“Kronikleşme Patogenezi”

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İstanbul Tıp Fakültesi
İnfeksiyon Hastalıkları
Ve Klinik Mikrobiyoloji Anabilim Dalı

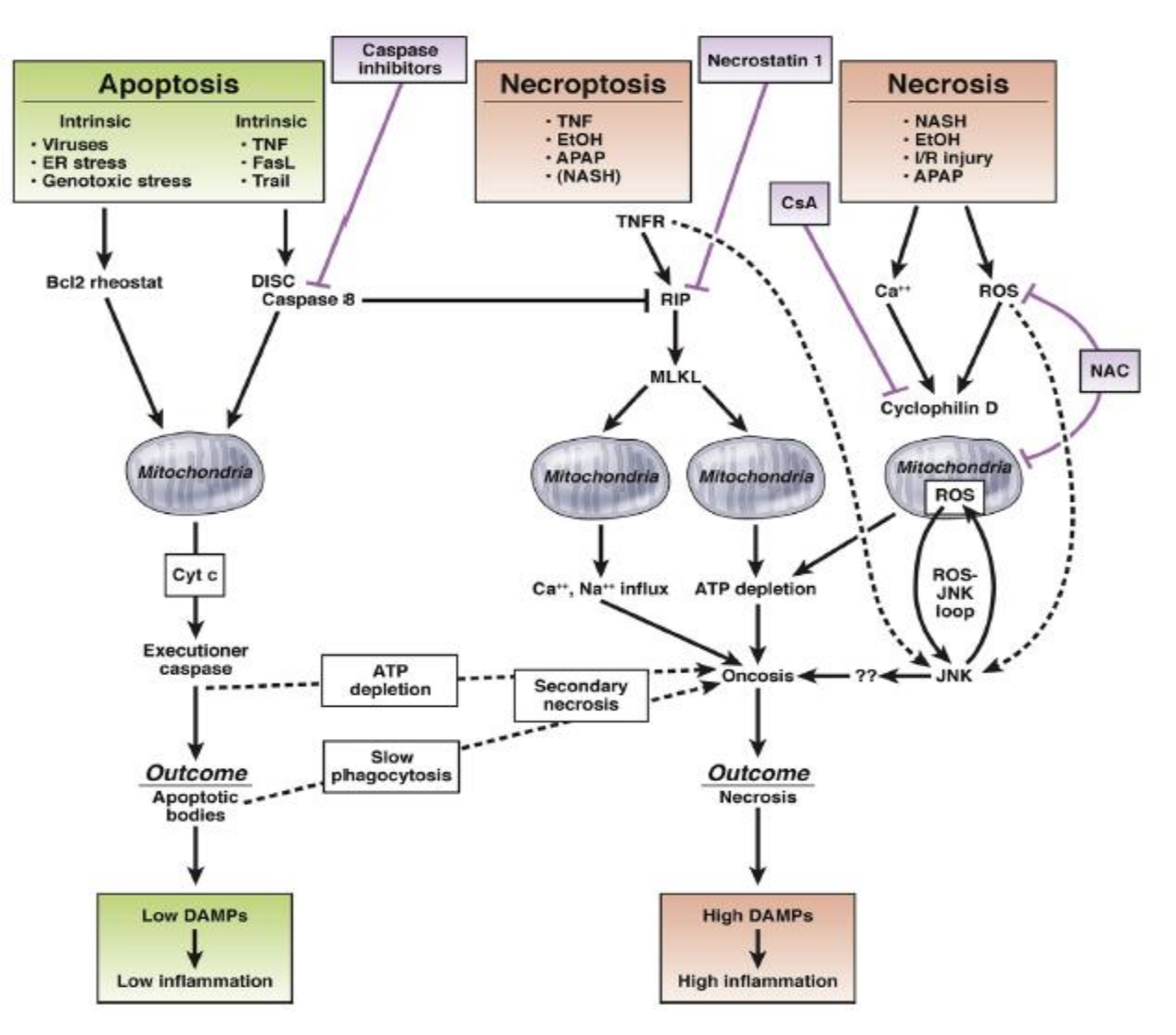
Sunum Taslağı

- HBV ve HCV Kronikleşme Sıklığı
- Kronikleşme ve Hücre Ölümü
- HBV Kronikleşme Patogenezi
- HCV Kronikleşme Patogenezi

Kronikleşme Hızı

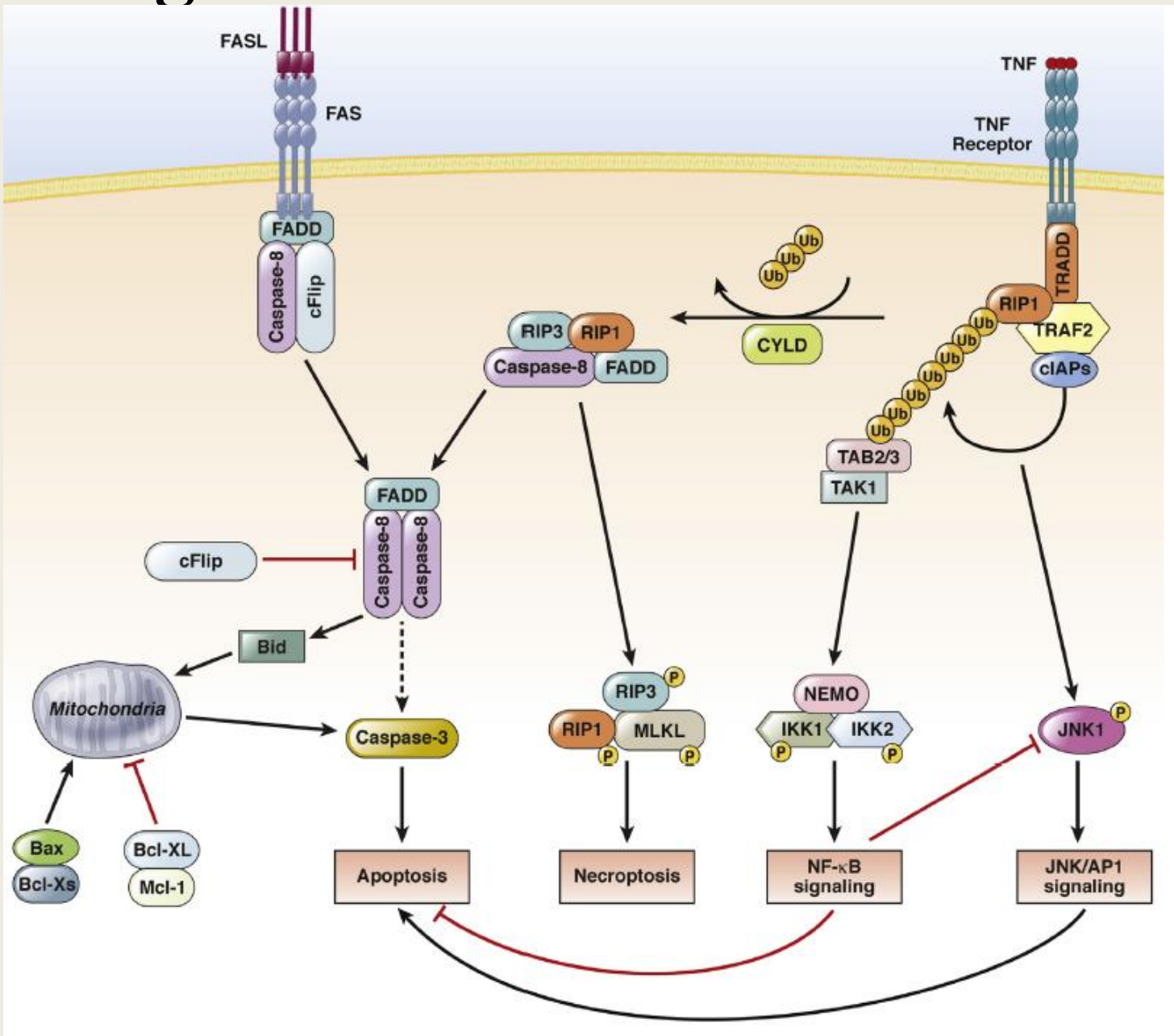
HBV	
Çocuklarda	%90
Erişkinlerde	%5-10
HCV	
Çocuklarda	%80-90
Erişkinlerde	%75-85
HDV	
Çocuklarda	%2
Erişkinlerde	%90

