HBV İNFEKSİYONU

AKUT VE KRONİK İNFEKSİYONDA PATOGENEZ

Ediz Tütüncü

KLİMİK Hepatit Akademisi 2025

14 Şubat 2025, Eskişehir

JOURNAL OF VIROLOGY, Oct. 2009, p. 9652–9662 Vol. 83, No. 19
0022-538X/09/$08.00+0 doi:10.1128/JVI.00867-09

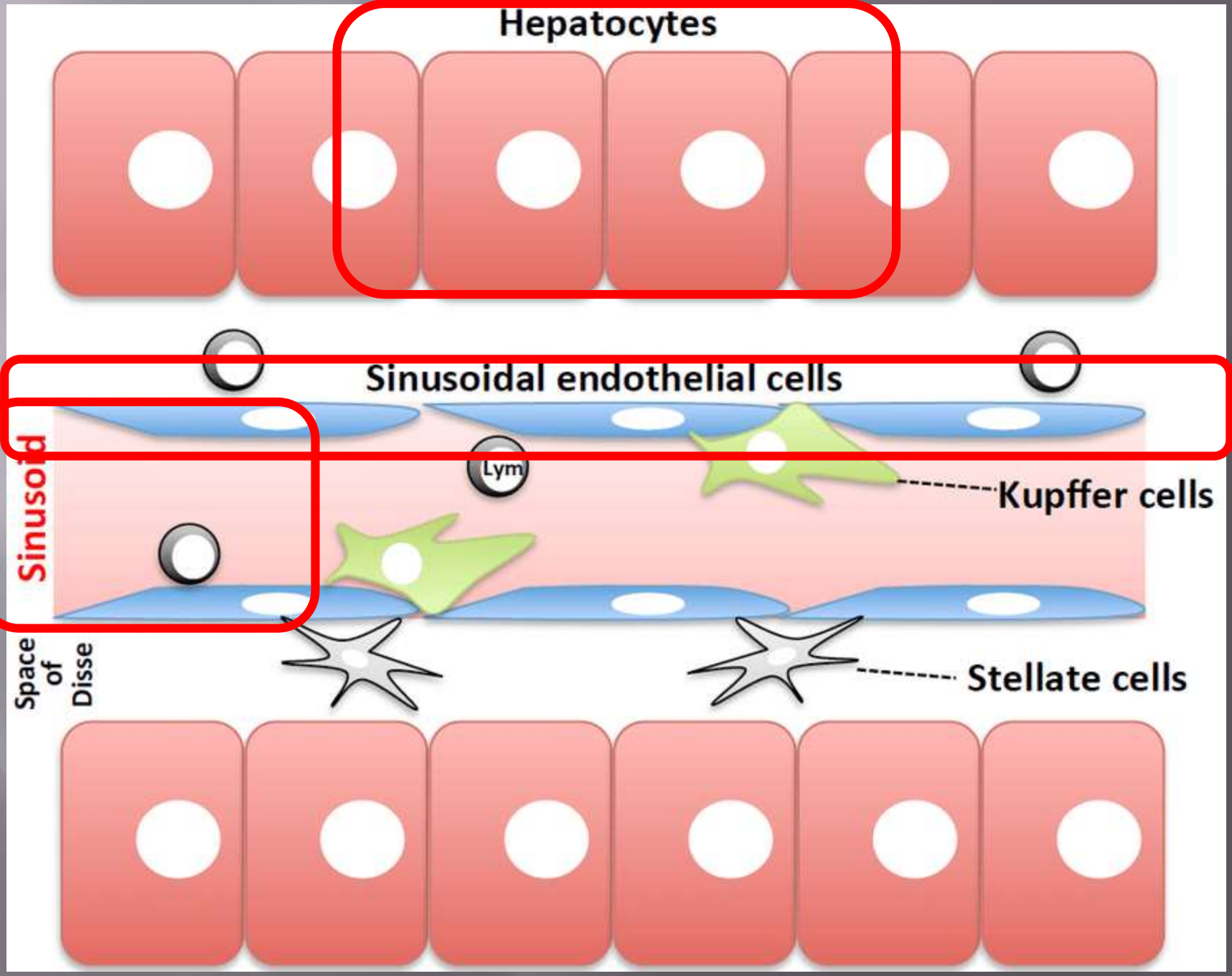
The Size of the Viral Inoculum Contributes to the Outcome of Hepatitis B Virus Infection▽†

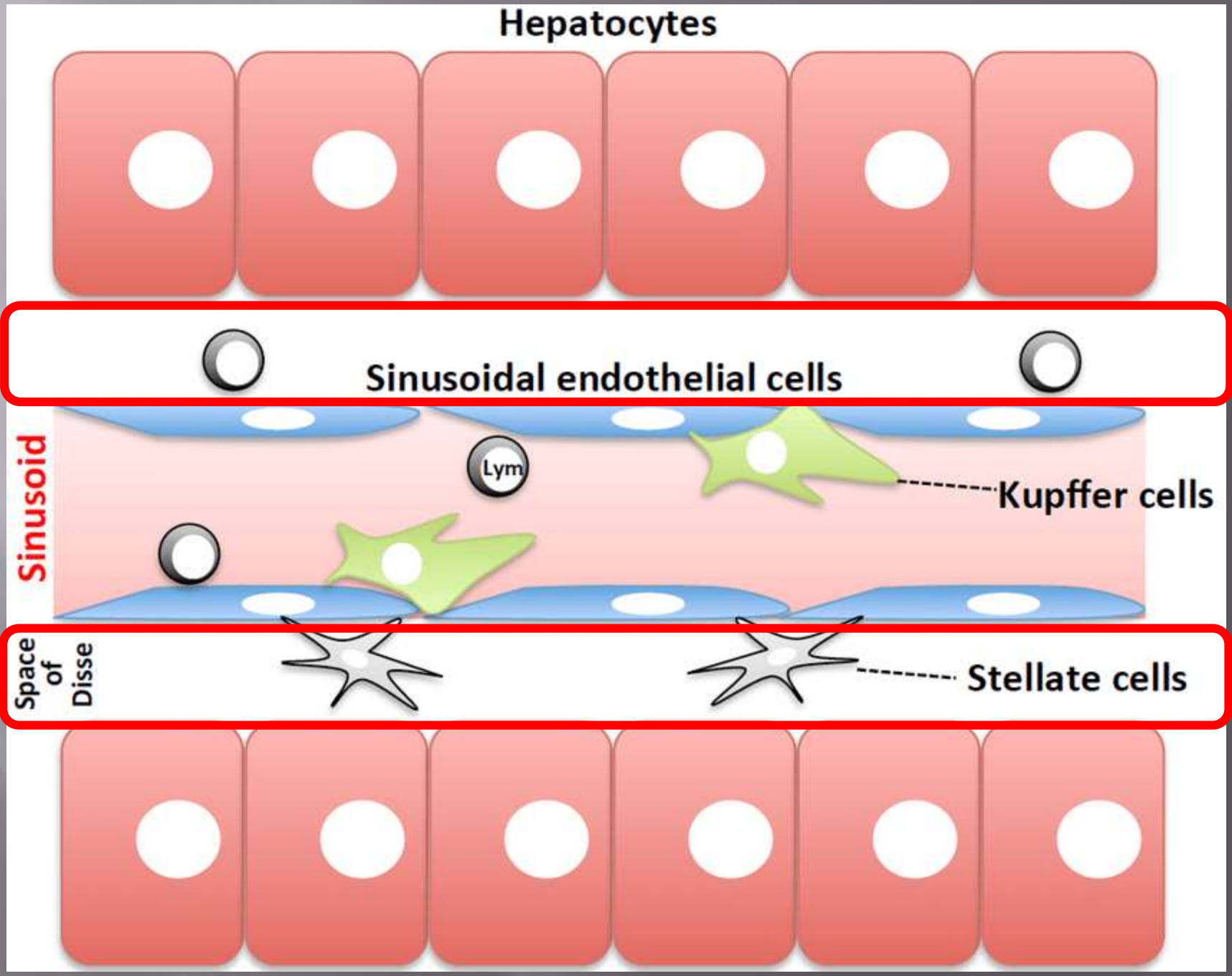
Shinichi Asabe,[1] Stefan F. Wieland,[1] Pratip K. Chattopadhyay,[2] Mario Roederer,[2] Ronald E. Engle,[3] Robert H. Purcell,[3] and Francis V. Chisari[1]*

Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, California 92037[1]; Immuno Technology Section, Laboratory of Immunology, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892[2]; and Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892[3]

Tek bir HBV virionu ile inoküle edilen şempanzelerde prodüktif infeksiyon gelişir.

Asabe S et al. J Virol 2009;83:9652


Hepatocytes
Sinusoidal endothelial cells
Sinusoid
Lym
Kupffer cells
Space of Disse
Stellate cells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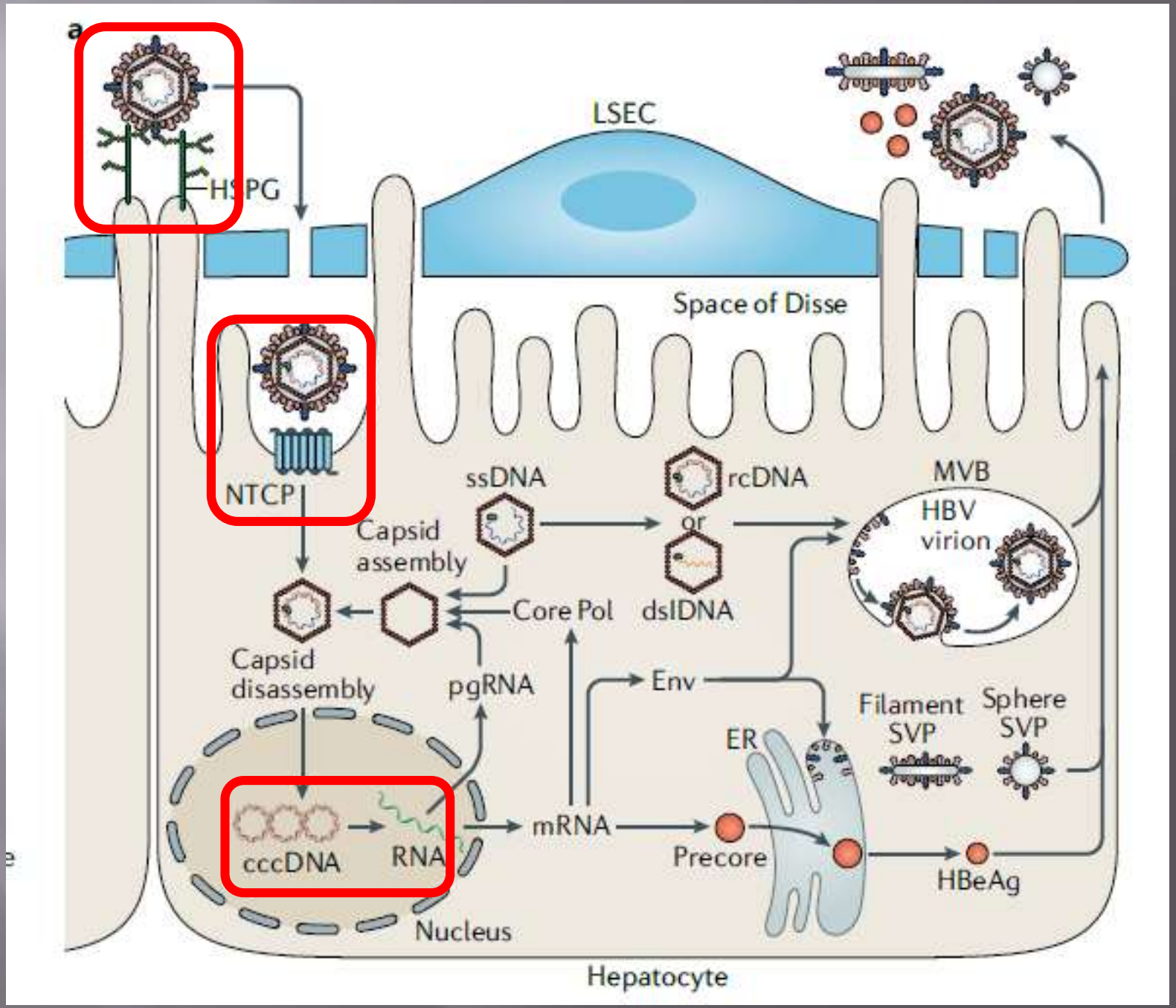


Iannacone M et al. Nat Rev Immunol 2022;22:19

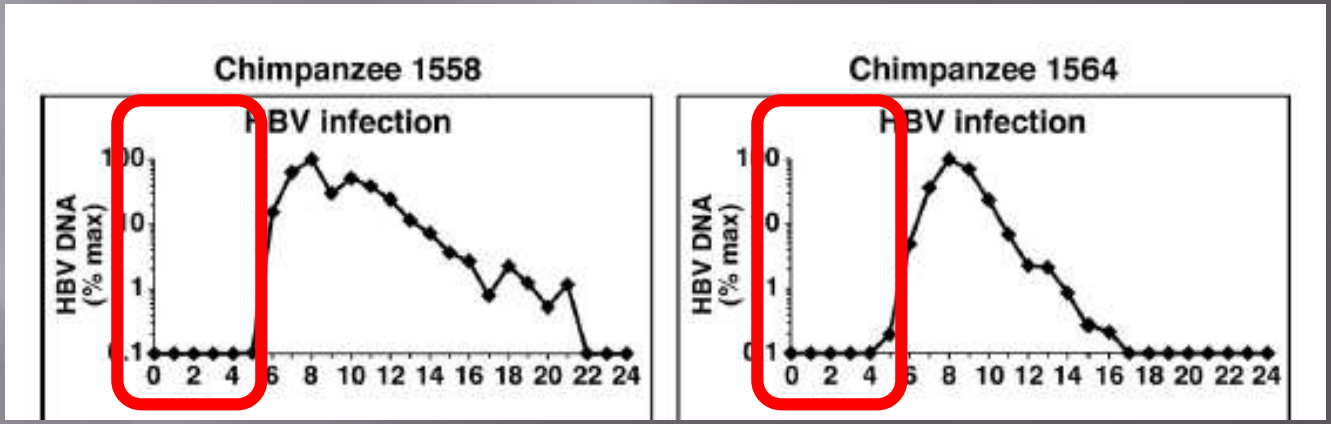
JOURNAL OF VIROLOGY, Aug. 2005, p. 9369–9380 Vol. 79, No. 15
0022-538X/05/$08.00+0 doi:10.1128/JVI.79.15.9369–9380.2005

MINIREVIEW

Stealth and Cunning: Hepatitis B and Hepatitis C Viruses

Stefan F. Wieland and Francis V. Chisari*

Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California



İnokülasyon sonrası HBV 4-7 hafta kadar etkin bir replikasyona başlamaz (Lag fazı)

Wieland SF et al. J Virol 2005;79:9369

Journal of General Virology (2006), 87, 1439–1449 DOI 10.1099/vir.0.81920-0

Review

The immune response during hepatitis B virus infection

Antonio Bertoletti and Adam J. Gehring

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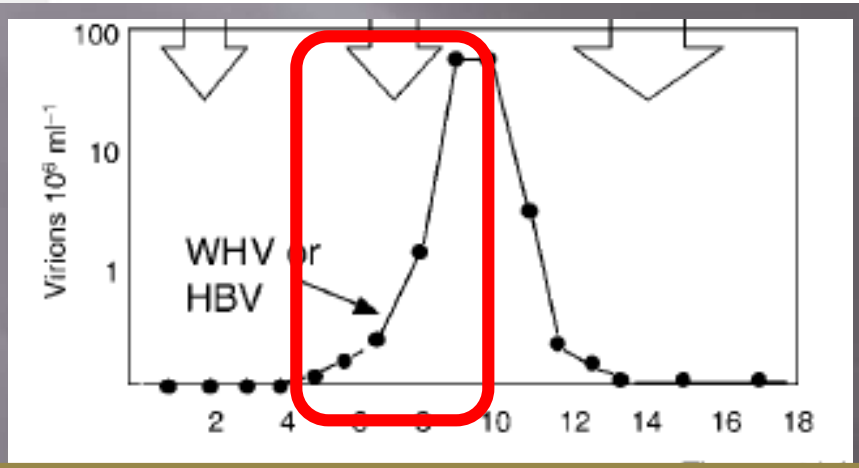


Ardından logaritmik bir ekspansiyon fazı ile hızla yükselerek 10^9-10^{10} kopya/ml düzeylerine ulaşır.

