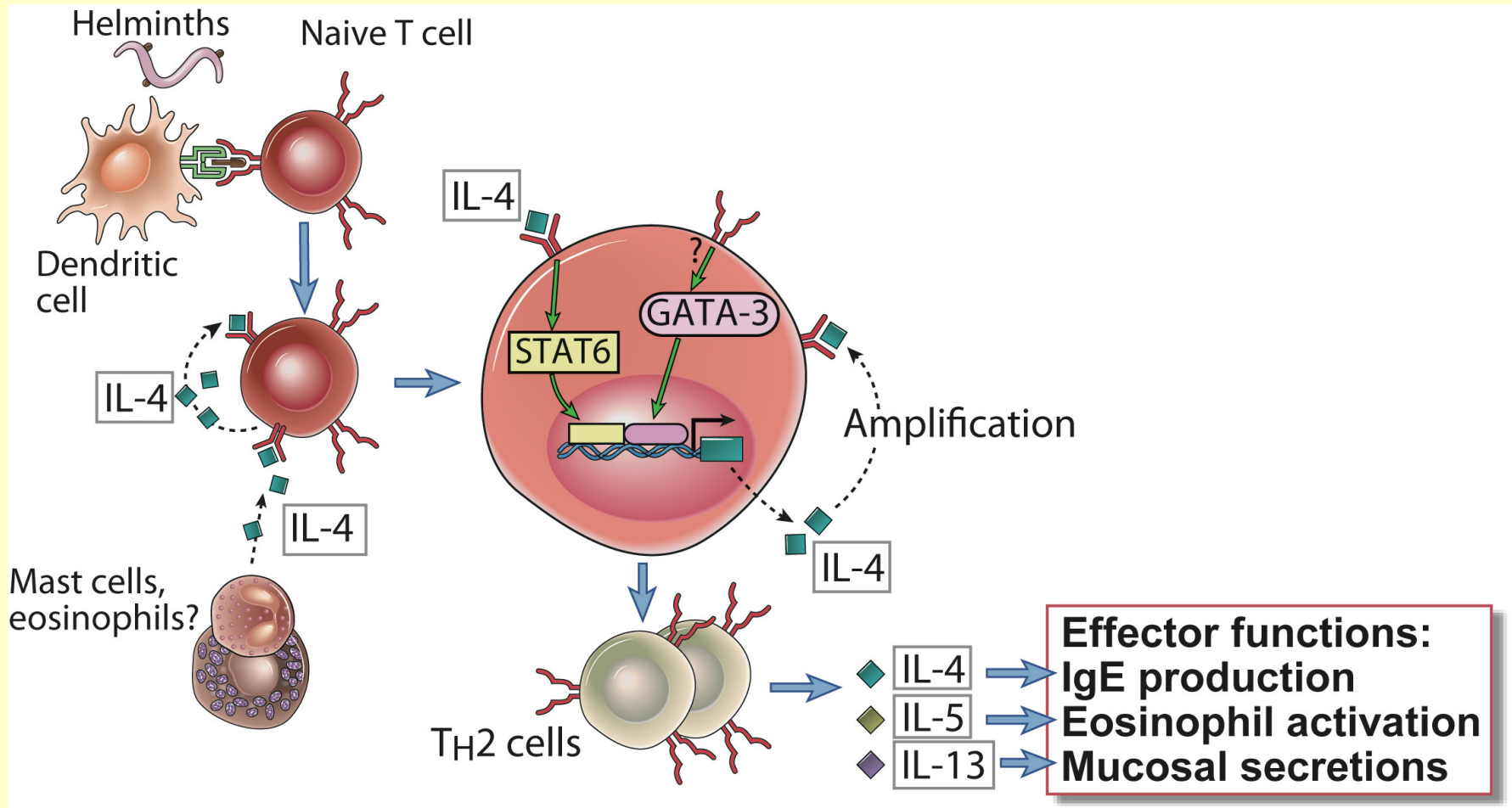
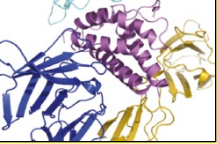