Karaciğerde Hücre Ölüm Modelleri



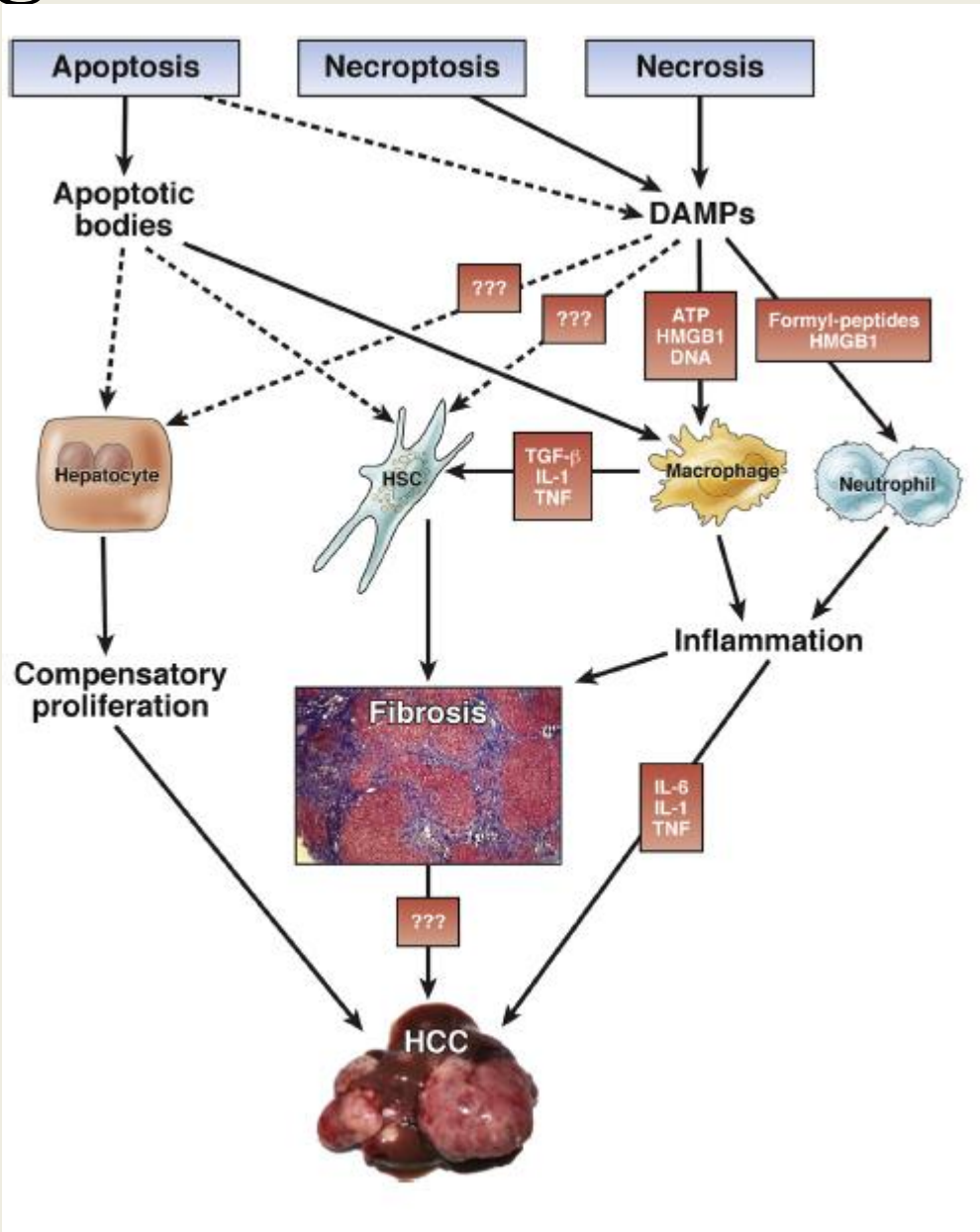
Gastroenterology 2014;147:765–783

Karaciğerde Hücre Ölüm Modelleri



Gastroenterology 2014;147:765–783

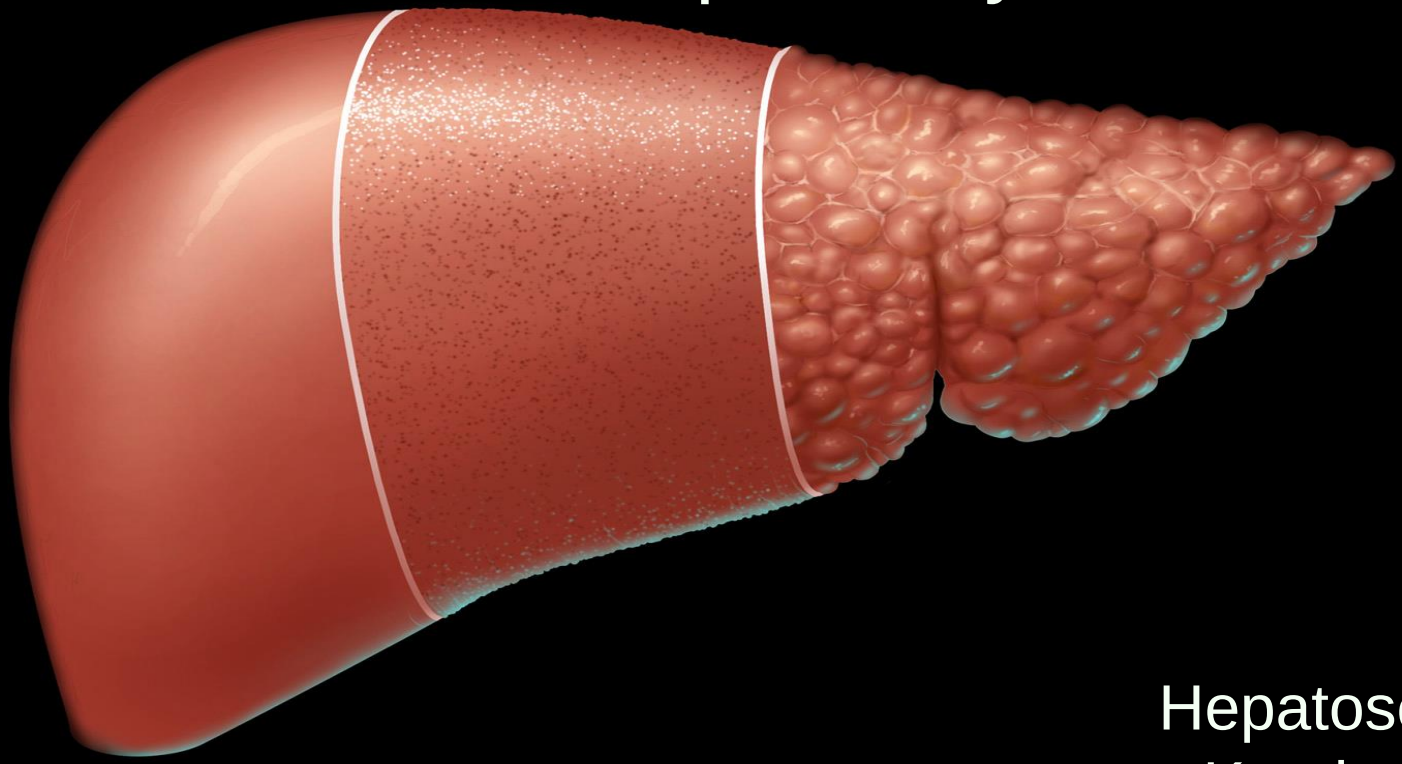
Karaciğerde Hücre Ölüm Modelleri



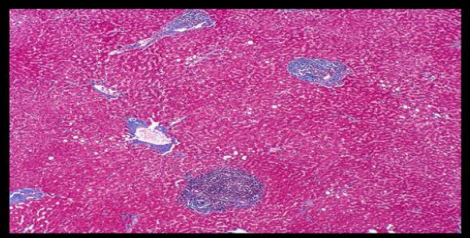
Gastroenterology 2014;147:765–783

Kronik Hepatit Seyri

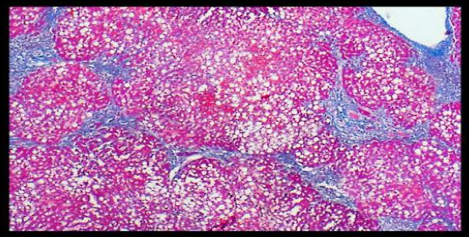
HBV
HCV
HDV



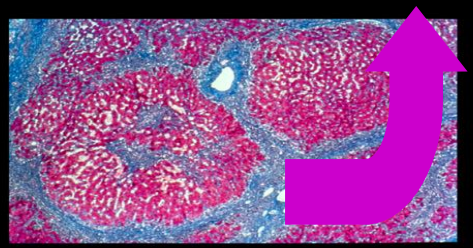
Hepatoselüler Karsinoma



Normal Karaciğer

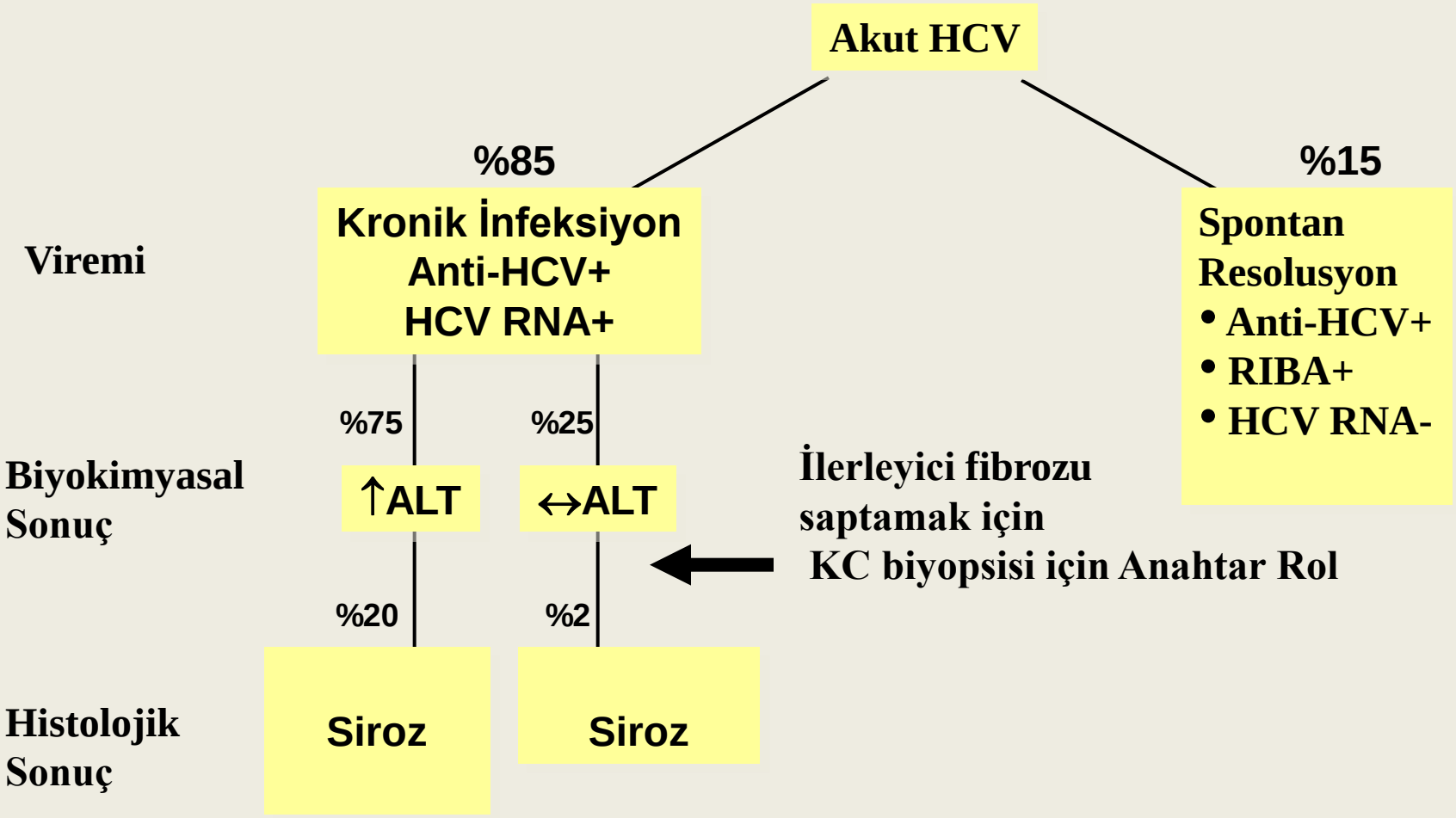


Kronik Hepatit

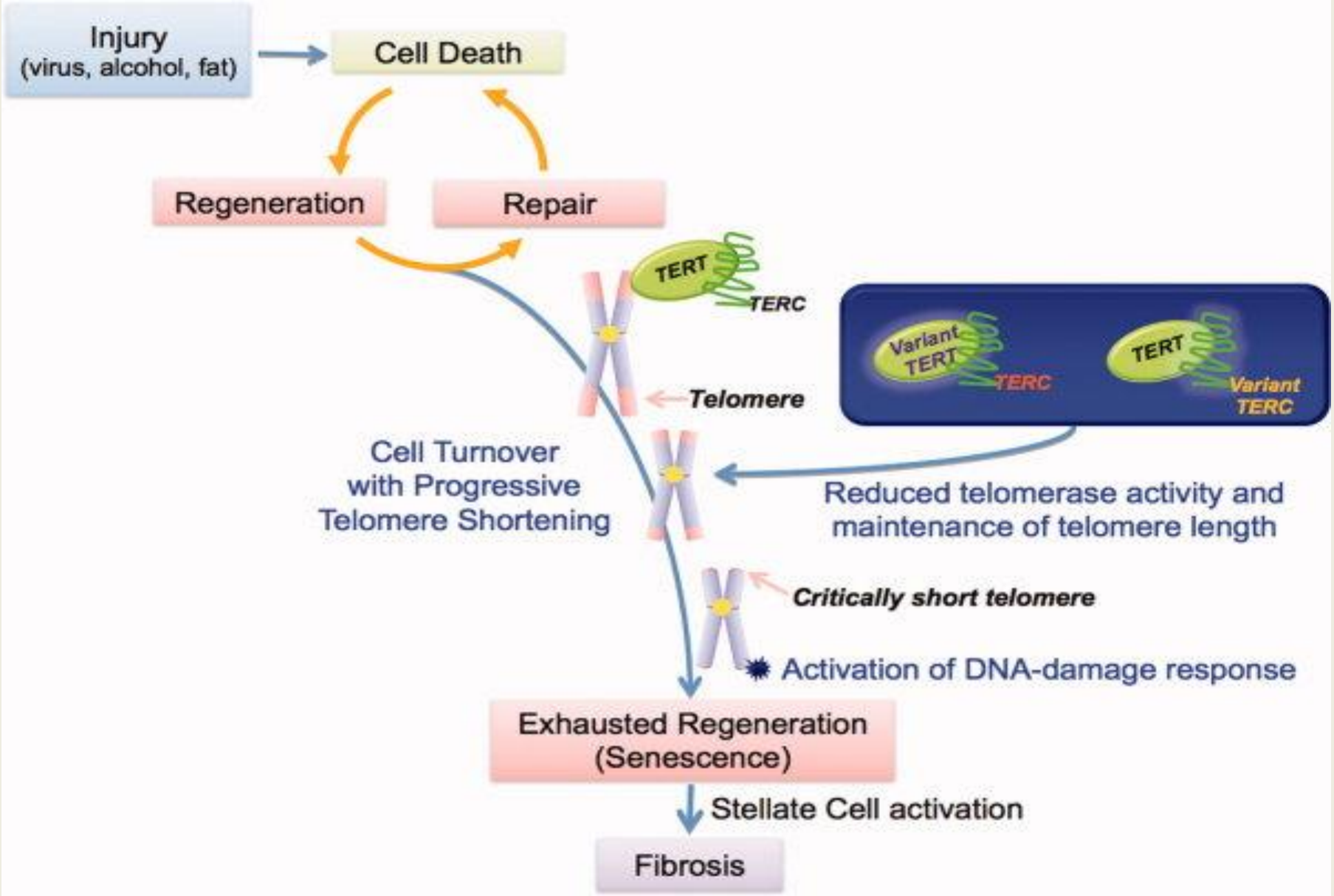


Siroz

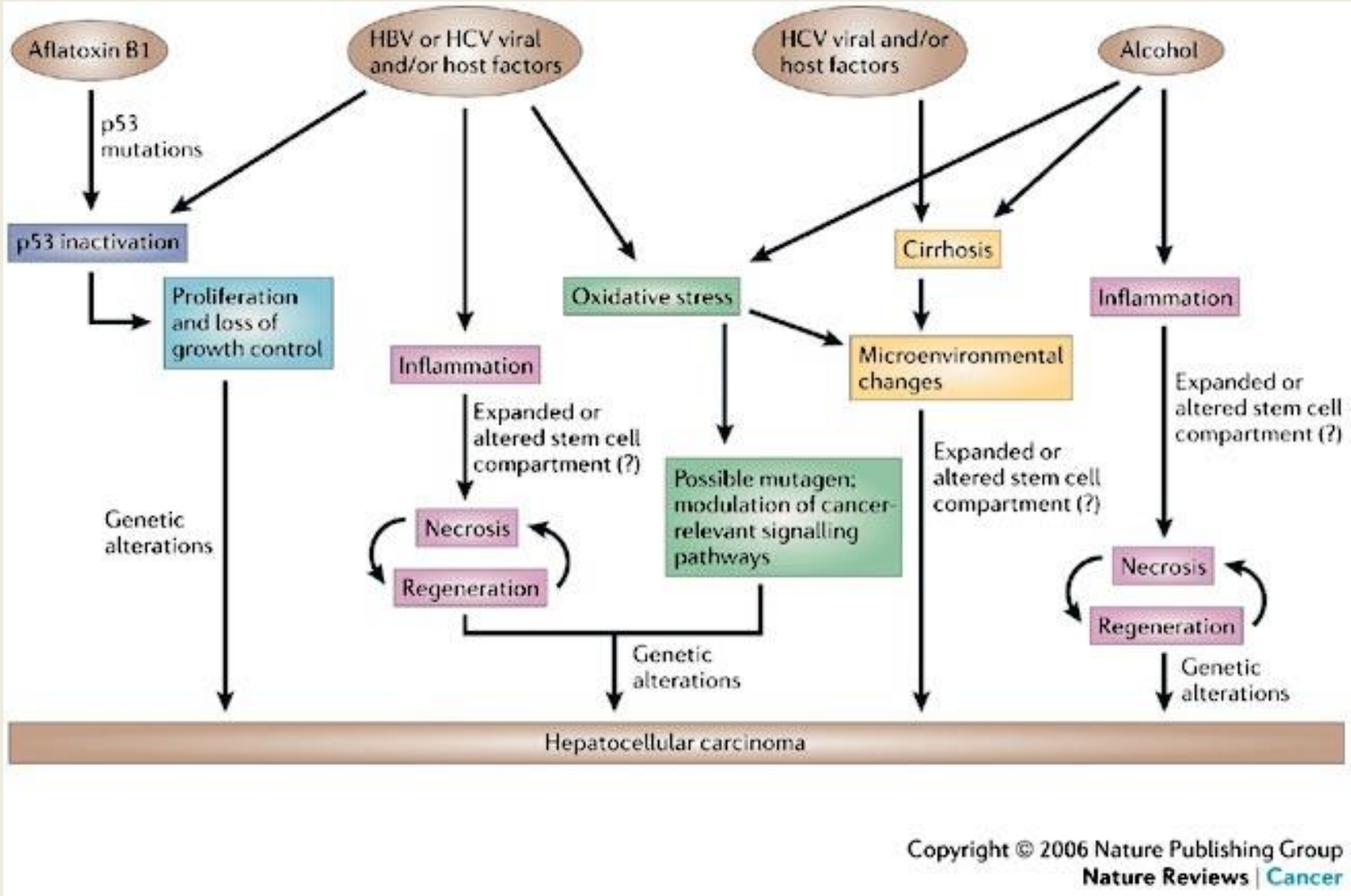
HCV İnfeksiyonunun Doğal Hikayesi



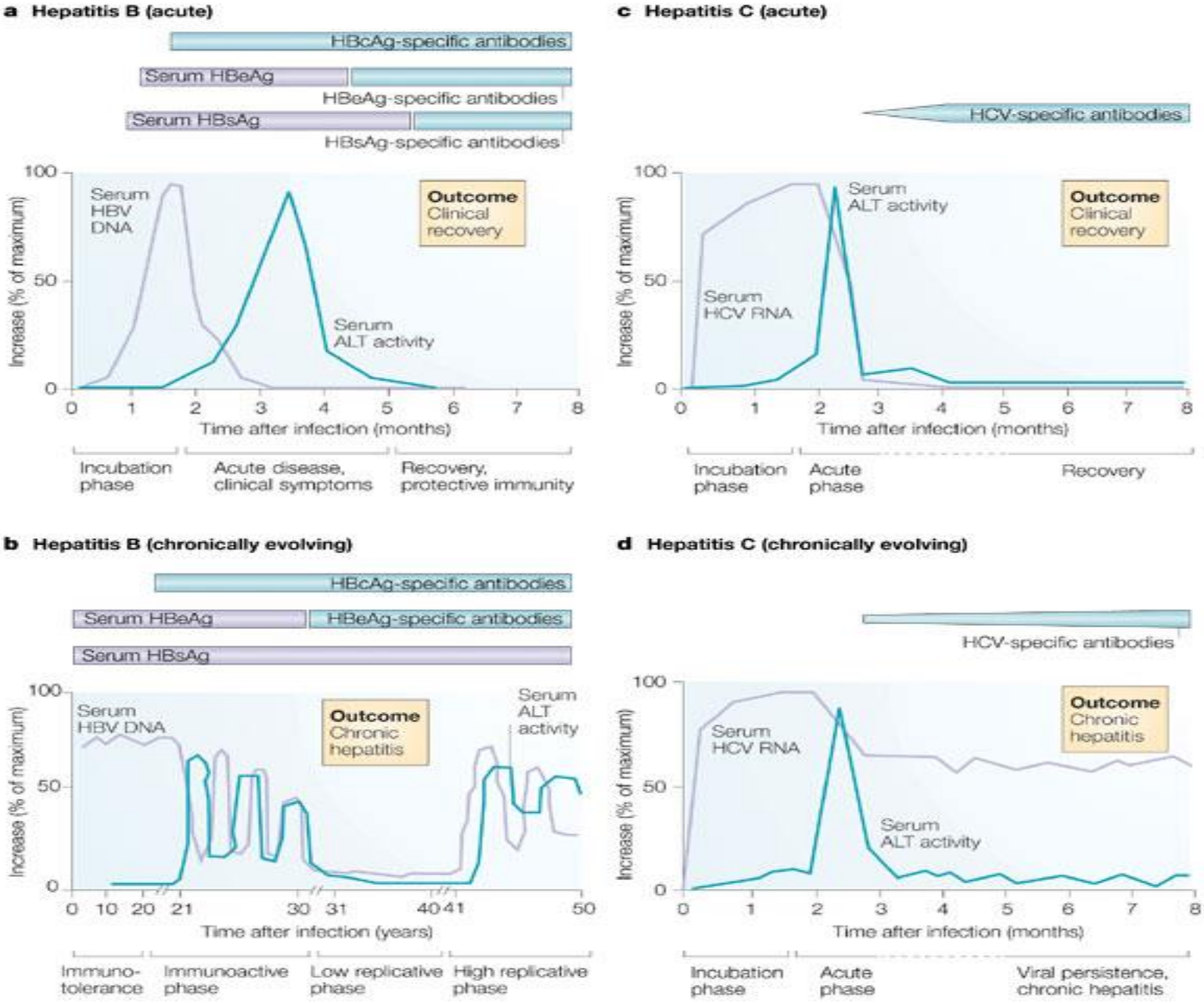
Fibroz Gelişiminde Ana Mekanizma



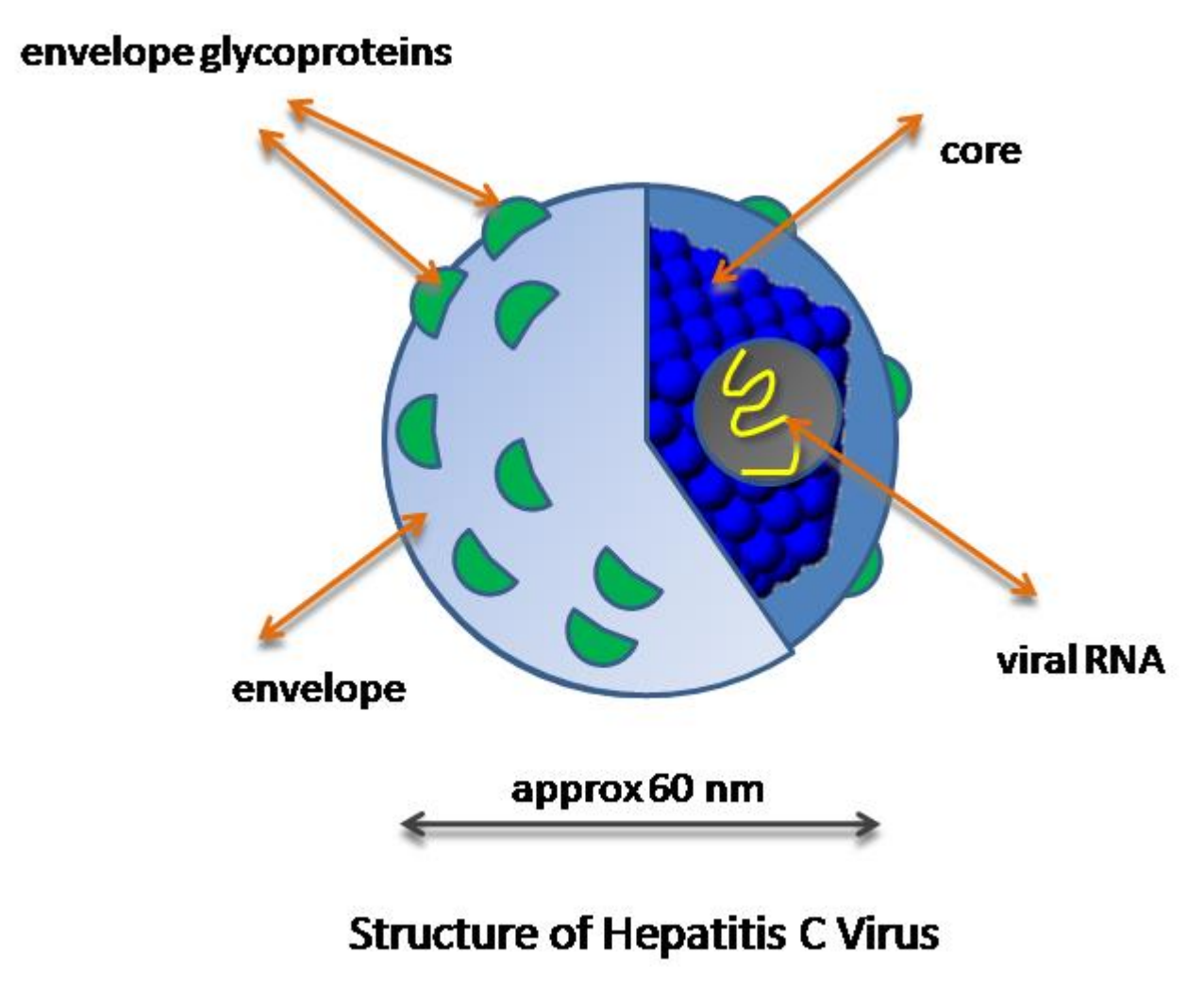
HBV ve HCV Kronik Süreci



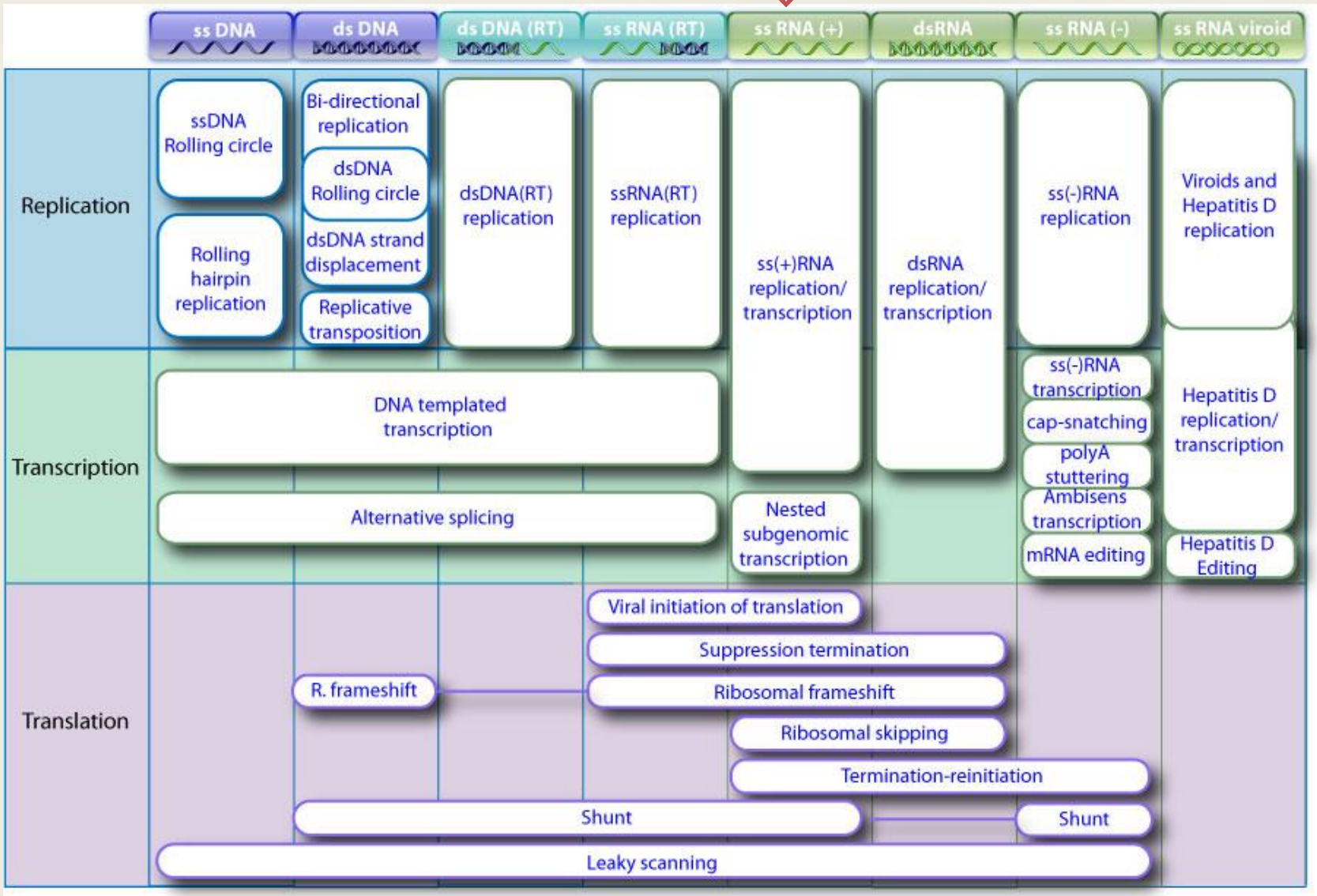
HBV ve HCV Akut-Kronik Hepatit Seyri

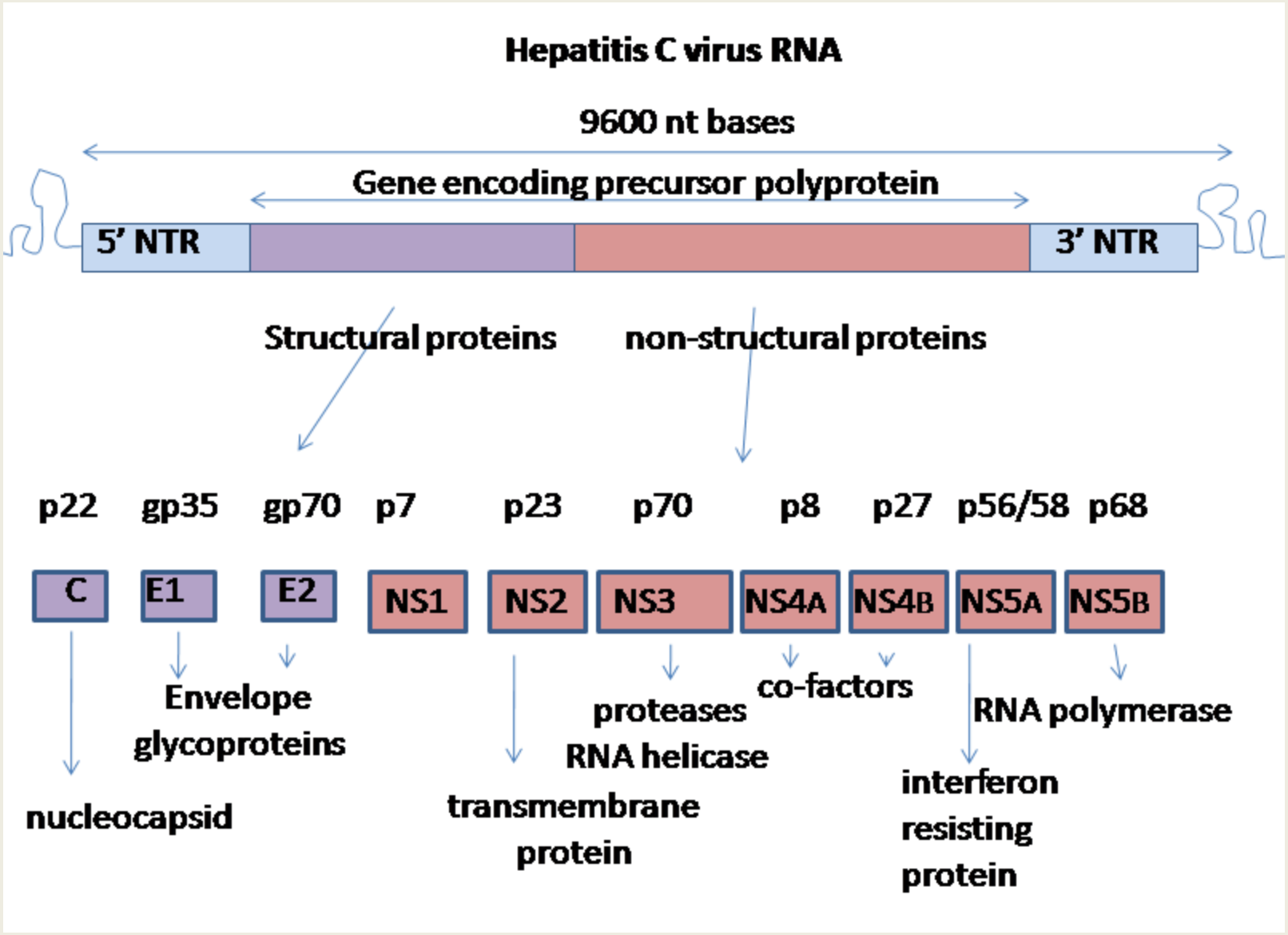


HCV Molekülü

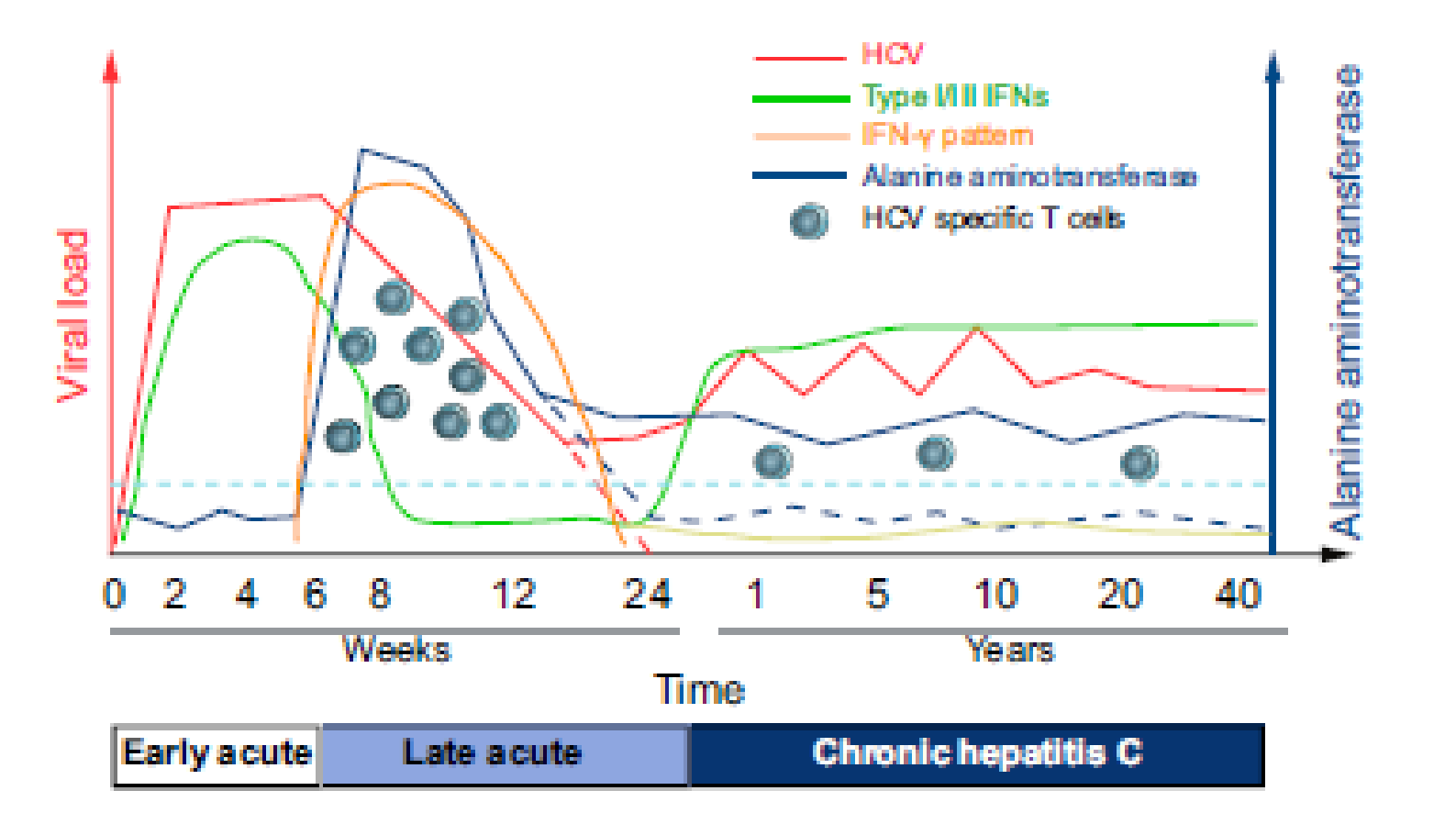


HCV


ss DNA
ds DNA
ds DNA (RT)
ss RNA (RT)
ss RNA (+)
dsRNA
ss RNA (-)
ss RNA viroid
Replication
Transcription
Translation
ssDNA Rolling circle
Rolling hairpin replication
Bi-directional replication
dsDNA Rolling circle
dsDNA strand displacement
Replicative transposition
dsDNA(RT) replication
ssRNA(RT) replication
ss(+)RNA replication/ transcription
dsRNA replication/ transcription
ss(-)RNA replication
Viroids and Hepatitis D replication
DNA templated transcription
Alternative splicing
Nested subgenomic transcription
ss(-)RNA transcription
cap-snatching
polyA stuttering
Ambisens transcription
mRNA editing
Hepatitis D replication/ transcription
Hepatitis D Editing
Viral initiation of translation
Suppression termination
R. frameshift
Ribosomal frameshift
Ribosomal skipping
Termination-reinitiation
Shunt
Shunt
Leaky scanning