Bertoletti A et al. J Gen Virol 2006;87:1439

Dynamics of hepatitis B virus clearance in chimpanzees

John M. Murray*†, Stefan F. Wieland‡, Robert H. Purcell§, and Francis V. Chisari‡¶

*School of Mathematics, University of New South Wales, Sydney NSW 2052, Australia; †National Centre in HIV Epidemiology and Clinical Research, Level 2, 376 Victoria Street, Darlinghurst NSW 2010, Australia; ‡Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA 92037; and §National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-8009

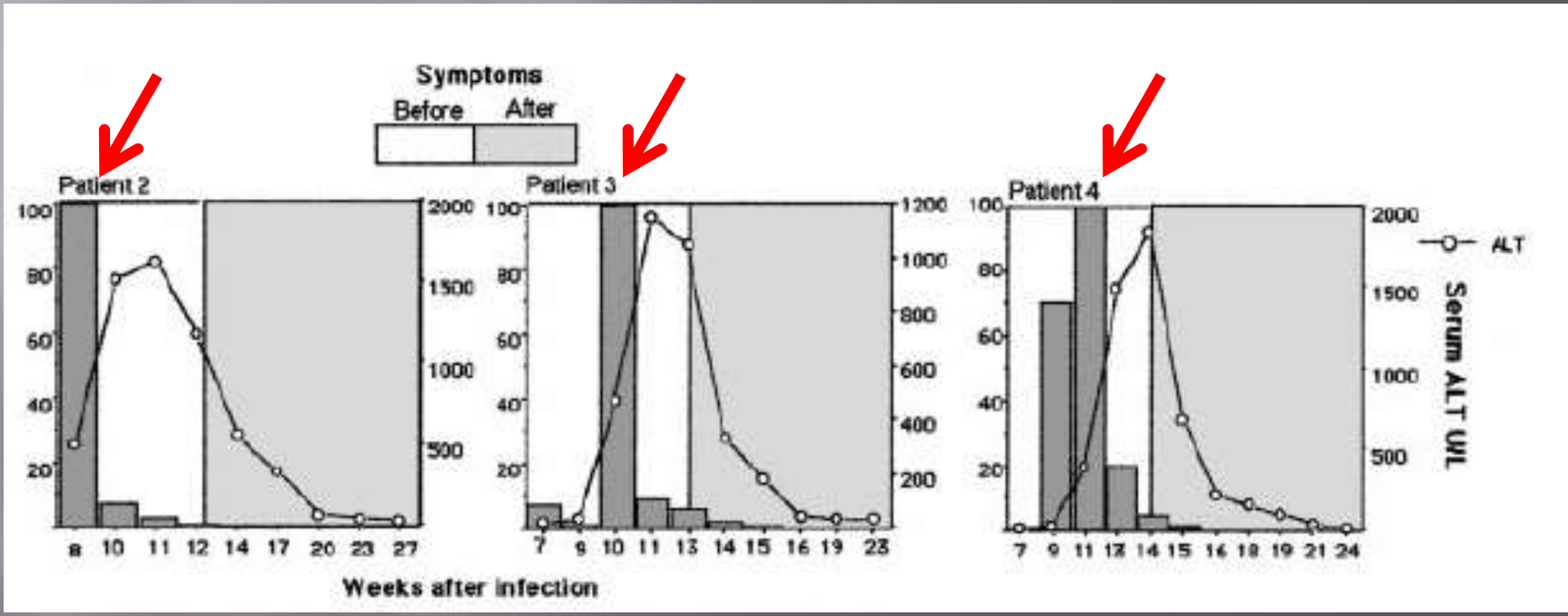
Contributed by Francis V. Chisari, October 14, 2005

7-10 haftalık bir süre içinde, hepatosellüler bir hasar olmaksızın, hepatositlerin %100'ünü infekte eder.

Proc. Natl Acad. Sci. USA 2005;102:17780

Incubation Phase of Acute Hepatitis B in Man: Dynamic of Cellular Immune Mechanisms

GEORGE J. M. WEBSTER,[1] STEPHANIE REIGNAT,[4] MALA K. MAINI,[4] SIMON A. WHALLEY,[1] GRAHAM S. OGG,[3] ABIGAIL KING,[3] DAVID BROWN,[1] PETER L. AMLOT,[2] ROGER WILLIAMS,[4] DIEGO VERGANI,[4] GEOFFREY M. DUSHEIKO,[1] AND ANTONIO BERTOLETTI[4]



HBV DNA'nın hızla yükseldiği bu dönemde hastalığın klinik semptomları izlenmez.

Webster GJM et al. Hepatology 2000;32:1117

Genomic analysis of the host response to hepatitis B virus infection

Stefan Wieland*, Robert Thimme*†, Robert H. Purcell‡, and Francis V. Chisari*§

*Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA 92037; and ‡Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institutes of Health, Bethesda, MD 20892-8009

Contributed by Francis V. Chisari, March 12, 2004

Hayvan deneylerinde infeksiyonun lag fazında karaciğerde hiçbir hücresel gen aktivasyonu saptanmaması, HBV'nin doğal bağışıklığı uyarmadığını gösterir.

Wieland et al. Proc. Natl Acad. Sci. USA 2004;101:6669

Doğal bağışık yanıt

Doğal bağışık yanıt, infeksiyonun başlangıç evresinde kontrolü ve izleyecek olan adaptif immün yanıtın aktivasyonu için son derece önemlidir.

PAMPs

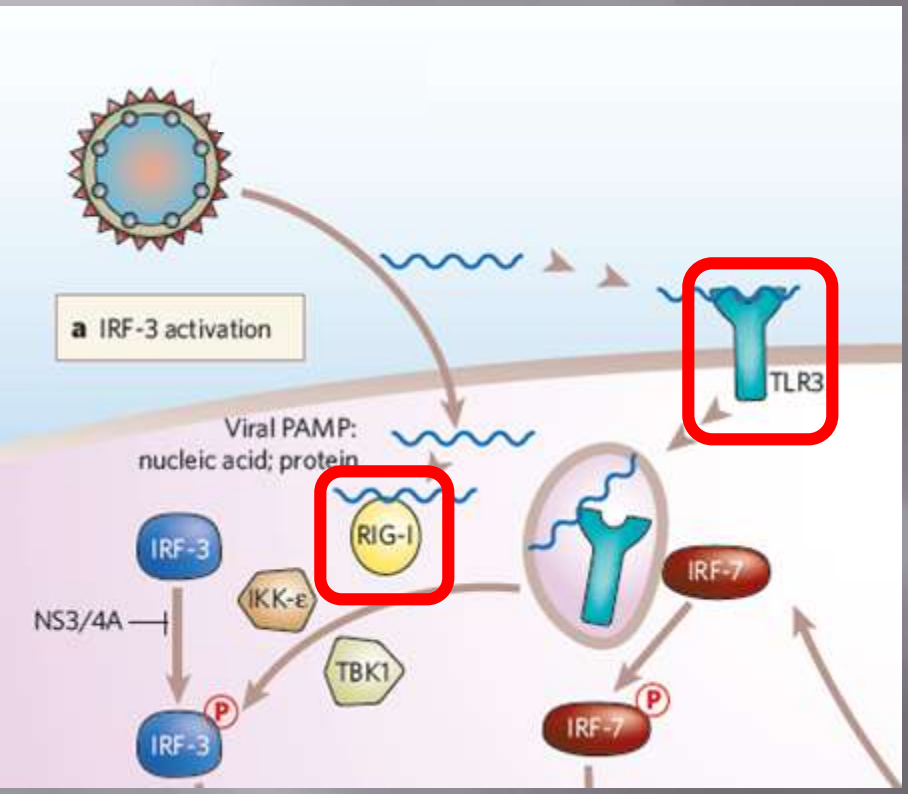
PAMPs
Pathogen-associated molecular patterns
(Patojen ilişkili moleküler kalıplar)

Prokaryotik yaşam biçimlerinde ve virüslerde var olan ve konakta olmayan, patojene özgü, tekrarlayan ve özgün moleküler yapılar

PRRs

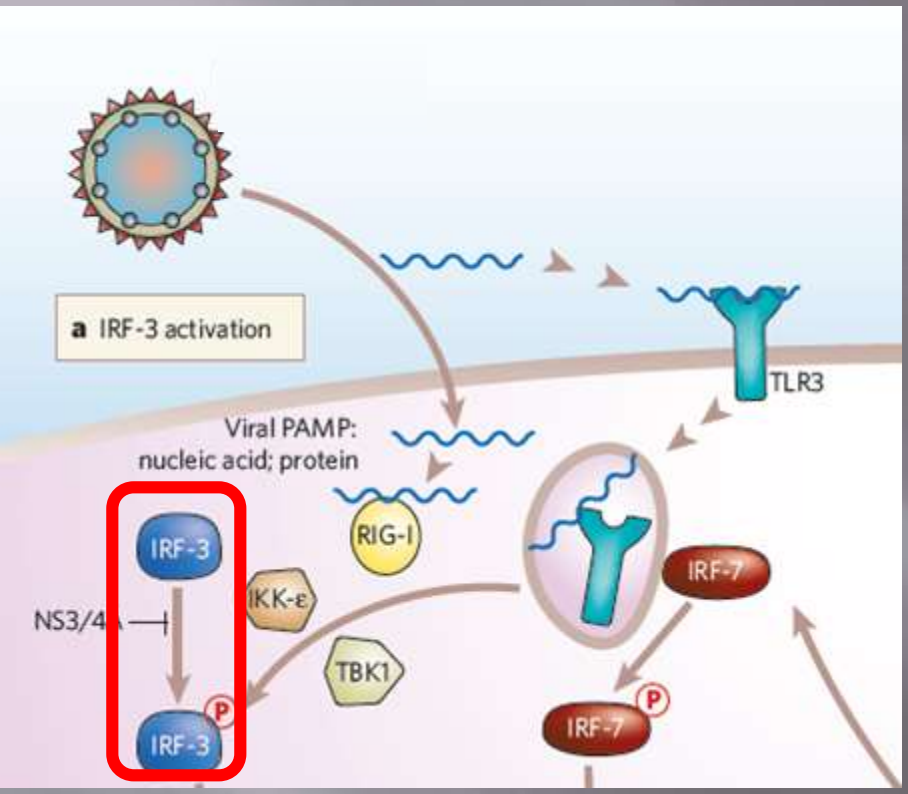
PRRs
Pattern recognition receptors
(Kalıp tanımlayıcı reseptörler)

- Toll-like reseptörler (TLRs)
- Nükleotid oligomerizasyon domain (NODLR)
- Retinoik asit inducible gen-1 benzeri helikazlar (RHLs)
- C tip lektin reseptörleri



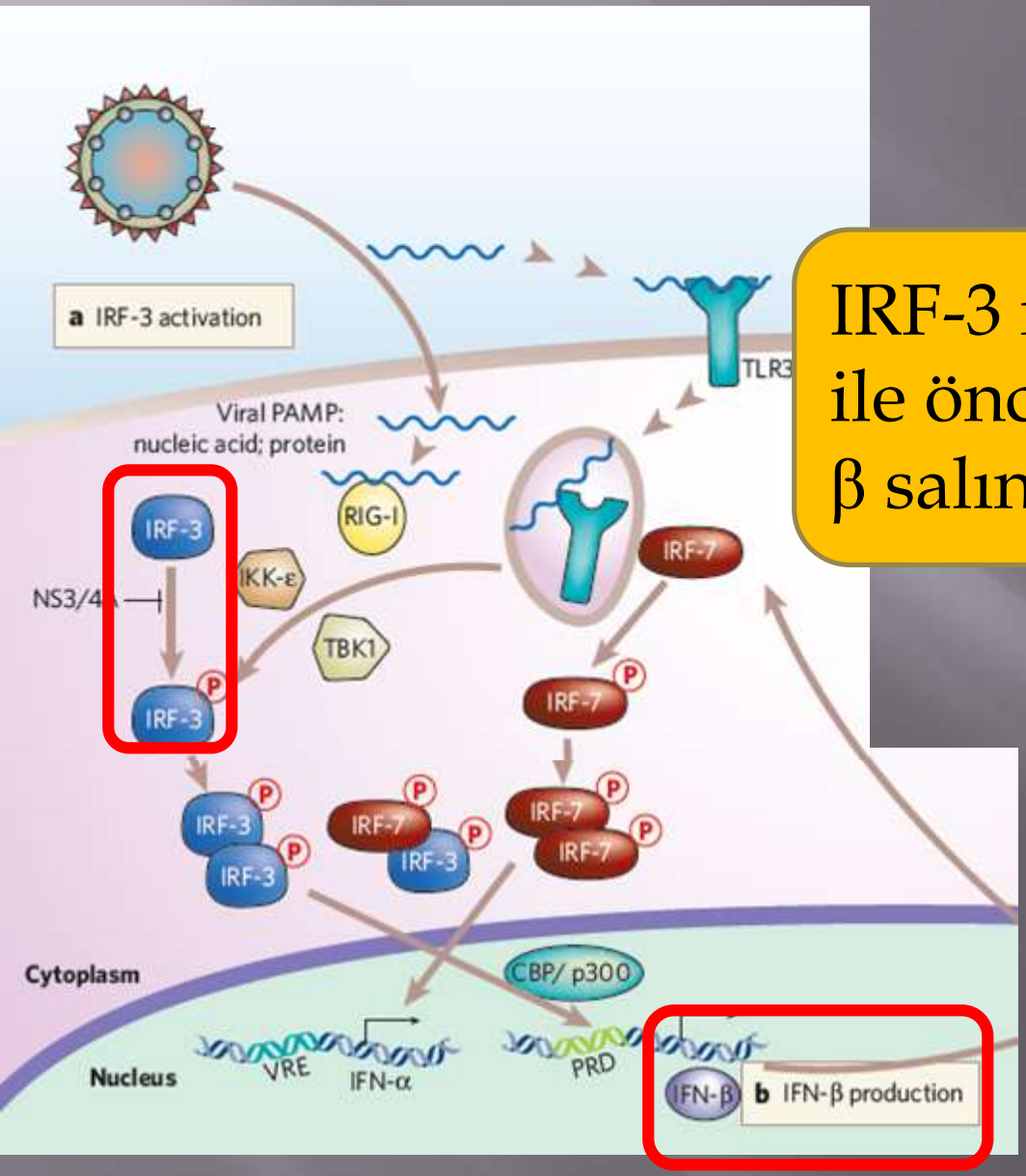
Konak yanıtı, virüse ait "Patojen ilişkili moleküler kalıp (PAMP)"'ların, konak hücredeki spesifik reseptörlerce tanınması ile tetiklenir.

Gale MJ. Nature 2005;436:939



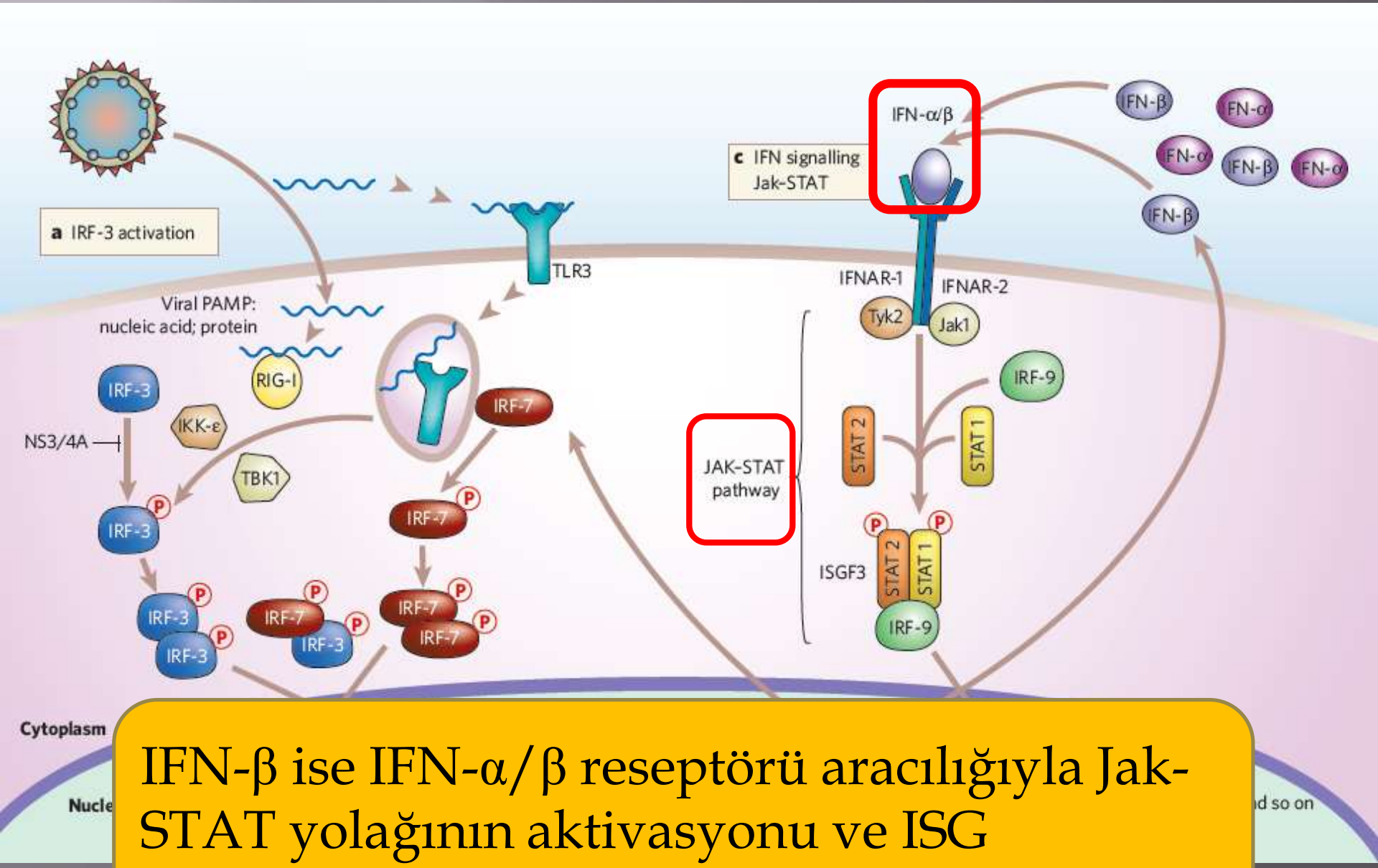
PAMP/PRR ilişkisi sonrası latent hücresel transkripsiyon faktörleri (IRF-3) aktive olur.

