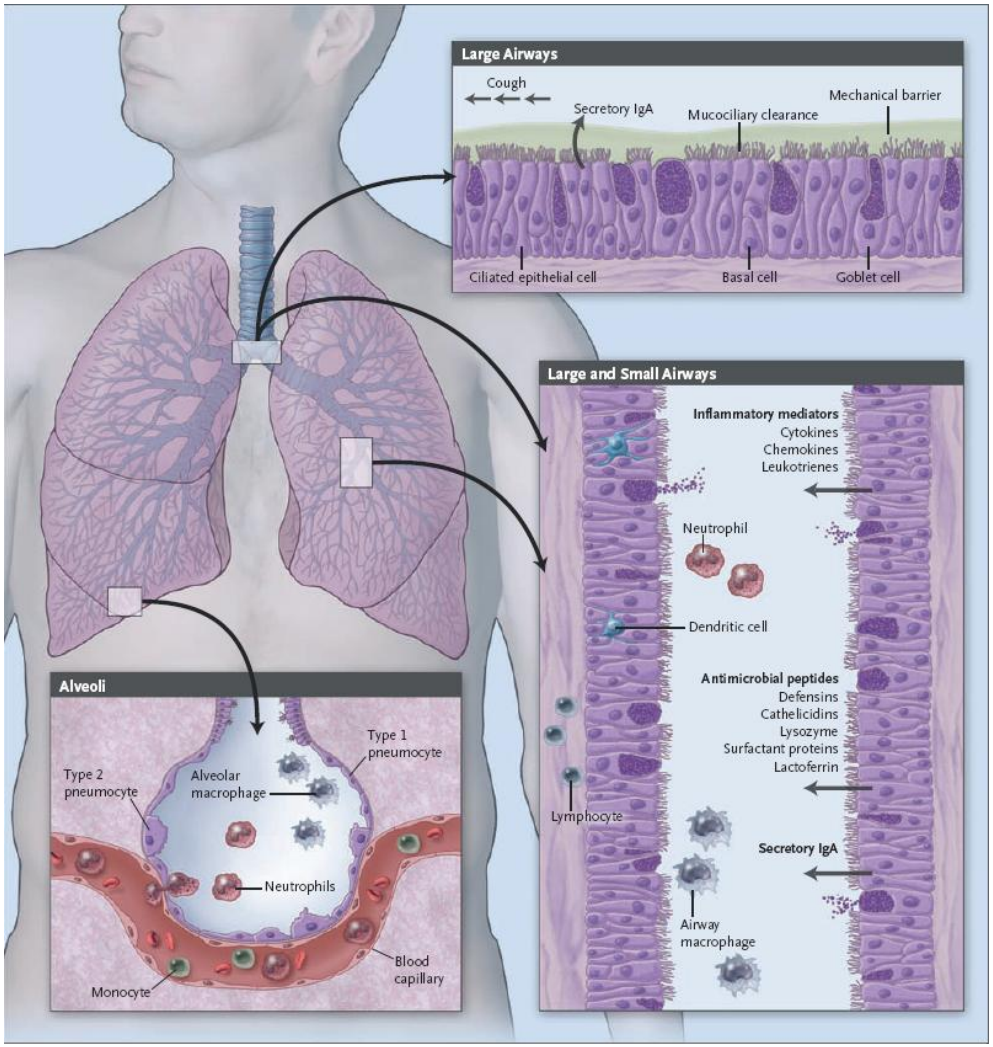
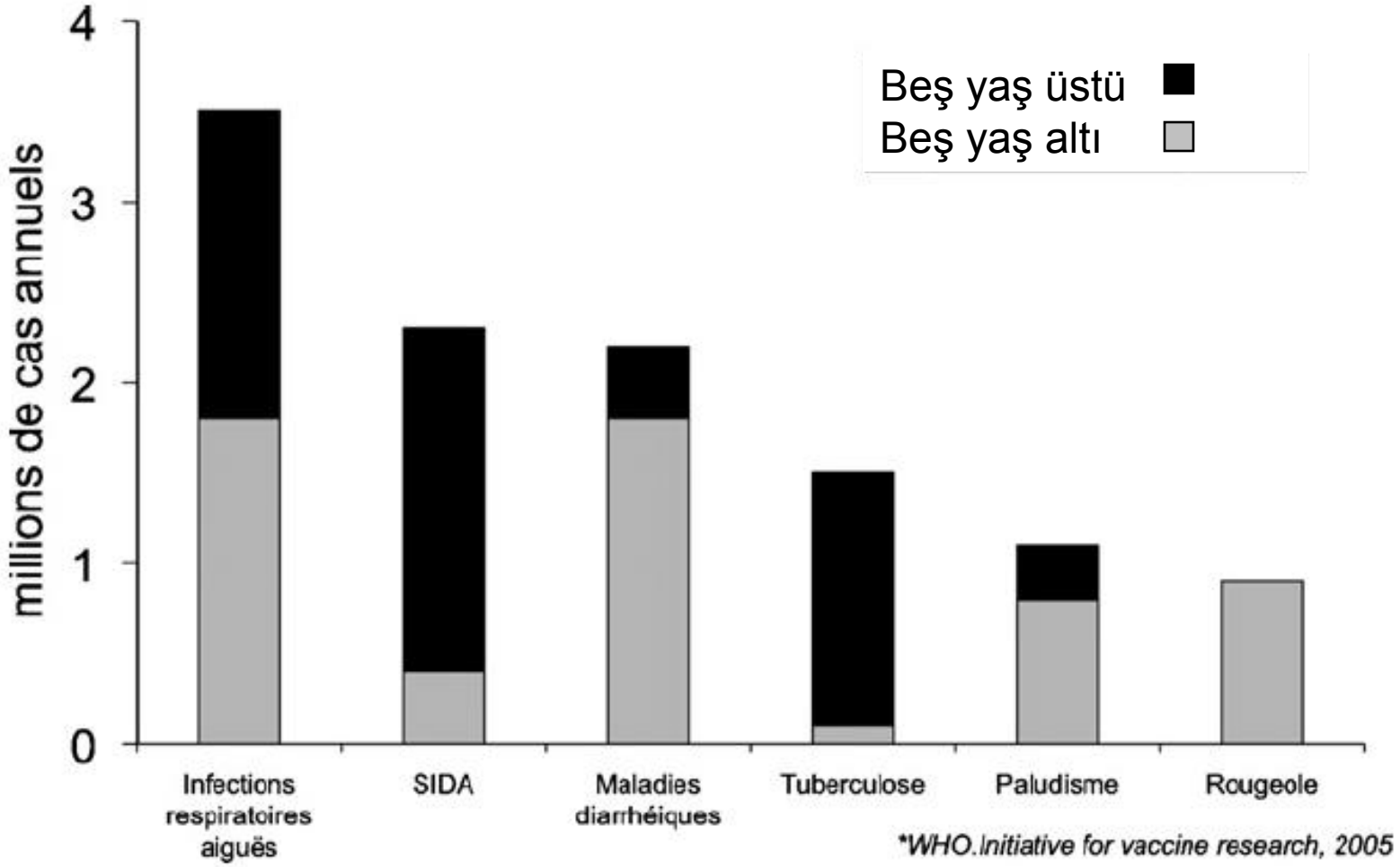
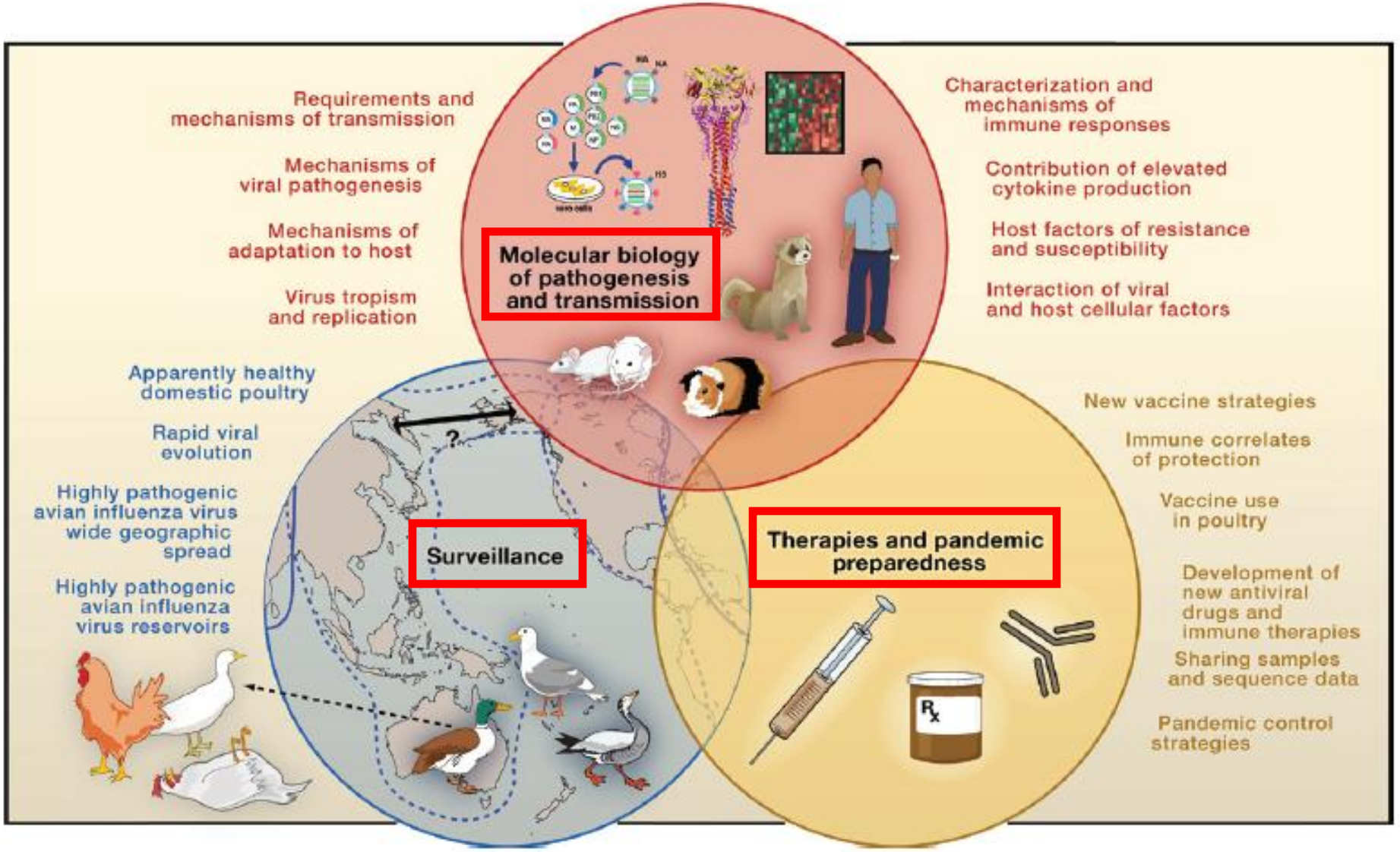
Solunum Yolları Enfeksiyonlarında İmmünopatogenez



Enfeksiyon Hastalıklarında Mortalite





Cell 2009;136: 402

20./21. Yüzyılda Pandemiler

1918

“Spanish Flu”

>40 milyon ölüm

A(H1N1)

1957

“Asian Flu”

1-4 milyon ölüm

A(H2N2)

1968

“Hong Kong Flu”

1-4milyon ölüm

A(H3N2)

2009

”Mexican Flu”

???

A(H1N1)

Bu insanlar neden öldü?

- **Sorumlu: Pandemi etkeni**
  - Virülansı yüksek
  - Viral pnömoni
  - Etkenin yol açtığı doğal enfeksiyon
- **Ancak bazı gözlemler:**
  - Grip insidansı artarken, invaziv pnömokok ve meningokok enfeksiyonları da artıyor
  - Grip = septisemi ve meninjit için kofaktör
  - Influenza virüslerinin fizyopatolojik etkileri, koenfeksiyon etkenlerinin ***davranışlarını*** değişime uğratıyor

Influenza Virüsleri Bakterilerin İşlerini Kolaylaştırıyor

Mechanism Responsible for Polymicrobial Synergy

- Hypothesis: Influenza infection causes pulmonary injury by inducing necrosis of the lung epithelium and this tissue injury then allows bacterial pathogens to gain direct access to the lung via the bronchial tree (MacCallum, 1919; Opie, 1921).

EMERGING INFECTIOUS DISEASES
August 2008
Vol 14, No. 8

Deaths from Bacterial Pneumonia during 1918-19 Influenza Pandemic

John F. Brundage and G. Dennis Shanks

Bacterial Pneumonia and Pandemic Influenza Planning

Ravindra K. Gupta, Robert George and Jonathan S. Nguyen-Van-Tam

Published online
August 18, 2008
The Journal of Infectious Diseases

Predominant Role of Bacterial Pneumonia as a Cause of Death in Pandemic Influenza: Implications for Pandemic Influenza Preparedness

David M. Morens, Jeffery K. Taubenberger and Anthony S. Fauci

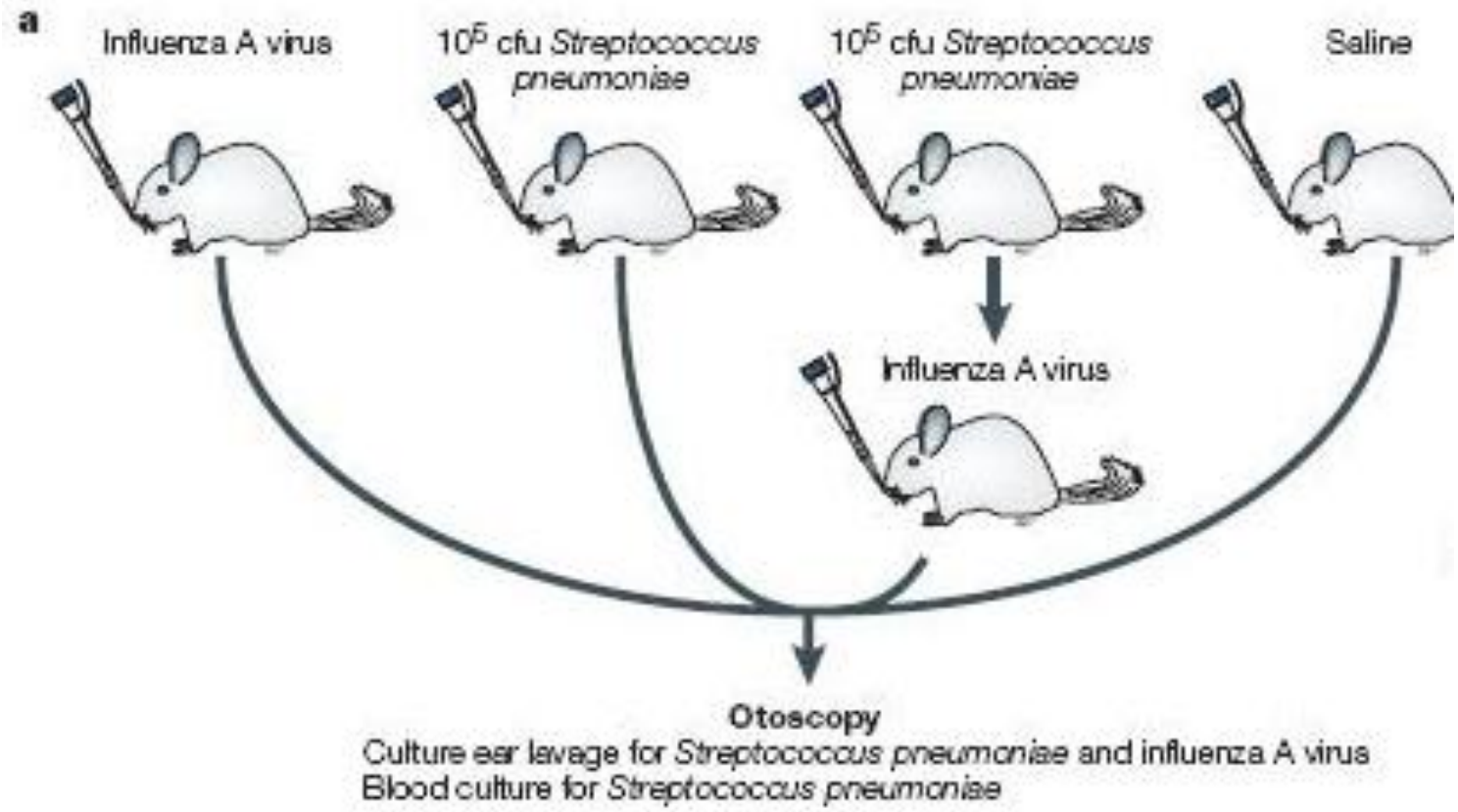
Planning for an Influenza Pandemic: Thinking beyond the Virus

INFLUENZA VİRÜSLERİNDE PATOGENEZ

1- Bakterilerin işini nasıl kolaylaştırırlar?

2- Kendileri nasıl bu denli patojen olabiliyorlar?

1. Örnek: Çinçilia modelinde deneysel OM



Çinçiliaların IN enfeksiyonu:

-Inf A ile inoküle edilenlerin % 4'ü

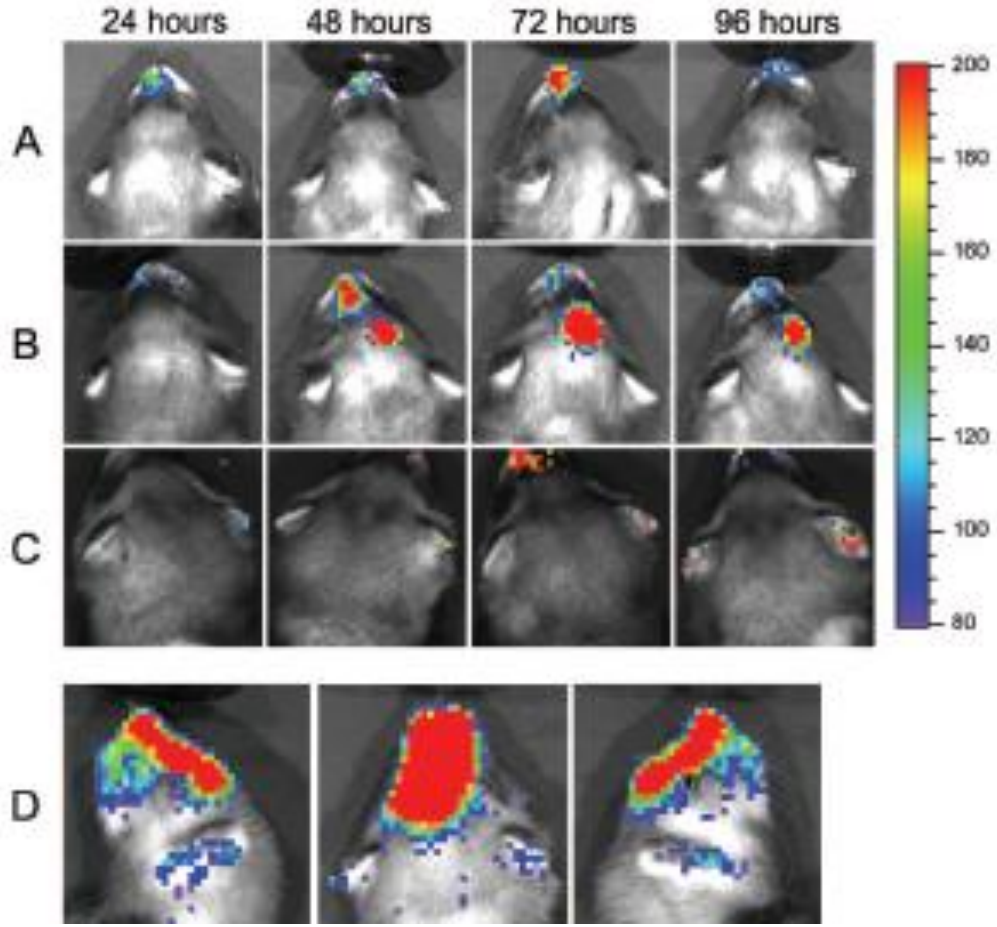
-S.pneumoniae ile inoküle edilenlerin % 21'i

-Koinfekte edilenlerin % 67'si OM geliştiriyor.

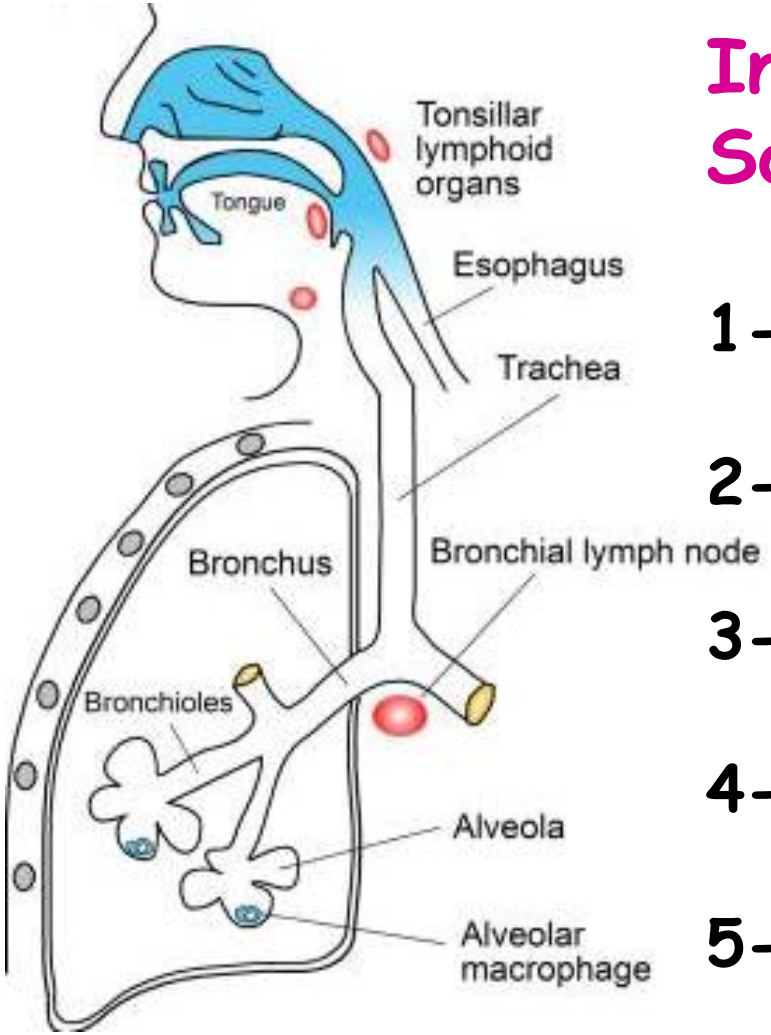
Nat Rev Microbiol 2004; 2: 552

2. Örnek: Gelincik modelinde deneysel OM

- S. pneumoniae, N.meningitidis' e dirençli deney hayvanları,
  sub-letal Inf.A inokülasyonunun 7. günü, bakterilere duyarlı hale geçiyor
- Gribin neden olduğu inflamasyon sürecinde süperenfeksiyona duyarlılık söz konusu...
- IFN-γ ve IL-1 artışı



Infect Immunity 2006; 74:2562



Influenza enfeksiyonunu takiben Solunum yollarında farklılaşma:

1- Epitel hasarı/sitotoksisite

2- Solunum fonkl.değişimler

3- Reseptör ekspresyonunda artış

4- Doğal direncin baskılanması

5- Nötrofillerin apoptozu

BAKTERİ ENFEKSİYONLARINDA ARTIŞ

http://www.influenzareport.com/ir/pathogen.htm

INFLUENZA VİRÜSLERİNDE PATOGENEZ

1- Bakterilerin işini nasıl kolaylaştırırlar?

2- Kendileri nasıl bu denli patojen olabiliyorlar?

•1951 de Iowa Üniv.'den JOHAN HULTIN: Alaska'ya "1918 suşunu" aramaya gider
•Yaşamını yitirenler "permafrost tabakasında"
•Sonuç : BAŞARISIZ

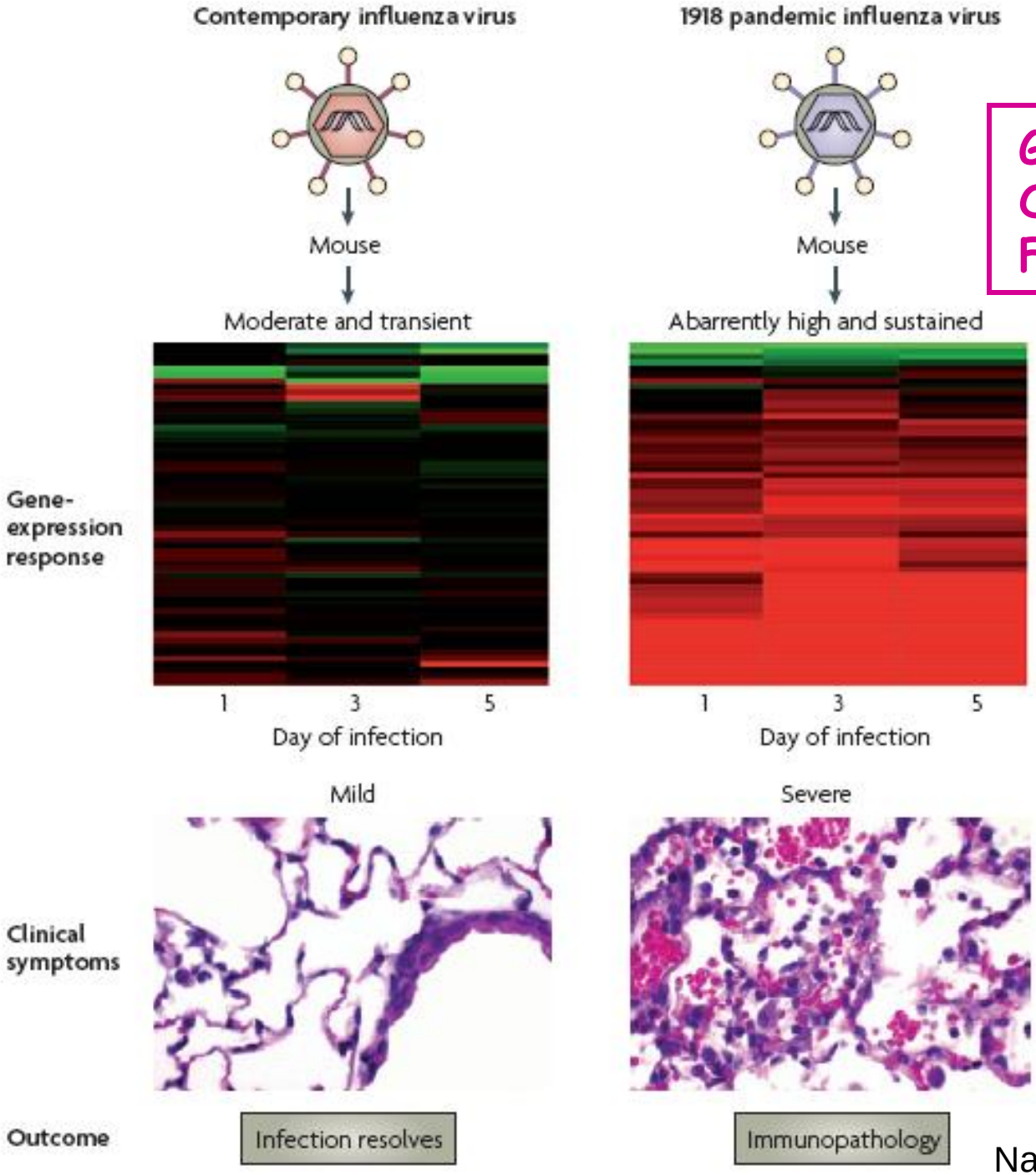
•1995'de Washington Üniv., 1918'den kalan doku örnekleri incelenir
•1996'da pandemide ölen bir askerin akciğer dokusundan etkenin 5 genine ait nükleotid sekansları elde edilir ; ancak virüsün tüm genom sekansının eldesi mümkün olmaz.

- Artık 73 yaşında olan J HULTIN yeniden Alaska'ya gider
- İlk araştırmasından tam 46 yıl sonra yaşamını yitirmiş 4 kişinin donmuş akciğerlerinden aldığı biyopsilerde

1918 suşunun tüm genomunu sekanslar

Bu suş neden bu kadar PATOJEN?

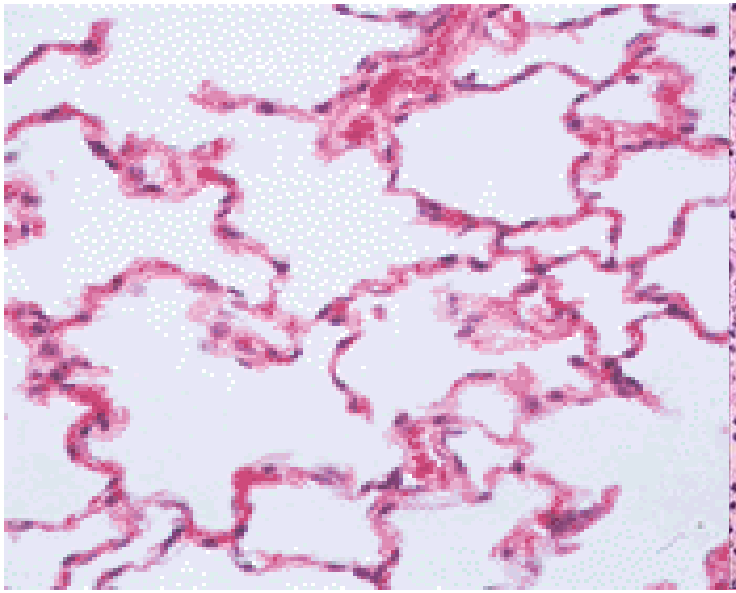
- Önce farklı "patojenliği arttırıcı" mutasyonlar aranmış...
- Sonra her farklı gen bölgesi, başka virüslere integre edilip, bu virüsteki değişim incelenmiş
- Sonuçta 1918/HA geninin yoğun inflamatuar yanıta neden olduğu gösterilmiş.