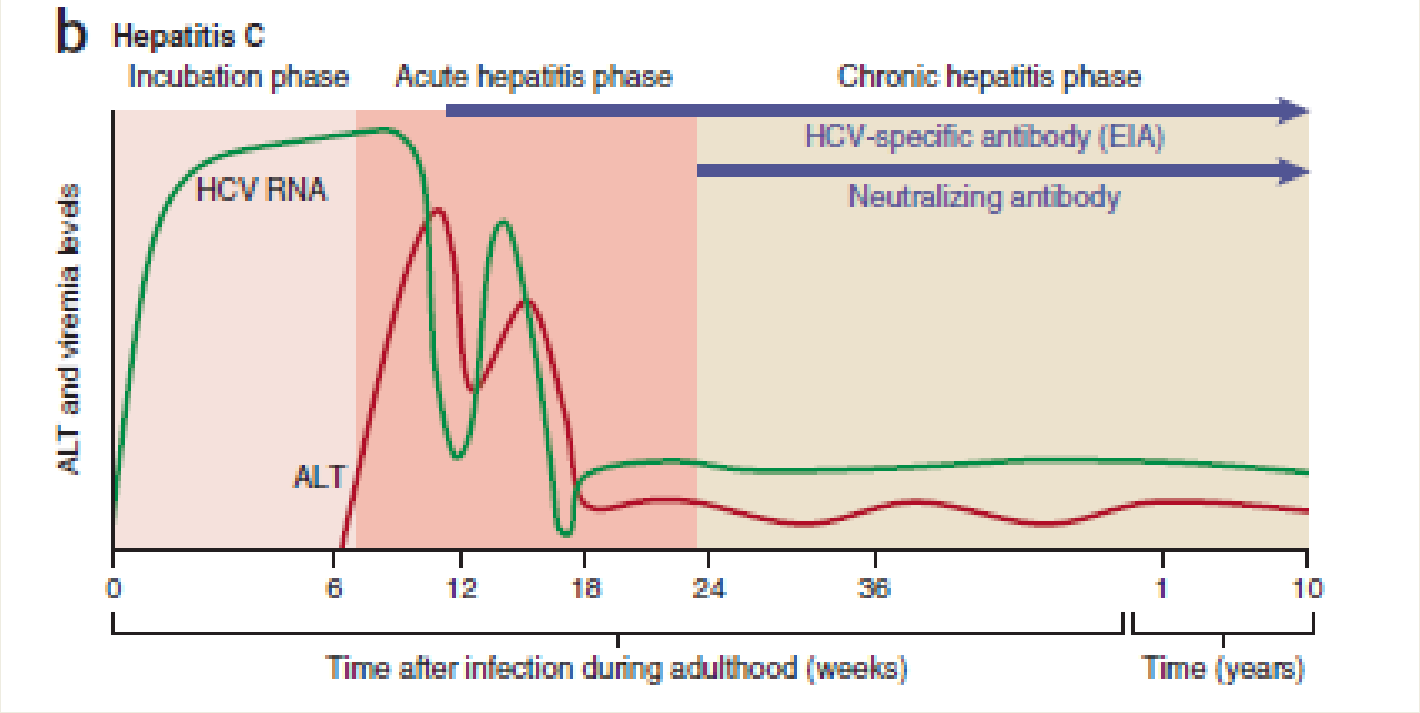

Hepatitis C virus RNA
9600 nt bases
Gene encoding precursor polyprotein
5' NTR
3' NTR
Structural proteins
non-structural proteins
p22
gp35
gp70
p7
p23
p70
p8
p27
p56/58
p68
C
E1
E2
NS1
NS2
NS3
NS4A
NS4B
NS5A
NS5B
nucleocapsid
Envelope glycoproteins
transmembrane protein
proteases
RNA helicase
co-factors
interferon resisting protein
RNA polymerase

HCV İnfeksiyonunun Doğal Seyri



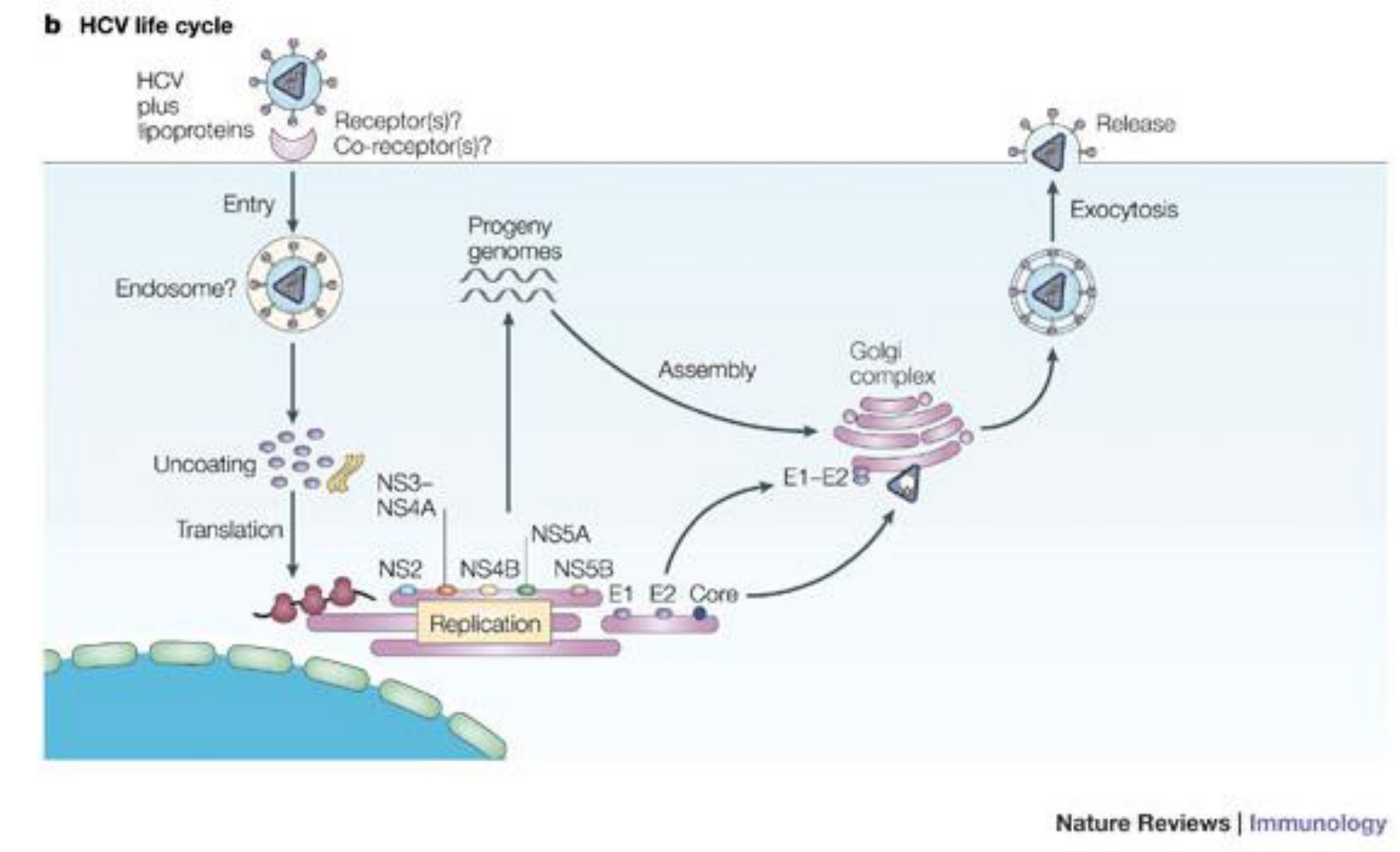
Journal of Hepatology 2014 vol. 61 j S14–S25

HCV İnfeksiyonunun Seyri

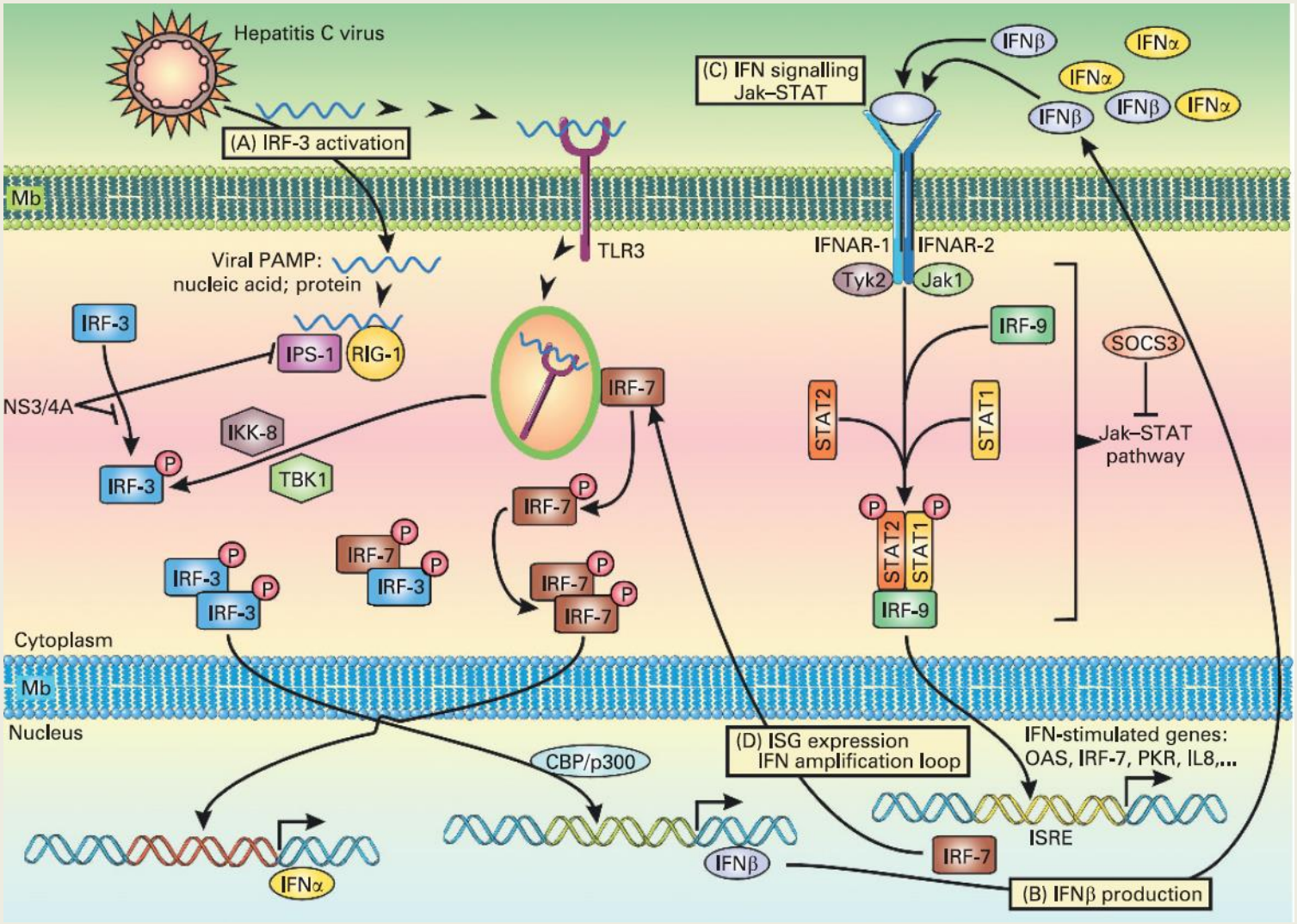


Nature Medicine, 2013;19 (7): 859-69

HCV İnfeksiyonunun Seyri

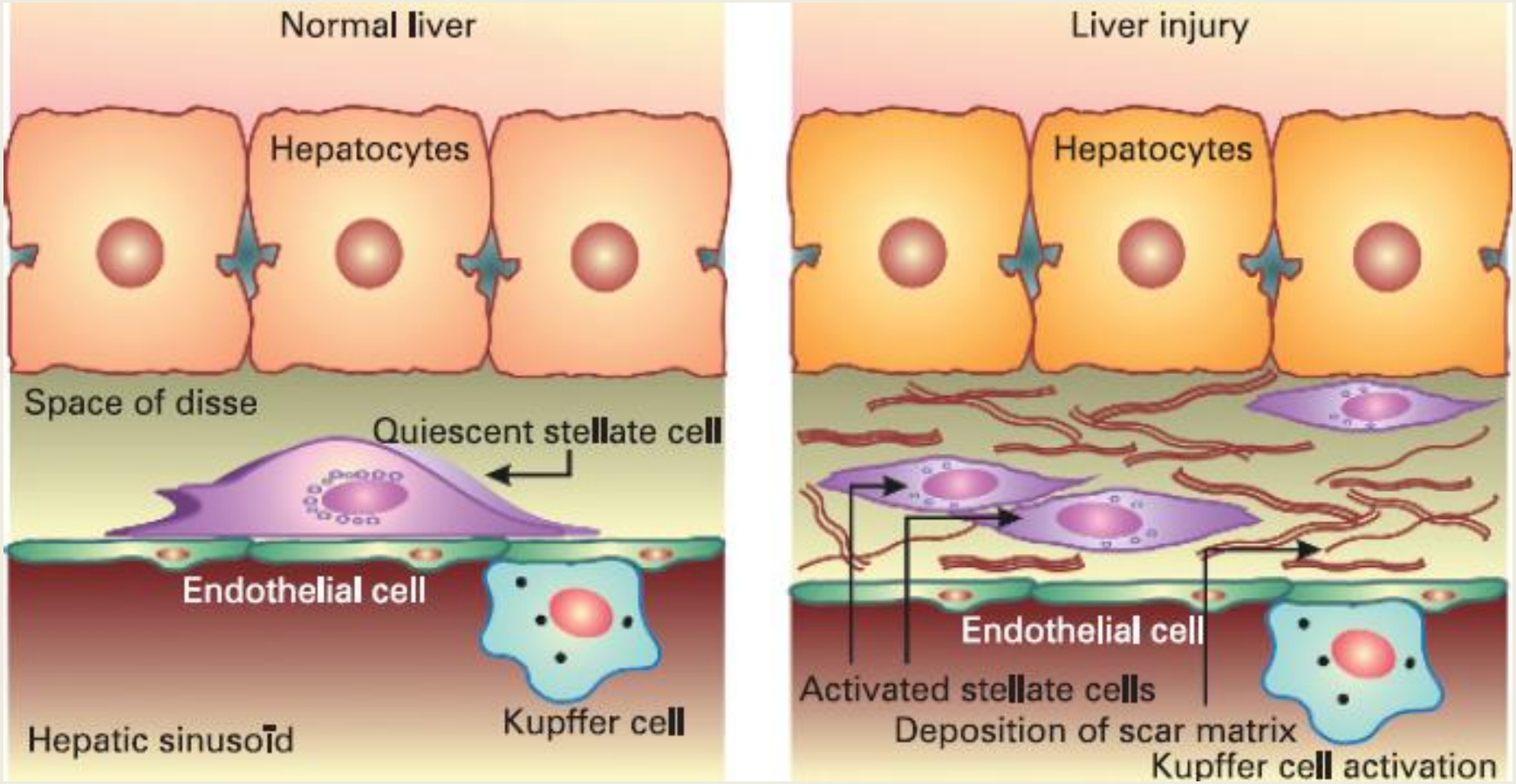


HCV ve Doğal İmmünite



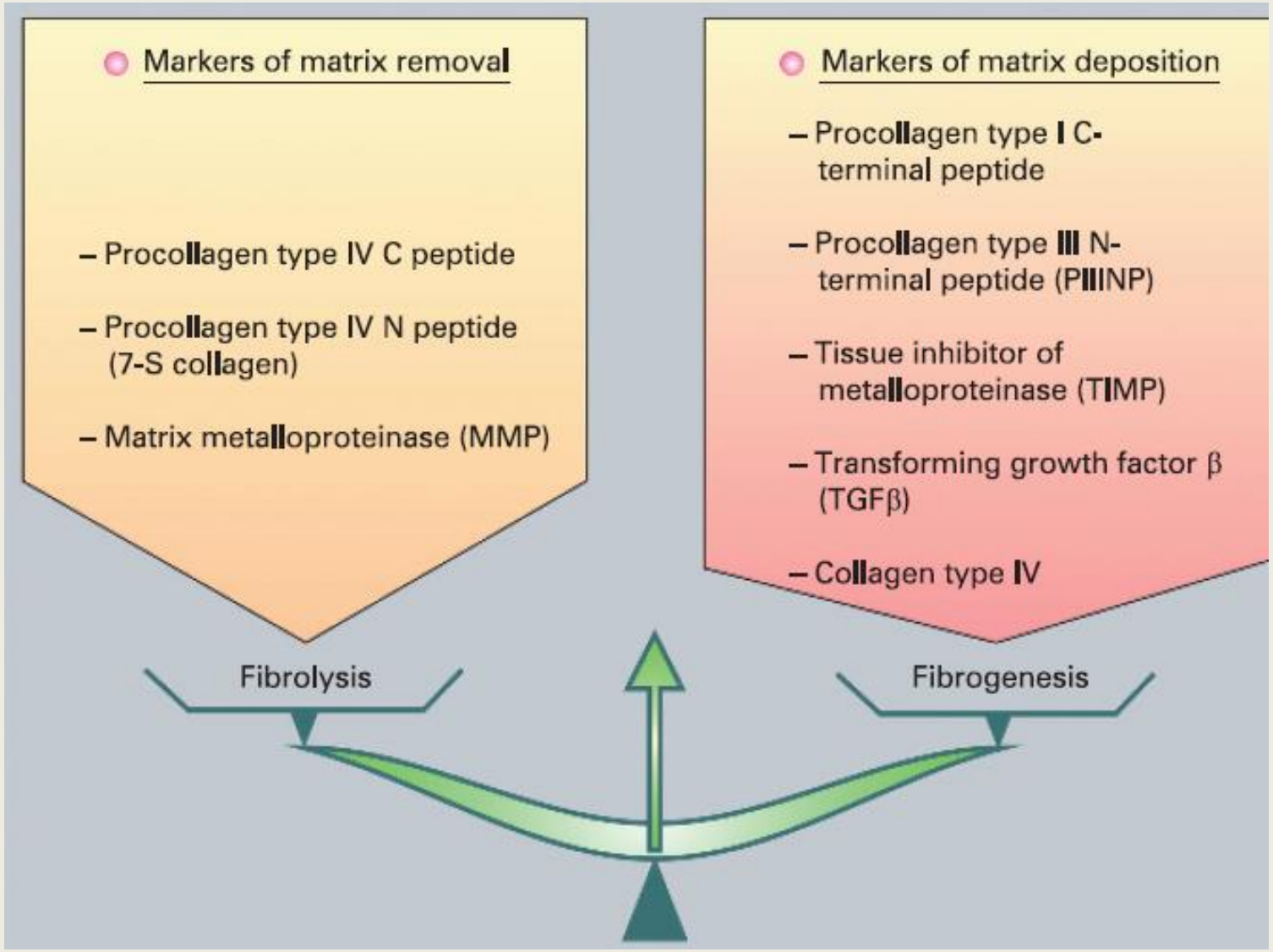
Gut 2009;58:846–858

‘’Stellate’’ Hücreleri ve Fibroz



Gut 2009;58:846–858

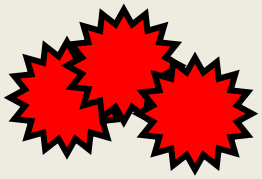
Fibroz Gelişimi



Gut 2009;58:846–858

HCV Patogenezi

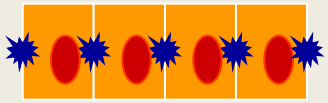
Infeksiyon mu Hastalık mı?