Gale MJ. Nature 2005;436:939



IRF-3 nükleus translokasyonu ile önce infekte hücreden IFN-β salınımını,

Gale MJ. Nature 2005;436:939



IFN-β ise IFN-α/β reseptörü aracılığıyla Jak-STAT yolağının aktivasyonu ve ISG ekspresyonunu tetikler.

5;436:939

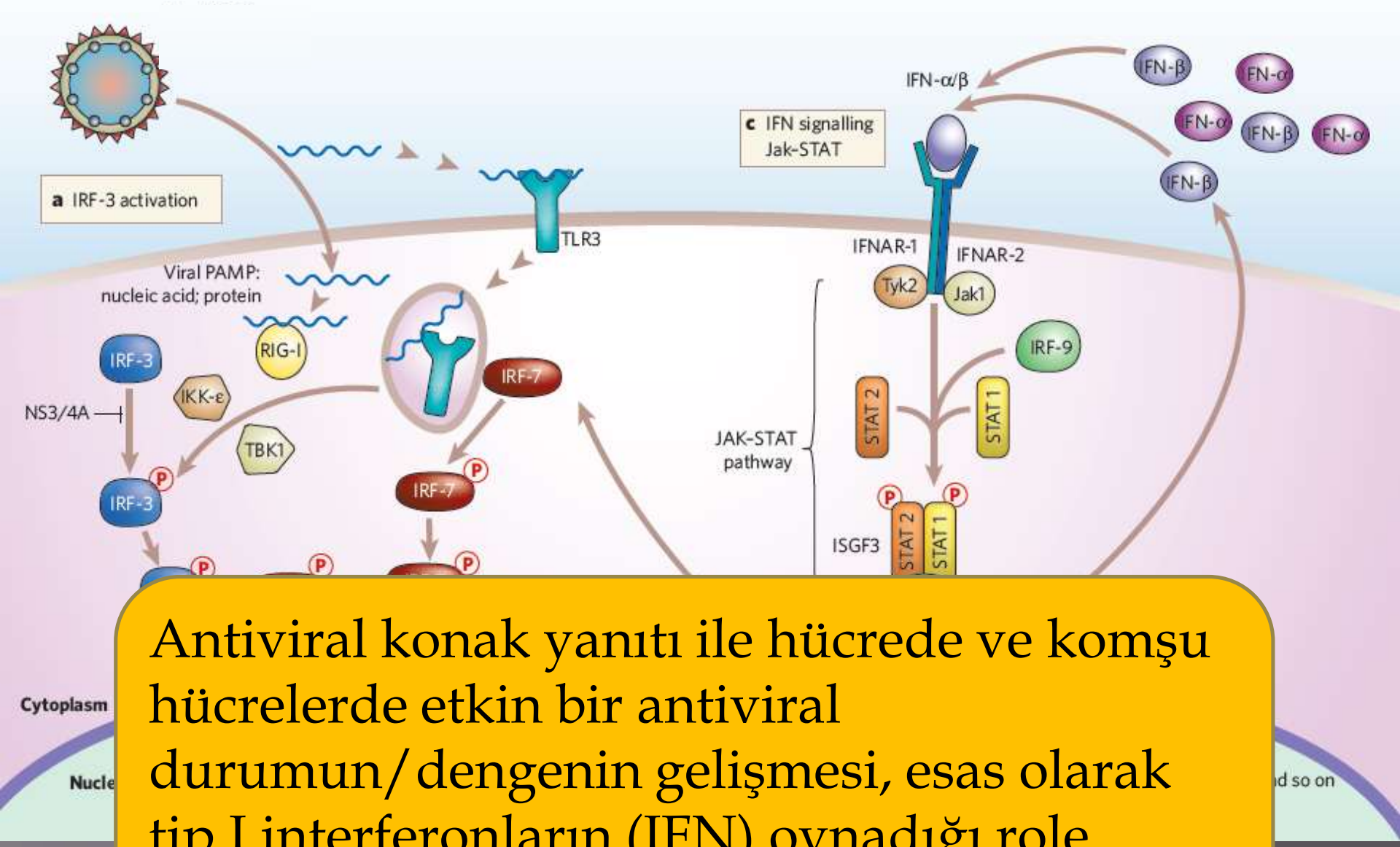
ISG ürünleri

2′-5′ oligoadenilat sentetaz,
viral RNA moleküllerini yıkar,

Protein kinaz R,
viral protein sentezini azaltır ve hücre içi RNA yıkımı,

p53 aktivitesi
Apoptozu indükler,

IRF-7,
IFN-α ekspresyonunu artırarak pozitif döngü yaratır; IFN üretimi ve etkisini ↑↑



Antiviral konak yanıtı ile hücrede ve komşu hücrelerde etkin bir antiviral durumun/dengenin gelişmesi, esas olarak tip I interferonların (IFN) oynadığı role bağlıdır.

JOURNAL OF VIROLOGY, Aug. 2005, p. 9369–9380 Vol. 79, No. 15
0022-538X/05/$08.00+0 doi:10.1128/JVI.79.15.9369–9380.2005

MINIREVIEW

Stealth and Cunning: Hepatitis B and Hepatitis C Viruses

Stefan F. Wieland and Francis V. Chisari*

Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California

HBV inkübasyon döneminin başlangıcında doğal bağışık yanıtı etkin biçimde stimüle etmez.

Bertoletti A et al. J Gen Virol 2006;87:1439

Wieland SF et al. J Virology 2005;79:9369

Molecular Biology of Hepatitis B Virus Infection

Christoph Seeger and **William S. Mason**
Fox Chase Cancer Center, Philadelphia, PA 19111

Abstract

Human hepatitis B virus (HBV) is the prototype of a family of small DNA viruses that productively infect hepatocytes, the major cell of the liver, and replicate by reverse transcription of a terminally redundant viral RNA, the pregenome. Upon infection, the circular, partially

Transkripsiyonel kalıp (cccDNA) çekirdek yerleşimlidir,

mRNA molekülleri konak mRNA'larına benzer biçimde poliadenile ve capped

Replikasyon ara ürünleri (RNA/DNA) nükleokapsid partikülleri içindedir.

Seeger C et al. Virology 2015;479:672

Liver INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER

Liver International ISSN 1478-3223

REVIEW ARTICLE

Management of acute hepatitis B and reactivation of hepatitis B

Ankur Jindal, Manoj Kumar and Shiv K. Sarin

Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

Haftalar boyu süren viremiye karşın klinik ya da biyokimyasal bulguların olmaması, HBV replikasyonunun tek başına sitopatik olmadığını gösterir.

Akut ya da kronik hastalıkta karaciğerde gelişen inflamasyon esas olarak konak immün yanıtı tarafından oluşturulur.

Jindal A et al. Liver Int 2013;33(S1):164

JOURNAL OF VIROLOGY, Aug. 2005, p. 9369–9380 Vol. 79, No. 15
0022-538X/05/$08.00+0 doi:10.1128/JVI.79.15.9369–9380.2005

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Wieland SF et al. J Virology 2005;79:9369

Viral Clearance Without Destruction of Infected Cells During Acute HBV Infection

Luca G. Guidotti,[1] Rosemary Rochford,[2] Josan Chung,[1]
Max Shapiro,[3] Robert Purcell,[4] Francis V. Chisari[1]*

Hastalığı kontrol eden şempanzelerde ekspansiyon fazı ile belirgin bir IFN-γ ve TNF-α aktivasyonu saptanır.

Guidotti LG et al. Science 1999;284:825

Viral Clearance Without Destruction of Infected Cells During Acute HBV Infection

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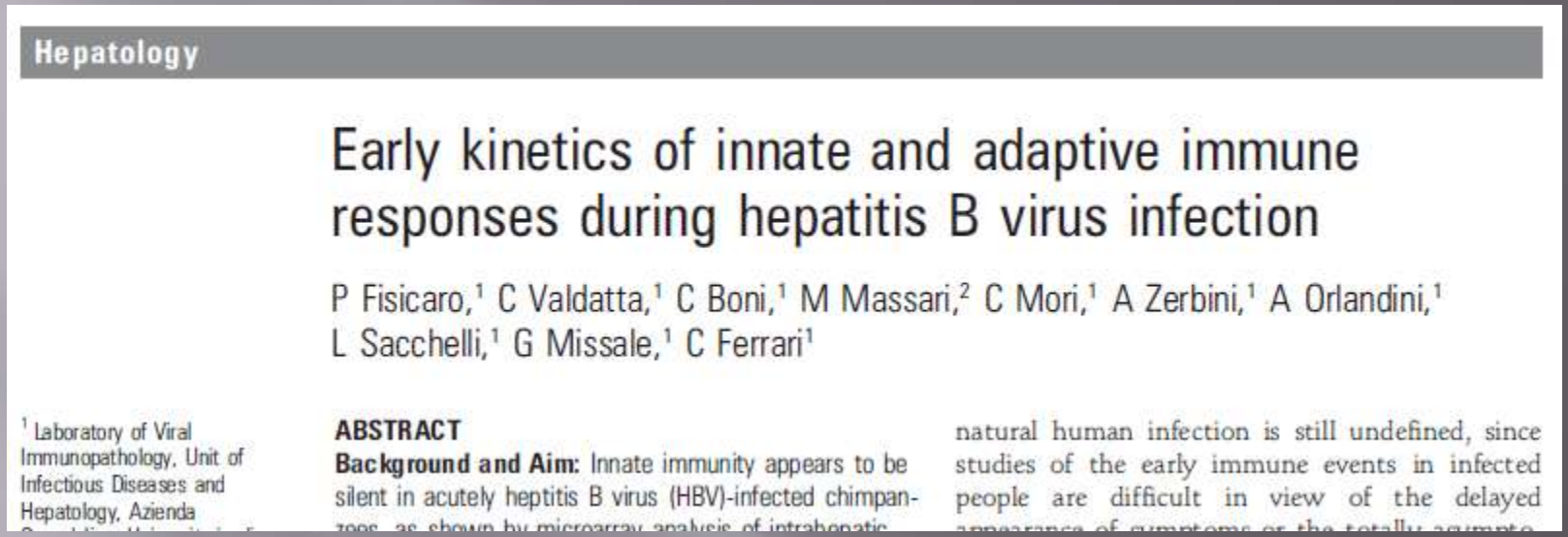
Max Shapiro,[3] Robert Purcell,[4] Francis V. Chisari[1]*

Akut infeksiyonu olan şempanzelerde intrahepatik IFN-γ üretiminin belirmesiyle viral replikasyonda belirgin düşüş olduğu,

T hücre yanıtından önce!!

Guidotti LG et al. Science 1999;284:825



Hepatology

Early kinetics of innate and adaptive immune responses during hepatitis B virus infection

P Fisicaro,[1] C Valdatta,[1] C Boni,[1] M Massari,[2] C Mori,[1] A Zerbini,[1] A Orlandini,[1] L Sacchelli,[1] G Missale,[1] C Ferrari[1]

[1] Laboratory of Viral Immunopathology, Unit of Infectious Diseases and Hepatology, Azienda

ABSTRACT

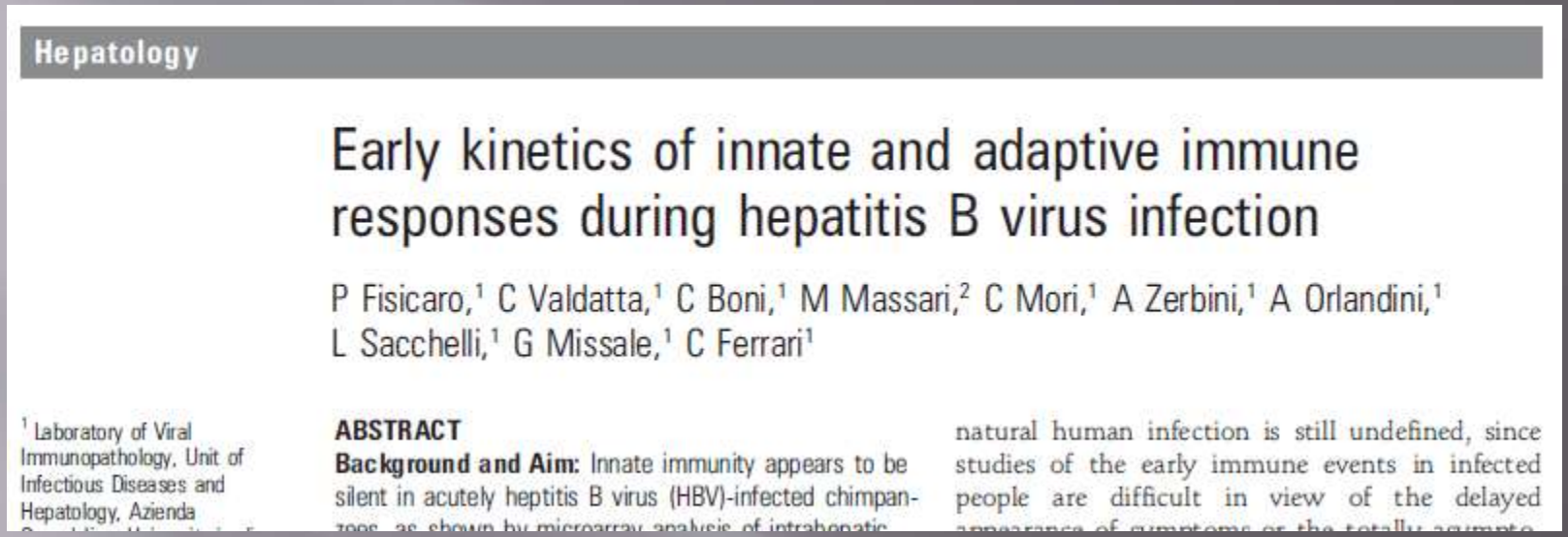
Background and Aim: Innate immunity appears to be silent in acutely heptitis B virus (HBV)-infected chimpanzees, as shown by microarray analysis of intrahepatic

natural human infection is still undefined, since studies of the early immune events in infected people are difficult in view of the delayed

HBV DNA en yüksek düzeylere erişmeden NK ve NK-T hücrelerde aktivasyon ve IFN-γ üretimi,

HBV spesifik T hücre yanıtlarının DNA düzeyleri düşüşe geçtiğinde maksimize olduğu belirlendi.

Fisicaro P et al. Gut 2009;58:974



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natural human infection is still undefined, since studies of the early immune events in infected people are difficult in view of the delayed

NK ve NK-T hücrelerinin HBV'ye karşı erken ve etkin bir yanıt geliştirdiği,

Doğal bağışık yanıtın erken ve etkin gelişiminin nonsitolitik mekanizmalarla infeksiyonun kontrolünü sağlayabileceği…

Fisicaro P et al. Gut 2009;58:974

Journal of General Virology (2006), 87, 1439–1449 DOI 10.1099/vir.0.81920-0

Review

The immune response during hepatitis B virus infection

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Doğal immün yanıtın aktivasyonu ve IFN-γ yanıtı, ardından gelişecek adaptif bağışık yanıtın indüksiyonu ve infeksiyonun kontrolü açısından önemlidir.

Bertoletti A et al. J Gen Virol 2006;87:1439

Journal of General Virology (2006), 87, 1439–1449 DOI 10.1099/vir.0.81920-0

Review

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Hayvan deneylerinde IFN-γ ve TNF-α üretiminde belirgin artış saptanmayanlarda hastalık kronikleşir.

Bertoletti A et al. J Gen Virol 2006;87:1439

JOURNAL OF VIROLOGY, Aug. 2005, p. 9369–9380 Vol. 79, No. 15
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MINIREVIEW

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HBV hepatositlerin neredeyse tamamını infekte eder, infekte hücrelerde HBV antijenleri yüksek düzeyde eksprese edilir.

Adaptif immün yanıt tarafından daha kolay tanınır.

Wieland SF et al. J Virology 2005;79:9369

JOURNAL OF VIROLOGY, Aug. 2005, p. 9369–9380 Vol. 79, No. 15
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HBV spesifik adaptif yanıtın şiddeti, kinetikleri ve efektör fonksiyonları yetişkinlerde infeksiyonun sonucu açısından belirleyicidir.

