DEFEKTE IN DER ANGEBORENEN IMMUNITÄT ALS URSACHE FÜR INFEKTANFÄLLIGKEIT BEIM ERWACHSENEN

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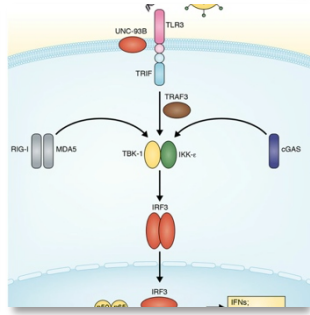
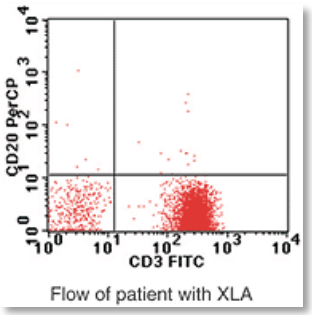
Med. Klinik und Poliklinik IV
Klinikum der Universität München

aida adulte immundefekt ambulanz





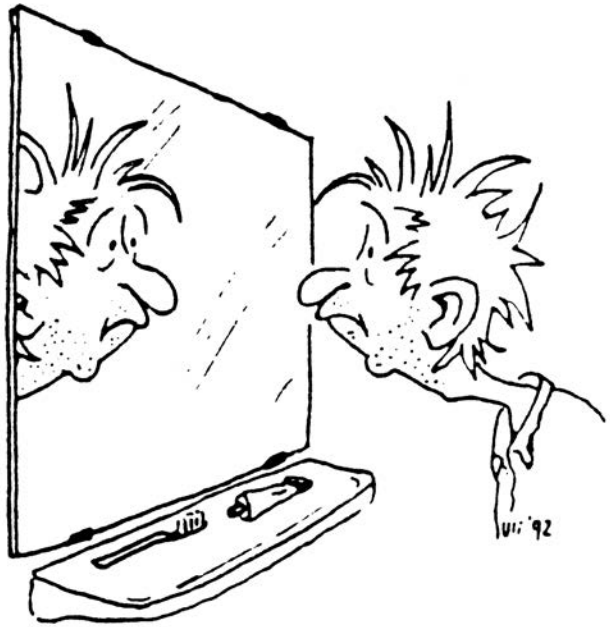
Flow of patient with XLA

AGENDA

Selbst und Fremd: Das Prinzip Mustererkennung in der angeborenen Immunität

Herpesenzephalitis – eine genetische Erkrankung des TLR-3 Signalwegs?

Pilzabwehr: was passiert bei zu viel pStat1?



Relevanz der *Selbst-Fremd* Unterscheidung für das Immunsystem

- Abwehr von Mikroben: Bakterien, Viren, Pilzen, Parasiten
- Barriere in der Transplantationsmedizin
- Wunder in der Schwangerschaft
- Krankheitsursache bei Autoimmunerkrankungen/ Allergien
- Schutz vor und möglicher Therapieansatz bei Tumoren

Prinzipien der *Selbst-Fremd*-Unterscheidung

- Erkennung aller Nicht-Selbst Strukturen

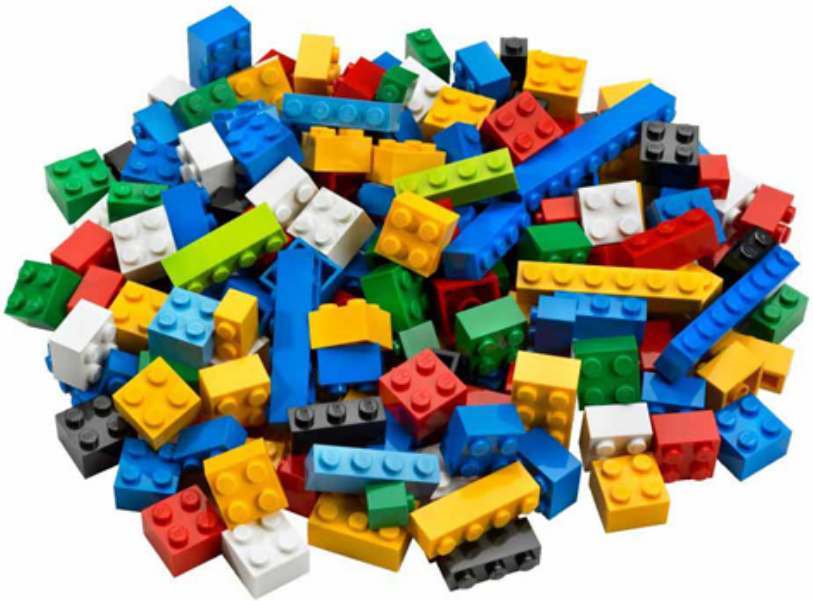
  gigantische Zahl der zu erkennenden Strukturen; Prinzip des adaptiven Immunsystems; verwendet von T- und B-Lymphozyten

- Erkennen nach dem *missing self*-Prinzip

  man muss nur ein *Selbst*-Merkmal (er)kennen; Prinzip wird von Natürlichen Killer Zellen (NK-Zellen) verwendet

- Erkennen von molekularen Mustern die mit Pathogenen oder für den Organismus schädlichen Zuständen assoziiert sind;

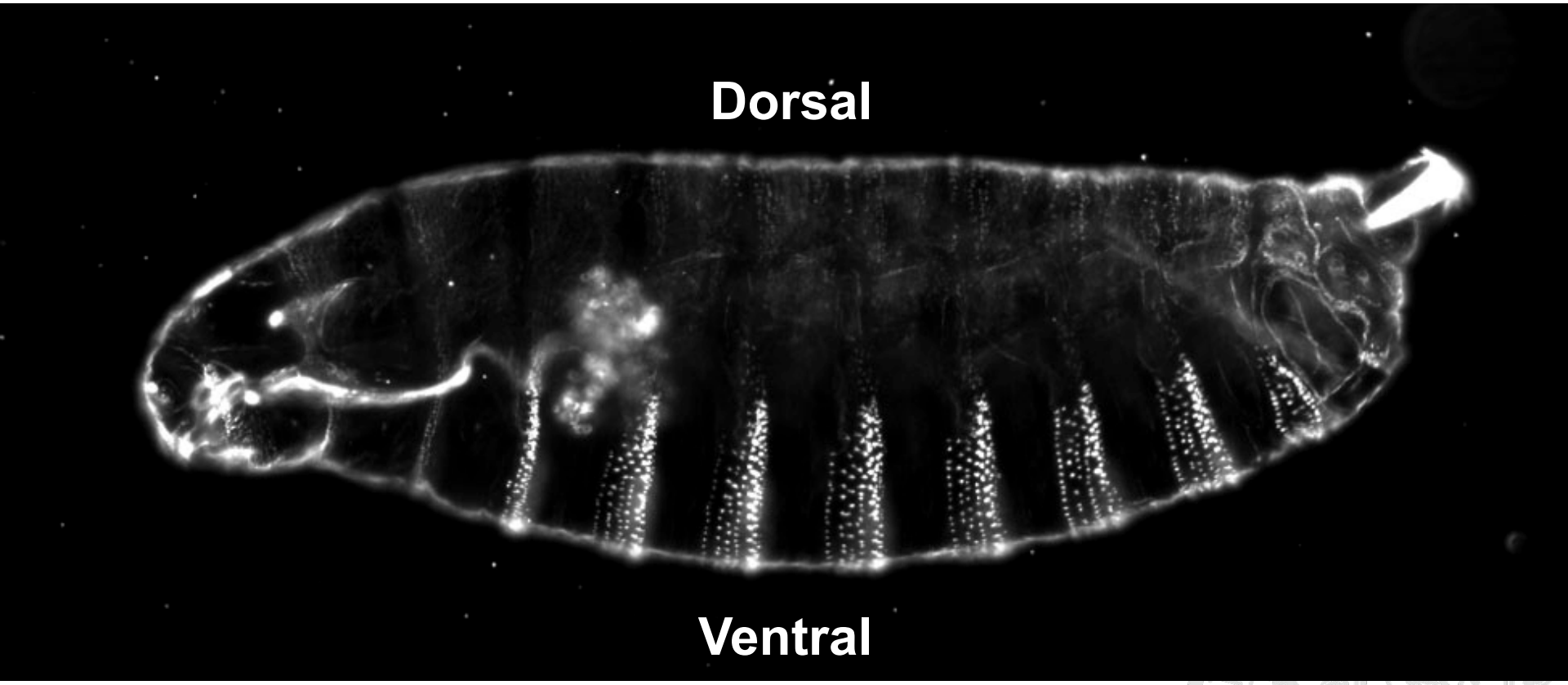
  begrenzte Anzahl erkannter Muster; von der Evolution selektioniert; Prinzip des angeborenen Immunsystems



