Autoinflammatory Diseases – Periodic Fever Syndromes

Athens, April 30th 2010

Tim Niehues MD

Autoinflammatory Disease and Periodic Fever Syndromes

- Definitions
- Molecular Pathology and Classification
- Phenotype
- Challenges

Definition immune systems

- Adaptive immune system
  - Ability to adapt immunoglobulins and receptors postnatally by somatic mutation and gene rearrangement: Highly diverse repertoire and memory
  - **Dysregulation: Autoantibodies/Autoreactive T cells**
- Innate immune system
  - Inherited receptors on phagocytes, NK cells, complement
  - Phylogenetically ancient, hardwired, rapid-response system distinct from but, in mammals, intertwined with adaptive immunity
  - **Dysregulation: Autoinflammation**

Definition Autoinflammatory disease

is characterised by

- both mendelian and complex genetic variants of the innate immune system without high titer autoantibodies or antigen specific T cells
- seemingly unprovoked episodes of inflammation

Periodic Fever Syndromes

are characterised by

- self-limitig recurrent fever episodes
- symptomfree interval
- multisystemic Inflammation
- increased inflammatory parameters
- no infectuous agent

Provisional molecular/functional classification (Masters, 2009)

Type 1: Inflammasomopathies including Periodic Fever Syndromes

Type 2: NF-κB activation disorders

- Crohn's disease
  - *NOD2* (16p12), *ATG16L1*, *IRGM*
- Blau syndrome, FCAS2 (Guadaloupe periodic fever)
  - *NOD2, NLRP12* (NALP12)

Type 3: Protein folding disorders of the innate immune system

- TRAPSq
  - *TNFRSF1A* (TNFR1, p55, CD120a)

Type 4-6: Disorders of Complement, cytokine signalling, Macrophage activation

- Atypical HUS, Cherubism, Familial HLH

Unclassified

PFAPA, systemic onset Juvenile Idiopathic Arthritis

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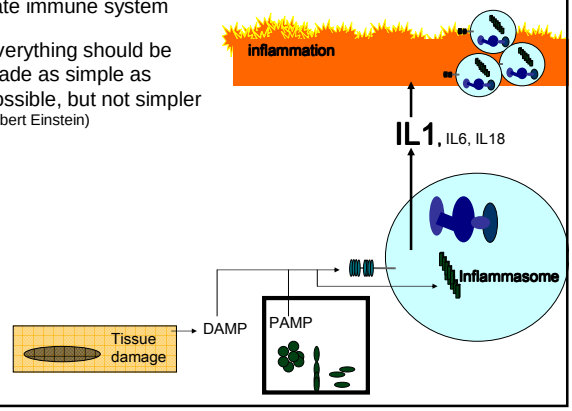
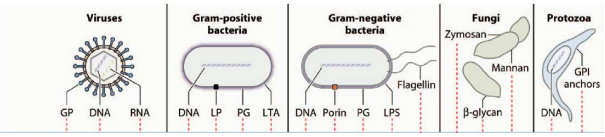
Innate immune system

- Everything should be made as simple as possible, but not simpler
(Albert Einstein)



Pathogen associated molecular patterns (PAMPs)



- **nucleic acids**, including DNA, dsRNA, ssRNA, and 5-triphosphate RNA
- **surface glycoproteins (GP)**
- **lipoproteins (LP)**
- membrane components (**peptidoglycans [PG], lipoteichoic acid [LTA], LPS, and GPI anchors**).

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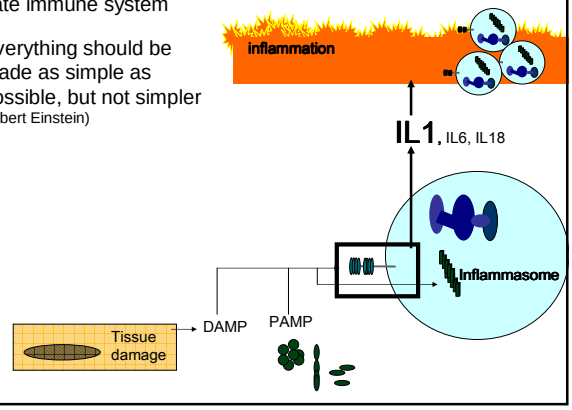
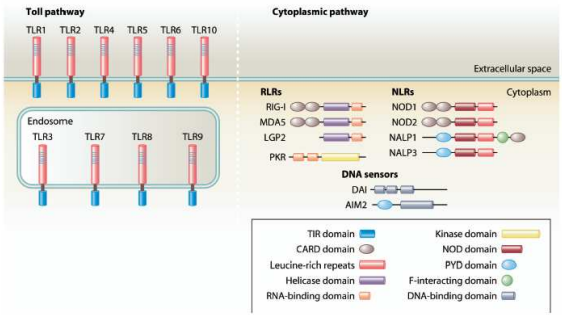