Wieland SF et al. J Virology 2005;79:9369

CD4 T hücreleri,
efektör sitotoksik CD8 T hücre yanıtı ile B hücre antikor üretimi

CD8 T hücreleri,
sitolitik ve nonsitolitik yollarla infekte hepatositlerin eliminasyonu

B hücreleri,
serbest viral partiküllerin nötralizasyonu ve reinfeksiyonun önlenmesi

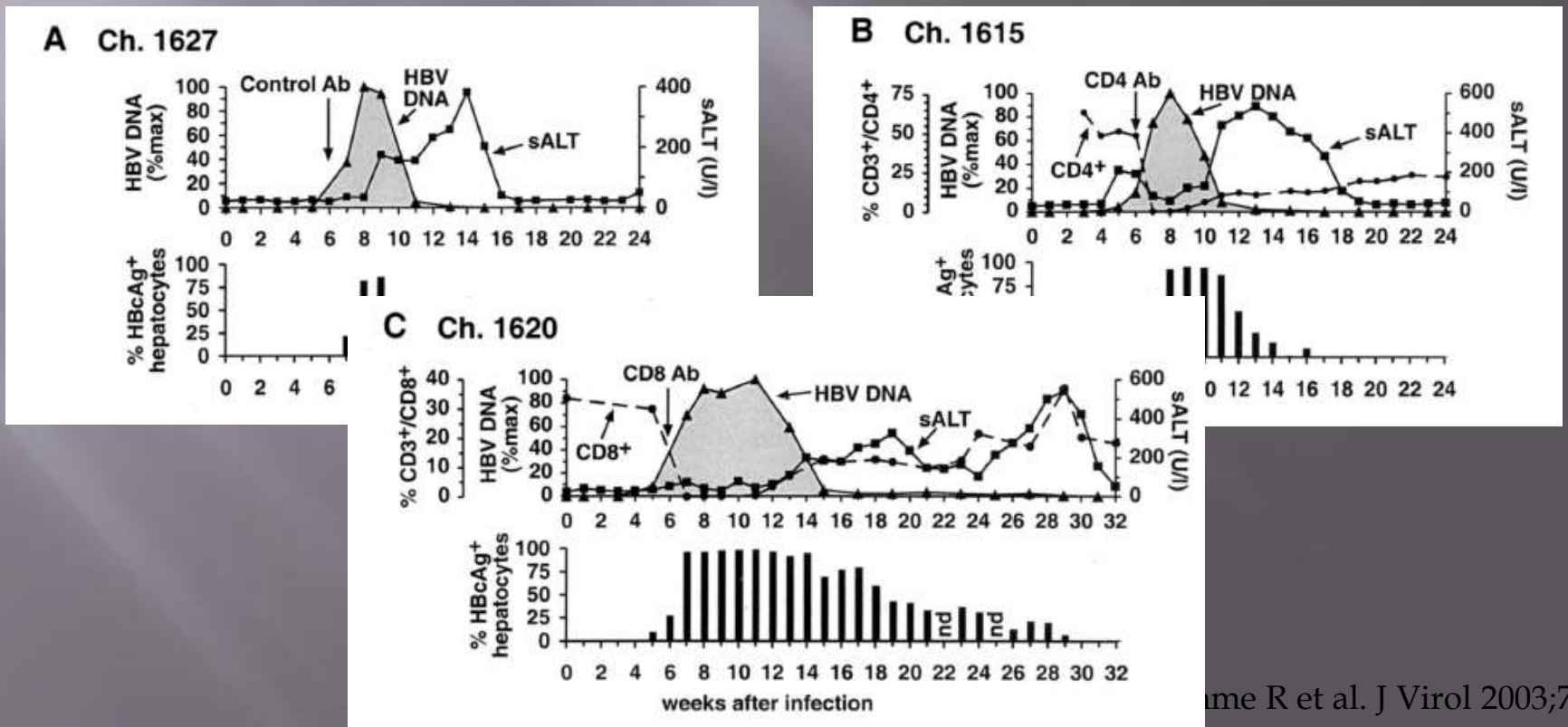
JOURNAL OF VIROLOGY, Jan. 2003, p. 68–76
0022-538X/03/$08.00+0 DOI: 10.1128/JVI.77.1.68–76.2003

Vol. 77, No. 1

CD8$^+$ T Cells Mediate Viral Clearance and Disease Pathogenesis during Acute Hepatitis B Virus Infection†

Robert Thimme,[1]‡ Stefan Wieland,[1] Carola Steiger,[1] John Ghrayeb,[2] Keith A. Reimann,[3] Robert H. Purcell,[4] and Francis V. Chisari[1]*

Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California[1]; Centocor, Malvern, Pennsylvania[2]; Division of Viral Pathogenesis, Beth Israel Deaconess Medical Center, Boston, Massachusetts[3]; and Hepatitis Viruses Section, Laboratory of Infectious Diseases, National Institutes of Health, Bethesda, Maryland[4]



JOURNAL OF VIROLOGY, Jan. 2003, p. 68–76 Vol. 77, No. 1
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Akut hepatit B'de hastalık patogenezi ve viral klirensten esas olarak CD8 T hücreleri sorumludur,

IFN-γ salınımı ile HBV gen ekspresyonu non-sitopatik olarak inhibe edilir, transkripsiyon kalıbı cccDNA düzeyleri düşer.

Thimme R et al. J Virol 2003;77:68

JOURNAL OF VIROLOGY, Aug. 2005, p. 9369–9380 Vol. 79, No. 15
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İnfekte hepatositlerin >%90 non-sitolitik mekanizmalar ile temizlenir.

Wieland SF et al. J Virology 2005;79:9369

Naiv CD8 T hücrelerinin spesifik olarak duyarlılaştırılması (priming) ve efektör hücrelere dönüşümü, antijen sunan hücrelerce Ag sunumunu ve CD4 T hücre yardımını gerektirir.

JOURNAL OF VIROLOGY, Oct. 2009, p. 9652–9662 Vol. 83, No. 19
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The Size of the Viral Inoculum Contributes to the Outcome of Hepatitis B Virus Infection▽†

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CD4 T hücre deplesyonu yapılması, T hücre priming'ini önleyerek persistan infeksiyona yol açmaktadır.

Asabe S et al. J Virol 2009;83:9652

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Profesyonel APC, DC tarafından MHC sınıf I molekülleri üzerinde viral Ag'lerin sunumu sekonder lenfoid organlarda gerçekleşir.

Dynamics and genomic landscape of CD8+ T cells undergoing hepatic priming

Alexandre P. Bénéchet[#1], Giorgia De Simone[#1,2], Pietro Di Lucia[1], Francesco Cilenti[2,3], Giulia Barbiera[3], Nina Le Bert[4], Valeria Fumagalli[1,2], Eleonora Lusito[3], Federica Moalli[1], Valentina Bianchessi[2,3], Francesco Andreata[1], Paola Zordan[1], Elisa Bono[1], Leonardo Giustini[1], Weldy V. Bonilla[5], Camille Bleriot[6], Kamini Kunasegaran[4], Gloria Gonzalez-Aseguinolaza[7], Daniel D. Pinschewer[5], Patrick T.F. Kennedy[8], Luigi Naldini[2,3], Mirela Kuka[1,2], Florent Ginhoux[6,9], Alessio Cantore[2,3], Antonio Bertoletti[4,6], Renato Ostuni[2,3,†], Luca G. Guidotti[1,2,†], Matteo Iannacone[1,2,10,†,‡]

Naiv CD8 T hücre duyarlılaştırılması, non-lenfoid organlarda endotelyal bariyer nedeniyle gerçekleşmez.

Benechet AP et al. Nature 2019;574:200

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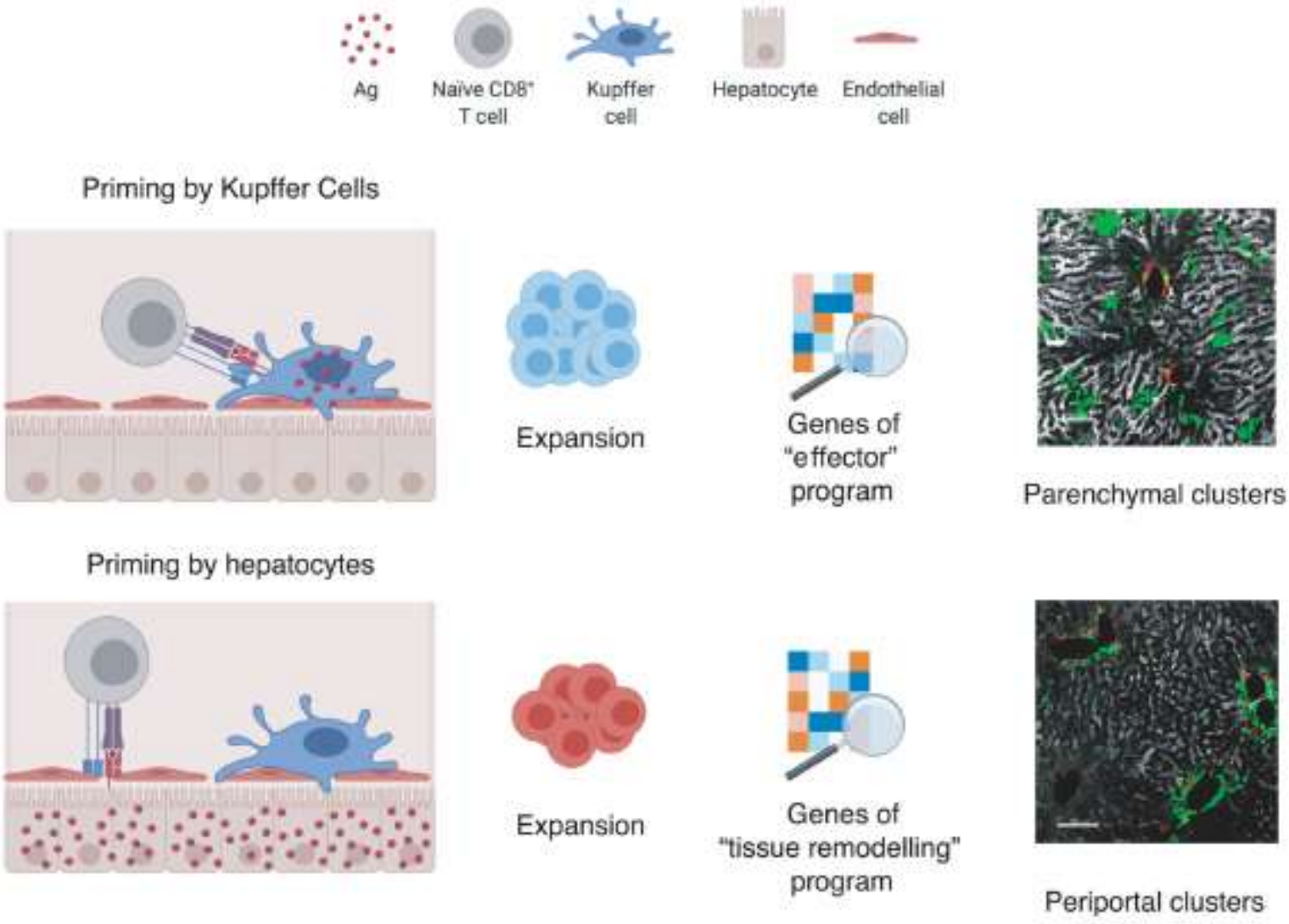

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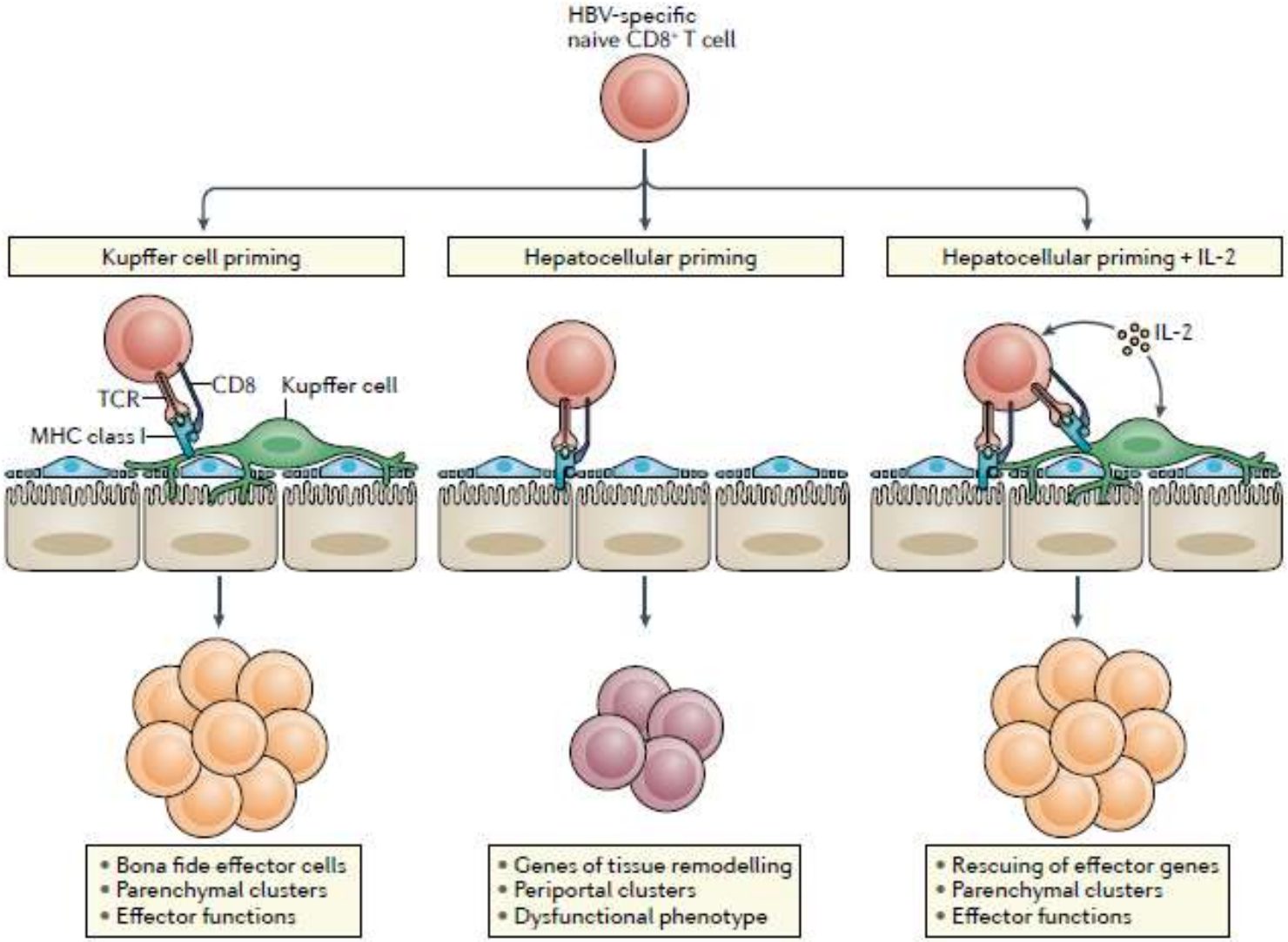
Immunobiology and pathogenesis of hepatitis B virus infection



Iannacone M et al. Nat Rev Immunol 2022;22:19

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Hepatositlerce duyarlılaştırılan naiv CD8 T hücreleri efektör hücrelere dönüşmezler,

Doku gelişimi, remodelling ve yara iyileşmesi ile ilişkili genler aktive olur, "doku koruma" programı öne çıkar.

Benechet AP et al. Nature 2019;574:200

B hücrelerinin HBsAg'ye karşı nötralizan antikor üretimi serbest viral partiküllerin nötralizasyonu ve reinfeksiyonun önlenmesi

Yuen MF et al. Nature Rev 2018;4:18035

Immunobiology and pathogenesis of hepatitis B virus infection

Matteo Iannacone[1,2,3] ✉ *and Luca G. Guidotti*[1,2] ✉

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Nerede duyarlılaştırıldığından bağımsız olarak, CD8 T hücrelerinin antiviral etkilerini göstermeleri için hepatosellüler antijenleri tanımaları gereklidir.

