Doenças Autoinflamatórias

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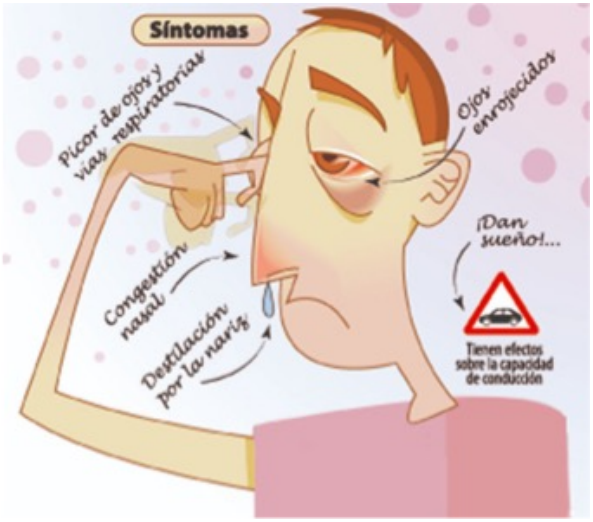
Disciplina BMI 102

Instituto de Ciências Biomédicas - USP / 2025

Hipersensibilidade

Resposta imune exagerada contra antígenos e que envolvem Patologias Complexas

Mediada pelo Sistema Imune Adaptativo



AUTOIMUNIDADE

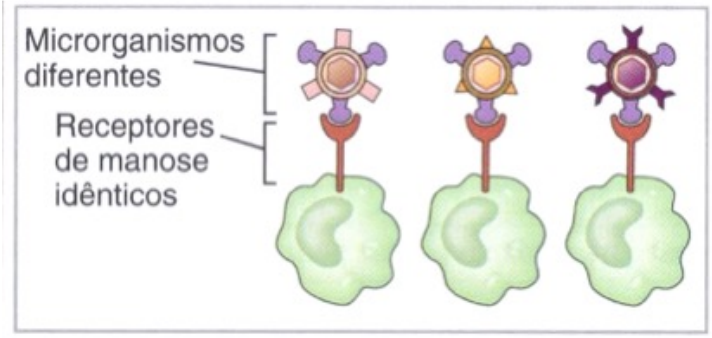
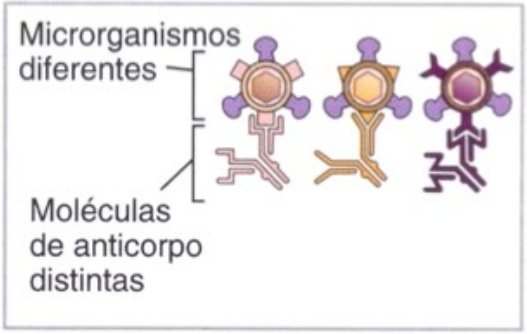
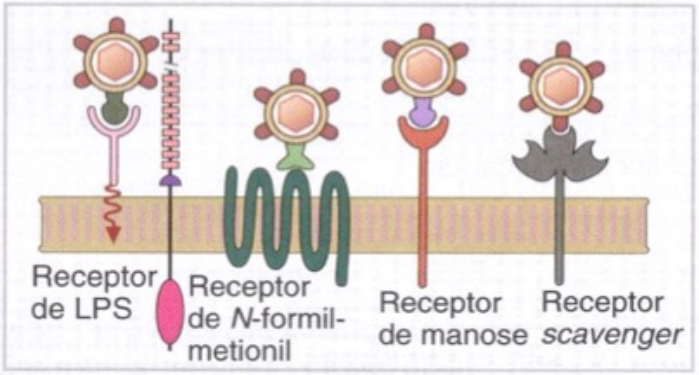
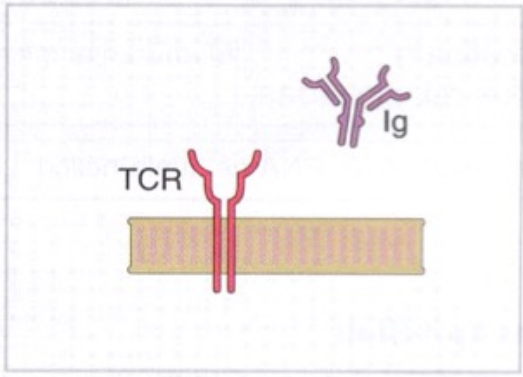
Doenças Autoimunes x Autoinflamatórias

Doenças Autoimunes são desordens sistêmicas originadas no Sistema Imune Adaptativo

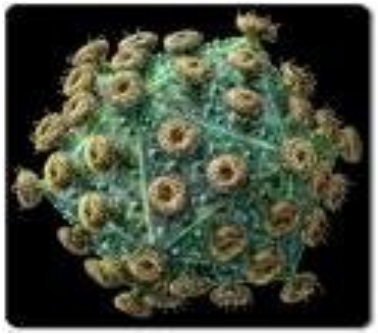
Respostas de linfócitos T ou B tecido-específicos

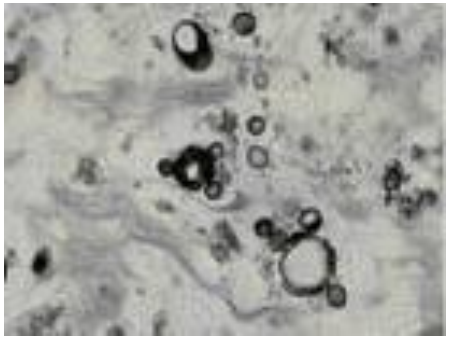
Doenças Autoinflamatórias são geradas a partir de desregulação nos mecanismos da Imunidade Inata

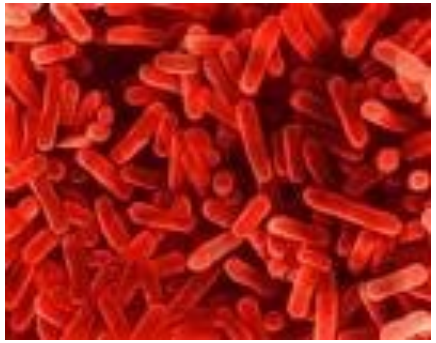
Ativação descontrolada de receptores da imunidade inata

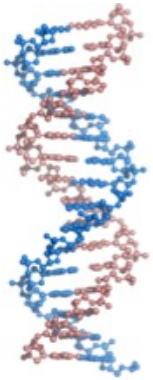
	Imunidade Inata	Imunidade Adaptativa
Especificidade	Padrões moleculares 	Detalhes estruturais 
Diversidade	Codificados na linhagem germinativa Diversidade limitada (10^3)	Codificados por genes que sofrem rec. somática grande diversidade (10^7-10^9)
Distribuição receptores	 Não clonal, receptores iguais em todas as células de uma linhag.	 clonal, cada clone de linfócito tem especificidade diferente
Discriminação próprio	Sim, células próprias não são reconhecidas ou apresentam mecanismos de prevenção	Sim, por seleção contra antígenos próprios (pode ser Imperfeita)
Especialização	++	+++
Memória	-/+	+++
Auto-limitação	+	+++

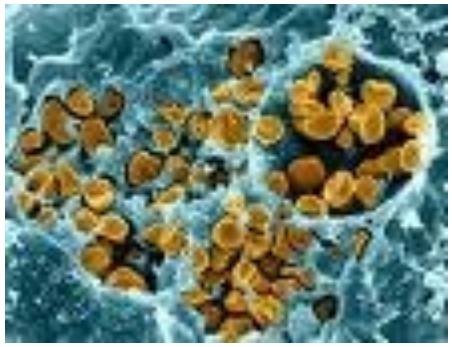
Receptores da Imunidade Inata

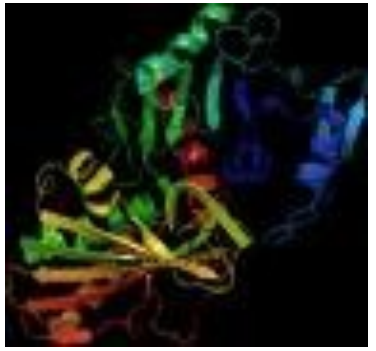












Solúveis

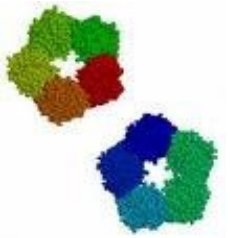
Associados a membrana

Intra-citoplasmático

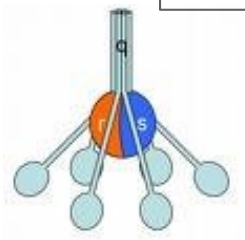
Receptores da Imunidade Inata

- Determinados na linhagem germinativa
- Especificidade limitada
- Reconhecem padrões moleculares conservados associados aos patógenos (PAMPs) ou ao dano celular (DAMPs)

PCR



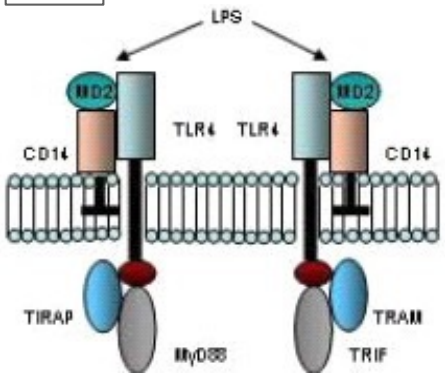
C1q



MBL

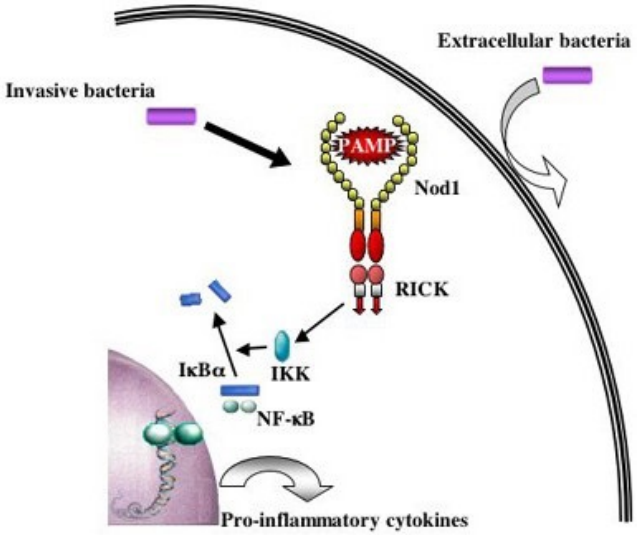
Solúveis

TLR

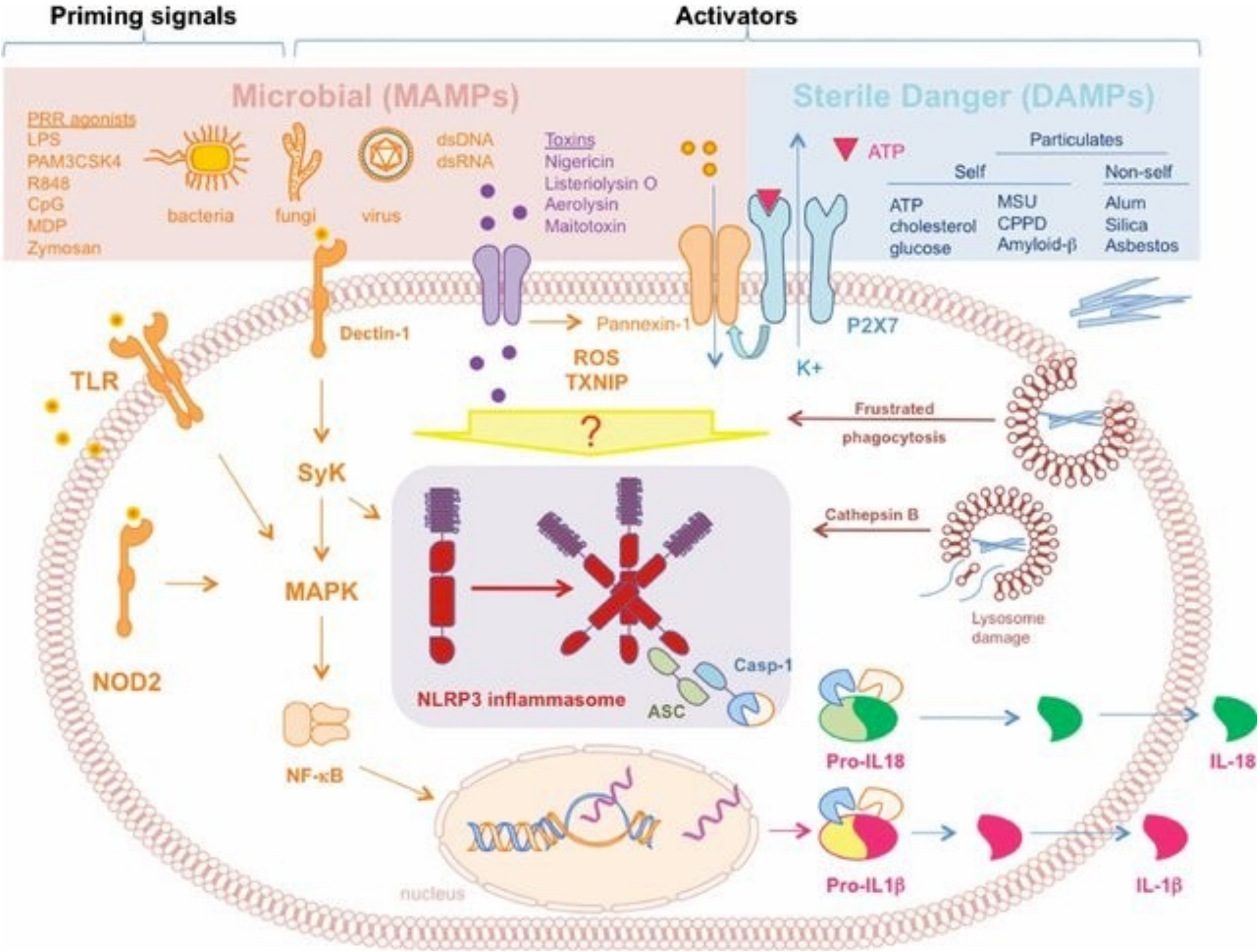


Associados a membrana

NOD



Intra-citoplasmático


Priming signals
Activators
Microbial (MAMPs)
Sterile Danger (DAMPs)
PRR agonists
LPS
PAM3CSK4
R848
CpG
MDP
Zymosan
bacteria
fungi
virus
dsDNA
dsRNA
Toxins
Nigericin
Listeriolysin O
Aerolysin
Maitotoxin
ATP
Particulates
Self
Non-self
ATP
cholesterol
glucose
MSU
CPPD
Amyloid-β
Alum
Silica
Asbestos
Dectin-1
TLR
Pannexin-1
ROS
TXNIP
P2X7
K+
?
Frustrated
phagocytosis
SyK
MAPK
NOD2
NF-κB
Cathepsin B
Lysosome
damage
NLRP3 inflammasome
ASC
Casp-1
Pro-IL18
IL-18
nucleus
Pro-IL1β
IL-1β