Muster-Erkennung der angeborenen Immunität

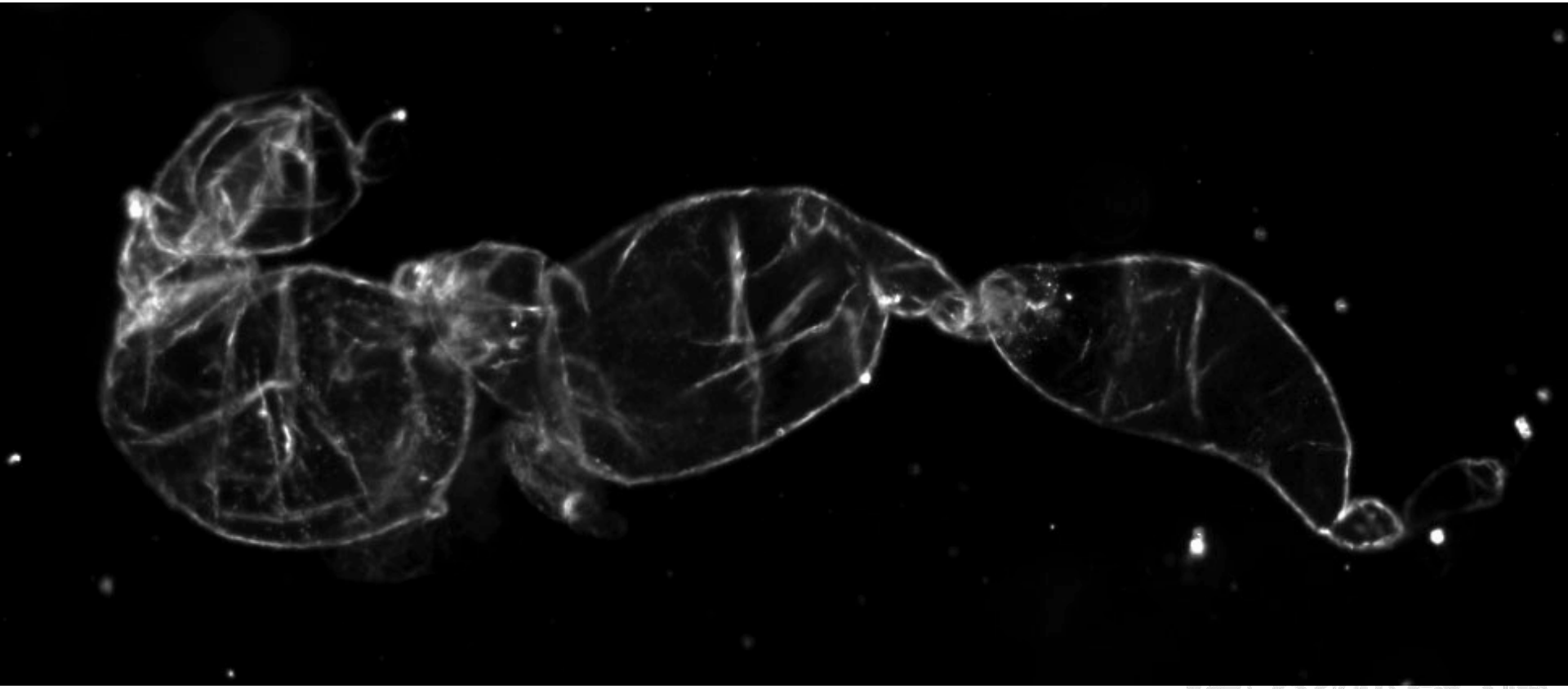
- Keimbahnkodierte Rezeptoren
  - beschränkte Anzahl (durch Evolution selektiert)
- Erkennung konservierter Strukturen die
  - mit Pathogenen assoziiert sind (PAMPs)
  - mit zellulärem Schaden assoziiert sind (DAMPs)
  - bei Viren Nukleinsäuren
- Fremd-Selbst Unterscheidung durch:
  - Strukturdiskriminierung
  - Ortsdiskriminierung
  - Mengendiskriminierung
- Toll-like Rezeptoren

Wildtyp *Drosophila* larvae



Christiane Nüsslein-Volhard, Nobelpreisträgerin für Medizin, 1995

mutante *Drosophila* larvae



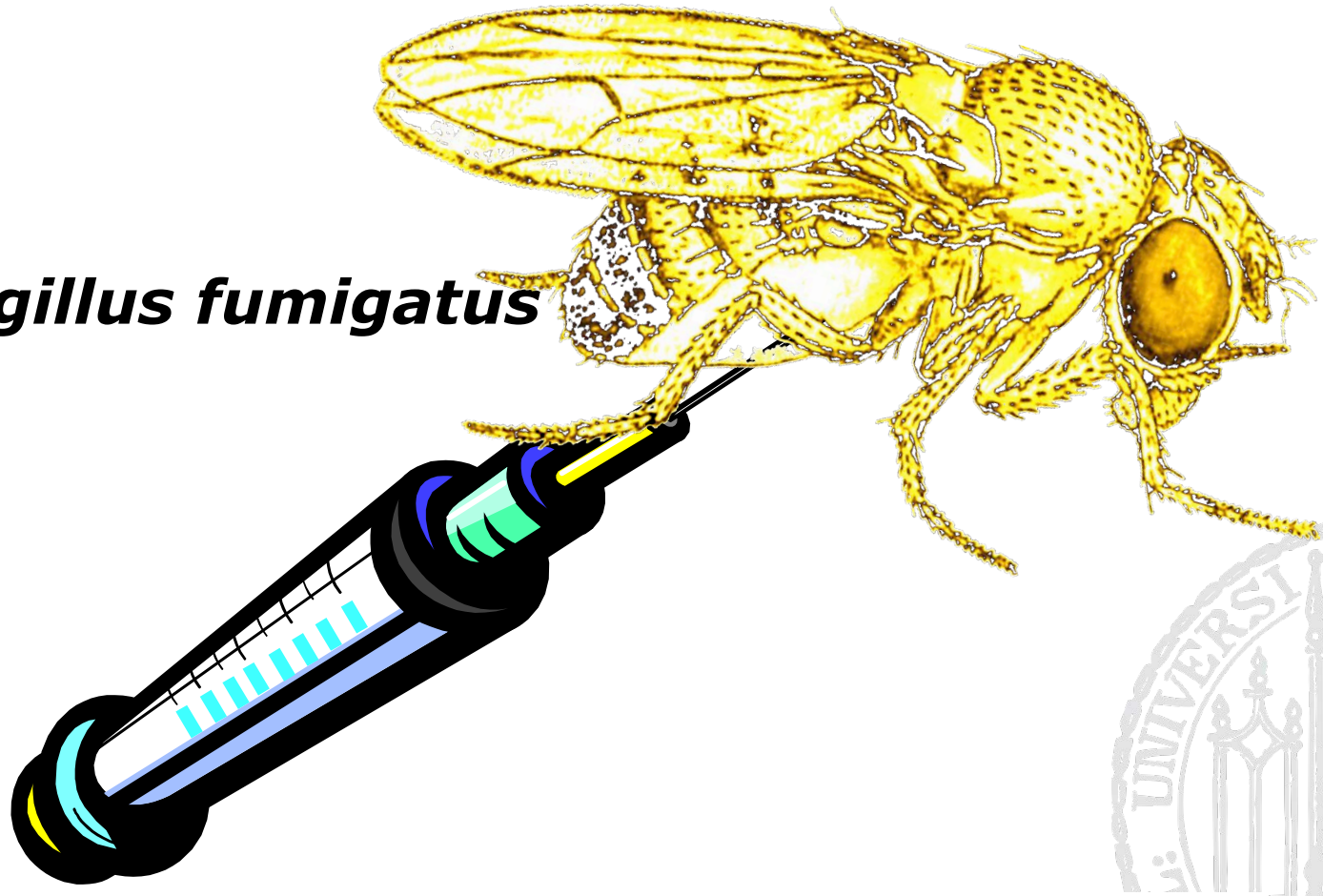
Anderson *et al. Cell* 1985; 42: 791-98

Christiane Nüsslein-Volhard, Nobel Laureate (Medicine, 1995)

Klonierung von *Toll*: Homologie zum humanen Interleukin-1 Rezeptor

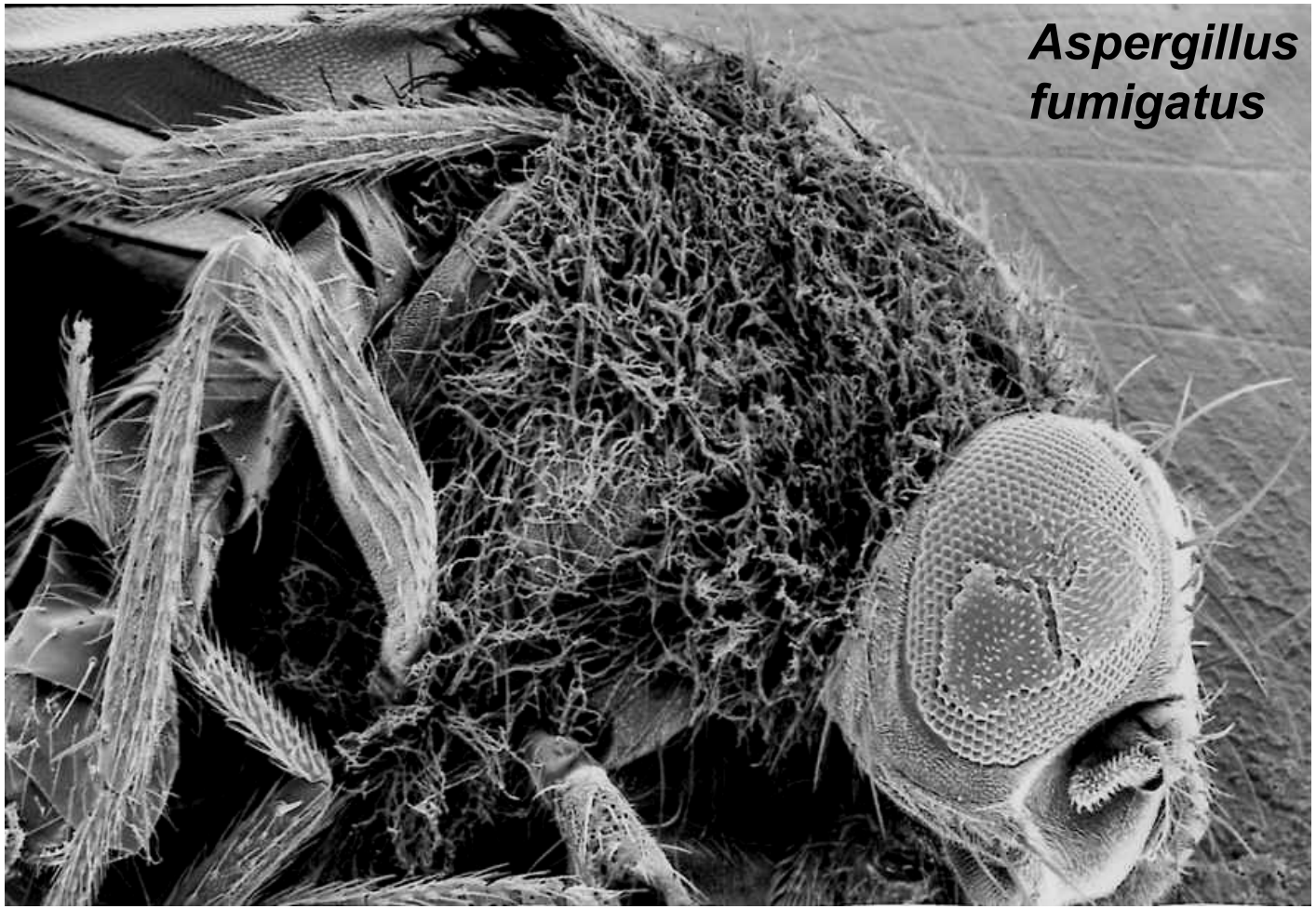
Lemaitre *et al*. *Cell* 1996; 86: 973-83