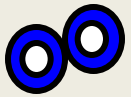
HCV

Farklı hücreleri infekte eder

Hepatosit

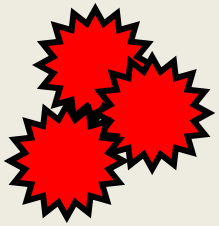


Lenfosit



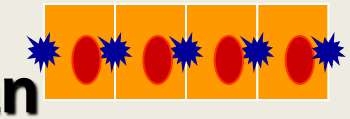
B hücreleri T hücreleri

Diğer Dokular:
Pankreas, Adrenal bez, Kemik iliği



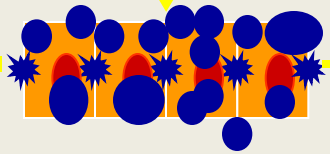
HCV

Hepatositler için sitopatik olmayan



Immün Yanıt

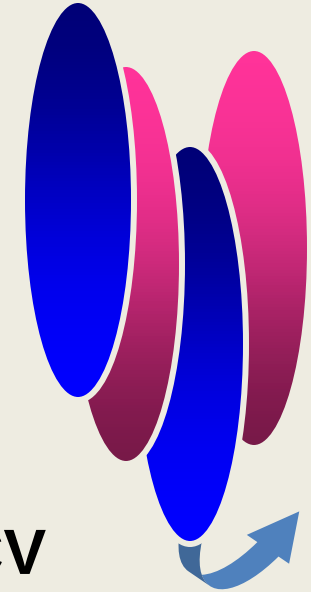
Minimal Fibroz



İleri Fibroz

HCV İnfeksiyonunun İmmünopatogenezi

HCV Antijenlerine Karşıt Hücre Aktivasyonu



HCV

- Core 21-40
- NS3 1253-1272
- NS3 1767-1286
- NS4 1909-1229

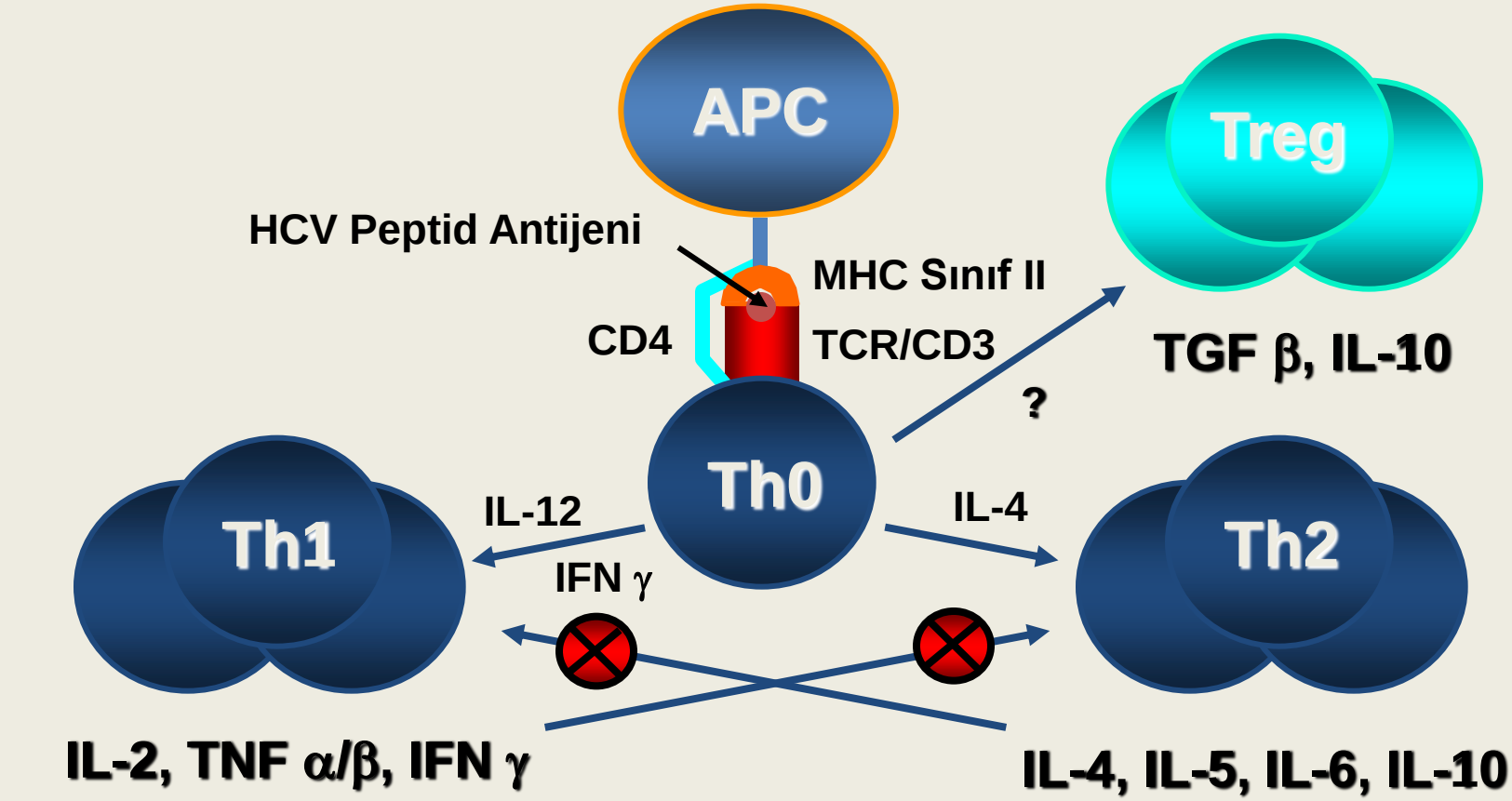
Sınıf II HLA

İmmün Yanıt

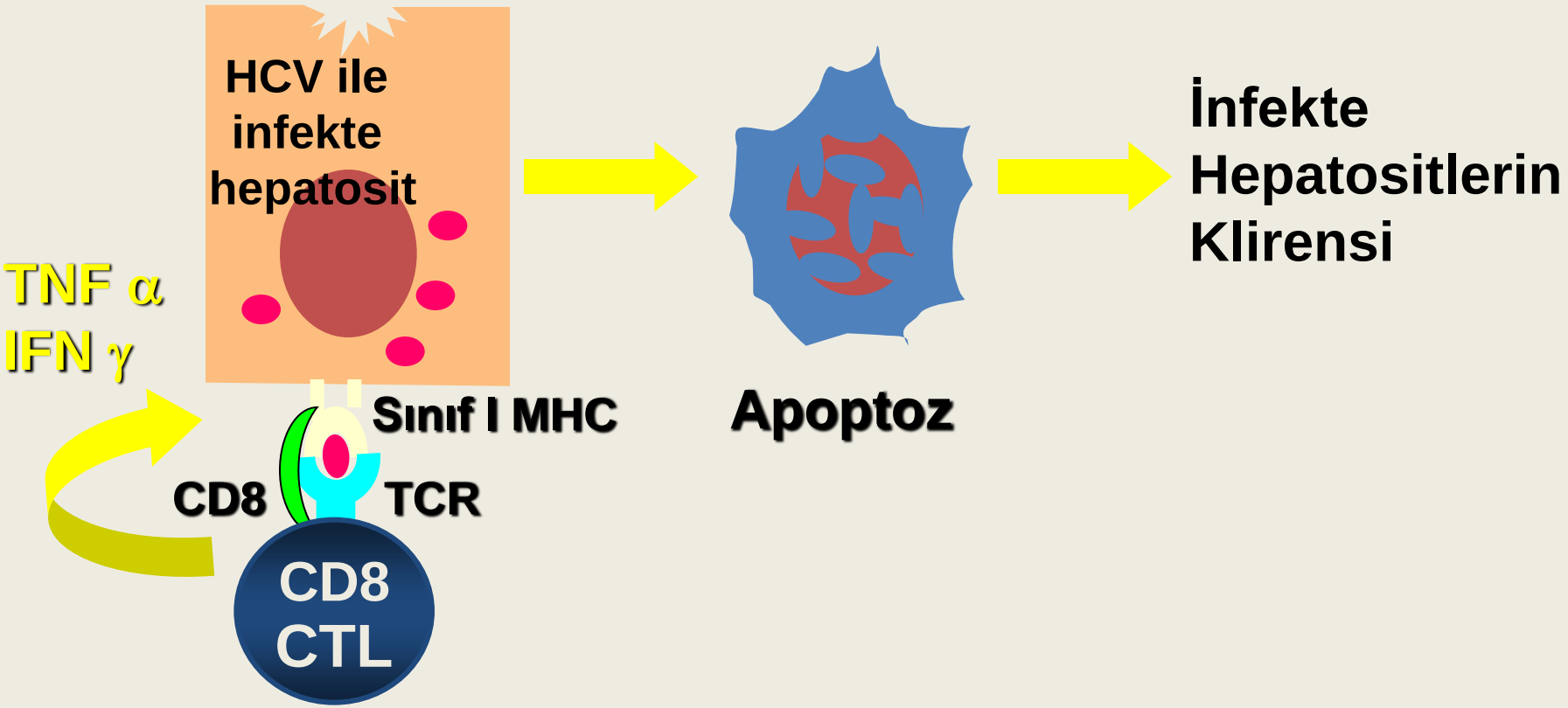
- Etkin
- Poliklonal
- Multispesifik

Sınıf I HLA

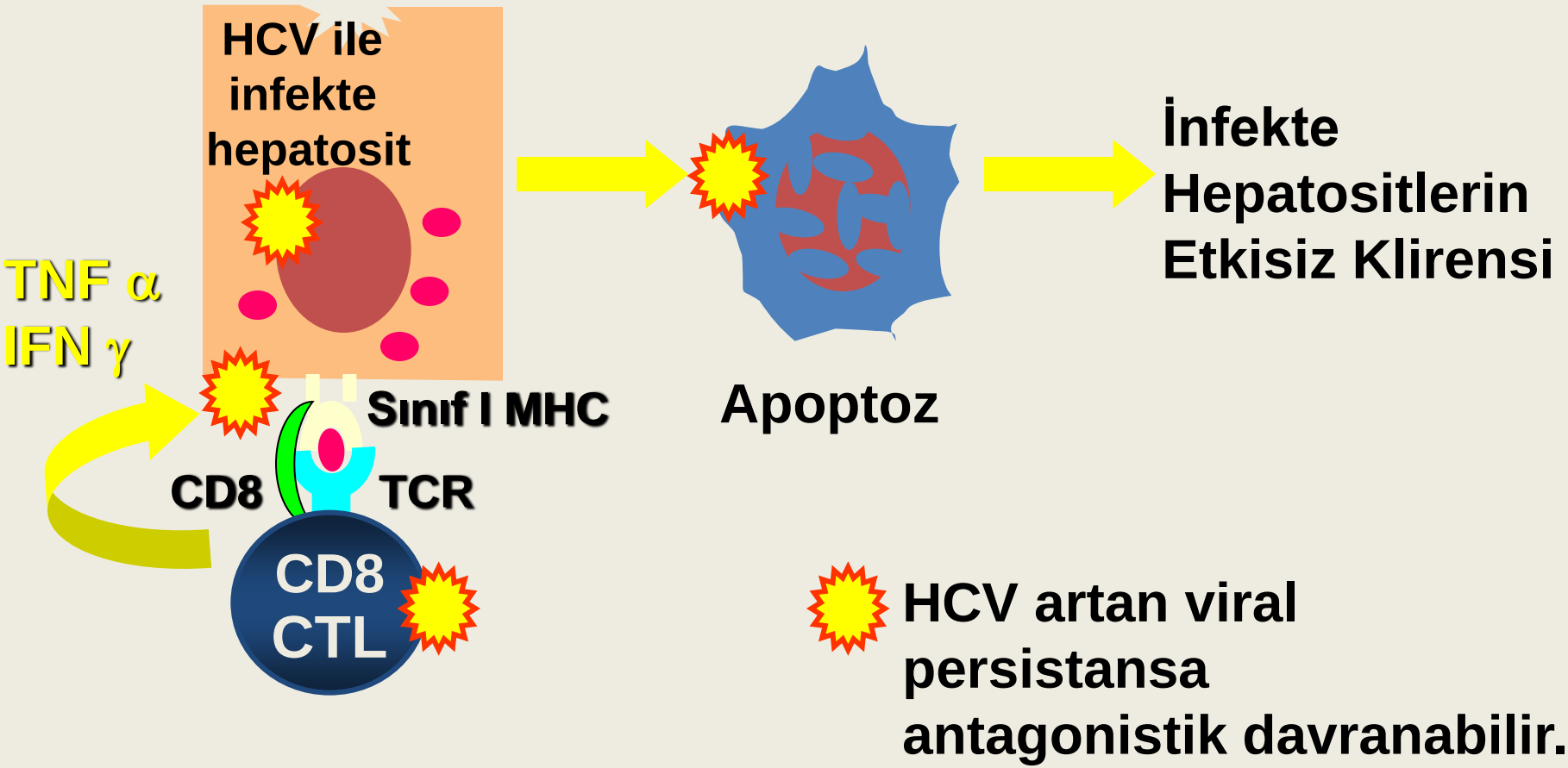
HCV İnfeksiyonunun İmmünopatogenezi
CD4 T-Helper Hücrelerinin Dinamik Dengesi



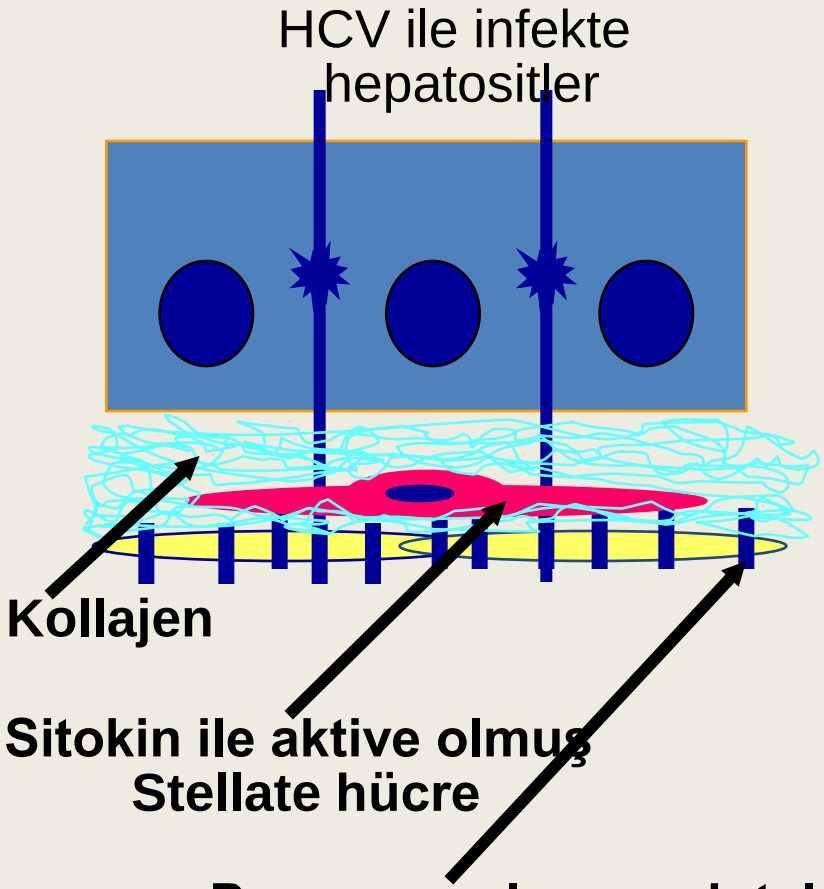
HCV'nin İmmünite Aracılığı ile Temizlenmesi



HCV'nin İmmünite Aracılığı ile Temizlenmesi



HCV İnfeksiyonu
Karaciğer Fibrozunun Interferon-α ile inhibisyonu



Antifibrotik Mekanizmalar

↓ mRNA Ekspresyonu:
- **TGF-β**
- **Prokollajen tip I**
- **Prokollajen III**
- **Prokollajen IV**

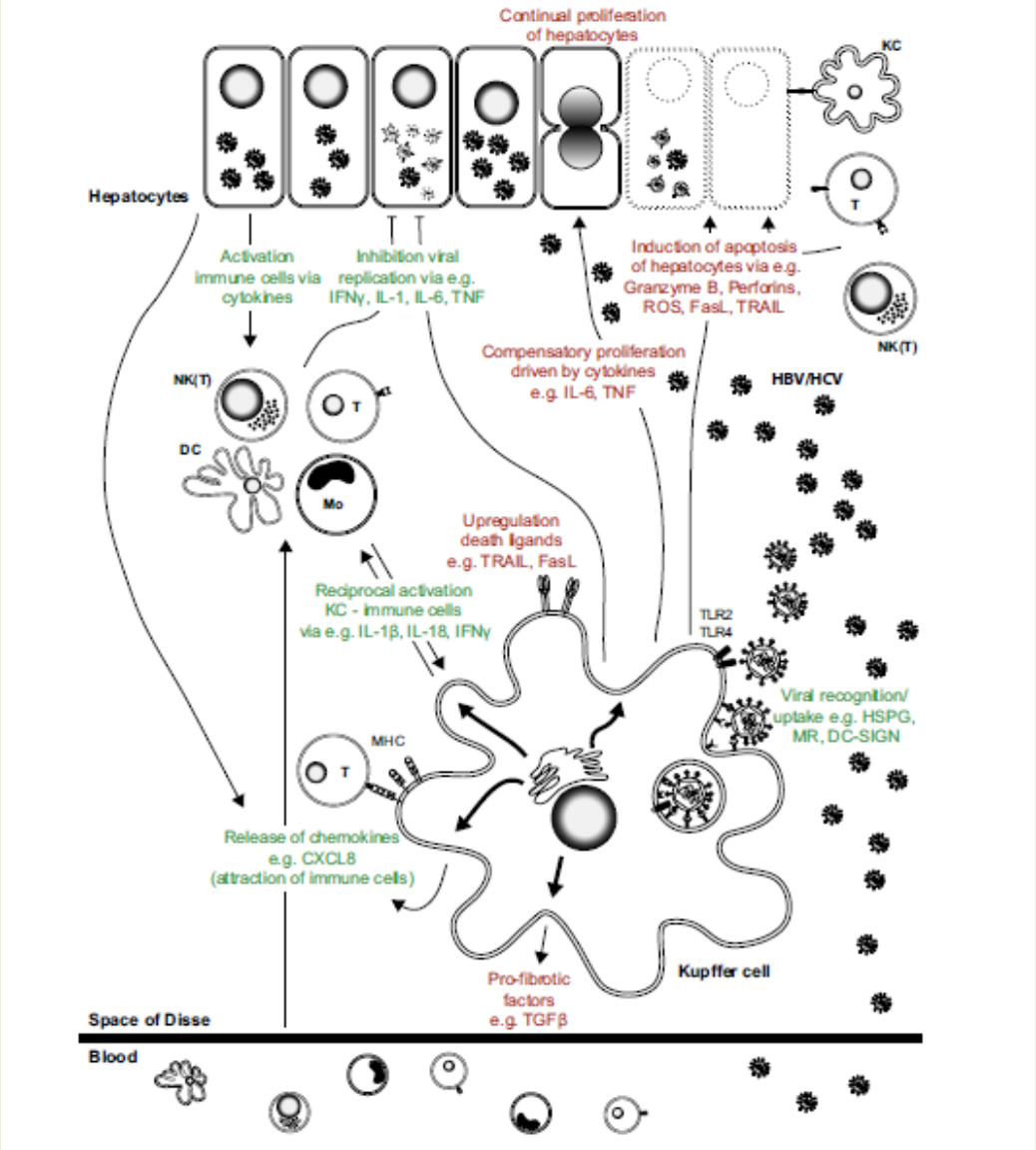
↓ Serum Seviyeleri:
- **Prokollajen tip III peptid**
- **Hyaluronik asit**
- **TIMP-1**

– mRNA Ekspresyonu:
- **Collagenase**
- **MMP**

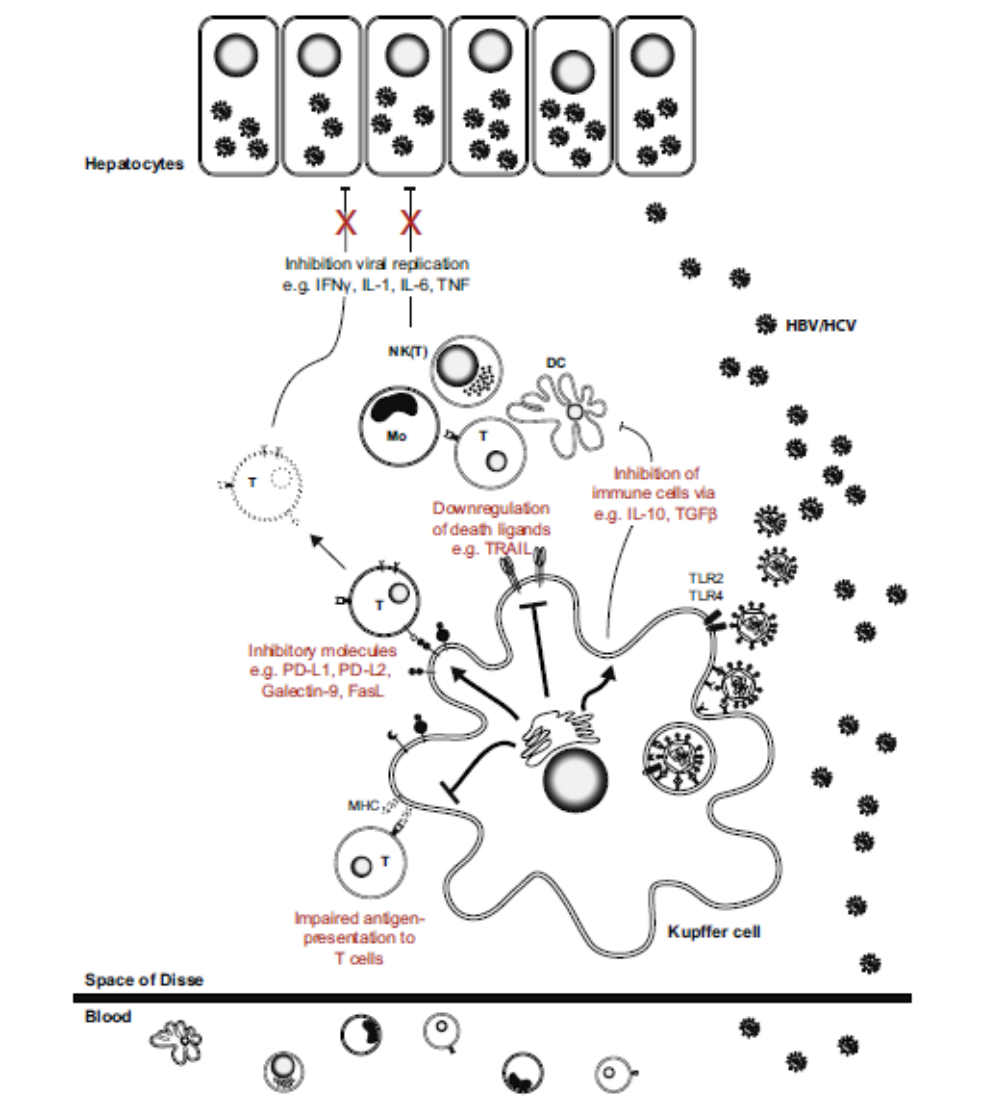
Kupffer Hücreleri ve HBV-HCV: Kronikleşme

