Genetics Susceptibility to Infectious Diseases

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Learning Objectives

- Define and classify primary immunodeficiency diseases
- Review the role of clinical laboratory in the diagnosis of primary immunodeficiency diseases
- Demonstrate the utility of molecular diagnosis in primary immunodeficiency diseases
- Review the genetics of
  - (1) Mendelian susceptibility to chronic mucocutaneous candidiasis
  - (2) Mendelian susceptibility to mycobacterial infections
  - (3) Herpes simples encephalitis

Definitions

- Primary immunodeficiency (PID): genetic

(Secondary immunodeficiency: infection, malignancy, iatrogenic)

- PID - changing definition:
  from very severe Mendelian traits to
  varying degree of susceptibility to infections

Identification of patients with PID

- Diagnosis of PIDs requires integration of data from clinical findings with laboratory immunological analyses and genetic testing

→ Infections

- recurrent
- life-threatening
- unusual

→Autoimmune diseases

→Malignancies

Primary immunodeficiencies

PIDs are like other genetic diseases, but

- Diagnosis:

  - secondary causes of ID are more common than primary (esp. in adults)

  - manifestations (infections) can be the same in both primary and secondary ID as well in “healthy” individuals

- Therapy(!):

  - Hematopoietic Stem Cell Transplantation (HSCT)
    (gene therapy)

  - Replacement, anti-microbials

Diagnosis of PIDs

Clinical and family history-based diagnostic approach

Diagnostic immunology lab supports, refine phenotype

Diagnosis of PIDs

Clinical and family history-based diagnostic approach

↓

Diagnostic immunology lab supports, refine phenotype

↓

Molecular lab

Mutation analysis in PIDs

- Definitive diagnosis (atypical presentations)
- Presymptomatic identification
- Carrier identification, genetic counseling, prenatal diagnosis
- Prognosis (strong genotype-phenotype correlation)
- Technical considerations (DNA stability vs. live cells)

Mutations in PIDs

- ~200 recognized PIDs, >250 genes (growing fast ~1/month)
  - candidate genes
  - mapping studies
  - novel technologies (genome/exome)

- Pathways not genes - Mendelian susceptibility to:
  - chronic mucocutaneous candidiasis
  - mycobacterial infections
  - herpes simplex encephalitis

- Normal vs. immune deficient (not all-or-nothing)
  - quantitative traits/pathways

Mendelian susceptibility to chronic mucocutaneous candidiasis (CMC)

- *Candida albicans* is present in GI flora and and reproductive mucosa of **healthy** subjects
- **Immunocompromised** patients *C albicans* can cause systemic or mucosal disease
- Systemic candidiasis is an acute, disseminated, and invasive

  - Candidemia is one of the most prevalent bloodstream infections in hospital settings and is associated with significant morbidity and mortality
- CMC is localized to the skin, nails, and mucous membranes (no predisposition to invasive disease, such as sepsis or pneumonia)

Immunity to candida

- Impaired T cell immunity: HIV/AIDS, SCID, DiGeorge syndrome, DOCK8 deficiency, etc.

- Congenital neutropenias or secondary neutropenia (e.g. after chemotherapy)

- Recognition:

  - mannans (outer portion of the cell wall)

    →TLR4, Mannose Receptor, DC-SIGN, and Dectin2

  - β-glucans (inner portion of the fungal cell wall)