Aspergillus fumigatus



Mutationen im *Toll*-Rezeptor prädisponieren zu Pilzinfektionen

Jules Hofmann



Lemaitre *et al*. *Cell* 1996; 86: 973-83

Toll-like Rezeptoren

- Bruce Beutler

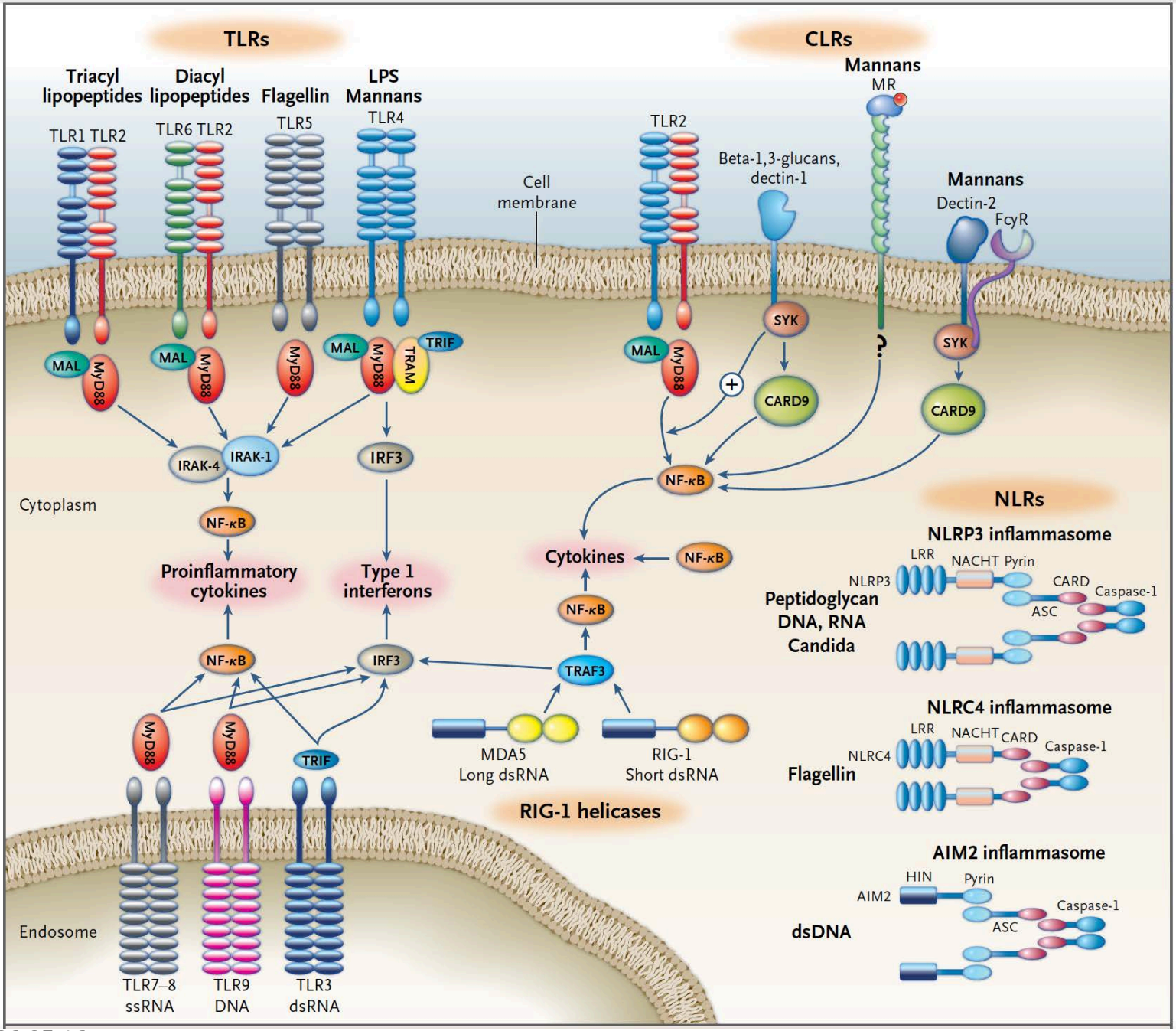
  Endotoxin resistente Maus C3H/HeJ; genetischer *Screen identifiziert TLR4*