Iannacone M et al. Nat Rev Immunol 2022;22:19

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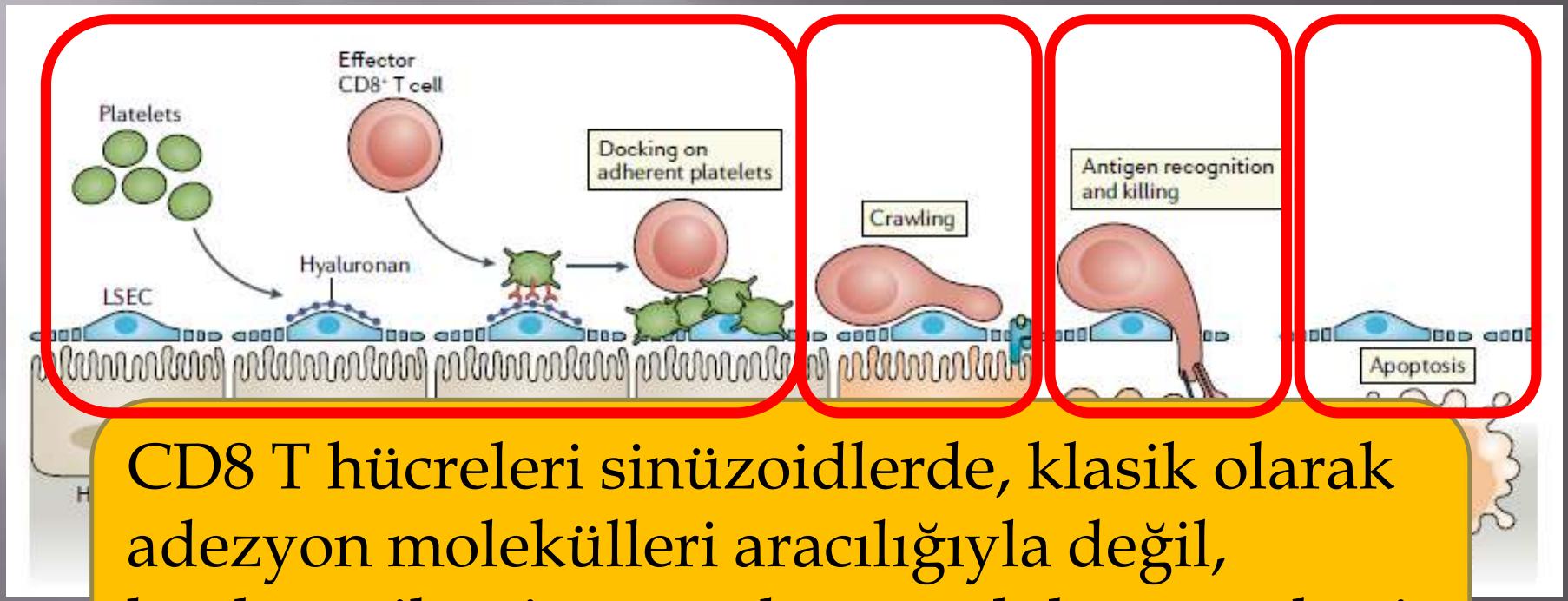
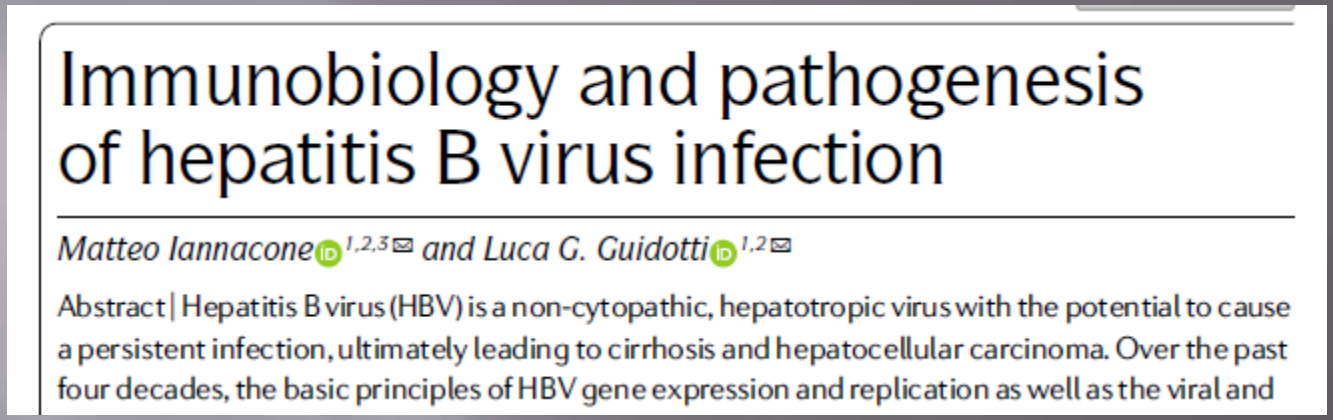


CD8 T hücreleri sinüzoidlerde, klasik olarak adezyon molekülleri aracılığıyla değil, hyaluronik asit uzantılarına takılan trombosit agregatlarına bağlanır.



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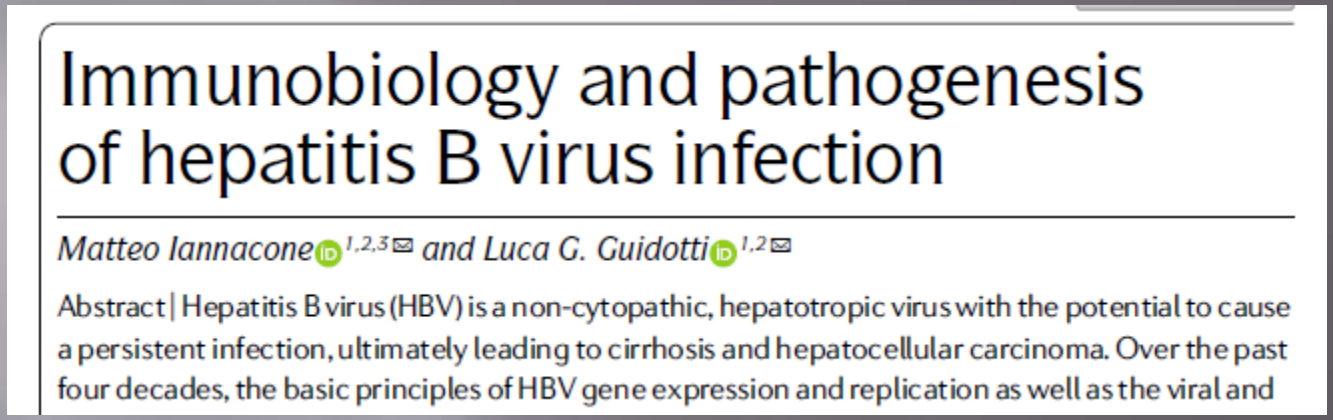
Ancak öldürme süreci etkin değildir çünkü T hücresi ile hepatositin fiziksel temasını gerektirir.

Iannacone M et al. Nat Rev Immunol 2022;22:19



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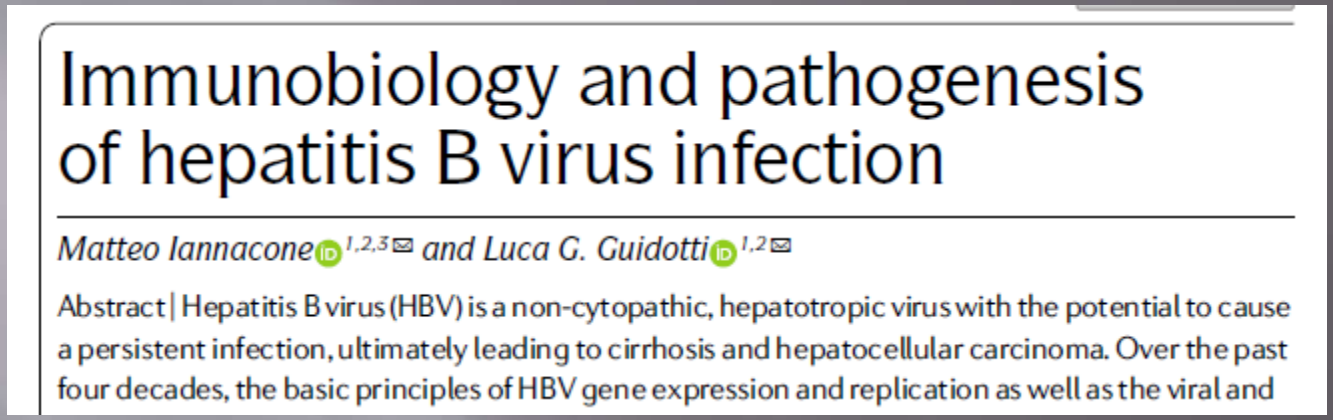
Viral replikasyonun efektör CD8 T hücreleri tarafından inhibisyonu esas olarak lokal IFNγ ve TNF üretimi ile nonsitolitik mekanizmalar aracılığıyla olur.

Iannacone M et al. Nat Rev Immunol 2022;22:19



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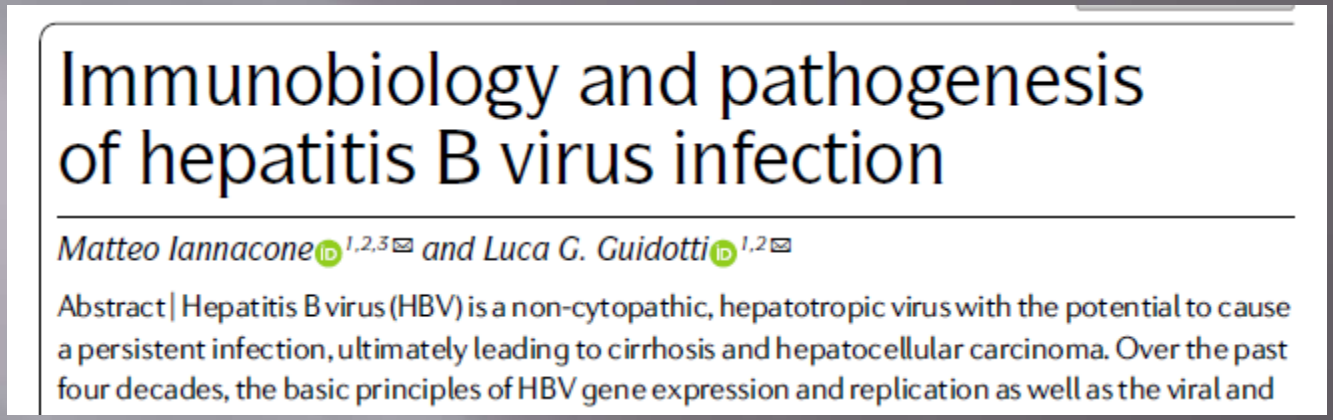
Hepatositte HBV RNA içeren nükleokapsidlerin biraraya gelmesi önlenir,

Stabilizasyonunu sağlayan SSB/La proteinin degredasyonu ile HBV RNA destabilize olur,

Nüklear APOBEC3 deaminaz aktivasyonu ile cccDNA'nın stabilizasyonu bozulur,

Iannacone M et al. Nat Rev Immunol 2022;22:19



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CD8 T hücreleri, antijen eksprese eden hepatositlern perforin/fas aracılı apoptozunu tetikler,

Ölen hepatositler Kuppfer hücrelerince ortadan kaldırılır,

Zamanla apoptotik hepatositler temizlenemez ve nekrotik odak haline gelirler

Iannacone M et al. Nat Rev Immunol 2022;22:19

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DAMP molekülleri nötrofil kemotaksisini sağlar,

İnflamatuvar mediatörler ve matriks metalloproteinazları matriks bileşenleri yıkılır

İntrahepatik inflamatuvar hücre birikimi ve lokal proinflamatuvar sitokinler ile hepatoselüler hasar gelişir.

Iannacone M et al. Nat Rev Immunol 2022;22:19

Liver INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER

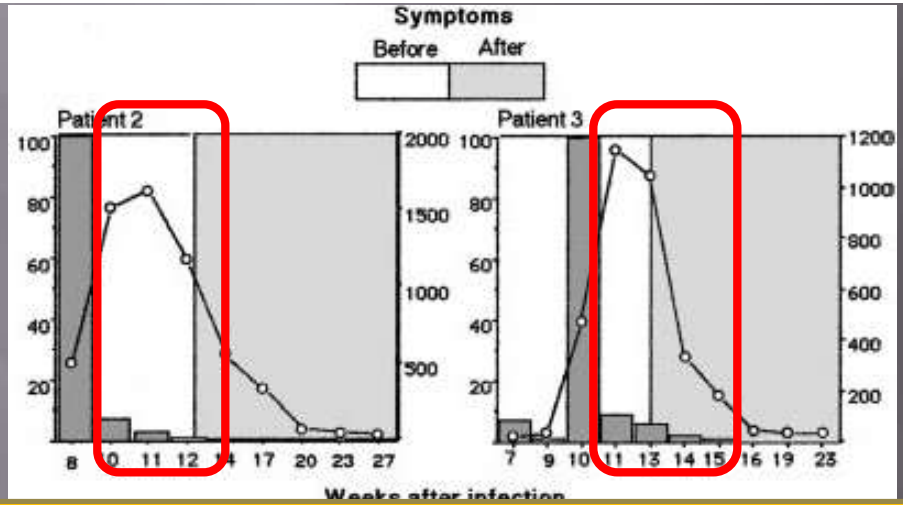
Liver International ISSN 1478-3223

REVIEW ARTICLE

Management of acute hepatitis B and reactivation of hepatitis B

Ankur Jindal, Manoj Kumar and Shiv K. Sarin

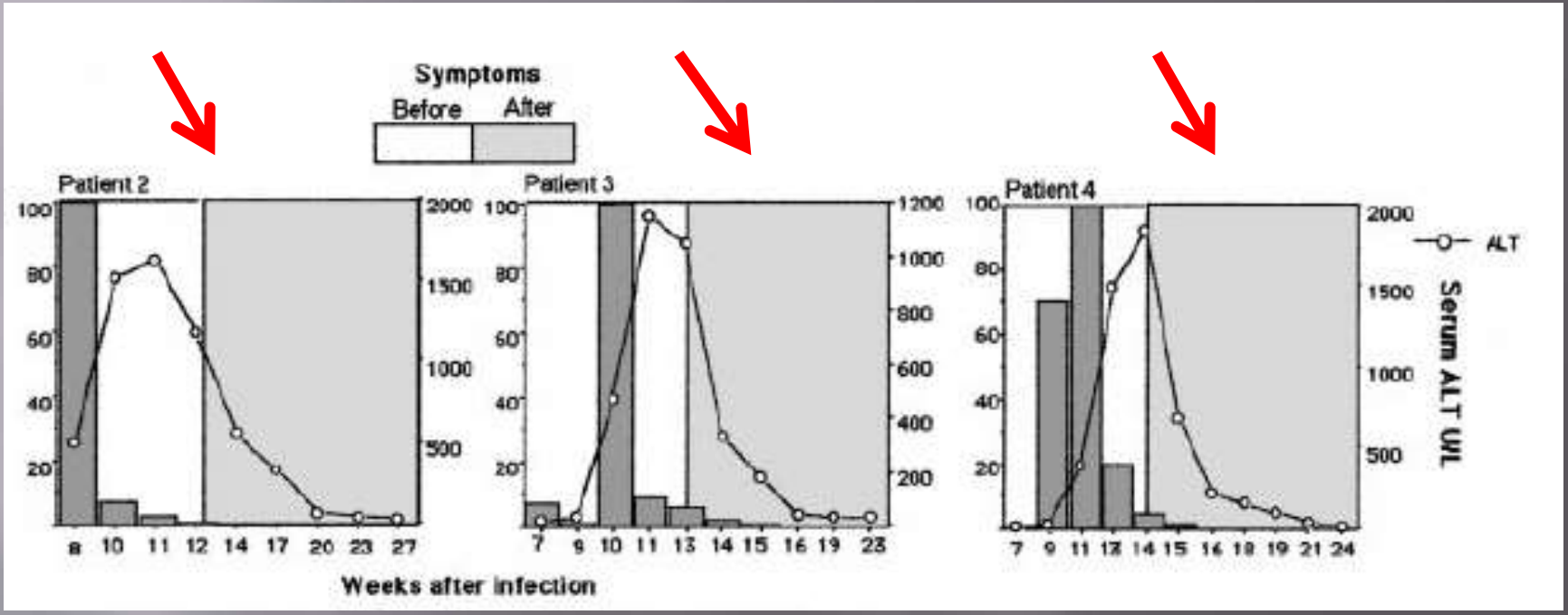
Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India



CTL aracılı sitolitik yanıt ve cccDNA içeren hepatositlerin yıkımı ile akut hepatit semptomları oluşur.

32:1117

Jindal A et al. Liver Int 2013;33(S1):164



Klinik semptomların başlangıcı, HBV DNA düzeyinin zirve yaptıktan sonra azalmaya başladığı döneme denk gelir.

Webster GJM et al. Hepatology 2000;32:1117

Journal of General Virology (2006), **87**, 1439–1449 DOI 10.1099/vir.0.81920-0

Review

The immune response during hepatitis B virus infection

Antonio Bertoletti and Adam J. Gehring

The UCL Institute of Hepatology, University College of London, 69–75 Chenies Mews, London WC1E 6HX, UK

Correspondence
Antonio Bertoletti
a.bertoletti@ucl.ac.uk

Sonuç olarak HBV infeksiyonunun kontrolü için adaptif immün yanıtın hem hücresel hem de humoral kollarının aktivasyonu gerekmektedir.