Fig. 9-16



# T<sub>H</sub>17-Zelle Differenzierung

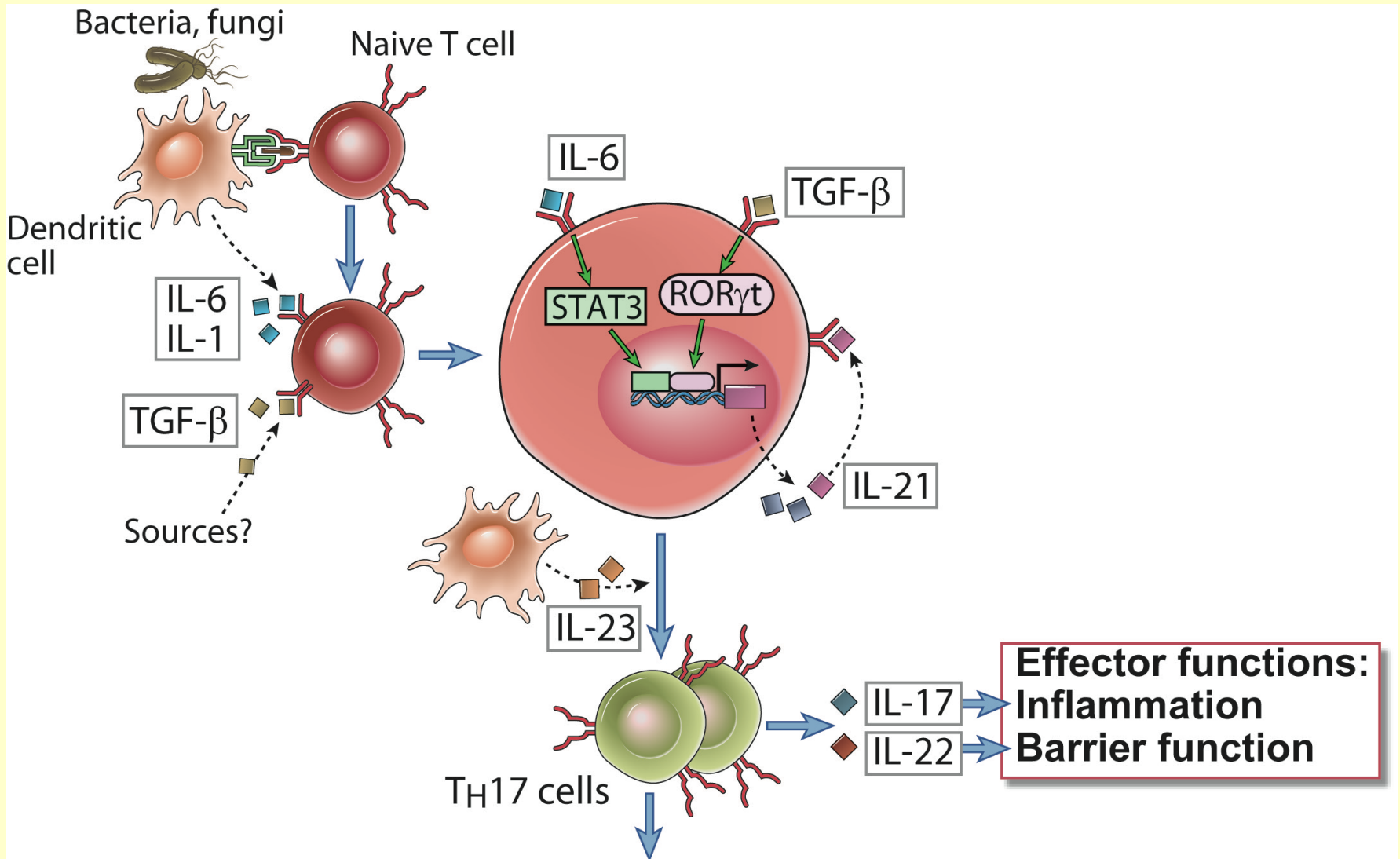
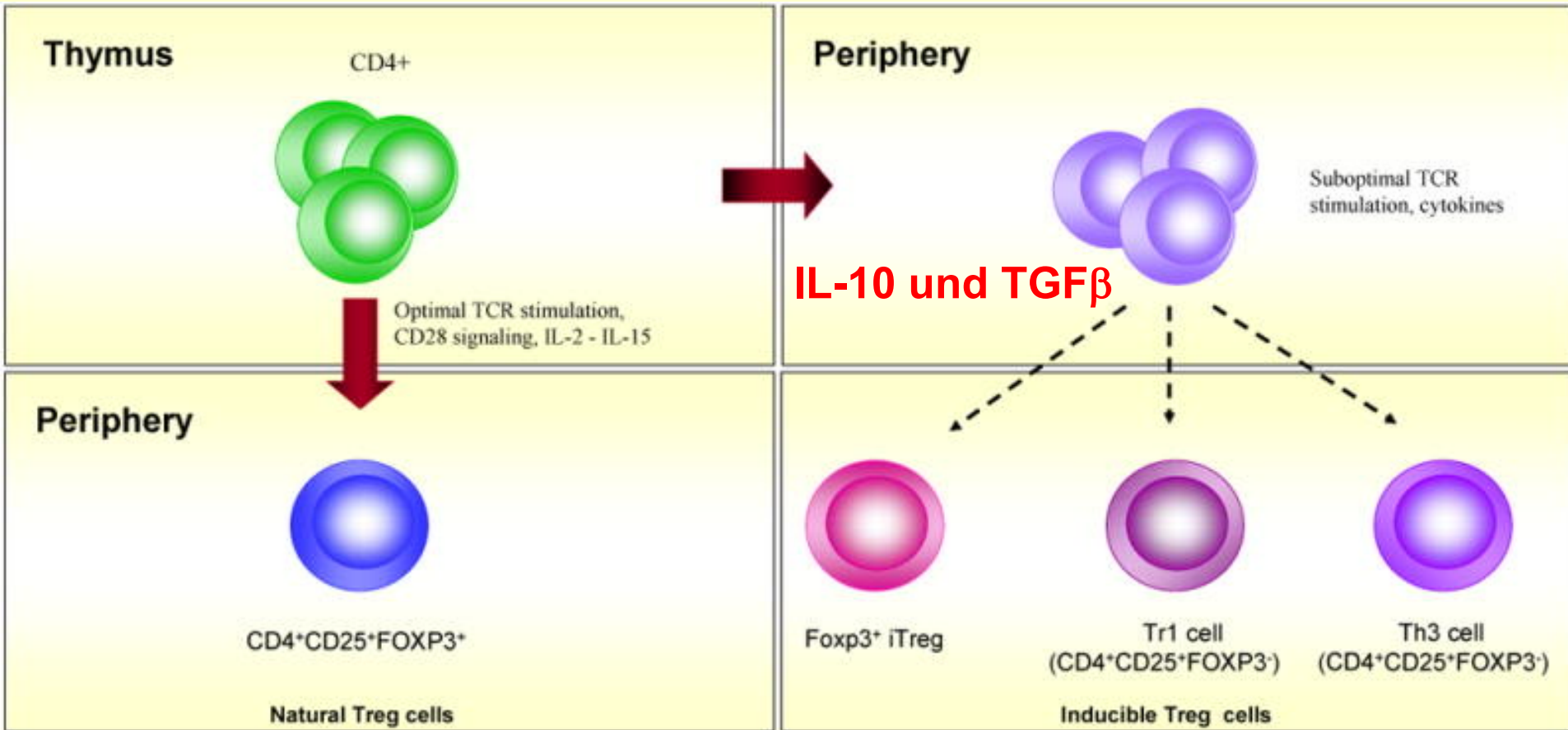