Pattern recognition receptors

- **TLR**s = Toll like receptors
- **RLR**s = Retinoid acid-inducible gene I (RIG-I)-like receptors
- **NLR**s =nucleotide-binding oligomerization domain (NOD)-like receptors
- **DNA sensors**, DAI (DNA-dependent activator of IFN-regulatory factors)

Pattern recognition receptors



Innate immune system

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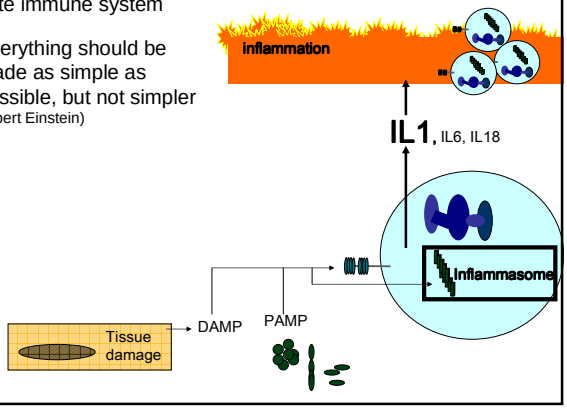
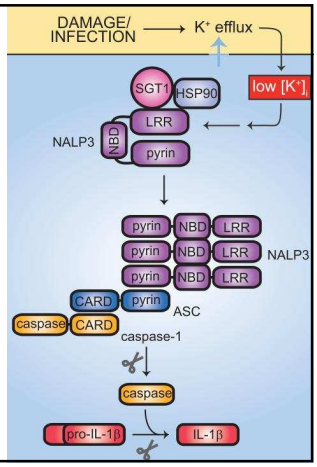


Inflammasomes

- Macromolecular complexes, that sense various microbial products and endogenous “danger signals” to activate caspase-1, thereby initiating IL-1β and IL-18 processing

IL-1β activation by the NRLP3 (NALP3) inflammasome

1. Autorepressed NRLP3
2. K+ efflux, low intracellular K+:
3. Dissociation of HSP90 and SGT1 from NALP3
4. NRLP3 recruits ASC
5. ASC recruits caspase 1
6. Caspase 1 cleaves pro-IL-1β



Inflammasomopathies

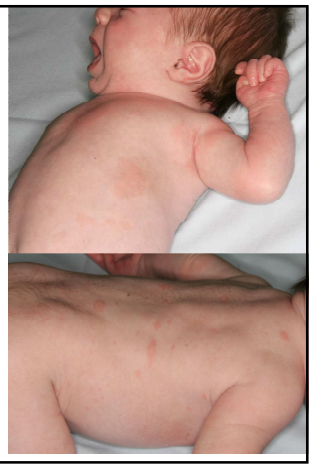
- Well-established autoinflammatory diseases
- caused by activating, gain-of-function mutations e.g in *NLRP3* (originally denoted *CIAS1* for cold-induced autoinflammatory syndrome 1)
- The NLRP3 inflammasome interacts with proteins mutated in other autoinflammatory diseases
  - Pyrin in FMF

Autoinflammatory Disease and Periodic Fever Syndromes

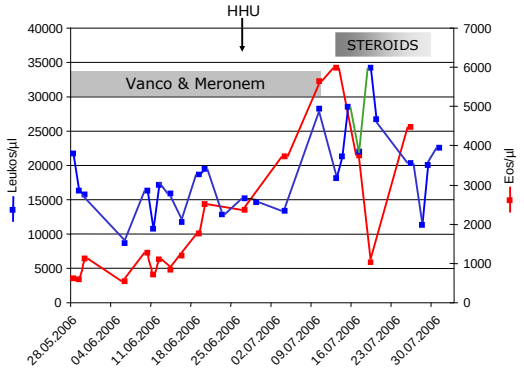
- Definitions
- Molecular Pathology and Classification
- Phenotype
- Challenges