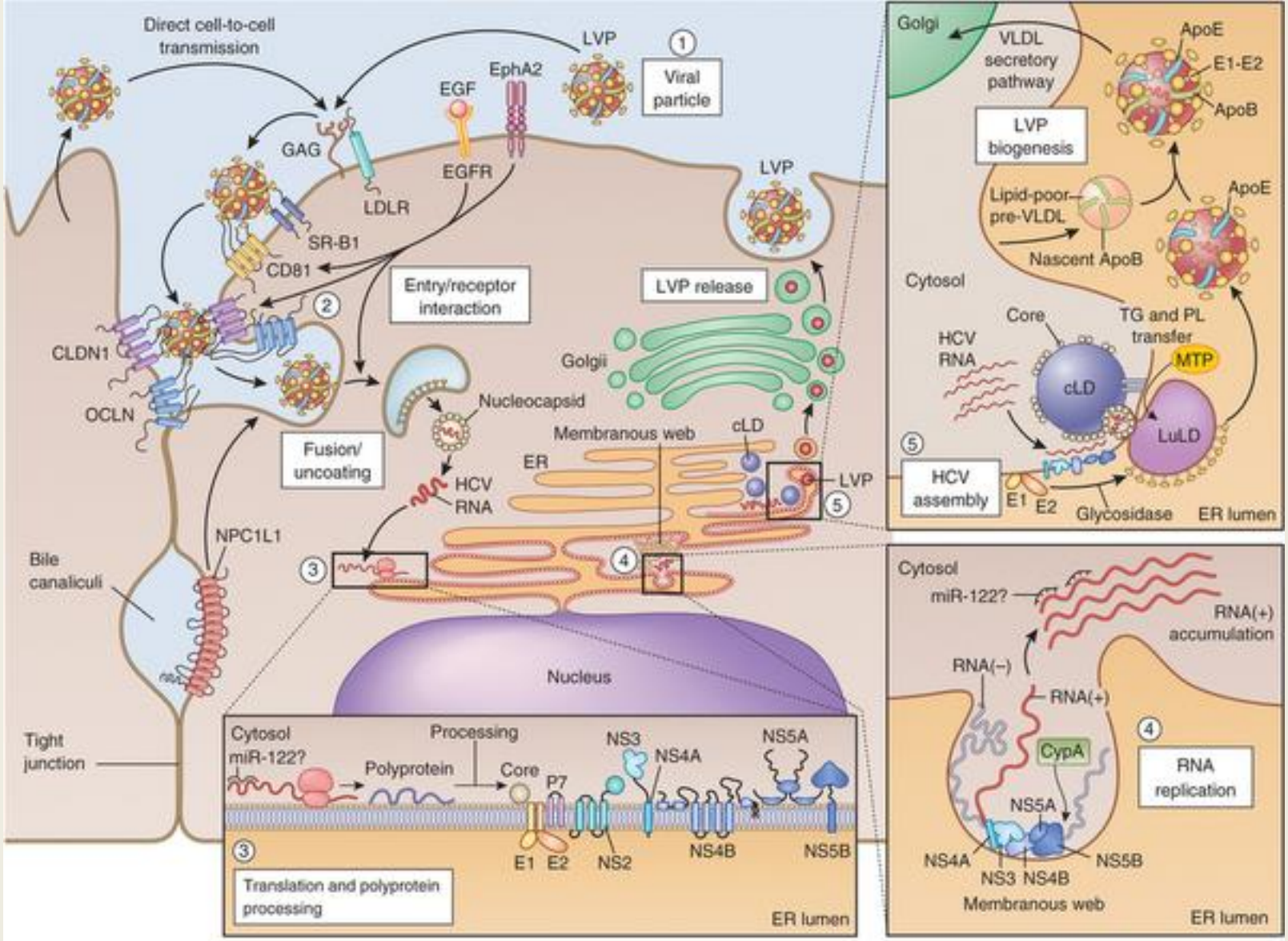
	HBV		HCV	
	Mediators	[Ref.]	Mediators	[Ref.]
Binding/uptake				
	HSPG	[79]	HSPG	[79]
	CD14	[9]	SR-B1	[82]
	mannose receptor	[69]	LDL-receptor	[81]
			DC-SIGN	[9, 85]
Pattern recognition receptors				
			TLR2	[84, 87]
			TLR4	[88]
Cytokines				
	IL-1β	[89]	IL-1β	[84, 100]
	IL-6	[89]	TNF	[84]
	TNF	[89]	IL-10	[84]
	TGFβ	[91]		
Chemokines				
	CXCL8	[89]		
Co-stimulatory molecules				
			CD40	[94]
			CD80	[94]
			MHC class II	[94]
Immune inhibition or promotion of tolerance				
	TGFβ	[91]	PD-L1	[84, 137]
	PD-L2	[30]	IL-10	[84]
	galectin-9	[135]	galectin-9	[120]
Liver damage				
	IL-6	[89]	TRAIL	[84]
	TRAIL	[84]	granzyme B	[105, 106]
	FasL	[106]	perforin	[105, 106]
	granzyme B	[105]		
	perforin	[105]		
	ROS	[54]		
	galectin-9	[135]		
	TGFβ	[91]		

Kupffer Hücreleri ve HBV-HCV: Kronikleşme



Kupffer Hücreleri ve HBV-HCV: Kronikleşme





Points of intervention in the HCV life cycle

① The viral particle (neutralizing antibodies, virocidal peptides)

② Entry and receptor interaction (antibodies and small molecules targeting receptors, kinase inhibitors)

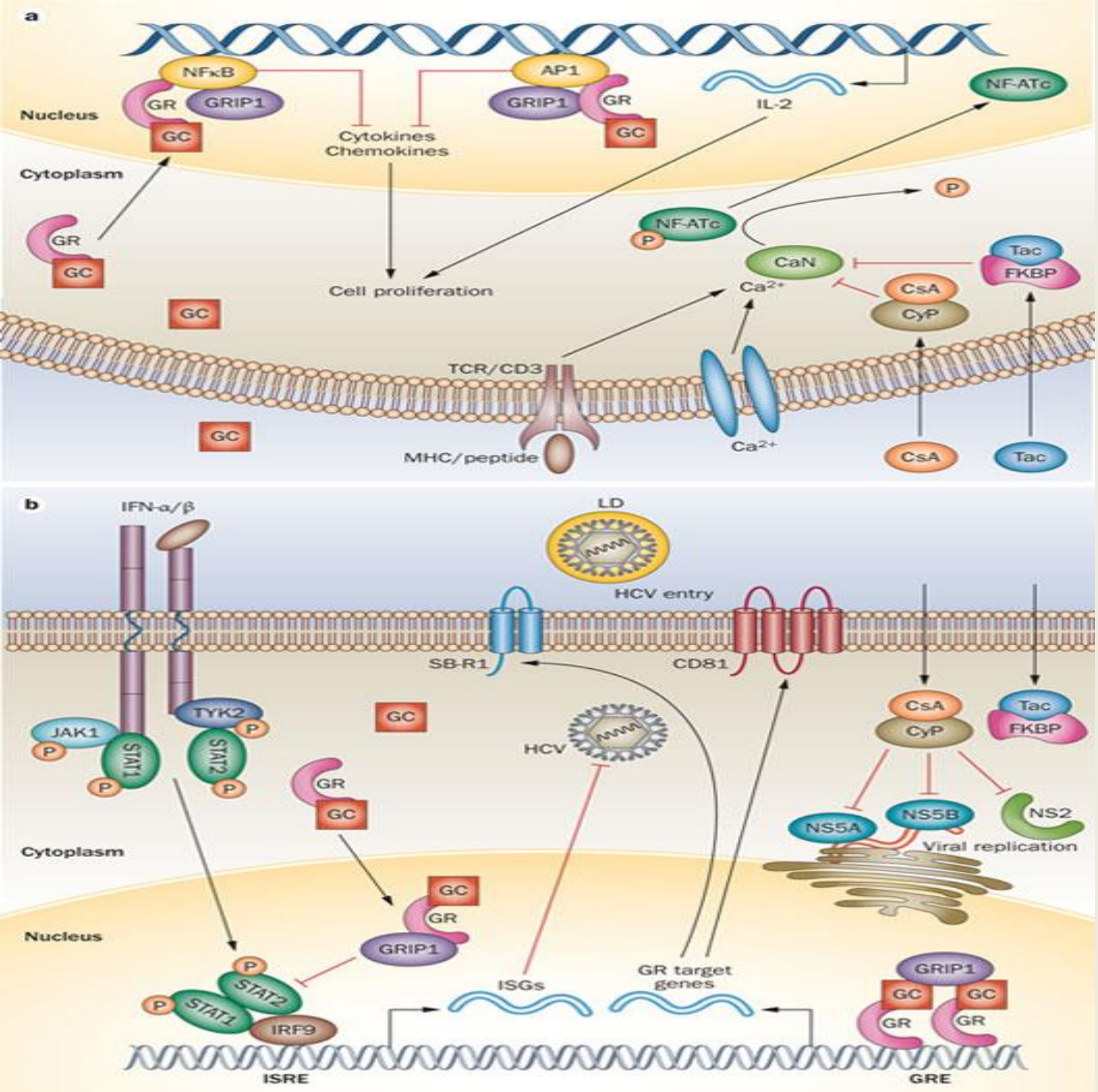
③ Translation and polyprotein processing (NS3-NS4A protease inhibitors)

④ HCV RNA replication (NS5B polymerase and NS5A inhibitors, miR-122 antagonists, cyclophilin inhibitors, statins, PI4KIIIα inhibitors)

⑤ Assembly and virion morphogenesis (NS5A inhibitors, DGAT1 inhibitors, glycosidase inhibitors, MTP inhibitors)

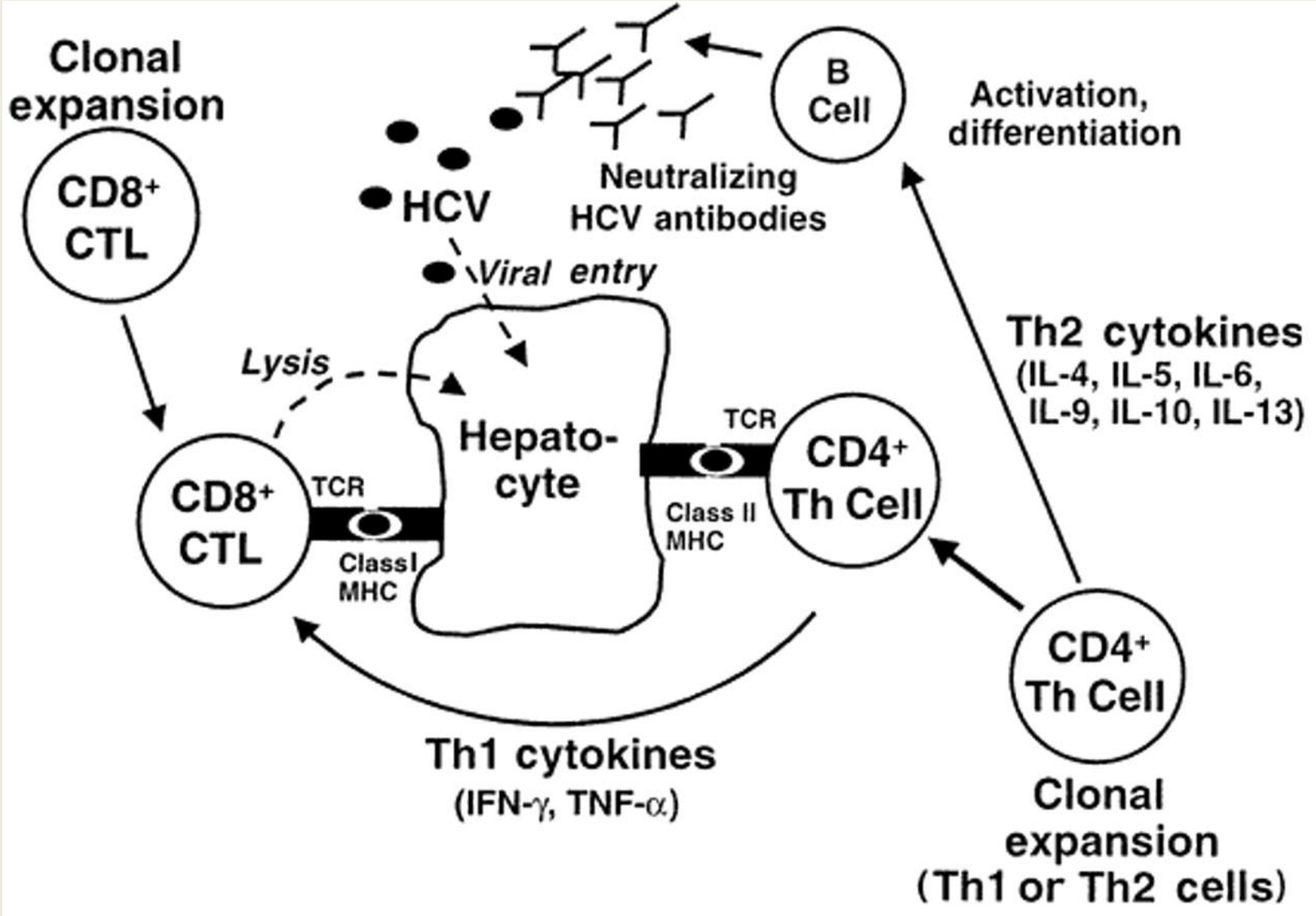
World J Gastroenterol 2014; 20(37): 13477-13492

HCV Siklüsü

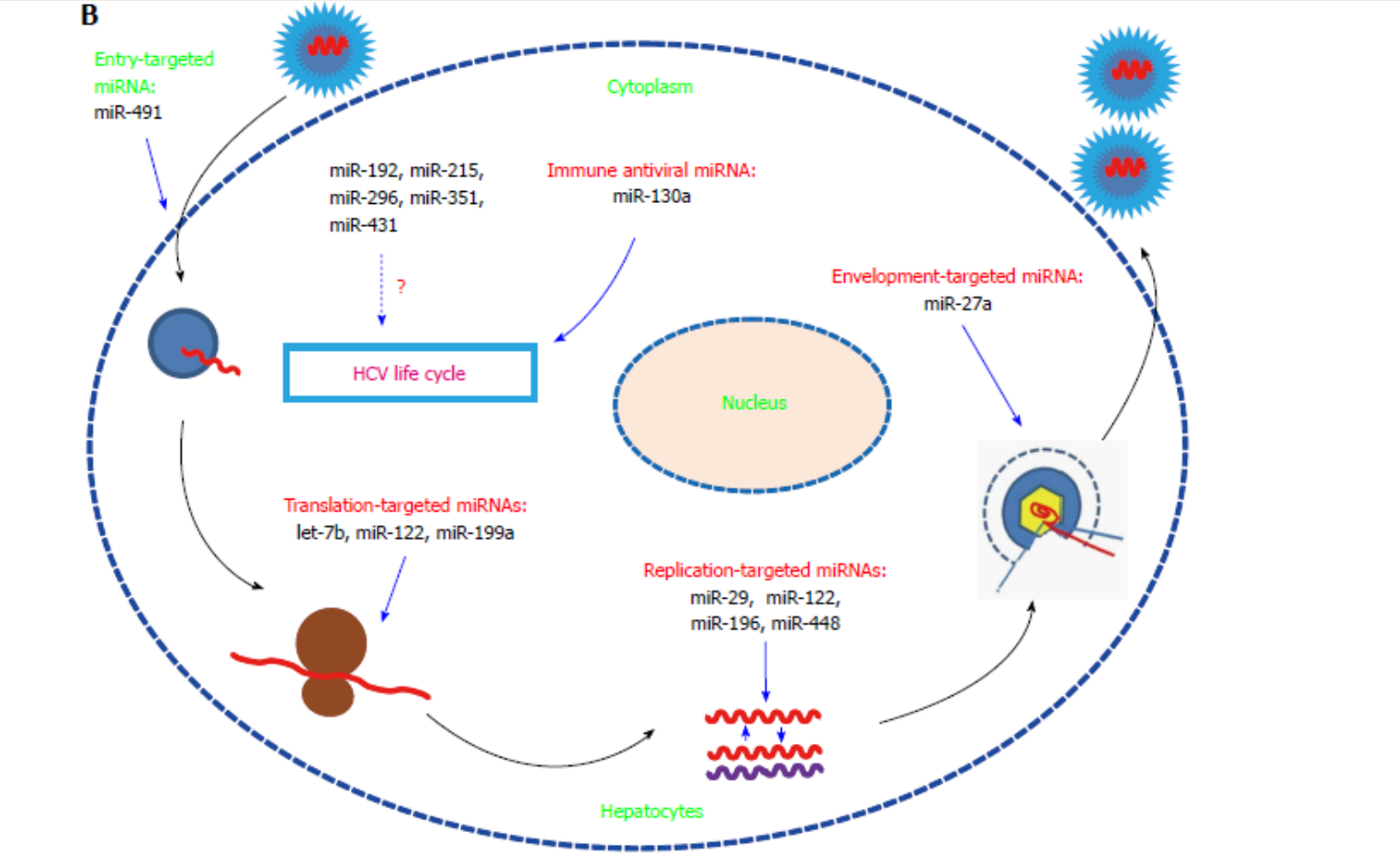


World J Gastroenterol 2014 October 7; 20(37): 13477-13492

HCV ve T Lenfositler

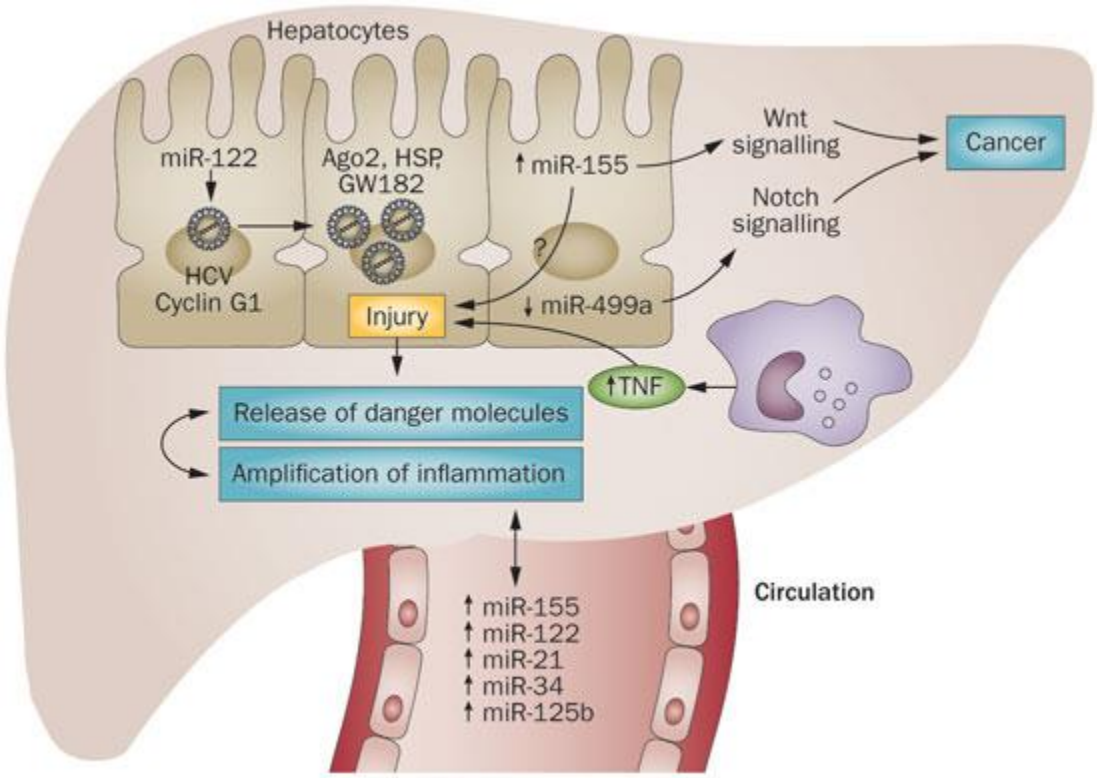


HCV İnfeksiyonu

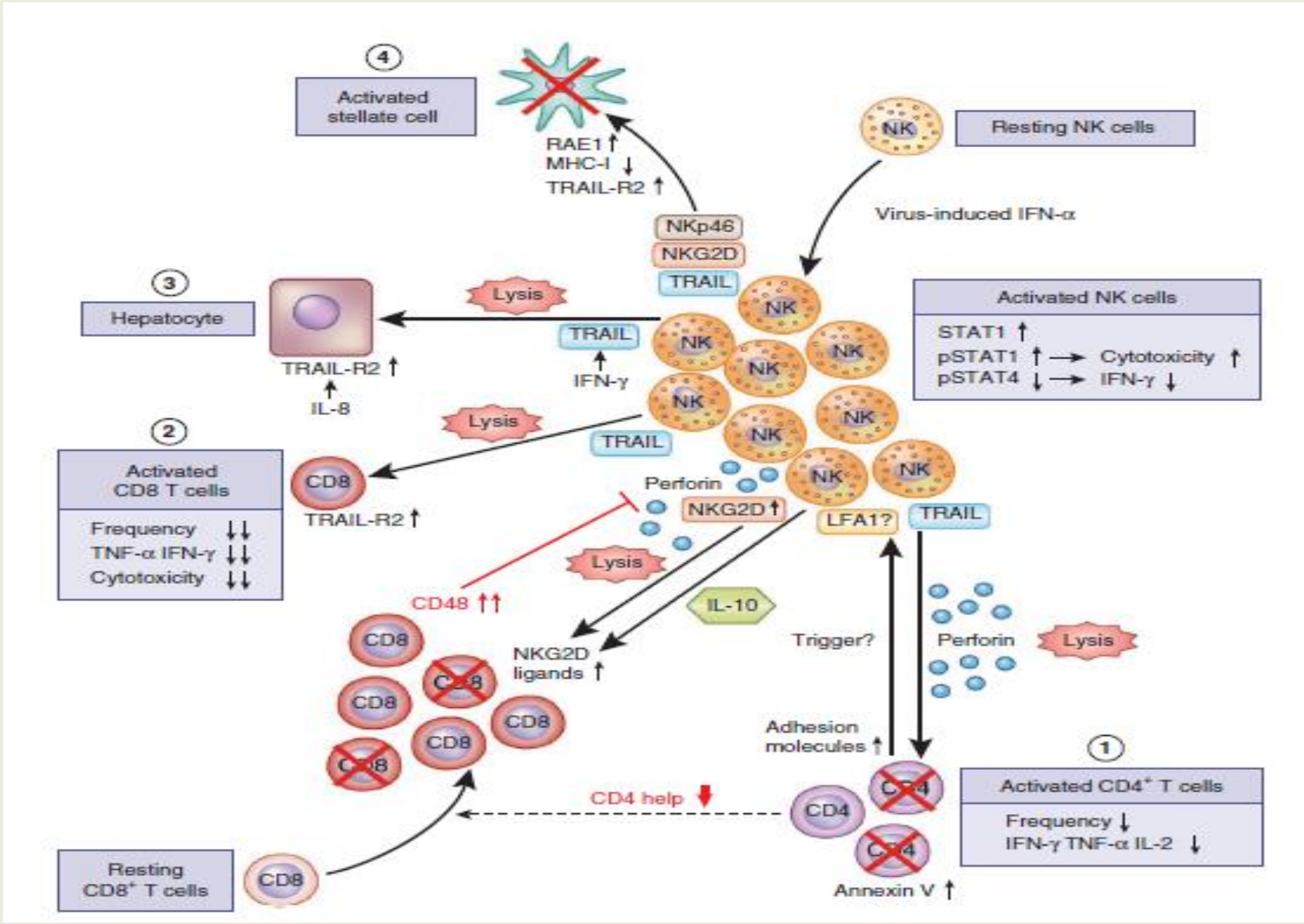


World J Gastroenterol 2014 October 7; 20(37): 13477-13492

miRNA


Hepatocytes
miR-122
Ago2, HSP, GW182
↑ miR-155
Wnt signalling
Cancer
Notch signalling
HCV
Cyclin G1
?
↓ miR-499a
Injury
↑TNF
Release of danger molecules
Amplification of inflammation
↑ miR-155
↑ miR-122
↑ miR-21
↑ miR-34
↑ miR-125b
Circulation

HCV ve NK Hücreler



Nature Medicine, 2013;19 (7): 859-69

a

Presence of NK cells	Absence of NK cells
High-dose LCMV (5×10^6 PFU) Drives $CD8^+$ T cell exhaustion in absence of $CD4^+$ T cell help	
Viremia high (day 8) Pathology minimal (day 15) Survival	Reduced viremia (day 8) Pathology ↑↑↑ (day 15) Death (58% mice)
LCMV-specific T cells: Frequency ↓↓ TNF-α IFN-γ ↓↓ Cytotoxicity ↓↓	LCMV-specific T cells: Frequency ↑↑ TNF-α IFN-γ ↑↑ Cytotoxicity ↑↑
Medium-dose LCMV (5×10^5 PFU) Not sufficient for T cell exhaustion	
Viremia high (day 15) Pathology ↑↑ (day 15) Death (23% mice)	Virus clearance (day 8) No pathology (day 15) Survival
Low-dose LCMV (5×10^4 PFU)	
Virus clearance Pathology minimal (day 15) Survival	Virus clearance rapid (<day 7) Pathology minimal (day 15) Survival