- Ruslan Medzhnitov (Charles Janeway)
  TLR-4 kontrolliert Ko-stimulation

- Shizuo Akira

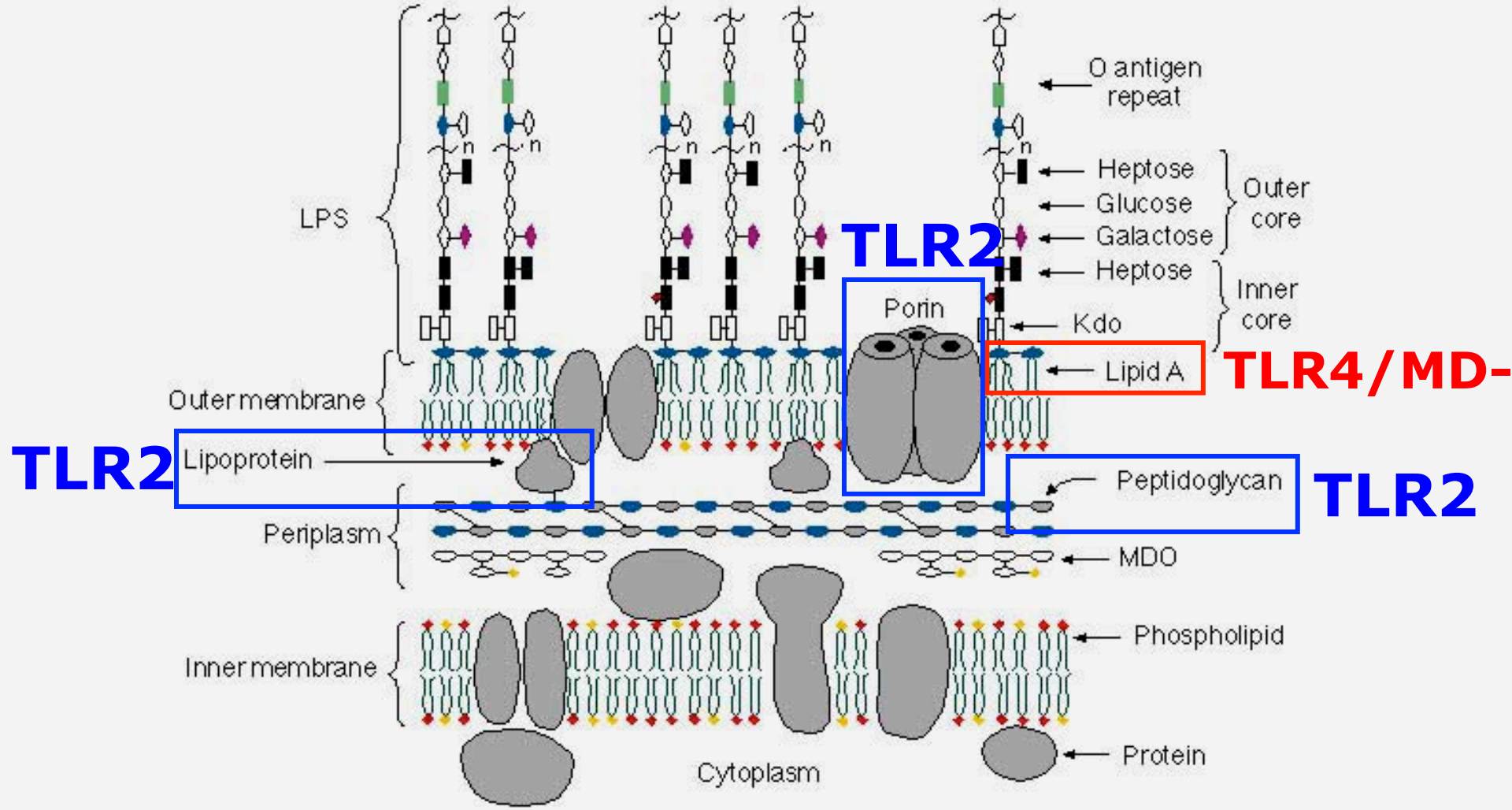
  TLR K.O Mäuse

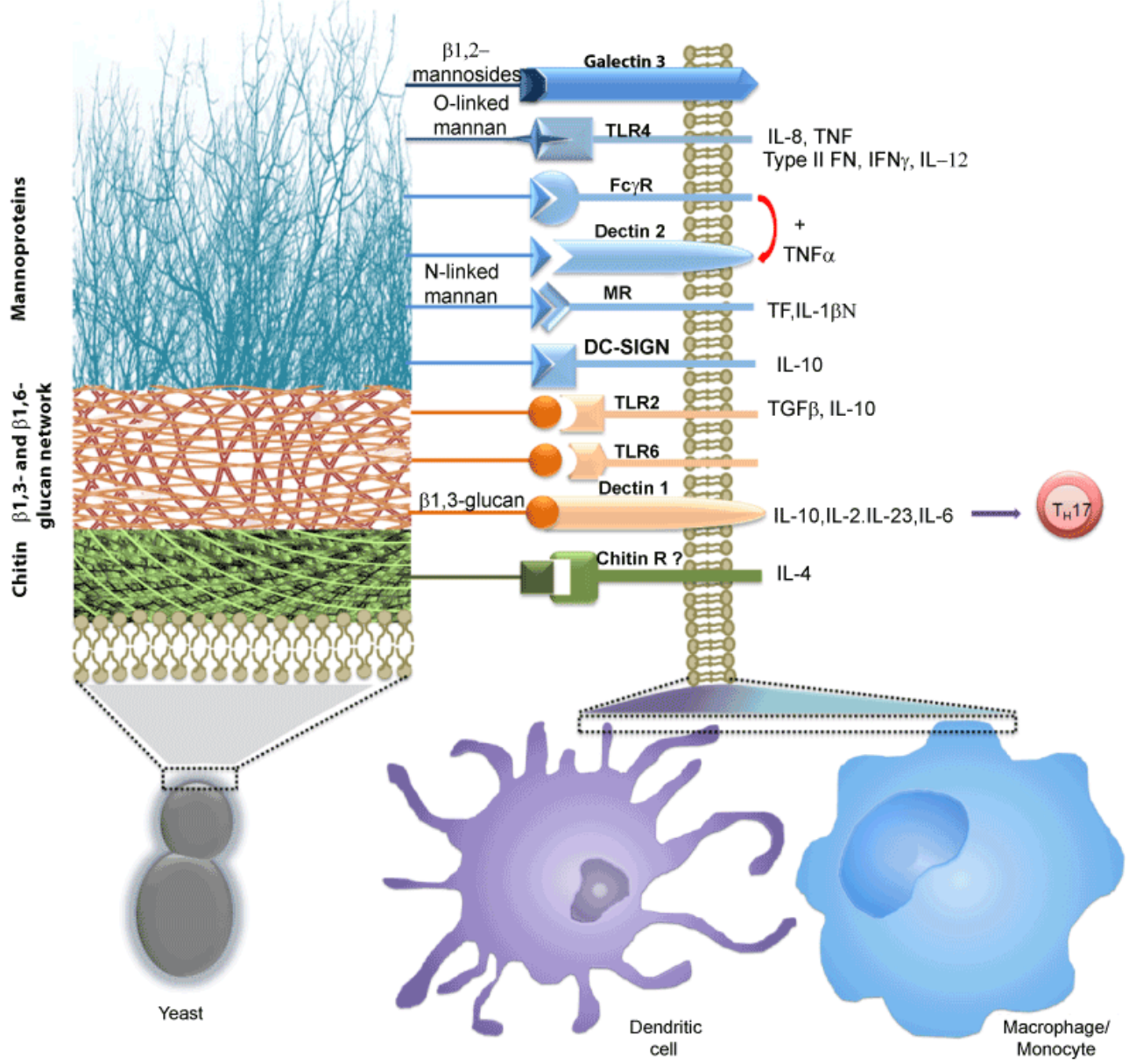
Nobel Price 2011: Bruce A. Beutler and Jules A. Hoffmann



N Engl J Med 2011;364:60-70.

Gram-negative Cell Envelope





Perez-Garcia LA, et al. J Glycobiology doi: 10.4172/2168-958X.1000102

AGENDA

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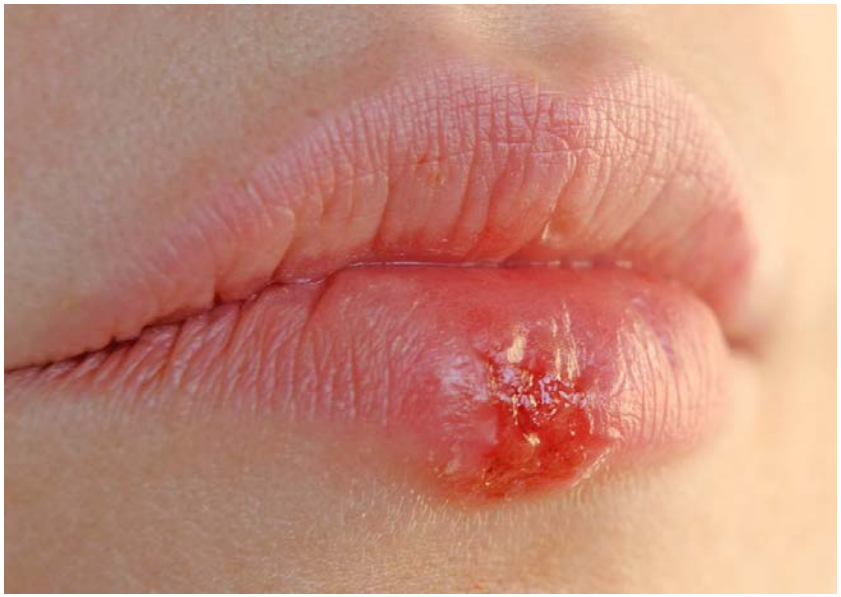
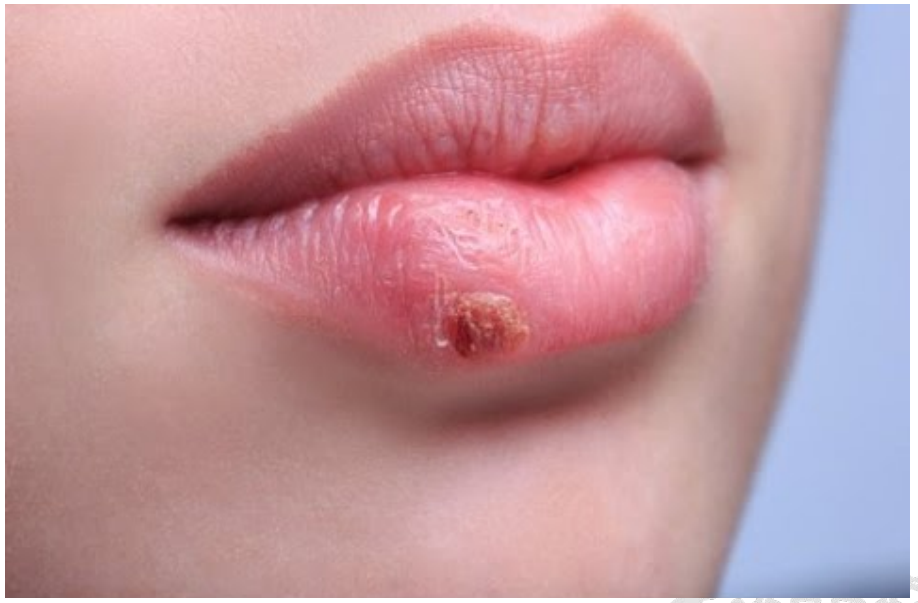
Herpesenzephalitis – eine genetische Erkrankung des TLR-3 Signalwegs?

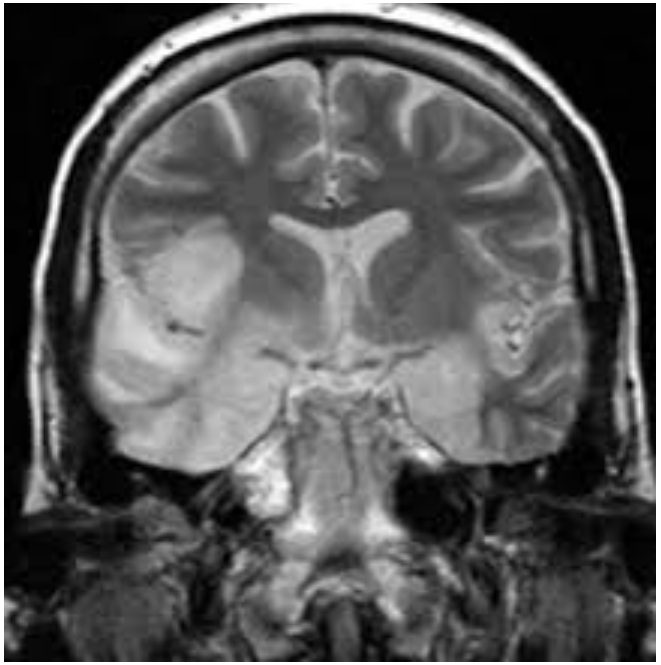
Pilzabwehr: was passiert bei zu viel pStat1?





- 60-90 % der Bevölkerung HSV1 oder HSV2 positiv
- Latentes Überleben der Viren in Neuronen
- Herpesschübe ausgelöst durch Triggerfaktoren

HERPES ENZEPHALITIS



- Herpes Enzephalitis: Inzidenz 2-4 pro 1 Mio Einwohner/pro Jahr
- Primäre Infektion und Reaktivierung
- Selbst bei korrekter Behandlung: Sterblichkeit 20%; bleibende Schäden

HERPESENZEPHALITIS; HSV 1 UND HSV2

- Patienten bekommen eine Herpesenzephalitis – dies wir durch das Virus verursacht. Es ist eine Infektionserkrankung.

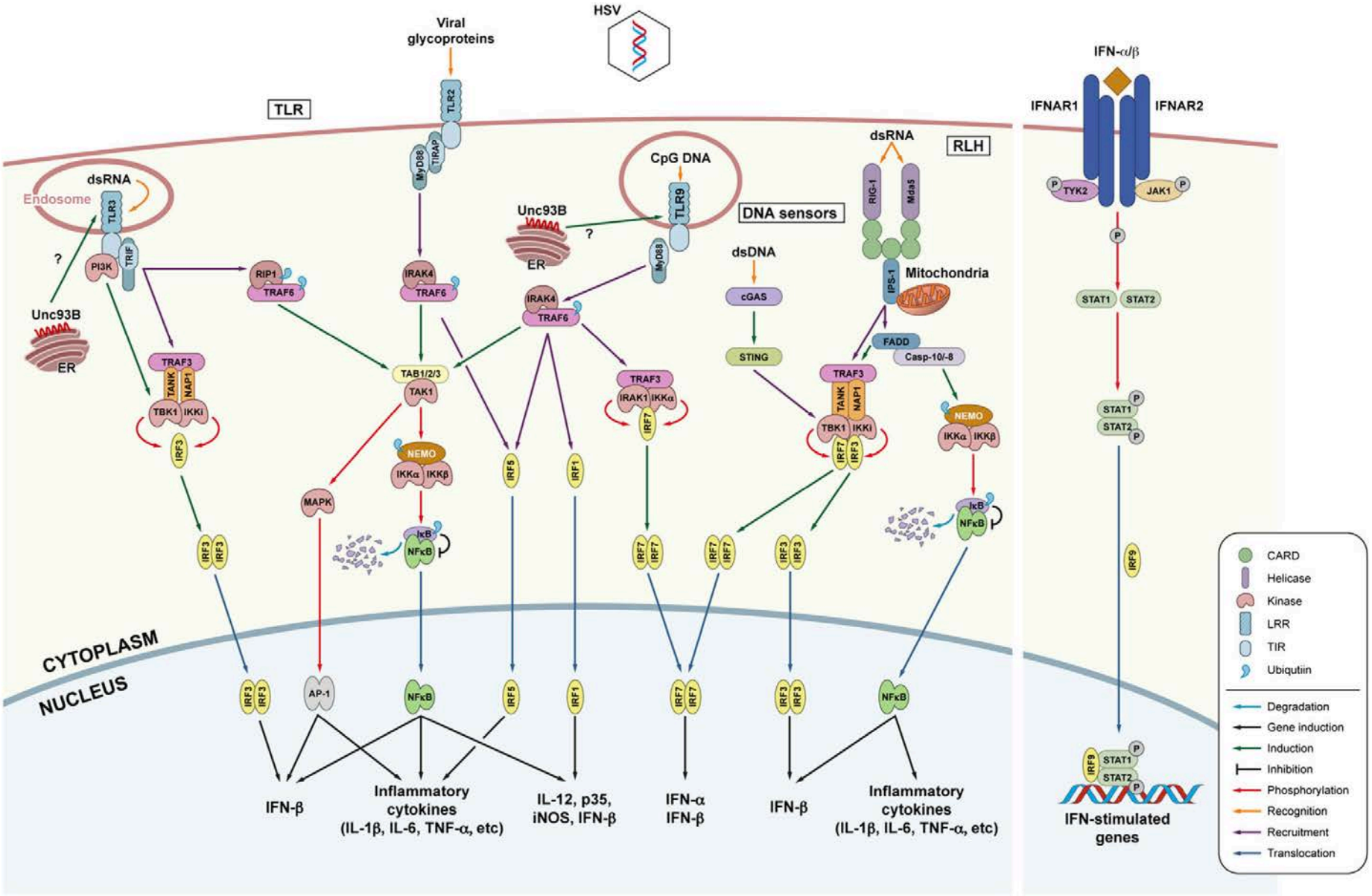
- Warum bekommt nicht jeder Patient eine Enzephalitis?