Georgios, 2 month-old

- From birth on continuous fever episodes
- Drug history: Many antibiotics, Fluconazole
- Urticaria in changing locations
- Leucocytes: 20.000-40000. Elevated inflammation markers (e.g. CRP)



Differential blood count: Hypereosinophilic syndrome



Georgios, 3 month-old

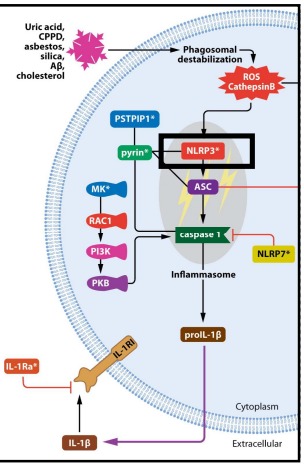
- No effect of antibiotics
- Steroid dependent

➢ Anakinra (IL1 Receptor antagonist)

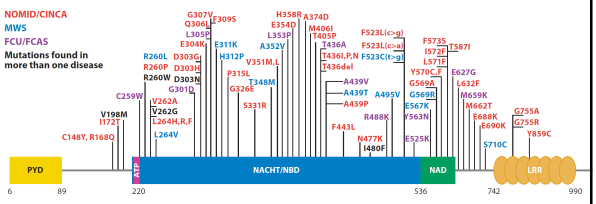
- Fever and inflammation gone for good…..
- Mutation in *NLPR3*

NLRP3 (NALP3; cryopyrin) Inflammasome

- **CAPS, :** cryopyrin associated periodic syndrome =**cryopyrinopathy**
- caused by autosomal dominant de novo mutations in *NLRP3*



NLRP3

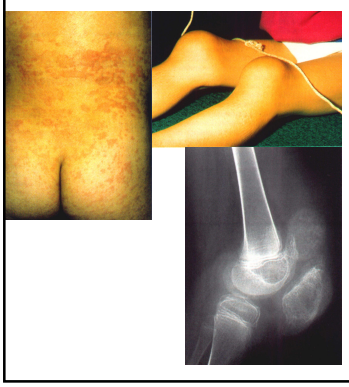


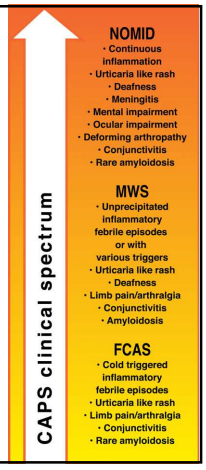
Chronic infantile neurological cutaneous and articular- Syndrom (**CINCA**)= Neonatal onset multisystem inflammatory Disease (**NOMID**)

Familiäres kälteinduziertes autoinflammatorisches Syndrom (**FCAS**)

Muckle-Wells Syndrom (**MWS**)

Spectrum cryopyrinopathies (CPAS)

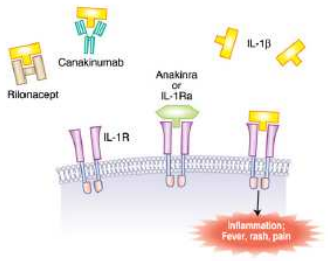




Response to IL1 blocking therapy can be dramatic

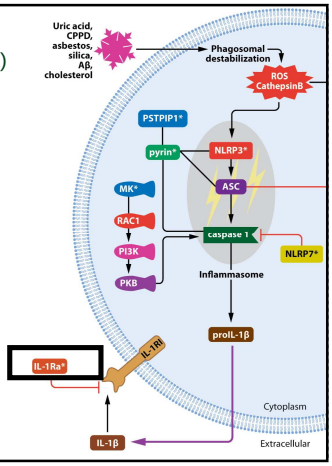
End-organ damage	Preventable Partially reversible if damage not permanent Further progression is halted
Amyloidosis in 30%	Yes*
Retinal scarring, corneal clouding	Yes*
Progressive optic nerve atrophy	Yes*
Progressive permanent hearing loss	Yes*
Hydrocephalus, brain atrophy, cognitive impairment	Leptomeningitis is fully reversible, hydrocephalus only when treated early, evidence of halting further progression is emerging
Deformities, contractures	Maybe preventable with early treatment, but once a lesions is formed, progression is not halted with treatment.