    → Dectin1, and MINCLE

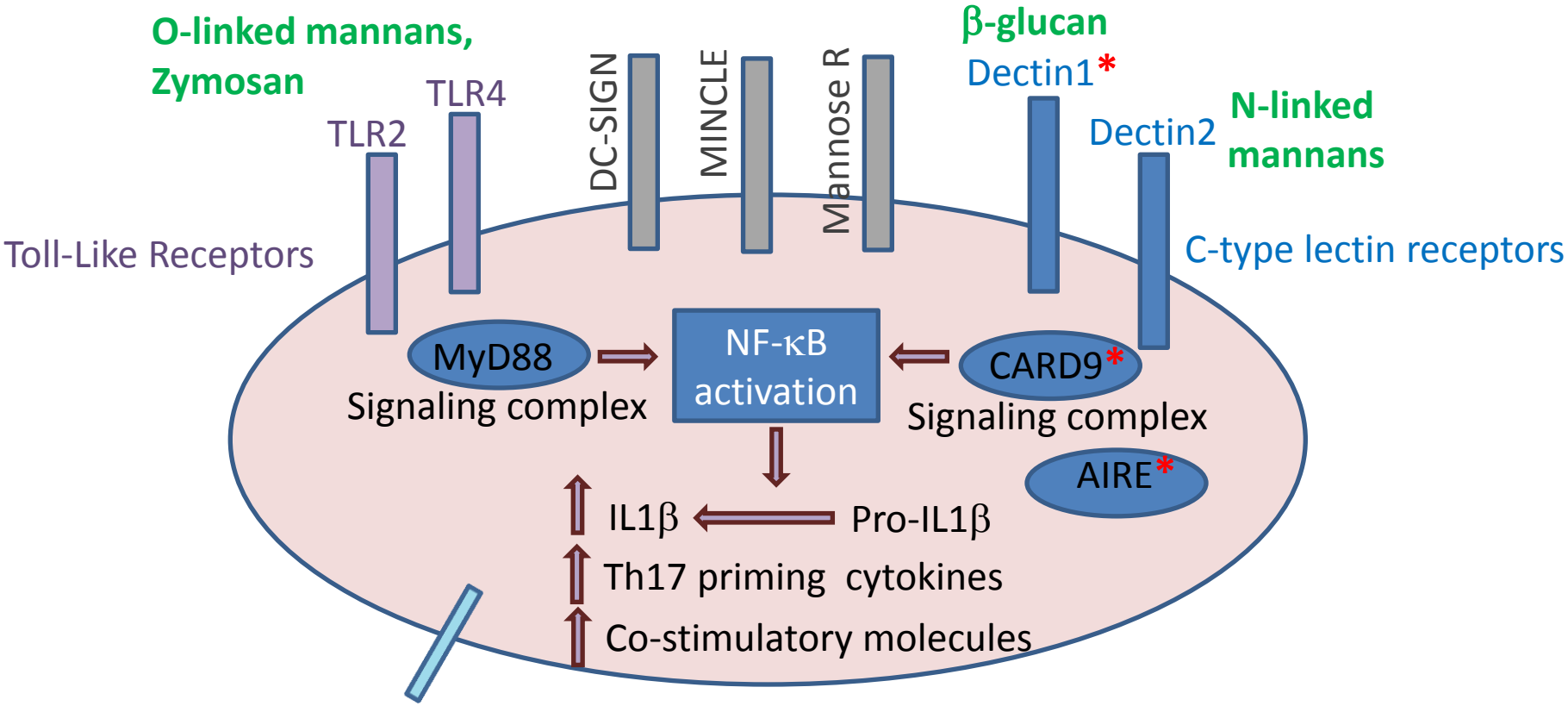
Genetics of CMC

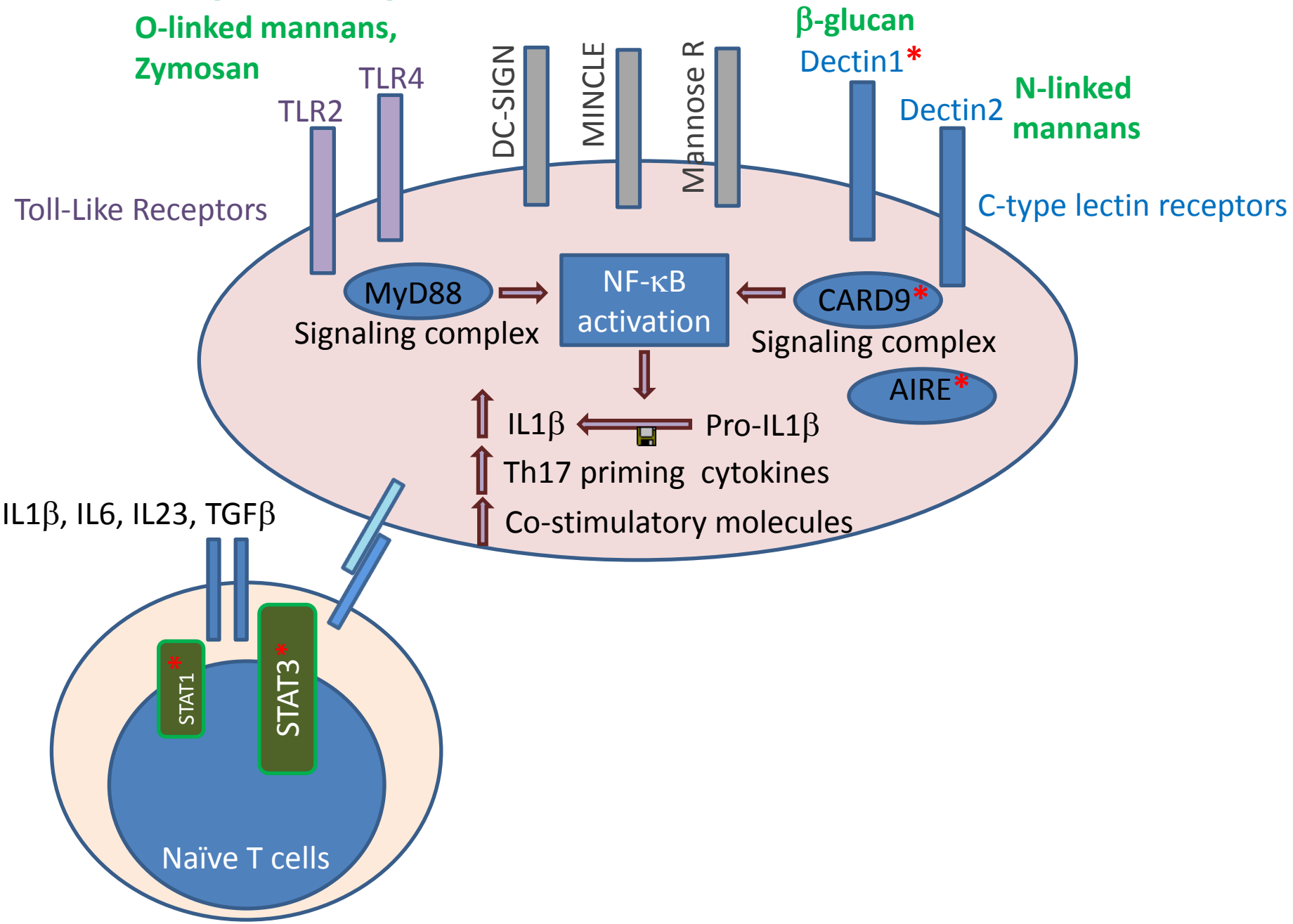
- Dectin-1 deficiency (AR)
- CARD-9 deficiency (AR)
- AD Hyper IgE syndrome or Job syndrome: STAT3 deficiency
- AR Hyper IgE syndrome: DOCK8 deficiency
- STAT1 mutations (AD)
- IL-17F deficiency (AR)
- IL-17RA deficiency (AR)
- APECED (or APS type I): AIRE deficiency (AR)