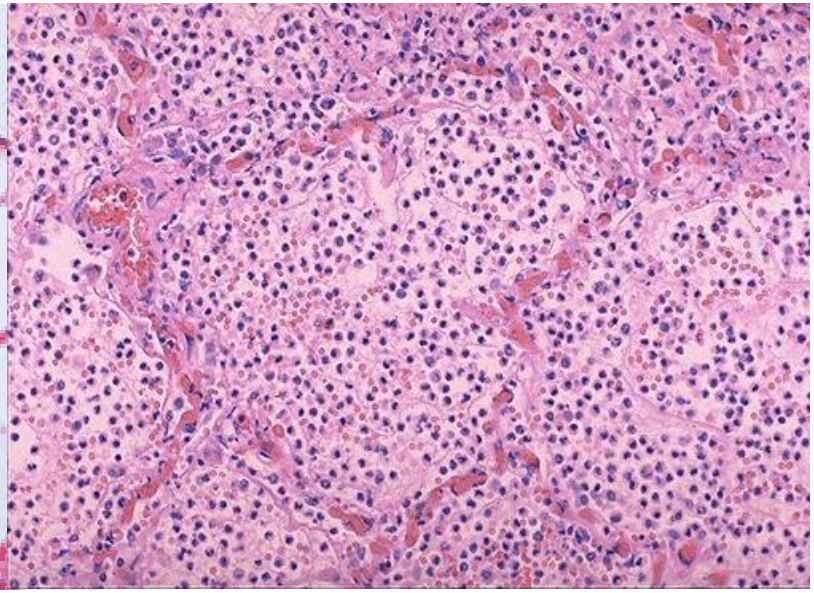


GEN EKSPRESYON ORANLARI FARKLI

Nat Rev Immunol 2008;8: 644

Abartılı İmmün Yanıtın Sonuçları





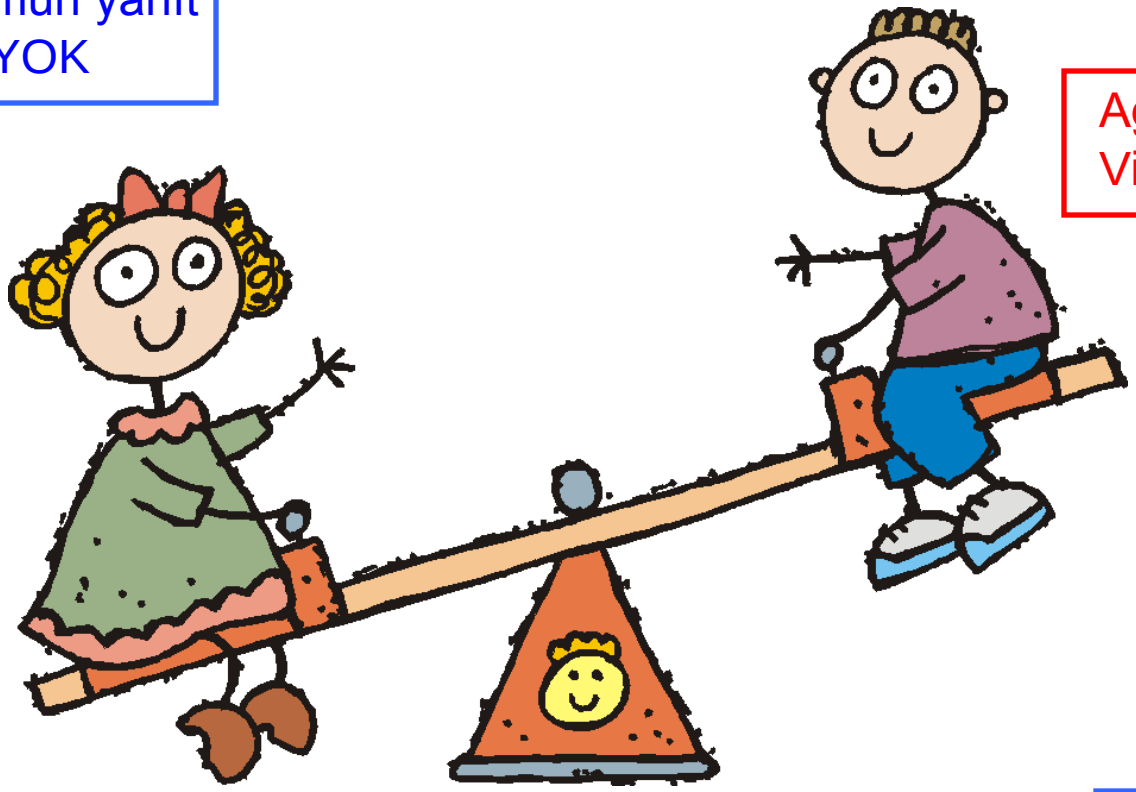
- Hipersitokinemi
- Hemofagositik sendrom
- ARDS/MOSF
- Yaygın pülmoner ödem
- Alveoler hemoraji

- Yoğun lökosit infiltrasyonu
- Böbrek yetmezliği
- Kardiak disfonksiyon

Patojenin Yıkımı vs Immünopatoloji: Hassas Denge

Yetersiz immün yanıt
Hasar YOK

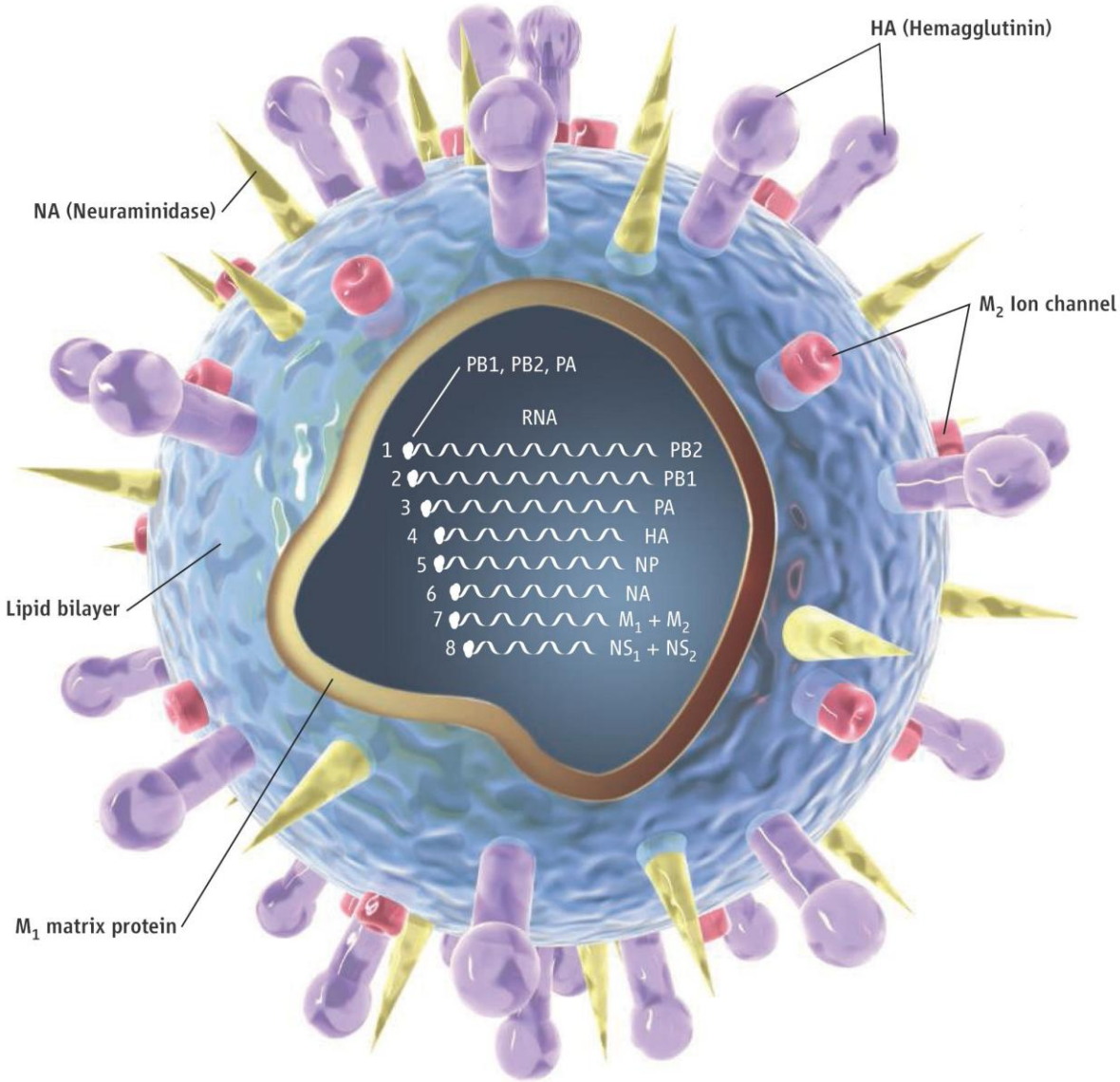
Ağır immünopatoloji
Viral hasarda azalma



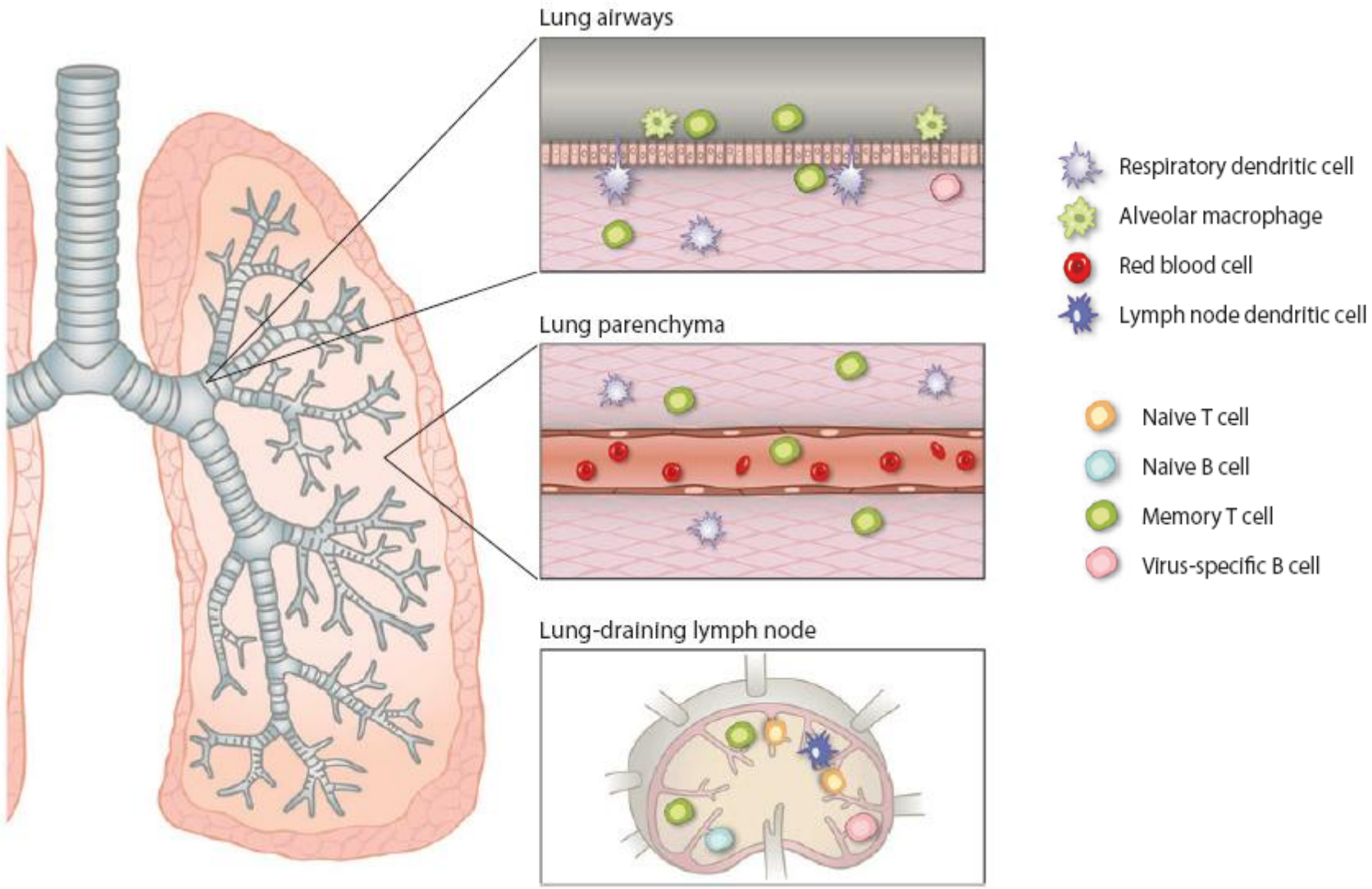
Abartılı immün yanıt

Viral yük artışı

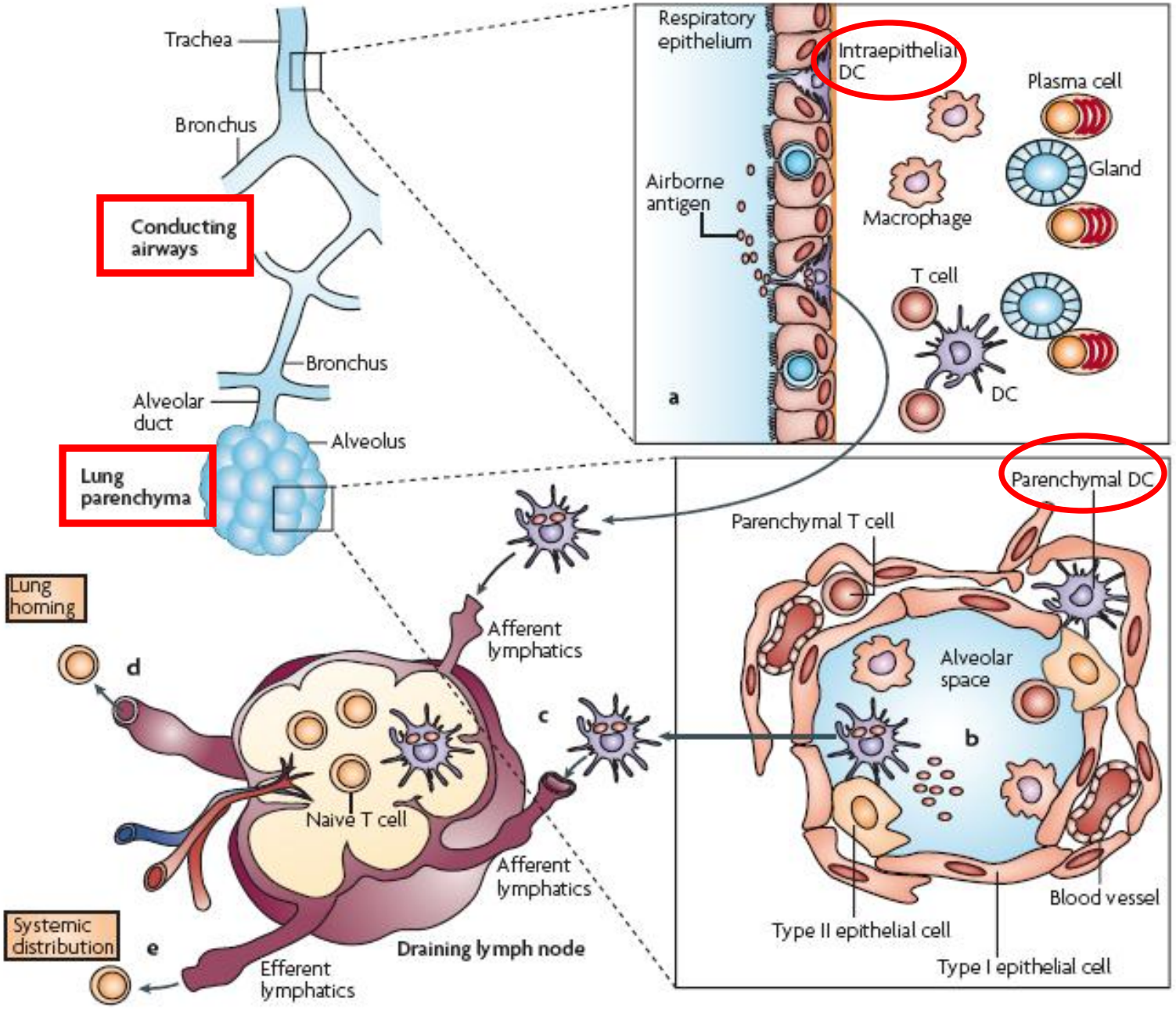
Influenza A Virüsü



Solunum Yolları ve Immün donanım

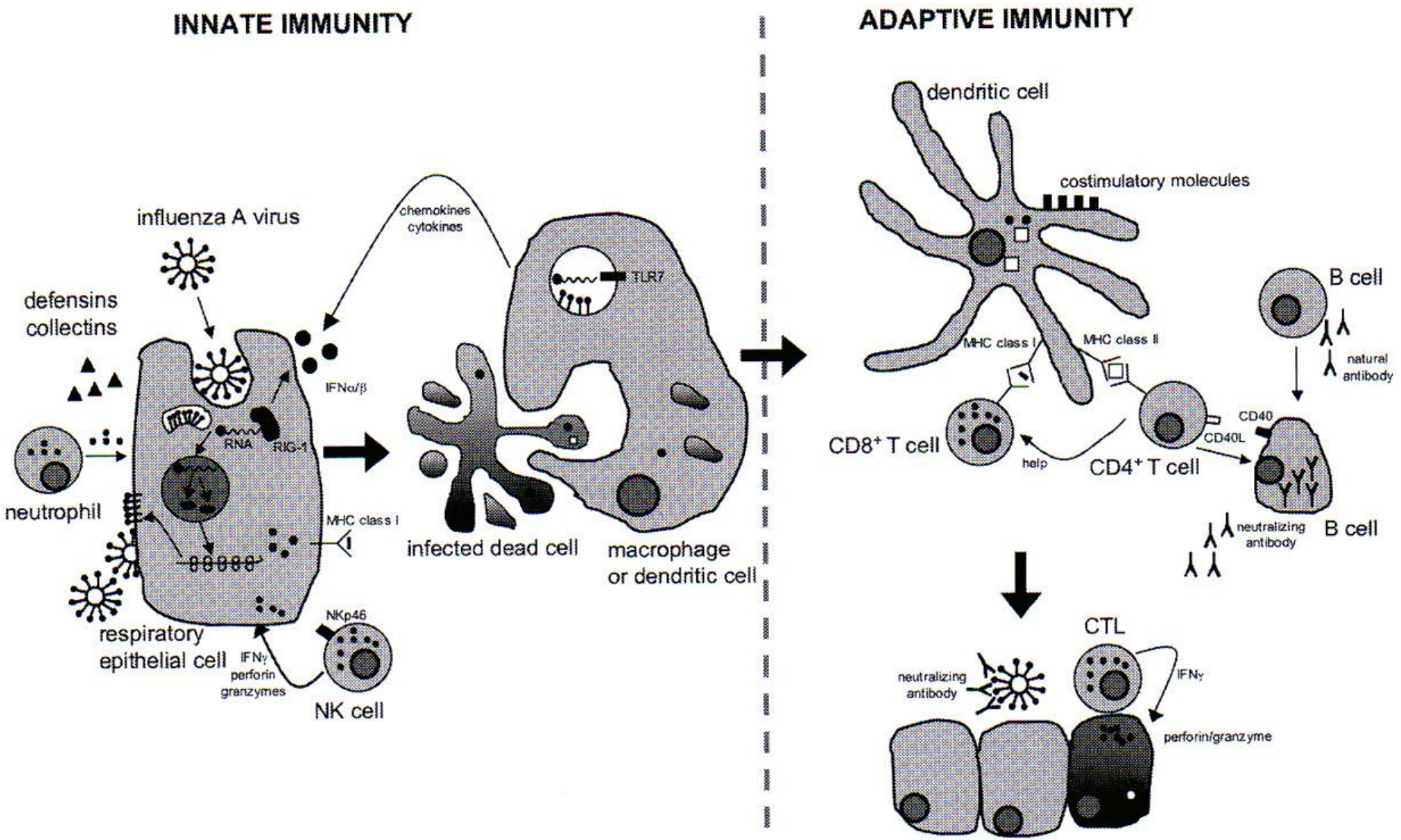


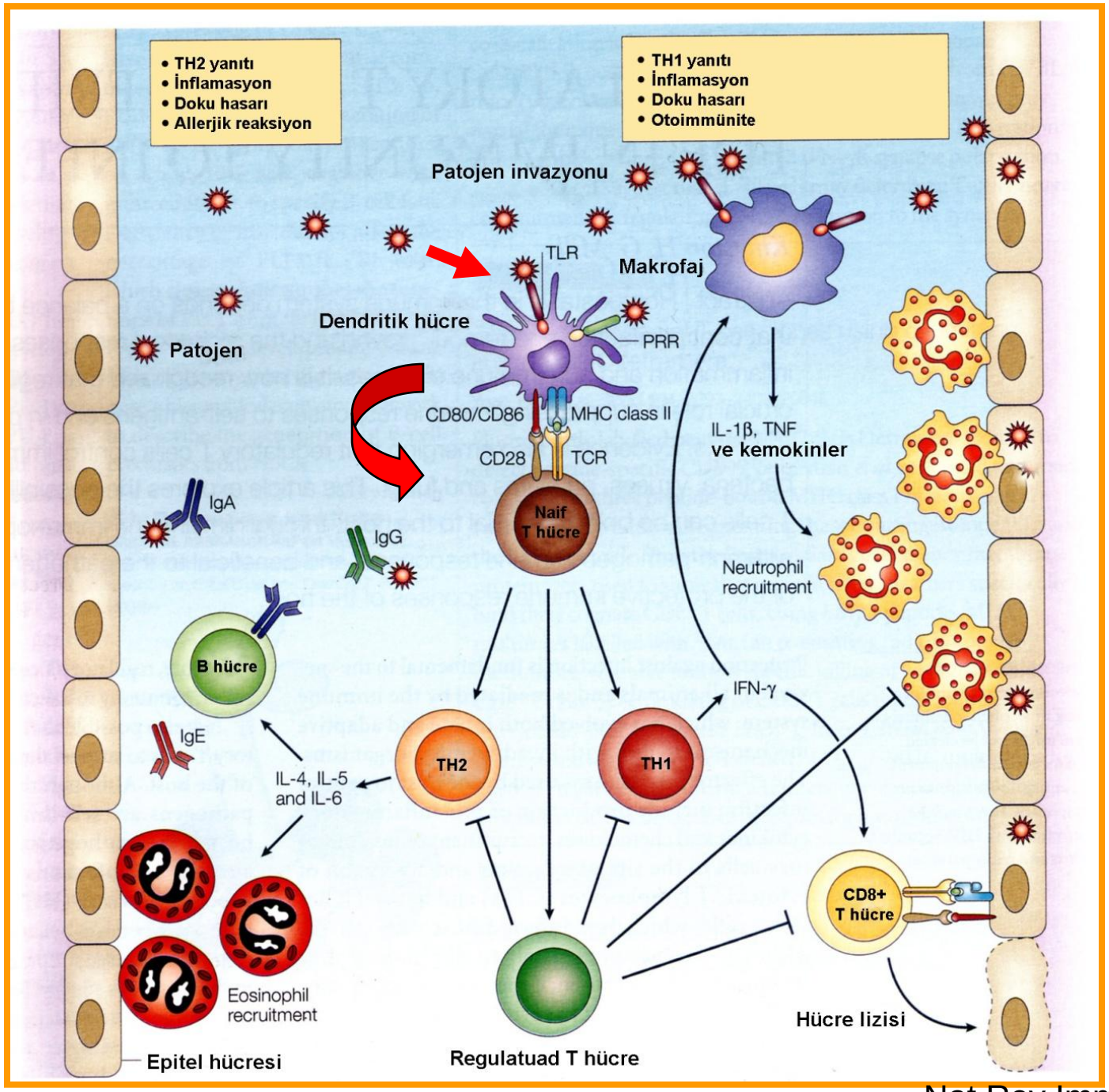
Annu Rev Immunol 2009;27: 61



Nat Rev Immunol 2008;8: 142

Influenza Enfeksiyonlarında İmmün Yanıt





Nat Rev Immunol 2004;4:841

Influenza Virüslerine Karşı Oluşan Yanıtın Aşamaları

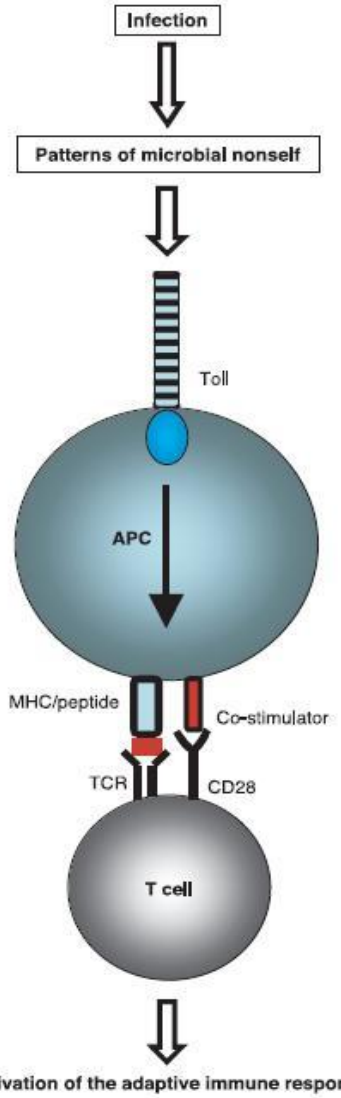
1- Doğal direnç hücrelerinin Virüsleri tanıması

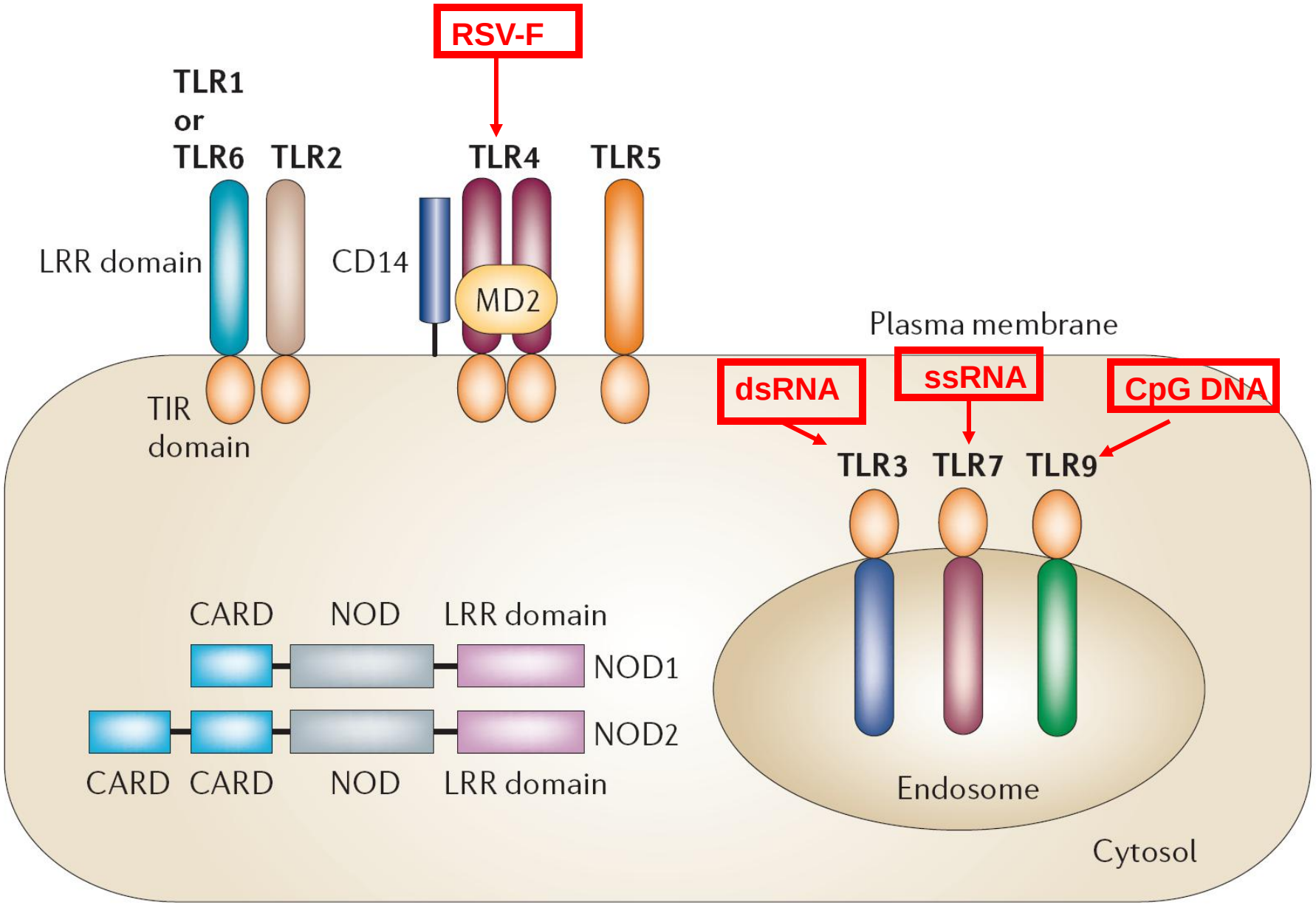
- dsRNA -TLR3
- ssRNA - RIG-1 ve TLR7

2- Doğal direnç mekanizmasının aktivasyonu

- NK'lar
- Nötrofiller
- Makrofajlar
- Kollektinler, defensinler

3- Özgül yanıtın (Edinsel bağışıklık) devreye girmesi





(Strober W et al: 2006)

Table 1 Host pathogen recognition receptors (PRRs) and their interaction with respiratory viruses

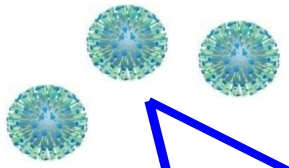
PRR	Viral PAMP	Viruses	PRR location	Signalling pathways triggered
TLR-4	F protein	RSV	Cell surface	NF-κB, AP-1
TLR-3	dsRNA	RNA viruses	Endosome	IRF-3, NF-κB
TLR-7	ssRNA	Influenza A	Endosome	IRF-7
TLR-9	Unmethylated DNA	Adenovirus	Endosome	IRF-7
RIG-I	dsRNA	RSV and influenza	Cytosol	IRF-3, IRF-7
MDA-5	dsRNA	Picornaviruses	Cytosol	IRF-3, IRF-7

AP, activating protein; dsRNA, double-stranded RNA; IRF, interferon response factor; MDA-5, melanoma-differentiation-associated gene 5; PAMP, pathogen-associated molecular pattern; RIG-I, retinoic-acid-inducible protein I; ssRNA, single-stranded RNA; TLR, Toll-like receptor.