Mechanisms of IL-1–targeted therapy

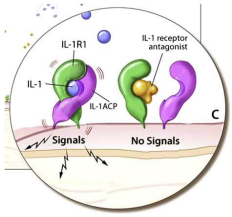


Deficiency of IL-1 receptor antagonist (DIRA)

- homozygous mutations in *IL1RN*

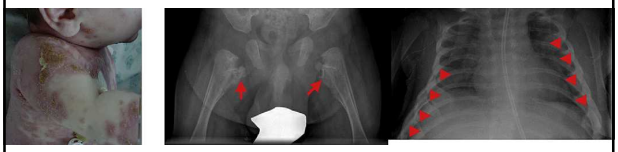


What if IL1RA is lacking? Continuous IL1 Signalling



- IL-1a and IL-1b can bind to the IL-1R1 receptor, which recruits the accessory receptor (IL-1ACP)
- However, binding of IL-1Ra to the IL-1R1 receptor inhibits IL-1 binding and does not allow for association with the accessory receptor

DIRA: Deficiency of IL-1 receptor antagonist



- pustular rash on the neck, arm, and trunk
- heterotopic bone formation and periosteal elevationon the proximal femurs bilaterally (red arrows).
- pathognomonic widening of multiple anterior ribs in a neonate (red arrowheads)
- No CNS involvement (as opposed to CINCA)

Familial Mediterranean Fever (FMF)

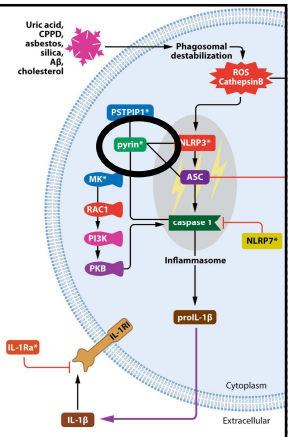
•Pyrin (= TRIM20) part of a larger family termed the TRIpartite Motif (TRIM) proteins

loss of function mutations with recessively inherited disease ??

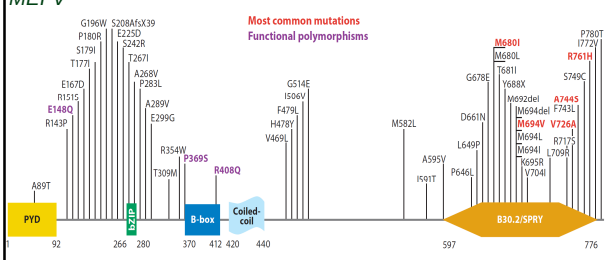
➢Antiinflammatory effect of wild-type pyrin

gain-of-function mutations with dominantly inherited disease ??

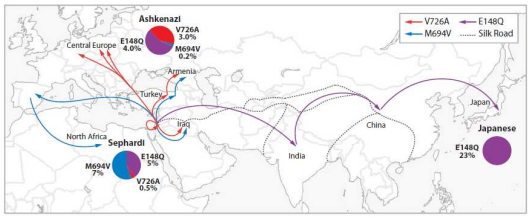
➢proinflammatory role of wild-type pyrin



MEFV



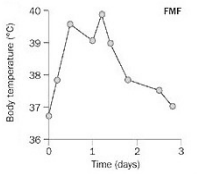
Geographical distribution

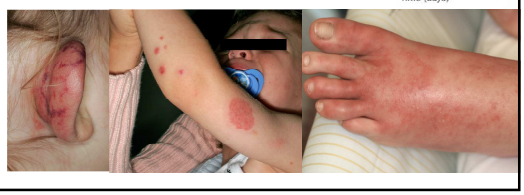


- TRIM family proteins exhibit the ability to affect the retroviral life cycle
- Hypothesis: TRIM proteins confer innate immune resistance to retroviruses

Familial Mediterranean Fever (FMF)