Propriedades das Doenças Autoinflamatórias

Doenças “raras”, de difícil diagnóstico;

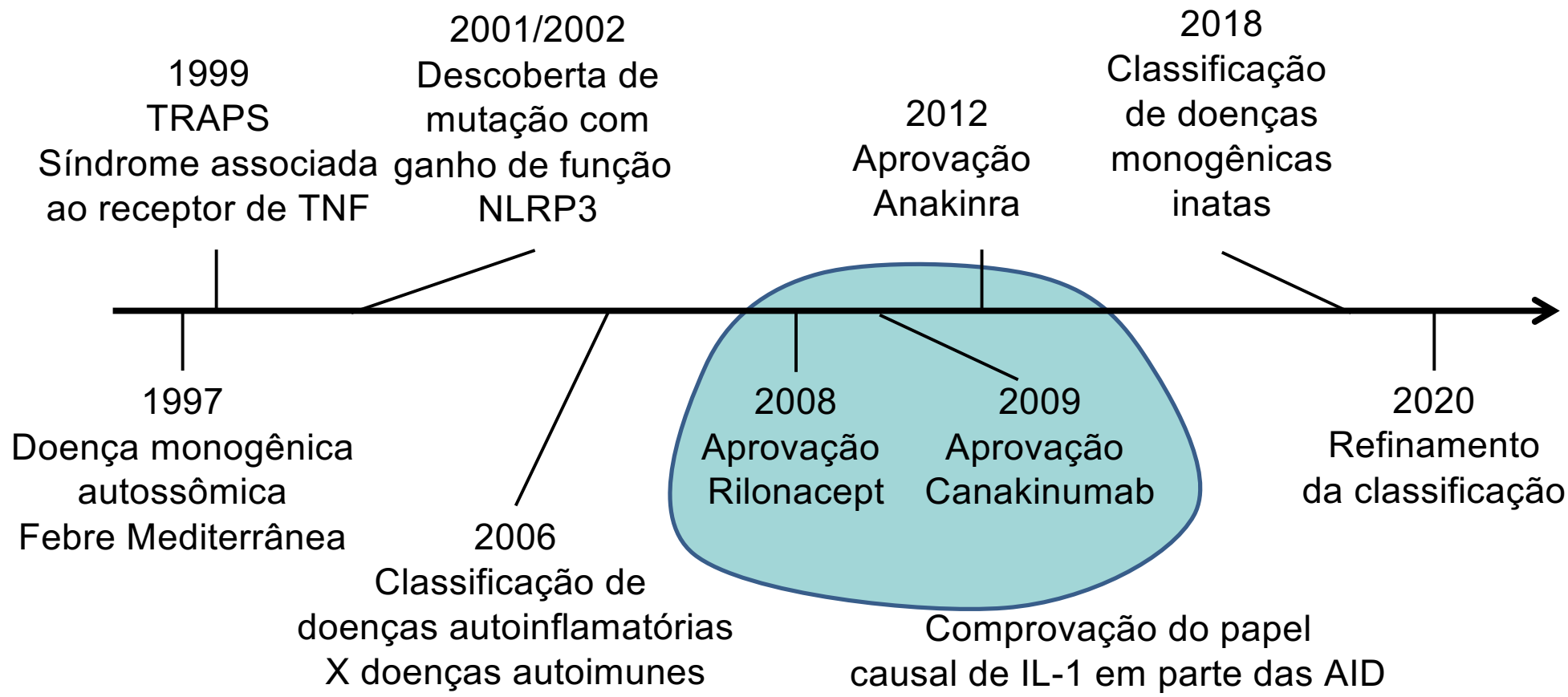
Inflamação **estéril**: persistente ou recorrente não explicada por infecções ou câncer ou outra causa;

Febre, irritação na pele, inflamação da pleura ou peritôneo, artrite, meningite, uveite, enterocolite, acidence vascular e hemorragia, vasculite, cacificação de estruturas do SNC;

Pode haver linfoanenopatia ou esplenomegalia;

Níveis elevados de proteína C reativa, taxa de sedimentação de eritrócitos aumentanda durante os surtos;

Não se observa, em geral, relação com MHC, e não se observa acúmulo de autoanticorpos.



Medicamento	Tipo	Alvo principal	Como age
Anakinra	Antagonista do receptor	IL-1α e IL-1β	Compete com a IL-1 no receptor (bloqueia os dois tipos)
Canakinumabe	Anticorpo monoclonal	IL-1β	Neutraliza seletivamente a IL-1β
Rilonacepte	Receptor-armadilha (proteína de fusão)	IL-1β (e IL-1α em menor grau)	"Captura" IL-1 no sangue antes de alcançar os receptores

TRAPS: TNF receptor–associated periodic syndrome

Inflammasomopathies
Interferonpathies
NF-κB-opahties
Cytoskelopathies
Enzymatic deficiencies
Others

Table 1. Heat map of autoinflammatory syndromes discussed in the main text.

Category	Autoinflammatory Condition	Gene	Clinical Features: Fever	Joint	Rash	Ulcer	Eye	GI	CNS	Vasculitis	Lung	Bone	HLH	Infection	Lipodystrophy	Thrombocytopenia	DD	Other
Inflammasomopathies	FMF	*MEFV*																
	PAPA	*PSTPIP1*																
	CAPS	*NLRP3*																
	Majeed syndrome	*LPIN2*																Anemia
	NLRP12-related AID	*NLRP12*																
	DPP9 deficiency[a]	*DPP9*																Eczema, allergies, fair hair, short stature, dysmorphic
	PMVK-related AID[a]	*PMVK*																Lymphoma, elevated IgD
IL-1 pathway	DIRA	*IL1RN*																
IL-18 pathway	AIFEC	*NLRC4*																
	FCAS4	*NLRC4*																
	X-linked proliferative disease 2	*XIAP*																
	IL-18BP deficiency	*IL18BP*																Viral hepatitis
	NLRP1-associated autoinflammation with arthritis and dyskeratosis	*N LRP1*																Dyskeratosis
Interferonopathies	AGS	*TREX1, SAMHD1, RNASEH2A, RNASEH2B, ADAR1, IF1H1*																Hepatitis, chilblains
	STAT2 gain-of-function disease	*STAT2*																Brain calcifications
	Pseudo-TORCH	*USP18*																Brain calcifications
	SAVI	*TMEM173*																
	SMS	*IFIH1, DDX38*																Dental dysplasia, aortic calcification
	PRAAS	*PSMB4, PSMA3, POMP, PSMG, PSMB8, PSMB9*[a]*, PSMB10*																
	COPA syndrome	*COPA*																Kidney dysfunction
	OPAID[a]	*OAS1*																FTT
	ATAD3A deficiency[a]	*ATAD3A*																Dystonia, thyroiditis, calcifications, HCM
	ZNFX1 deficiency[a]	*ZNFX1*																Renal disease
NF-κB–opathies	Haploinsufficiency of A20	*TNFAIP3*																
	RAID	*RELA*																
	RIPK1 deficiency	*RIPK1*																
	RIPK1 gain-of-function	*RIPK1*																
	Otulipenia	*FAM105B*																Lymphadenopathy
	Blau syndrome	*NOD2*																Sarcoidosis
	CARD14-mediated pustular psoriasis	*CARD14*																
	SYK-associated AID[a]	*SYK*																Lymphoma
	TBK1 deficiency[a]	*TBK1*																Short stature
	DEX[a]	*ELF4*																Perianal abscesses
	ROSAH[a]	*ALPK1*																Splenomegaly, anhidrosis
	NDAS[a]	*IKBKG*																Panniculitis
Cytoskelopathies	NOCARH	*CDC42*																
	ARPC1B deficiency	*ARPC1B*																
	NCKAP1 deficiency	*NCKAP1*																
	PFIT	*WDR1*																
Enzymatic deficiencies	MKD	*MVK*																Elevated IgD
	DADA2	*CECR1*																
	SIFD	*TRNT1*																Sideroblastic anemia
	PLAID	*PLCG2*																
	APLAID	*PLCG2*																
Other	TRAPS	*TNFRSF1A*																
	VEXAS	*UBA1*																Deep vein thrombosis
	C2orf69 deficiency[a]	*C2orf69*																Hypomyelination, microcephaly, DWS, FTT
	HCK-associated AID[a]	*HCK*																Hepatosplenomegaly
	IL-33 gain-of-function[a]	*IL33*																Eosinophilic dermatitis, IgE
	STAT6 gain-of-function[a]	*STAT6*																IgE, allergy
	DPM[a]	*STAT4*																Poor wound healing, hypogammaglobulinemia
	LAVLI[a]	LYN																Hepatosplenomegaly

Autoinflammatory syndromes are arranged by pathway with colored boxes representing main clinical features. It is important to note that many conditions may fall into multiple categories and that this heat map is a representation of the predominant mechanism at play. [a] Conditions discovered since 2021. AGS: Aicardi-Goutières syndrome; AID: autoinflammatory disease; AIFEC: autoinflammation with infantile enterocolitis; APLAID: autoinflammation and PLAID; CAPS: cryopyrin-associated periodic syndrome; CNS: central nervous system; COPA: coatomer protein subunit alpha; DADA2: deficiency of adenosine deaminase 2; DD: developmental delay; DEX: deficiency of ELF4, X-linked; DIRA: deficiency of IL-1 receptor antagonist; DPM: disabling pansclerotic morphea; DWS: Dandy-Walker syndrome; FCAS4: familial cold autoinflammatory syndrome 4; FMF: familial Mediterranean fever; FTT: failure to thrive; GI: gastrointestinal; HCM: hypertrophic cardiomyopathy; HLH: hemophagocytic lymphohistiocytosis; IL: interleukin; LAVLI: Lyn kinase–associated vasculopathy and liver fibrosis; MKD: mevalonate kinase deficiency; NDAS: NEMO deleted exon 5 autoinflammatory syndrome; NF: nuclear factor; NOCARH: neonatal onset of pancytopenia, autoinflammation, rash, and hemophagocytosis; OPAID: *OAS1*-associated polymorphic autoinflammatory immunodeficiency disorder; PAPA: pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; PFIT: periodic fevers, immunodeficiency, thrombocytopenia; PLAID: *PLCG2*-associated antibody deficiency and immune dysregulation; PRAAS: proteosome-associated autoinflammatory syndromes; RAID: *RELA*-associated inflammatory disease; ROSAH: retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and migraine headaches; SAVI: stimulator of IFN genes–associated vasculopathy with onset in infancy; SIFD: sideroblastic anemia, immunodeficiency, fevers, and developmental delay; SMS: Singleton-Merton syndrome; STAT: signal transducer and activator of transcription; TORCH: toxoplasmosis, other, rubella, cytomegalovirus, and herpes simplex; TRAPS: tumor necrosis factor receptor–associated periodic syndrome; VEXAS: vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