Bertoletti A et al. J Gen Virol 2006;87:1439

JOURNAL OF VIROLOGY, Aug. 2005, p. 9369–9380 Vol. 79, No. 15
0022-538X/05/$08.00+0 doi:10.1128/JVI.79.15.9369–9380.2005

MINIREVIEW

Stealth and Cunning: Hepatitis B and Hepatitis C Viruses

Stefan F. Wieland and Francis V. Chisari*

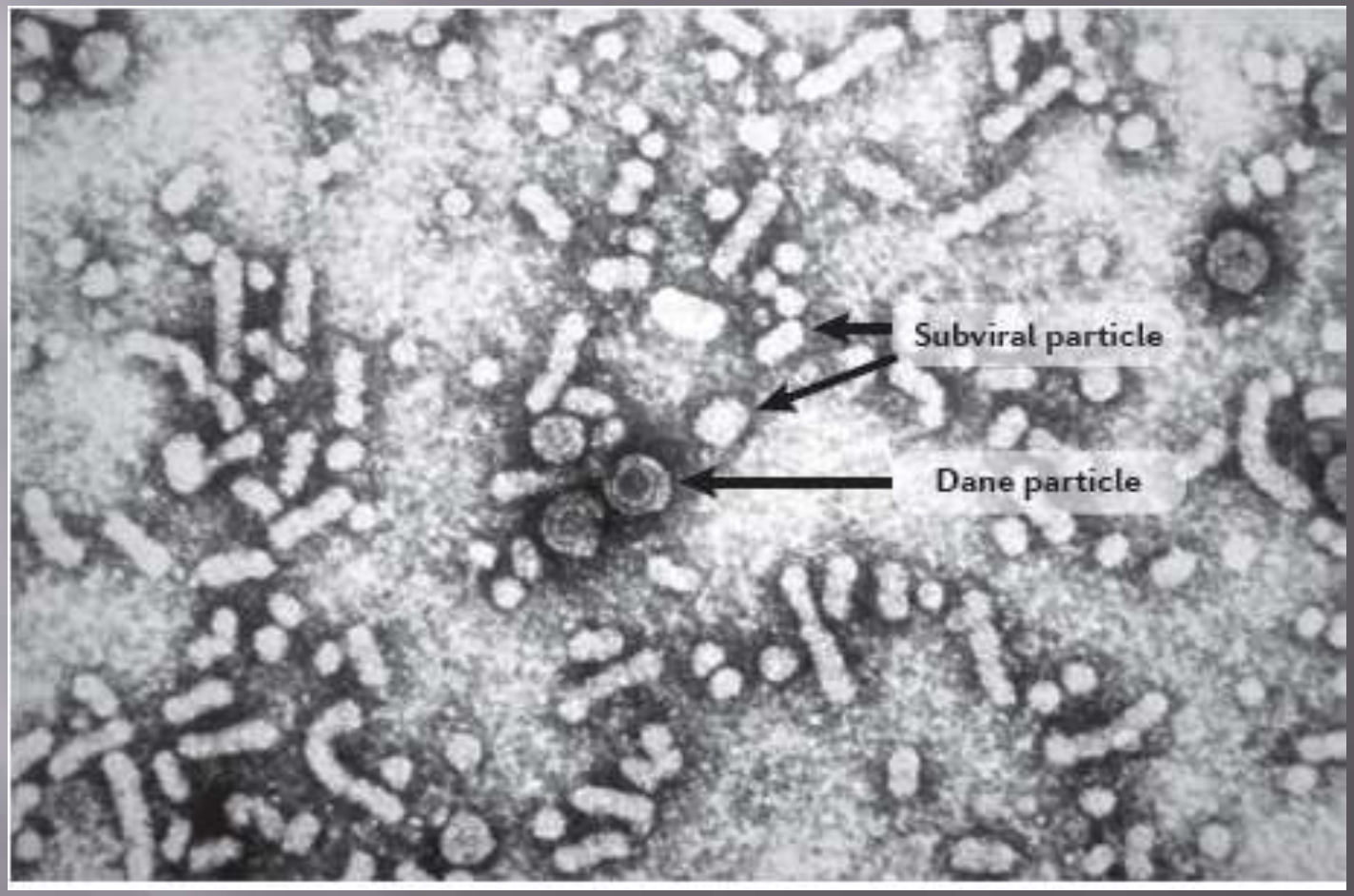
Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California

HBV

- doğal bağışık yanıtı indüklemeyerek,
- adaptif bağışık yanıtı baskılayarak

Wieland SF et al. J Virology 2005;79:9369

Mechanisms leading to HBV chronicity



HBsAg'nin aşırı miktarda üretimi

"virionların 10^3-10^6 katı HBsAg partikülü"

Yuen MF et al. Nature Rev 2018;4:18035

PRIMER

Hepatitis B virus infection

HBV spesifik humoral immün yanıt için yanlış hedef,

Ag spesifik T hücre reseptör sinyal yolaklarının sürekli uyarımıyla HBV spesifik T hücre anerjisi ve delesyonuna yol açar,

NF-kB, MAPK gibi doğal bağışık yanıt sinyal yolakları üzerinden TLR ile inflamatuvar sitokin ve ISG transkripsiyonunu baskılar.

A function of the hepatitis B virus precore protein is to regulate the immune response to the core antigen

Margaret T. Chen*†, Jean-Noel Billaud†, Matti Sällberg†‡, Luca G. Guidotti§, Francis V. Chisari§, Joyce Jones†, Janice Hughes†, and David R. Milich†¶

*Karolinska Institute and Swedish Institute for Infectious Disease Control, 171 82 Solna, Sweden; †Vaccine Research Institute of San Diego, San Diego, CA 92109; ‡Division of Clinical Virology, F68, Karolinska Institute at Karolinska University Hospital, Huddinge, SE-141 86 Stockholm, Sweden; and §Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA 92037

Contributed by Francis V. Chisari, September 2, 2004

Precore/HBeAg, nükleoproteinin sekretuvar formudur.

HBc/HBeAg spesifik CD8 T hücrelerinde toleransa yol açar, intrasellüler nükleokapside karşı immün yanıtı regüle eder.

Chen MT et al. Proc Natl Acad Sci USA 2004;101:14913

JOURNAL OF VIROLOGY, Aug. 2005, p. 9369–9380 Vol. 79, No. 15
0022-538X/05/$08.00+0 doi:10.1128/JVI.79.15.9369–9380.2005

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HBcAg/HBeAg çapraz-reaktif T hücre anerjisi,

Transgenik farelerde Th-1 hücrelerin delesyonu ve Th-2 sitokinlerin üretimini indükler.

Wieland SF et al. J Virol 2005;79:9369

Proc. Natl. Acad. Sci. USA
Vol. 88, pp. 4186–4190, May 1991
Medical Sciences

Wild-type and e antigen-minus hepatitis B viruses and course of chronic hepatitis

(hepatitis B virus DNA/hepatitis B virus variant)

MAURIZIA ROSSANA BRUNETTO*, MANUELA MARIA GIARIN*, FILIPPO OLIVERI*, ELISABETTA CHIABERGE*, MAURIZIO BALDI*, ALDA ALFARANO†, ANNA SERRA†, GIORGIO SARACCO*, GIORGIO VERME*, HANS WILL‡, AND FERRUCCIO BONINO*§

*Division of Gastroenterology, Molinette Hospital, 10126 Torino, Italy; †Medical Clinic of the University of Turin, Torino, Italy; and ‡Max-Plank-Institute fur Biochemie, Martinsried, Munich, Federal Republic of Germany

HBeAg negatif varyantlarla neonatal infeksiyonlar sıklıkla viral klirensle sonlanır.

HBeAg serokonversiyonlarına alevlenmeler eşlik eder.

Brunetto MR et al. Proc Natl Acad Sci USA 1991;88:4186

MICROBIOLOGY AND MOLECULAR BIOLOGY REVIEWS, Mar. 2000, p. 51–68 Vol. 64, No. 1
1092-2172/00/$04.00+0

Hepatitis B Virus Biology

CHRISTOPH SEEGER* AND WILLIAM S. MASON
Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111

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THE LIVER AS A TARGET FOR HEPADNAVIRUS INFECTION 52
GENOME REPLICATION 53
Introduction 53
Infection 53
Formation of cccDNA 55
Viral Gene Expression 55
Viral Proteins 56

HBx proteininin, viral proteinlerin proteazom degredasyonunu inhibe ederek HBV antijen sunumunu bozduğu,

Seeger C et al. Microbiol Mol Biol Rev 2000;64:51

Hepatitis B virus polymerase inhibits RIG-I- and Toll-like receptor 3-mediated beta interferon induction in human hepatocytes through interference with interferon regulatory factor 3 activation and dampening of the interaction between TBK1/IKKε and DDX3

Shiyan Yu,[1,2]† Jieliang Chen,[1,2]† Min Wu,[2] Hui Chen,[1,2] Nobuyuki Kato[3] and Zhenghong Yuan[1,2,4]

HBV polimerazın RIG-1 ve TLR-3 aracılı IRF aktivasyonunu ve IFN-β yanıtını bozduğu,

Yu S et al. J Gen Virol 2010;91:2080

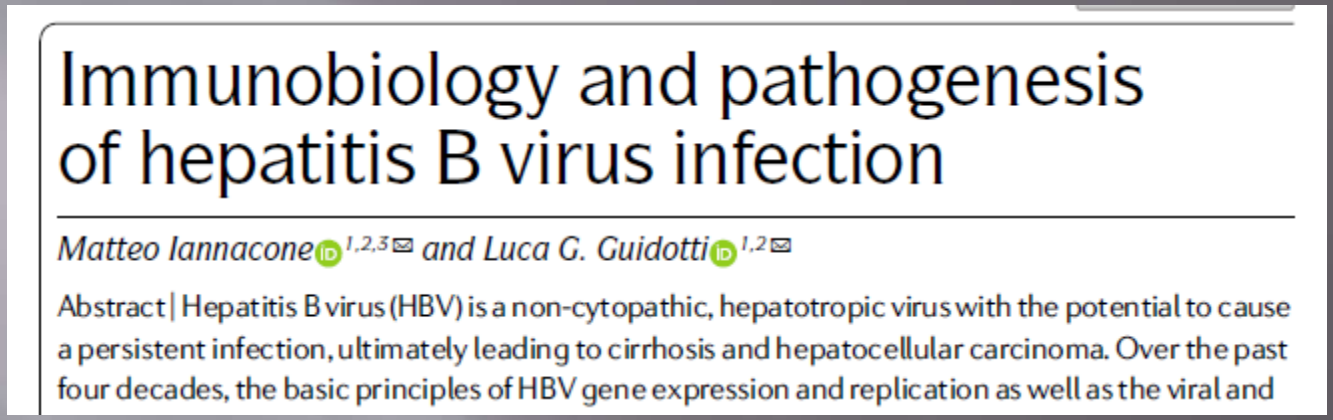
Intrahepatic innate immune response pathways are downregulated in untreated chronic hepatitis B

Fanny Lebossé[1,2,3,†], Barbara Testoni[1,3,†], Judith Fresquet[1,3], Floriana Facchetti[4], Enrico Galmozzi[4], Maëlenn Fournier[1,3], Valérie Hervieu[3,5], Pascale Berthillon[1], Françoise Berby[1], Isabelle Bordes[1], David Durantel[1,3], Massimo Levrero[1,2,6], Pietro Lampertico[4], Fabien Zoulim[1,2,3,*]

[1]*INSERM U1052-Cancer Research Center of Lyon (CRCL), 69008 Lyon, France;* [2]*Department of Hepatology, Croix Rousse Hospital, Hospices Civils de Lyon, France;* [3]*University of Lyon, UMR_S1052, CRCL, 69008 Lyon, France;* [4]*Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy;* [5]*Department of Pathology, Edouard Heriot Hospital, Hospices Civils de Lyon, France;* [6]*Department of Internal Medicine – DMISM and the IIT Center for Life Nanoscience (CLNS), Sapienza University, Rome, Italy*

Antiviral efektör moleküllerin, ISG ve TLR / PRR yolaklarını güçlü biçimde baskıladığı,

Lebosse F et al. J Hepatol 2017;66:897



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KHB'de CD8 T hücreleri sayıca belirgin az ve efektör fonksiyonları bozulmuştur.

Iannacone M et al. Nat Rev Immunol 2022;22:19

Immunity, Vol. 23, 53–63, July, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.immuni.2005.05.005

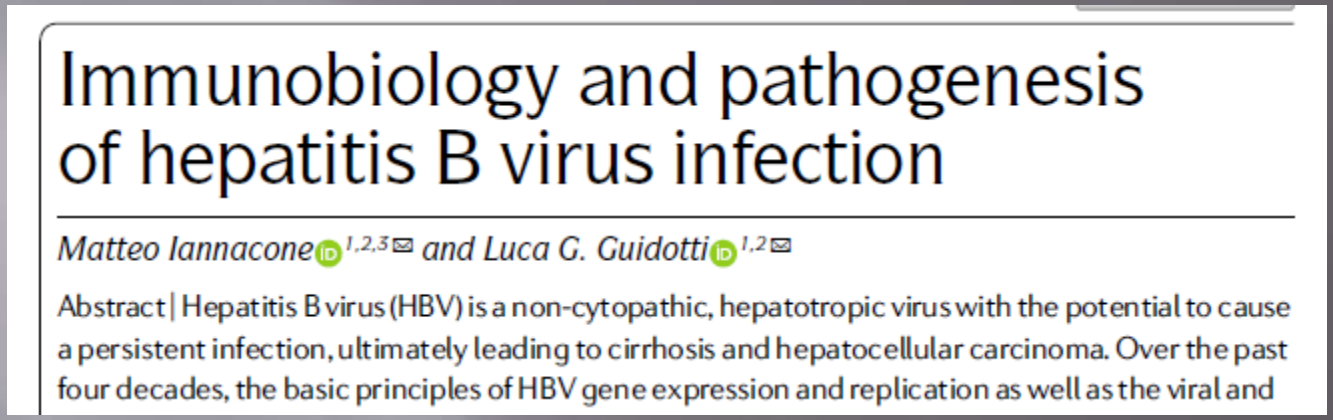
Oscillating CD8+ T Cell Effector Functions after Antigen Recognition in the Liver

Masanori Isogawa, Yoshihiro Furuichi, and Francis V. Chisari*
Department of Molecular and Experimental Medicine
The Scripps Research Institute
La Jolla, California 92037

suggest that regulation of these two effector fu
is fundamentally different, the relative importan
kinetics of CD8+ T cell-mediated IFNγ producti
cytolytic activity in controlling virus infection h
mained elusive. For example, although the rapi

Sürekli antijen stimülasyonu HBV spesifik CD8 T hücrelerinin IFNγ ve TNF sekresyon yeteneğini tamamen bozarken, sitotoksik fonksiyonlarını kısmen etkiler.

Isogawa M et al. Immunity 2005;23:53



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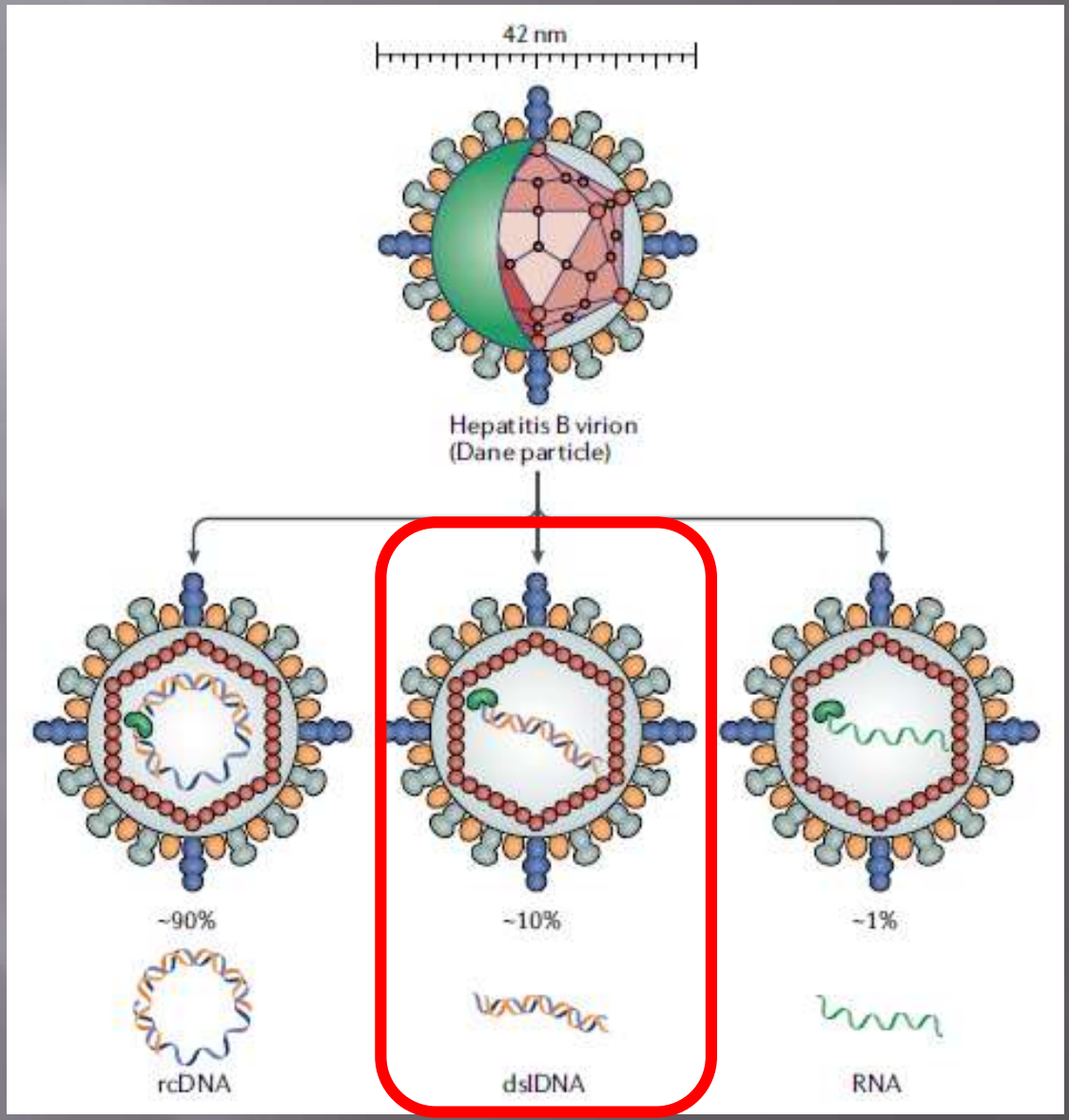
Az sayıda ve sitokin salgılayamayan CD8 T hücreleri HBV proteinlerini eksprese eden hepatositleri elimine etmek için saldırır,

Viral klirensi sağlayamadıkları halde, uzun dönemli immünopatolojik yanıtları sürdürür.