Molecular testing → diagnosis, prognosis, inheritance

Immune response: receptors → signaling → effector functions

Fungal Pathogen Associated Molecular Patterns (PAMPs)

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Zymosan
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Dectin1*
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mannans
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C-type lectin receptors
MyD88
Signaling complex
NF-κB
activation
CARD9*
Signaling complex
AIRE*
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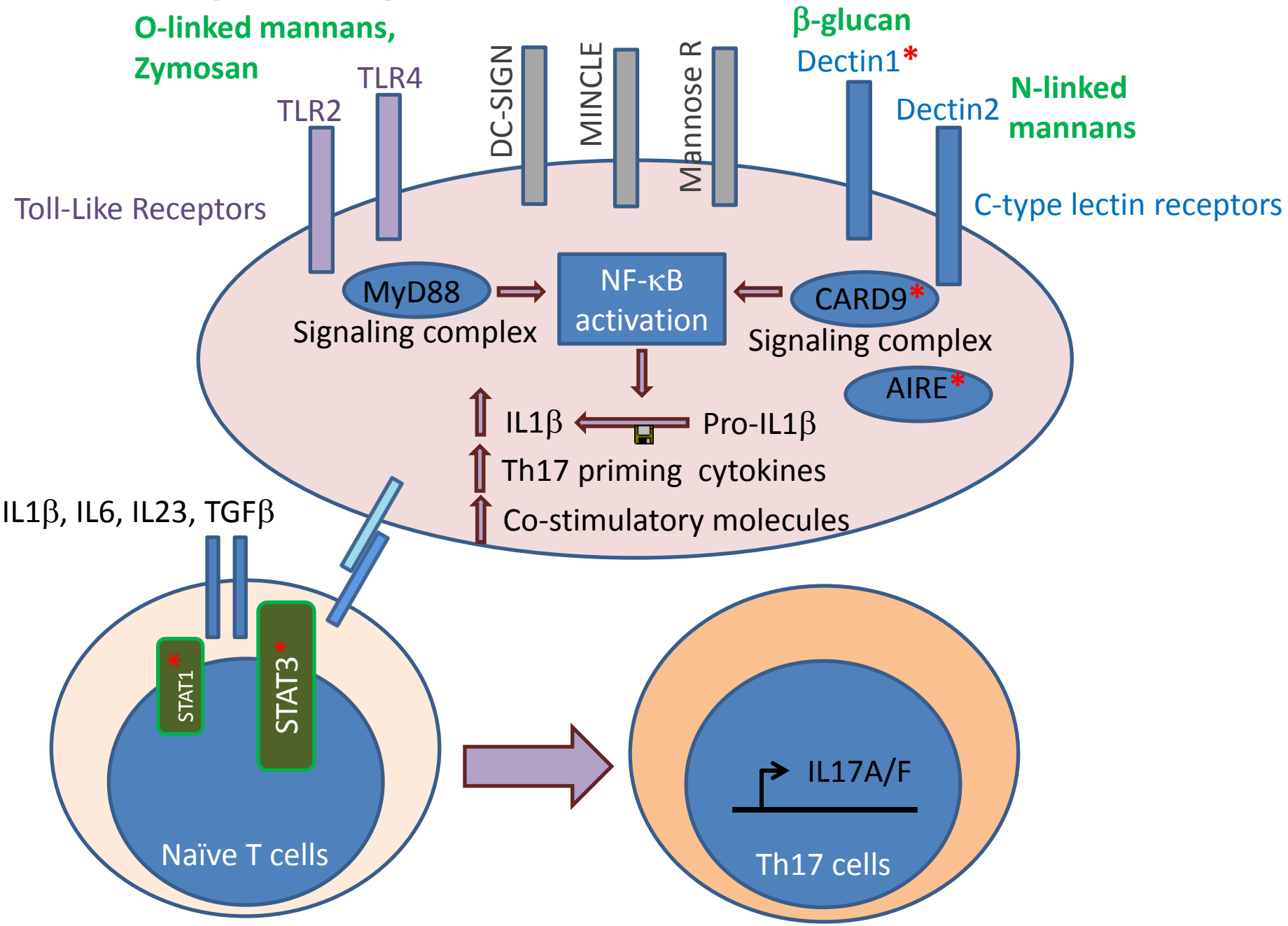
Pro-IL1β
Th17 priming cytokines
Co-stimulatory molecules
IL1β, IL6, IL23, TGFβ
STAT1*
STAT3*
Naïve T cells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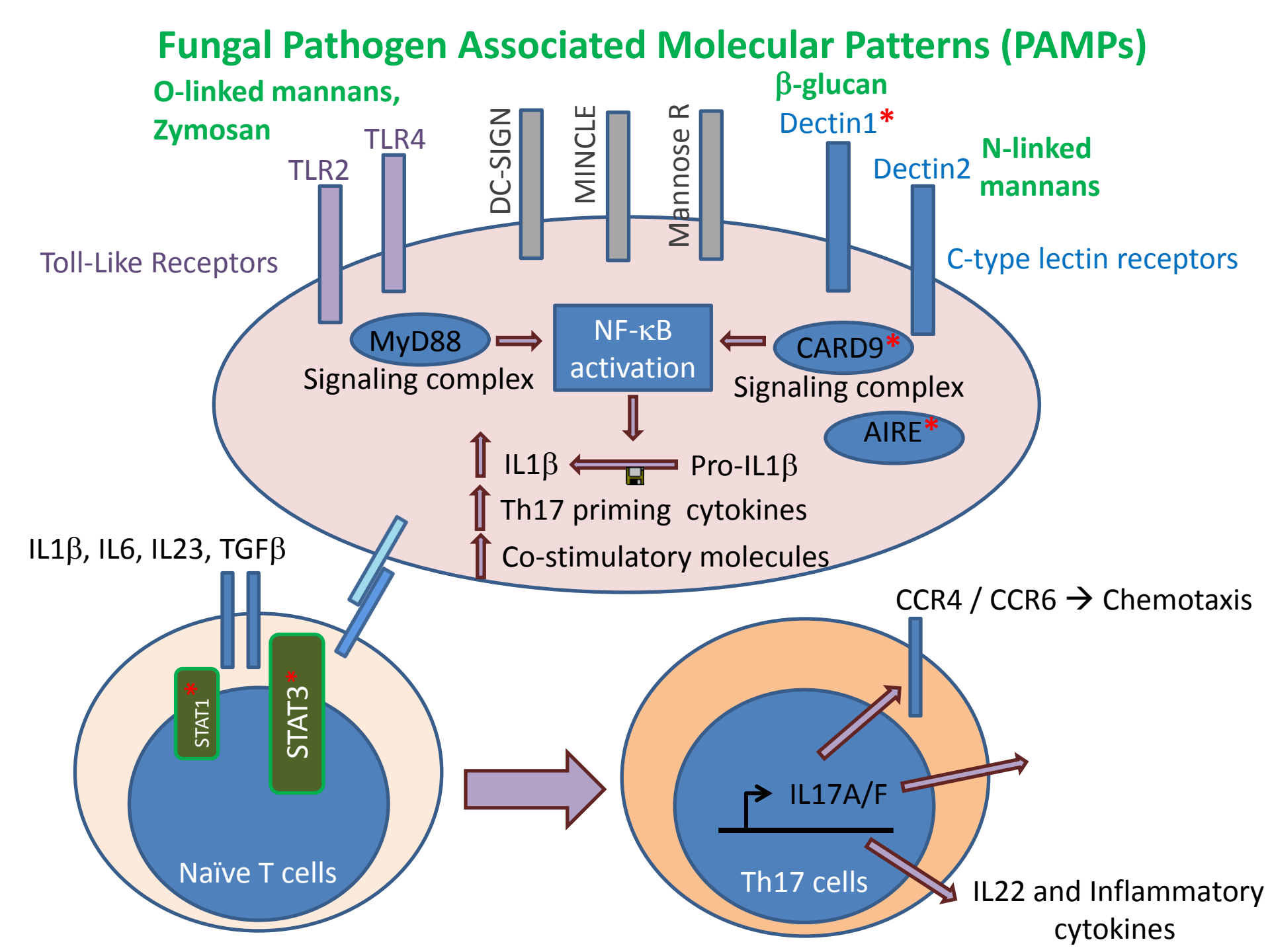
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IL1β, IL6, IL23, TGFβ
CCR4 / CCR6 → Chemotaxis