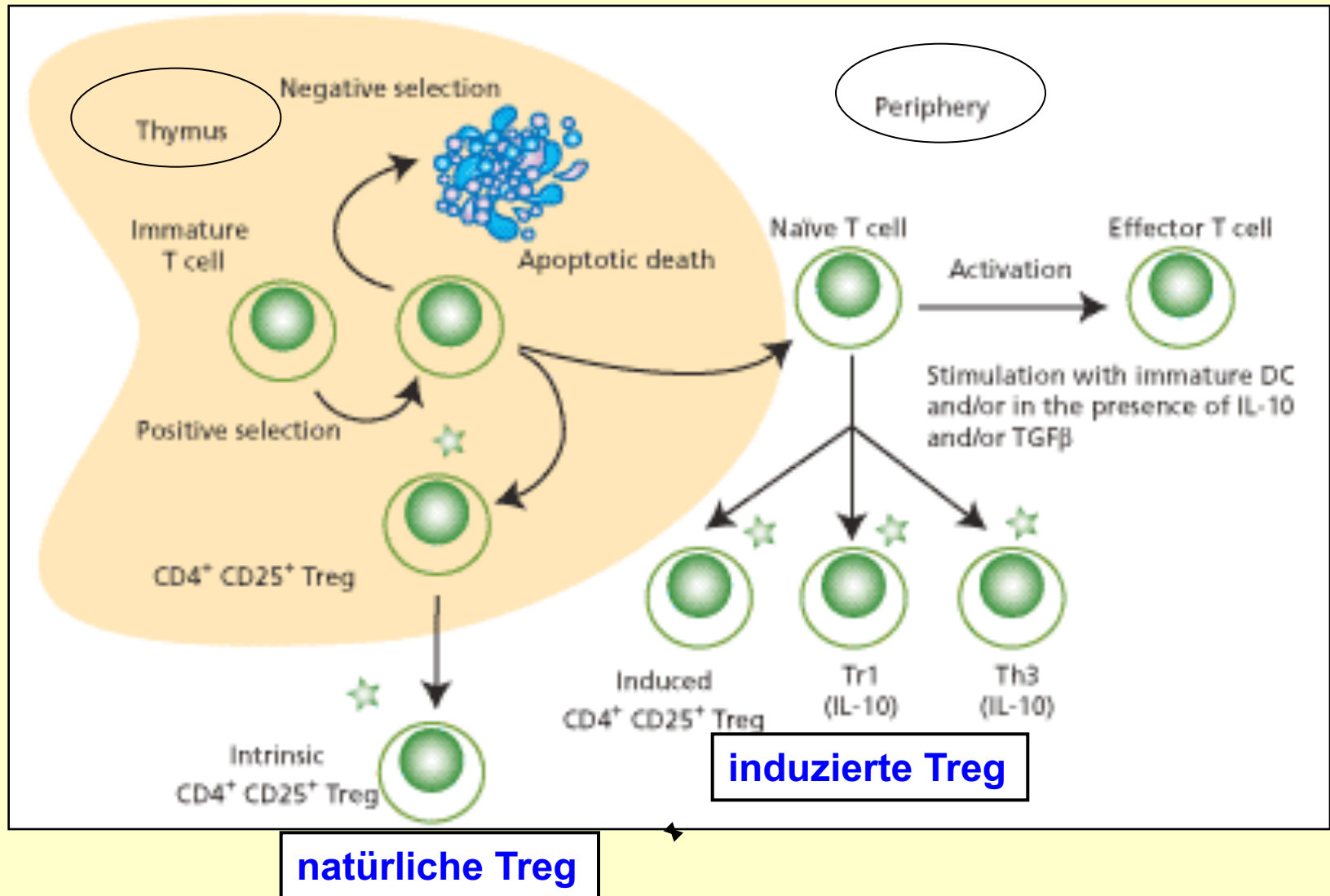
Fig. 9-17

# Regulatorische T-Zelle (Treg) Differenzierung

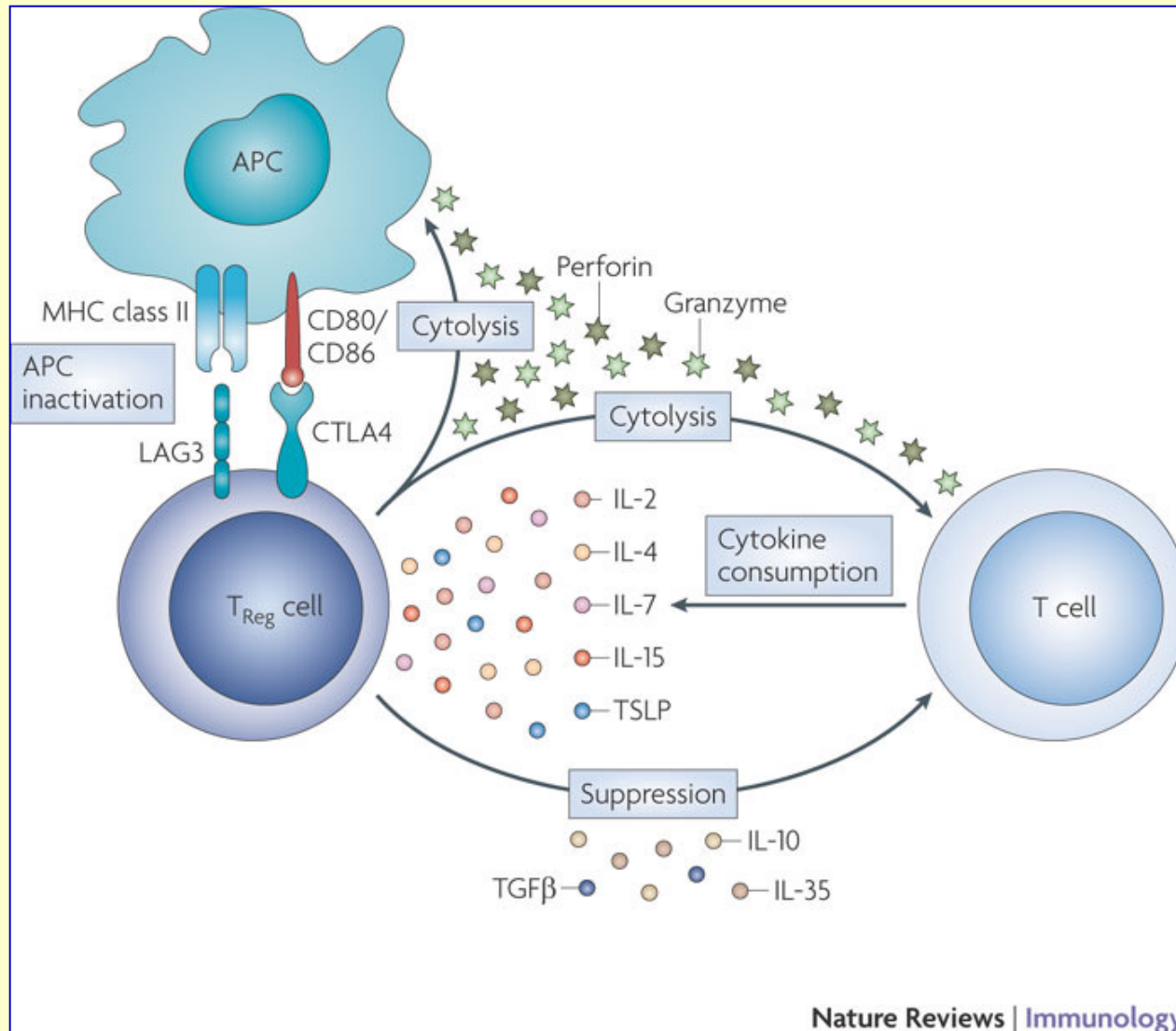




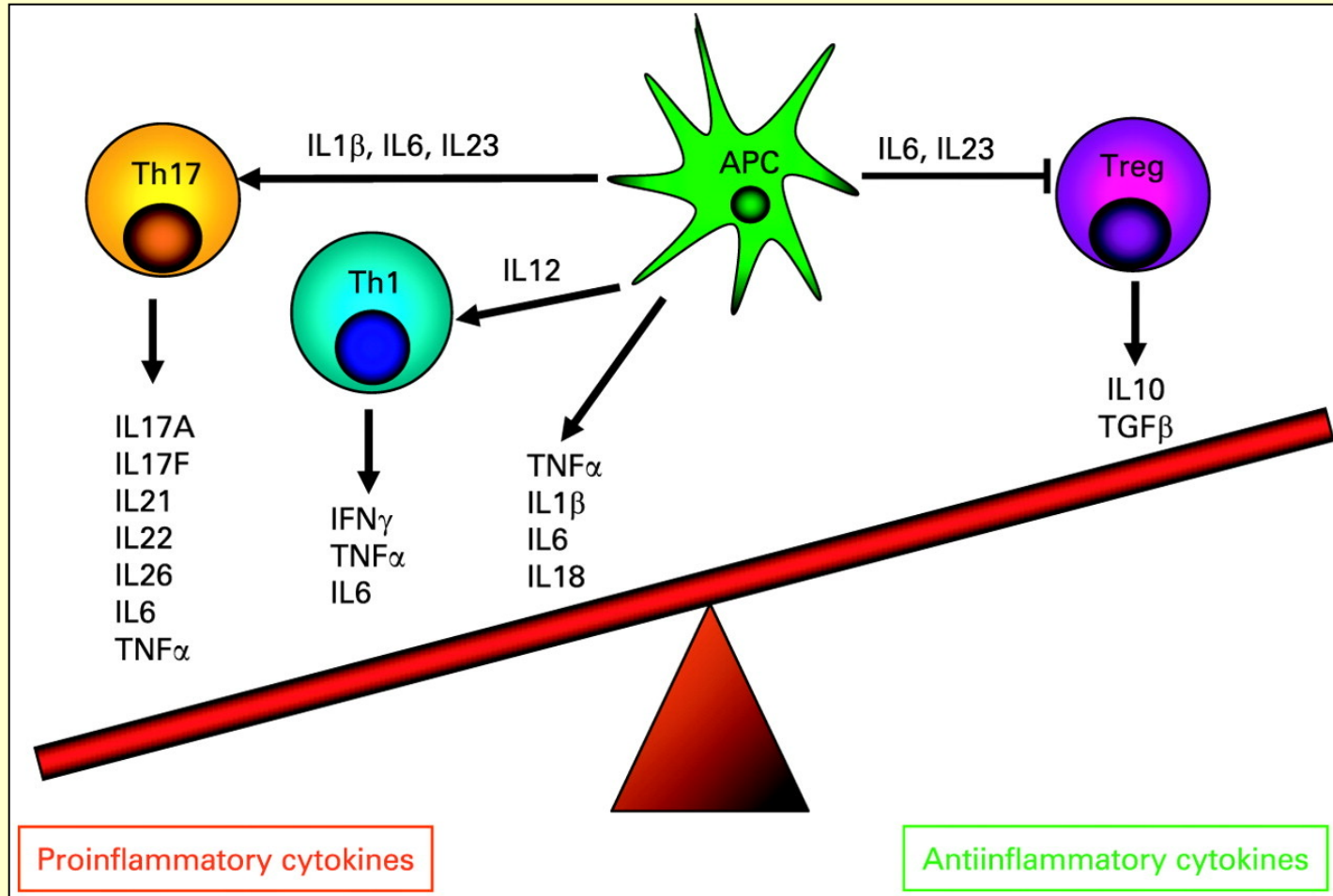
# Regulatorische T-Zelle (Treg) Differenzierung

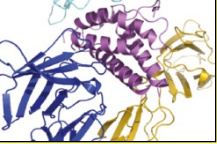


# Treg Suppression Mechanisms



# Immunologische Balance

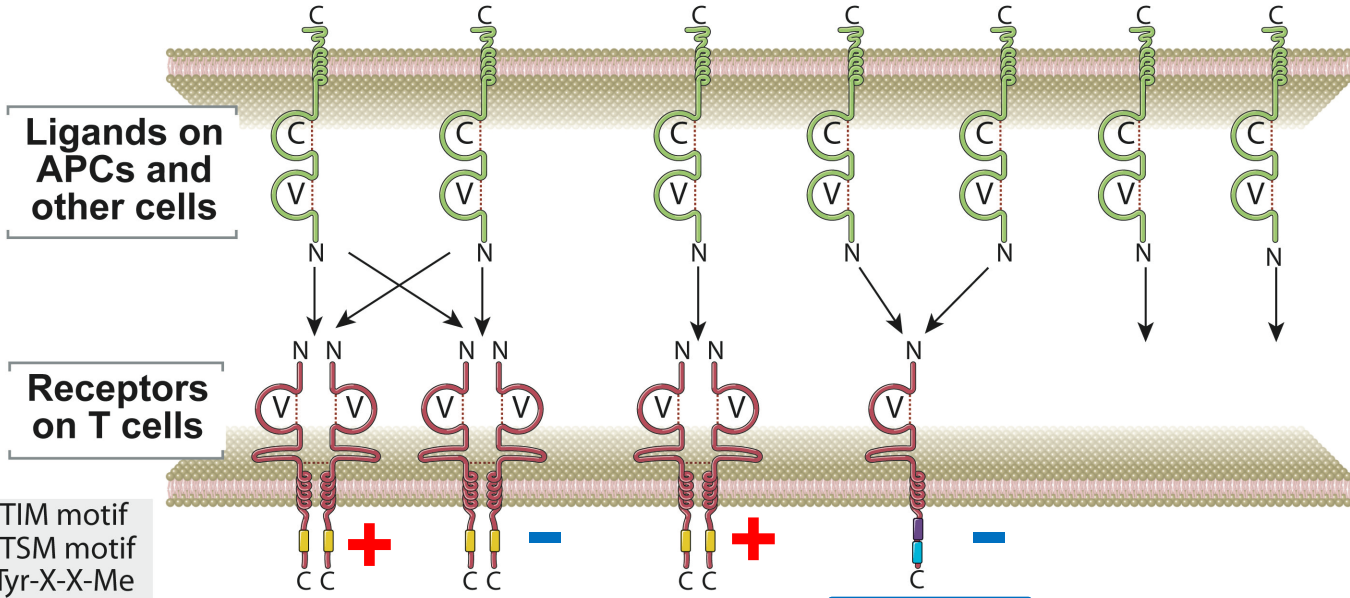




# B7 und CD28 Familien

APC

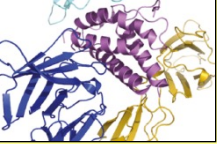
Expression	DCs, Macs, B cells	DCs, Macs, B cells	DCs; Macs, B cells	Many cell types	DCs; Macs, B cells	DCs; other cells	DCs; other cells
Name	<b>B7-1 (CD80)</b>	<b>B7-2 (CD86)</b>	<b>ICOS-L (CD275)</b>	<b>PD-L1 (B7-H1, CD274)</b>	<b>PD-L2 (B7-DC, CD273)</b>	<b>B7-H3</b>	<b>B7-H4</b>