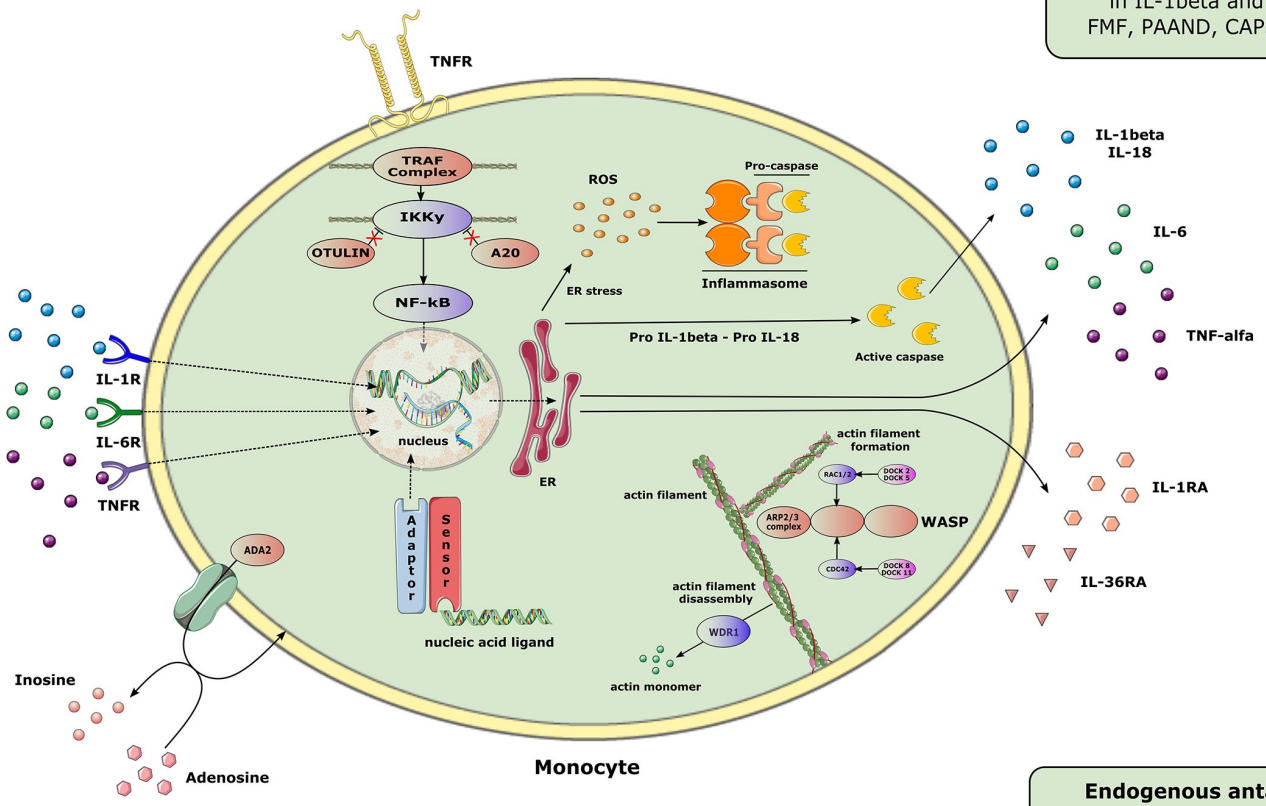
Jason An et al. J Rheumatol 2024;51:848-861

ER stress *
Defective post-tranlational modification or protein misfolding generates ER stress and results in ROS and IL-1beta production
TRAPS

NF-kB-related disorders *
NF-kB pathway activation through ubiquitination disorders or dysregulated NOD2 signaling.
HA20, ORAS, LUBAC deficiency, CRIA

Inflammasomopathies *
Gain-of-function mutations in the inflammasome (pyrin, NACHT) generates increased inflammasome activity and results in IL-1beta and IL-18 production
FMF, PAAND, CAPS, NLRP12-AD, HIDS

ADA2 deficiency *
Reduced ADA2 enzymatic activity resulting in defective differentiation of M2 anti-inflammatory macrophages and impaired secretion of pro-inflammatory cytokines by neutrophils
DADA2

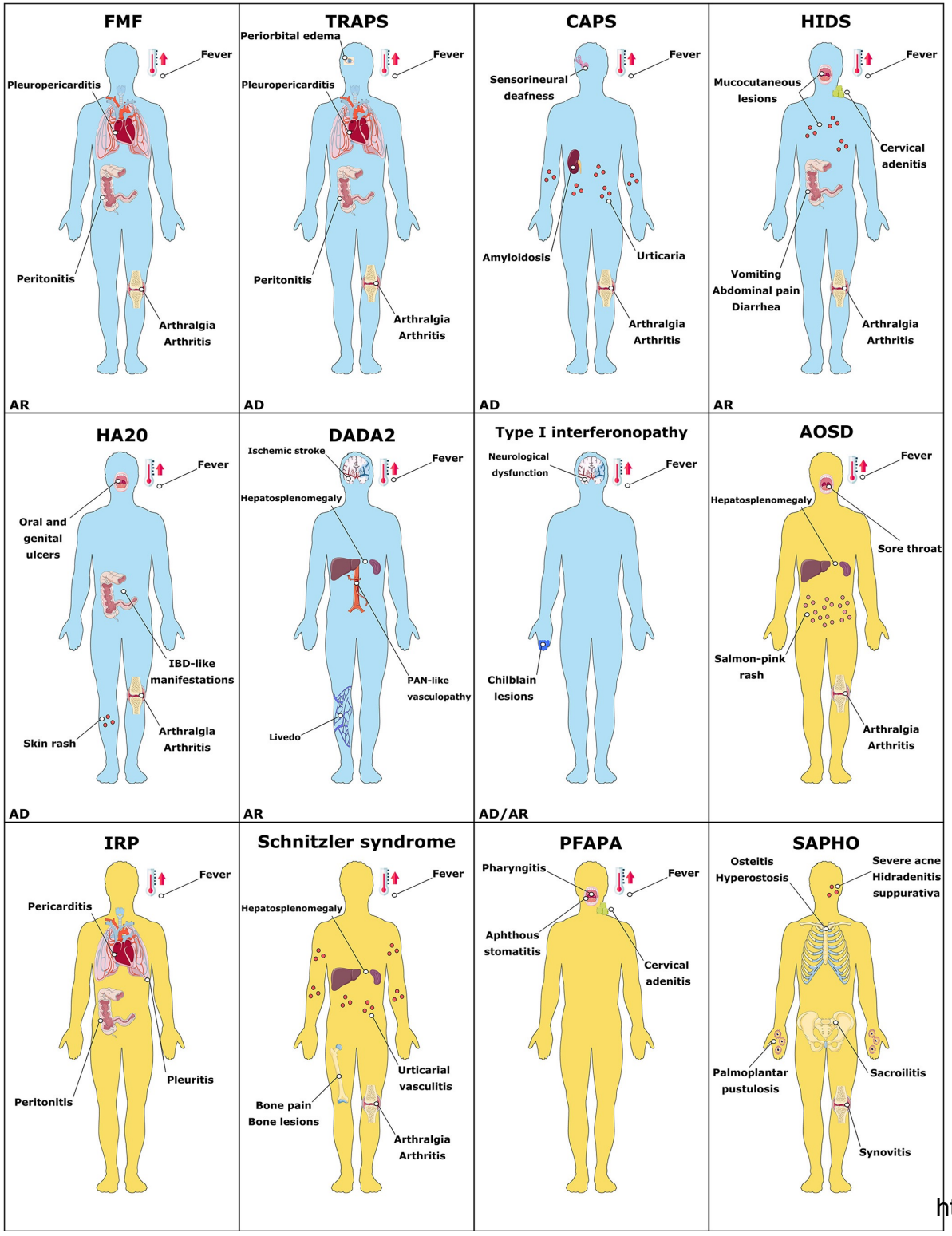


Endogenous antagonist mutations
Loss-of-function mutations in genes encoding endogenous cytokine antagonist impair the antagonization of proinflammatory signals
DIRA, DITRA

Type I interferonopathies *
Enhanced IFN gene expression due to accumulation of endogenous nucleic acids (TREX1), enhanced sensitivity or constitutive activation of a nucleic acid (IFIH1) or non-nucleic (TMEM173) acid receptor of the IFN signaling pathway
AGS, CANDLE, SAVI, RVCL

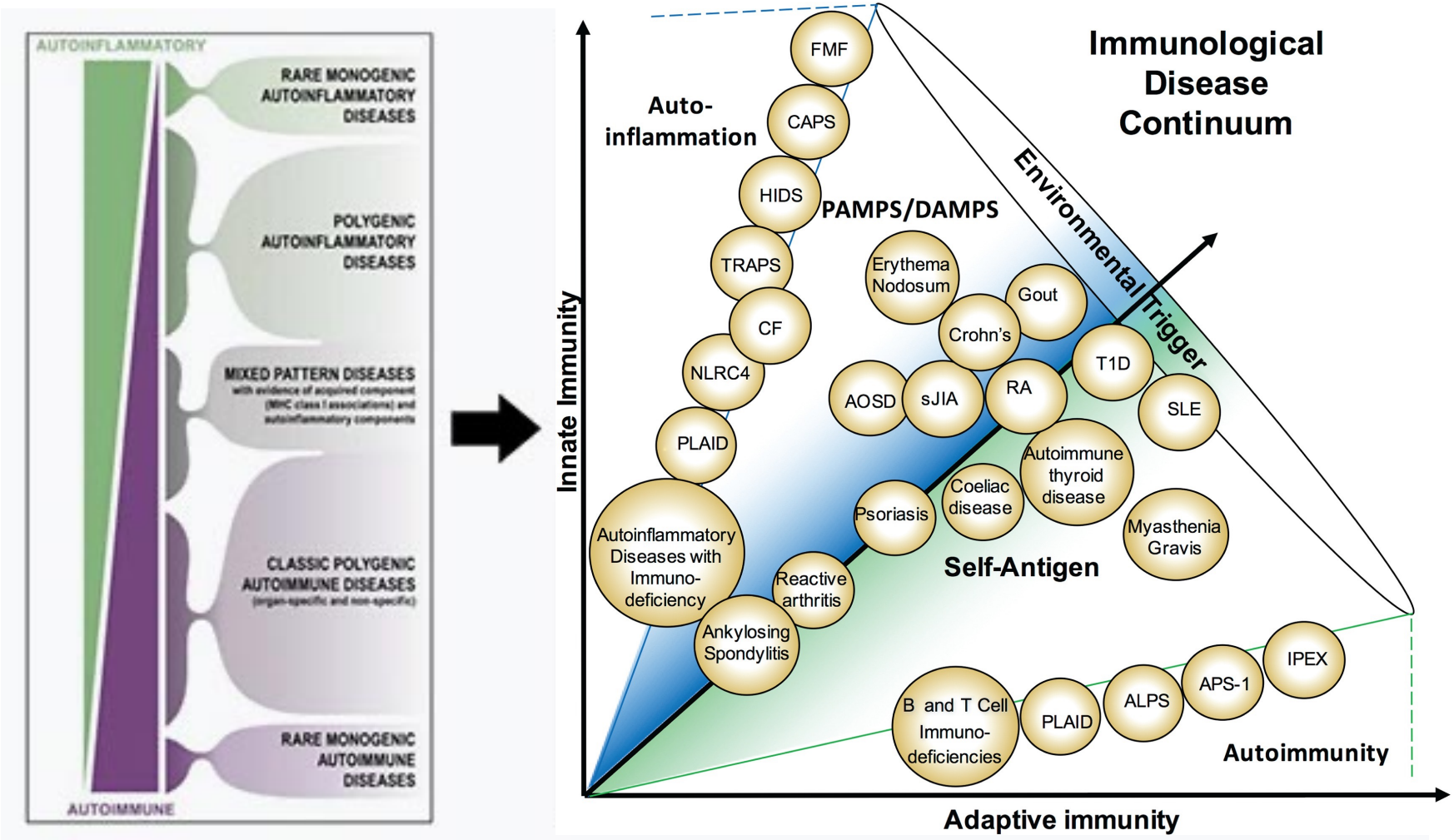
Actinopathies
Mutations in genes involved in the regulation of actin filament formation and disassembly
CDC42 deficiency, WDR1 deficiency, ARPC1B deficiency