Paediatr Resp Rev 2008;9: 243

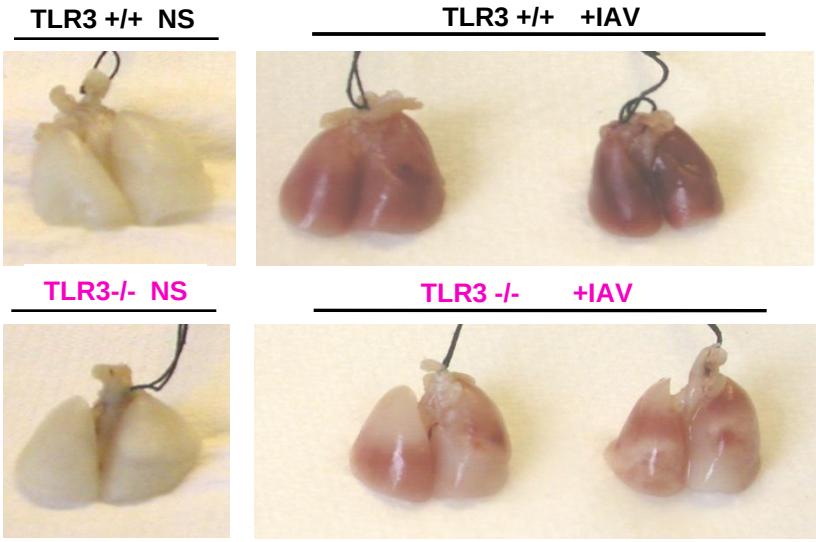
Influenza A (H3N2)
(IN inokülasyon)

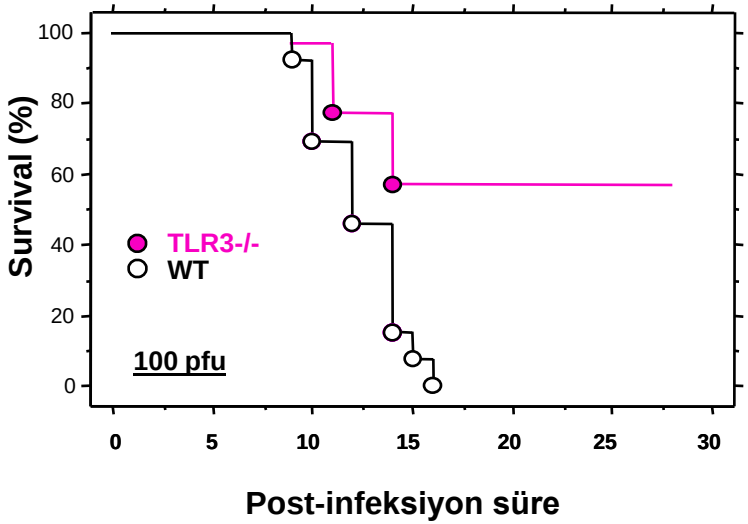
TLR3'ün Influenza enfeksiyonu sürecindeki önemi



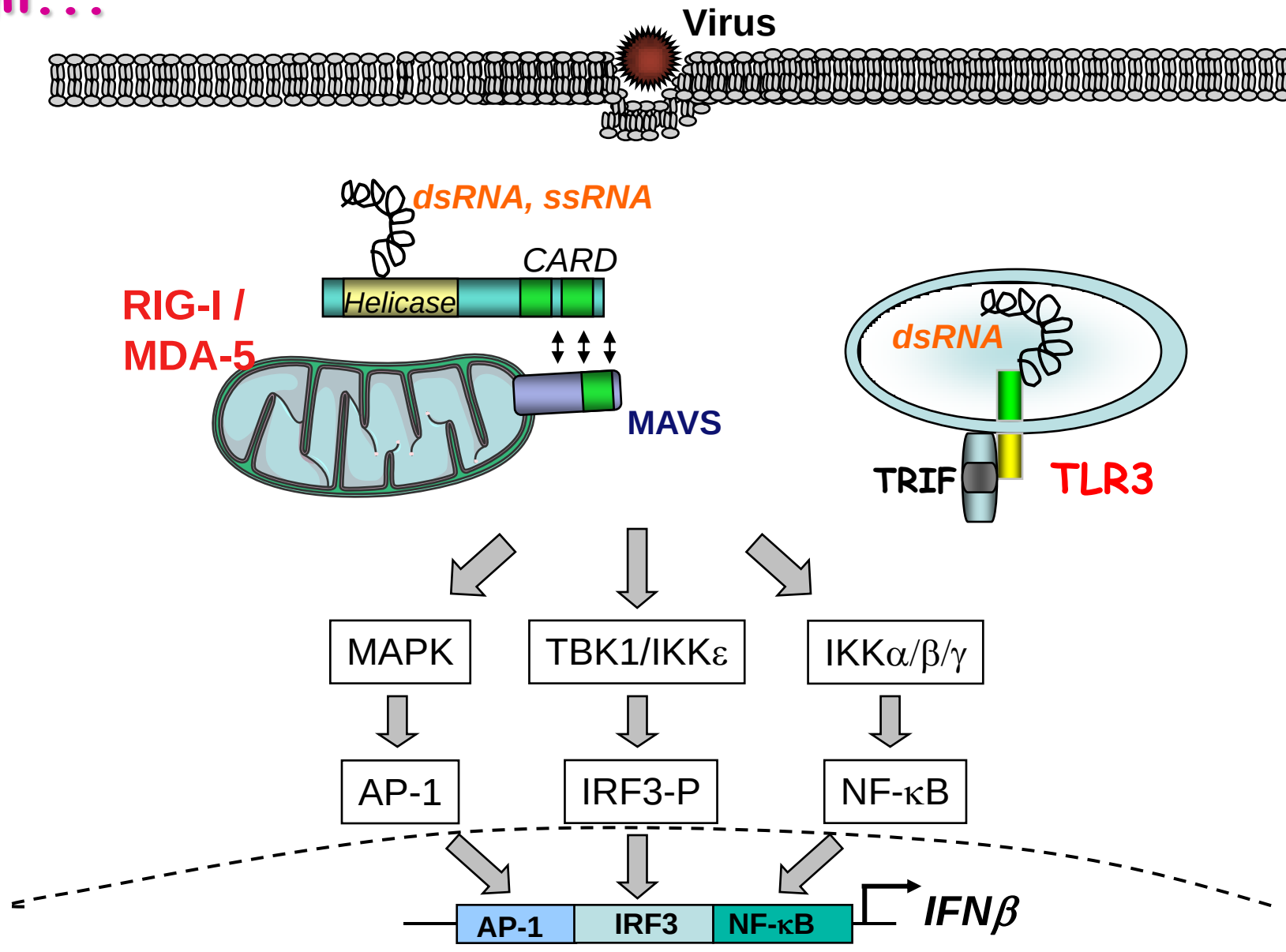
TLR3 -/-

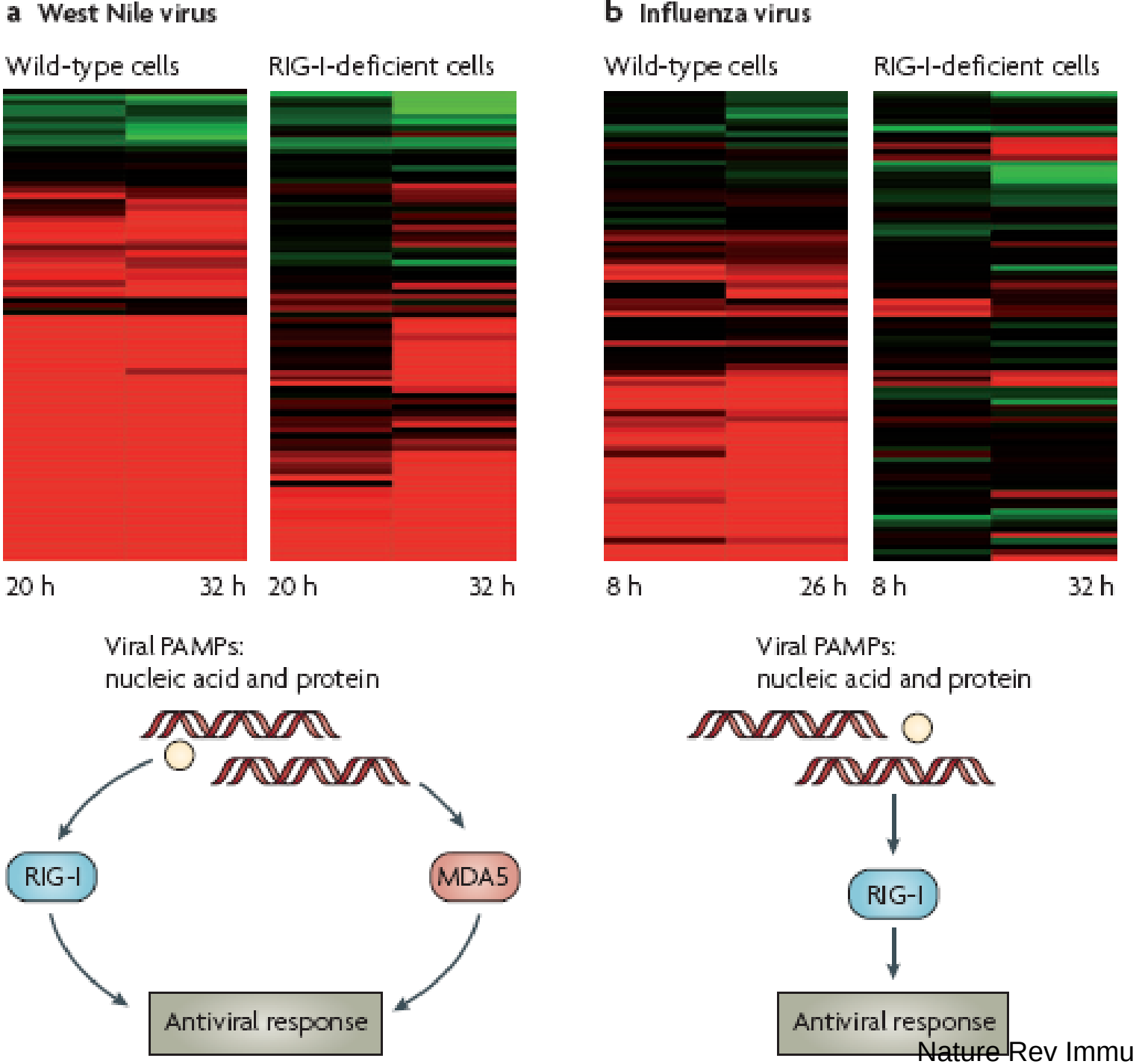
TLR3 +/+





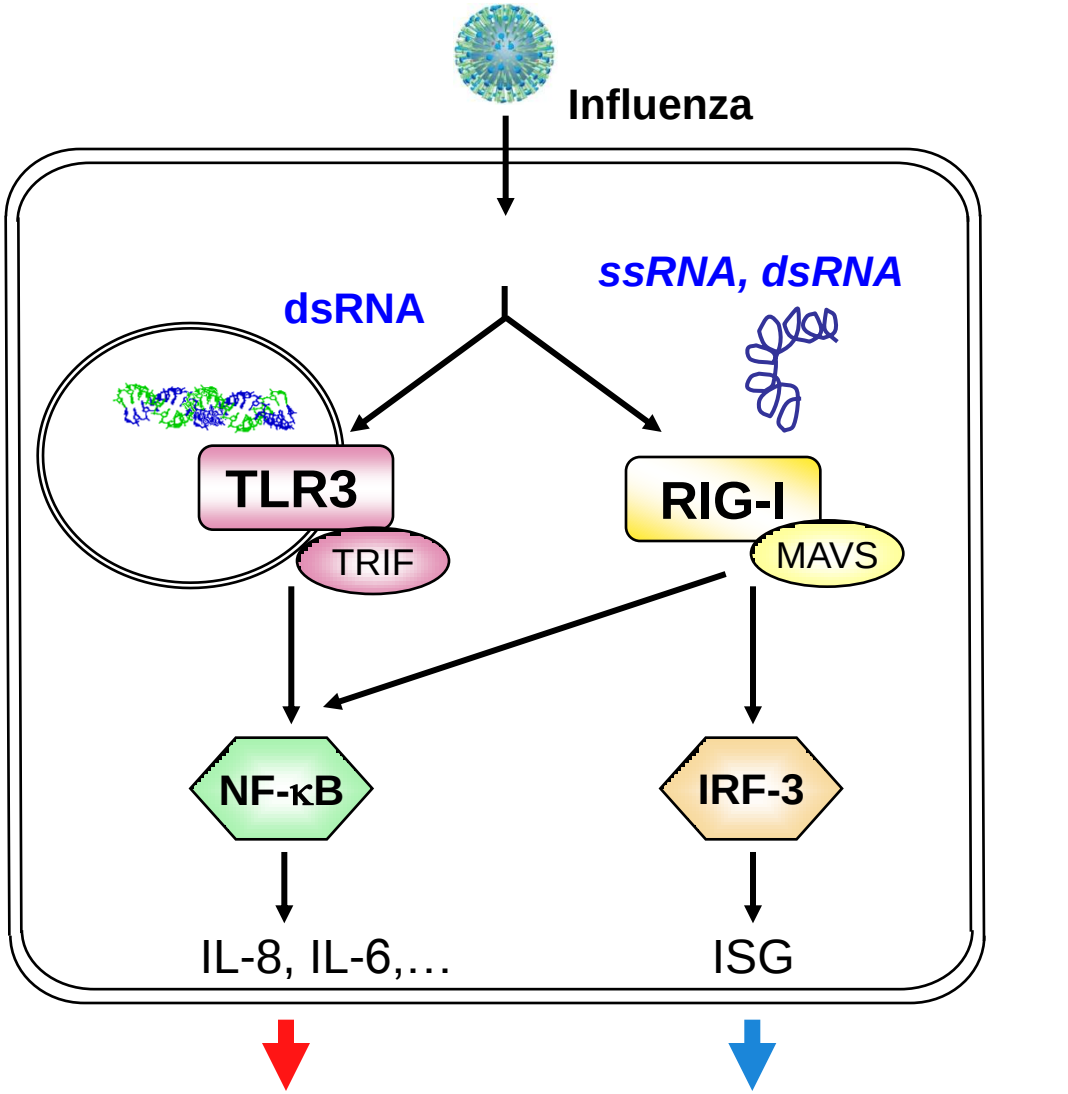
Viral Nükleik Asidi tanıyan tek Reseptör TLR değil...





Nature Rev Immunol 2008;8: 644

Reseptörlerin ligandları ile birleşmesi sonucu...



Acute Respiratory Distress Syndrome Induced by Avian Influenza A (H5N1) Virus in Mice

Tong Xu, Jian Qiao, Lihong Zhao, Guirong Wang, Guimei He, Kai Li, Yong Tian, Mingyu Gao, Jianlin Wang, Hulyu Wang, and Changgui Dong

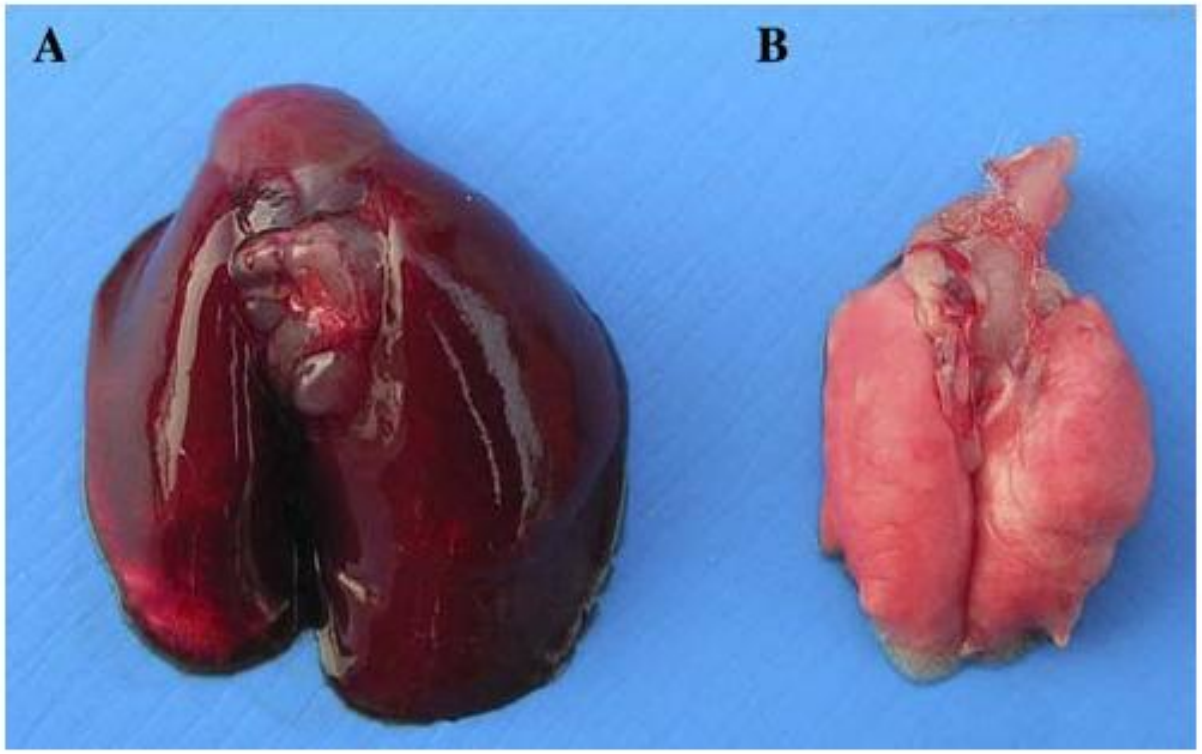
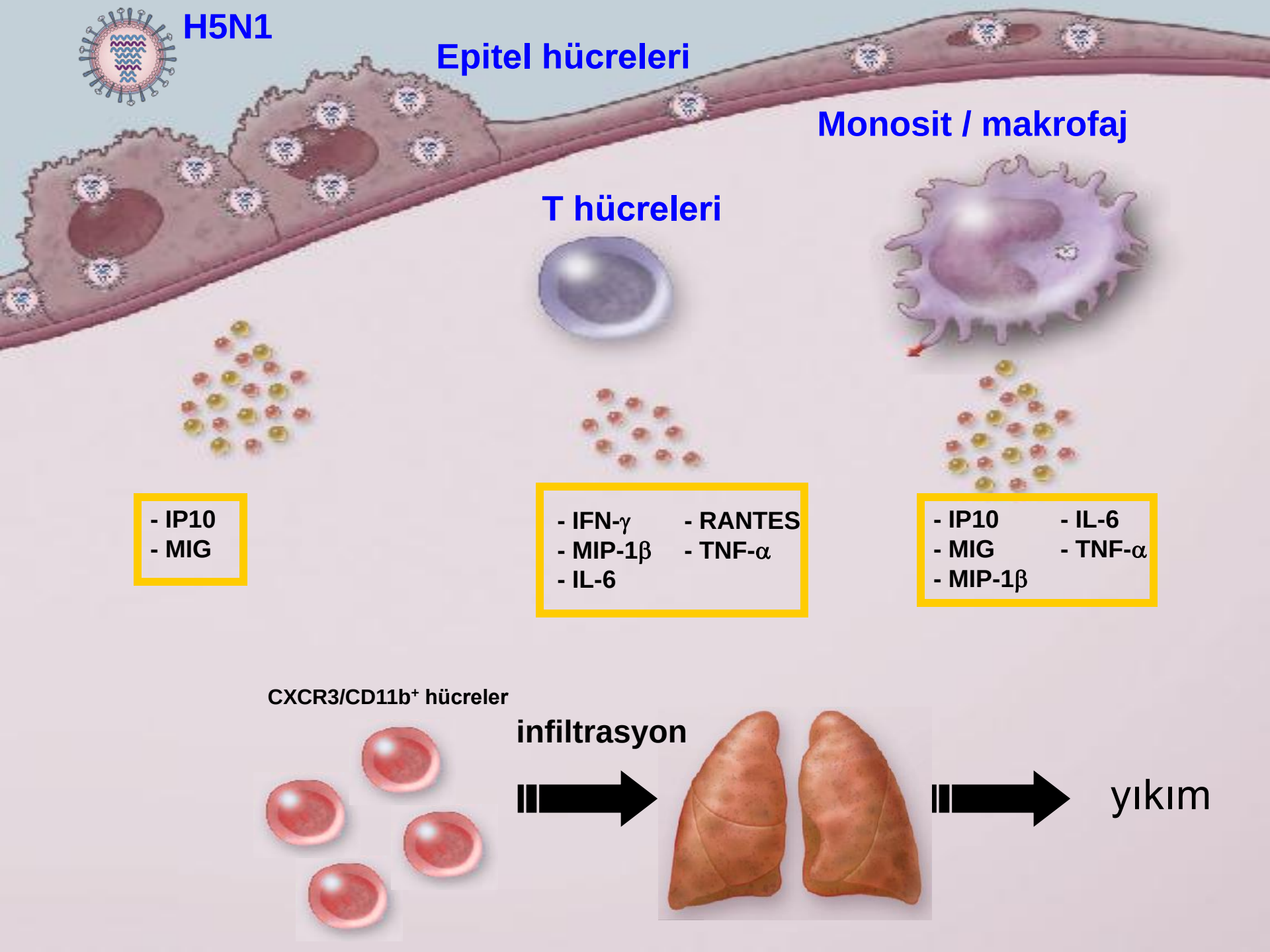


Figure 1. Gross pathology of H5N1 virus–infected lung. (*A*) H5N1 virus–infected lung 6 d postinoculation, displaying highly edematous, congestive, and hemorrhagic changes. (*B*) Noninfectious allantoic fluid–inoculated control lung 6 d postinoculation.

Am J Respir Crit Care Med 2006;174: 1011

Sitokin bombardımanı- I

- Virüsün neden olacağı patolojilerden daha ağır hasarı pülmoner filtratlarda saptanan **inflamatuar sitokinler** gerçekleştiriyor.
- **Aşırı inflamatuar anti-viral aktivite** yarardan çok zarara yol açar!.
- Hayvan modellerinde 1918 Influenza A / H5N1 suşlarının yüksek titrede sitokin / kemokin salımına neden olduğu gösterilmiş (IFN-γ, TNF-α, IL-1, IL-6, IL-12, IL-18, GCSF,MIP-2, MIP-1α/β, MCP-1)


H5N1
Epitel hücreleri
Monosit / makrofaj
T hücreleri
- IP10
- MIG
- IFN-γ
- MIP-1β
- IL-6
- RANTES
- TNF-α
- IP10
- MIG
- MIP-1β
- IL-6
- TNF-α
CXCR3/CD11b+ hücreler
infiltrasyon
yıkım

Sitokin bombardımanı- II

- Çok sayıda sitokin indüksiyonu, **sitokin genlerinin transaktivasyonunu sağlayan bir transkripsiyon faktörünün (NF-kB), viral HA tarafından aktive edilmesinden** kaynaklanır.
- Ayrıca **viral NP** de, **monositlerden** TNF ve IL-1 üretimini uyarmaktadır.

Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia

Menno D de Jong[1], Cameron P Simmons[1], Tran Tan Thanh[1], Vo Minh Hien[2], Gavin J D Smith[3], Tran Nguyen Bich Chau[1], Dang Minh Hoang[1], Nguyen Van Vinh Chau[2], Truong Huu Khanh[4], Vo Cong Dong[5], Phan Tu Qui[4], Bach Van Cam[4], Do Quang Ha[1], Yi Guan[3], J S Malik Peiris[3], Nguyen Tran Chinh[2], Tran Tinh Hien[2] & Jeremy Farrar[1]

Table 3 Levels of chemokines and cytokines in the peripheral blood

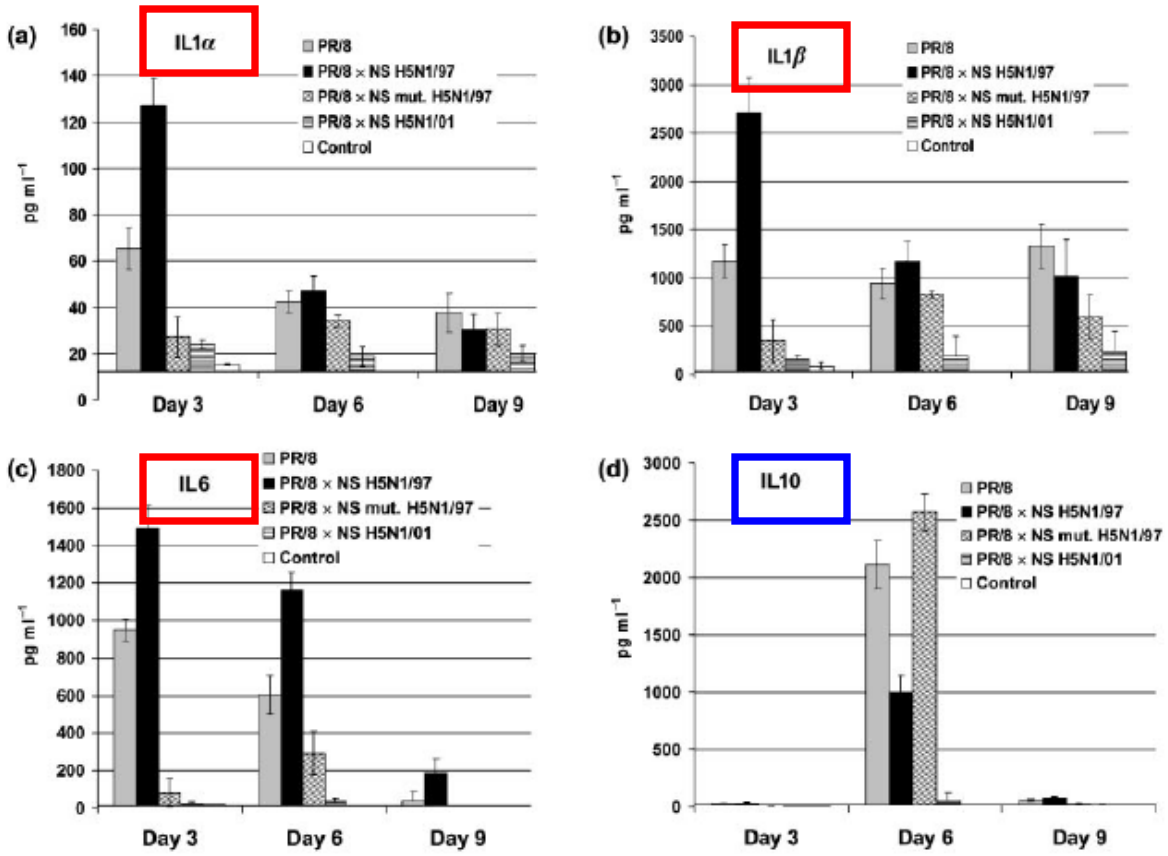
						H5N1		
	H5N1[a] ($n = 16$)	P^b	H3/H1 ($n = 6$)	P^c	Controls ($n = 15$)	Fatal ($n = 11$)	Not fatal ($n = 5$)	P
IP-10	5.1 (3.5–6.3)	0.005	3.8 (3.4–4.6)	0.001	2.7 (2.4–3.8)	5.4 (3.5–6.3)	4.2 (4.0–5.0)	0.031
MCP-1	2.4 (1.5–4.0)	0.083	1.9 (und.–2.4)	0.045	1.4 (und.–2.0)	2.8 (2.0–4.0)	1.8 (1.5–2.3)	0.015
MIG	4.3 (3.1–5.2)	0.013	3.2 (2.9–3.9)	0.002	2.6 (2.2–3.3)	4.6 (3.3–5.2)	3.3 (3.1–4.2)	0.011
IL-8	2.0 (0.7–3.2)	0.001	0.8 (0.4–1.5)	0.34	0.7 (und.–1.0)	2.4 (1.1–3.2)	1.7 (0.7–1.9)	0.020
IL-10	1.5 (und.–2.8)	0.002	–1.0 (und.–0.4)	0.85	–1.0 (und.–1.0)	1.6 (und.–2.8)	0.8 (und.–2.2)	0.6
IL-6	2.1 (und.–3.7)	0.001	–0.2 (und.–0.7)	0.30	–1.0 (und.–1.0)	2.2 (1.5–3.7)	1.0 (und.–2.4)	0.054
IFN-γ	2.0 (und.–4.2)	0.029	0.1 (und.–2.4)	0.42	–1.0 (und.–1.4)	2.3 (1.0–4.2)	2.0 (und.–2.6)	0.2

Levels of chemokines and cytokines in the peripheral blood of patients with influenza H5N1 and H3N2 or H1N1. Levels are given as median $\log_{10}$ pg per ml (range).
[a]Plasma levels of chemokines and cytokines in H5N1 patients were all higher than in healthy controls at <0.001 significance levels. [b]Comparison between H5N1 and H3/H1 patients. [c]Comparison between H3/H1 patients and healthy controls. und., undetectable.