Nature Medicine, 2013;19 (7): 859-69

a

Presence of NK cells	Absence of NK cells
High-dose LCMV (5×10^6 PFU) Drives $CD8^+$ T cell exhaustion in absence of $CD4^+$ T cell help	
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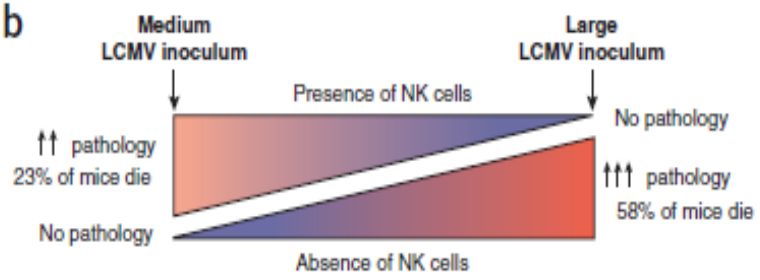
Low-dose LCMV (5×10^4 PFU)	
Virus clearance Pathology minimal (day 15) Survival	Virus clearance rapid (<day 7) Pathology minimal (day 15) Survival

b



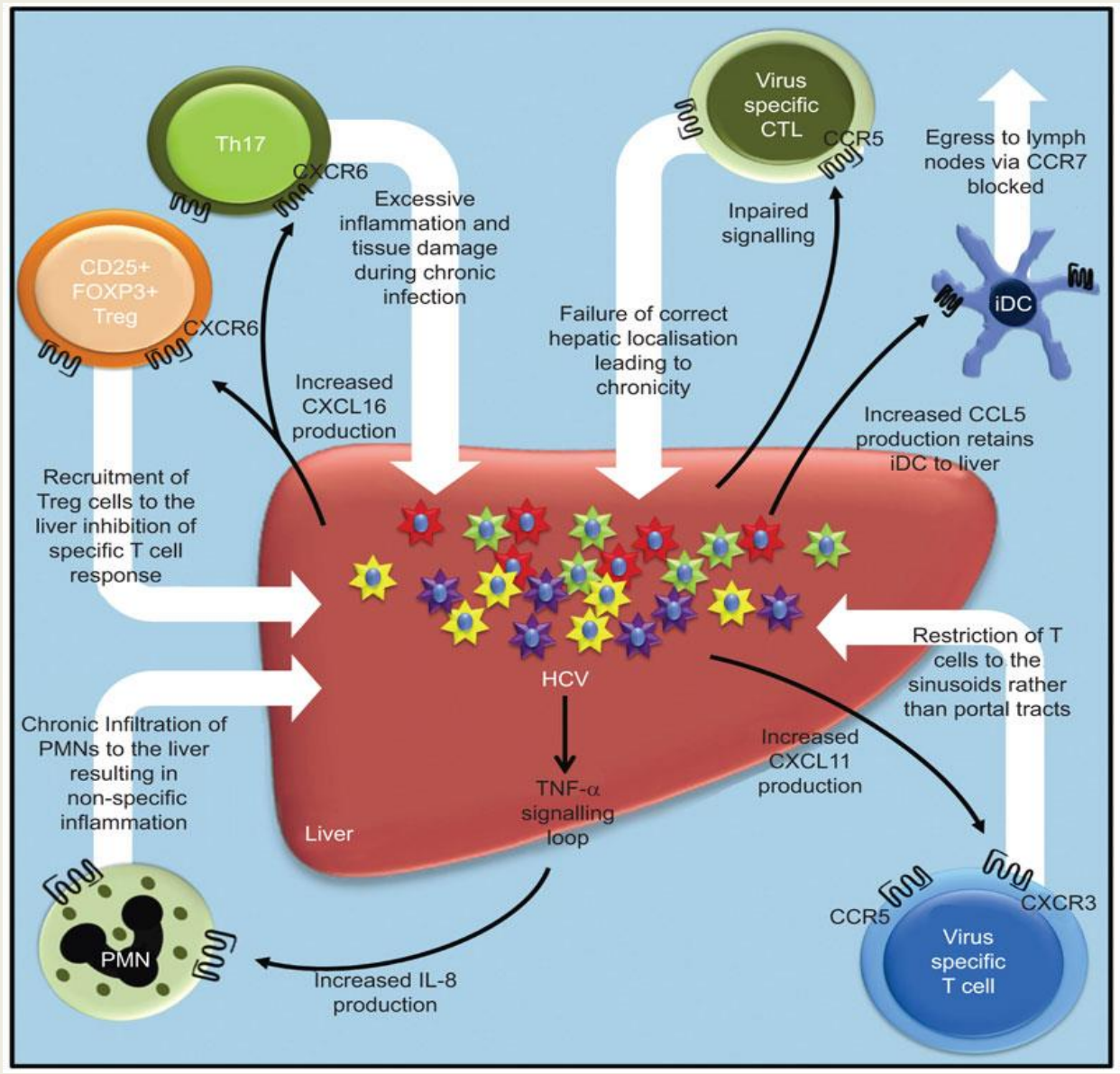
Nature Medicine, 2013;19 (7): 859-69

Kronik Karaciğer Hastalığında İlgili Kemokinlerin Rolü

Chemokine	Alternative name(s)	Main chemokine receptor(s)	Target cell(s)	Suggested involvement in liver disease
CCL1	I-309, TCA-3	CCR8	Monocytes/macrophages	Fibrosis
CCL2	MCP-1	CCR2	Monocytes/macrophages, HSCs	Initiation of inflammation, fibrosis, NAFLD/NASH
CCL3	MIP-1α	CCR1, CCR5	NK, Th1, CD8 T	HCV, HBV, NAFLD/NASH, fibrosis
CCL4	MIP-1β	CCR1, CCR5	NK, Th1, CD8 T	HCV, HBV, NAFLD/NASH, fibrosis
CCL5	RANTES	CCR1, CCR5	NK, Th1, CD8 T, HSCs	HCV, HBV, NAFLD/NASH, fibrosis
CCL17	TARC	CCR4	Treg	HCV
CCL19	ELC	CCR7	CD8 T, DCs	HCV
CCL20	MIP-3α	CCR6	$\gamma\delta$ T, Th17, HSCs	Cholestatic, HCV, alcohol, fibrosis
CCL21	SLC	CCR7	CD8 T, DCs	HCV, fibrosis
CCL22	MDC	CCR4	Treg	HCV
CCL25	TECK	CCR9	Monocytes/macrophages, HSCs	Fibrosis
CXCL1	Gro-α	CXCR2	Neutrophils, monocytes	Initiation of inflammation, alcohol
CXCL2	Gro-β	CXCR2	Neutrophils, monocytes	Initiation of inflammation, alcohol
CXCL5	ENA-78	CXCR2	Neutrophils	Alcohol, fibrosis
CXCL6	GCP-2	CXCR1, CXCR2	Neutrophils, monocytes	alcohol
CXCL8	IL-8	CXCR1, CXCR2	Neutrophils, monocytes	Initiation of inflammation, alcohol, HBV
CXCL9	MIG	CXCR3	NK, Th1, Th17	HCV, fibrosis
CXCL10	IP-10	CXCR3	NK, Th1, Th17, HSCs	Cholestatic, HCV, HBV, fibrosis
CXCL11	I-TAC	CXCR3	NK, Th1, Th17	HCV, fibrosis
CXCL12	SDF-1	CXCR4, CXCR7	HSCs, LSECs, HCCs	Fibrosis, regeneration, HCC
CXCL13	BCA-1	CXCR5	B cells	HCV
CXCL16	SRPSOX	CXCR6	NKT cells	HCV, fibrosis
CX3CL1	Fractalkine, neurotactin	CX3CR1	Monocytes/macrophages	HCV, fibrosis