https://www.sciencedirect.com/science/article/pii/S1568997221000379



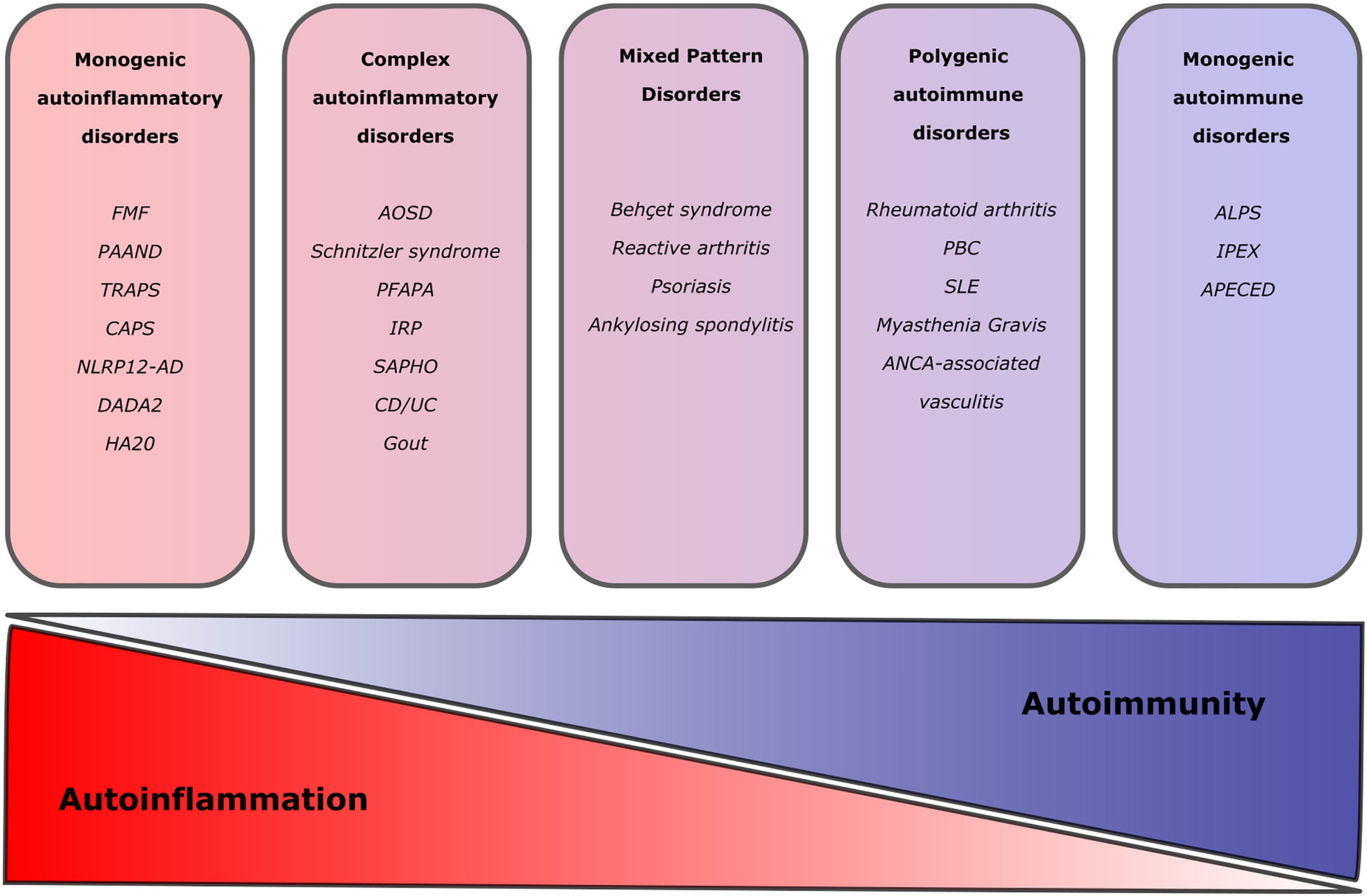
TRAPS: Tumor necrosis factor Receptor–Associated Periodic Syndrome
CAPS: Cryopyrin-Associated Periodic Syndromes
HIDS: Hyper IgD Syndrome (MVK)
HA20 é uma **doença autoinflamatória monogênica rara**, causada por **mutações no gene *TNFAIP3***, que codifica a **proteína A20**.
DADA2: Deficiência de ADA2
AOSD: Adult-Onset Still Disease
IRP: Inflamação Recorrente Periódica
PFAP: Síndrome Periódica Febre, Aftas, Faringite, Adenite
SAPHO: Sinovite, Acne, Pustulose, Hiperostose, Osteíte

https://www.sciencedirect.com/science/article/pii/S1568997221000379



Differences between autoinflammatory and autoimmune diseases [4–10].

	Autoinflammation	Autoimmunity
Immune dysregulation	Innate immune system	Adaptive immune system
Predominant cell types	Monocytes, macrophages, neutrophils	T cells, B cells
Cytokine targets used therapeutically	TNF, IFNαβ, IL-1, IL-2, IL-12, IL-23, IL-18	IFNγ, TNFα, IL-1, IL-2, IL-4, IL-6, IL-5, IL-9, IL-10, IL-12, IL-13, IL-17, IL-22, IL-23
Pathogenesis of organ damage	Neutrophil- and macrophage-mediated	Autoantibody- or autoantigen-specific T cell-mediated


Monogenic autoinflammatory disorders
FMF
PAAND
TRAPS
CAPS
NLRP12-AD
DADA2
HA20
Complex autoinflammatory disorders
AOSD
Schnitzler syndrome
PFAPA
IRP
SAPHO
CD/UC
Gout
Mixed Pattern Disorders
Behçet syndrome
Reactive arthritis
Psoriasis
Ankylosing spondylitis
Polygenic autoimmune disorders
Rheumatoid arthritis
PBC
SLE
Myasthenia Gravis
ANCA-associated vasculitis
Monogenic autoimmune disorders
ALPS
IPEX
APECED
Autoimmunity
Autoinflammation

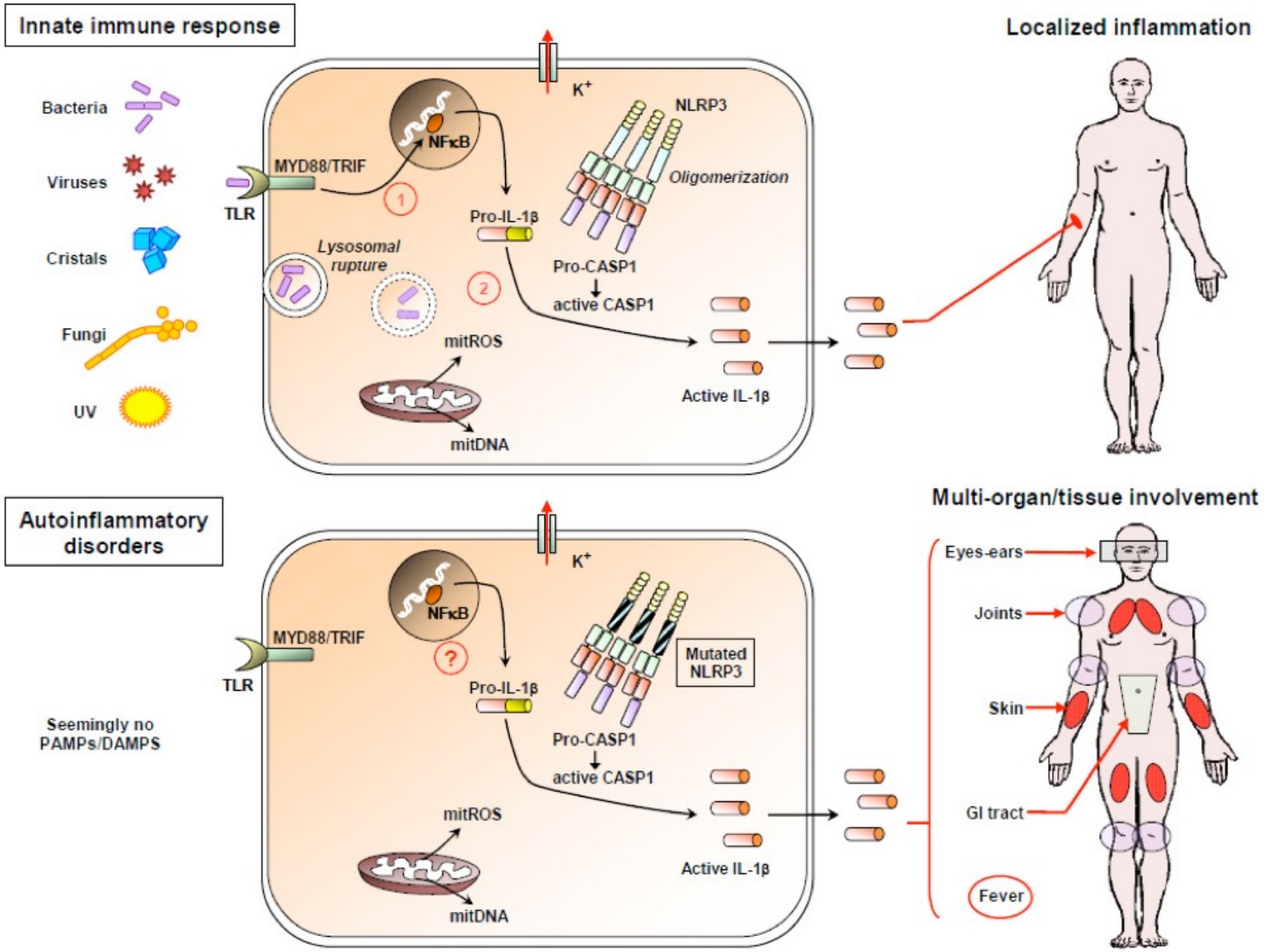
Doenças Autoimunes x Autoinflamatórias

Table 2. A comparison of autoimmunity and autoinflammation.

		Autoinflammation	Autoimmunity
Etiology	Genetics	Mutations in germline encoded elements of innate immune system	Generation of self-reactive lymphocyte receptors by somatic recombination
		Monogenic > polygenic	Polygenic > monogenic
	Immunology	Failure of autoinhibitory mechanisms ± constitutive inflammatory cytokine signaling	Failure of immune tolerance and lymphocyte-driven tissue damage
			Self-reactive lymphocytes and autoantibodies
Demographics	Age of onset	Pediatric > adult	Adult > pediatric
	Family history	+++	+/–
Clinical features	Triggers	Stress, infections, cold, physical exertion or trauma, vaccination, menses, pregnancy	Stress, infections, pregnancy
	Recurrent fevers	+++	Usually not the presenting complaint
	Ocular	Conjunctivitis, periorbital edema	Episcleritis/scleritis, retinitis, iritis
	Oral/genital ulcers	+++	+
	Gastrointestinal	Colitis in children, peritonitis	IBD in adults
	Bone inflammation	++	–
	Other	Rashes, synovitis, neurologic and renal involvement	
Tests	Elevated inflammatory markers	During attacks	Low grade at baseline
	Autoantibodies	–	+++
	Yield of genetic testing	+++	–
Response to treatment	Colchicine, IL-1 blockers	+++	+
	Antimetabolites[a], HCQ, CSA, tacrolimus	–	+++
	JAKi/TNFi, steroids	+++	

https://www.jrheum.org/content/jrheum/51/9/848.full.pdf

Inflamação Fisiológica e Síndromes Autoinflamatórias



Auto-inflamação "*Horror Autoinflammaticus*" - *Daniel L. Kastner 1999*

"Horror autotoxicus=horror à autoimunidade (Paul Ehrlich, 1890)

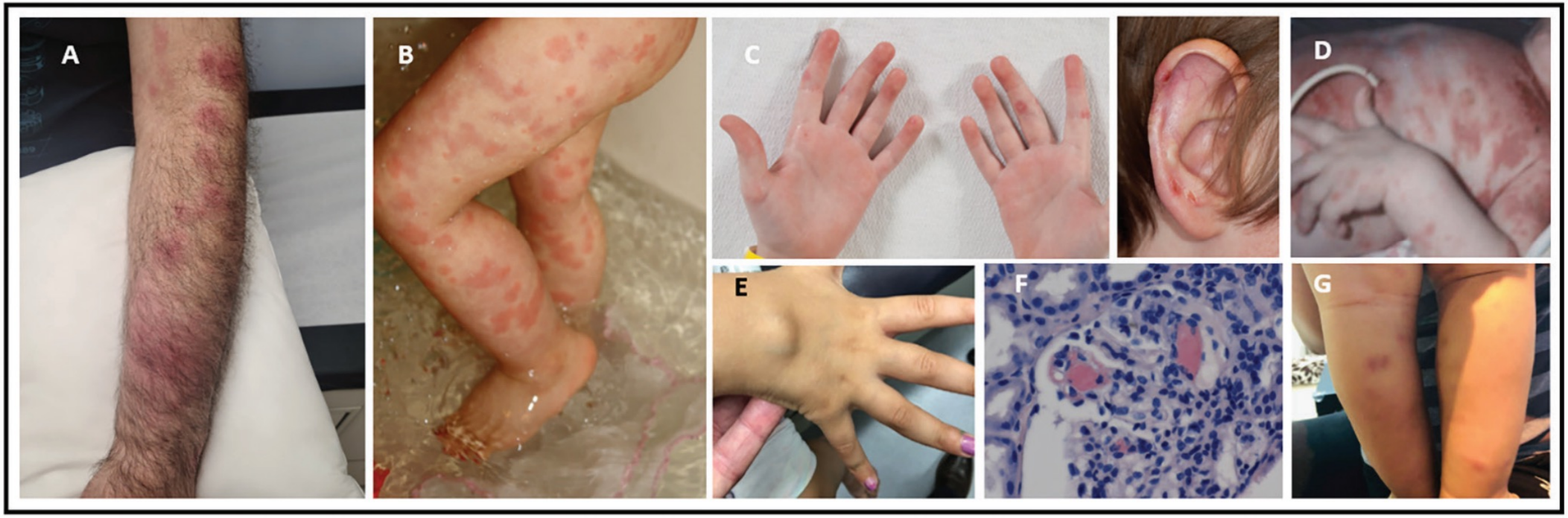


Figure 1. Clinical images of select AIDs. Patient consent was obtained to publish these images. (A) A 68-year-old man with Sweet syndrome related to VEXAS. (B) A 21-month-old girl with urticaria-like lesions characteristic of Muckle-Wells syndrome. (C) A 10-year-old boy with Aicardi-Goutières syndrome (compound heterozygous variants in *SAMHD1*) showing chilblain lesions of the hands and pinna. (D) Severe psoriatic rash in a 2-year-old boy with DIRA. (E) Extensor tenosynovitis in a 3-year-old girl with Blau syndrome. (F) A glomerulus with segmental mesangial amyloid deposition; salmon pink staining of amyloid with Congo red in a 10-year-old boy with TRAPS. (G) Purpuric subcutaneous nodules in a 15-month-old boy with DADA2. AID: autoinflammatory disease; DADA2: deficiency of adenosine deaminase 2; DIRA: deficiency of IL-1 receptor antagonist; TRAPS: tumor necrosis factor receptor–associated periodic syndrome; VEXAS: vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