Name	<b>CD28</b>	<b>CTLA-4</b>	<b>ICOS</b>	<b>PD-1</b>	?	?
Expression	T cells	T cells; (activated)	T cells; (activated)	T cells, B cells, myeloid cells; (activated)		
Major function	Costimulation of naive T cells; generation of Treg	Neg. regulation of immune responses; self-tolerance	Costimulation of effector T cells and Treg; generation of T <sub>FH</sub>	Neg. regulation of T cells	?	Neg. regulation of T cells

T-Zelle

Fig. 9-5



# Therapeutic Costimulatory Blockade

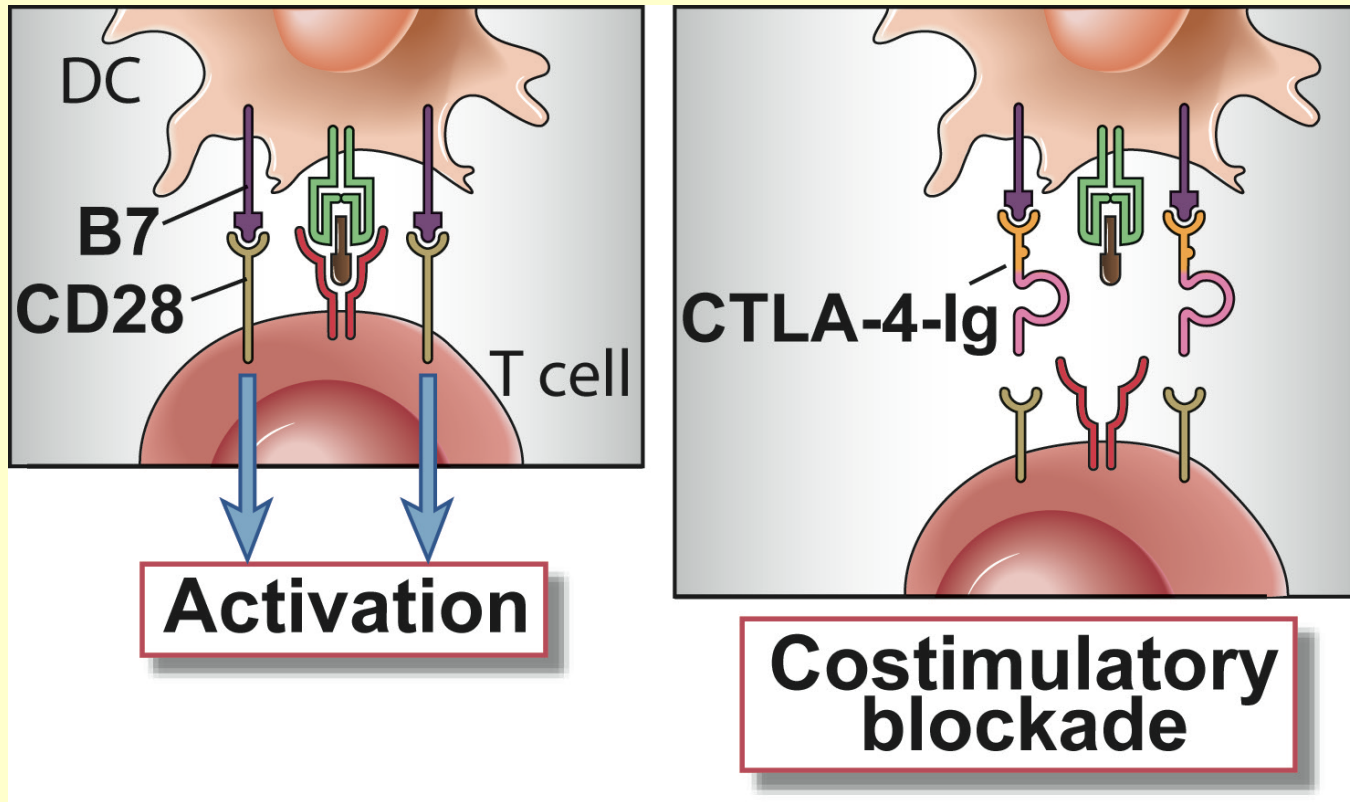
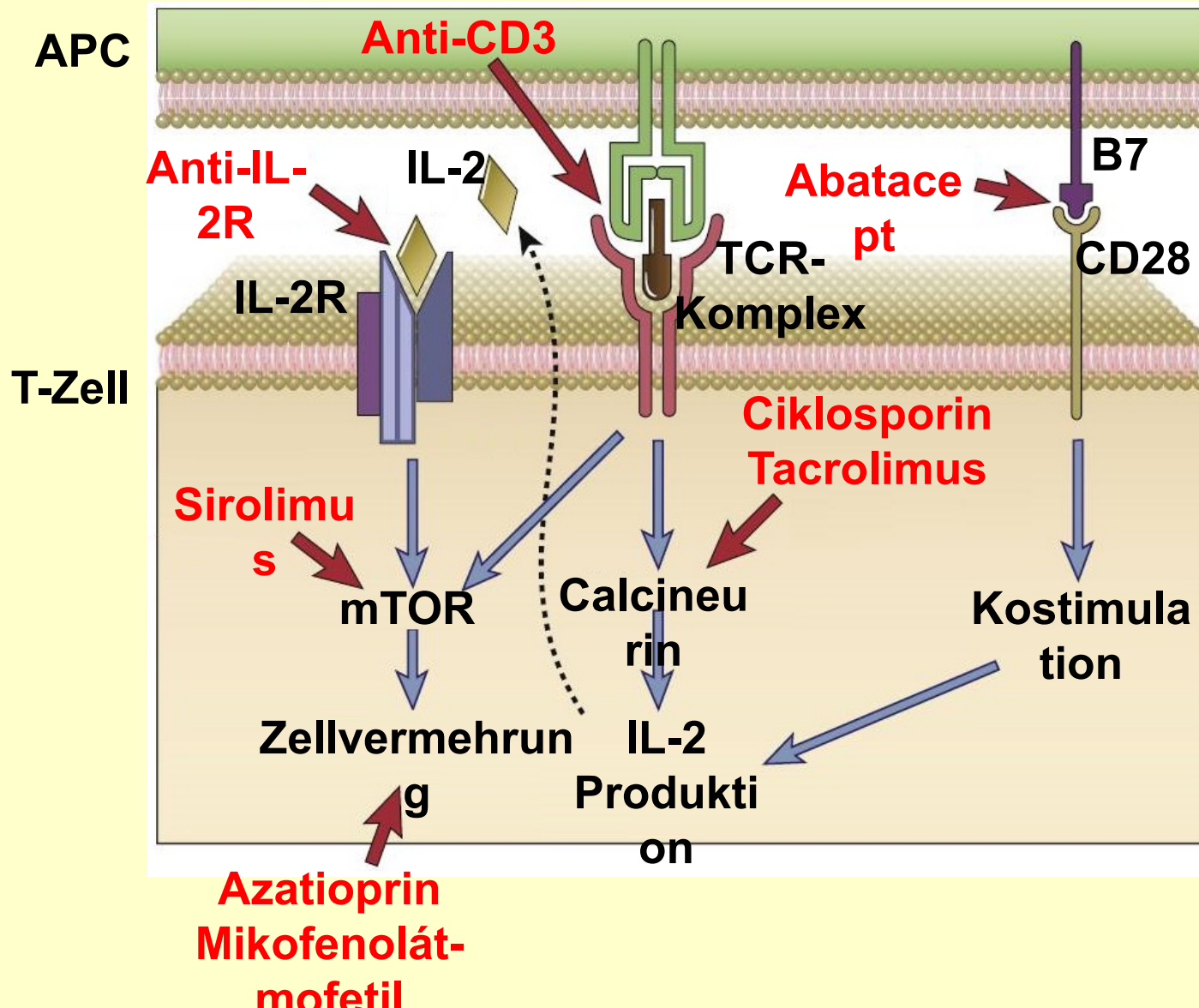