Jean-Laurent Casanova

- These: „Jede lebensbedrohliche Infektion ist durch einen Immundefekt verursacht “

HERPES; HSV 1 UND HSV2

- Es ist ein DNA Virus.
- HSV Viren triggern eine Vielzahl von Mustererkennungsrezeptoren

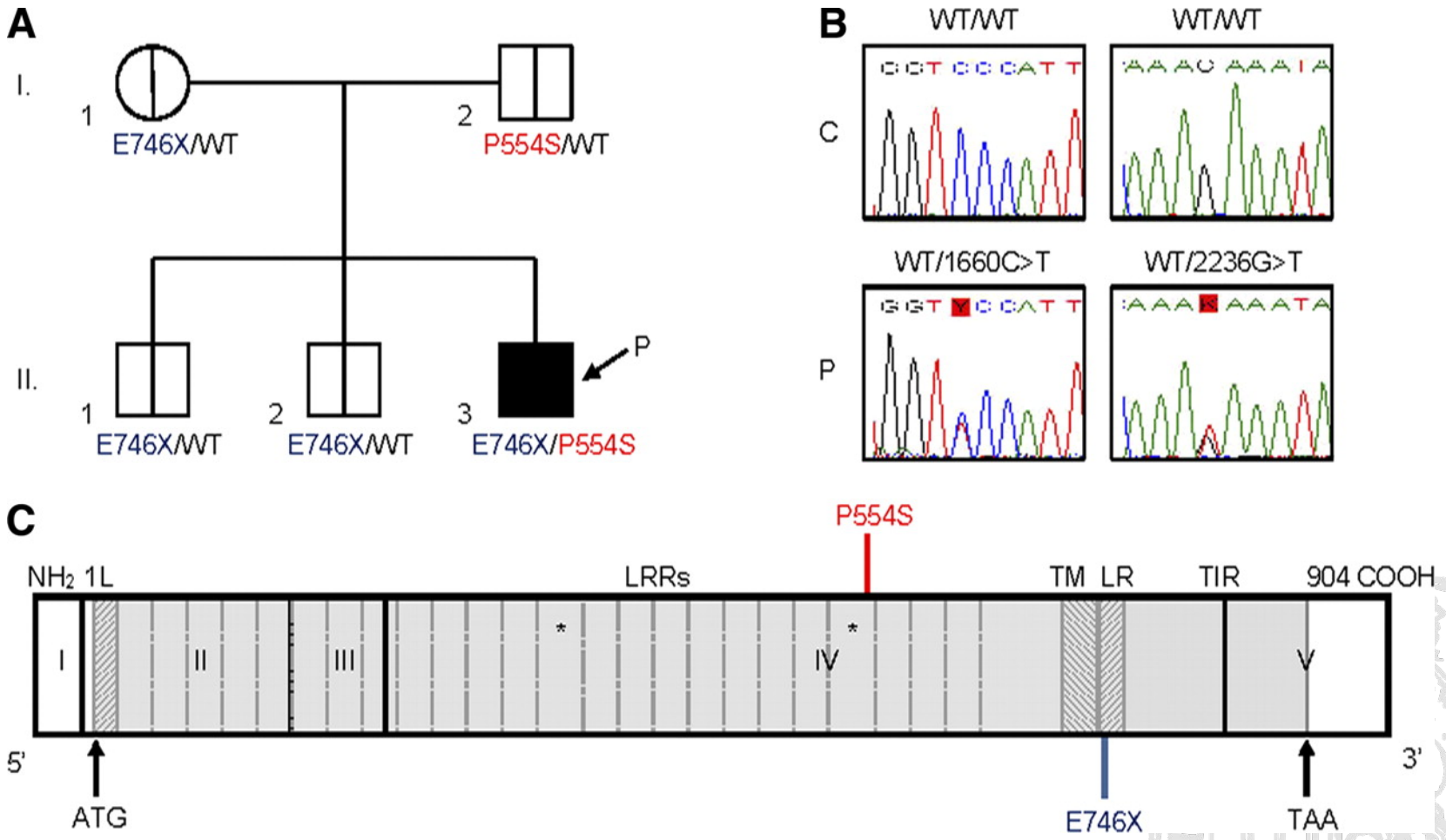

HSV
Viral glycoproteins
TLR
TLR2
MyD88
TIRAP
dsRNA
Endosome
TLR3
TRIF
PI3K
?
Unc93B
ER
RIP1
TRAF6
IRAK4
TRAF6
TAB1/2/3
TAK1
TRAF3
TANK
NAP1
TBK1
IKKi
IRF3
NEMO
IKKα
IKKβ
IκB
NFκB
MAPK
IRF5
IRF1
CpG DNA
TLR9
Unc93B
ER
?
MyD88
IRAK4
TRAF6
TRAF3
IRAK1
IKKα
IRF7
DNA sensors
dsDNA
cGAS
STING
dsRNA
RLH
RIG-1
Mda5
IPS-1
Mitochondria
FADD
Casp-10/-8
TRAF3
TANK
NAP1
TBK1
IKKi
IRF7
IRF3
NEMO
IKKα
IKKβ
IκB
NFκB
IRF3 IRF3
AP-1
NFκB
IRF5
IRF1
IRF7 IRF7
IRF7 IRF7
IRF3 IRF3
NFκB
CYTOPLASM
NUCLEUS
IFN-β
Inflammatory cytokines (IL-1β, IL-6, TNF-α, etc)
IL-12, p35, iNOS, IFN-β
IFN-α IFN-β
IFN-β
Inflammatory cytokines (IL-1β, IL-6, TNF-α, etc)
IFN-α/β
IFNAR1
IFNAR2
TYK2
JAK1
P
STAT1
STAT2
IRF9
IFN-stimulated genes
CARD
Helicase
Kinase
LRR
TIR
Ubiqutiin
Degradation
Gene induction
Induction
Inhibition
Phosphorylation
Recognition
Recruitment
Translocation

Herpes simplex virus encephalitis in a patient with complete TLR3 deficiency: TLR3 is otherwise redundant in protective immunity

by Yiqi Guo, Magali Audry, Michael Ciancanelli, Laia Alsina, Joana Azevedo, Melina Herman, Esperanza Anguiano, Vanessa Sancho-Shimizu, Lazaro Lorenzo, Elodie Pauwels, Paul Bastard Philippe, Rebeca Pérez de Diego, Annabelle Cardon, Guillaume Vogt, Capucine Picard, Zafitsara Zo Andrianirina, Flore Rozenberg, Pierre Lebon, Sabine Plancoulaine, Marc Tardieu, Valérie Doireau, Emmanuelle Jouanguy, Damien Chaussabel, Frederic Geissmann, Laurent Abel, Jean-Laurent Casanova, and Shen-Ying Zhang

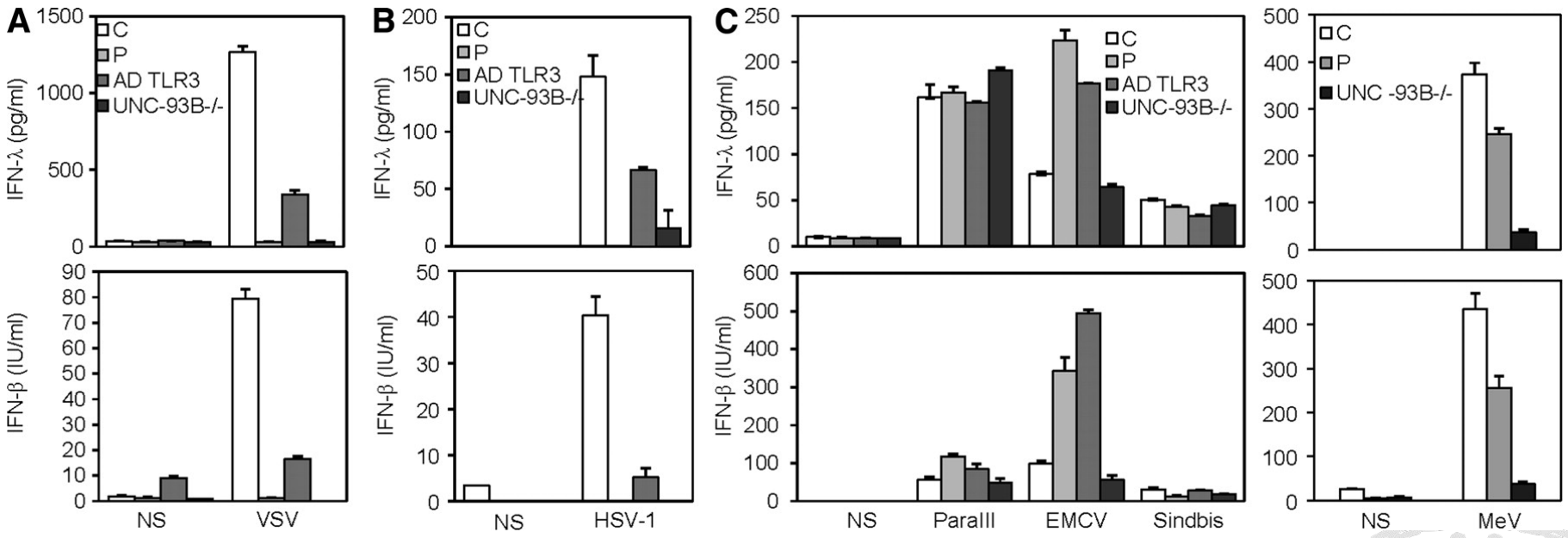
JEM
Volume 208(10):2083-2098
September 26, 2011

Compound heterozygous mutations in TLR3 in a child with HSE. (A) Family pedigree with allele segregation.