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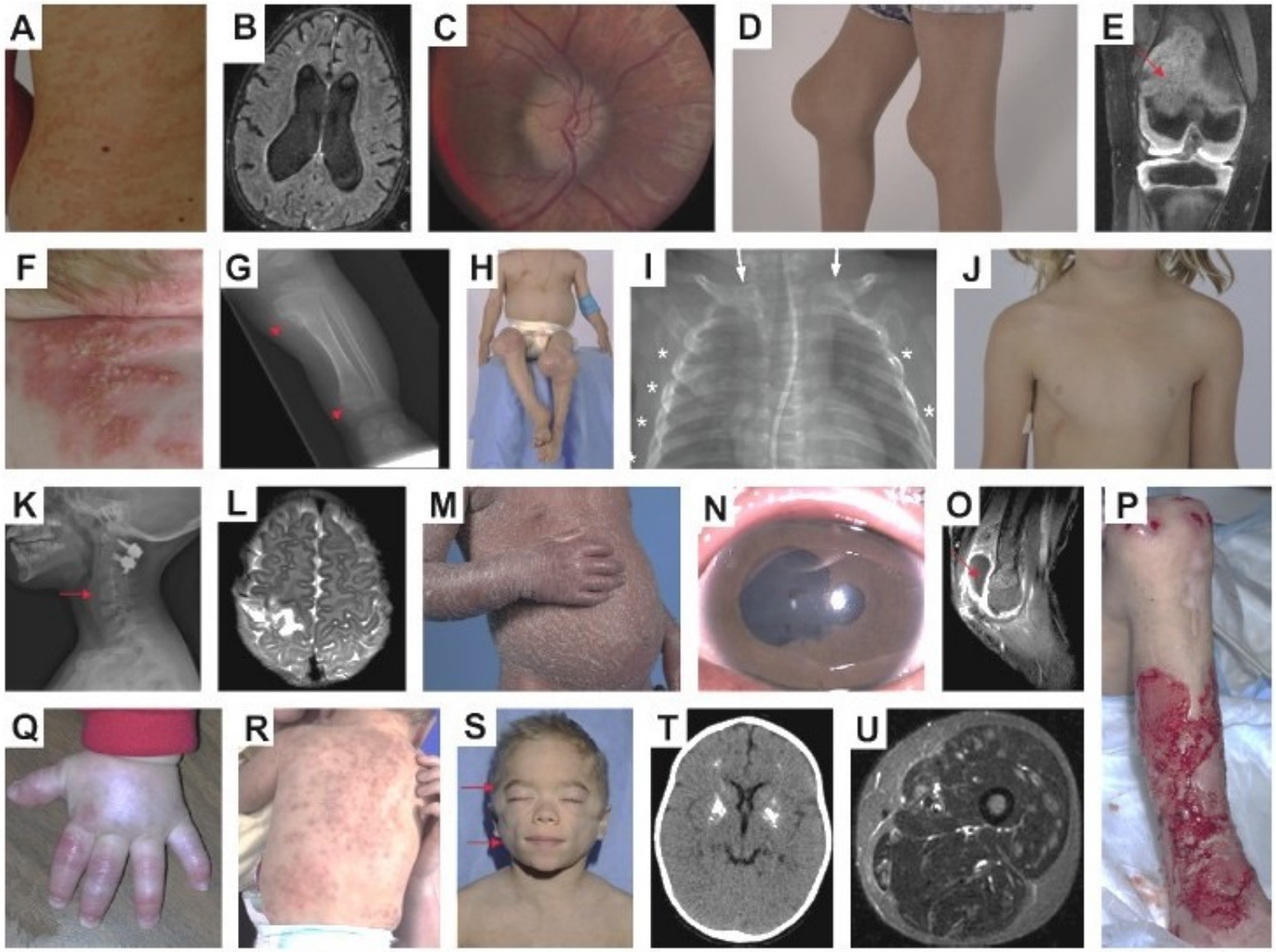


Montalegre Sanchez, 2013

Síndromes Autoinflamatórias

❖ Termo proposto por Michael Mc Dermoth e Daniel Kastner em 1999 para descrever um novo grupo de doenças imunológicas diferentes conceitualmente, clinicamente e mecanisticamente das outras doenças imunológicas.

❖ "DAI são desordens clínicas caracterizadas por aumento de inflamação induzida por agentes endógenos ou exógenos mediada predominantemente por células e moléculas **do SI Inato**, com uma signfificativa **predisposição genética** do hospedeiro".

❖ **São** condições caracterizadas por episódios não provocados de inflamação, sem altos títulos de auto-anticorpos ou de linfócitos T específicos.

❖ **Doenças auto-imunes-** Desvios da **Imunidade Adquirida**

❖ **Doenças Auto-Inflamatórias-** Desvios da **Imunidade Inata**

Doenças Autoinflamatórias

Características Clínicas

Episódios recorrentes de febre, Inflamação sistêmica e sintomas tais como rash cutâneo, dor abdominal, lifadenopatia, artrite.

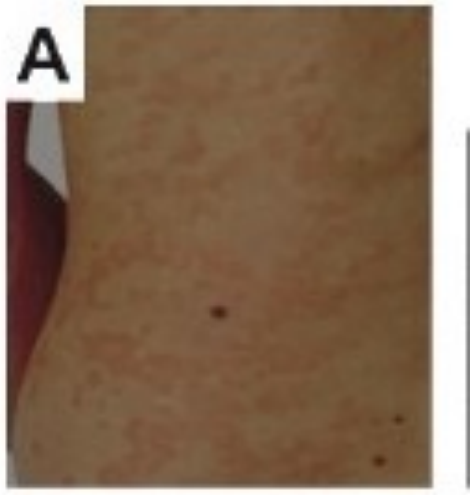
Há DAI com expressão contínua de sintomas e inflamação branda

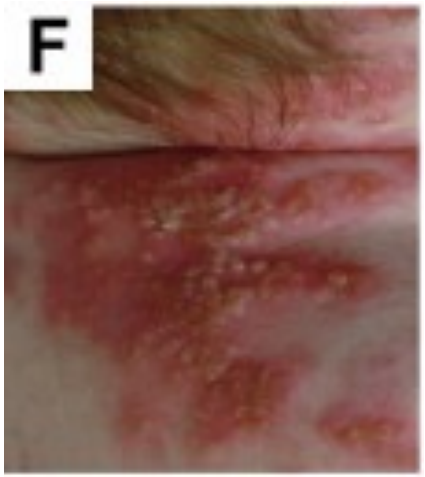
Resposta ao Tratamento

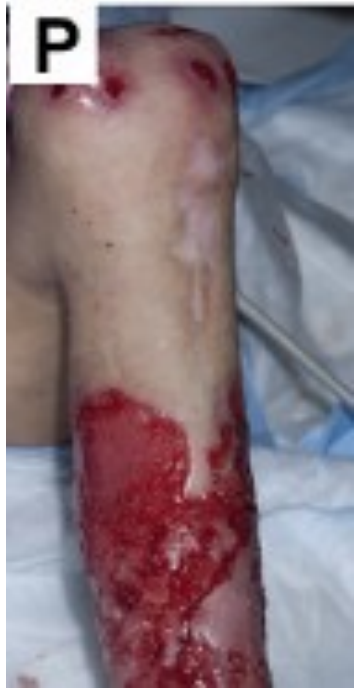
Doenças **Auto-imunes** respondem ao **Anti-TNF-**α
e
Doenças **Auto-Inflamatórias** respondem ao **Anti-IL-1**β

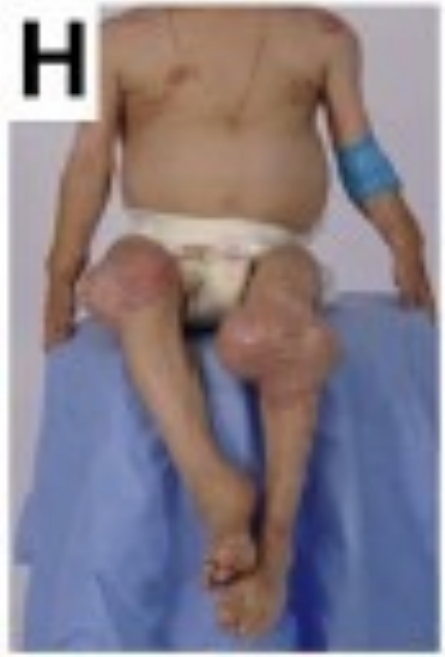
Síndromes Autoinflamatórias

- ✓ Episódios de febre e inflamação aparentemente “sem causa”
- ✓ Lesões “estéreis” e não malígnas
- ✓ Ausência de auto-anticorpos circulantes e linfócitos T auto- reativos
- ✓ Inflamação sistêmica grave

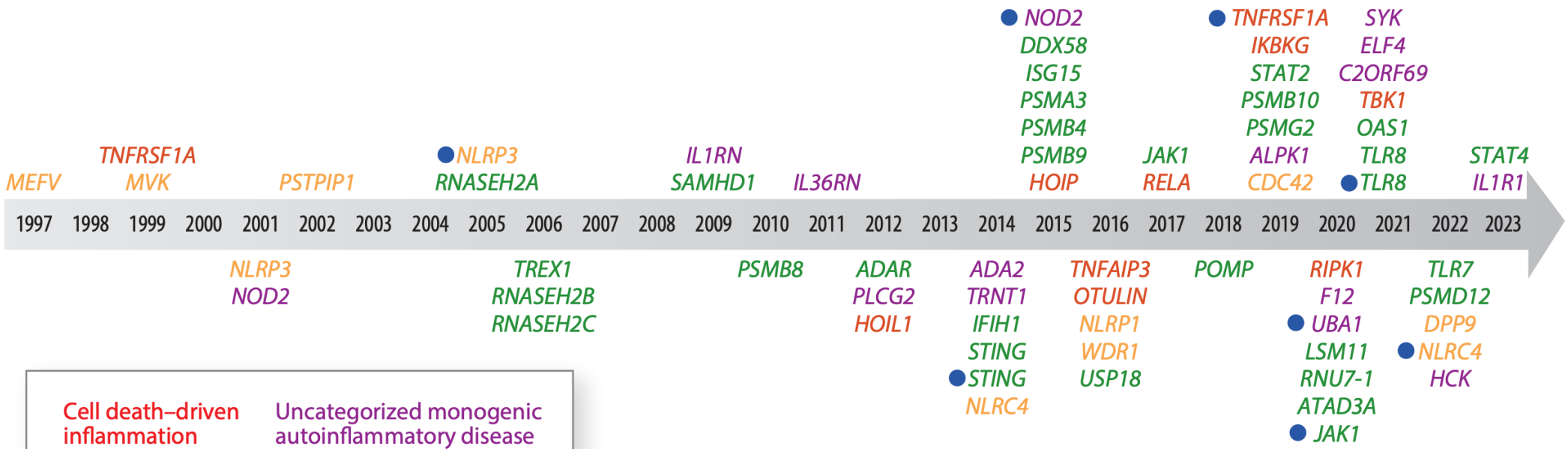








Montalegre Sanchez, 2013


MEFV
TNFRSF1A
MVK
PSTPIP1
NLRP3
RNASEH2A
IL1RN
SAMHD1
IL36RN
NOD2
DDX58
ISG15
PSMA3
PSMB4
PSMB9
HOIP
JAK1
RELA
TNFRSF1A
IKBKG
STAT2
PSMB10
PSMG2
ALPK1
CDC42
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ELF4
C2ORF69
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RNASEH2B
RNASEH2C
PSMB8
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PLCG2
HOIL1
ADA2
TRNT1
IFIH1
STING
STING
NLRC4
TNFAIP3
OTULIN
NLRP1
WDR1
USP18
POMP
RIPK1
F12
UBA1
LSM11
RNU7-1
ATAD3A
JAK1
TLR7
PSMD12
DPP9
NLRC4
HCK
Cell death–driven inflammation
Uncategorized monogenic autoinflammatory disease
Type I interferonopathy
Inflammasomopathy
Somatic mutation

Doenças Autoinflamatórias

- ✓ Lista em continuo aumento…
- ✓ Doenças “antigas” e «novas» classificadas como síndrome auto-inflamatórias
- ✓ *Mendelianas ou Multifatoriais*
- ✓ **Disregulaçao do sistema imune inato**

6 categorias (Master et al, 2009)

- **defeitos de ativação de IL-1ß (inflamassomopatias)**
- **síndromes de ativação de NF-kB**
- **defeitos de “misfolding” das proteínas**
- **defeitos de regulação do complemento**
- **defeitos de sinalização das citocinas**
- **síndromes de ativação dos macrófagos**

novas doenças (Montealegre Sanchez et al, 2013)

- **defeitos de proteasoma/IFN-mediata**
- **defeito de IL36RA ***
- **Psoríase com defeito de CARD14***
- **Early onset IBD (def. IL-10)**
- **Defeito in PLCy2**

Novas vias de sinalizaçao
Células não imunes (*keratinócitos)

Inflammasomopathies
Interferonpathies
NF-κB-opahties
Cytoskelopathies
Enzymatic deficiencies
Others

Table 1. Heat map of autoinflammatory syndromes discussed in the main text.