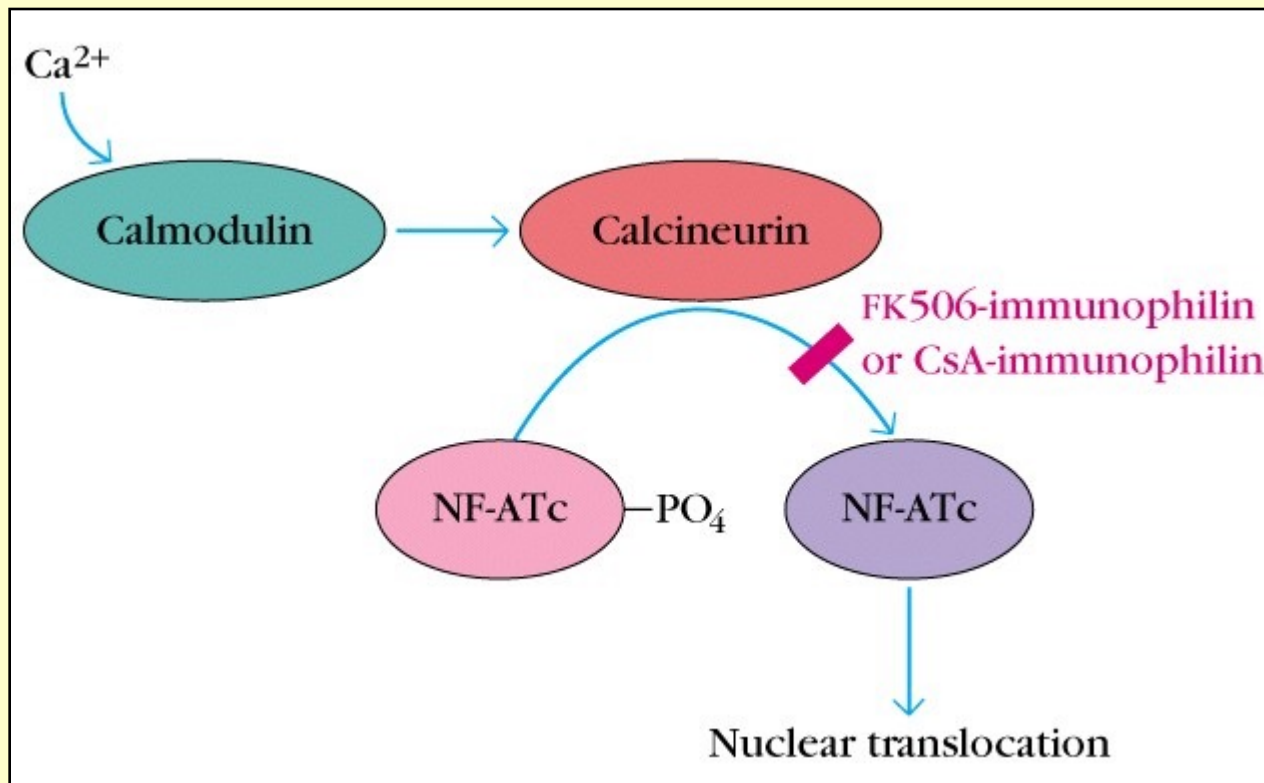
Fig. 9-7

# Möglichkeiten in der Hemmung von T-Zellen



# Mechanismus der Immunsuppression von Cyclosporin A (CsA) und FK-506:

- Immunophiline
- Blockierung der Phosphataseaktivität von Calcineurin –  
Prävention der NF-Atc-Produktion