Yiqi Guo et al. J Exp Med 2011;208:2083-2098

Fehlende TLR3-Aktivierung in Fibroblasten des Patienten

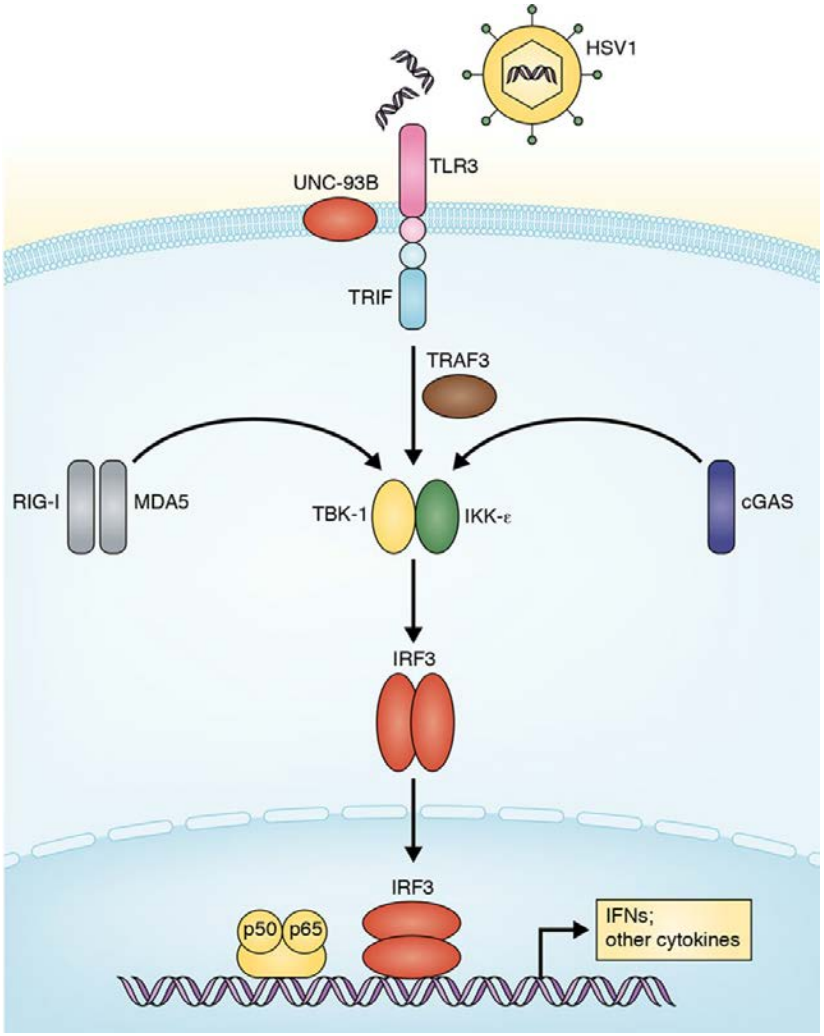


Yiqi Guo et al. J Exp Med 2011;208:2083-2098

KLINIKUM DER UNIVERSITÄT MÜNCHEN®

JEM

Mutationen in TLR3, UNC93B1, TRIF, TRAF3, TBK1, IRF3, Stat1, alle involviert in den TLR3-Signalweg, sowie in MAVS wurden in HSE patients beschrieben .



Shen-Ying Zhang, and Jean-Laurent Casanova J Exp Med 2015;212:1342-1343

TLR3 deficiency in herpes simplex encephalitis

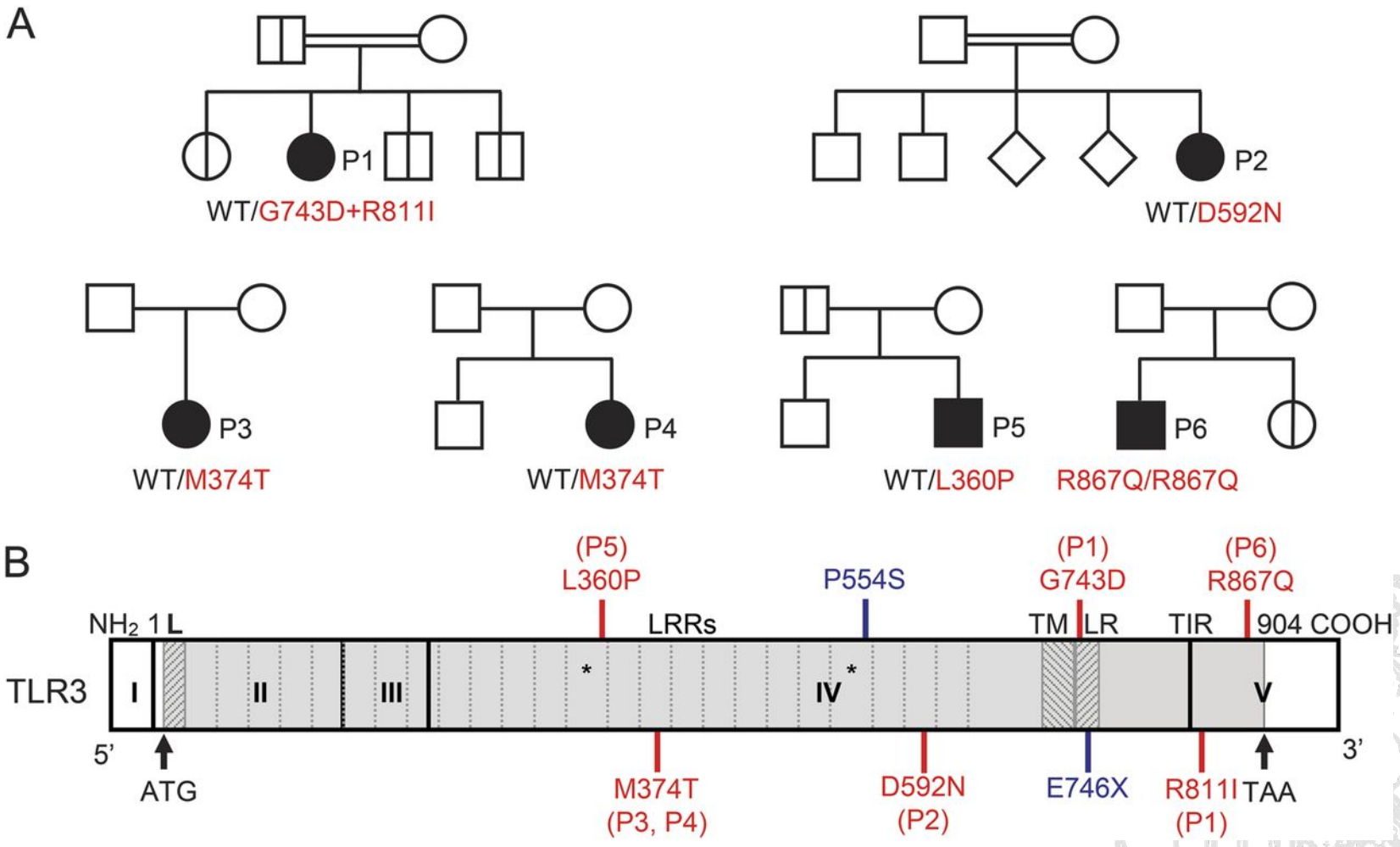
High allelic heterogeneity and recurrence risk

ABSTRACT

Objective: To determine the proportion of children with herpes simplex encephalitis (HSE) displaying TLR3 deficiency, the extent of TLR3 allelic heterogeneity, and the specific clinical features of TLR3 deficiency.

Methods: We determined the sequence of all exons of *TLR3* in 110 of the 120 patients with HSE enrolled in our study who do not carry any of the previously described HSE-predisposing mutations of TLR3 pathway genes (*TLR3*, *UNC93B1*, *TRIF*, *TRAF3*, and *TBK1*). All the new mutant TLR3 alleles detected were characterized experimentally in-depth to establish the causal relationship between the genotype and phenotype.

Figure 1 Five novel TLR3 mutant alleles in 6 unrelated patients with herpes simplex encephalitis(A) Family pedigrees with allele segregation in the 6 families.



Hye Kyung Lim et al. Neurology 2014;83:1888-1897

ORIGINAL ARTICLE

Mutations in the TLR3 signaling pathway and beyond in adult patients with herpes simplex encephalitis

N Mørk[1], E Kofod-Olsen[2], KB Sørensen[1], E Bach[1], TF Ørntoft[3], L Østergaard[1,2], SR Paludan[4], M Christiansen[2,5] and TH Mogensen[1,2,4]

Herpes simplex encephalitis (HSE) in children has previously been linked to defects in type I interferon production downstream of Toll-like receptor (TLR)3. In the present study, we used whole-exome sequencing to investigate the genetic profile of 16 adult patients with a history of HSE. We identified novel mutations in IRF3, TYK2 and MAVS, molecules involved in generating innate antiviral immune responses, which have not previously been associated with HSE. Moreover, data revealed mutations in TLR3, TRIF, TBK1 and STAT1 known to be associated with HSE in children but not previously described in adults. All discovered mutations were heterozygous missense mutations, the majority of which were associated with significantly decreased antiviral responses to HSV-1 infection and/or the TLR3 agonist poly(I:C) in patient peripheral blood mononuclear cells compared with controls. Altogether, this study demonstrates novel mutations in the TLR3 signaling pathway in molecules previously identified in children, suggesting that impaired innate immunity to HSV-1 may also increase susceptibility to HSE in adults. Importantly, the identification of mutations in innate signaling molecules not directly involved in TLR3 signaling suggests the existence of innate immunodeficiencies predisposing to HSE beyond the TLR3 pathway.