Nature Med 2006;12: 1203

Pathogenesis of Hong Kong H5N1 influenza virus NS gene reassortants in mice: the role of cytokines and B- and T-cell responses

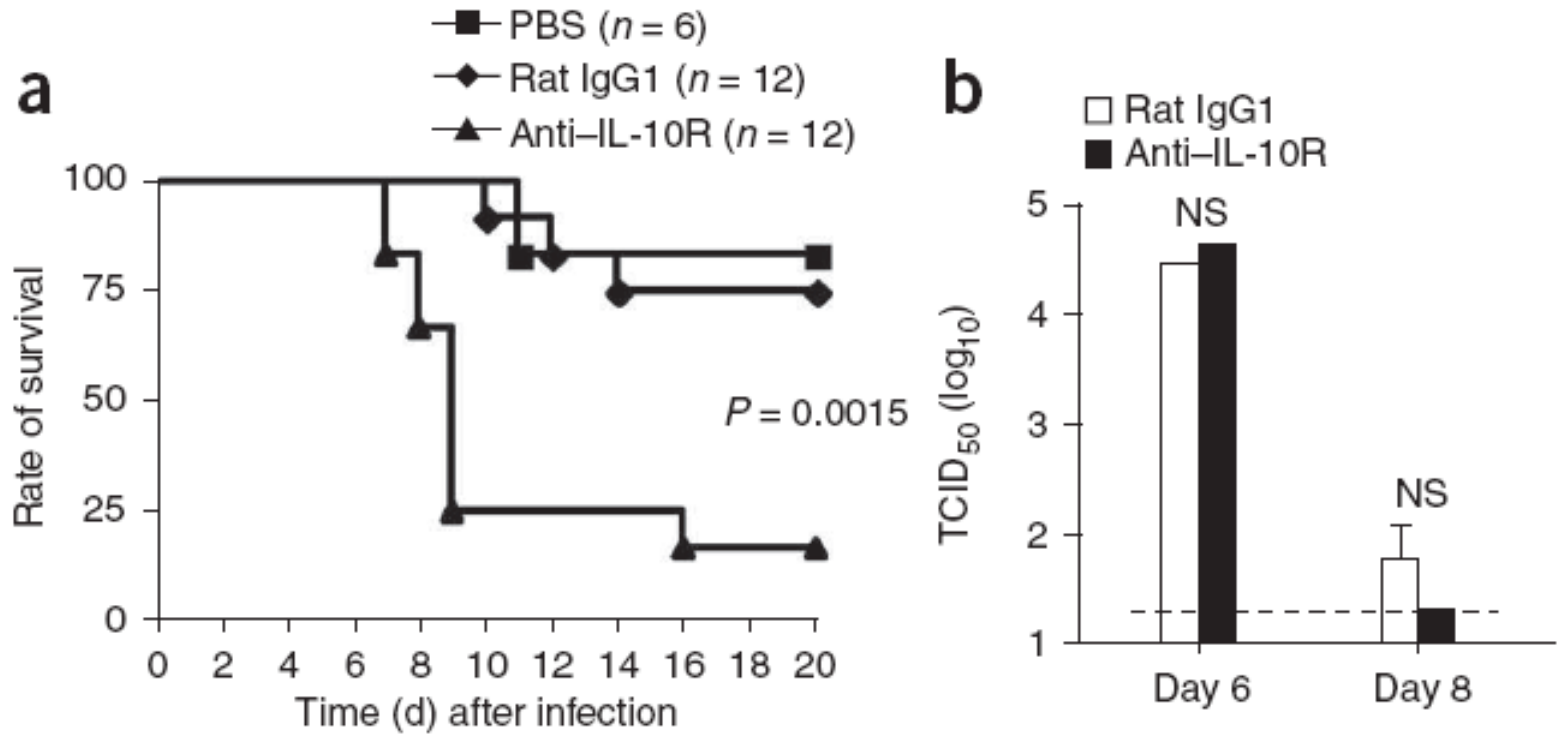
Aleksandr S. Lipatov,[1] Samita Andreansky,[2]† Richard J. Webby,[1] Diane J. Hulse,[1] Jerold E. Rehg,[3] Scott Krauss,[1] Daniel R. Perez,[1]‡ Peter C. Doherty,[2,5] Robert G. Webster[1,4] and Mark Y. Sangster[2]§



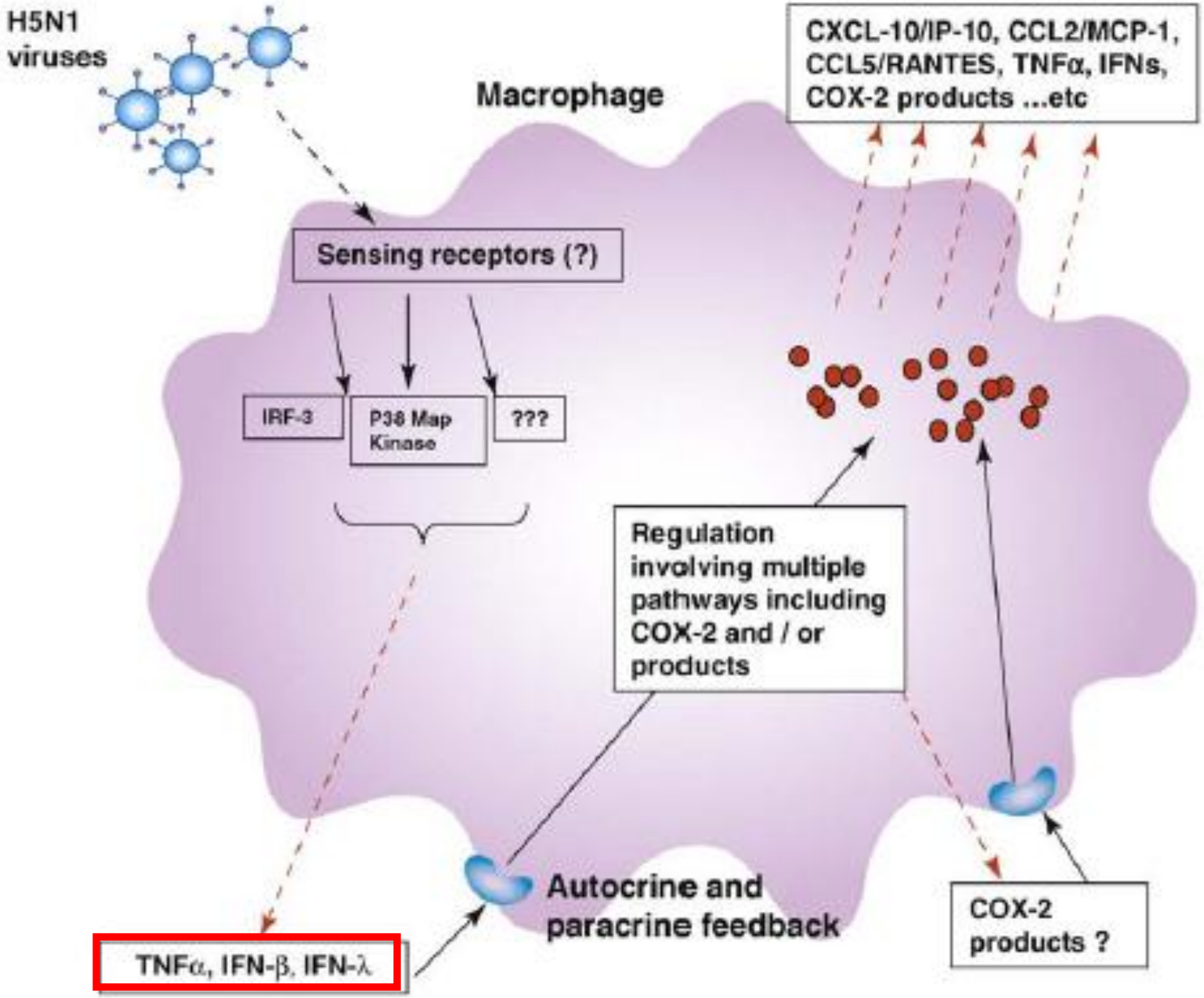
J Gen Virol 2005;86: 1121

Effector T cells control lung inflammation during acute influenza virus infection by producing IL-10

Jie Sun[1], Rajat Madan[2], Christopher L Karp[2] & Thomas J Braciale[1,3]

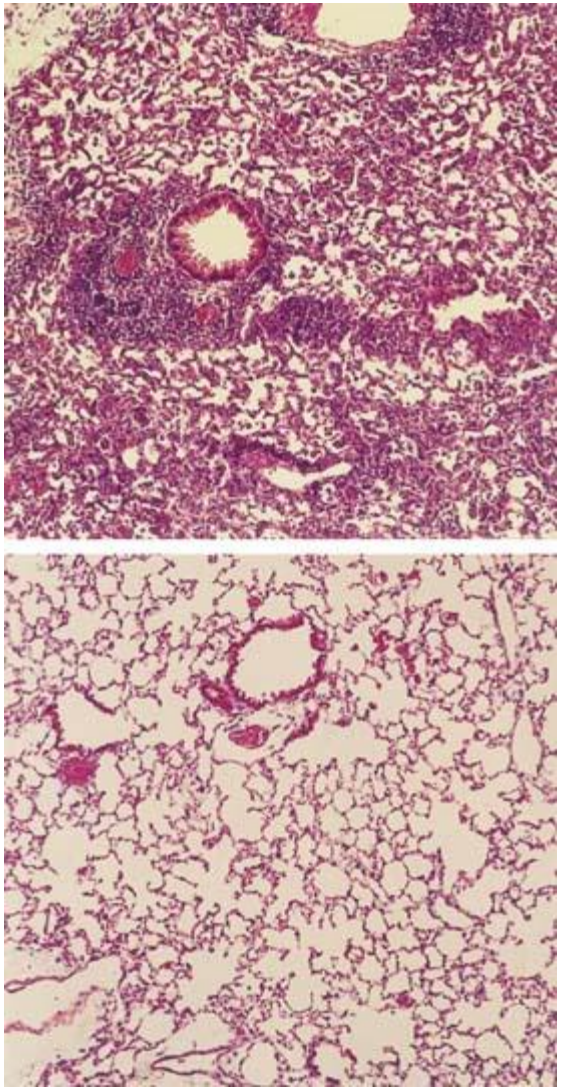


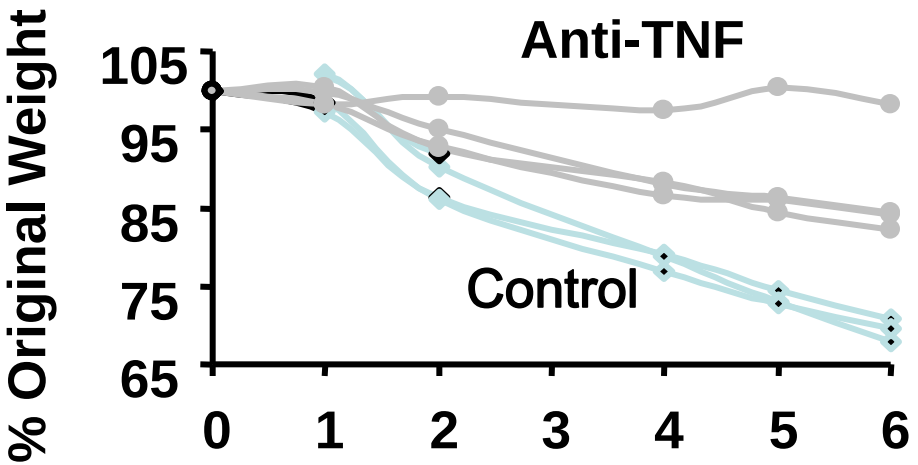
Nature Med 2009;15: 277

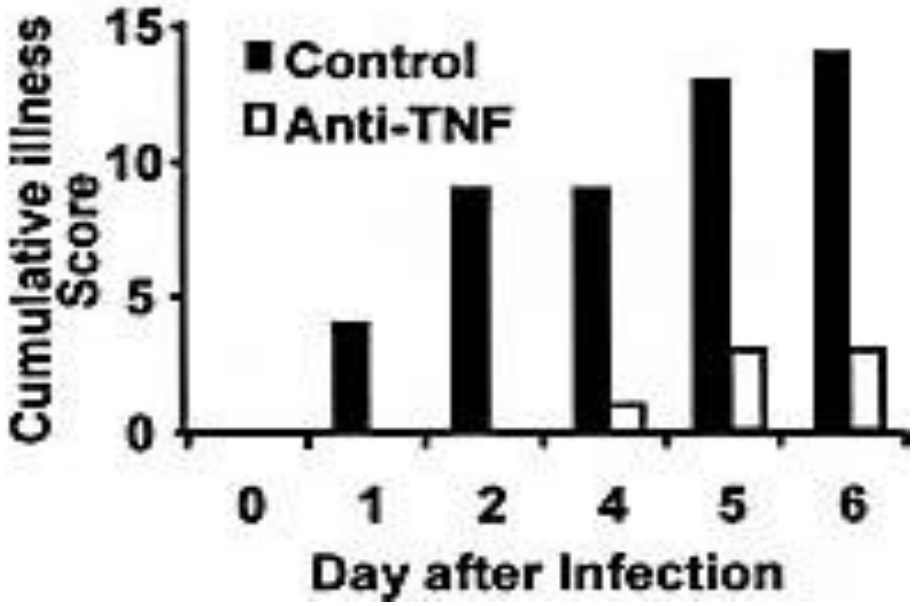


Trends Immunol 2009;30: 574

Farede Anti-TNF uygulaması kilo kaybını engelliyor

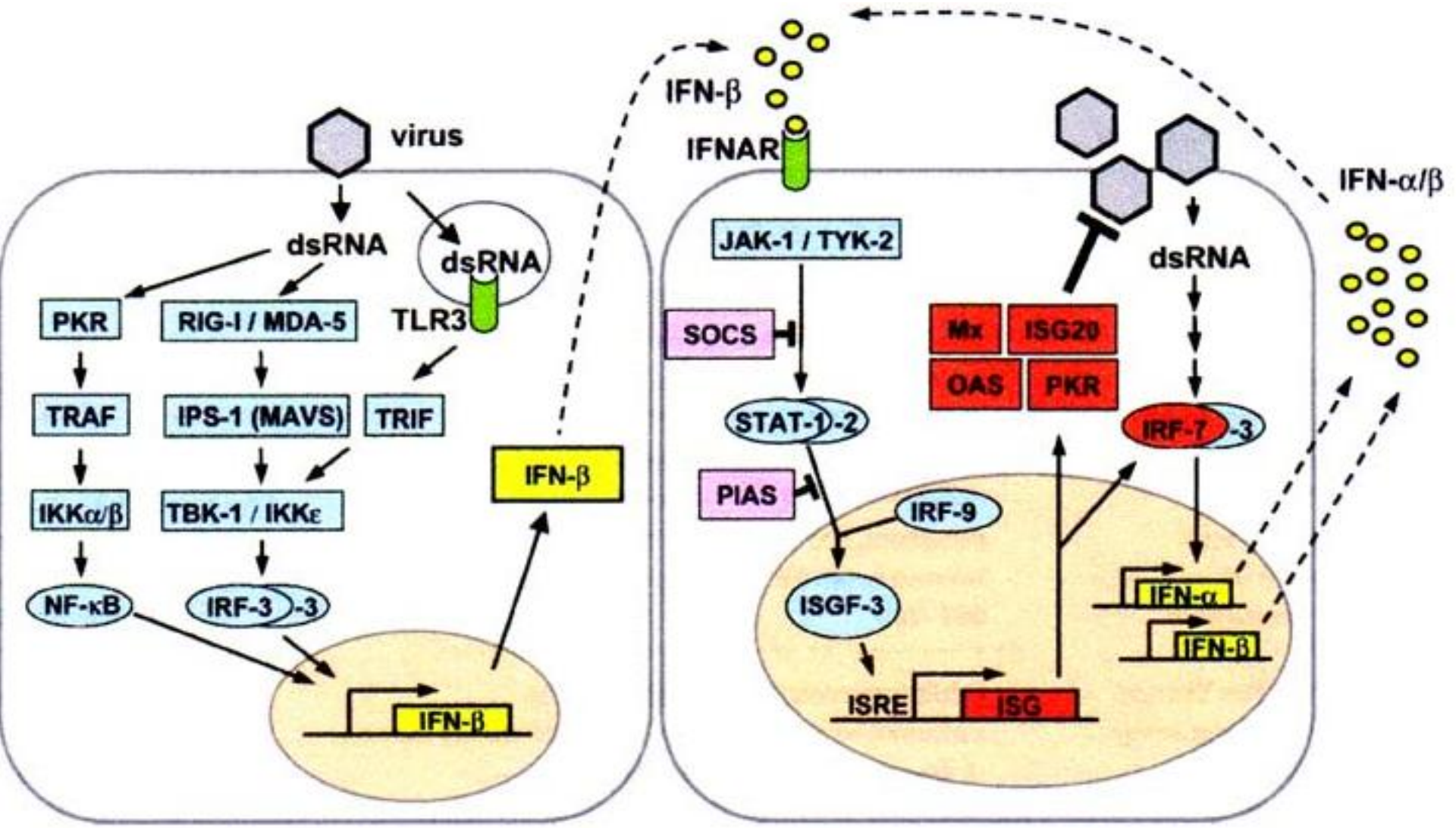




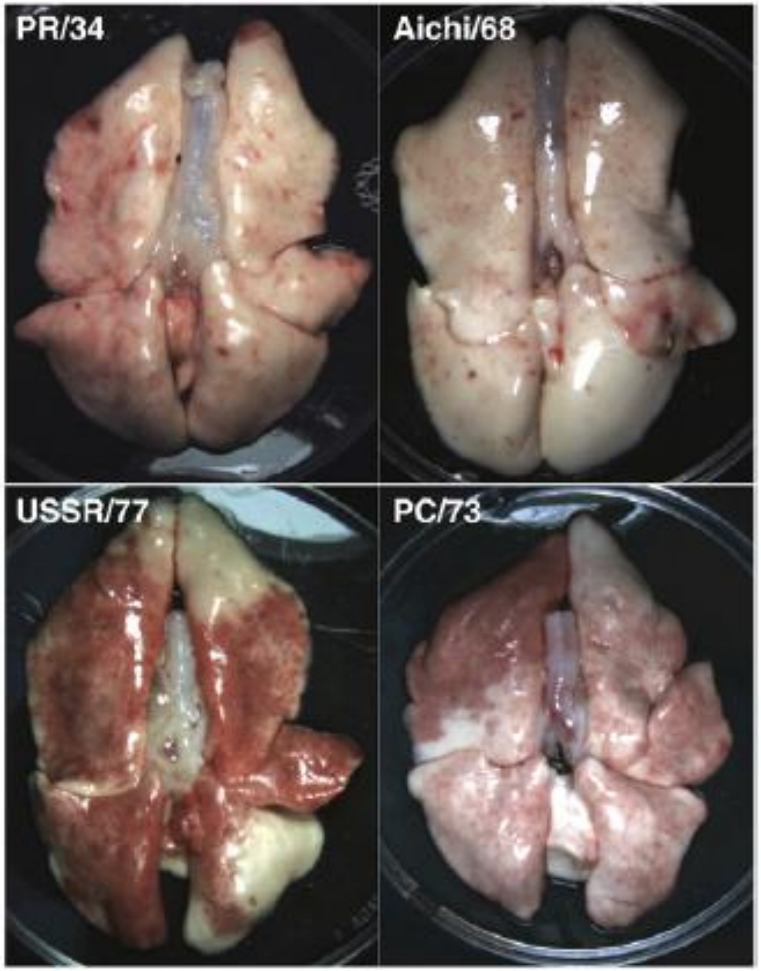


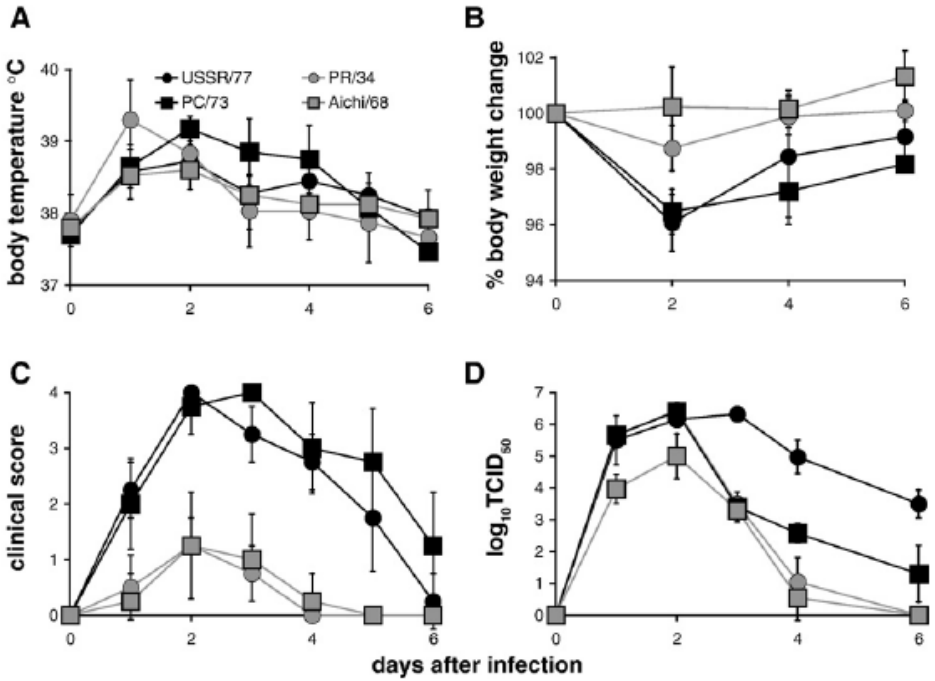
J Immunol 2001; 31: 2566

INFLUENZA enfeksiyonlarında INTERFERON'ların ayrı bir önemi var...



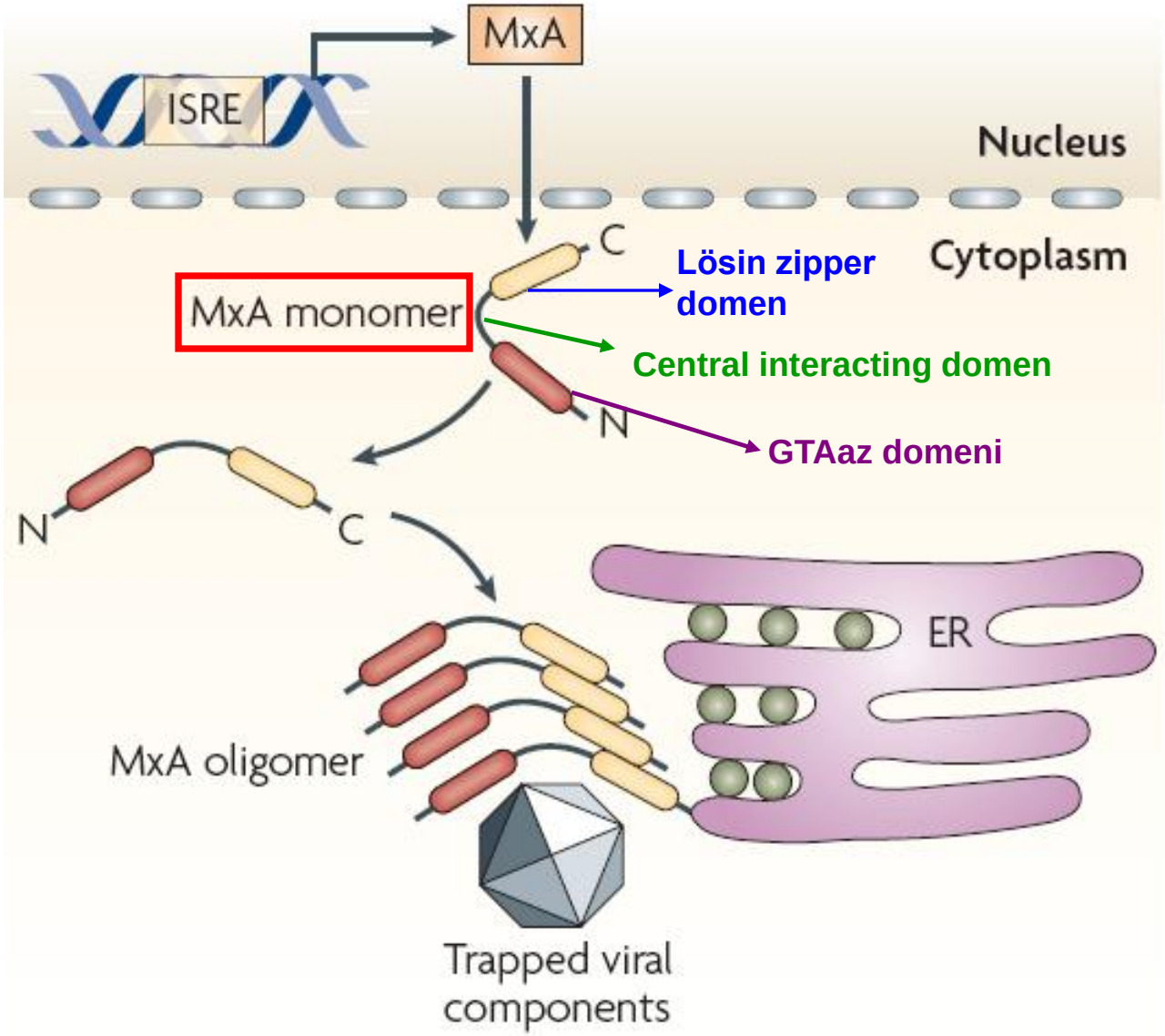
Severe seasonal influenza in ferrets correlates with reduced interferon and increased IL-6 induction





Virology 2008;376: 53

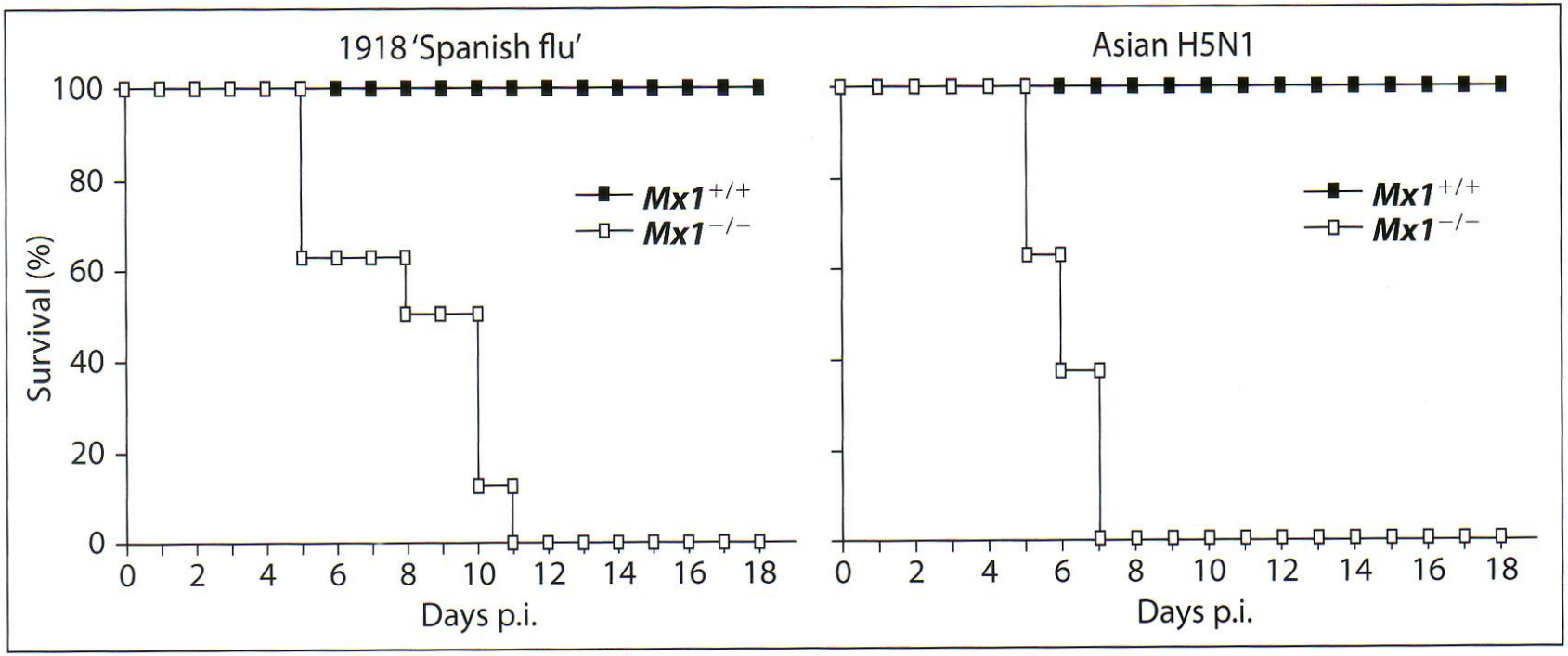
Tip I IFN'ların uyarısı sonucu oluşan proteinlere bir örnek: Mx