# Beginn der Signaltransduktion im B-Zelle

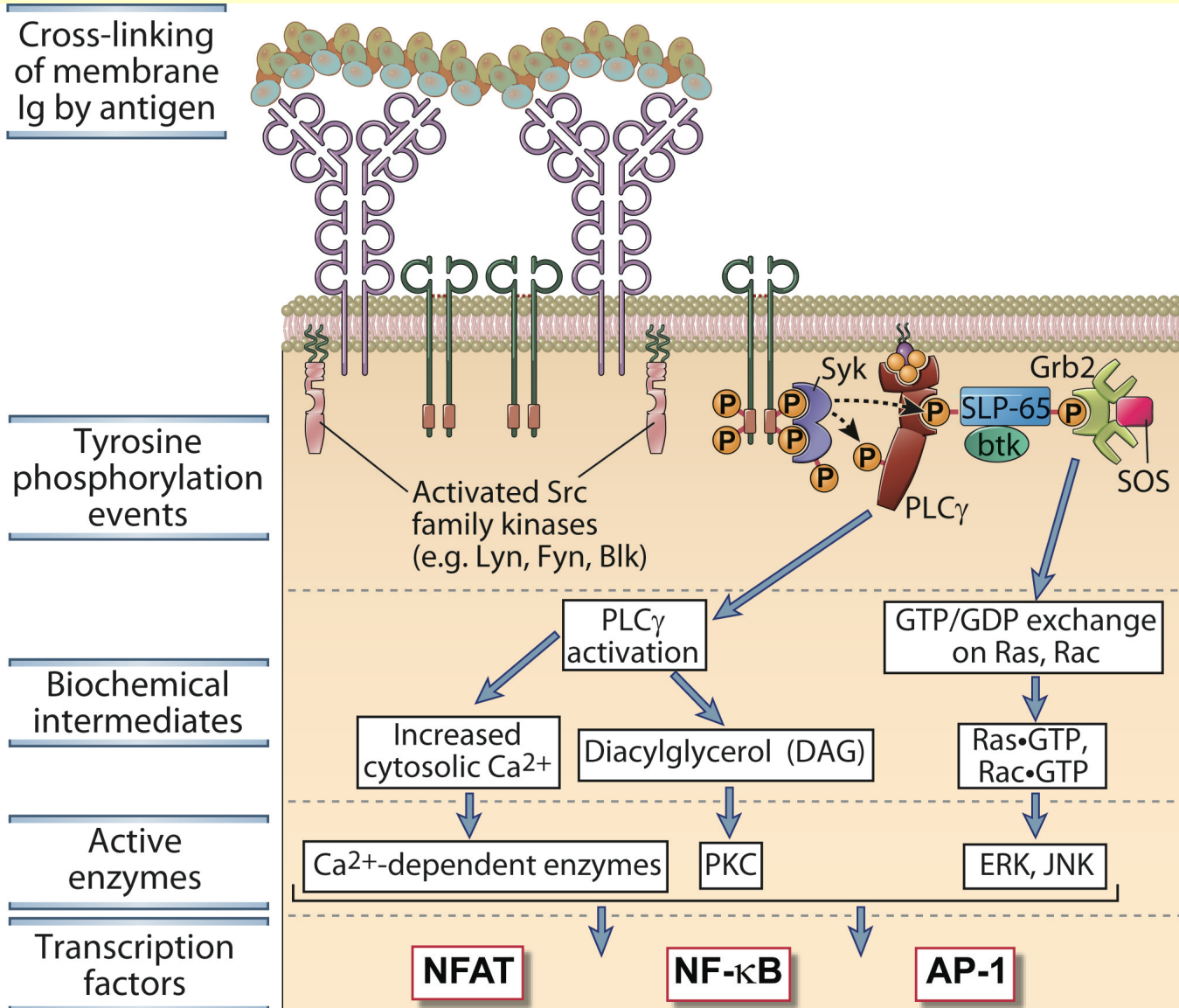


Fig. 7-19



# Beginn der Signaltransduktion im B-Zelle 2.

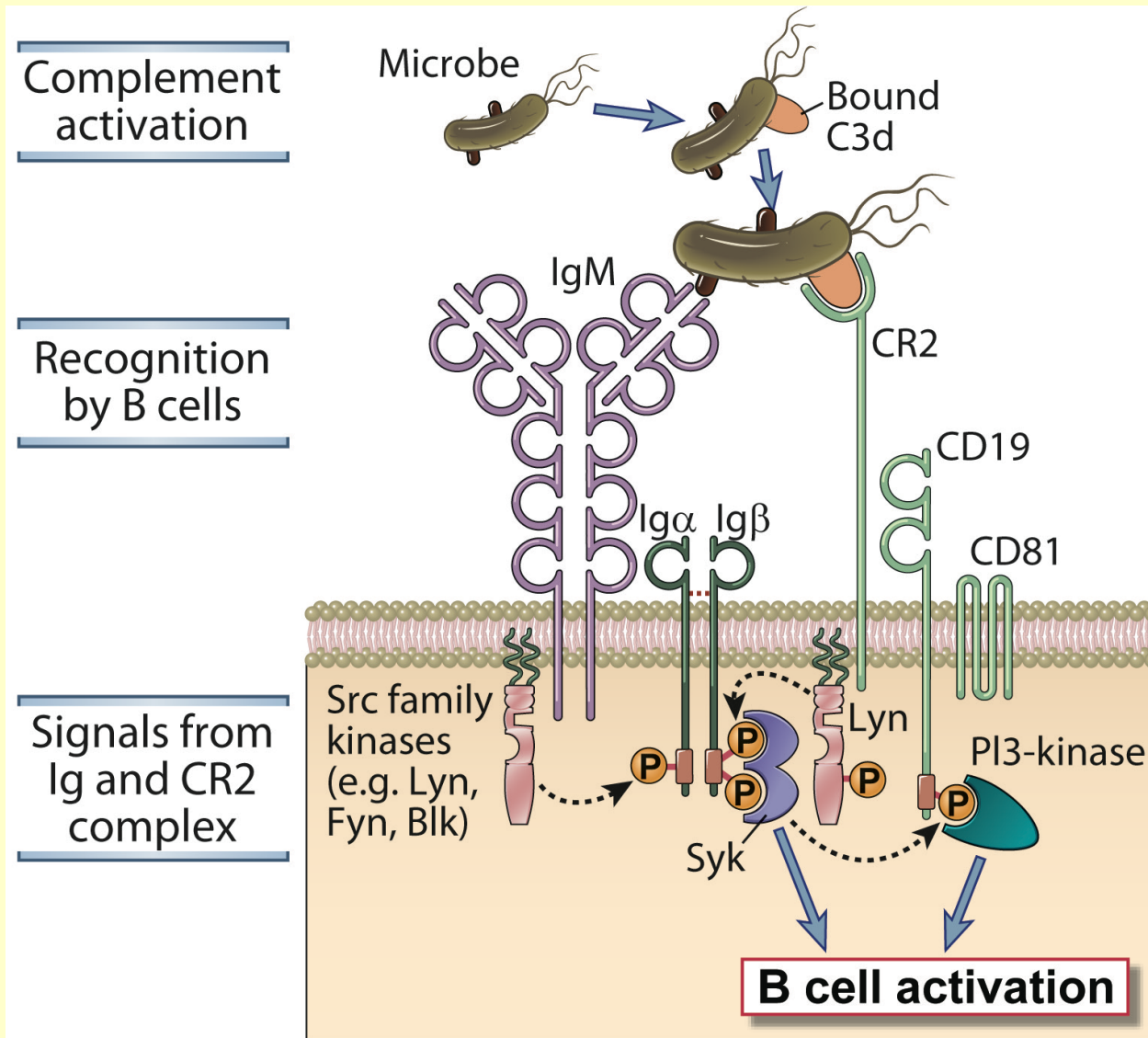
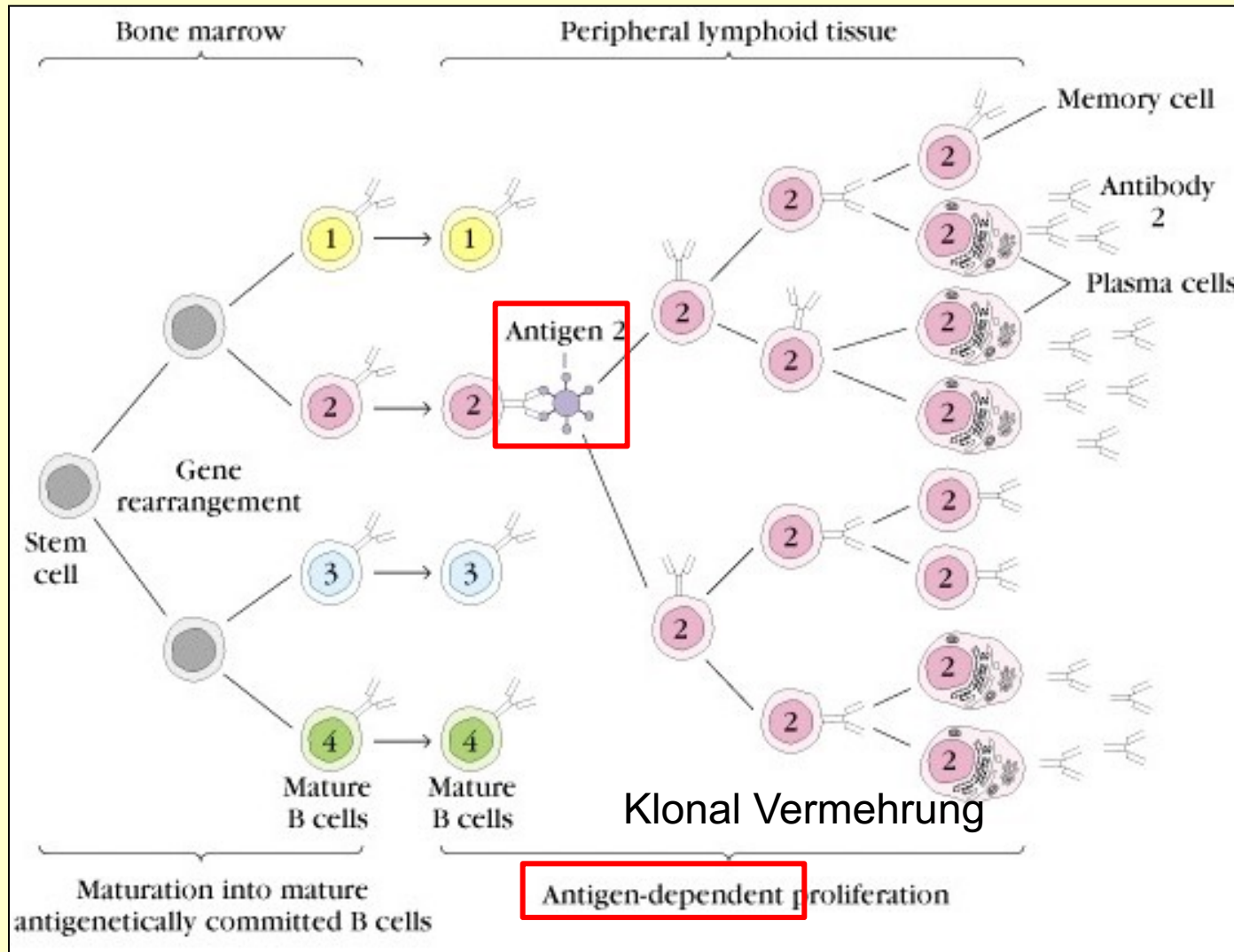