Iannacone M et al. Nat Rev Immunol 2022;22:19



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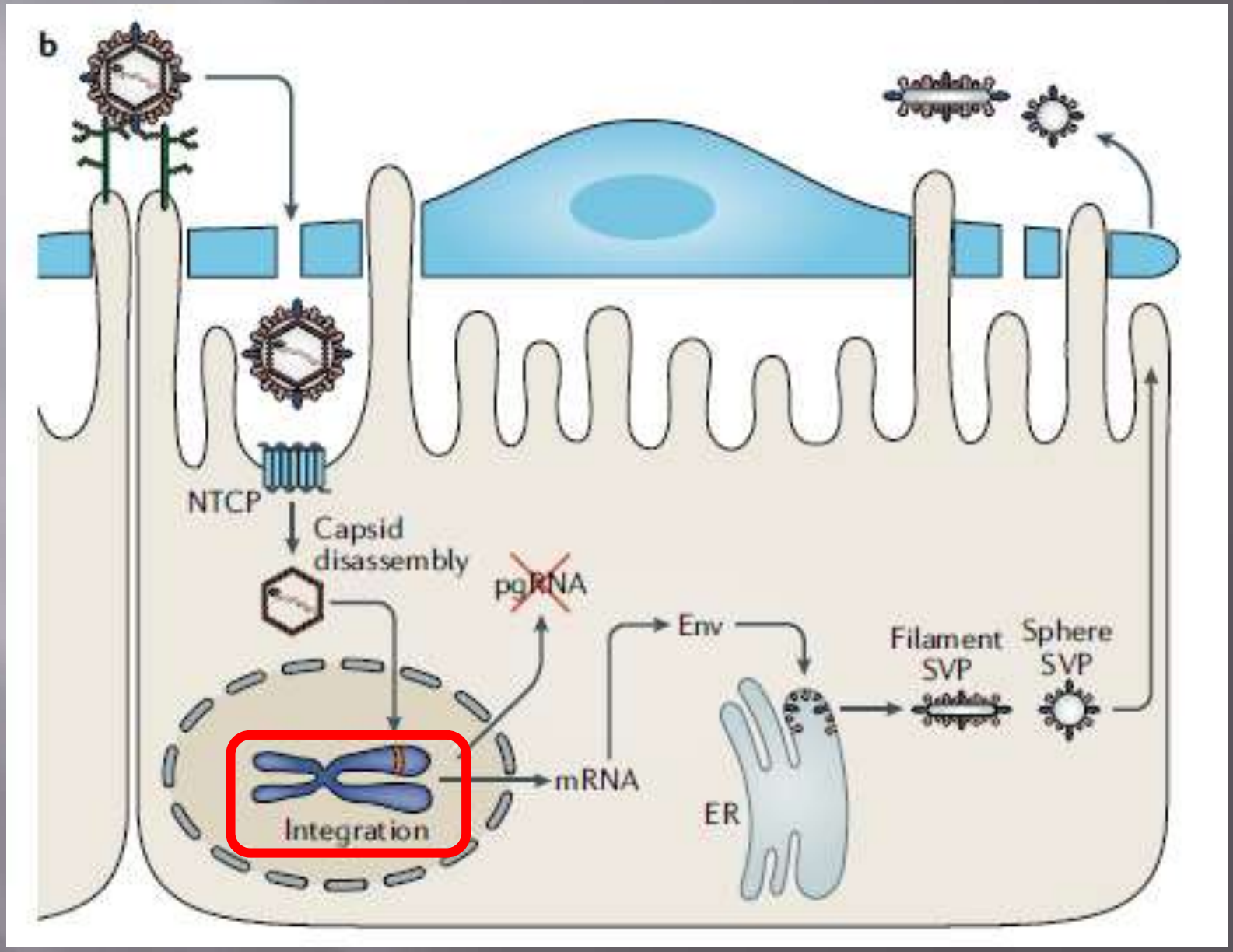

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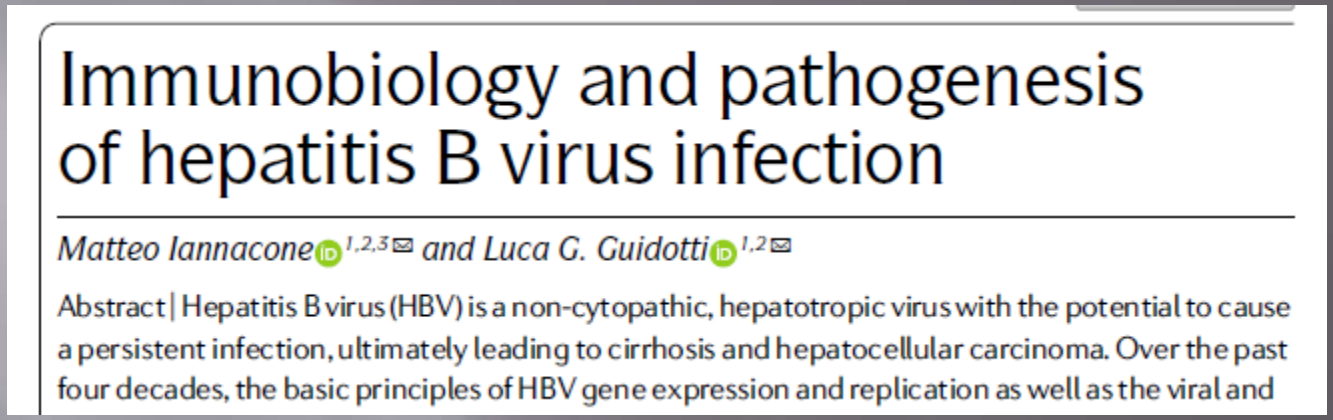

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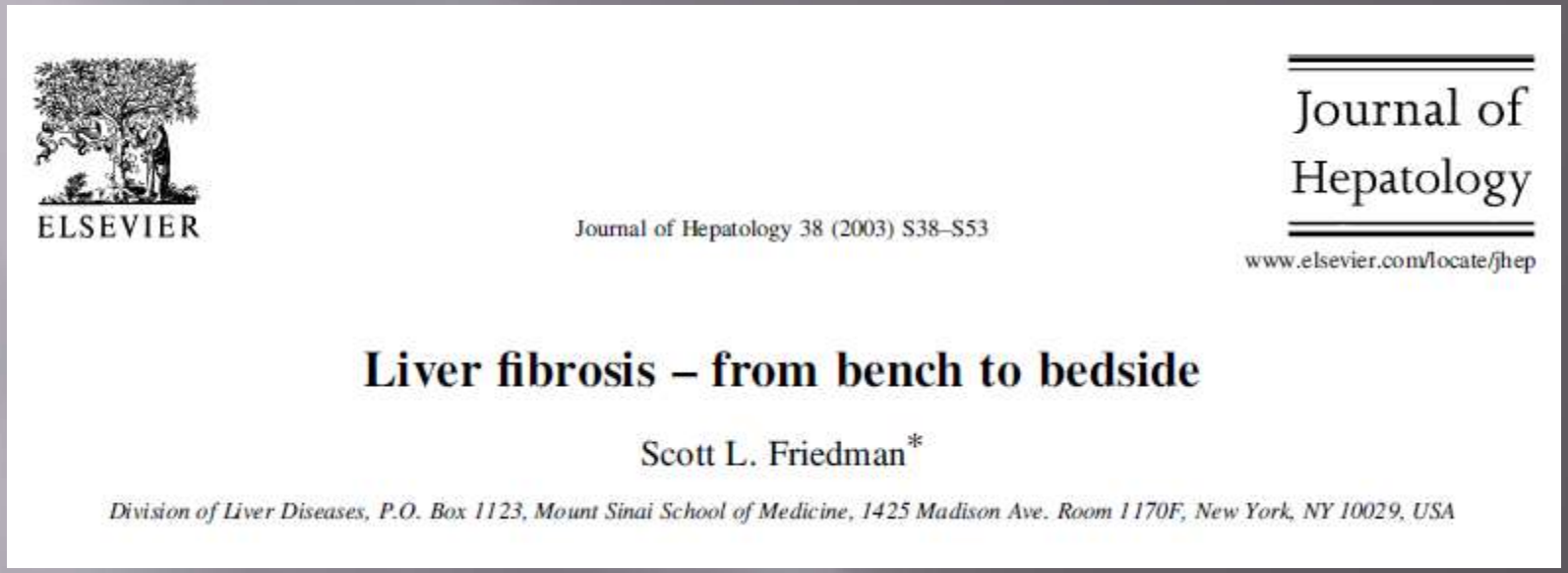
Orta şiddette ancak sürekli devam eden CD8 T hücre bağımlı hepatosit hasarı, nekroz ve rejenerasyon süreçleri ile ilerler,

Nekroz, rejenerasyon ve inflamasyonun eş zamanlı birlikteliği anormal tamir süreçlerini ve random genetik hasarı getirir.

= fibroz → siroz → HCC

Iannacone M et al. Nat Rev Immunol 2022;22:19



ELSEVIER

Journal of Hepatology 38 (2003) S38–S53

Journal of Hepatology

www.elsevier.com/locate/jhep

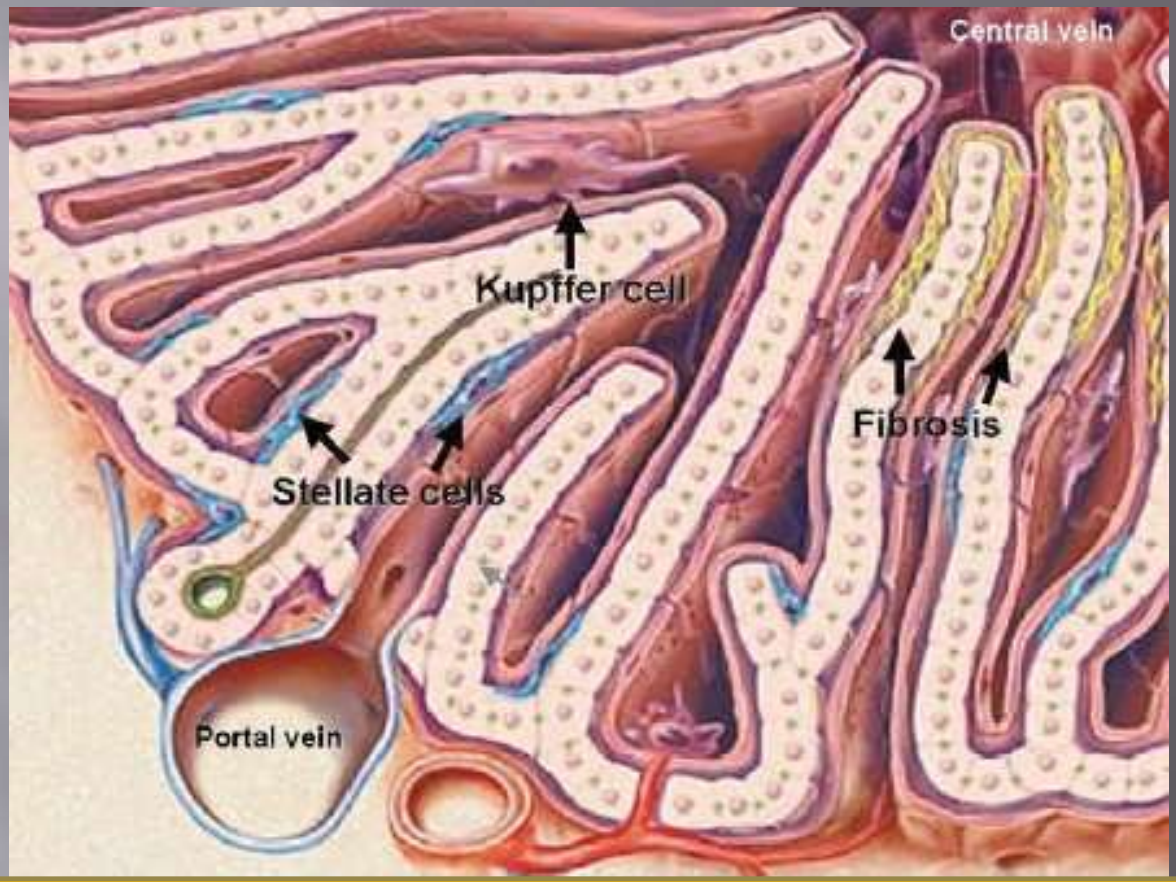
Liver fibrosis – from bench to bedside

Scott L. Friedman*

Division of Liver Diseases, P.O. Box 1123, Mount Sinai School of Medicine, 1425 Madison Ave. Room 1170F, New York, NY 10029, USA

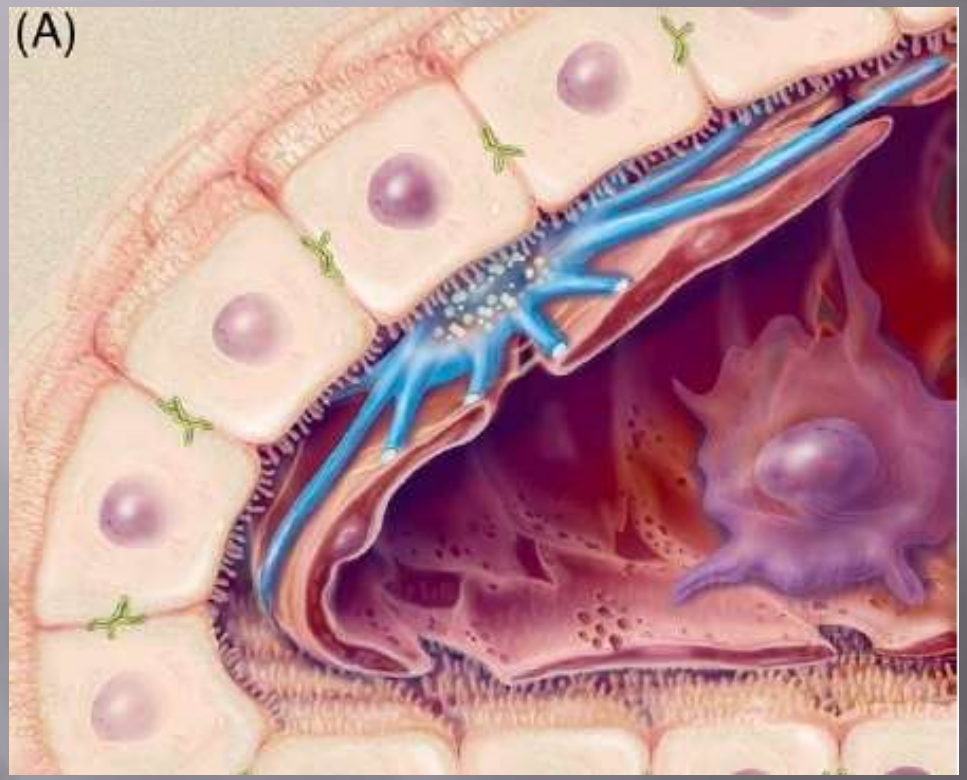
Kronik hepatit seyrinde görülen hepatik fibrozis, süregiden karaciğer hasarına karşı gelişen tipik bir yara iyileşmesi sürecidir.

Friedmann SL. J Hepatol 2003;38:S38



Hepatik stellat hücreleri subendotelyal Disse aralığında, Kupffer hücreleri intrasinüsoidal yerleşimlidir.