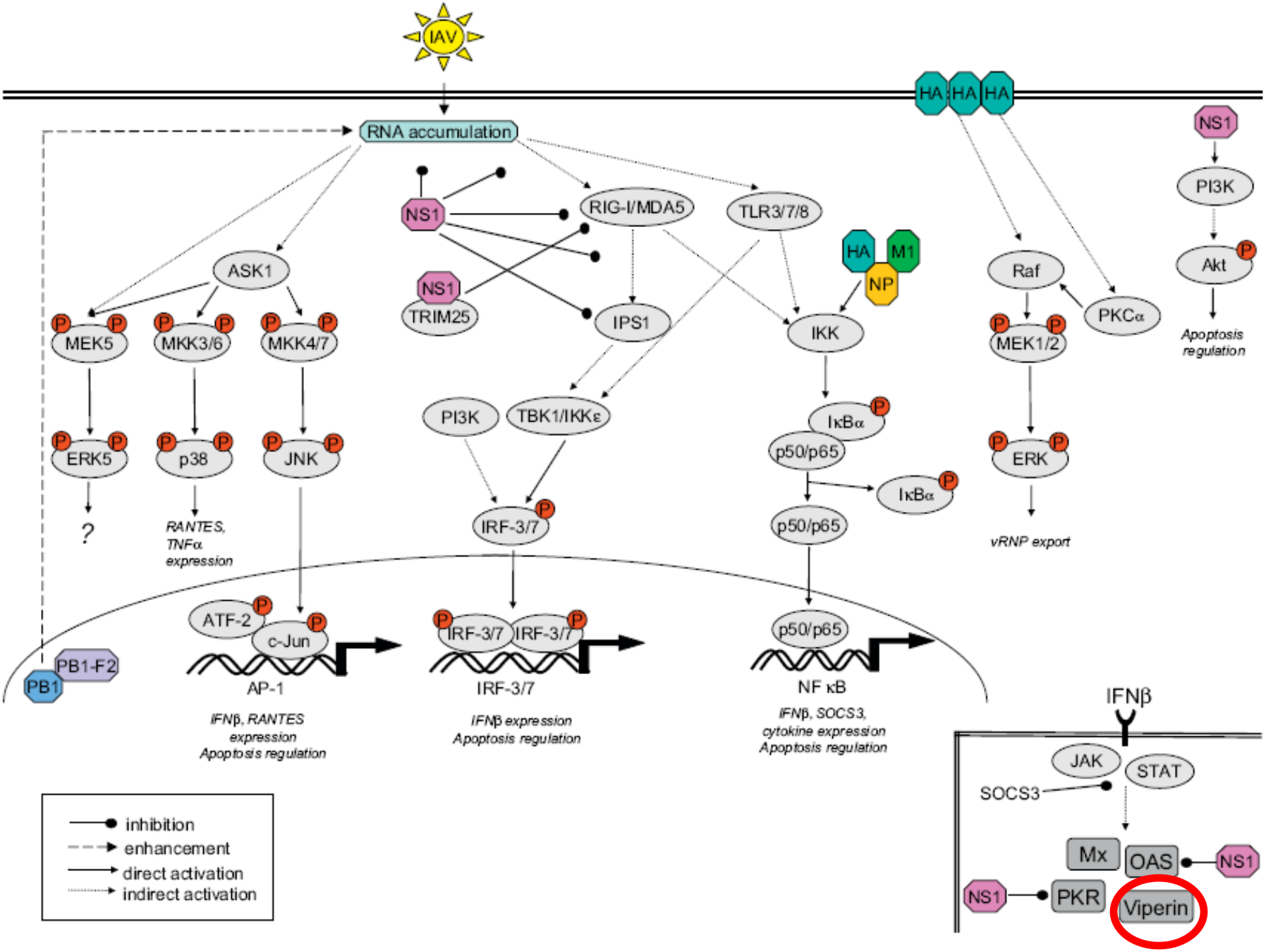


Mx'ler: - viral PB2 polimerazın transkripsiyonunu inhibe ederler
- viral nükleokapside bağlanıp, parçalarlar

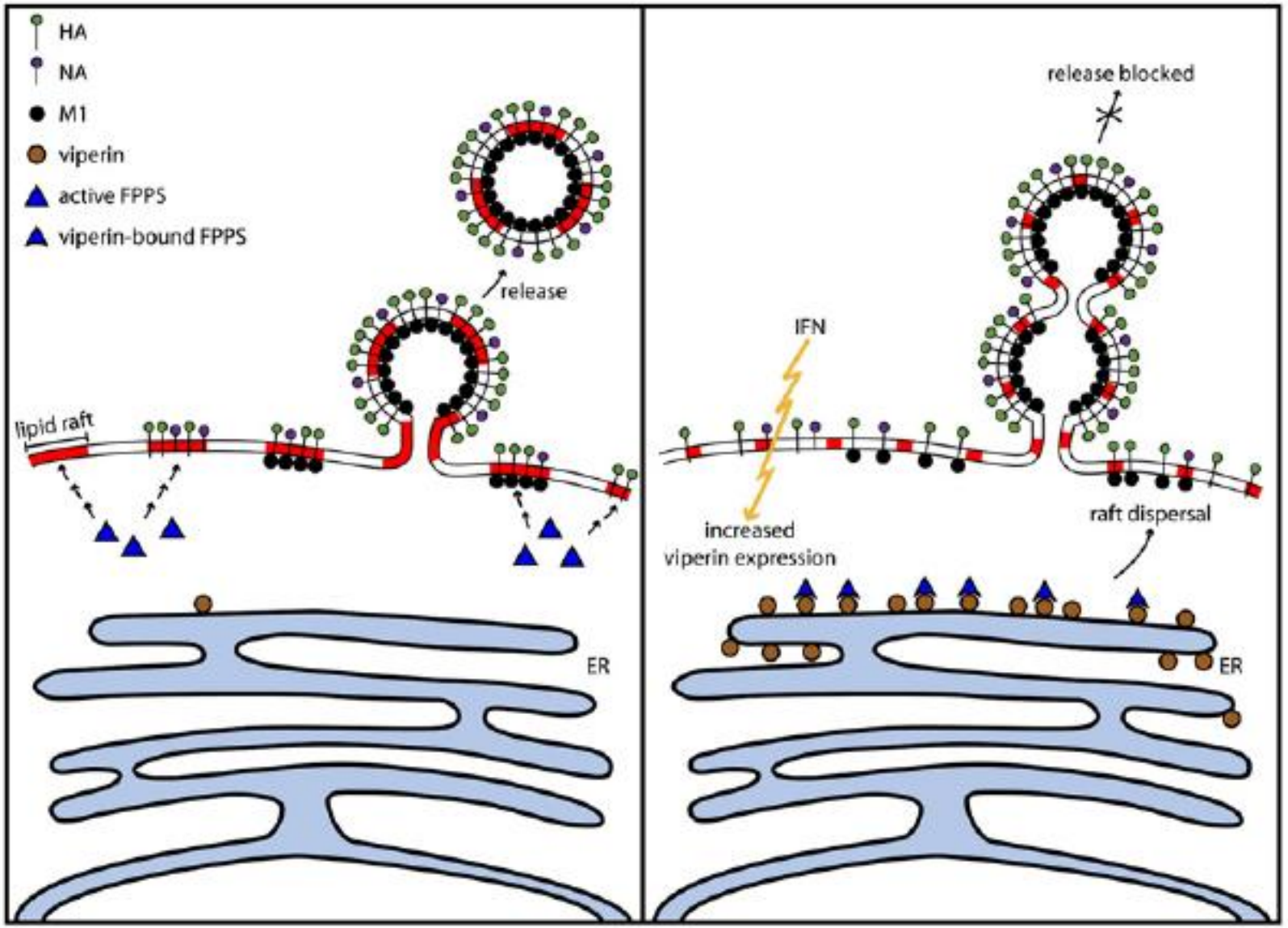
Nat Rev Immunol 2008;8: 559

- Mx (-) fareler Influenza'ya daha duyarlıdırlar
- Letal hastalık oluşturmak için Mx (+) farelere 100-1000 kez daha fazla virüs gerekli



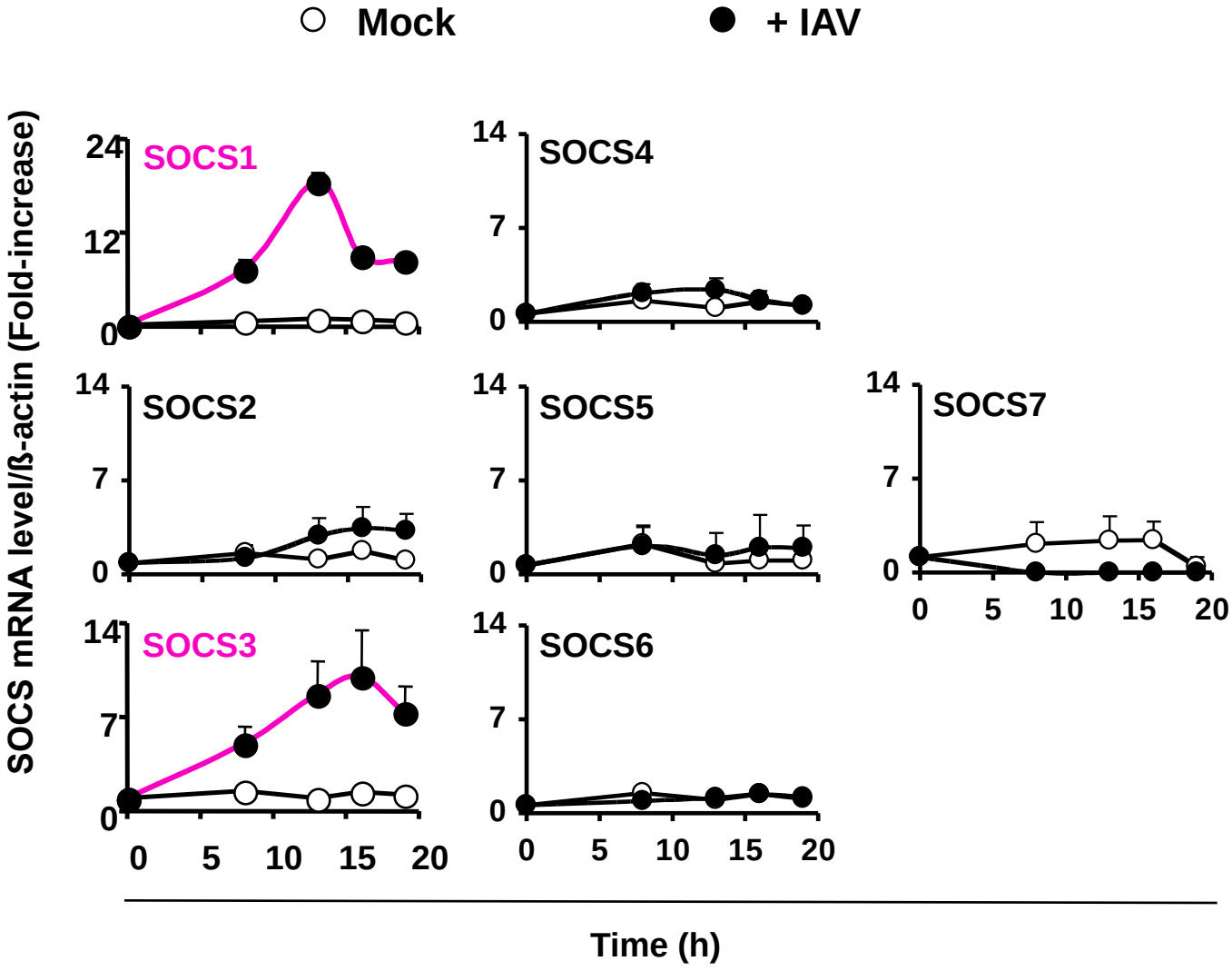


Microbes Infect 2010;12: 81

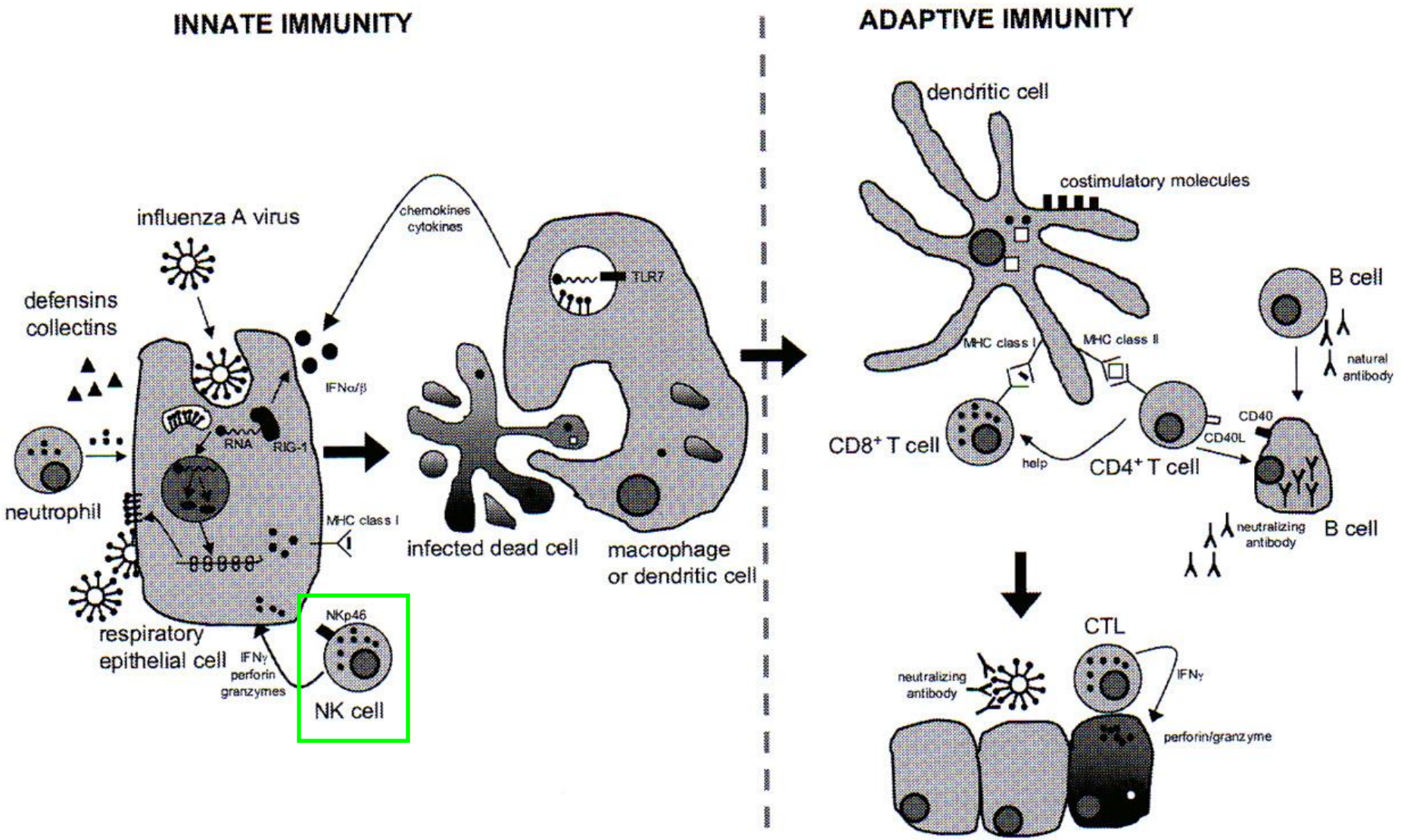


Cell Host Microbe 2007;2: 71

Influenza A enfeksiyonu, akciğer epitel hücrelerinde SOCS1 ve SOCS3 sentezini arttırıyor



Influenza Enfeksiyonlarında İmmün Yanıt



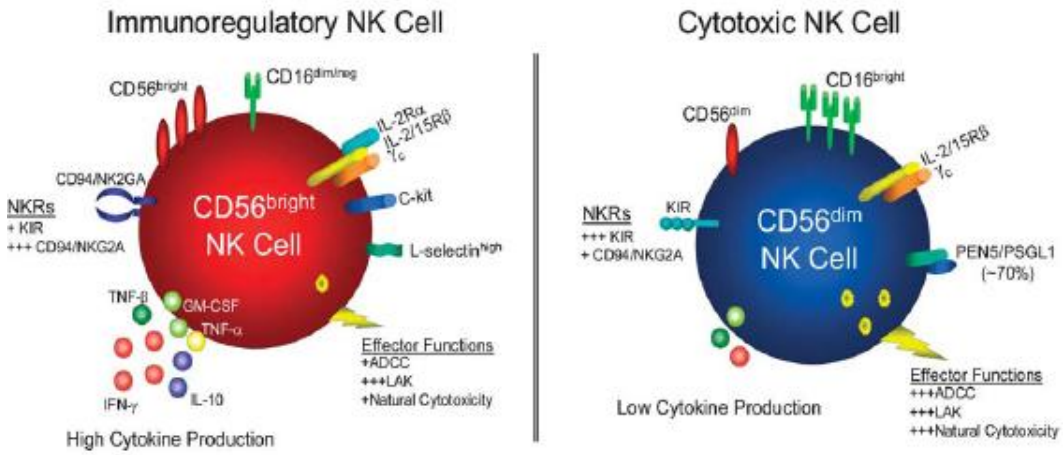
NK'ların işlevleri

1- Sitokin üretimi

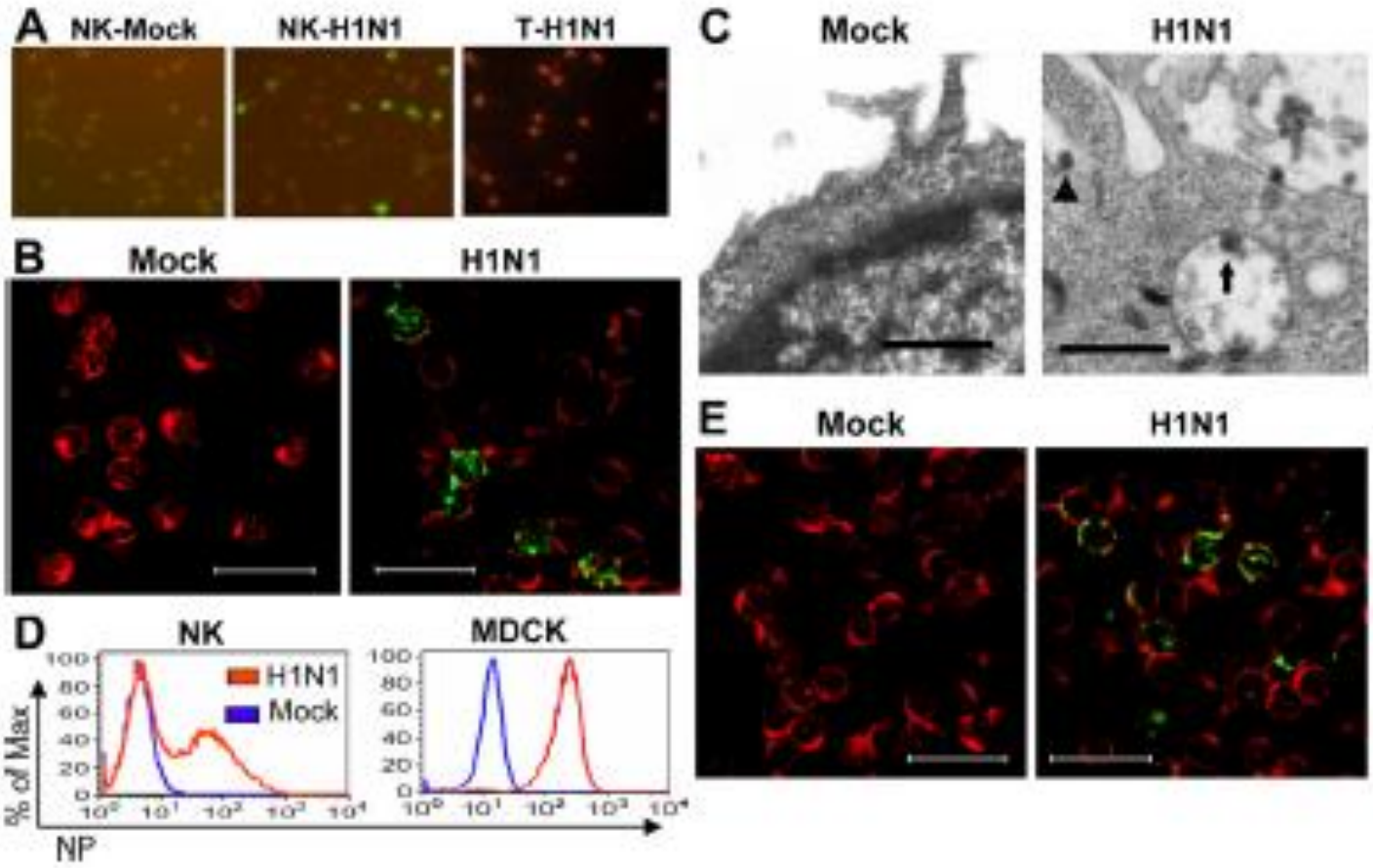
2- Hedef hücre yıkımı

* granül ekzositozu ile (granzim A, B)
* ölüm reseptörlerini (FasL, TRAIL) devreye sokarak
* antikora bağımlı hücresel sitotoksisite (FcγRIII ile)

3- DC'ler ile etkileşim

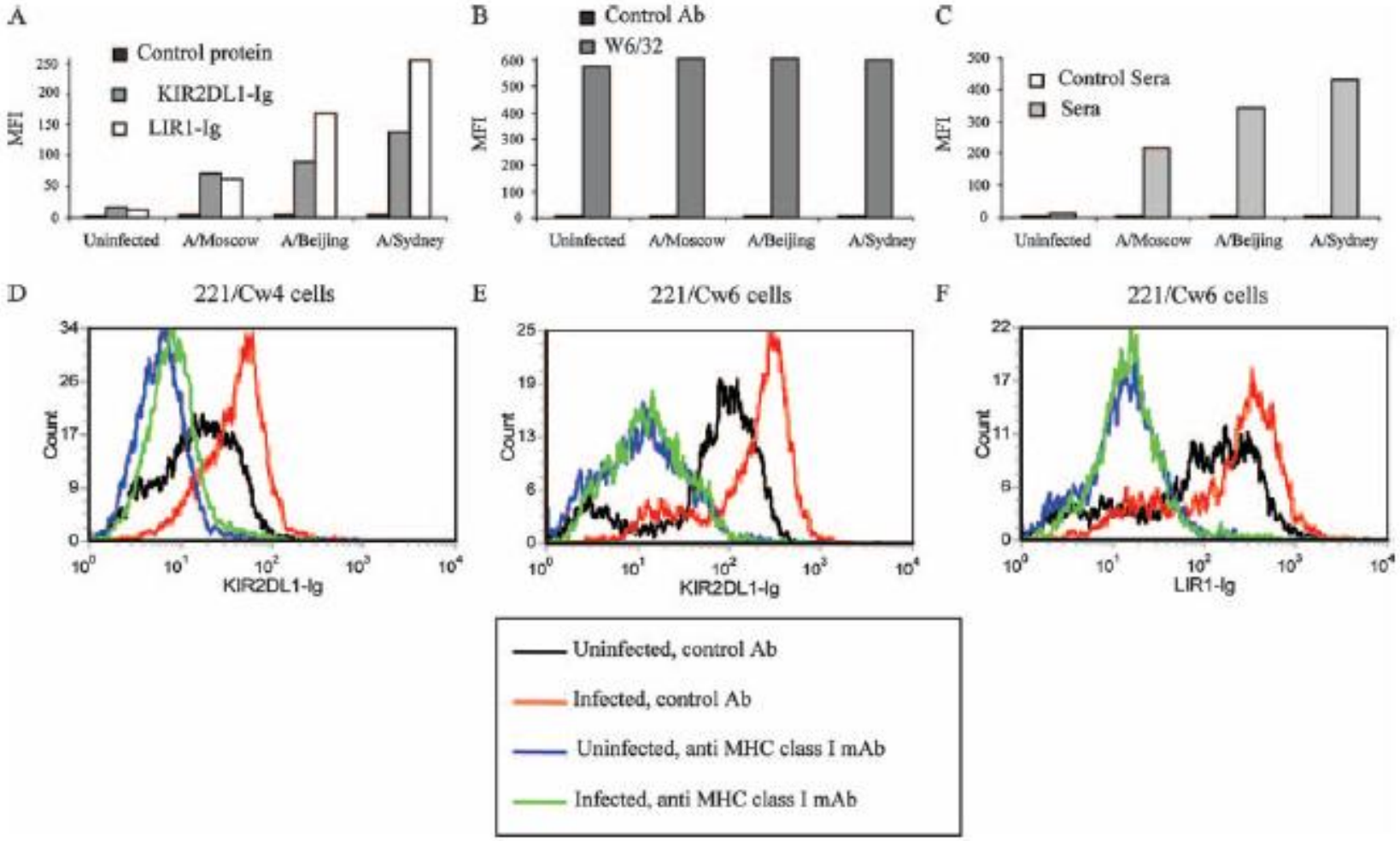


Influenza Virus Directly Infects Human Natural Killer Cells and Induces Cell Apoptosis[▽]



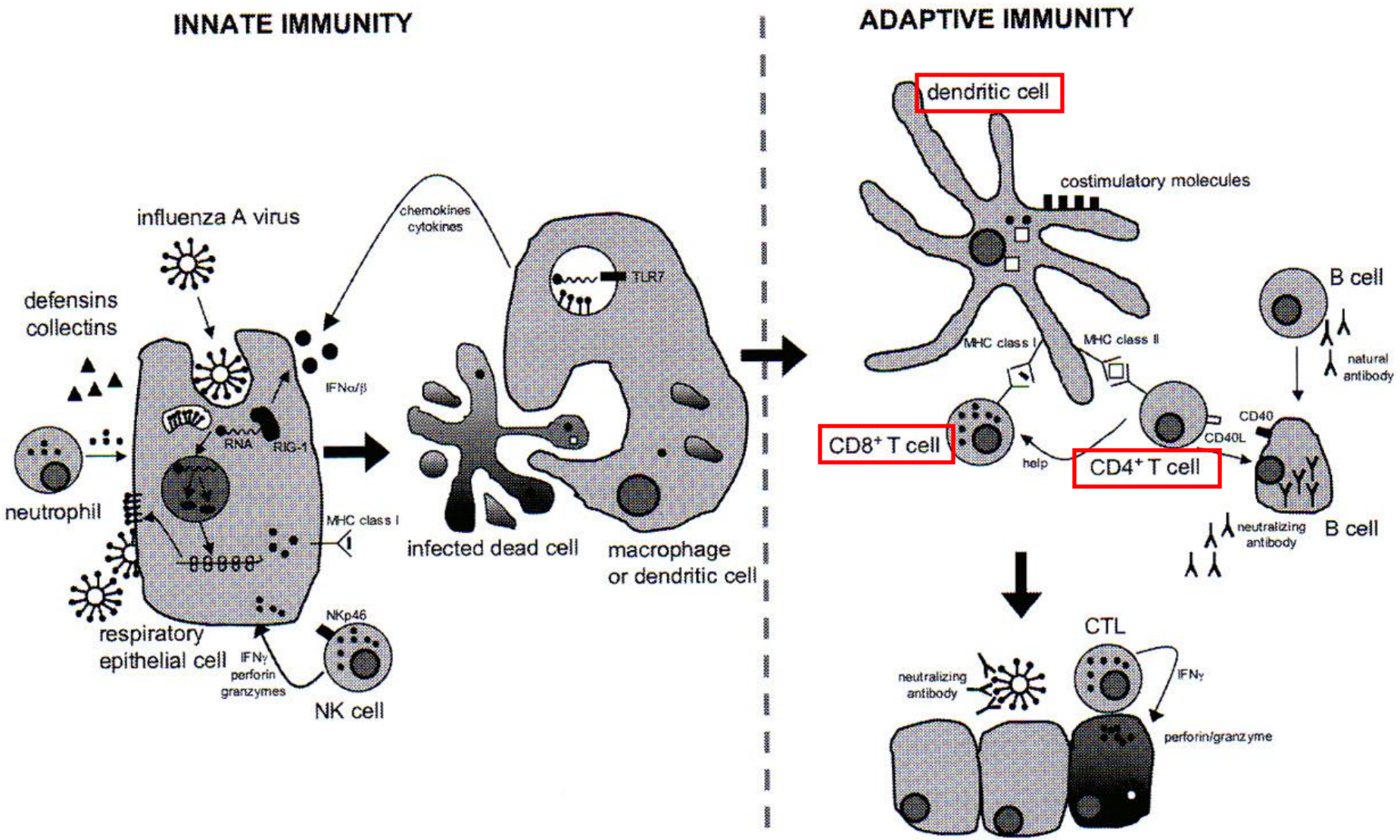
J Virol 2009;83: 9215

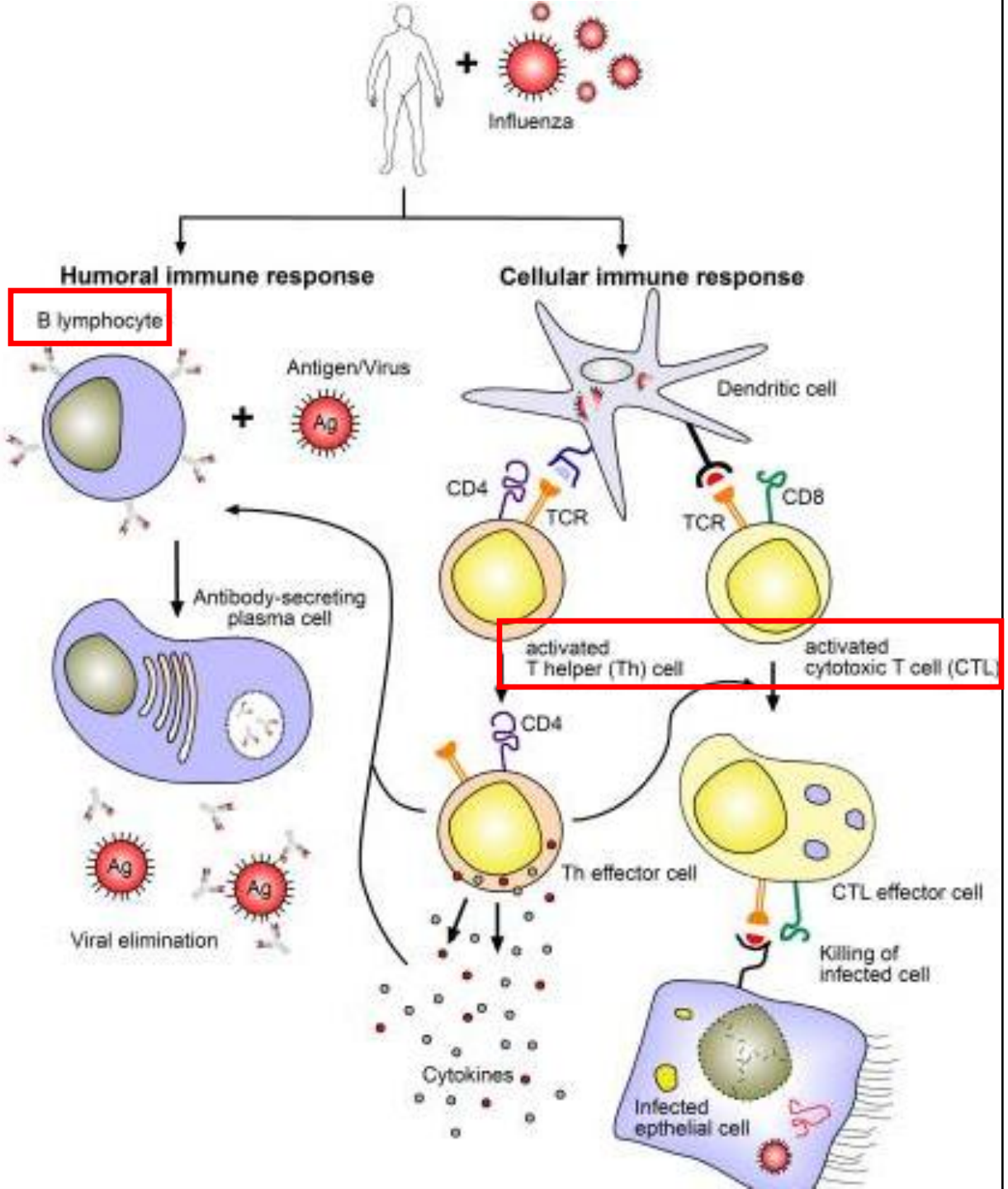
Influenza Virus Infection Augments NK Cell Inhibition through Reorganization of Major Histocompatibility Complex Class I Proteins[▽]