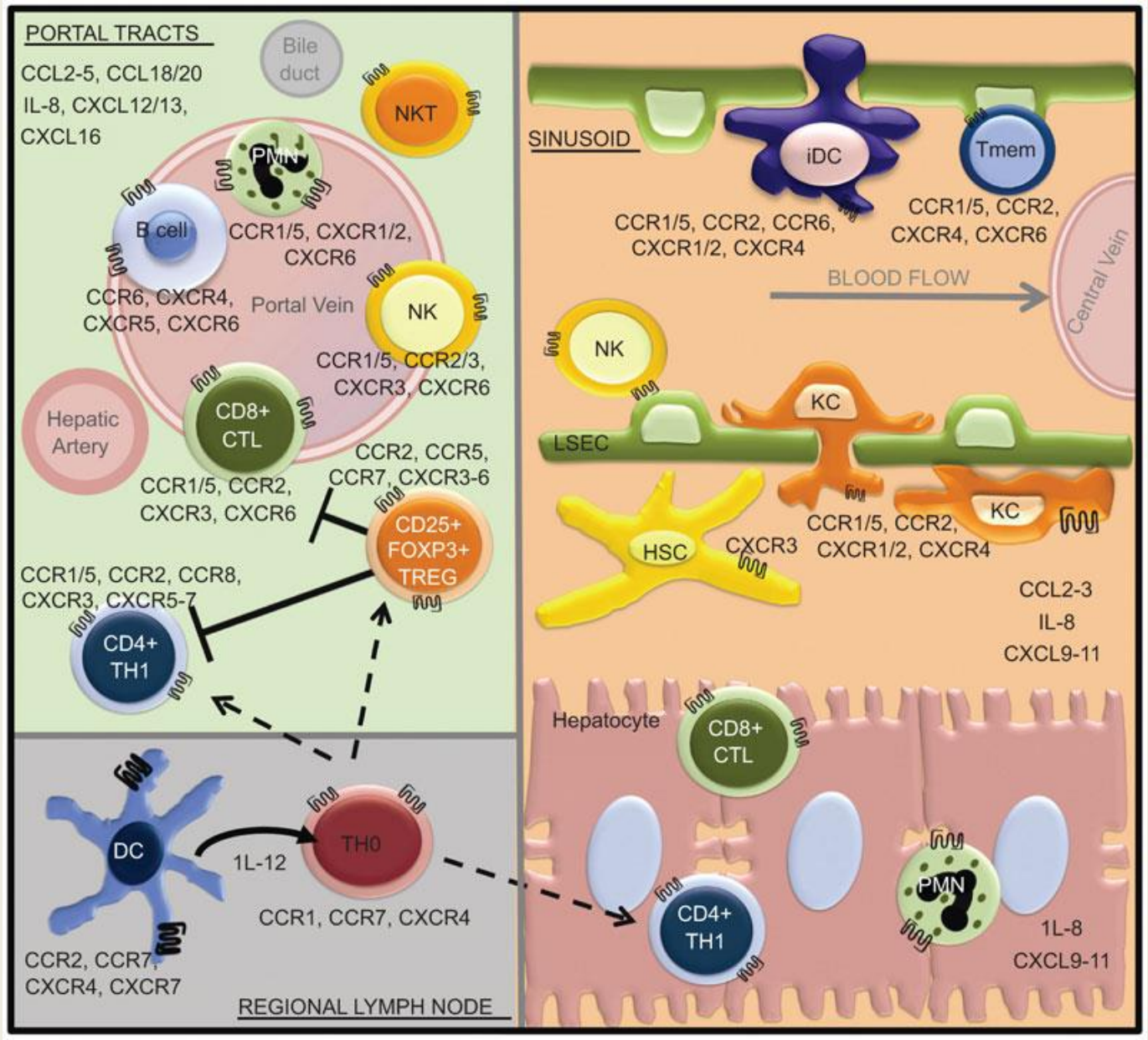
Gastroenterology 2014;147:577–594

HCV ve Kemokinler

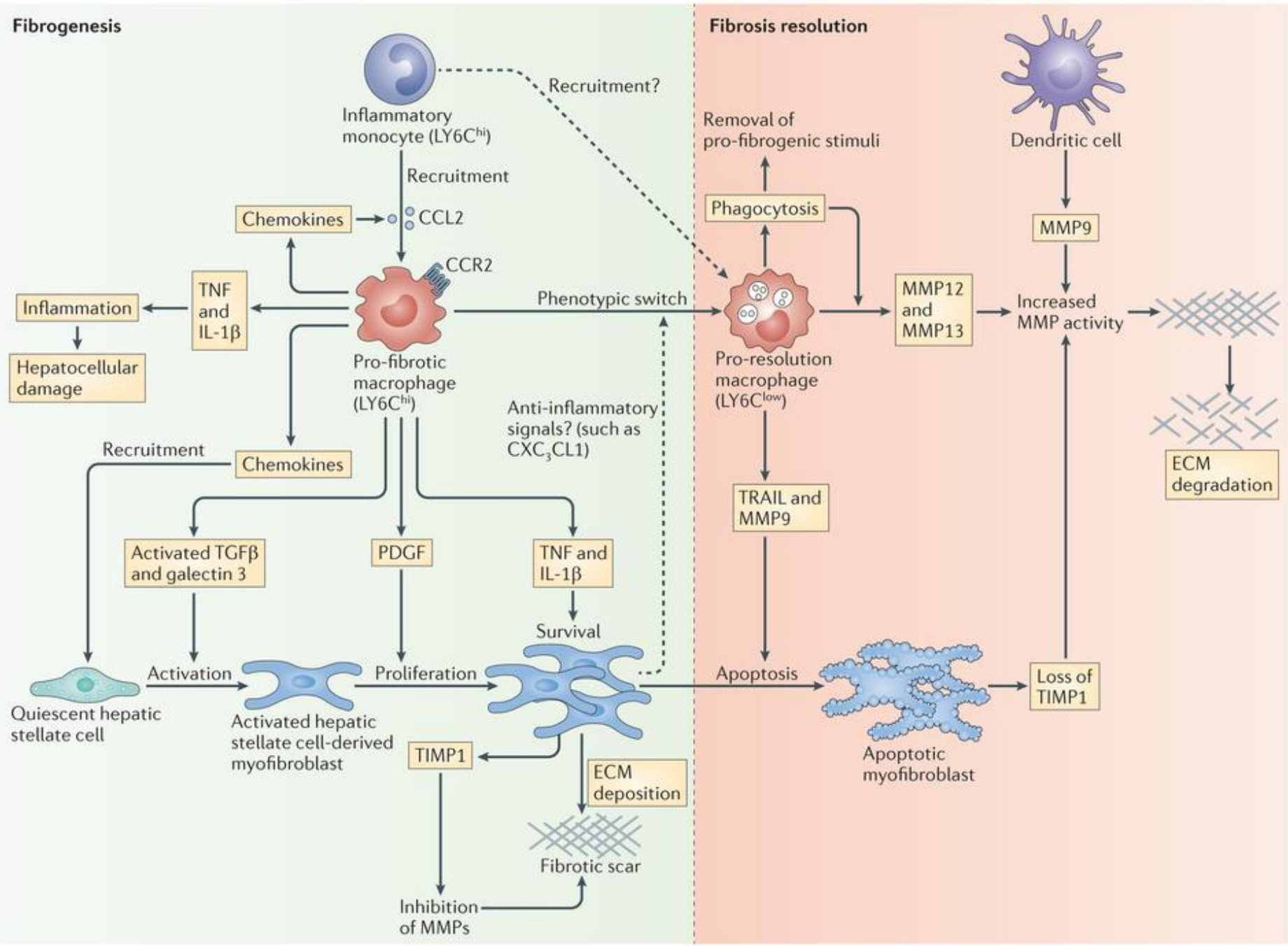


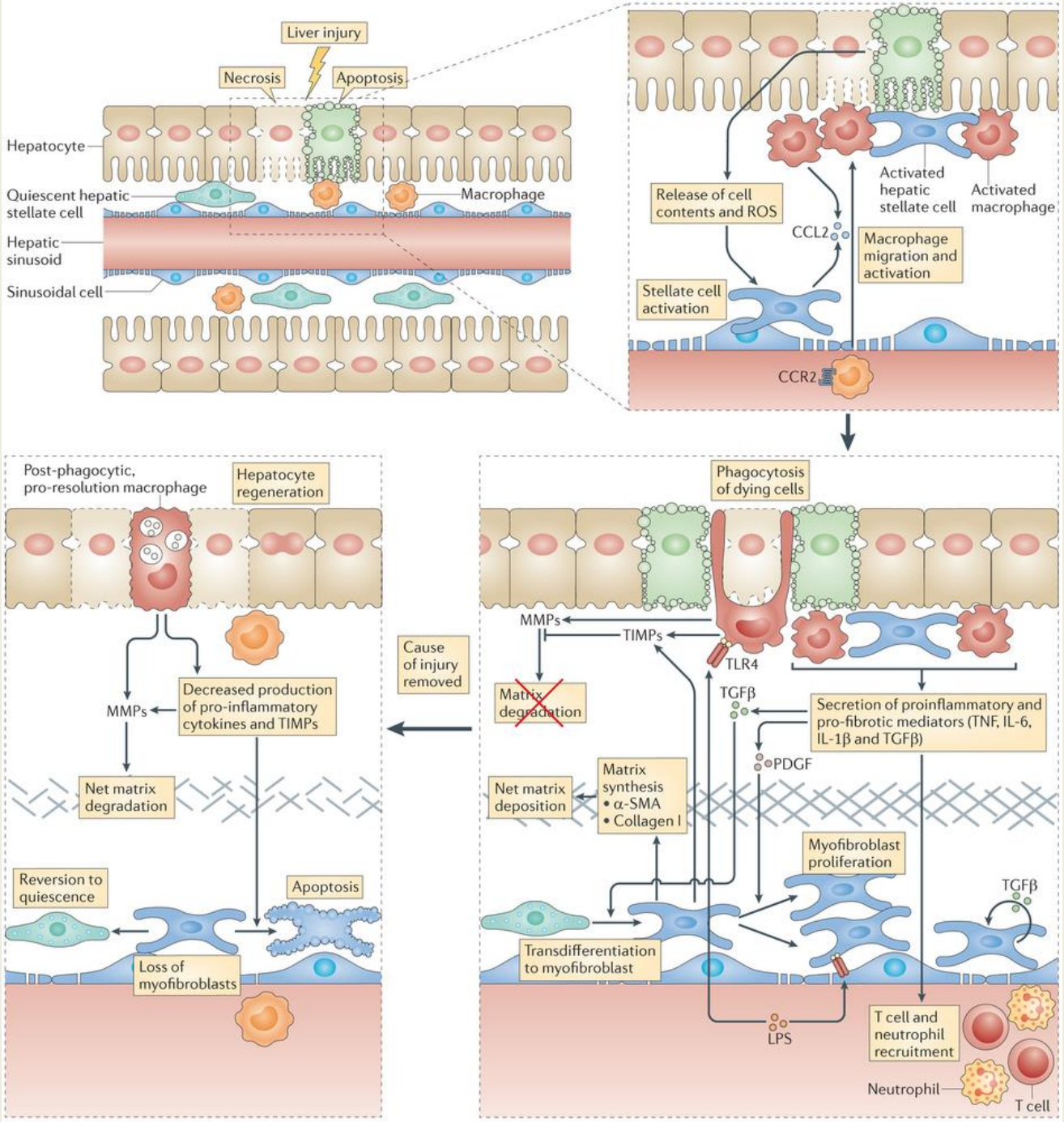
Nature Medicine, 2013;19 (7): 859-69

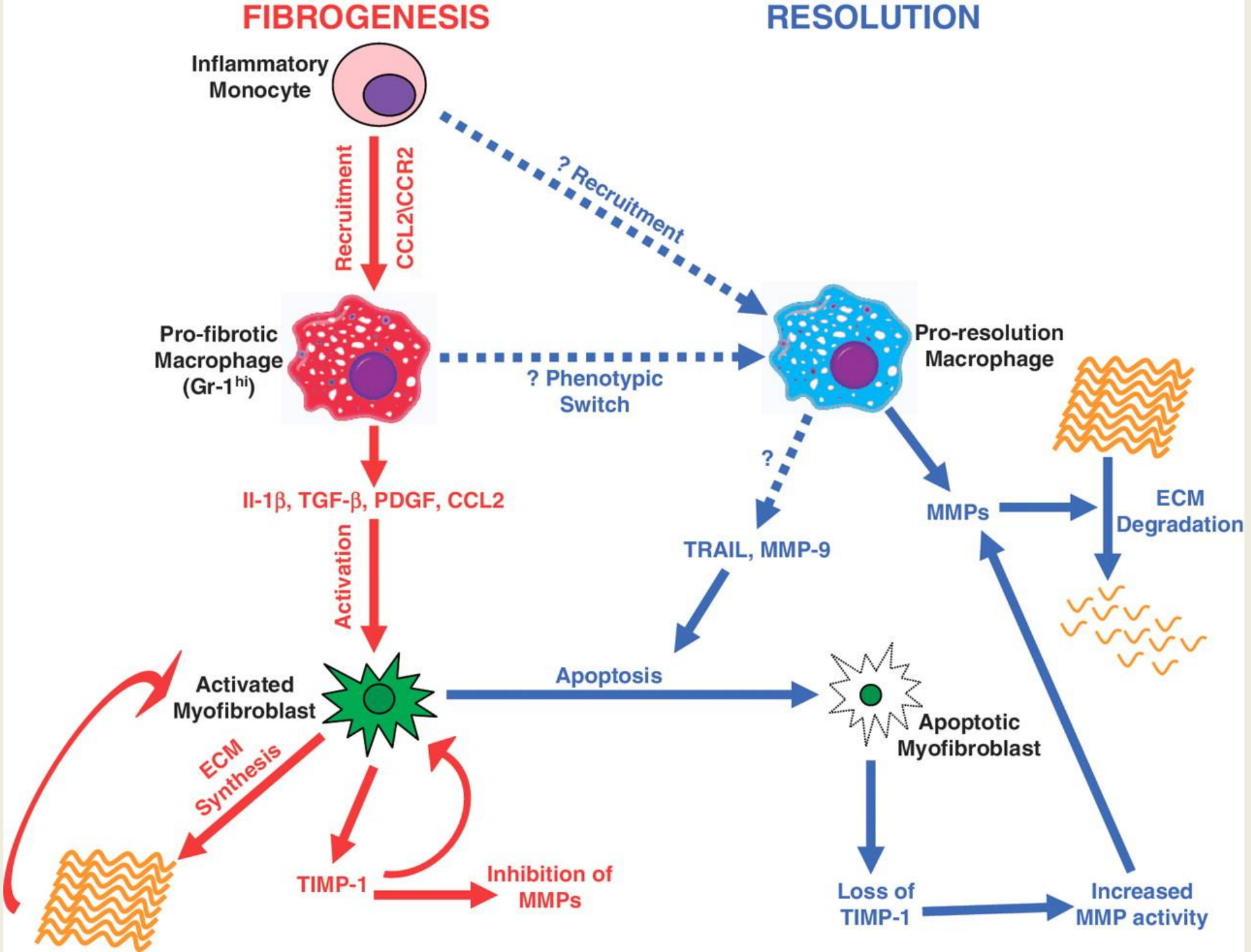
HCV ve Kemokinler



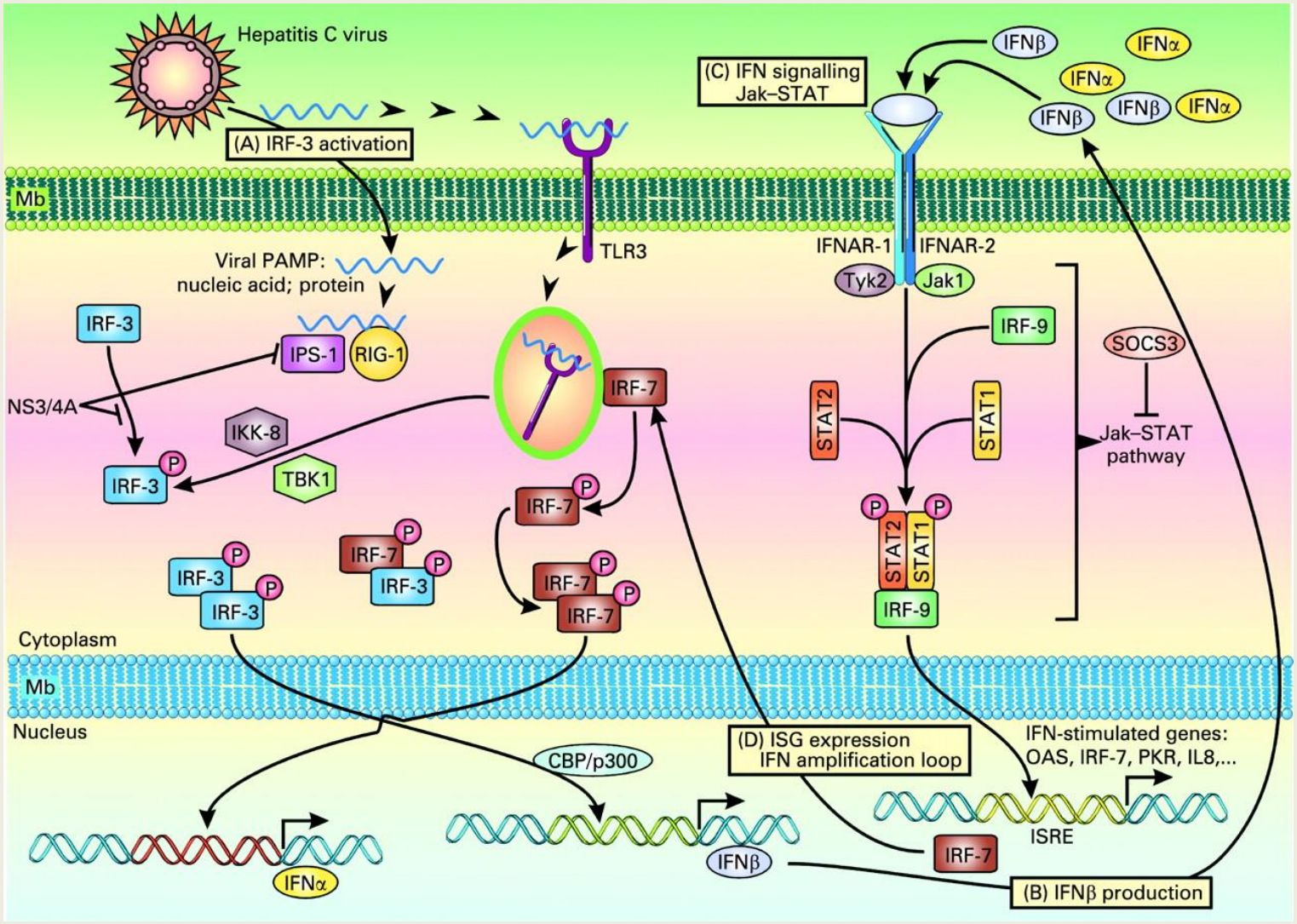
Nature Medicine, 2013;19 (7): 859-69


Fibrogenesis
Fibrosis resolution
Inflammatory monocyte (LY6C^{hi})
Recruitment?
Recruitment
Chemokines
CCL2
CCR2
TNF and IL-1β
Inflammation
Hepatocellular damage
Pro-fibrotic macrophage (LY6C^{hi})
Phenotypic switch
Anti-inflammatory signals? (such as CXC$_3$CL1)
Recruitment
Chemokines
Activated TGFβ and galectin 3
PDGF
TNF and IL-1β
Survival
Activation
Proliferation
Quiescent hepatic stellate cell
Activated hepatic stellate cell-derived myofibroblast
TIMP1
ECM deposition
Fibrotic scar
Inhibition of MMPs
Removal of pro-fibrogenic stimuli
Phagocytosis
Pro-resolution macrophage (LY6C^{low})
TRAIL and MMP9
Apoptosis
Apoptotic myofibroblast
Dendritic cell
MMP9
MMP12 and MMP13
Increased MMP activity
ECM degradation
Loss of TIMP1

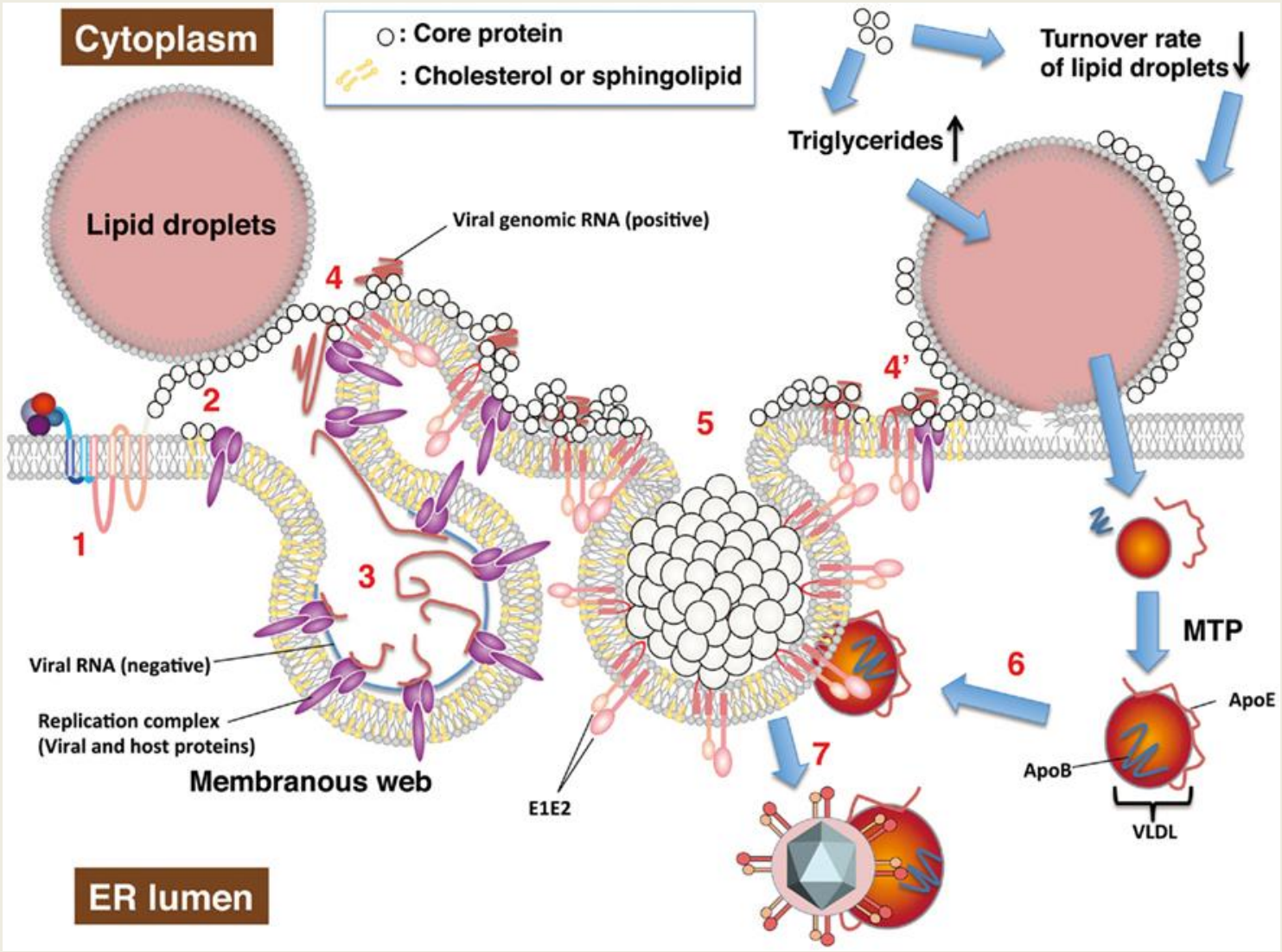

Liver injury
Necrosis
Apoptosis
Hepatocyte
Quiescent hepatic stellate cell
Hepatic sinusoid
Sinusoidal cell
Macrophage
Release of cell contents and ROS
CCL2
Activated hepatic stellate cell
Activated macrophage
Macrophage migration and activation
Stellate cell activation
CCR2
Post-phagocytic, pro-resolution macrophage
Hepatocyte regeneration
MMPs
Decreased production of pro-inflammatory cytokines and TIMPs
Net matrix degradation
Reversion to quiescence
Apoptosis
Loss of myofibroblasts
Cause of injury removed
Phagocytosis of dying cells
MMPs
TIMPs
TLR4
Matrix degradation
TGFβ
Secretion of proinflammatory and pro-fibrotic mediators (TNF, IL-6, IL-1β and TGFβ)
PDGF
Net matrix deposition
Matrix synthesis
• α-SMA
• Collagen I
Myofibroblast proliferation
TGFβ
Transdifferentiation to myofibroblast
LPS
T cell and neutrophil recruitment
Neutrophil
T cell


FIBROGENESIS
RESOLUTION
Inflammatory Monocyte
Recruitment
CCL2\CCR2
? Recruitment
Pro-fibrotic Macrophage (Gr-1hi)
? Phenotypic Switch
Pro-resolution Macrophage
Il-1β, TGF-β, PDGF, CCL2
Activation
?
TRAIL, MMP-9
MMPs
ECM Degradation
Activated Myofibroblast
Apoptosis
Apoptotic Myofibroblast
ECM Synthesis
TIMP-1
Inhibition of MMPs
Loss of TIMP-1
Increased MMP activity