Fig. 7-20

# Peripherale B Lymphozytendifferenzierung

Primäre (Zentrale) und Peripherale Lymphozytendifferenzierung



# Follikular T<sub>H</sub>-Zelle (T<sub>FH</sub>) Induktion und Funktion

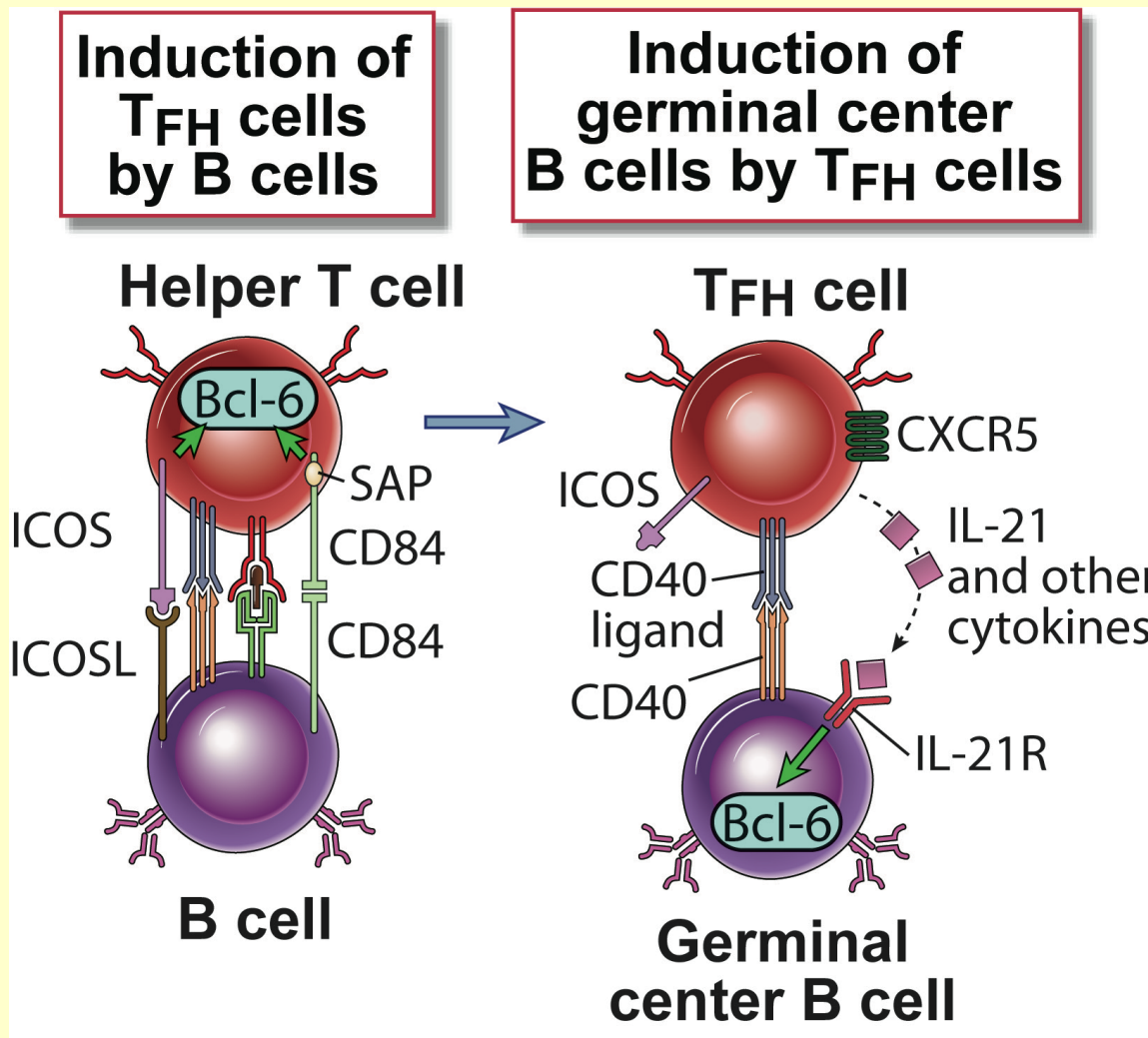


Fig. 11-13