J Virol 2008;82: 8030

Influenza Enfeksiyonlarında İmmün Yanıt





- **$CD4^+$ T hücreleri:**

-Sitokin üretimi (IL-2, TNF, IL-10, IFN-γ)

-$CD8^+$ ve B hücre yanıtının güçlendirilmesi

- **$CD8^+$ T hücreleri:**

-Enf hücrelerin lizisi

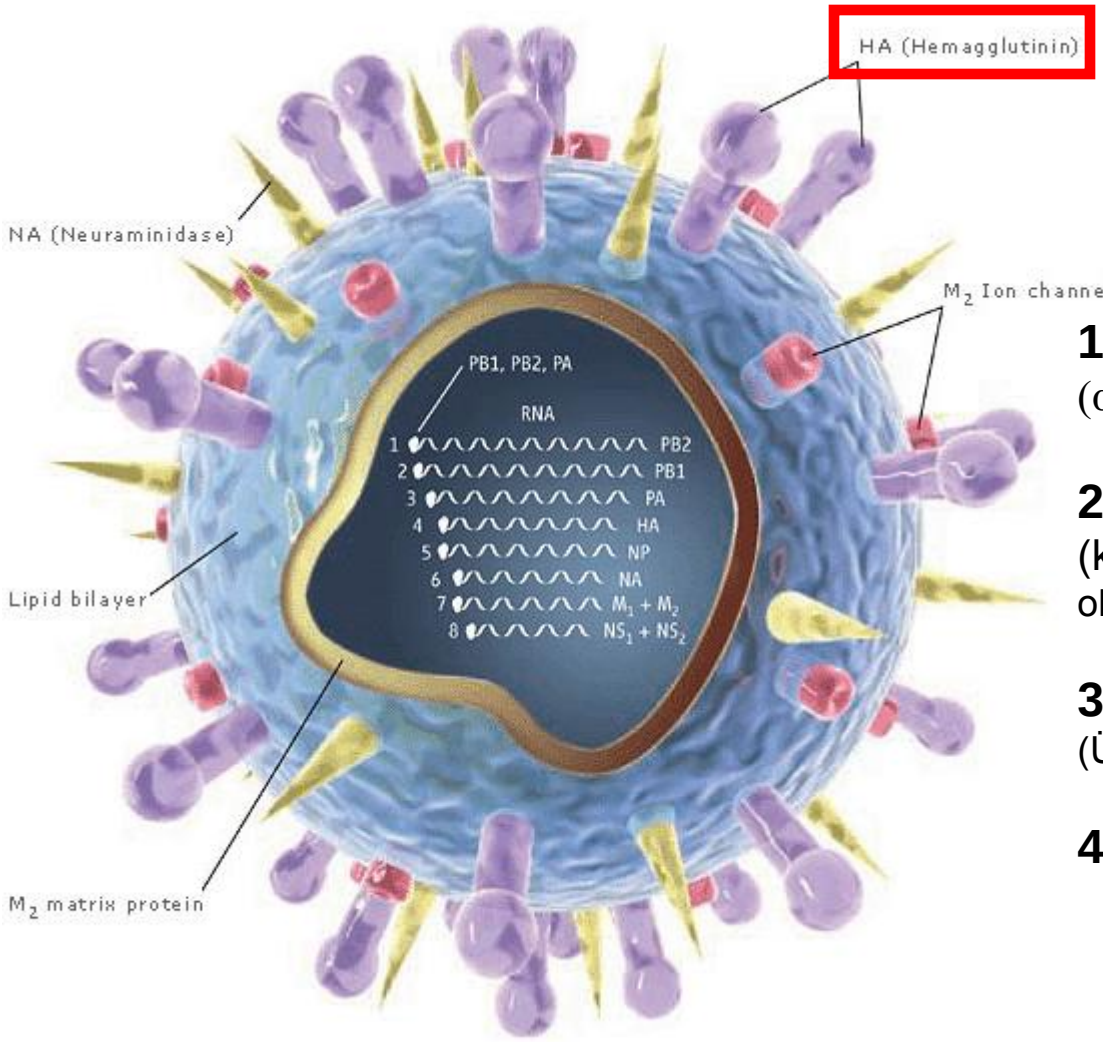
-Anti-viral sitokin üretimi (TNF, IFN-γ)

- **B hücreleri:**

-Antikor üretimi

-Antijen sunumu

Virülans ve Patogenezde rol oynayan viral proteinler



Hemaglütinin (HA)

Reseptör spesifisitesini belirler

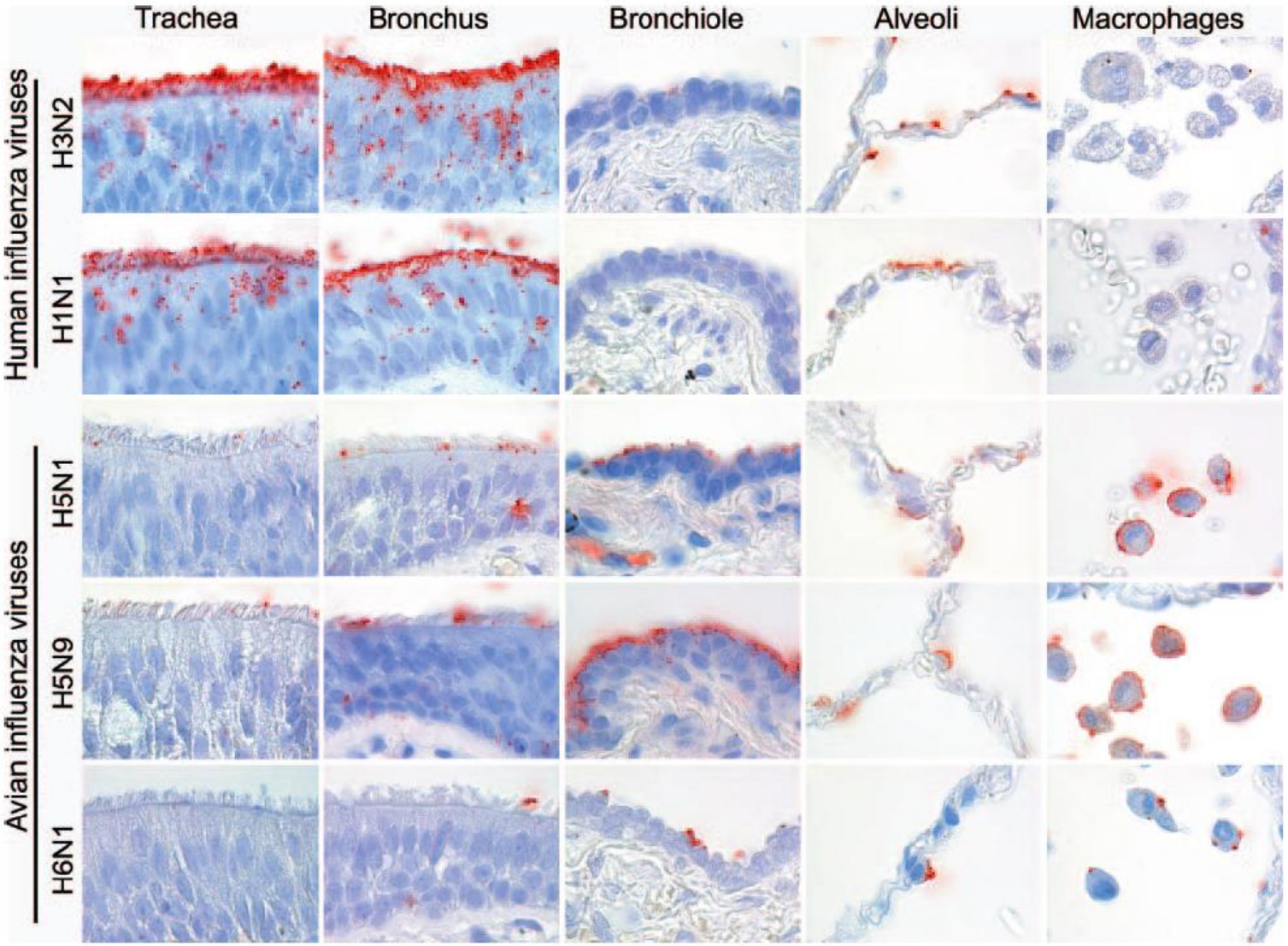
1- Konak özgüllüğünü belirler
(α2,3- vs α2,6-bağlı sialik asid)

2- Hücresel tropizmi belirler
(kırılma bölgesinin mülti-bazik özelliğine bağlı olarak, akciğer dışı yayılımın varlığı)

3- Replikasyon bölgesini belirler
(Üst/alt sol yol'da reseptör ekspresyonu)

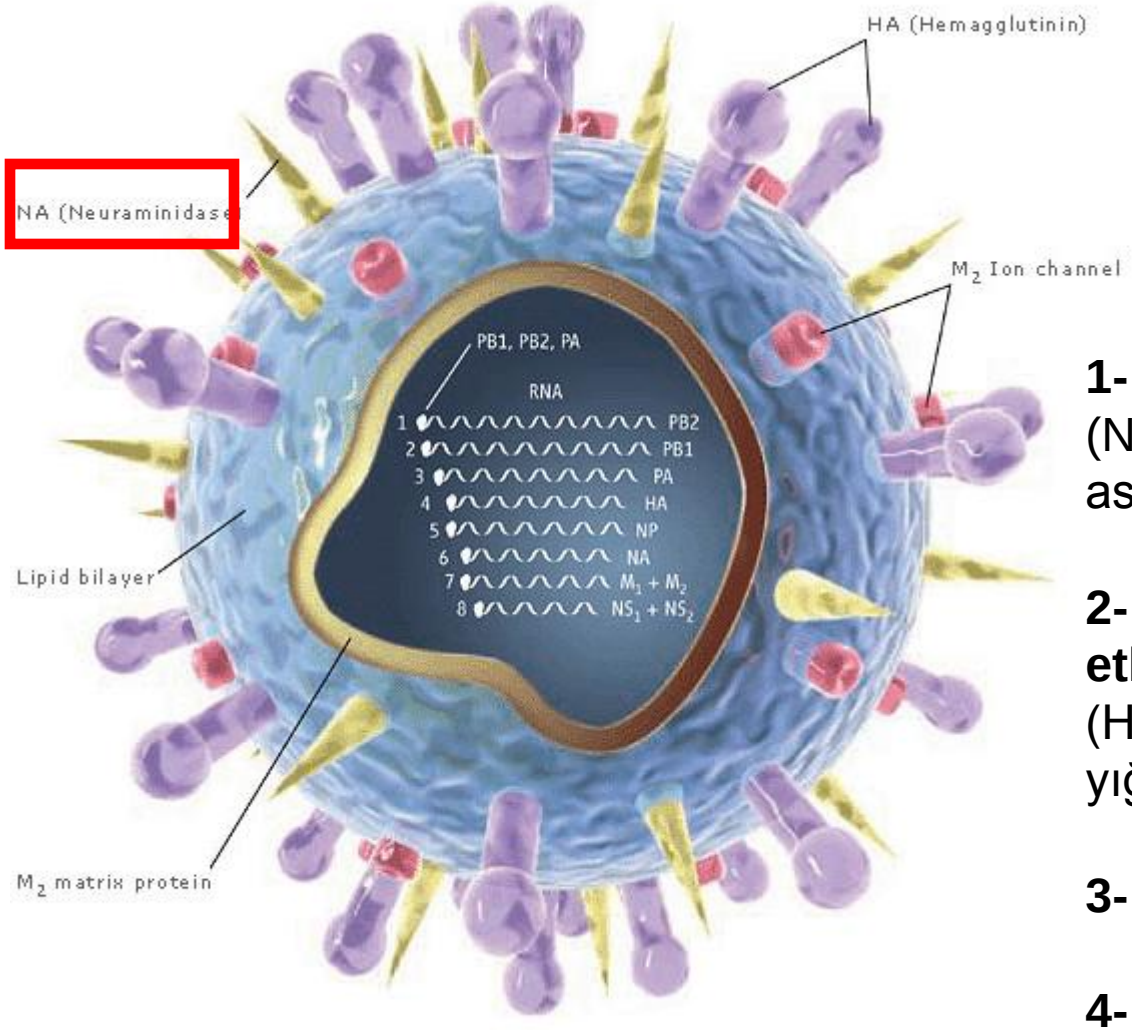
4- İnflamatuar yanıtı uyarır

Influenza A H5N1 virüsü: HA – Respt. spesifisitesi



Nature 2006, Science 2006, Am J Pathol 2007, Am J Pathol 2009

Virülans ve Patogenezde rol oynayan viral proteinler



Nöraminidaz (NA)

Yeni viral partiküllerin hücreden salınımında rol oynar

1- Viral yayılımı etkiler
(NA-HA oranı yeni partiküllerin sialik aside bağlanmalarına etkilidir)

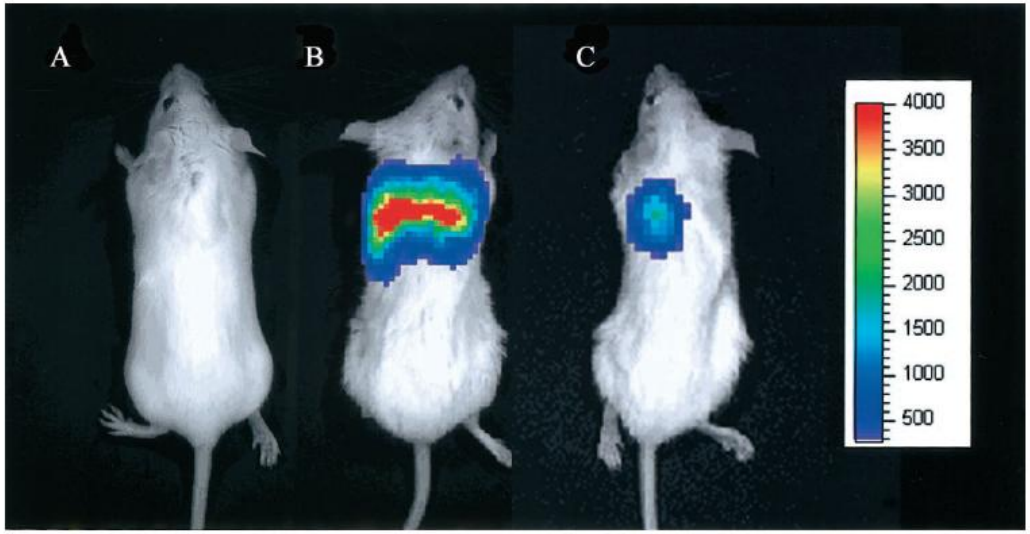
2- Virüslerin hücrelere girişini etkiler
(HA kırılması için gerekli proteazların yığımını sağlar)

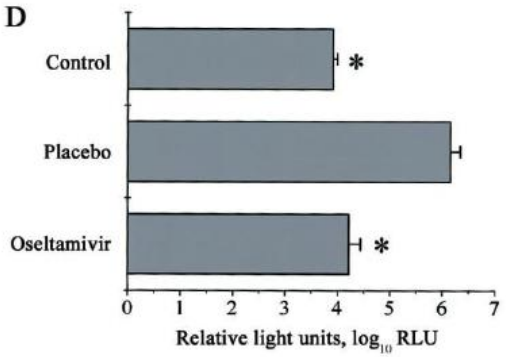
3- Apoptozu arttırır

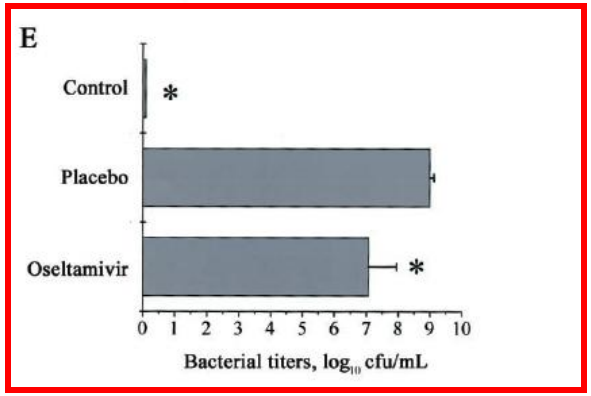
4- Bakteri enfeksiyonlarını kolaylaştırır, reseptörlerini açığa çıkarır

Role of Neuraminidase in Lethal Synergism between Influenza Virus and *Streptococcus pneumoniae*

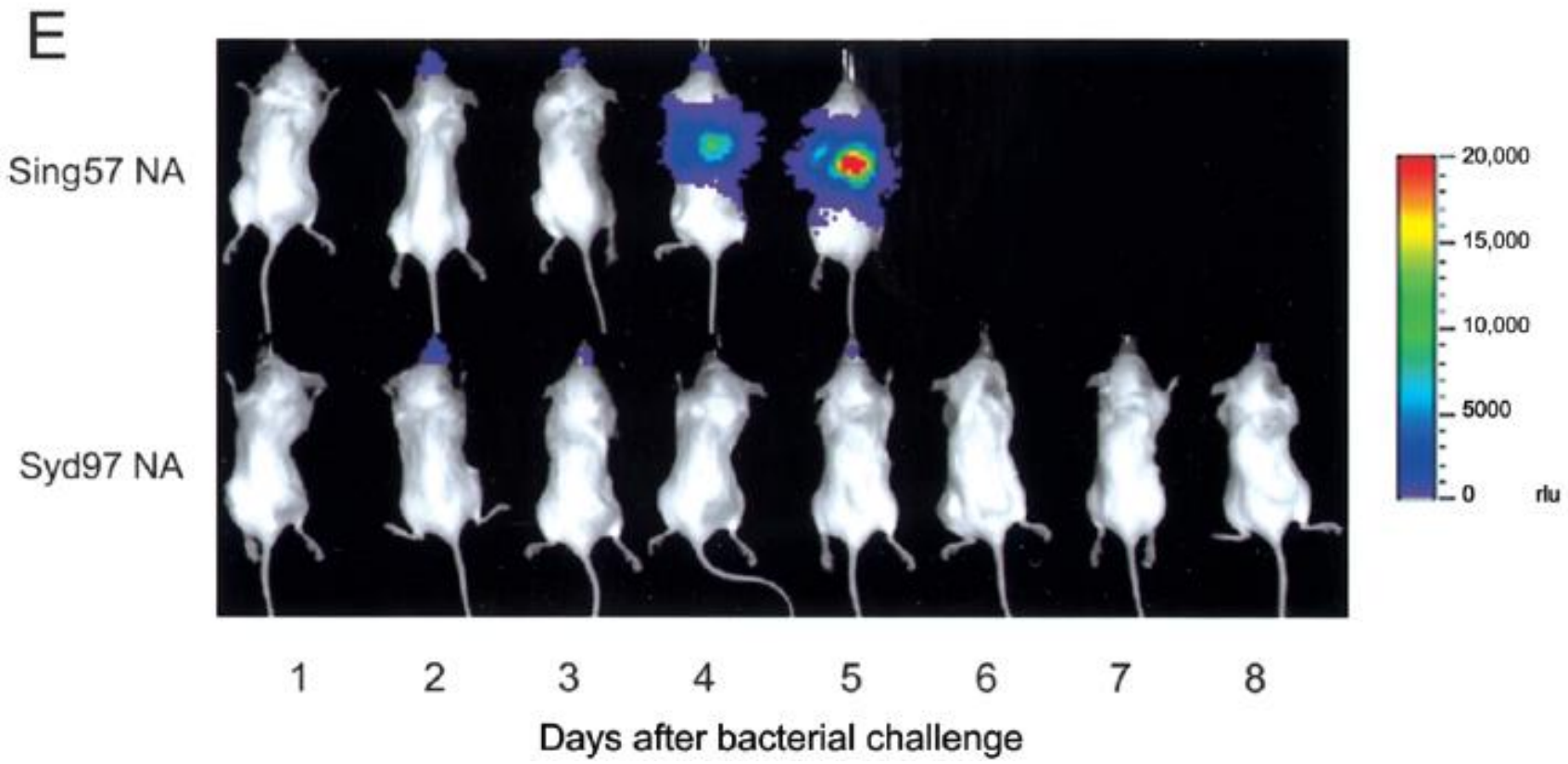
Jonathan A. McCullers and Kimberly C. Bartmess







Farklı NA aktivitesine sahip suşların etki farkı-II



Sing57 : Yüksek NA aktivitesine sahip suş
Syd97 : Düşük NA aktivitesine sahip suş

J Infec Dis 2005; 192: 249

Table 2. Comparison of neuraminidase (NA) activity with excess mortality from influenza.

Season	Circulating influenza virus	NA activity,[a] %	Deaths[b]	Excess mortality/ 100,000 persons	Reference
1957–1958	Sing57	100	66,000	39	[34]
1962–1963	Eng62	24	46,000	25	[34]
1968–1969	HK68	12	28,100	14	[34]
1972–1973	Mem72	37	20,700	10	[35]
1987–1988	Len86	41	30,800	13	[2]
1997–1998	Syd97	71	72,400	27	[2]

[a] NA activity was measured in recombinant influenza viruses with a common background of hemagglutinin and internal genes.

[b] Excess deaths by all causes in the United States above the seasonal baseline attributable to influenza. Excess mortality was calculated by Thompson et al. [2] by a method slightly different from that used by Liu et al. [35] and Housworth et al. [34]. These methods provide comparable estimates of mortality caused by influenza [2].

Influenza Virüslerinin önemli iki Virülans Faktörü

1) NS1

NS1 Protein of Influenza A Virus Inhibits the Function of Intracytoplasmic Pathogen Sensor, RIG-I

Zhu Guo, Li-mei Chen, Hui Zeng, Jorge A. Gomez, Julie Plowden, Takashi Fujita, Jacqueline M. Katz, Ruben O. Donis, and Suryaprakash Sambhara

Am J Respir Cell Mol Biol 2007;36: 263

Inhibition of Retinoic Acid-Inducible Gene I-Mediated Induction of Beta Interferon by the NS1 Protein of Influenza A Virus[▽]

Masaki Mibayashi,[1] Luis Martínez-Sobrido,[1] Yueh-Ming Loo,[2] Washington B. Cárdenas,[1] Michael Gale, Jr.,[2] and Adolfo García-Sastre[1]*

J Virol 2007;81: 514

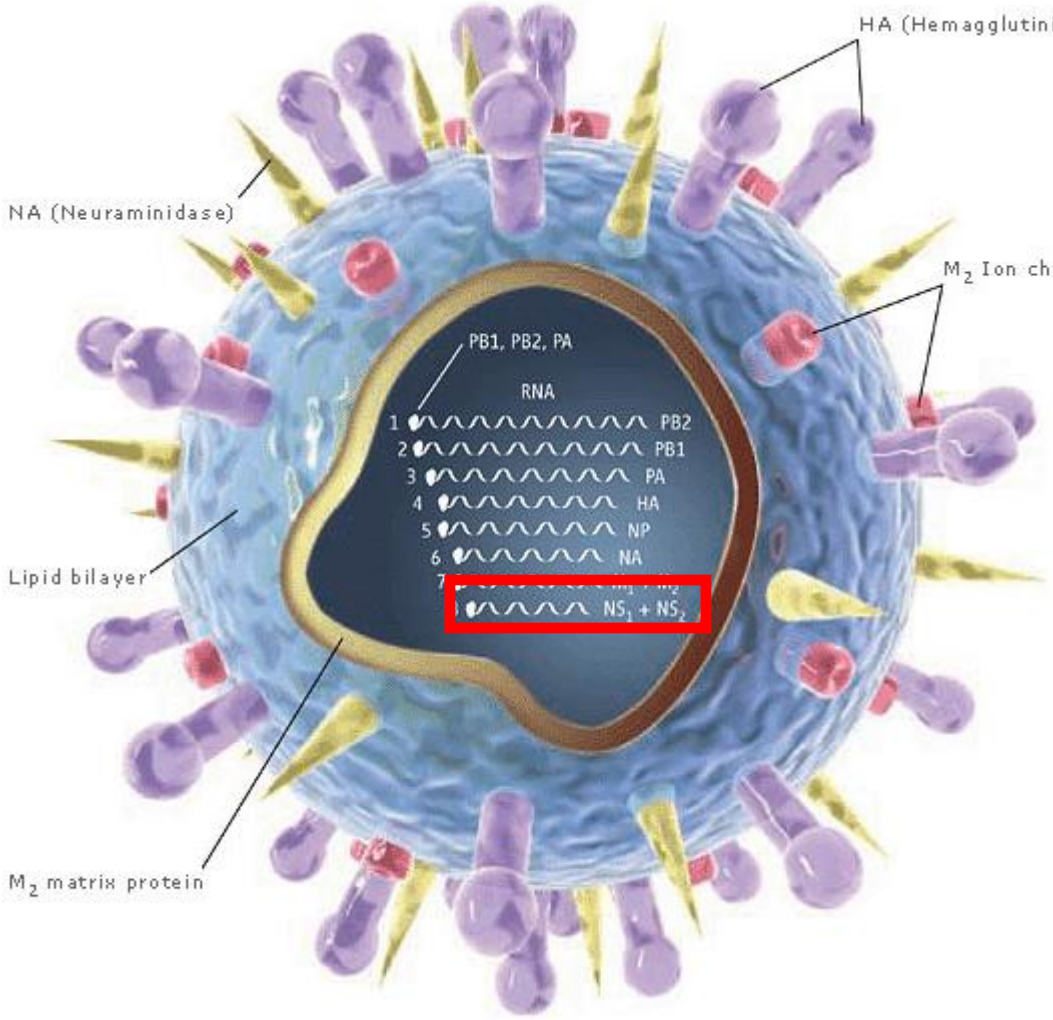
The NS1 Gene Contributes to the Virulence of H5N1 Avian Influenza Viruses[▽]

Zejun Li, Yongping Jiang, Peirong Jiao, Aiqin Wang, Fengju Zhao, Guobin Tian, Xijun Wang, Kangzhen Yu, Zhigao Bu,* and Hualan Chen*