Category	Autoinflammatory Condition	Gene	Clinical Features: Fever	Joint	Rash	Ulcer	Eye	GI	CNS	Vasculitis	Lung	Bone	HLH	Infection	Lipodystrophy	Thrombocytopenia	DD	Other
Inflammasomopathies	FMF	*MEFV*																
	PAPA	*PSTPIP1*																
	CAPS	*NLRP3*																
	Majeed syndrome	*LPIN2*																Anemia
	NLRP12-related AID	*NLRP12*																
	DPP9 deficiency[a]	*DPP9*																Eczema, allergies, fair hair, short stature, dysmorphic
	PMVK-related AID[a]	*PMVK*																Lymphoma, elevated IgD
IL-1 pathway	DIRA	*IL1RN*																
IL-18 pathway	AIFEC	*NLRC4*																
	FCAS4	*NLRC4*																
	X-linked proliferative disease 2	*XIAP*																
	IL-18BP deficiency	*IL18BP*																Viral hepatitis
	NLRP1-associated autoinflammation with arthritis and dyskeratosis	*N LRP1*																Dyskeratosis
Interferonopathies	AGS	*TREX1, SAMHD1, RNASEH2A, RNASEH2B, ADAR1, IF1H1*																Hepatitis, chilblains
	STAT2 gain-of-function disease	*STAT2*																Brain calcifications
	Pseudo-TORCH	*USP18*																Brain calcifications
	SAVI	*TMEM173*																
	SMS	*IFIH1, DDX38*																Dental dysplasia, aortic calcification
	PRAAS	*PSMB4, PSMA3, POMP, PSMG, PSMB8, PSMB9*[a]*, PSMB10*																
	COPA syndrome	*COPA*																Kidney dysfunction
	OPAID[a]	*OAS1*																FTT
	ATAD3A deficiency[a]	*ATAD3A*																Dystonia, thyroiditis, calcifications, HCM
	ZNFX1 deficiency[a]	*ZNFX1*																Renal disease
NF-κB–opathies	Haploinsufficiency of A20	*TNFAIP3*																
	RAID	*RELA*																
	RIPK1 deficiency	*RIPK1*																
	RIPK1 gain-of-function	*RIPK1*																
	Otulipenia	*FAM105B*																Lymphadenopathy
	Blau syndrome	*NOD2*																Sarcoidosis
	CARD14-mediated pustular psoriasis	*CARD14*																
	SYK-associated AID[a]	*SYK*																Lymphoma
	TBK1 deficiency[a]	*TBK1*																Short stature
	DEX[a]	*ELF4*																Perianal abscesses
	ROSAH[a]	*ALPK1*																Splenomegaly, anhidrosis
	NDAS[a]	*IKBKG*																Panniculitis
Cytoskelopathies	NOCARH	*CDC42*																
	ARPC1B deficiency	*ARPC1B*																
	NCKAP1 deficiency	*NCKAP1*																
	PFIT	*WDR1*																
Enzymatic deficiencies	MKD	*MVK*																Elevated IgD
	DADA2	*CECR1*																
	SIFD	*TRNT1*																Sideroblastic anemia
	PLAID	*PLCG2*																
	APLAID	*PLCG2*																
Other	TRAPS	*TNFRSF1A*																
	VEXAS	*UBA1*																Deep vein thrombosis
	C2orf69 deficiency[a]	*C2orf69*																Hypomyelination, microcephaly, DWS, FTT
	HCK-associated AID[a]	*HCK*																Hepatosplenomegaly
	IL-33 gain-of-function[a]	*IL33*																Eosinophilic dermatitis, IgE
	STAT6 gain-of-function[a]	*STAT6*																IgE, allergy
	DPM[a]	*STAT4*																Poor wound healing, hypogammaglobulinemia
	LAVLI[a]	LYN																Hepatosplenomegaly

Autoinflammatory syndromes are arranged by pathway with colored boxes representing main clinical features. It is important to note that many conditions may fall into multiple categories and that this heat map is a representation of the predominant mechanism at play. [a] Conditions discovered since 2021. AGS: Aicardi-Goutières syndrome; AID: autoinflammatory disease; AIFEC: autoinflammation with infantile enterocolitis; APLAID: autoinflammation and PLAID; CAPS: cryopyrin-associated periodic syndrome; CNS: central nervous system; COPA: coatomer protein subunit alpha; DADA2: deficiency of adenosine deaminase 2; DD: developmental delay; DEX: deficiency of ELF4, X-linked; DIRA: deficiency of IL-1 receptor antagonist; DPM: disabling pansclerotic morphea; DWS: Dandy-Walker syndrome; FCAS4: familial cold autoinflammatory syndrome 4; FMF: familial Mediterranean fever; FTT: failure to thrive; GI: gastrointestinal; HCM: hypertrophic cardiomyopathy; HLH: hemophagocytic lymphohistiocytosis; IL: interleukin; LAVLI: Lyn kinase–associated vasculopathy and liver fibrosis; MKD: mevalonate kinase deficiency; NDAS: NEMO deleted exon 5 autoinflammatory syndrome; NF: nuclear factor; NOCARH: neonatal onset of pancytopenia, autoinflammation, rash, and hemophagocytosis; OPAID: *OAS1*-associated polymorphic autoinflammatory immunodeficiency disorder; PAPA: pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; PFIT: periodic fevers, immunodeficiency, thrombocytopenia; PLAID: *PLCG2*-associated antibody deficiency and immune dysregulation; PRAAS: proteosome-associated autoinflammatory syndromes; RAID: *RELA*-associated inflammatory disease; ROSAH: retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and migraine headaches; SAVI: stimulator of IFN genes–associated vasculopathy with onset in infancy; SIFD: sideroblastic anemia, immunodeficiency, fevers, and developmental delay; SMS: Singleton-Merton syndrome; STAT: signal transducer and activator of transcription; TORCH: toxoplasmosis, other, rubella, cytomegalovirus, and herpes simplex; TRAPS: tumor necrosis factor receptor–associated periodic syndrome; VEXAS: vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

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Mecanismos das doenças Autoinflamatórias monogênicas

Table 3 The mechanisms in monogenic autoinflammatory diseases

Innate mechanism	Component	Mechanism
Intracellular sensor function defects		
CAPS (FCAS, MWS, NOMID/CINCA)	NLRP3 (cryopyrin)	Activation of NLRP3 inflammasome (gain-of-function) leading to IL-1β production
FMF	Pyrin	Inflammasome activation, increased IL-1β production
BS/PGA	NOD2	NF-κB and RIP2K activation
CAMPS	Adaptor molecule C CARD14	Increased NF-κB
Accumulation of intracellular triggers		
TRAPS	Folding defect and accumulation of TNFR1	MAPK activation, Increased production of mROS, ER stress
CANDLE/PRAAS	Proteasome dysfunction	IFN response gene induction
HIDS/MKD	Mevalonate kinase	Lack of prenylation leads to cytoskeletal changes and inflammasome activation
Loss of a negative regulator of inflammation		
DIRA	Loss of IL-1 antagonism	Uncontrolled IL-1 signalling
DITRA	Loss of IL-36 antagonism	Uncontrolled IL-36 signalling
EO-IBD	Loss of IL-10 or IL-10 receptor antagonist	Decreased IL-10 signalling
Effects on signalling molecules that upregulate innate immune cell function		
AGS	Type I interferonopathy-related proteins	Increased INF type I production

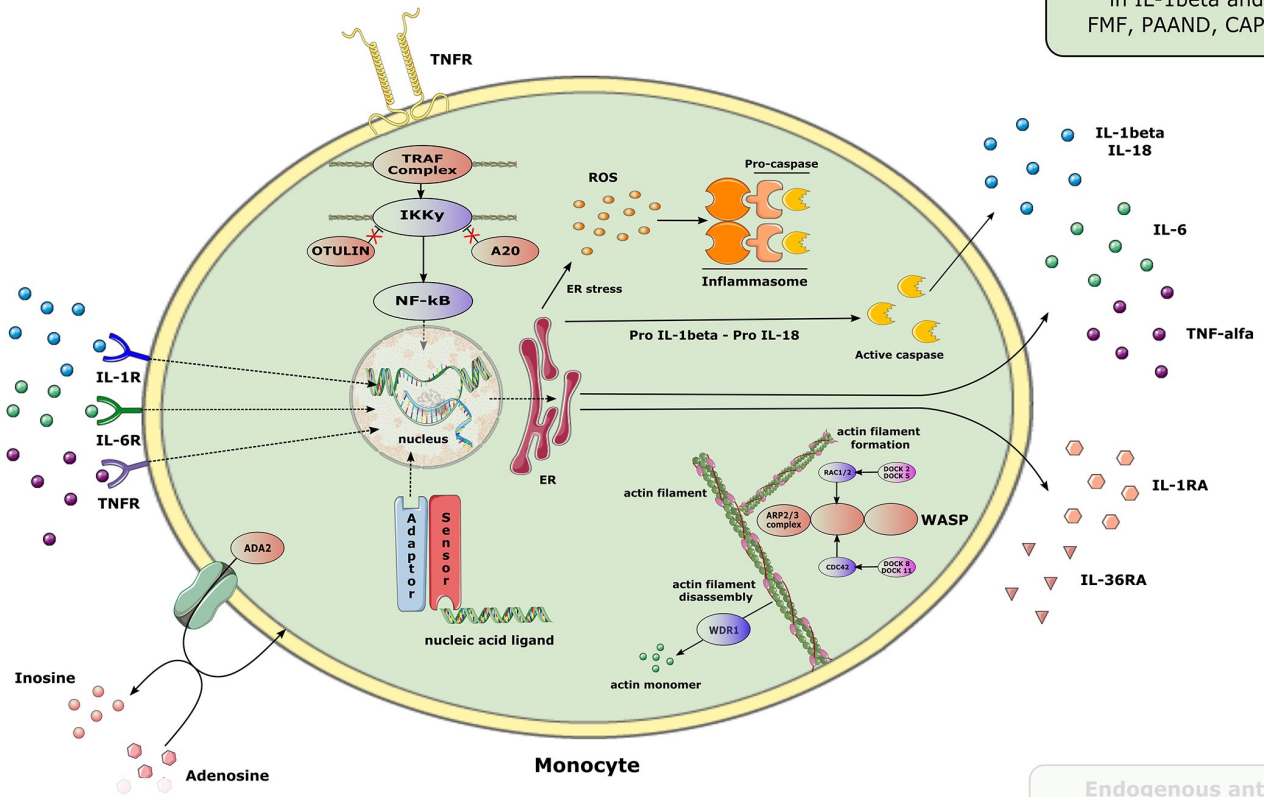
TNF receptor–associated periodic syndrome
CAPS Cryopyrin-associated periodic syndrome
DIRA Deficiency in the IL-1-receptor antagonist

ER stress *
Defective post-tranlational modification or protein misfolding generates ER stress and results in ROS and IL-1beta production
TRAPS

NF-kB-related disorders *
NF-kB pathway activation through ubiquitination disorders or dysregulated NOD2 signaling.
HA20, ORAS, LUBAC deficiency, CRIA

Inflammasomopathies *
Gain-of-function mutations in the inflammasome (pyrin, NACHT) generates increased inflammasome activity and results in IL-1beta and IL-18 production
FMF, PAAND, CAPS, NLRP12-AD, HIDS

ADA2 deficiency *
Reduced ADA2 enzymatic activity resulting in defective differentiation of M2 anti-inflammatory macrophages and impaired secretion of pro-inflammatory cytokines by neutrophils
DADA2



Endogenous antagonist mutations
Loss-of-function mutations in genes encoding endogenous cytokine antagonist impair the antagonization of proinflammatory signals
DIRA, DITRA

Type I interferonopathies *
Enhanced IFN gene expression due to accumulation of endogenous nucleic acids (TREX1), enhanced sensitivity or constitutive activation of a nucleic acid (IFIH1) or non-nucleic (TMEM173) acid receptor of the IFN signaling pathway
AGS, CANDLE, SAVI, RVCL

Actinopathies
Mutations in genes involved in the regulation of actin filament formation and disassembly
CDC42 deficiency, WDR1 deficiency, ARPC1B deficiency

https://www.sciencedirect.com/science/article/pii/S1568997221000379

Doenças Autoinflamatórias mediadas pelo Inflamassomas

Disease	Gene (chromosome)	Protein (synonyms) or *pathogenic stimulus*
Type 1: IL-1β activation disorders (inflammasomopathies)		
Intrinsic		
FCAS[a], MWS[b], NOMID[c]/CINCA[d]	*NLRP3/CIAS1* (1q44)	NLRP3[e] (cryopyrin, NALP3, PYPAF1)
Extrinsic		
FMF[f]	*MEFV* (16p13.3)	Pyrin (marenostrin)
PAPA[g]	*PSTPIP1* (15q24–25.1)	PSTPIP1[h] (CD2BP1[i])
CRMO[j]/SAPHO[k]	Complex	
Majeed syndrome	*LPIN2* (18p11.31)	Lipin-2
HIDS[l]	*MVK* (12q24)	Mevalonate kinase
Recurrent hydatidiform mole	*NLRP7* (19q13)	NLRP7 (NALP7, PYPAF3, NOD12)
DIRA[m]	*IL1RN*	IL-1Ra
Complex/acquired		
Gout, pseudogout	Complex	*Uric acid/CPPD*
Fibrosing disorders	Complex	*Asbestos/silica*
Type 2 diabetes mellitus	Complex	*Hyperglycemia*
Schnitzler syndrome	Sporadic	

Deficiency in the IL-1-receptor antagonist

Doenças Autoinflamatórias mediadas pelo Inflamassomas

Table 1 Inflammasome-driven diseases

Inflammasome	Associated proteins	Associated human syndrome	Evidence
NLRP1	ASC, procaspase-1, procaspase-5	Vitiligo Addison's disease Autoimmune thyroid disease Type 1 diabetes	Genetic and ex vivo (human) Genetic (human) Genetic (human) Genetic (human)
NLRP3	ASC, procaspase-1	CAPS Schnitzler's syndrome	Genetic (human); ex vivo and in vitro (human, mouse); and in vivo (mouse) Genetic (human)
NLRP6	ASC, procaspase-1	None identified to date	
NLRP7	ASC, procaspase-1	Familial biparental hydatidiform mole	Genetic (human)
NLRC4	ASC, procaspase-1, NAIP	MAS-like syndrome Enterocolitis	Genetic, ex vivo, and in vitro (human)
NLRP12	ASC, procaspase-1	Periodic fevers with urticaria (CAPS-like syndrome)	Genetic, ex vivo, and in vitro (human)
AIM2	ASC, procaspase-1	SLE, psoriasis	In vitro (human)
Pyrin (*MEFV*)	ASC, procaspase-1	Familial Mediterranean fever	Genetic (human); ex vivo and in vitro (human, mouse); and in vivo (mouse)

Abbreviations: AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (CARD); CAPS, cryopyrin-associated periodic syndromes; MAS, macrophage-activation syndrome; NLR, NOD-like receptor; NAIP, NLR family, apoptosis inhibitory protein; SLE, systemic lupus erythematosus.