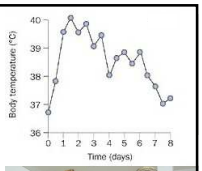
- Age: 5 years (90% < 20 years)
- Peritonitis, serositis
- Synovitis, asymmetric arthritis
- Erysipeloid efflorescences,
- Henoch Schönlein Purpura, Polyarteriitis nodosum

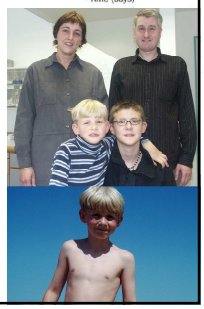




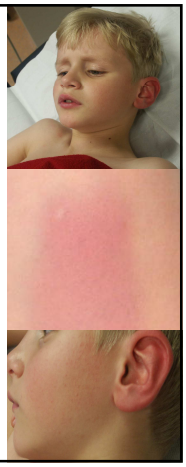
Nicolai, 10 years

- Since newborn age 40-41° C in weekly to monthly intervals (every 2-12 weeks); duration 3-5 days
- Pharyngitis, feinfleckiges Exanthem an Armen, Oberschenkel, Füßen, Fußsohlen und im Gesicht, Kopf-, Bauchschmerzen, Myalgien und Arthralgien
- Leucocytosis, raised ESR, CRP





Nicolai



IgD 665 mg/dl = 475 U/ml

(Normal <100 U/ml)

•Mevalonic acid in urine: 0,8 mmol/mol Creatinine

(Normal <0,29 mmol/mol)

Homozygous mutation Valin $_{377}$ → Isoleucin in Exon 11 of the Mevalonatkinase gene *MVK*

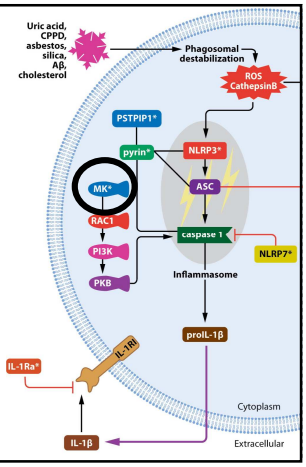
Mevalonate Kinase Deficiency Hyper IgD Syndrome

Classic type: MVK < 30% activity

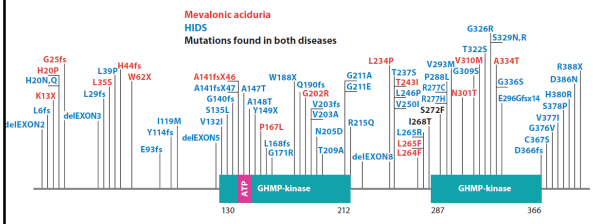
Mevalonic aciduria= MVK < 1% activity

(Dysmorphia, Dystrophy, psychomotor Delay, cerebellar ataxia, cataract)

Isoprenoid deficiency activates Rac1, PI3K, PKB and thus caspase 1



Mevalonate Kinase *MVK*



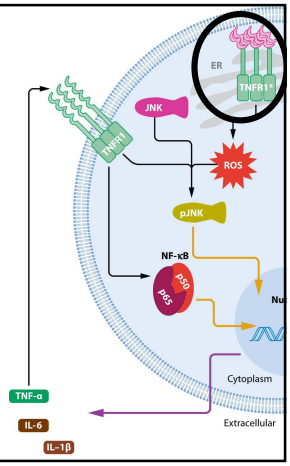
Autosomal recessive, most common: V377I

Geographical distribution: Northwestern Europe (Netherlands, France)

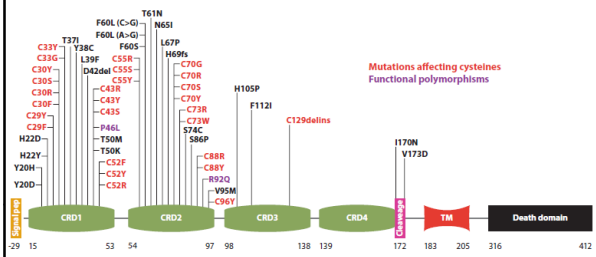
TRAPS (TNF receptor associated periodic syndome)

- Dominantly inherited heterozygous missense mutations, gain of function?
- Shedding hypothesis unlikely

- Mutations cause
  - TNFR1 to aggregate
  - inhibit TNFR1 trafficking to the cell membrane
  - JNK activation