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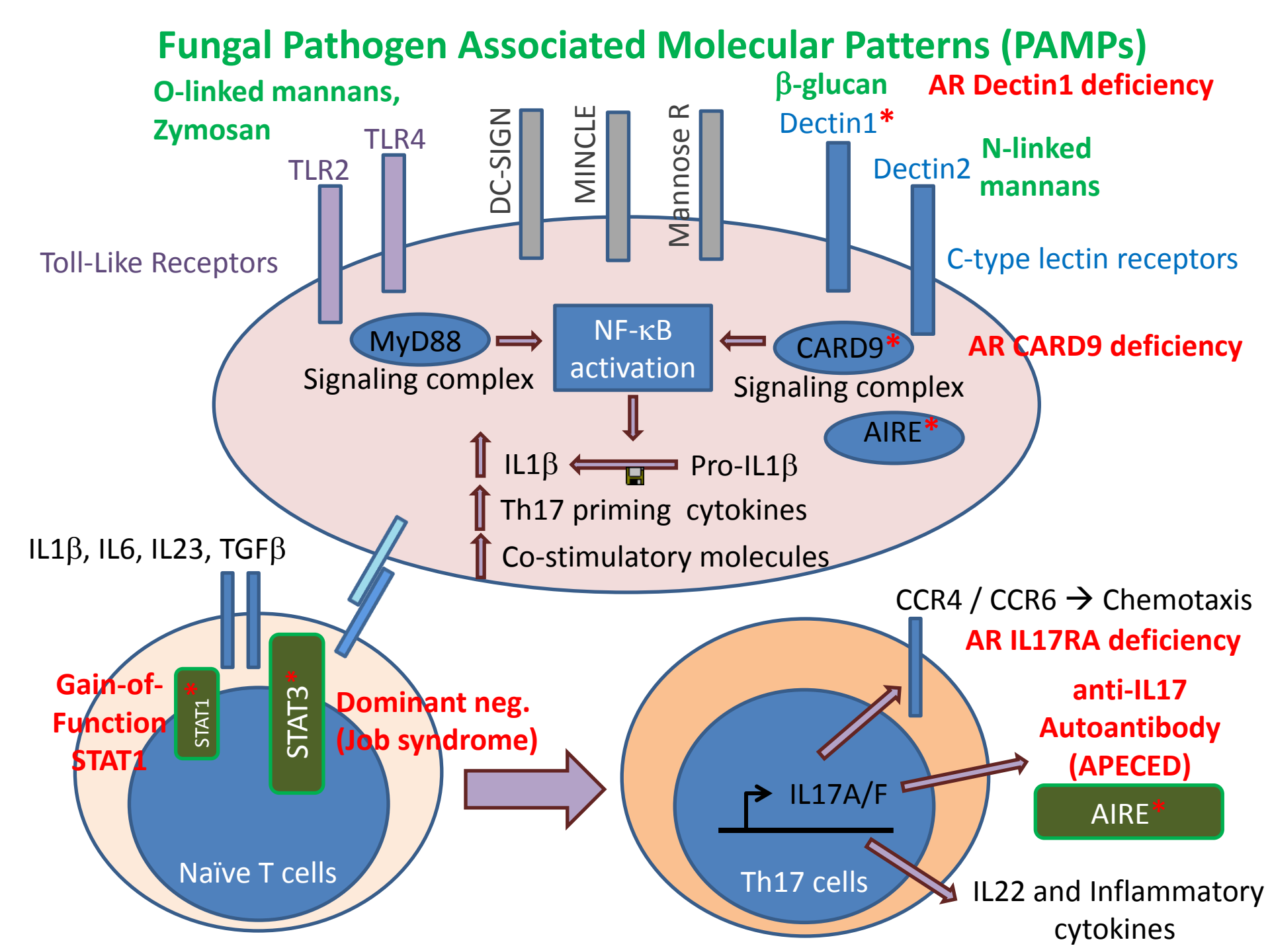
STAT3*
Naïve T cells
IL17A/F
Th17 cells
IL22 and Inflammatory
cytokines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IL1β, IL6, IL23, TGFβ
CCR4 / CCR6 → Chemotaxis
AR IL17RA deficiency
Gain-of-
Function
STAT1
STAT1*
STAT3*
Dominant neg.
(Job syndrome)
anti-IL17
Autoantibody
(APECED)
IL17A/F
AIRE*
Naïve T cells
Th17 cells
IL22 and Inflammatory
cytokines