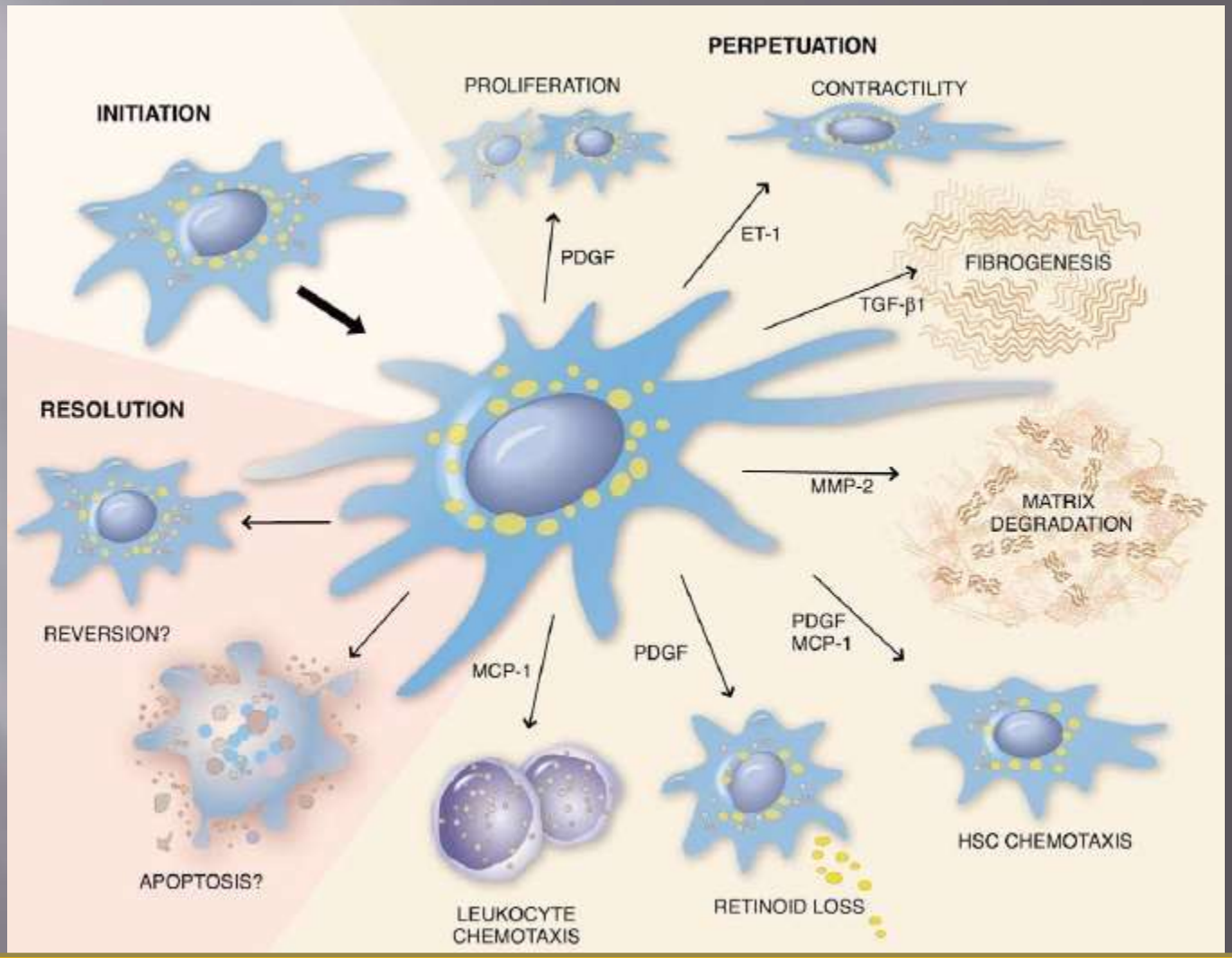
Friedmann SL. J Hepatol 2003;38:S38



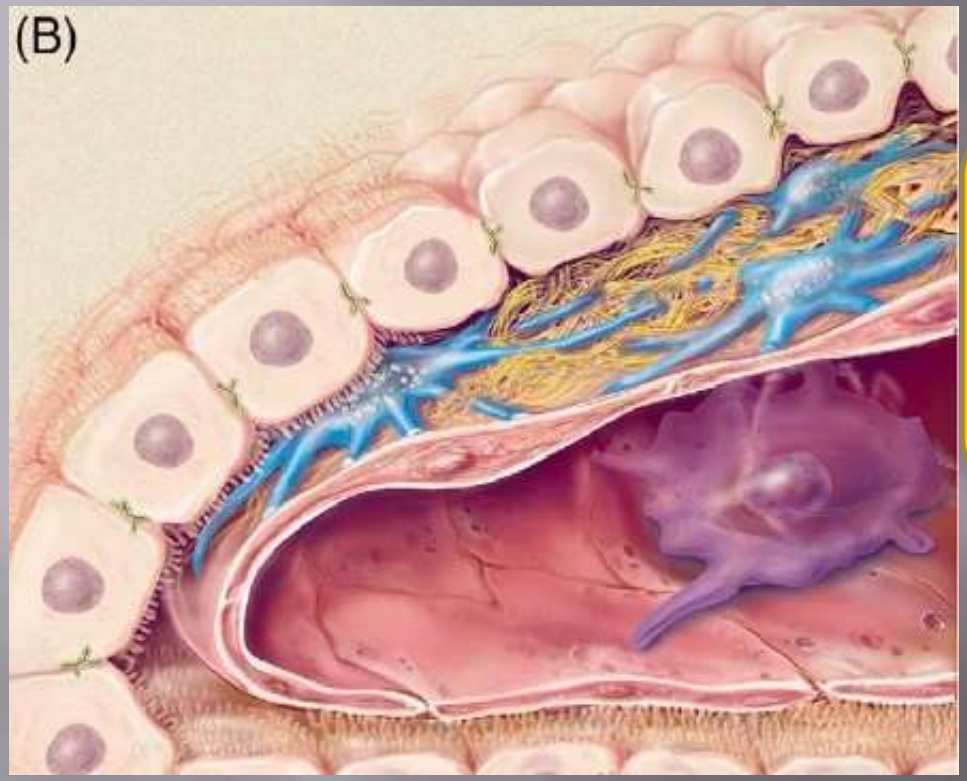
CD8 ve CD4 lenfositler
Sitokinler
Kemokinler
Reaktif O_2 metabolitleri

Stellat hücre aktivasyonu

Friedmann SL. J Hepatol 2003;38:S38



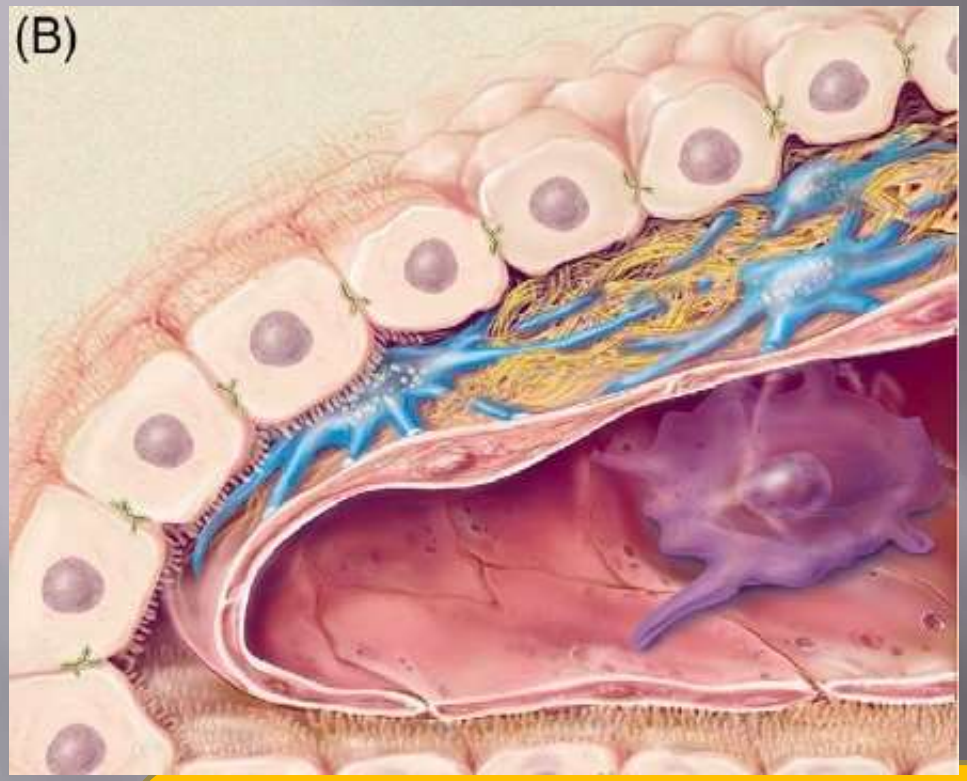
Stellat hücre aktivasyonu, bu hücrelerin fibrojenik myofibroblastlara dönüşümüdür.



Stellat hücre aktivasyonu ve proliferasyonu

Fibriler matriks birikimi

Friedmann SL. J Hepatol 2003;38:S38



Aktive olan stellat hücrelerle ilişkili olarak kontraktilitenin artması, karaciğerde portal direnci artırır ve portal kan akımını bozar.

Sinüzoidal kapillarizasyon / defenestrasyon

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Liver fibrosis – from bench to bedside

Scott L. Friedman*

Division of Liver Diseases, P.O. Box 1123, Mount Sinai School of Medicine, 1425 Madison Ave. Room 1170F, New York, NY 10029, USA

Karaciğer fibrozisi, subendotelyal boşluktaki ekstrasellüler matrikste, kollajen ve diğer proteinlerin birikimi ve ortadan kaldırılmasının söz konusu olduğu, dinamik ve kompleks sürecin net sonucudur.

Friedmann SL. J Hepatol 2003;38:S38

Sonuç

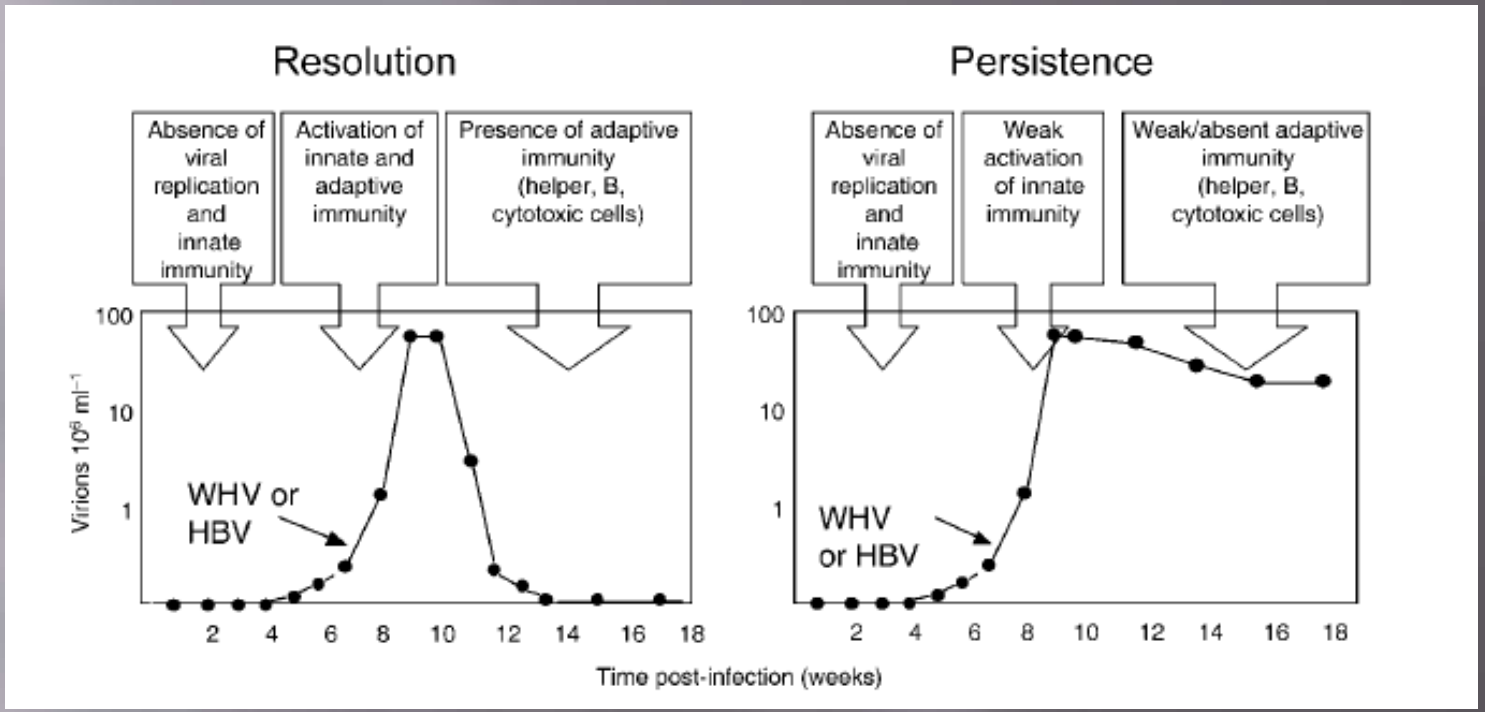
CONCISE REVIEW IN MECHANISMS OF DISEASE

Kinetics of the Immune Response During HBV and HCV Infection

Antonio Bertoletti[1] and Carlo Ferrari[2]

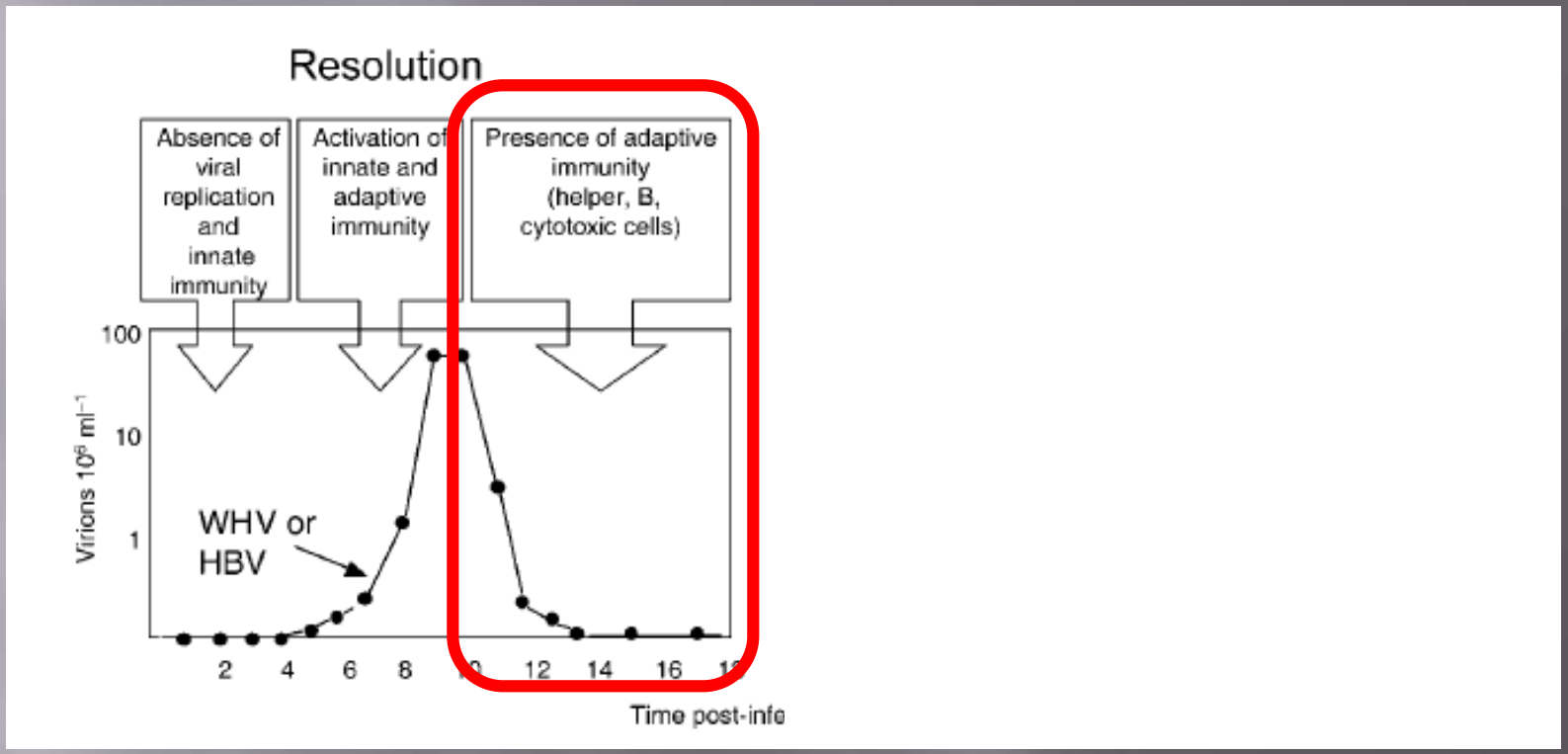
HBV infeksiyonunun kendiliğinden iyileştiği olgularda, erken, kuvvetli, poliklonal ve birden çok viral epitopa karşı multispesifik CD4 ve CD8 T lenfosit yanıtı ile Th-1 tipi sitokin profili olduğu gösterilmiştir.

Bertoletti A. Hepatology 2003;38:4



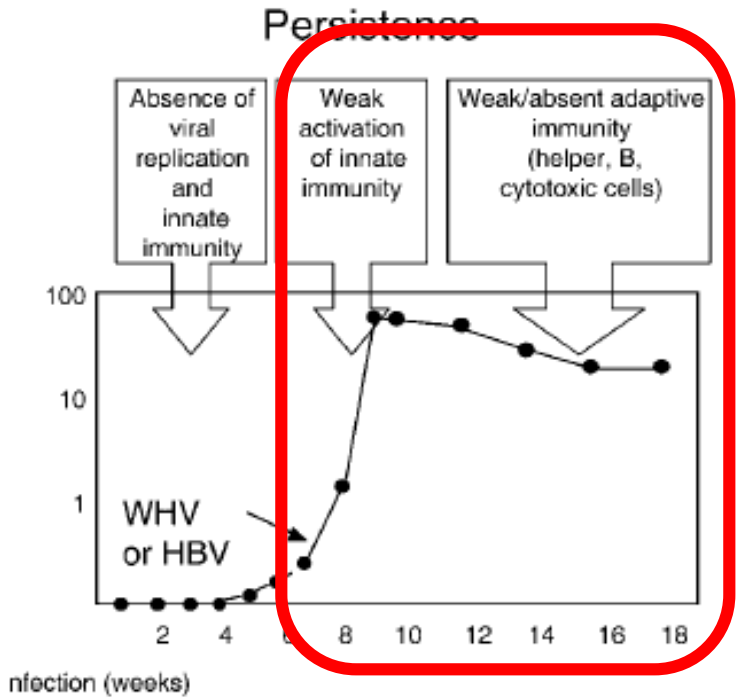
T hücre yanıtsızlığı ya da HBV spesifik T hücre ekspansiyonunun erken dönemde azalması kronikleşme ile ilişkilidir.

Bertoletti A et al. J Gen Virol 2006;87:1439



HBV infeksiyonunun kontrolünde esas sorumlu mekanizma, etkin ve sürekli bir hücresel immün yanıt geliştirme yeteneğidir.

Bertoletti A et al. J Gen Virol 2006;87:1439



Bu yanıtın yetersiz olması kronikleşme ile sonuçlanır.

Bertoletti A et al. J Gen Virol 2006;87:1439