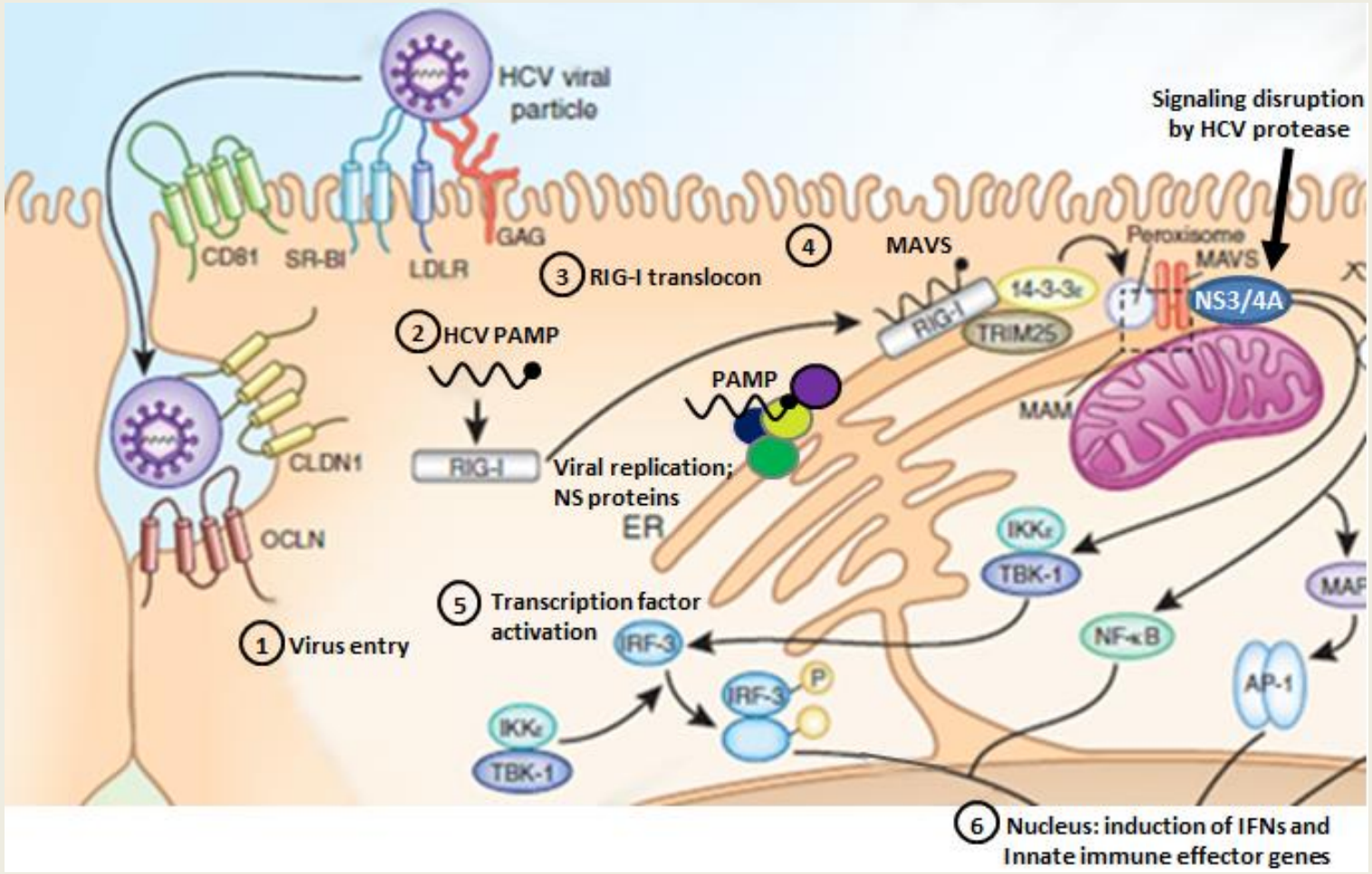
HCV ve Yolaklar



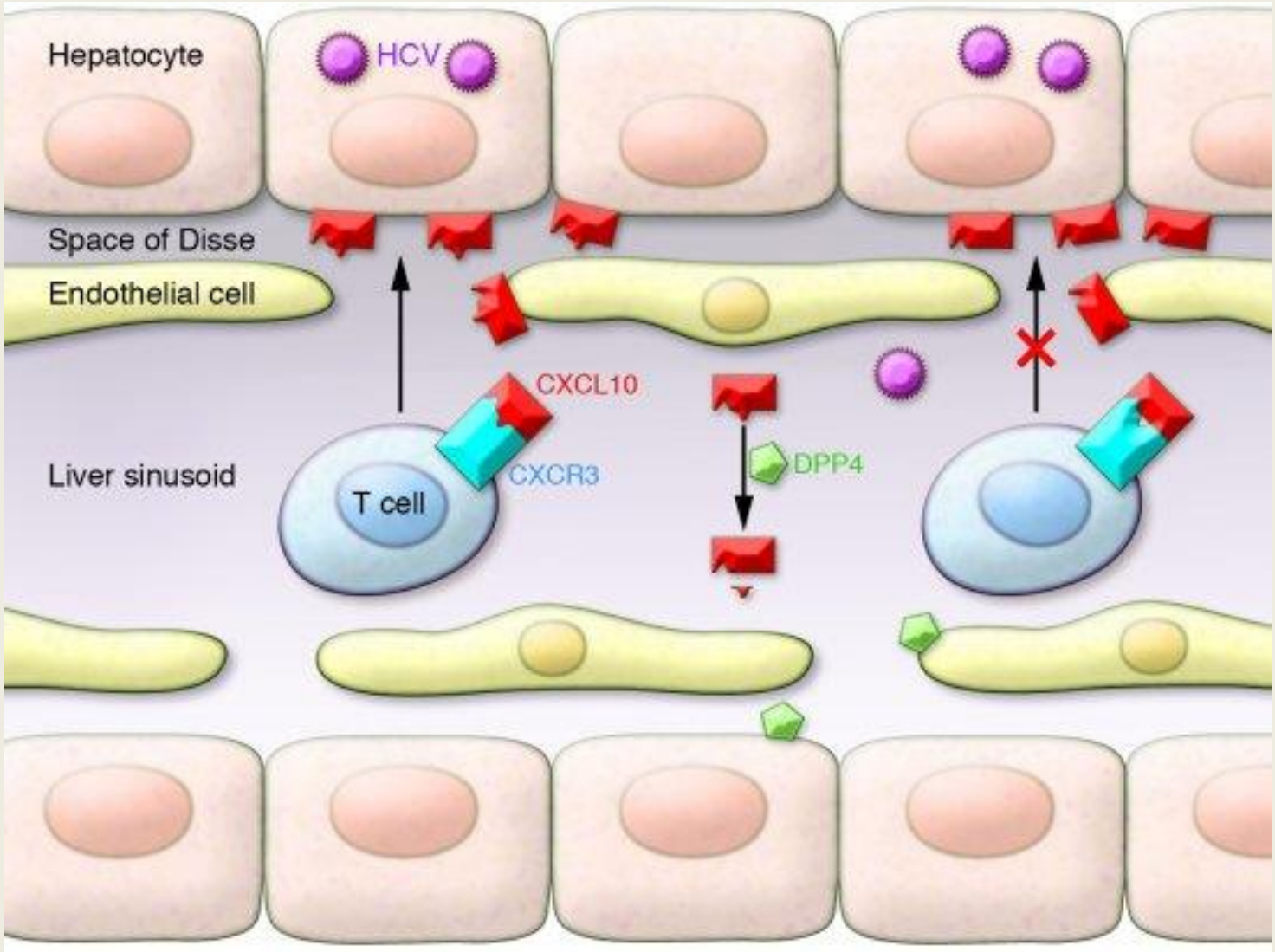
HCV ve Lipid Damlaları



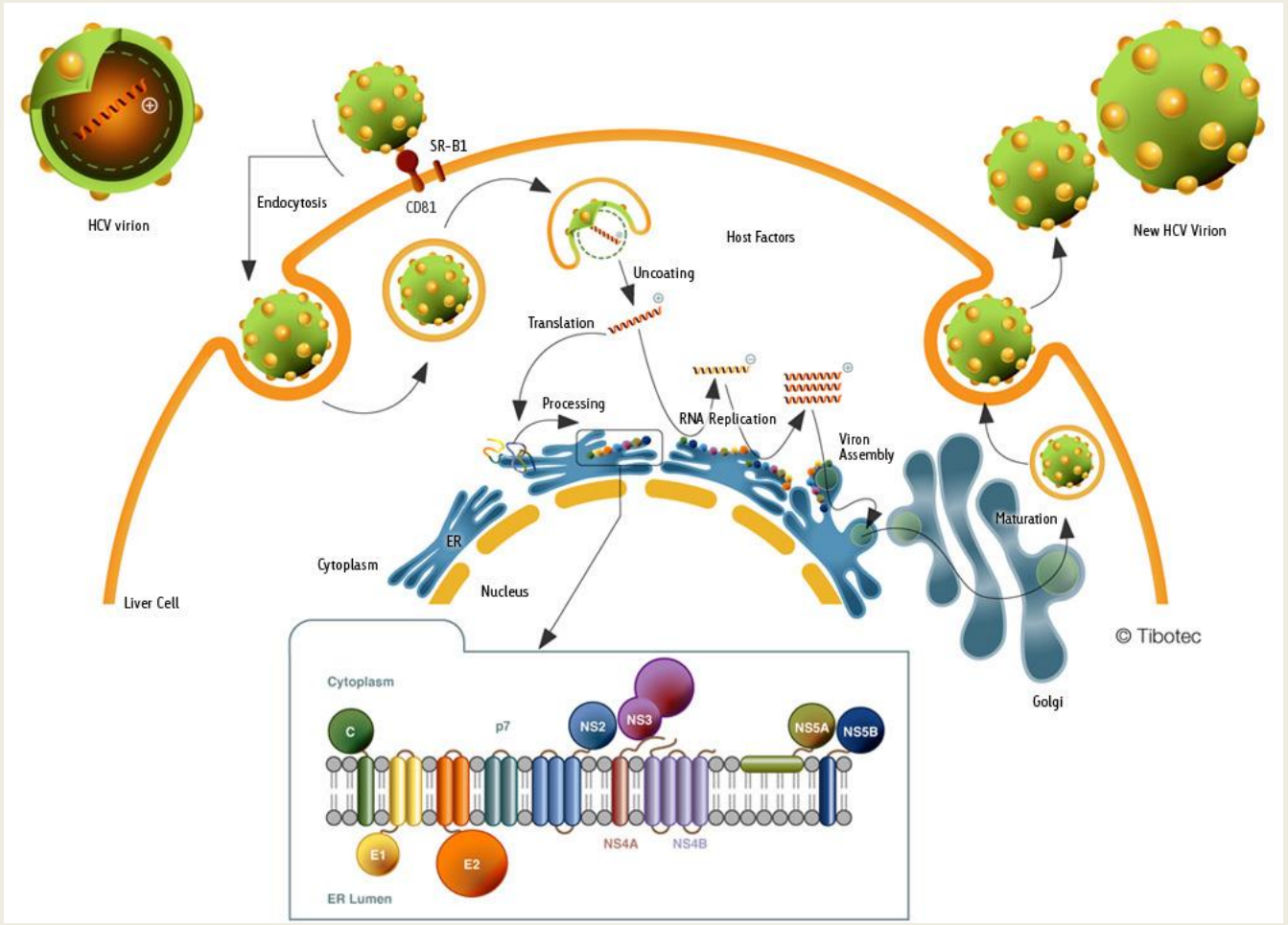
HCV Siklusu ve Doğal İmmünite

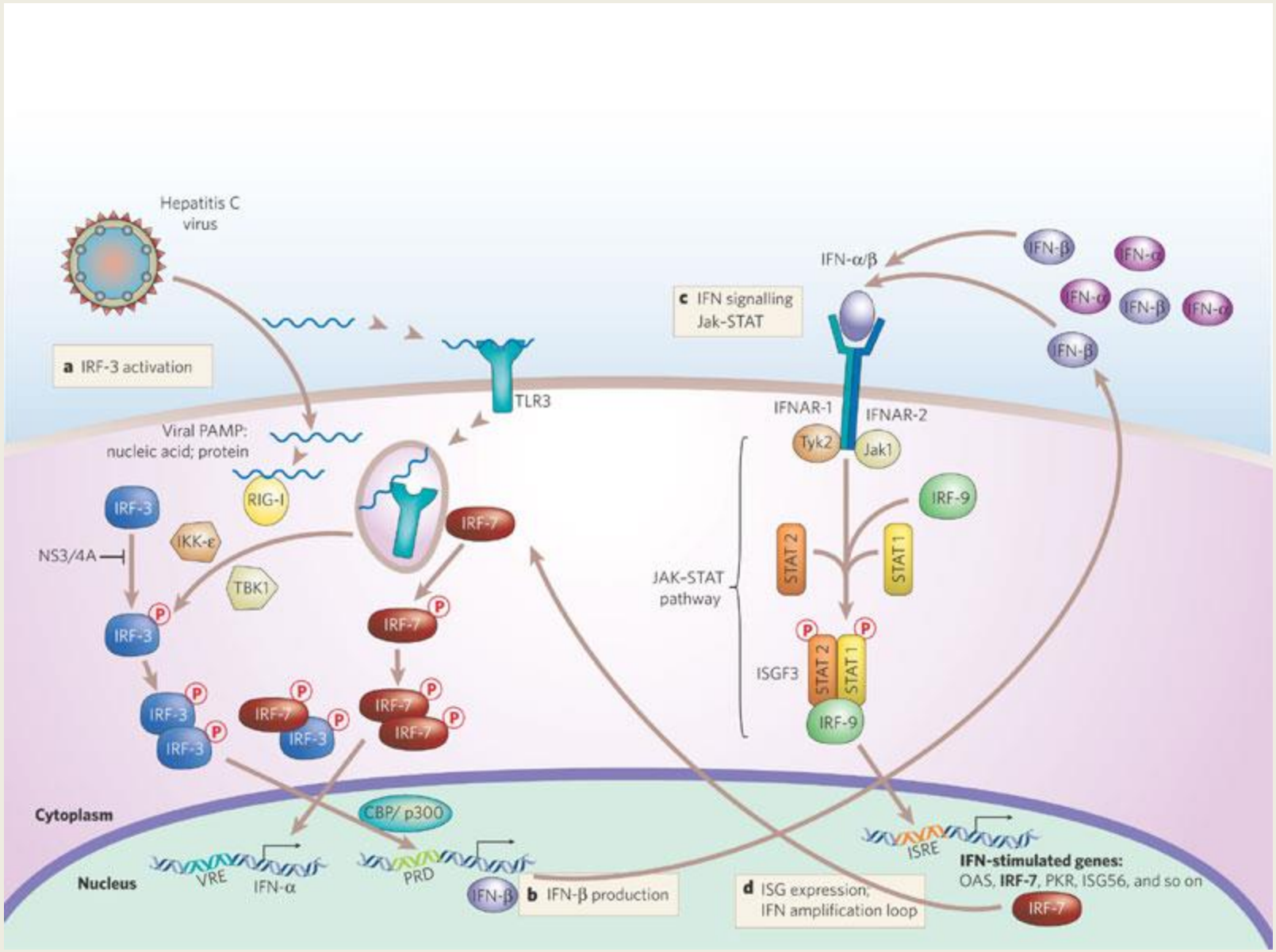


HCV

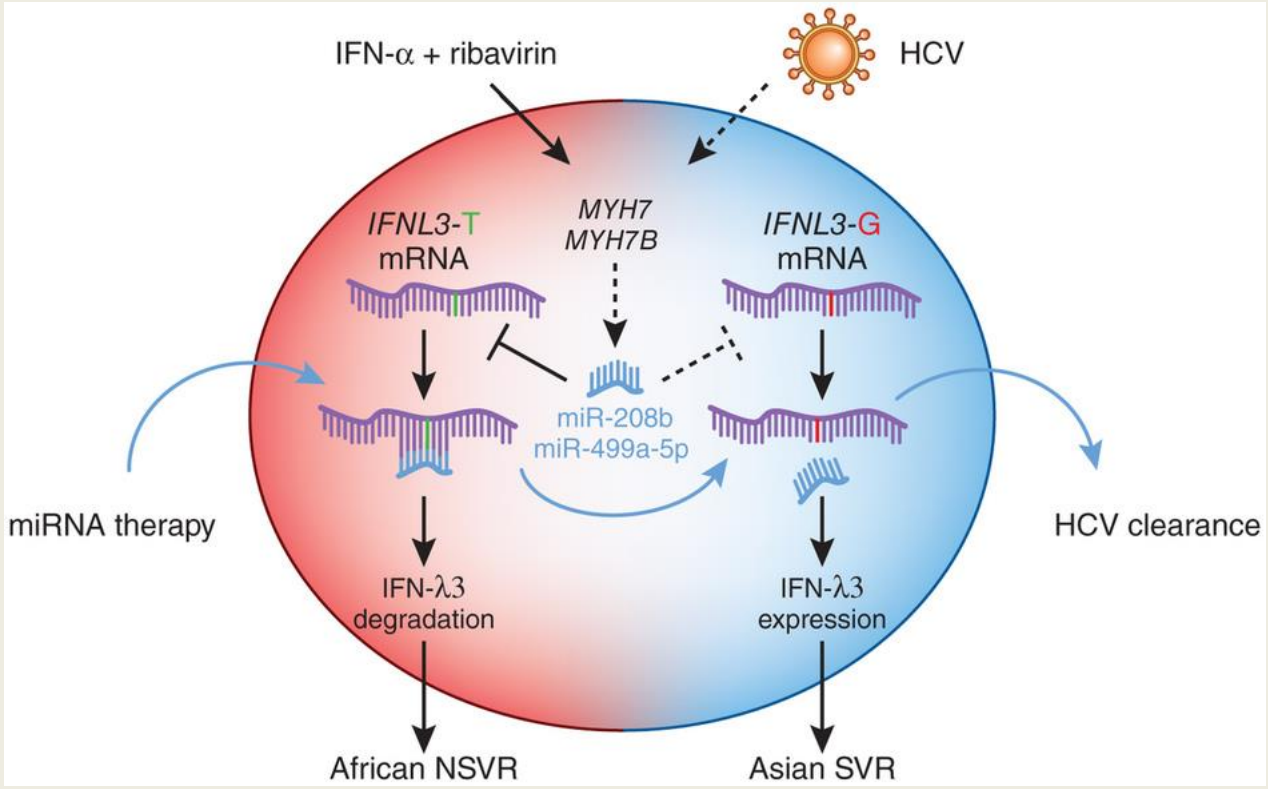

Hepatocyte
HCV
Space of Disse
Endothelial cell
CXCL10
CXCR3
Liver sinusoid
T cell
DPP4

HCV Siklüsü ve Tedavi Hedefleri

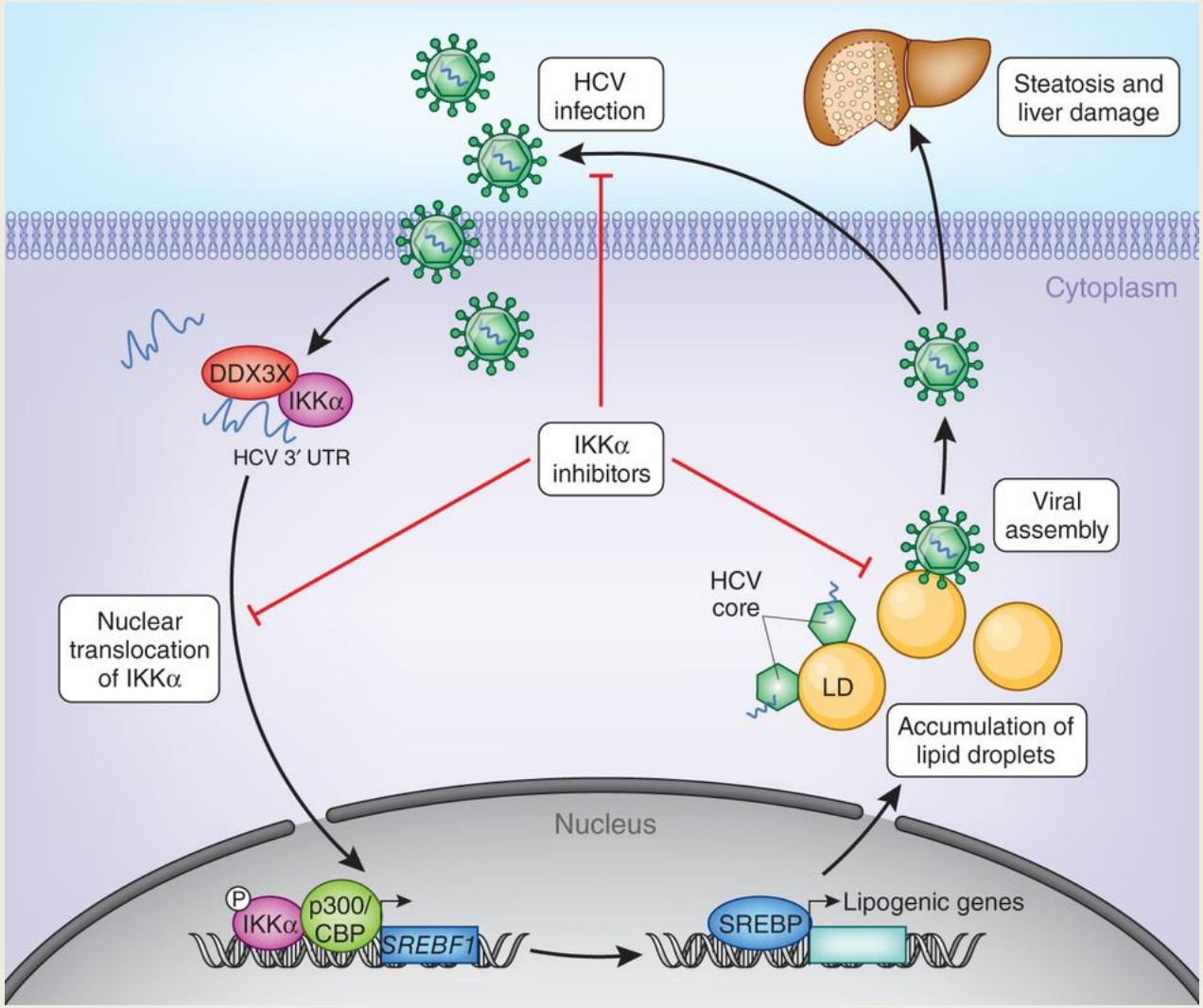



Hepatitis C virus
a IRF-3 activation
TLR3
Viral PAMP: nucleic acid; protein
RIG-I
IRF-3
IKK-ε
NS3/4A
TBK1
IRF-7
Cytoplasm
CBP/ p300
Nucleus
VRE
IFN-α
PRD
IFN-β
b IFN-β production
c IFN signalling Jak-STAT
IFN-α/β
IFNAR-1
IFNAR-2
Tyk2
Jak1
IRF-9
STAT 2
STAT 1
JAK-STAT pathway
ISGF3
ISRE
IFN-stimulated genes:
OAS, IRF-7, PKR, ISG56, and so on
d ISG expression; IFN amplification loop

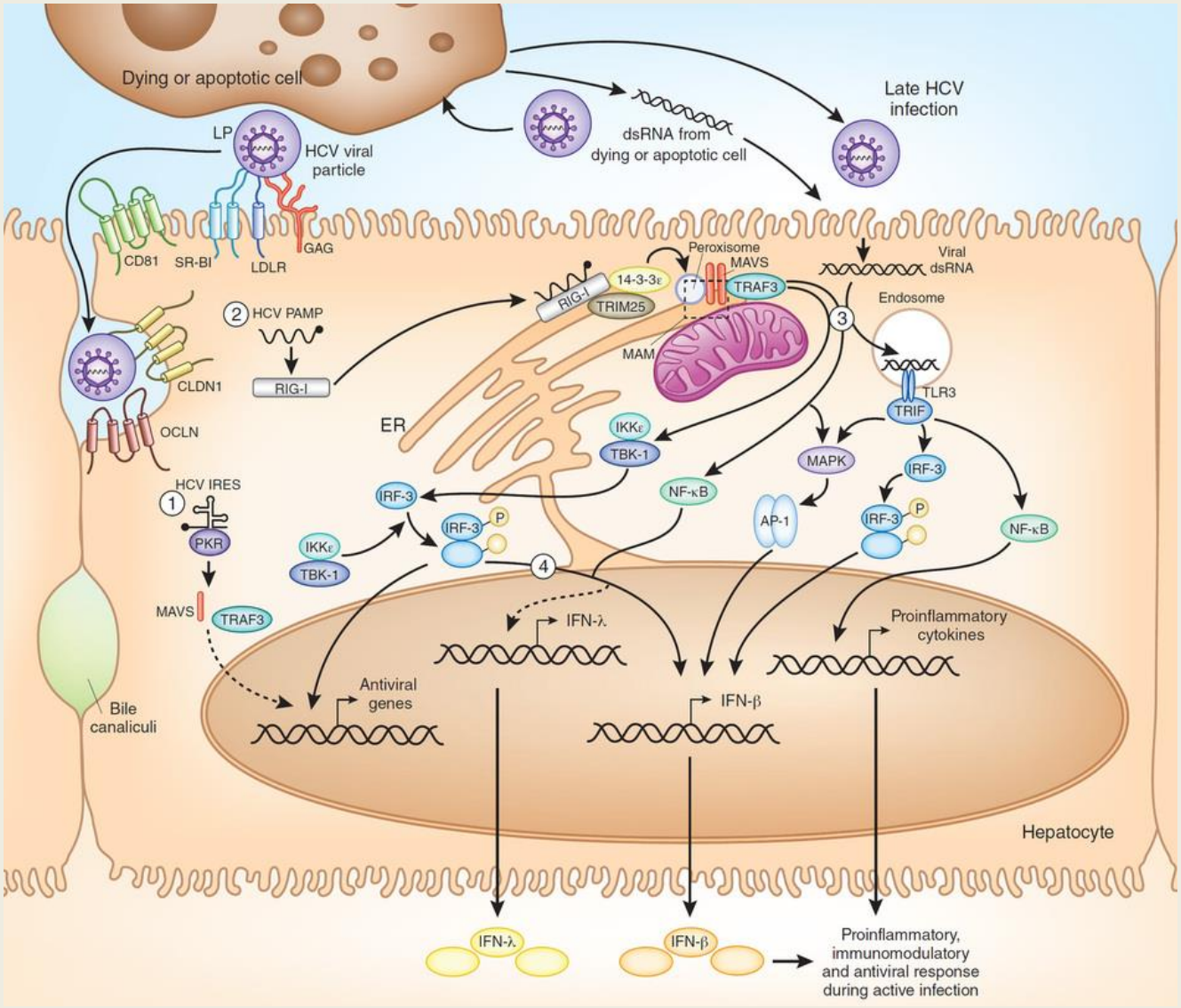
HCV Klirensi



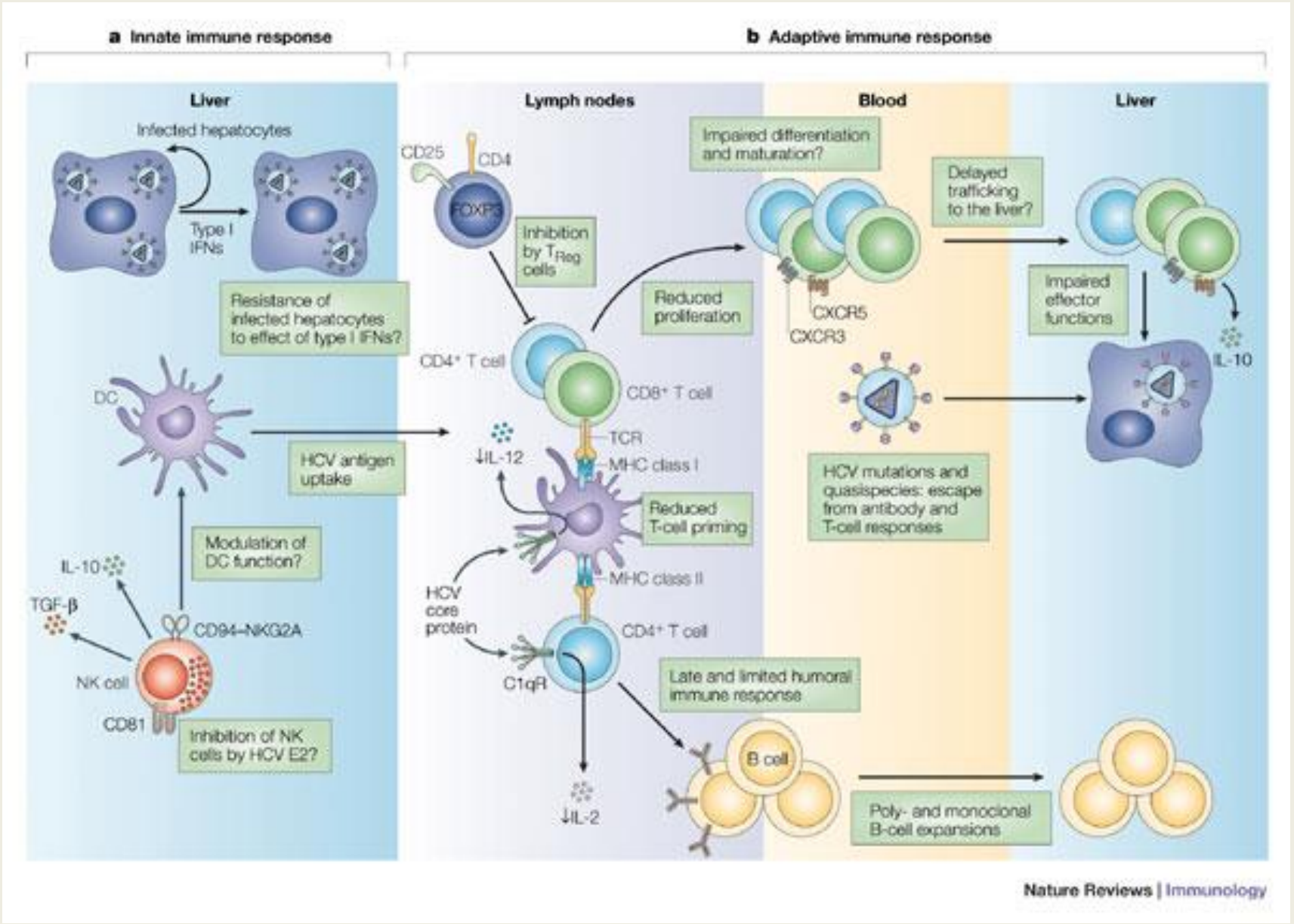
HCV ve IKK


HCV infection
Steatosis and liver damage
Cytoplasm
DDX3X
IKKα
HCV 3′ UTR
IKKα inhibitors
Viral assembly
Nuclear translocation of IKKα
HCV core
LD
Accumulation of lipid droplets
Nucleus
P
IKKα
p300/ CBP
SREBF1
SREBP
Lipogenic genes

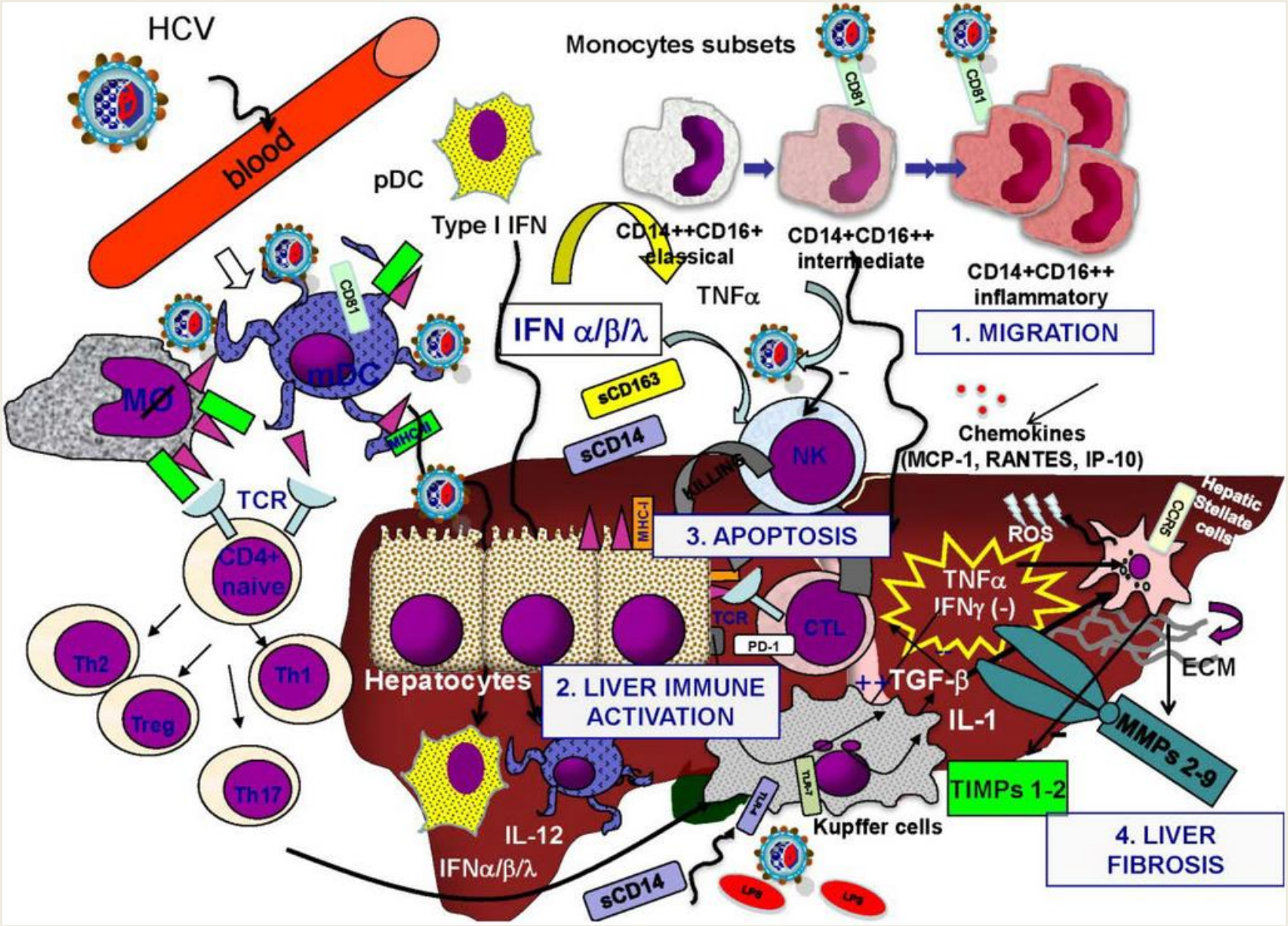
HCV ve Kronikleşme Patogenezi



HCV ve Kronikleşme Patogenezi



HCV


HCV
blood
pDC
Type I IFN
Monocytes subsets
CD81
CD14++CD16+ classical
CD14+CD16++ intermediate
CD14+CD16++ inflammatory
TNFα
IFN α/β/λ
1. MIGRATION
sCD163
sCD14
MØ
mDC
MHCII
TCR
CD4+ naive
Th2
Th1
Treg
Th17
NK
KILLING
Chemokines (MCP-1, RANTES, IP-10)
MHC-I
3. APOPTOSIS
ROS
Hepatic Stellate cells
CCR5
TNFα
IFNγ (-)
TCR
CTL
PD-1
Hepatocytes
2. LIVER IMMUNE ACTIVATION
++TGF-β
IL-1
ECM
MMPs 2-9
TIMPs 1-2
TLR-4
Kupffer cells
IL-12
IFNα/β/λ
sCD14
LPS
4. LIVER FIBROSIS

Dinlediğiniz için teşekkür ederim.

Kaynaklar

1.Q J Med 2012; 105:109–113
2.*Physiol Genomics 45: 1035–1048, 2013.*
3.Hepatobiliary Surg Nutr 2013;2(1):37-39
4.Frontiers in Physiology 2014;5:212-220
*5.*Gut 2009;58:846–858
6.*Int. J. Mol. Sci. 2014, 15, 9184-9208*
*7.J Clin Invest. 2011;*121(1):25–27.
8.Nature Cell Biology 2007;9:837--850
9.Nature Medicine 2013;19:879-889
10.*Viruses 2012, 4, 2485-2513*
*11.*Journal of Hepatology 2014 vol. 61 j 660–671
12.Antiviral Research 96 (2012) 405–413
13.Journal of Hepatology 49 (2008) 396–406
14.Cancer Letters 286 (2009) 69–79
15.Microbial Pathogenesis 74 (2014) 59e62
16.Biochimica et Biophysica Acta 1809 (2011) 678–685
17.J. Mol. Biol. (2014) 426, 1198–1209