Immunity to candida

- Gain-of-function STAT1 mutations:

  → dimorphic fungi: - coccidioidomycosis
  - histoplasmosis

- CARD9 deficiency:

  → increased risk of invasive candidiasis

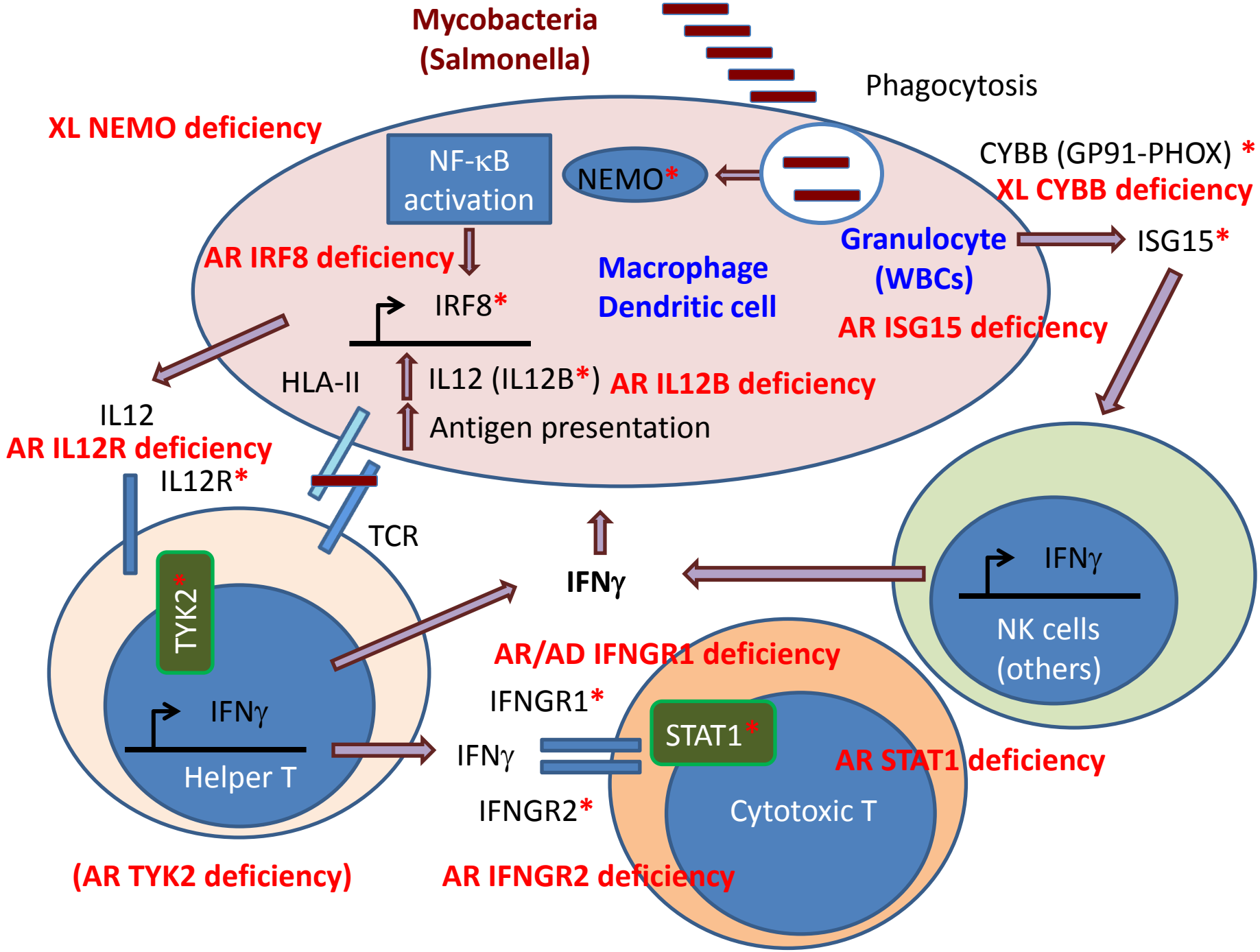
  (Candida dubliniensis meningoencephalitis)

(Sampaio EP et al. JACI 2013; Drewniak A et al. Blood 2013)

Mendelian susceptibility to mycobacterial disease

- Predisposition of otherwise apparently healthy individuals to infections caused by weakly virulent mycobacteria Bacille Calmette Guerin (BCG) and atypical (or nontuberculous) mycobacteria, *M. tuberculosis* and Salmonella
- Genes:
  - IFNGR1 (AR/AD)
  - IFNGR2 (AR)
  - STAT1 (AD)
  - IL12B (AR)
  - IL12RB1 (AR)*
  - NEMO (IKBKG) (XL)
  - CYBB (XL)
  - IRF8 (AR/AD)
  - ISG15 (AR)
  - TYK2 (AR)