Table 1. Heat map of autoinflammatory syndromes discussed in the main text.

Category	Autoinflammatory Condition	Gene	Clinical Features														
			Fever	Joint	Rash	Ulcer	Eye	GI	CNS	Vasculitis	Lung	Bone	HLH	Infection	Lipodystrophy	Thrombocytopenia	DD	Other
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	PAPA	*PSTPIP1*																
	CAPS	*NLRP3*																
	Majeed syndrome	*LPIN2*																Anemia
	NLRP12-related AID	*NLRP12*																
	DPP9 deficiency[a]	*DPP9*																Eczema, allergies, fair hair, short stature, dysmorphic
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IL-18 pathway	AIFEC	*NLRC4*																
	FCAS4	*NLRC4*																
	X-linked proliferative disease 2	*XIAP*																
	IL-18BP deficiency	*IL18BP*																Viral hepatitis
	NLRP1-associated autoinflammation with arthritis and dyskeratosis	*NLRP1*																Dyskeratosis

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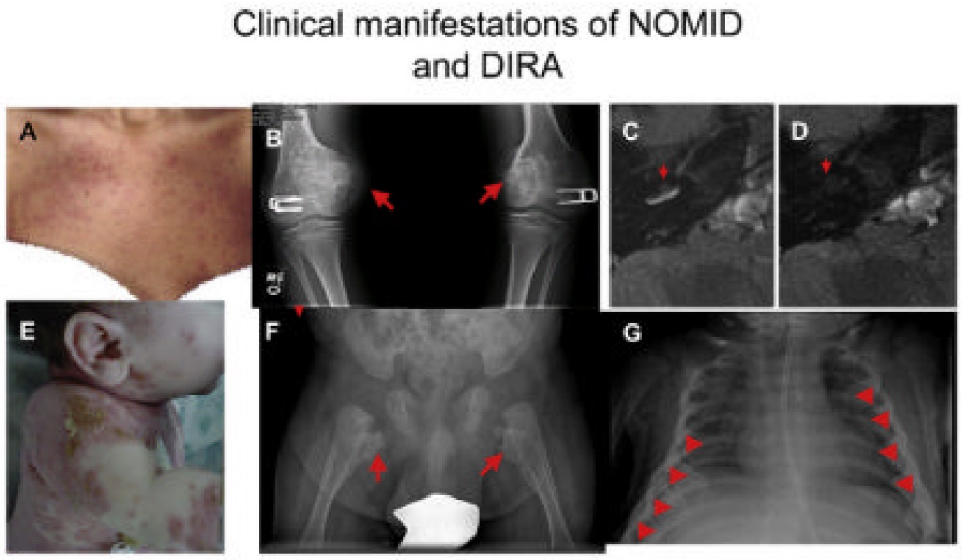

Muckle-Wells Syndrome (MWS): CAPS NLRP3 Gene

et disease

👥 As 3 formas principais do espectro CAPS:

Subtipo	Nome completo	Gravidade	Características principais
FCAS	*Familial Cold Autoinflammatory Syndrome*	Leve	Erupções induzidas por frio, febre leve
MWS	*Muckle-Wells Syndrome*	Moderada	Urticária, febre, surdez neurossensorial, risco de amiloidose
CINCA/NOMID	*Chronic Infantile Neurological Cutaneous Articular / Neonatal-Onset Multisystem Inflammatory Disease*	Grave	Inflamação sistêmica severa desde a infância: envolvimento neurológico, ósseo e cutâneo

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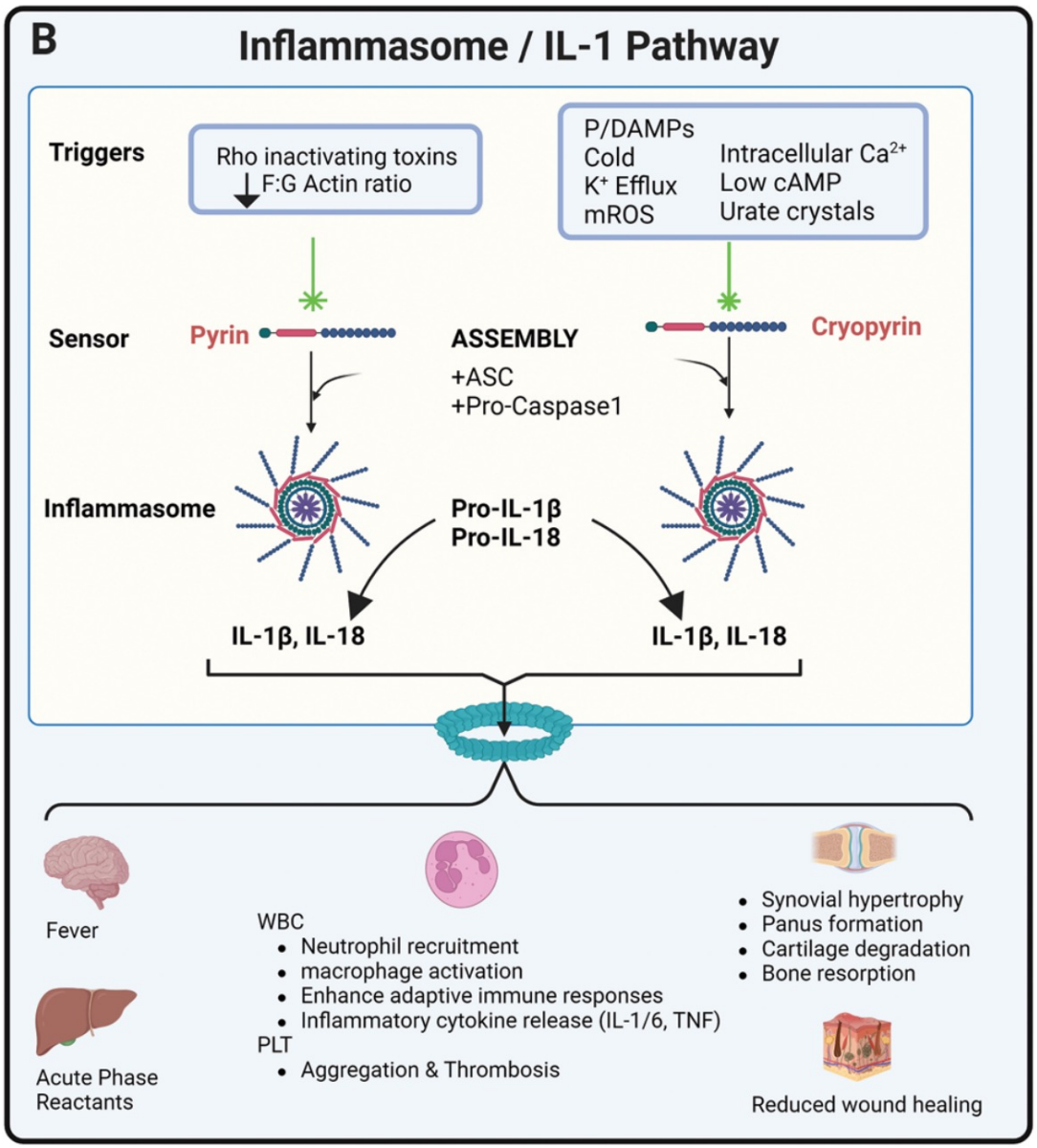
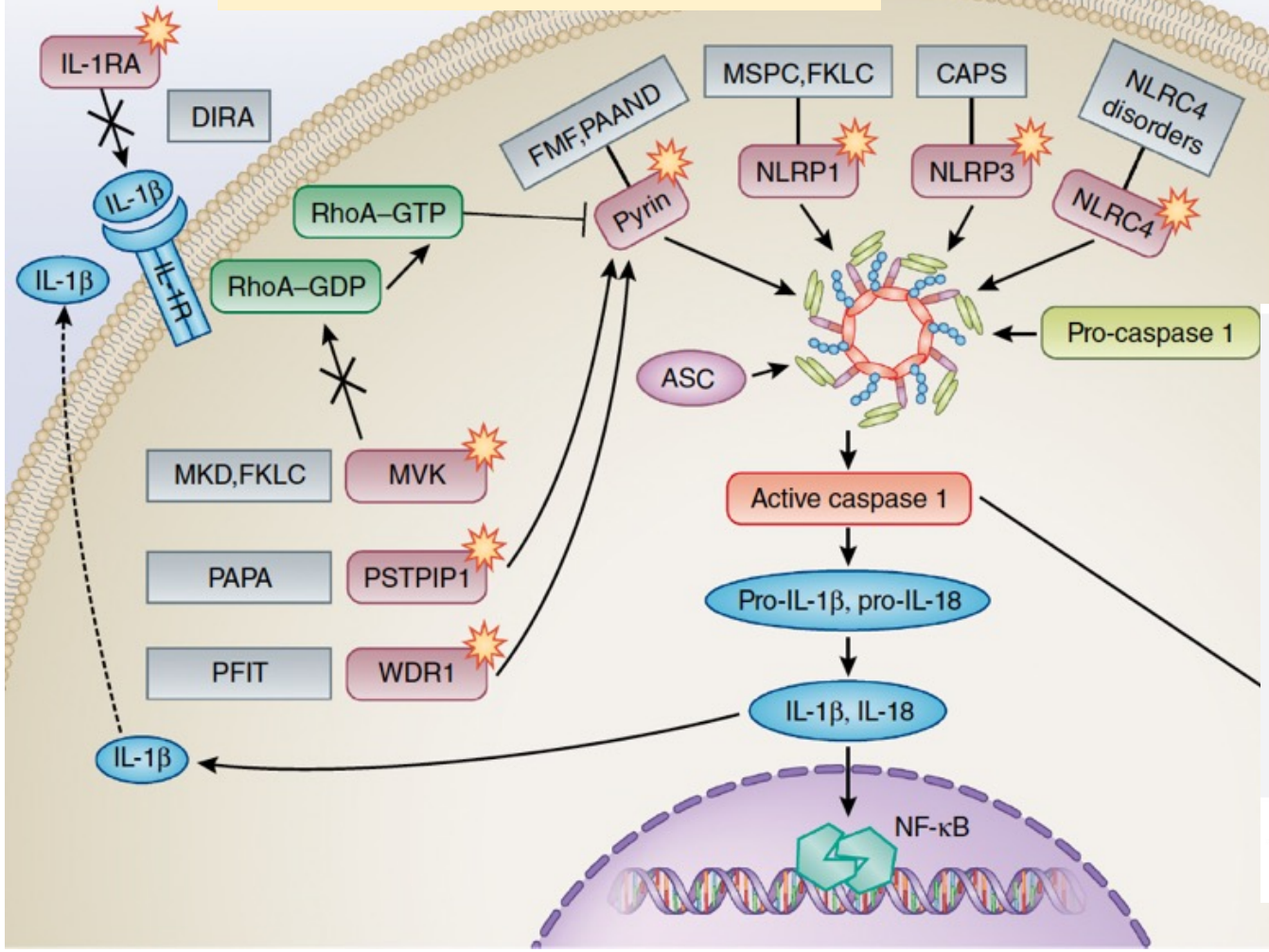
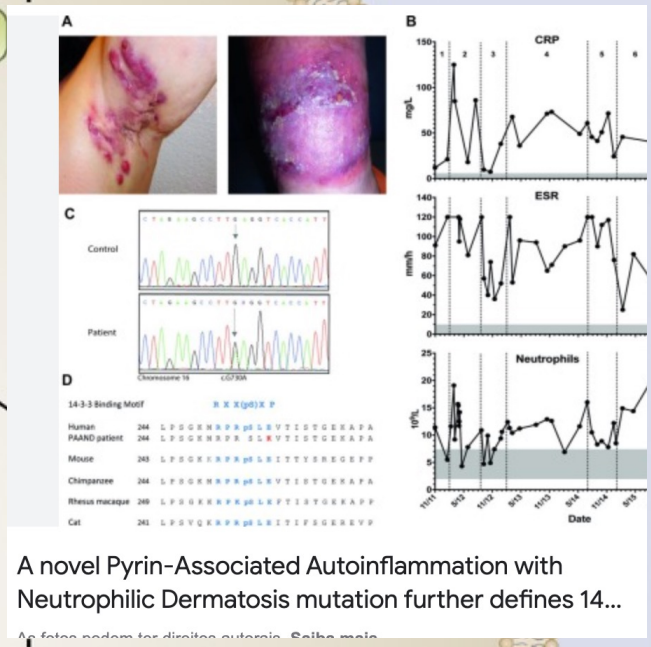


Figure 2B: The priming phase (not shown) occurs when the canonical NFκB pathway is activated, leading to expression and generation of inflammasome components and pro-IL-1β. Upon further stimulation, the activation phase is triggered (above). ASC and pro-caspase 1 are assembled with the sensor molecule into the mature inflammasome which then processes pro-IL-1β and pro-IL-18 into its active cytokine forms. There are many inflammasomes beyond pyrin and cryopyrin such as NLRP1, NLRP12, NLRC4, AIM2, IFI-16, and RIG-1 (not shown). Mutations in inflammasome sensors can lead to autoinflammatory disease.