Genes and Immunity (2015) **16,** 552–566; doi:10.1038/gene.2015.46; published online 29 October 2015

Table 1. Demographic, genetic and medical data on HSE patients included in the study together with overview of identified molecules with mutations

Figures and tables index | Next table

Patient ID	Age, Gender	Molecule	Transcript ID, Transcript variant, Protein variant	ExAC Frequency[a], Phred score[b]	CSF findings	MR findings (EEG if performed)	Treatment duration[c]
#1	15 years Female	IRF3	NM_001197122.1, c.854G>A, p. Arg285Gln	0.000066, 21.8	Virus: HSV-1 DNA Leukocytes: 197[d]Protein: 4.16[e]	MR: Diffuse severe changes consistent with HSE	21 days
#2	34 years Male	IRF3	NM_001197122.1, c.829G>A, p.Ala277Thr	0.0036, 7.6	Virus: HSV-1 DNA Leukocytes: 92 Protein: 0.97	No MR scan performed Normal EEG	14 days
#3	61 years Male	TYK2	NM_003331.4, c.157G>A, p.Ala53Thr	0.0080, 24.0	Virus: HSV-1 DNA Leukocytes: 52 Protein: 0.73	No MR scan CT: Edema and possible minor infarction at right temporal lobe Control CT: changes consistent with HSE	16 days
#4	24 years Female	MAVS	NM_020746.4, c.371C>T, p.Ala124Val	0.00014, 15.9	Virus: HSV-1 DNA Leukocytes: 550 Protein: 1.01	MR: Cyst in pineal gland, otherwise normal	14 days
#5	73 years Male	TICAM1/TRIF	NM_182919.3, c.1702G>A, p.Ala568Thr	0.0031, 23.6	Virus: HSV-1 DNA Leukocytes: 64 Protein: 0.73	CT with contrast; ischemic areas located at the temporal lobes Later MR scan with similar findings	29 days
#6	69 years Male	TICAM1/TRIF	NM_182919.3, c.749C>T, p.Ser160Phe	0.0024, 8.2	Virus: HSV-2 DNA Leukocytes: 136 Protein: 2.66	MR: Only partly successful, no abnormity observed in temporal lobes. Abnormal EEG	21 days
#7	68 years Male	STAT1	NM_007315.3, c.796G>A, p.Val266Ile	0.0020, 10.5	Virus: HSV-1 DNA Leukocytes: 115 Protein: 0.73	MR: Changes in left temporal cerebral hemisphere consistent with HSE	14 days
#8	65 years Male	STAT1	NM_007315.3, c.796G>A, p.Val266Ile	0.0020, 10.5	Virus: HSV DNA Leukocytes: 22.5 Protein: 0.52	MR: Changes after recent infarction/infection in left temporal region	14 days
#9	58 years Male	TLR3	NM_003265.2, c.889C>G, p.Leu297Val	0.0015, 24.2	Virus: HSV-1 DNA Leukocytes: 40 Protein: 0.59	MR: Signal changes in cortical structures bilateral, also edema. Consistent with HSE	26 days
#10	50 years Female	TBK1	NM_013254.3, c.619 A>G, p.Ile207Val	ND, 243	Virus: HSV-2 DNA Leukocytes: 258 Protein: 1.65	MR: Normal CT: Diffuse cerebral edema	14 days
#11	59 years Male		—		Virus: HSV-1 DNA Leukocytes: 88 Protein: 0.36	MR: Changes in left temporal lobe region	14 days
#12	52 years Male		—		Virus: HSV-1 DNA Leukocytes: 144 Protein: 0.44	MR: Classical fronto-temporal changes on right side	21 days
#13	40 years Female		—		Virus: HSV-2 DNA Leukocytes: 150 Protein: 0.75	No MR scan performed	10 days
#14	34 years Male		—		Virus: HSV-1 DNA Leukocytes: 294	MR: Abnormalities especially in cortex at left temporal lobe	14 days
#15	76 years Male		—		Virus: HSV-1 DNA Leukocytes:<5 Protein/albumin ratio slightly elevated	Normal MR	14 days
#16	41 years Female		—		Virus: HSV-1 DNA Leukocytes: 368 Protein: 1.12	No MR scan performed CT with changes in left temporal lobe	21 days

Abbreviations: CSF, cerebrospinal fluid; CT, CAT scan; EEG, electroencephalography; HSE, herpes simplex encephalitis; HSV-1/2, herpes simplex virus type 1/2; MR, magnetic resonance.

[a] Allele frequencies from the ExAC server of 60 000 exomes (ref Exome Aggregation Consortium (ExAC), Cambridge, MA (URL: http://exac.broadinstitute.org) (accessed 04, 2015).

[b] CADD software prediction of deleteriousness.

[c] acyclovir 10mg kg^{-1} × 3 intravenously.

- 10 of 16 patients show mutations in genes implicated in the TLR3 pathway

Genes and Immunity 2015

Lebensbedrohliche Infektionen
beruhen auf einem Immundefekt?

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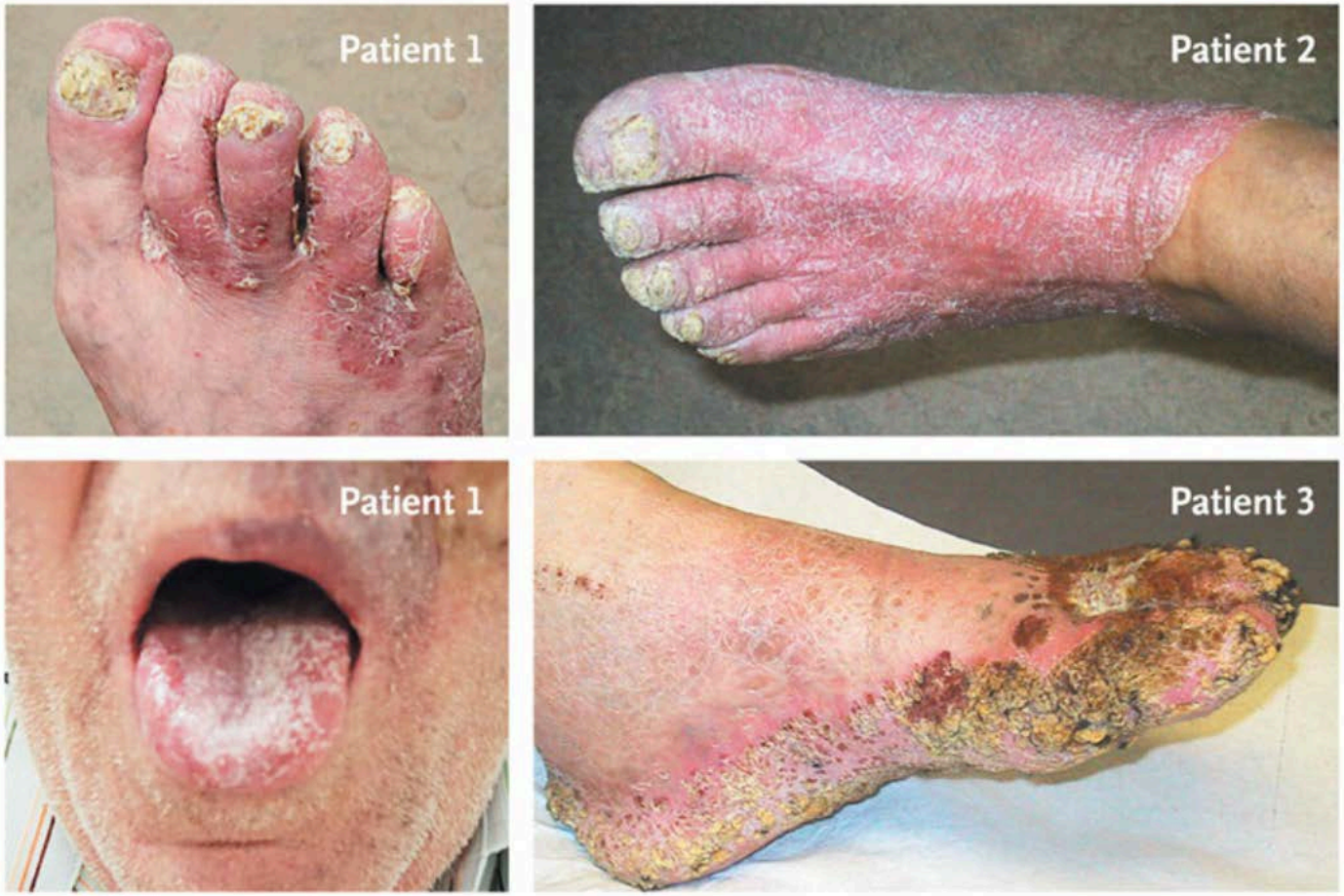
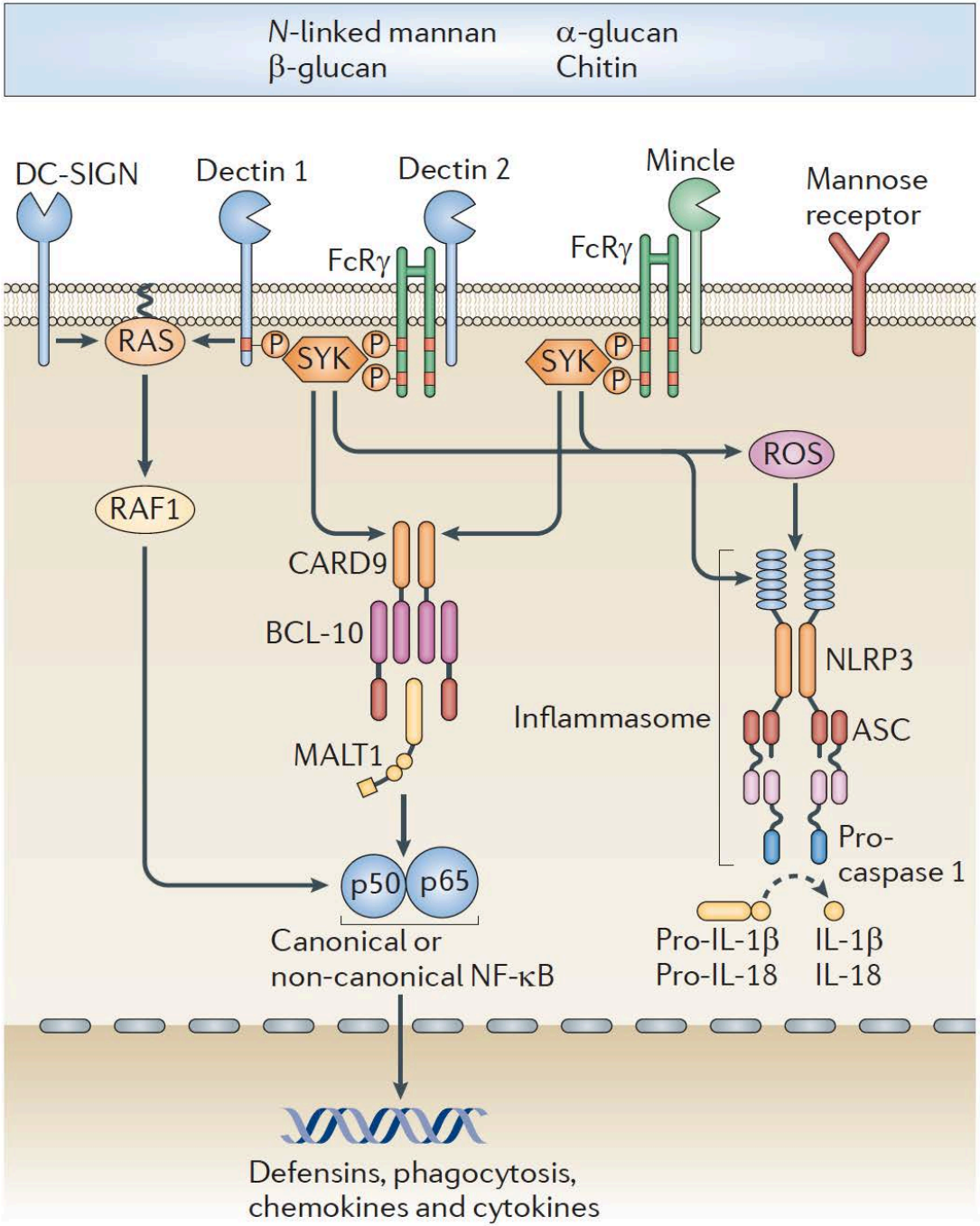
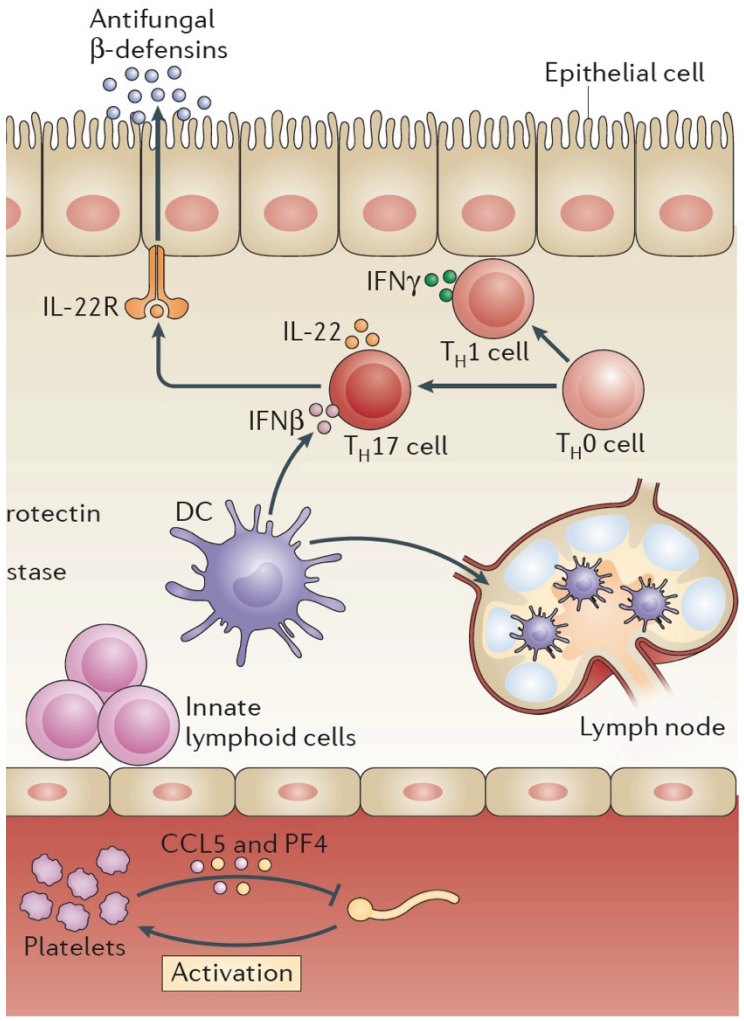
Candida spp.	Commensal of human gastrointestinal tract and vagina		• Disseminated infections • Mucocutaneous infections (oropharyngeal, skin and nail infections) • Vaginitis