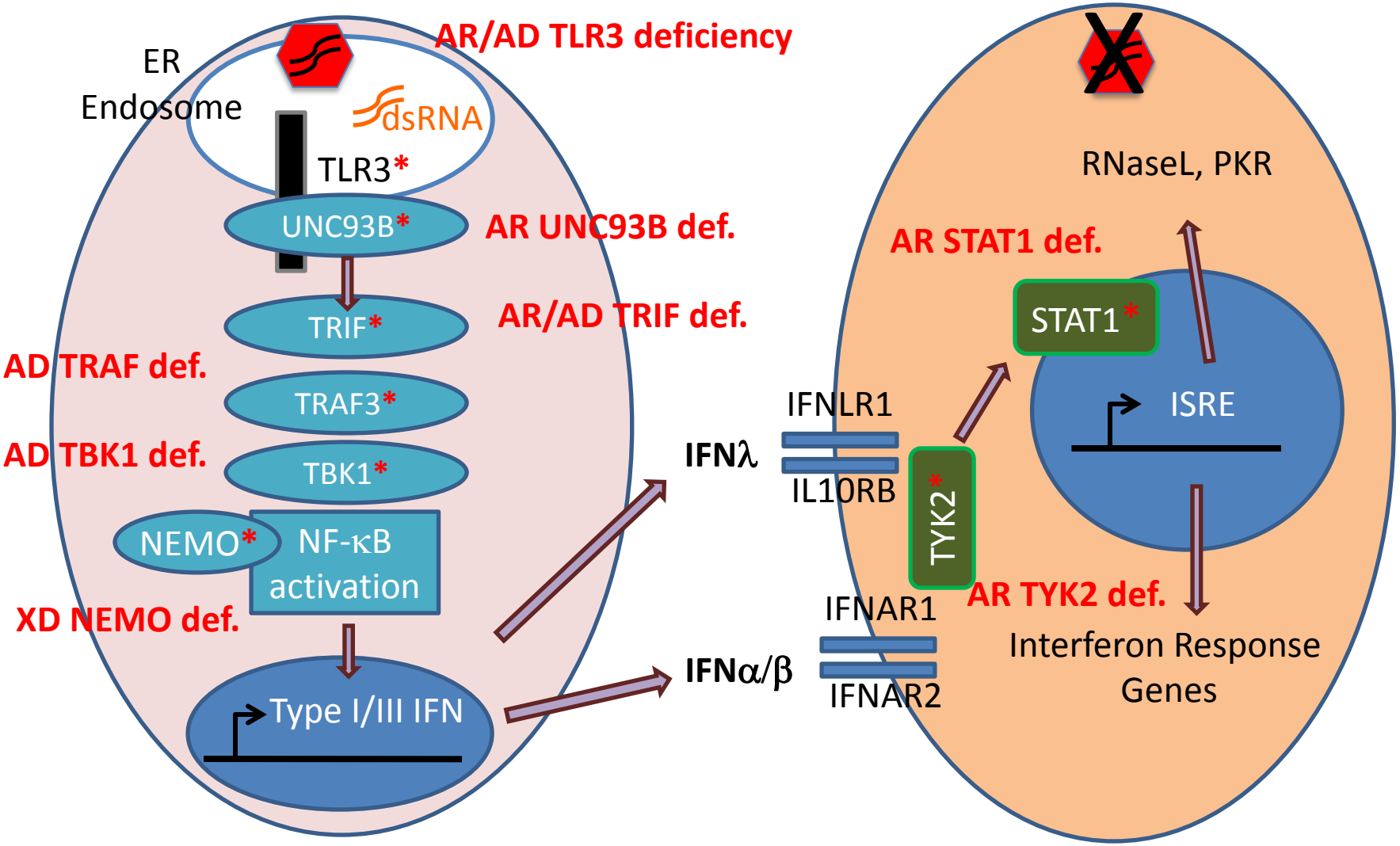
→ Impaired IFN-γ-mediated immunity (~50 % have unknown genetics)


Mycobacteria
(Salmonella)
Phagocytosis
XL NEMO deficiency
NF-κB
activation
NEMO*
CYBB (GP91-PHOX) *
XL CYBB deficiency
AR IRF8 deficiency
Granulocyte
(WBCs)
ISG15*
Macrophage
Dendritic cell
IRF8*
AR ISG15 deficiency
HLA-II
IL12 (IL12B*)
AR IL12B deficiency
Antigen presentation
IL12
AR IL12R deficiency
IL12R*
TCR
IFNγ
TYK2*
IFNγ
NK cells
(others)
AR/AD IFNGR1 deficiency
IFNGR1*
STAT1*
IFNγ
AR STAT1 deficiency
Helper T
IFNGR2*
Cytotoxic T
(AR TYK2 deficiency)
AR IFNGR2 deficiency

Herpes Simplex Encephalitis

- HSE is the most common cause of sporadic fatal encephalitis worldwide (70% mortality if untreated)
- Acyclovir
- Lifelong neurological sequelae of varying severity in survivors is common (>30%)
- Genes:
  - TLR3 (AR/AD)
  - UNC-93B (AR)
  - TRIF (AR/AD)
  - TRAF3 (AD)
  - TBK1 (AD)
  - NEMO (XR)
  - STAT1 (AR)
  - TYK2 (AR)