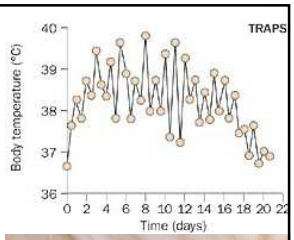
TNFRSF1A (TNF receptor Type I)

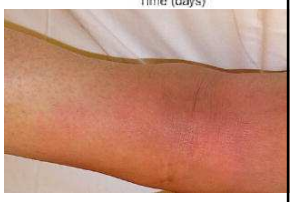


- affect almost every cysteine residue within the first two cysteine-rich domains of the extracellular region of the protein (*red*): **Protein folding affected**.
- I170N and V173D, can affect ectodomain cleavage that generates the soluble form of the receptor.

TRAPS

- Painful Erythemas
- Conjunctivitis, periorbital edema 80%
- Migratorischy exanthemas 60%
- Colicky abdominal pain





Summary I

- Severe enough to cause illness, but not so severe as to be embryonic lethal
- NLR proteins monitor homeostatic pathways that can be perturbed by individual PAMPs or DAMPs to trigger activity of the inflammasome.
- IL-1β occupies a special place
  - unique in the ability to trigger innate immunity without major provocation of the adaptive immune system
  - blockade highly succcessful

Summary II

Clinical clues

- Cryopyrinopathies (MWS, CINCA): urticaria-like rash, deafness, blindness
- FMF: Erysipelas like erythema
- Hyper IgD/Mevalonate Kinase deficiency: early age, Lymphadenopathy, Splenomegaly
- TRAPS: long attacks >1week, periorbital edema, conjunctivitis

Treatment

	Clinical studies (adults/children)	No. of patients
Hereditary fever disorders		
FMF	Colchicine-controlled trials, adults[8-10]	>100
	Colchicine open-label trials, children[11,12]	>100
	Anakinra case reports, both[20-25]	<10
	Rilonacept trial in progress	
TRAPS	Etanercept small trials, both[7,13]	>10
	Anakinra case reports, both[14,29,30]	<10
Hyper-IgD syndrome with periodic fever	Anakinra case reports, both[26-28]	<10
CAPS		
FCAS	Anakinra open-label trials, both[16,17]	>10
	Rilonacept controlled trials, both[18]	<100
	Canakinumab controlled trials, both[19]	<100
MWS	Anakinra open-label trials, both[16]	>10
	Rilonacept controlled trials, both[18]	<10
	Canakinumab controlled trials, both[19]	>10
NOMID	Anakinra open-label trial, children[15]	>10
	Canakinumab trials in progress	

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- Definitions
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To be explored

- The underlying genetic basis and pathophysiologic mechanisms for many inherited autoinflammatory syndromes
- Specific mechanisms underlying the activation of the inflammasome
- The long-term efficacy and safety of IL-1–targeted therapies
- The role of novel upstream and downstream inflammasome-targeted therapies in the future

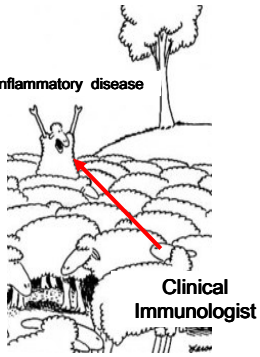
Recurrent fever

Presentation

Clinical score
Tel-Hashomer, Gattorno

Lab tests?
Lab tests!

Molecular genetics



Excellent Reviews

- Goldbach-Mansky, JACI 2009
- Hoffman, JACI 2009
- Morgensen, Microbiology Reviews 2009
- Masters, Ann. Rev. Immunol., 2009
- Rigante, Europ. Rev. Med. Pharmacolog. Sc., 2010