Chronische mukokutane Candidose
CMC



N Engl J Med 2011;365:54-61.





Nature reviews Immmunology

ORIGINAL ARTICLE

N Engl J Med 2011;365:54-61.

STAT1 Mutations in Autosomal Dominant Chronic Mucocutaneous Candidiasis

Frank L. van de Veerdonk, M.D., Ph.D., Theo S. Plantinga, Ph.D., Alexander Hoischen, Ph.D., Sanne P. Smeekens, M.Sc., Leo A.B. Joosten, Ph.D., Christian Gilissen, Ph.D., Peer Arts, Ph.D., Diana C. Rosentul, M.Sc., Andrew J. Carmichael, M.D., Chantal A.A. Smits-van der Graaf, M.D., Ph.D., Bart Jan Kullberg, M.D., Ph.D., Jos W.M. van der Meer, M.D., Ph.D., Desa Lilic, M.D., Ph.D., Joris A. Veltman, Ph.D., and Mihai G. Netea, M.D., Ph.D.

JEM

Article

Gain-of-function human *STAT1* mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis

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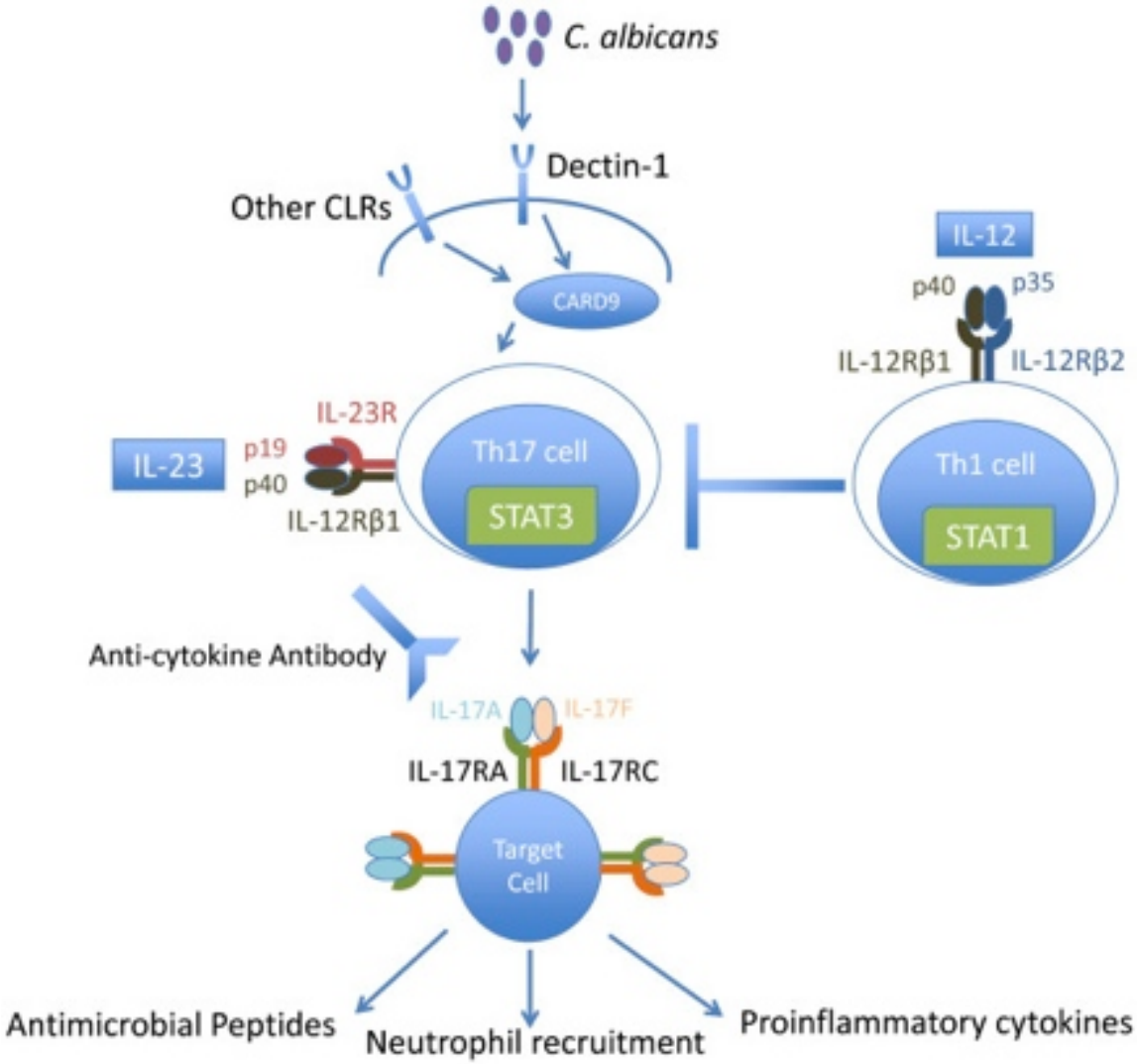

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ZUSAMMENFASSUNG

Selbst und Fremd: Das Prinzip Mustererkennung in der angeborenen Immunität

Herpesenzephalitis – in den meisten Fällen ein Immundefekt zu erwarten

Gain of function Mutationen in pStat1 führen zu einer Reduktion von TH17 Zellen und verursachen AD Chronische Mukokutane Candidose (CMC)

Vielen Dank für Ihre Aufmerksamkeit !

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