J Virol 2006;80: 11115

2) PB1-F2

Virülans ve Patogenezde rol oynayan viral proteinler

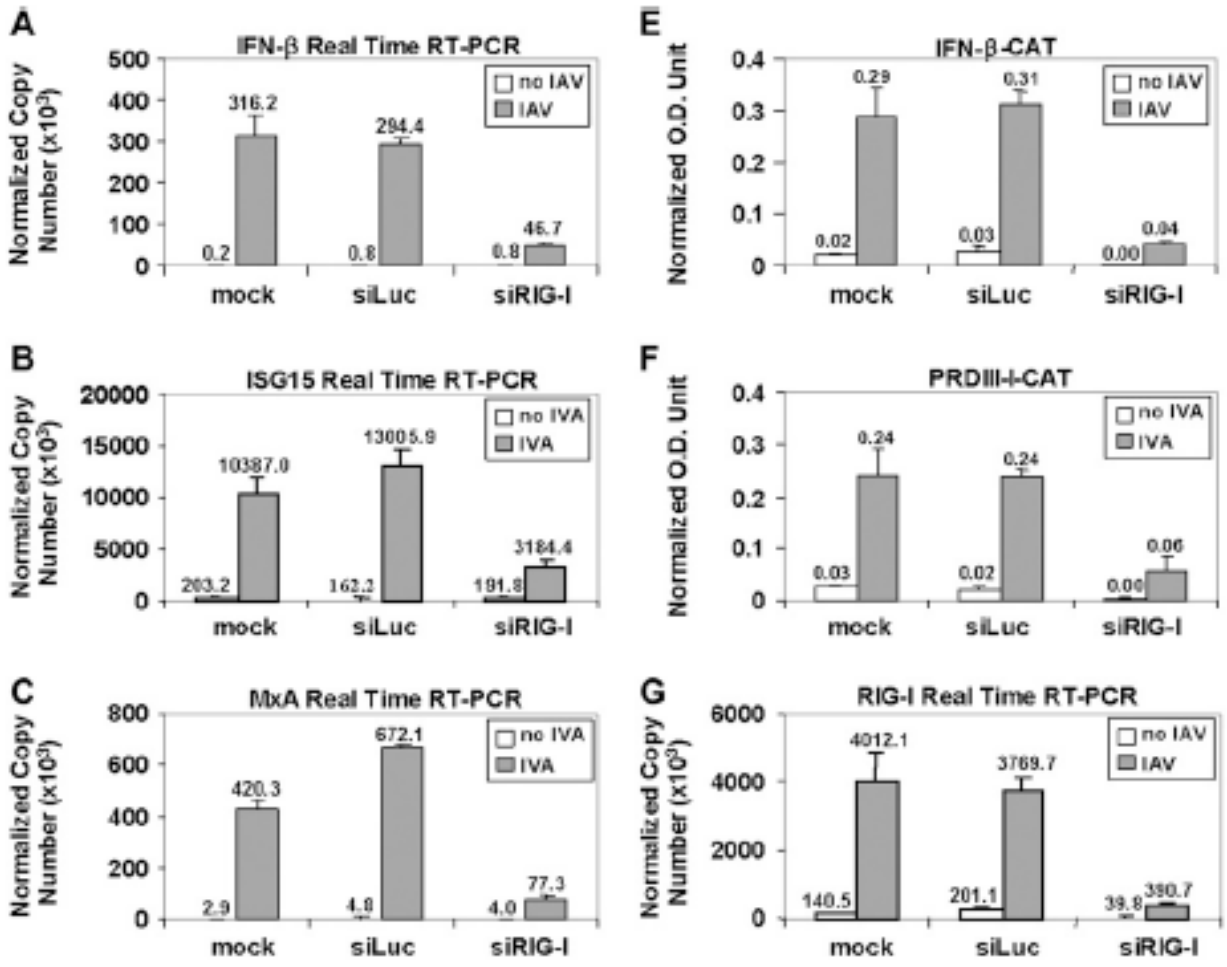


Yapısal olmayan protein 1 (NS1)

Konağın anti-viral yanıtını etkiler

1- Viral RNA üretimini etkiler
2- PI3 kinaza etki ederek virüsün uyardığı apoptozu geciktirir
3- RNaz L'nin OAS aktivasyonunu bloke eder
4- Tip I IFN yanıtını baskılar ve TNF/IFN a duyarlığı azaltır
5- RIG-1 aktivasyonunu baskılar
6- Aşırı sitokin üretimini kamçılar
7- PKR üzerinden gerçekleşen protein sentezi inhibisyonunu bloke eder
8-Konak mRNA poliadenilasyonunu bloke eder
9- DH olgunlaşmasını baskılayarak T hücre aktivasyonuna engel olur

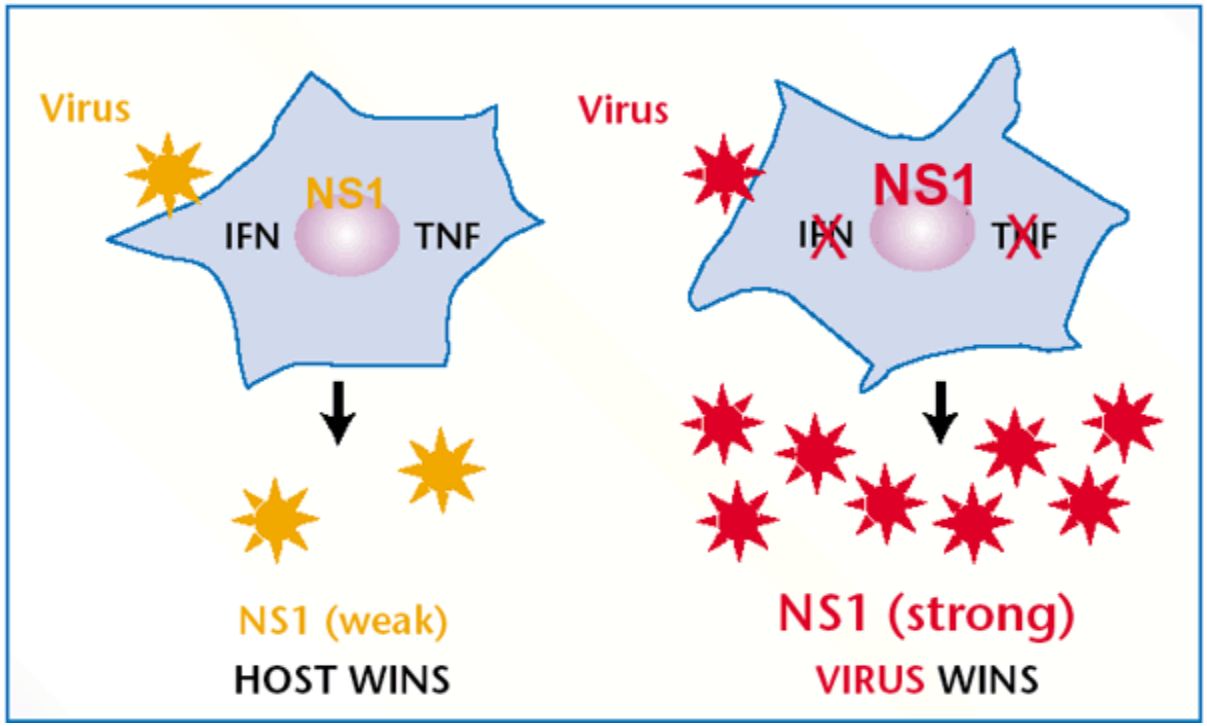
NS1 Protein of Influenza A Virus Inhibits the Function of Intracytoplasmic Pathogen Sensor, RIG-I



Am J Respir Cell Mol Biol 2007;36: 263

İmmünosüpresyona ÖRNEK:

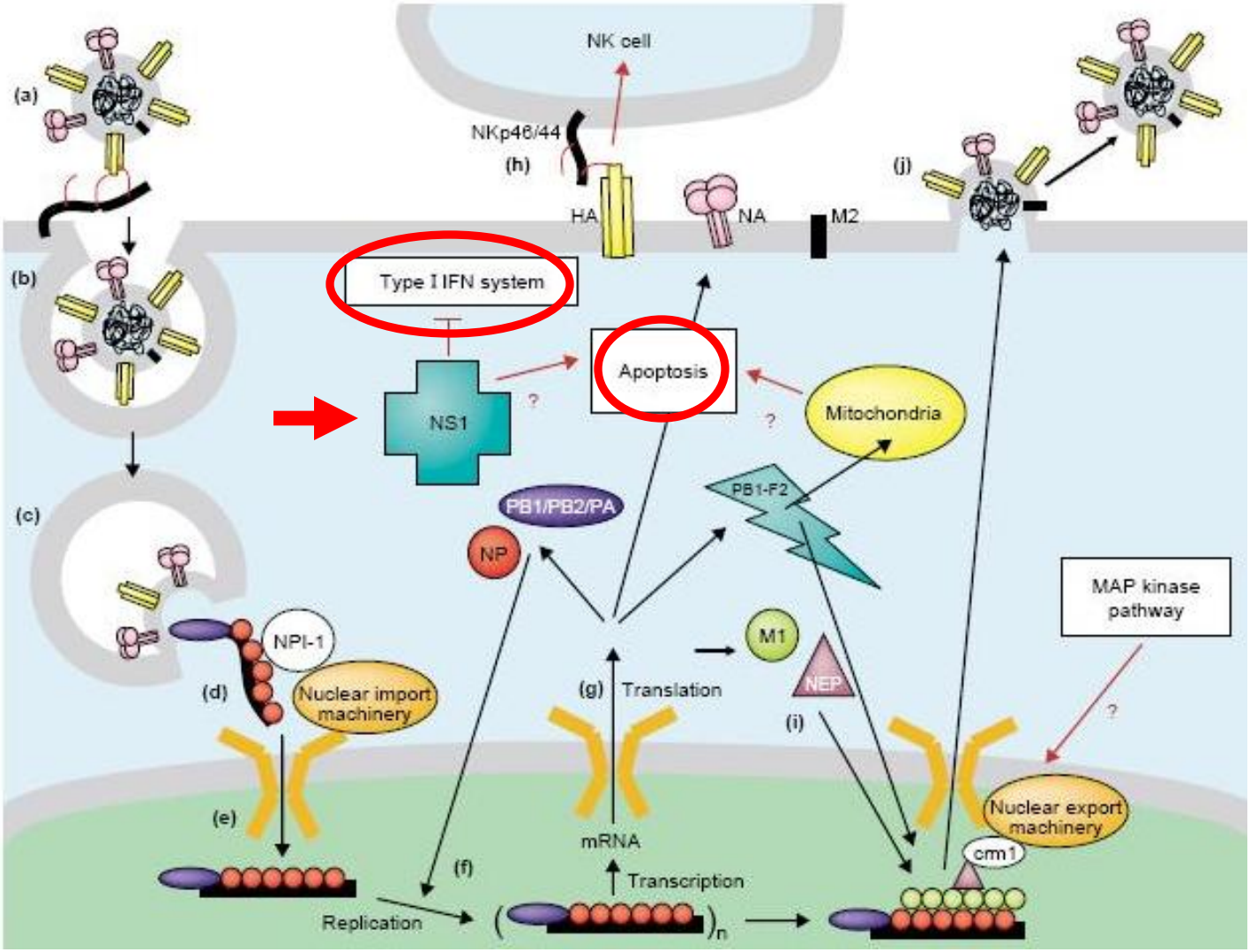
Viral patogenezde IFN antagonisti olan NS1 proteininin rolü



- NS1 kodlama özelliği zayıf olan tipler konağın savunma mekanizmalarına karşı koyamazlar; bu durum viral replikasyonun azalmasıyla sonuçlanır (solda).

- Buna karşın IFN antagonisti olan NS1'i yüksek düzeyde kodlama özelliği olan tipler konak savunmasını etkisiz hale getirir ve viral replikasyon hızla devam eder (sağda).

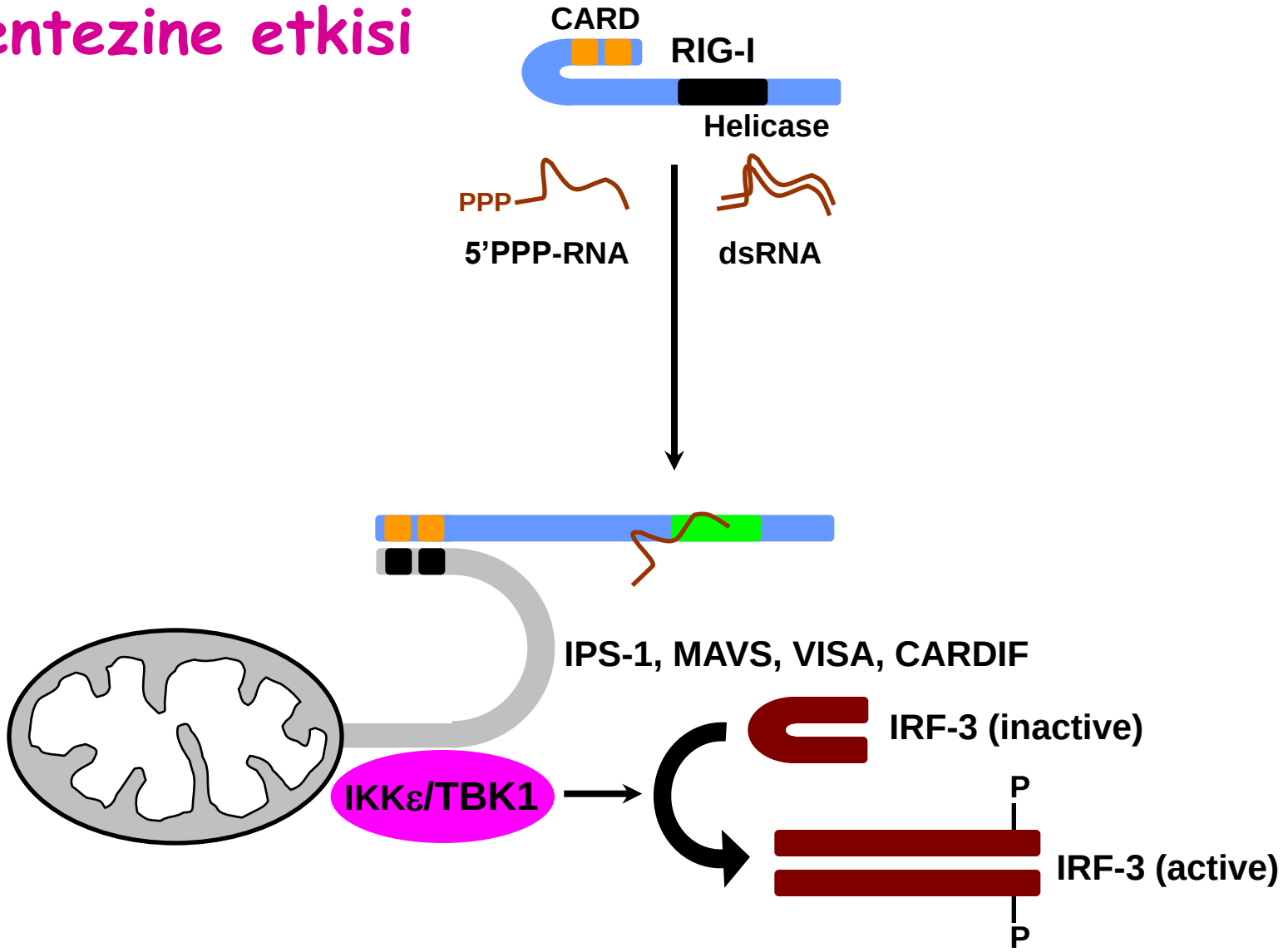
Nature Med 2002; 8; 927



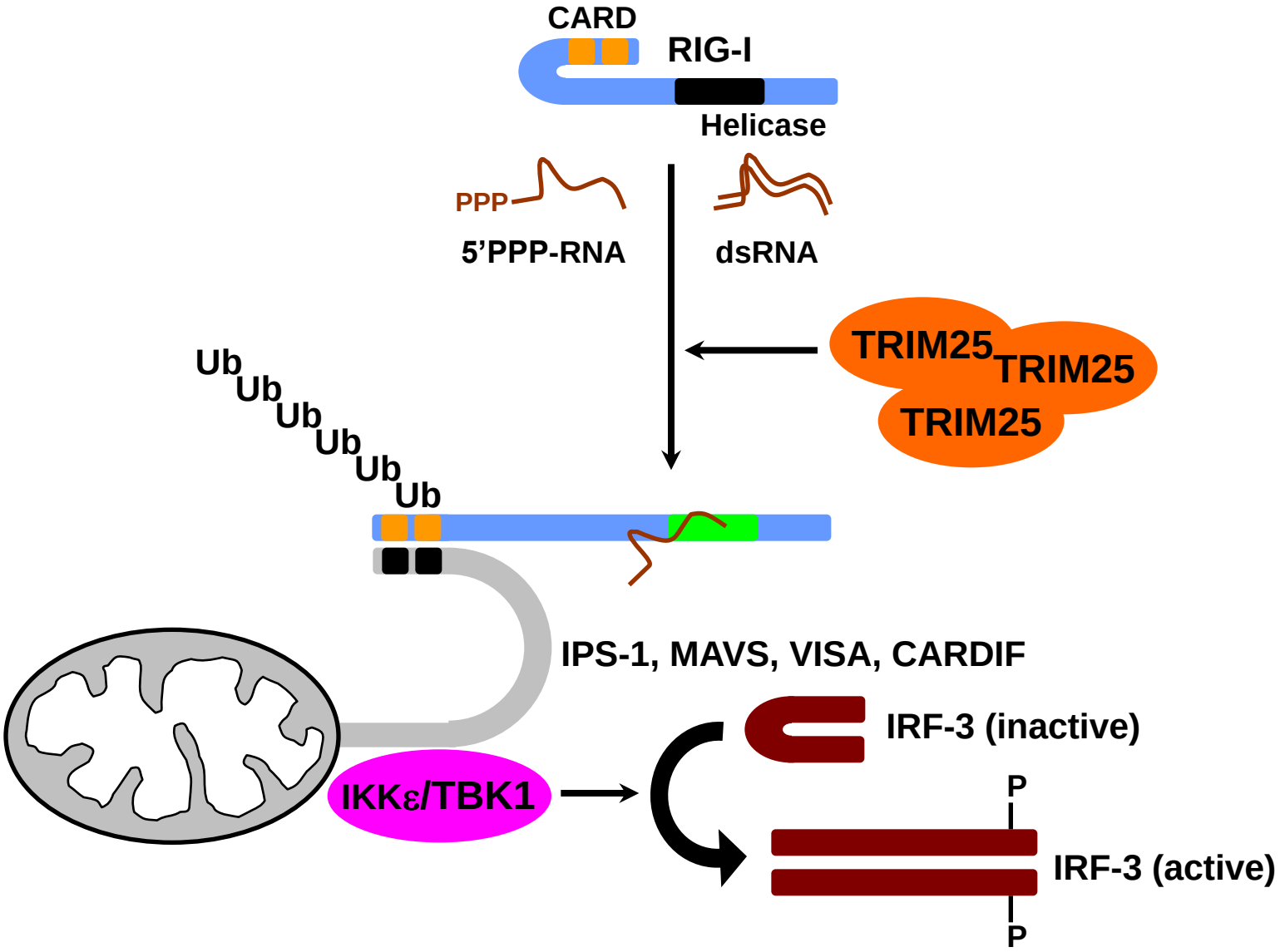
- **NS1 kodlama özelliği zayıf olan tipler konağın savunma mekanizmalarına karşı koyamazlar**
- **NS1'i yüksek düzeyde kodlama özelliği olan tipler konak savunmasını etkisiz hale getirir ve viral replikasyon sürer.**

Curr Opinion Microbiol 2002; 5: 414

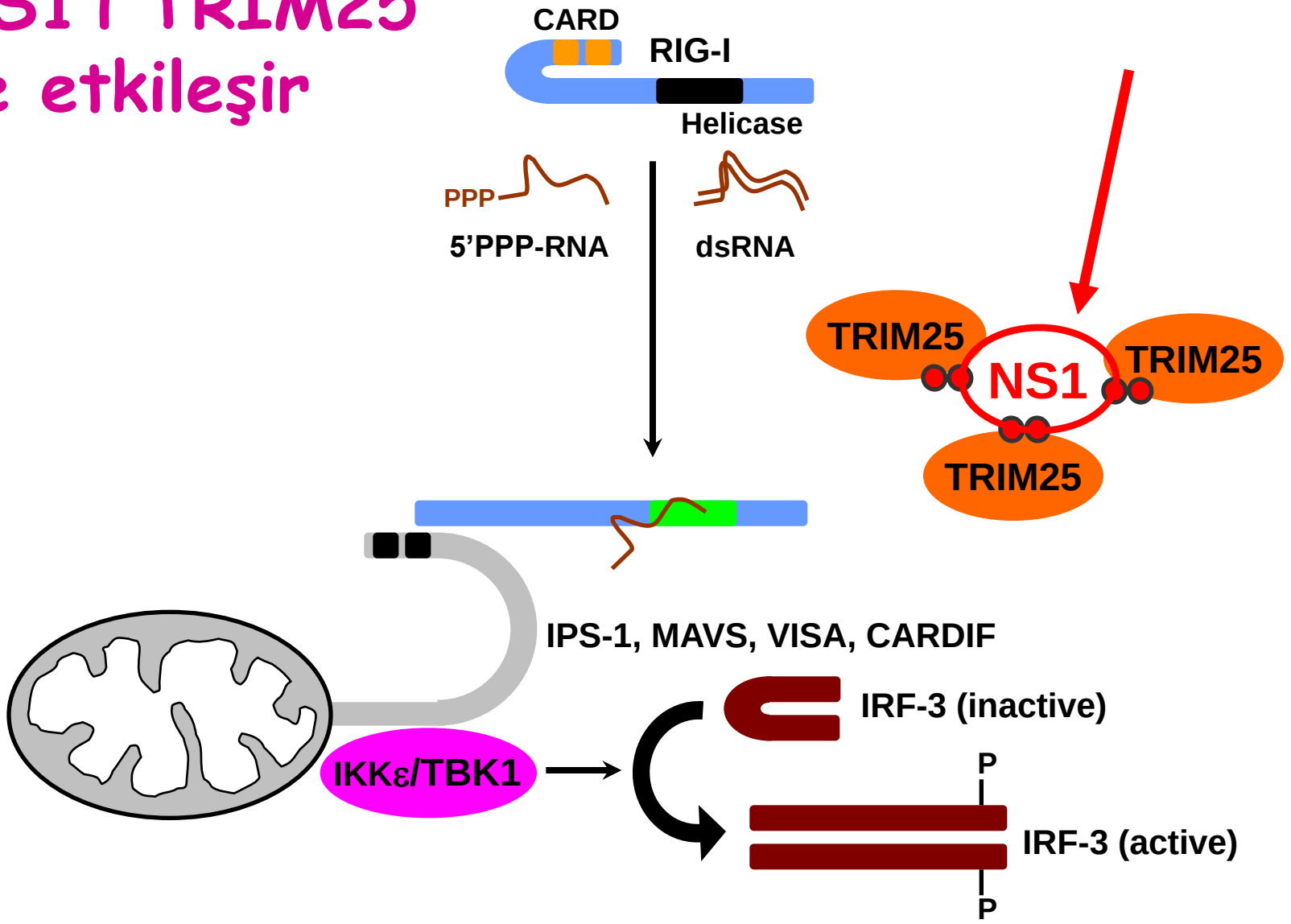
NS1'in INTERFERON Sentezine etkisi

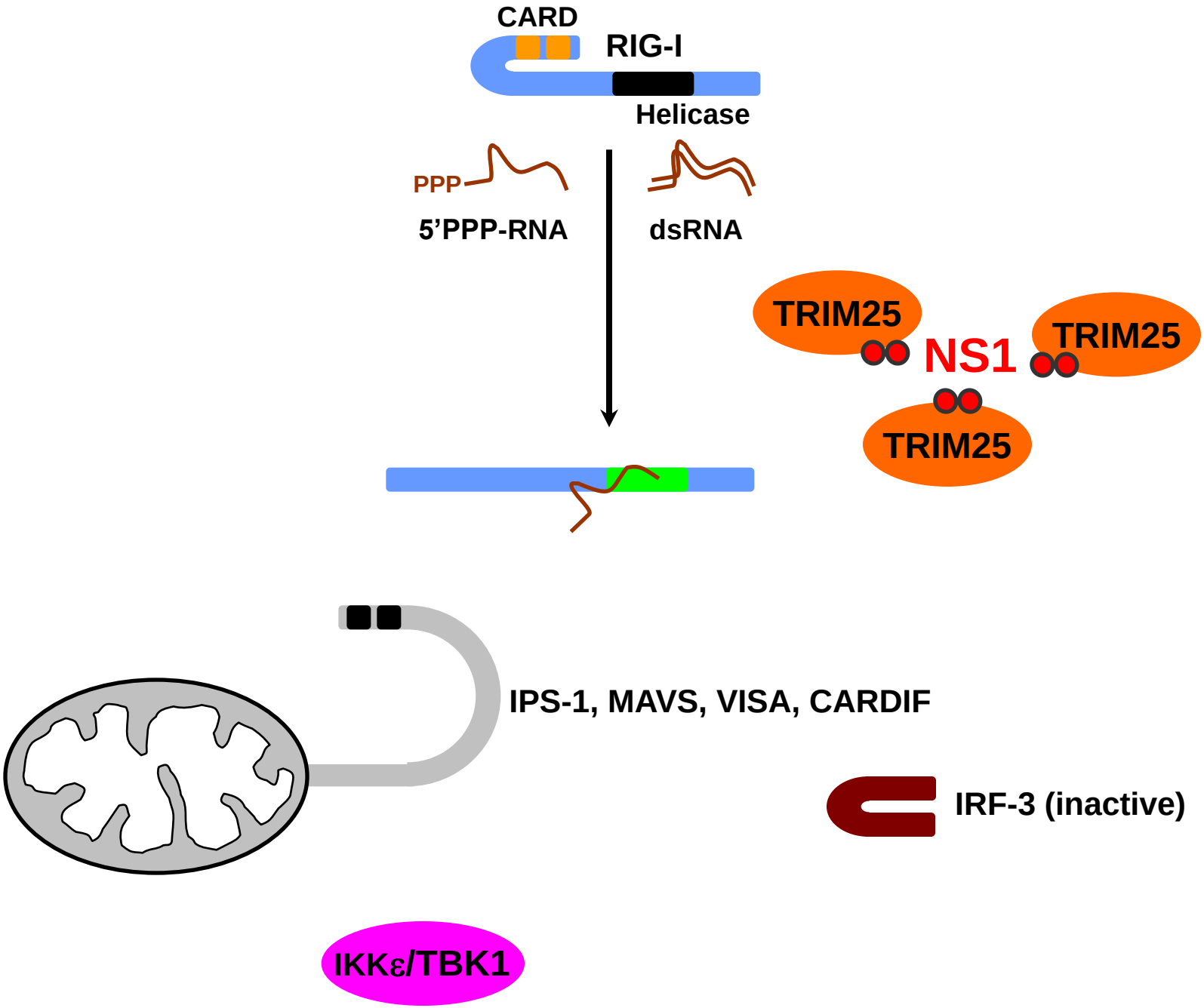


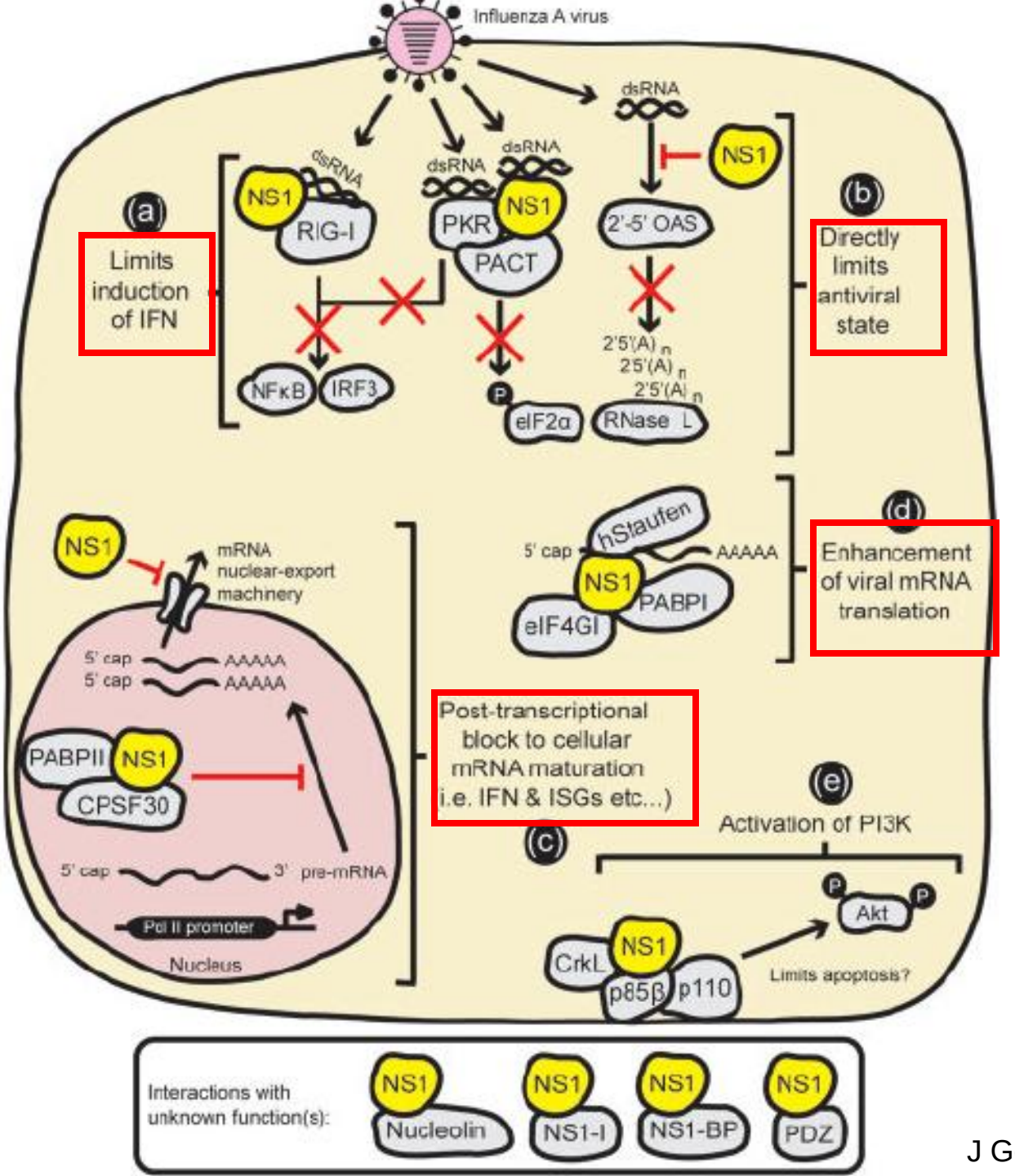
Nature 2007; 446: 916


CARD
RIG-I
Helicase
PPP
5'PPP-RNA
dsRNA
TRIM25
TRIM25
TRIM25
Ub
Ub
Ub
Ub
Ub
IPS-1, MAVS, VISA, CARDIF
IKKε/TBK1
IRF-3 (inactive)
P
IRF-3 (active)
P