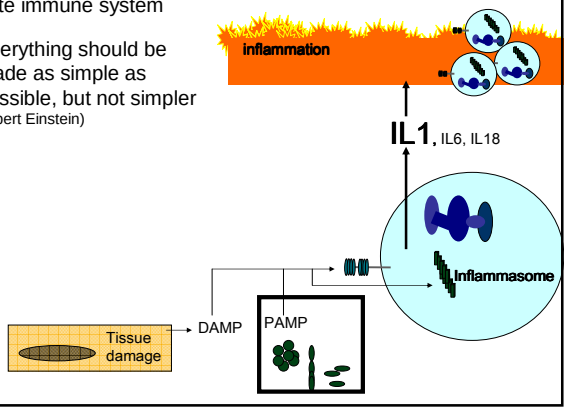
HELIOS Kliniken

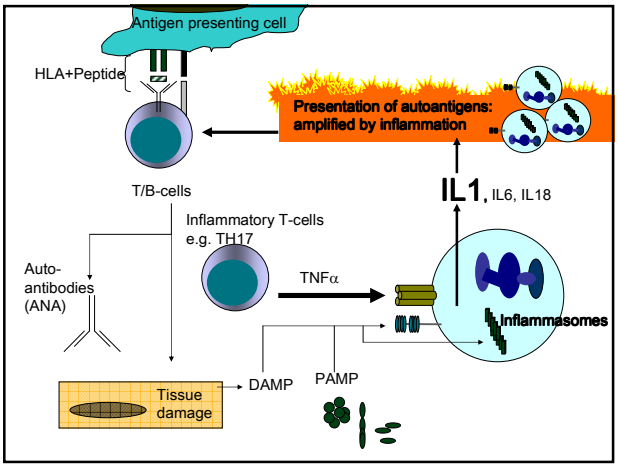
Efcharisto! Vielen Dank!

HELIOS Klinikum Krefeld, Germany
Krefeld Immunodeficiency Centre KIDZ
www.helios-kliniken.de

Innate immune system

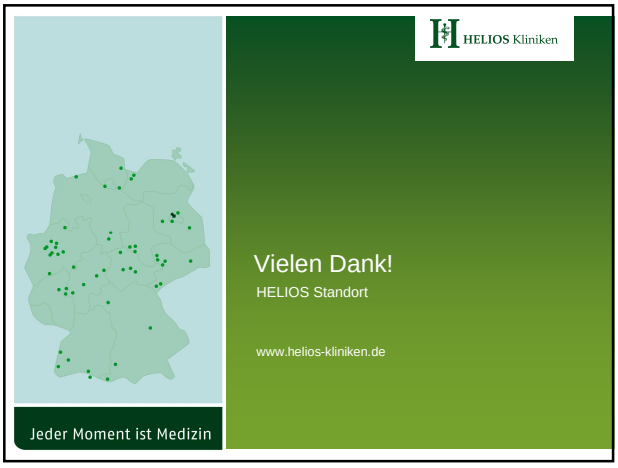
- Everything should be made as simple as possible, but not simpler
(Albert Einstein)





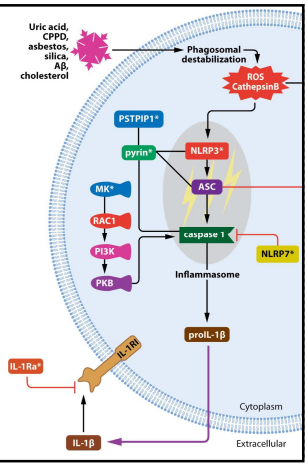
Innate immune system and Autoimmunity: seperate?

- association of *NLRP1* with vitiligo, and a range of other autoimmune diseases
- *NLRP1* is highly expressed in T cells,
- Allogeneic stem cell transplantation, recipient variants in *NLRP1*, as well as donor variants at *NLRP2* and *NLRP3*, have been shown to be important prognostic factors
- Variants at another *NLR* gene *NOD2/CARD15*, in both donor and recipient are associated with graft-versus-host disease and mortality



Extrinsic

- recurrent arthritis, sterile but purulent synovial fluid,
- pyoderma gangrenosum (large,open purulent lesions)
- severe cystic acne
- dominantly inherited mutations of CD2-binding protein 1 (CD2BP1) = **proline serine threonine phosphatase-interacting protein 1 (PSTPIP1),**



Pyogene sterile Arthritis, Pyoderma gangrenosum, Akne

http://dermnetnz.org

- recurrent arthritis, sterile but purulent synovial fluid,
- pyoderma gangrenosum (large,open purulent lesions)
- severe cystic acne
- dominantly inherited mutations of CD2-binding protein 1 (CD2BP1) = proline serine threonine phosphatase-interacting protein 1 (PSTPIP1),