Herpes Simplex Encephalitis



Different genes – same/similar clinical phenotype

- **CMC:**

  - IL-17RA, IL-17F, STAT1, DECTIN1, CARD9, STAT3, DOCK8, AIRE

- **MSMD:**

  - IFNGR1, IFNGR2, STAT1, IL12B**,** IL12RB1, NEMO, CYBB, IRF8, ISG15, TYK2

- **HSE:**

  -TLR3, UNC-93B, TRIF, TRAF3, TBK1, NEMO, STAT1

→ Molecular networks/pathways, not genes

→ Single gene testing vs. gene panels

One gene – multiple phenotypes

- AD STAT1 deficiency: dominant negative mutations
  → susceptibility to mycobacterial and salmonella infections

- AD STAT1 deficiency: gain-of-function mutations
  → chronic mucocutaneous candidiasis

- AR STAT1 deficiency: loss-of-function mutations
  → susceptibility to severe viral and mycobacterial disease

Genetic susceptibility

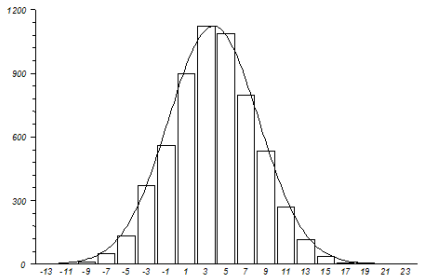
- Monogenic primary immunodeficiency diseases
  - Classic PIDs: opportunistic infections
  - Novel PIDs: restricted susceptibility/single organisms (e.g. HSE is genetic)

  → rare

- Immune response is a complex trait
  - complex traits (such as height and weight), arise from the combination of large number of (hundreds/thousands) of individual small genetic effects across the genome
  - Genome Wide Association Studies

  (GWAS) Increasing knowledge

  → Common (everybody!)



Genetic susceptibility

- Candida infections (Smeekens et al. 2013):
  - Dectin1 → Candida colonization
  - TLR1/2/3/4 → Susceptibility candidemia
  - IL4/MBL2/NLPR3 → Recurrent vulvo-vaginal candidiasis

- Tuberculosis susceptibility (Barreiro et al. 2012; Qu et al. 2011):
  - MSMD and TB: monozygotic/dizygotic twin studies
  - DUSP14 → pulmonary TB
  - HLA/NRAMP1/IFNG/IL12B/NOS2A

- Susceptibility to HSV encephalitis:
  - HSE (de Diego et al. 2013)
  - TLR3 variants → Resistance to HSV2 (Svensson et al. 2012)

→ Pathways

Genetic susceptibility

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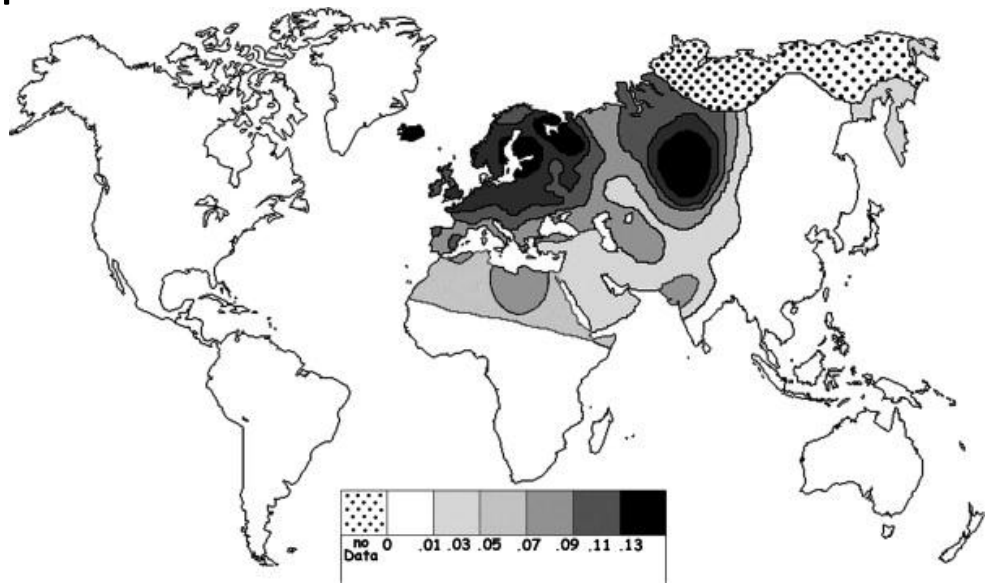
→ Pathways

Genetic susceptibility - Environment

- Genetic variants: ‘pathogenic’, ‘neutral’, ‘beneficial’
- HbS, HbC, and α-thalassemia → protection from malaria

- CCR5Δ32
  → Protection against HIV infection (Liu et al. 1996)
  → Increases risk of symptomatic West Nile virus infection (Glass et al. 2006)

→Europe 3-16%
allele frequencies
(south to north)



Faure & Royer-Carenzi 2008

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