NS1'i TRIM25 ile etkileşir

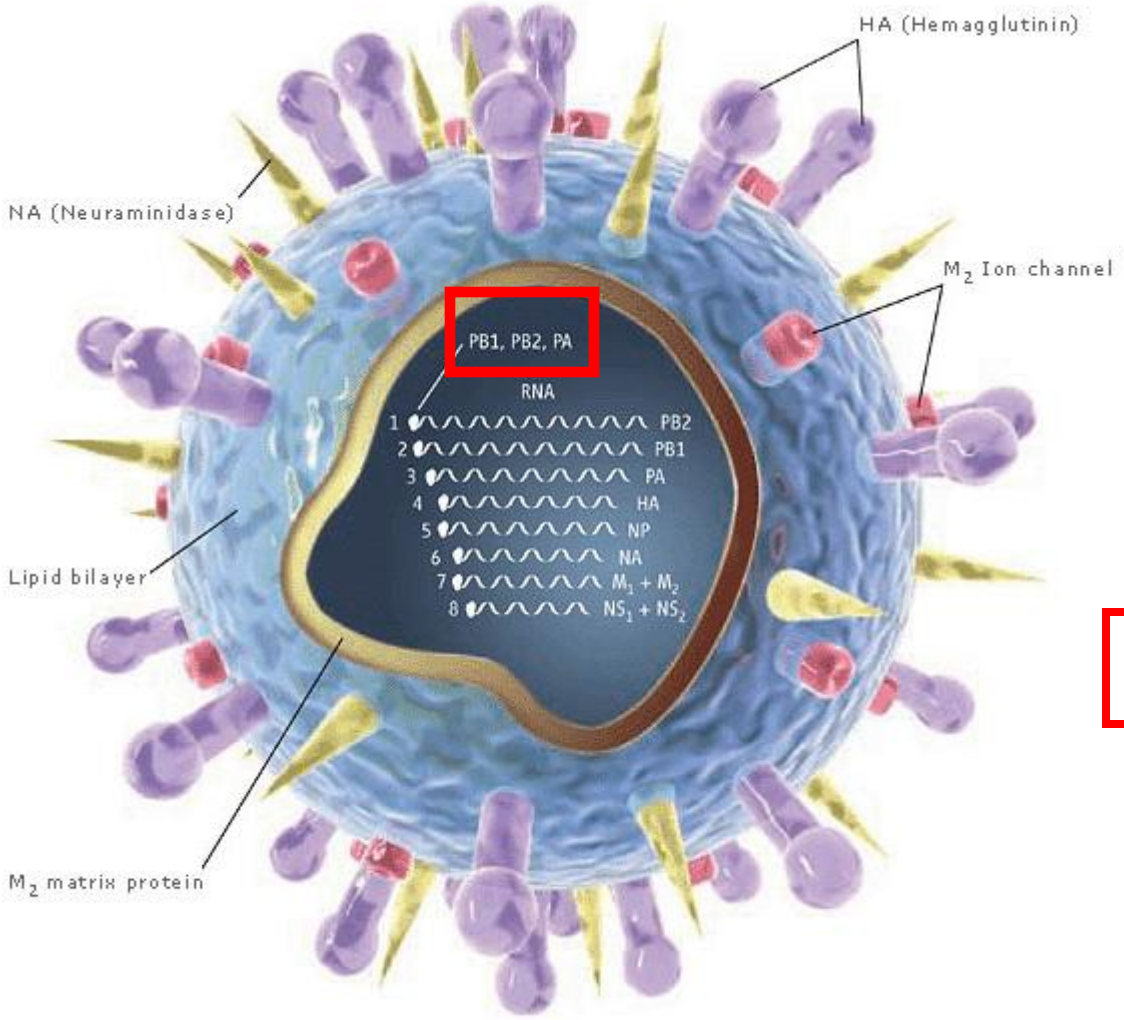



CARD
RIG-I
Helicase
PPP
5’PPP-RNA
dsRNA
TRIM25
NS1
TRIM25
TRIM25
IPS-1, MAVS, VISA, CARDIF
IRF-3 (inactive)
IKKε/TBK1



J Gen Virol 2008;89: 2359

Virülans ve Patogenezde rol oynayan viral proteinler



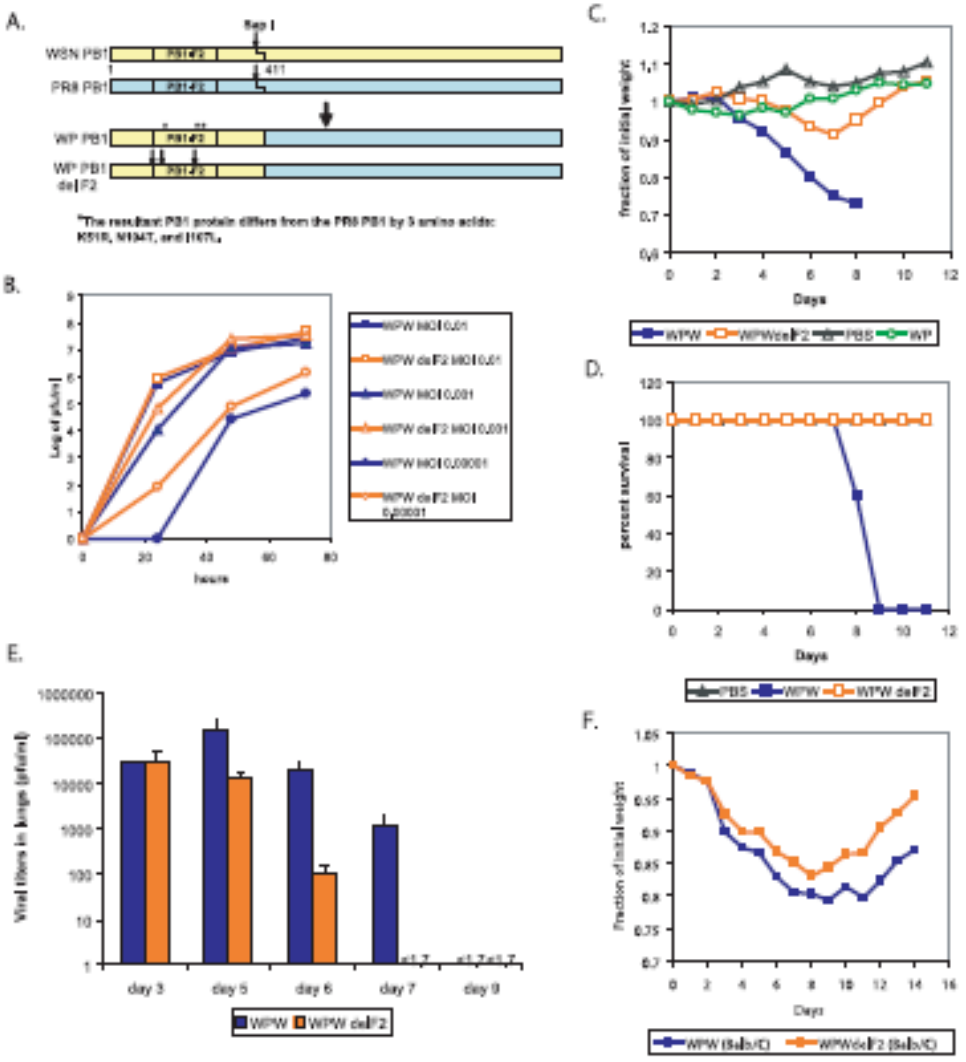
Viral Polimerazlar (PA, PB1, PB2)

1- Replikasyon yoğunluğunu belirler
(replikasyon arttıkca virülans artar)
2- Isıya duyarlığı belirler
(PB2 bölgesindeki tek bir aa değişimi düşük ısıda üremeyi sağlar)

PB1-F2

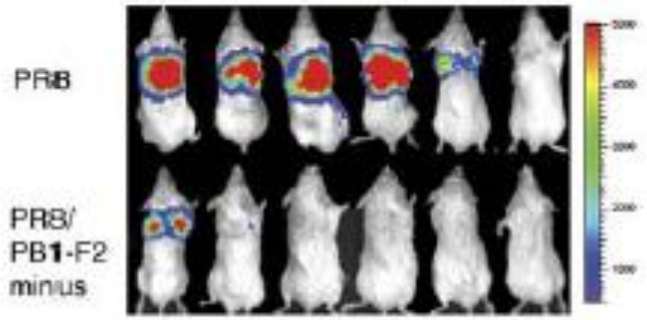
1- Polimeraz genindeki ORF a etki
2- Apoptozu etkiler
(C-terminal uç mitokondriyi hedef alan bölge içerir)
3- Viral polimerazı etkiler
4- Anti-viral immüniteyi etkiler
(PB1-F2, inflamatuar hücre akımını arttırır, immünopatolojide etkilidir)

Influenza A Virus PB1-F2 Protein Contributes to Viral Pathogenesis in Mice



J Virol 2006;80: 7976

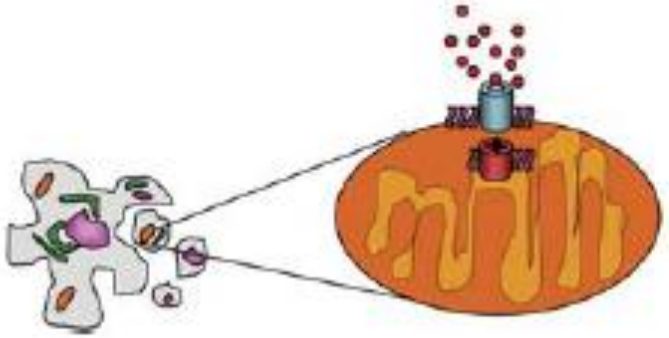
Increased secondary bacterial pneumonia



Increased macrophage and neutrophil lung infiltration during infection with a virus containing the 1918 pandemic virus PB1-F2

PB1-F2

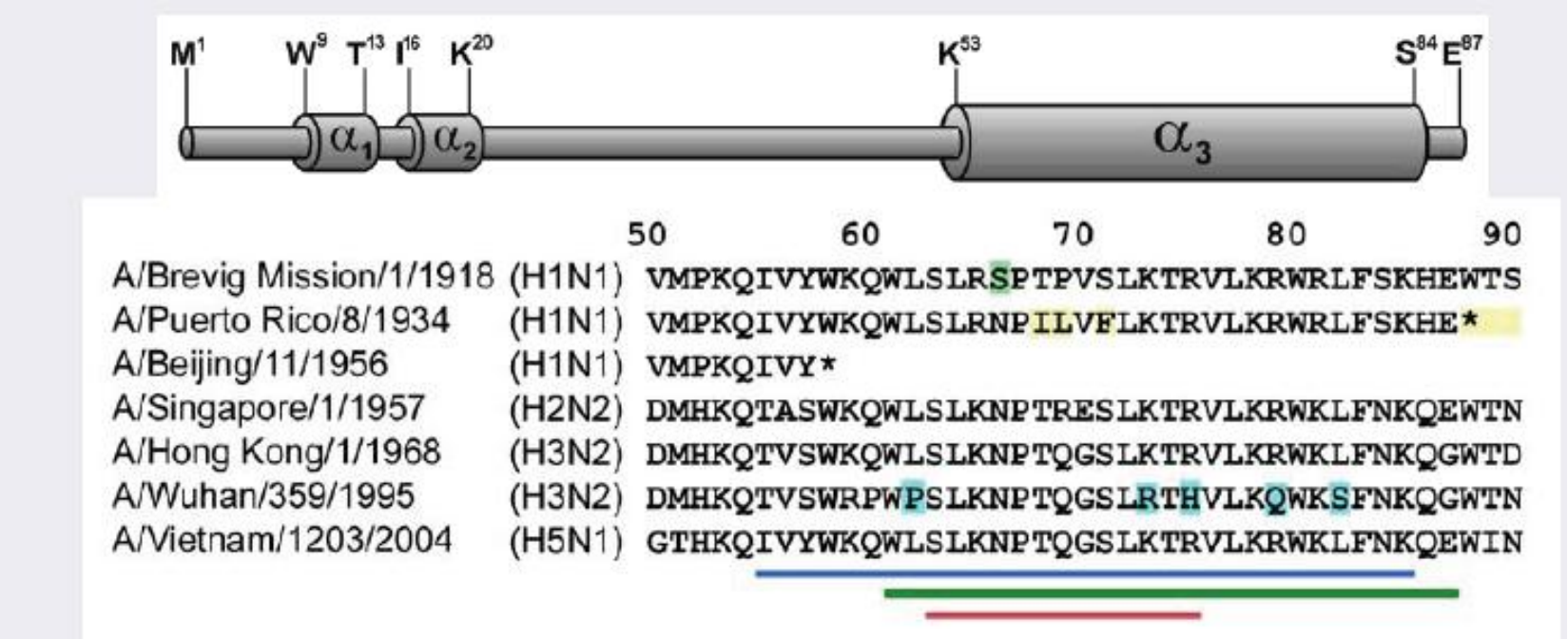
Induces apoptosis via mitochondrial pathway



Increased pathogenesis and cytokine dysregulation in mice

Cell Host Microbe 2007;2: 207

PB1-F2 Proteini

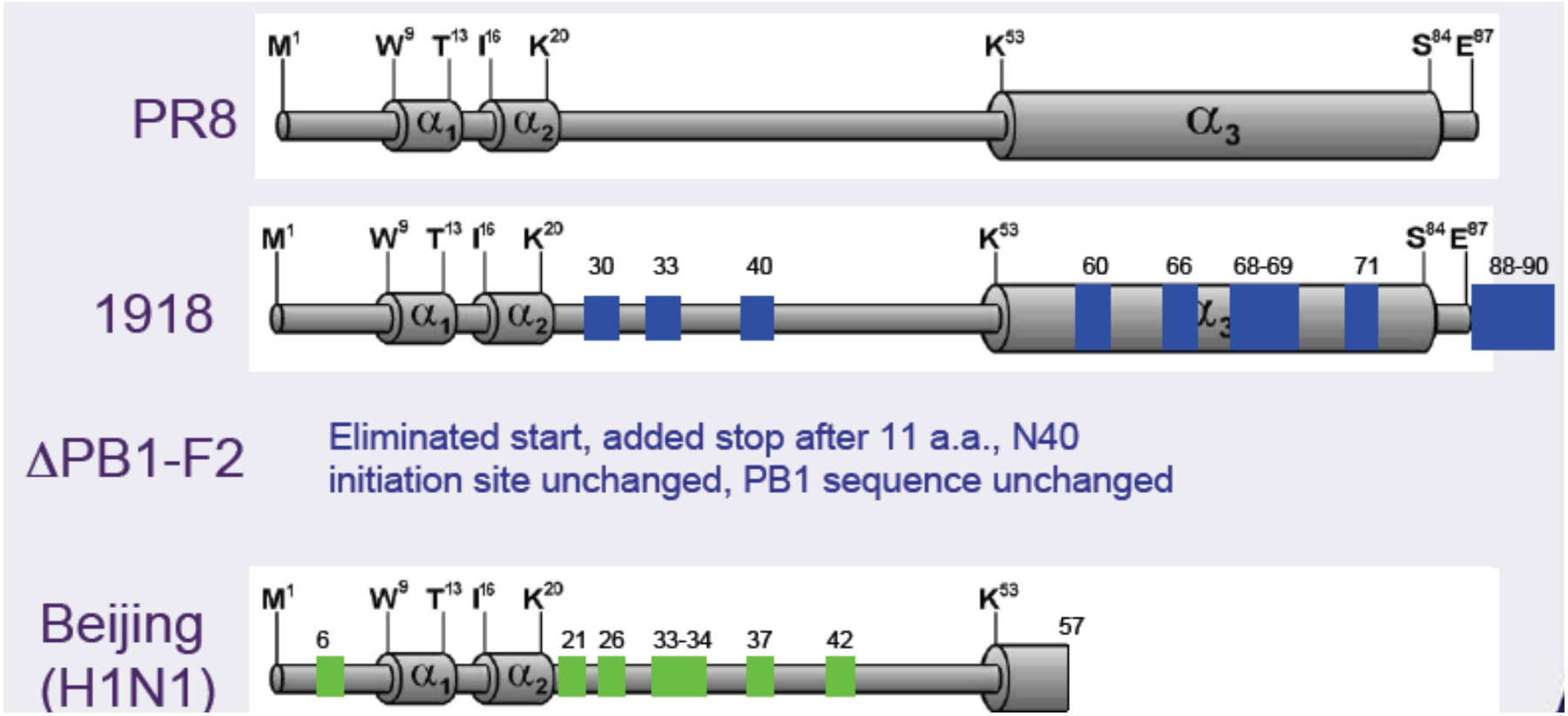


*** 87-90 aa'lik, C-terminal ucunda helikal domen taşıyan mitokondrial bir peptid**

*** Fare KC mitokondrileri + PB1- F2=**

- **Sitokrom C'nin açığa çıkışı**
- **Mitokondri membranında zedelenme**
- **tBid'in tetiklediği permeabilite artışı**

} **APOPTOZ**



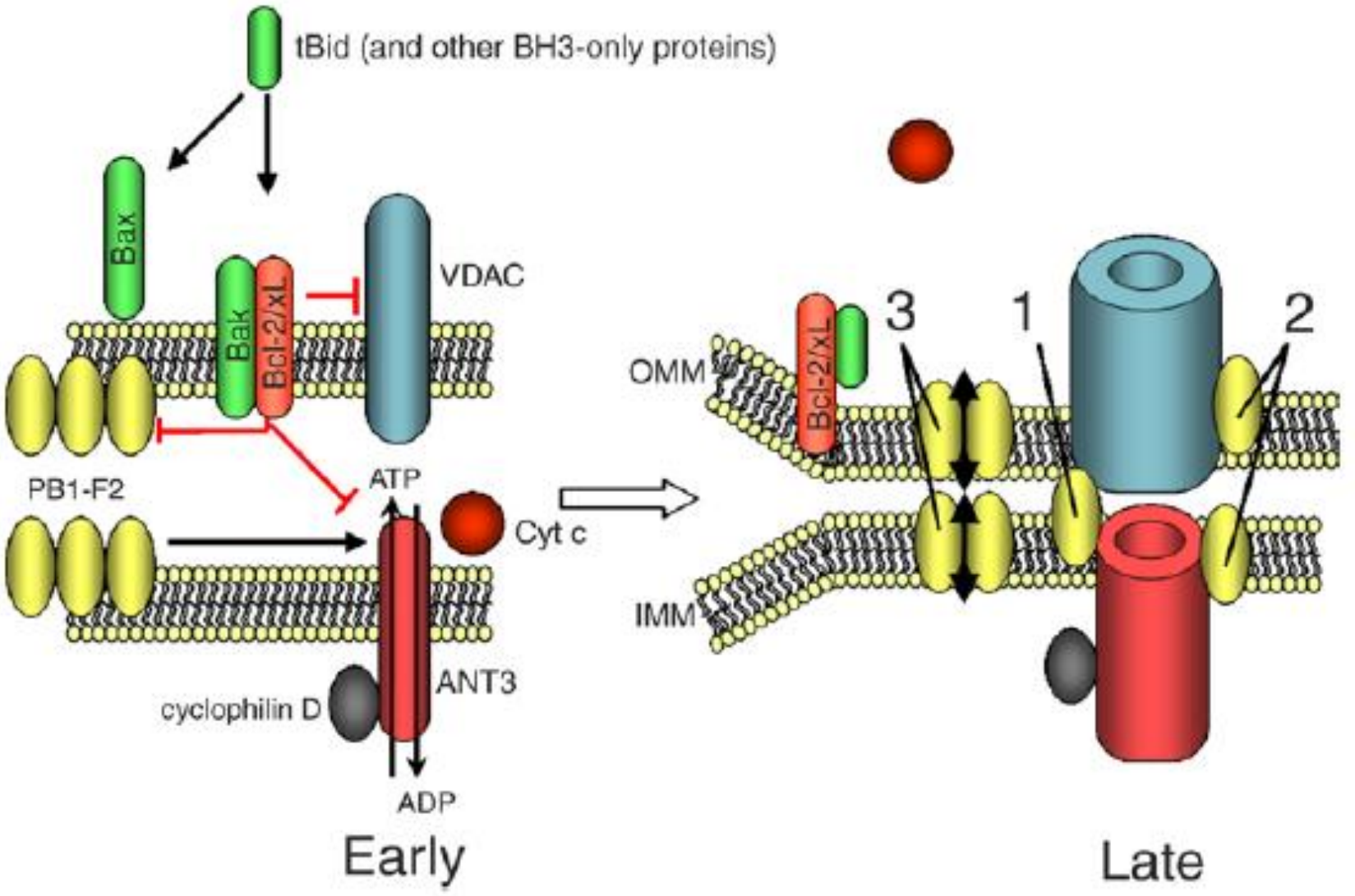
İŞLEVİ NEDİR?

1- Viral replikasyonu değiştirir : HAYIR

2- Hücre ölümüne neden olur : KISMEN

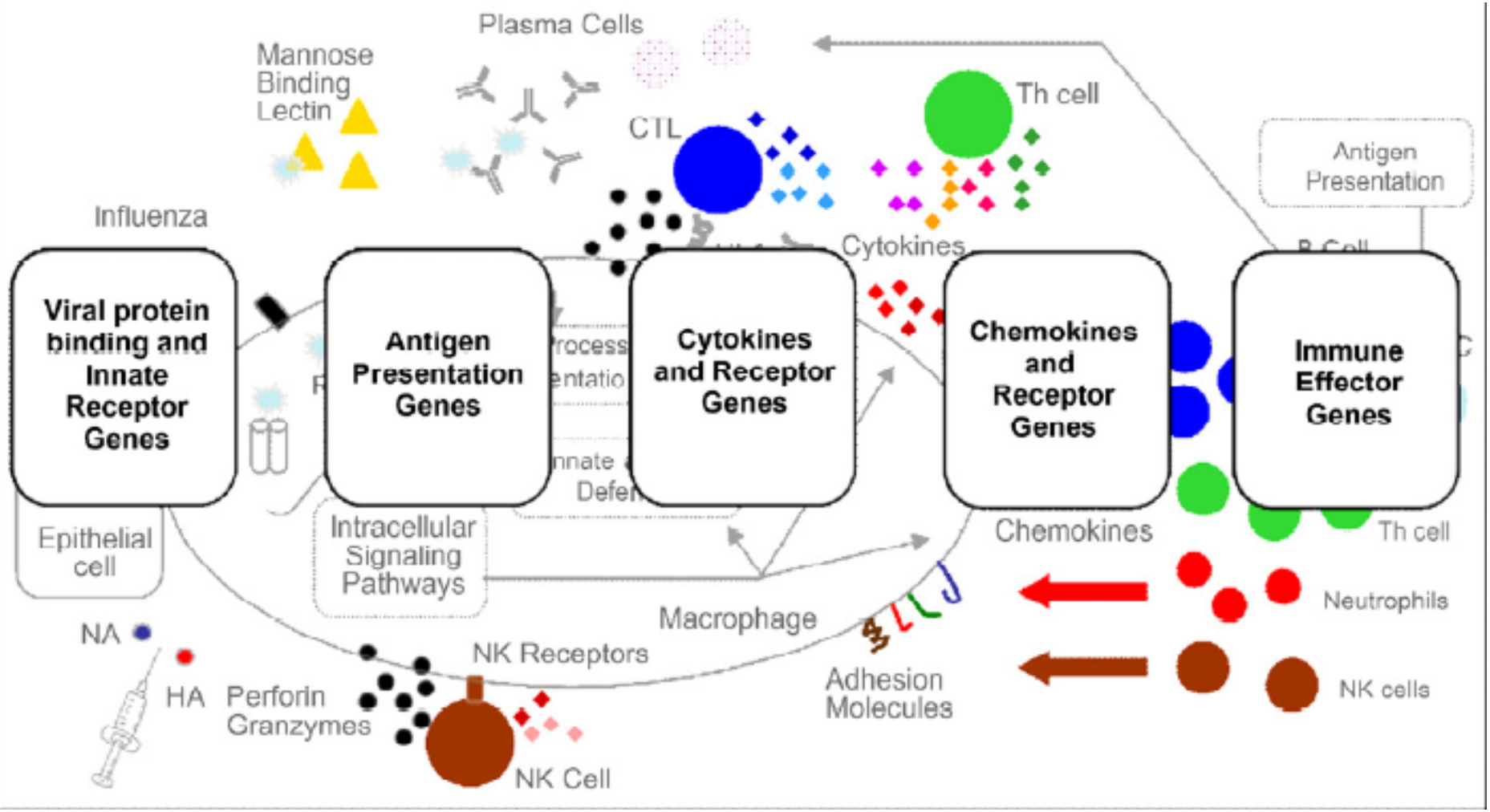
3- İmmünopatogeniteyi arttırır : EVET

Viral Protein:
Mitokondri iç membr. ADENİN NÜKLEOTİD TRANSLOKATÖR 3 (ANT3) ve
Mitokondri dış membr. VOLTAJ BAĞIMLI ANYON KANAL1 (VDAC1) ile ...
Her 2 mol. apoptozise götüren süreçte mitokondri permeabilitesine etkililer

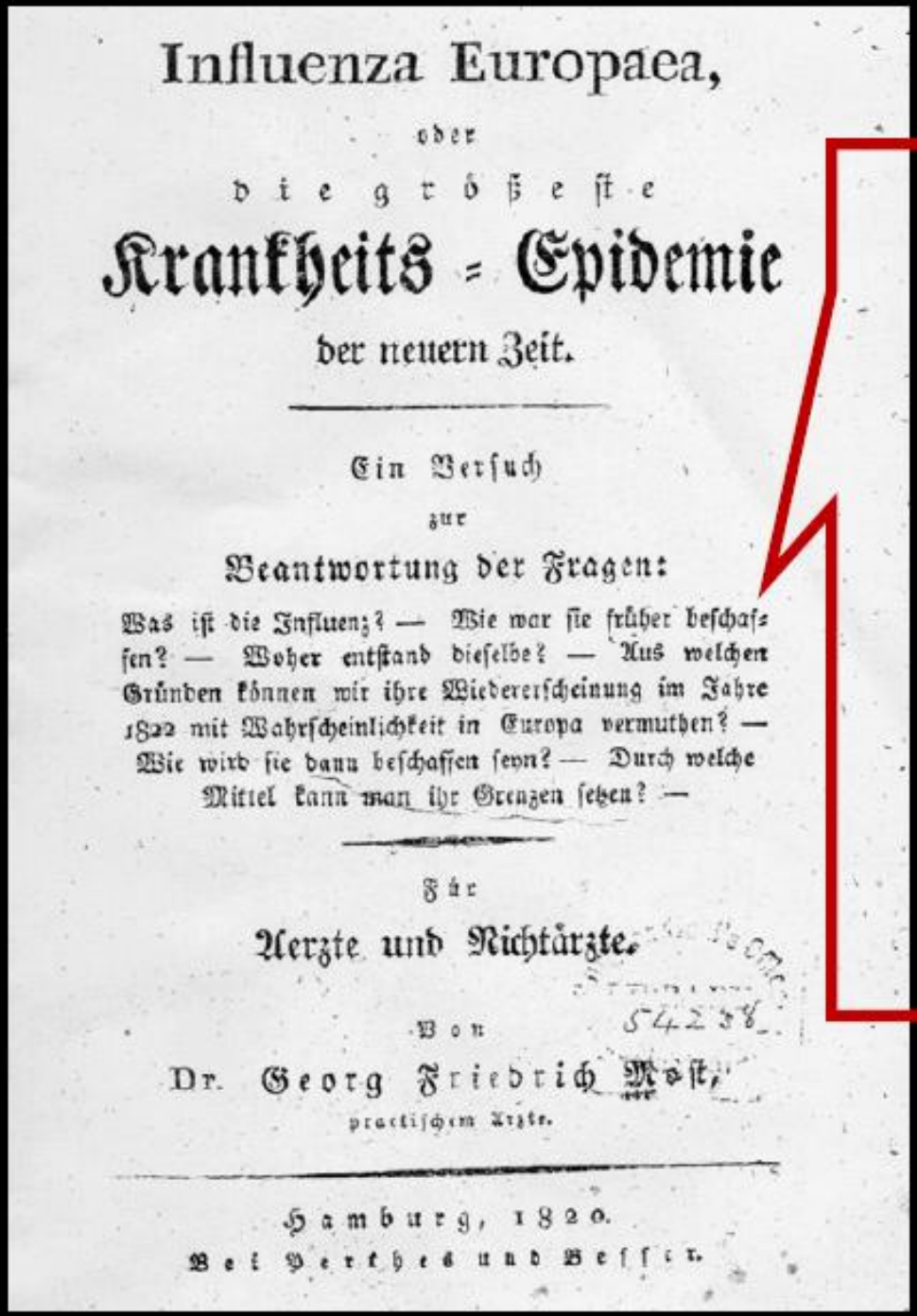


PLoS Pathogens 2005;1:e4

INFLUENZA ENFEKSİYONLARINDA
Doğal Bağışıklık ve Edinsel yanıtta etkili Genler



Vaccine 2008;26S: D35



Influenza Europaea,

oder

die größeste

Krankheits = Epidemie

der neuern Zeit.

Ein Versuch

zur

Beantwortung der Fragen:

Was ist die Influenz? — Wie war sie früher beschaffen? — Woher entstand dieselbe? — Aus welchen Gründen können wir ihre Wiedererscheinung im Jahre 1822 mit Wahrscheinlichkeit in Europa vermuthen? — Wie wird sie dann beschaffen seyn? — Durch welche Mittel kann man ihr Grenzen setzen? —

Für

Aerzte und Nichtärzte.

Von

Dr. Georg Friedrich Most,

practischem Arzte.

Hamburg, 1820.

Bei Perthes und Besser.

Questions posed in 1820:

What is influenza?

Where does influenza come from?

How did influenza behave in the past?

In what ways can we predict future occurrences...and how will future outbreaks behave?

Through what means can its spread be halted?