Síndromes Autoinflamatórias mediadas por Inflamassoma

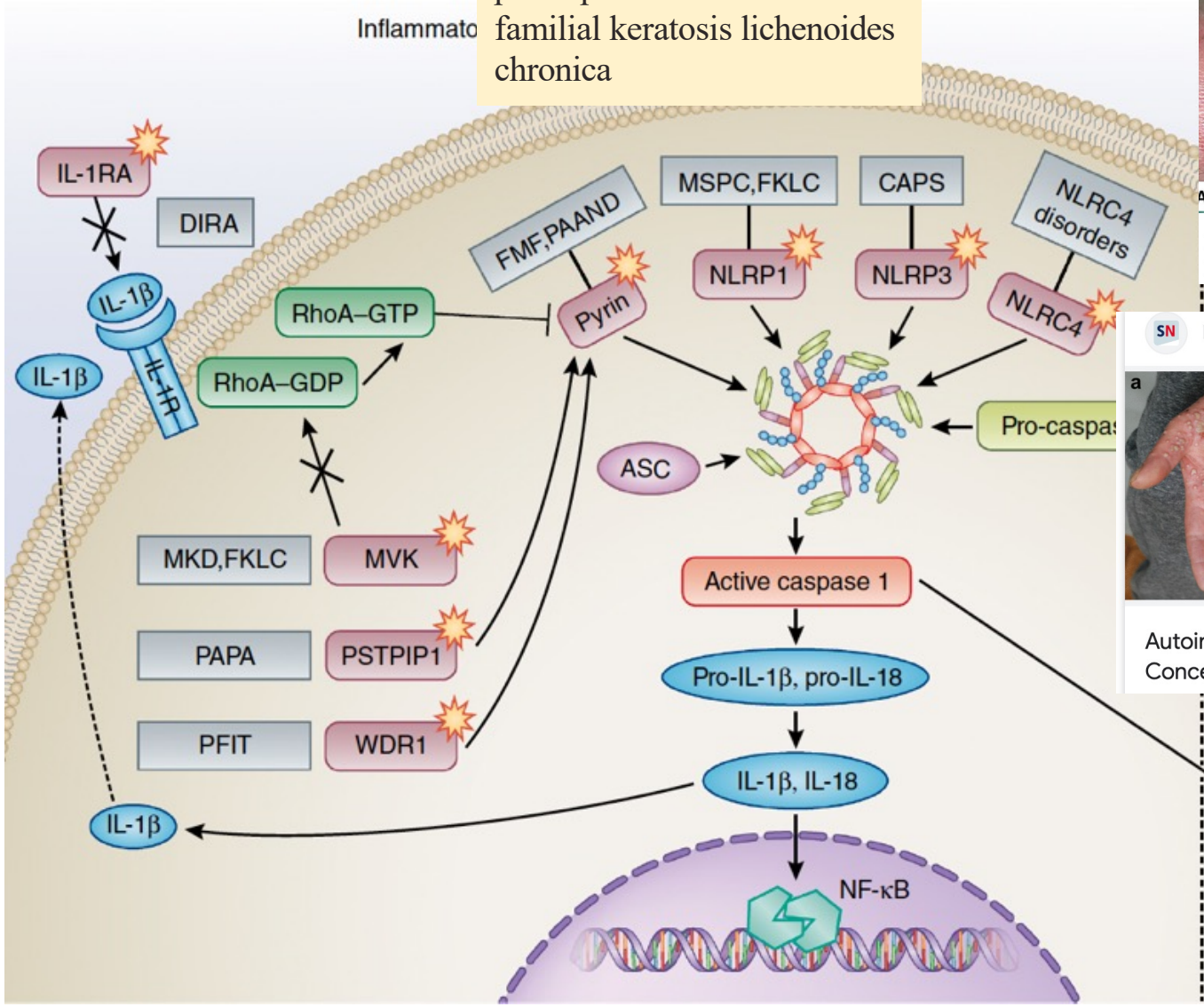
Familial Mediterranean Fever pyrin-associated Autoinflammation with Neutrophilic Dermatosis
PAAND

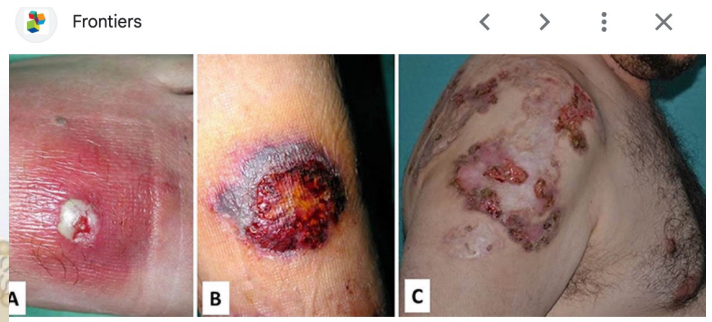




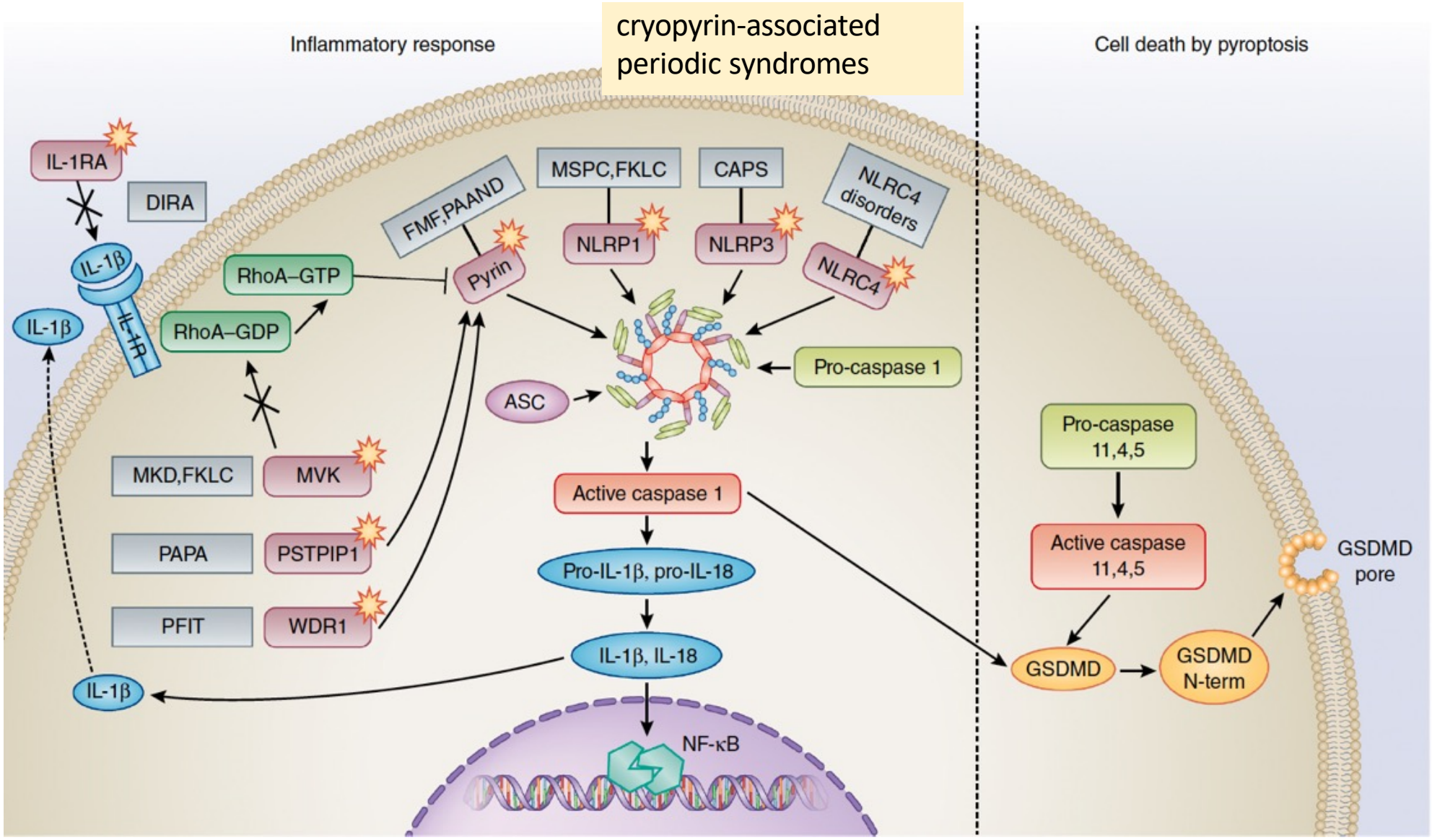
Síndromes Autoinflamatórias mediadas por Inflamassoma

multiple self-healing palmoplantar carcinoma
familial keratosis lichenoides chronica

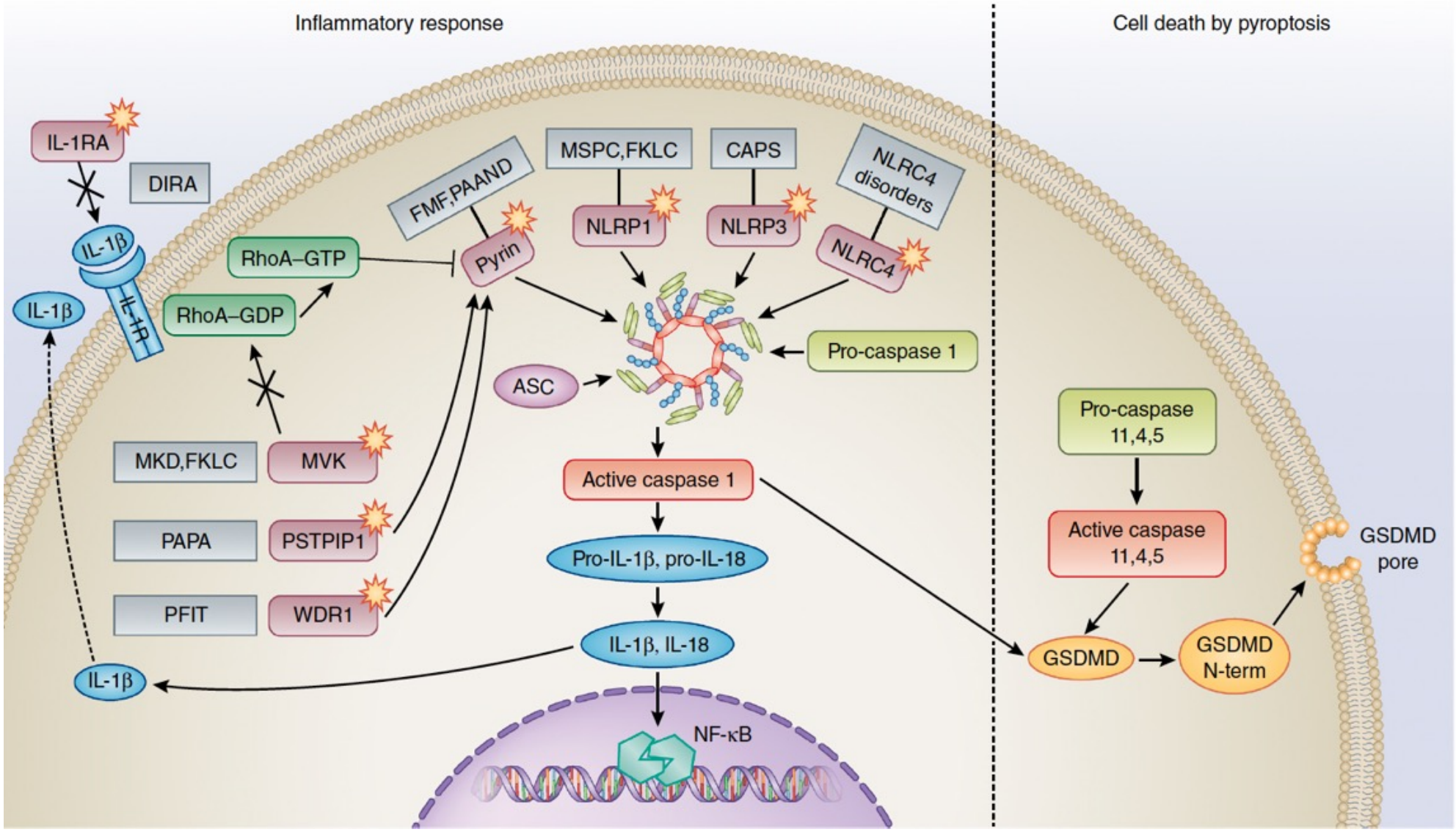




Síndromes Autoinflamatórias mediadas por Inflamassoma



Síndromes Autoinflamatórias mediadas por Inflamassoma



A ativação do inflamassoma leva à piroptose e liberação de partículas de inflamassoma contendo ASC (SPECK com ativação extracellular de caspase-1 e IL-1β. Fagocitose de SPECKs leva a ativação do inflamassoma

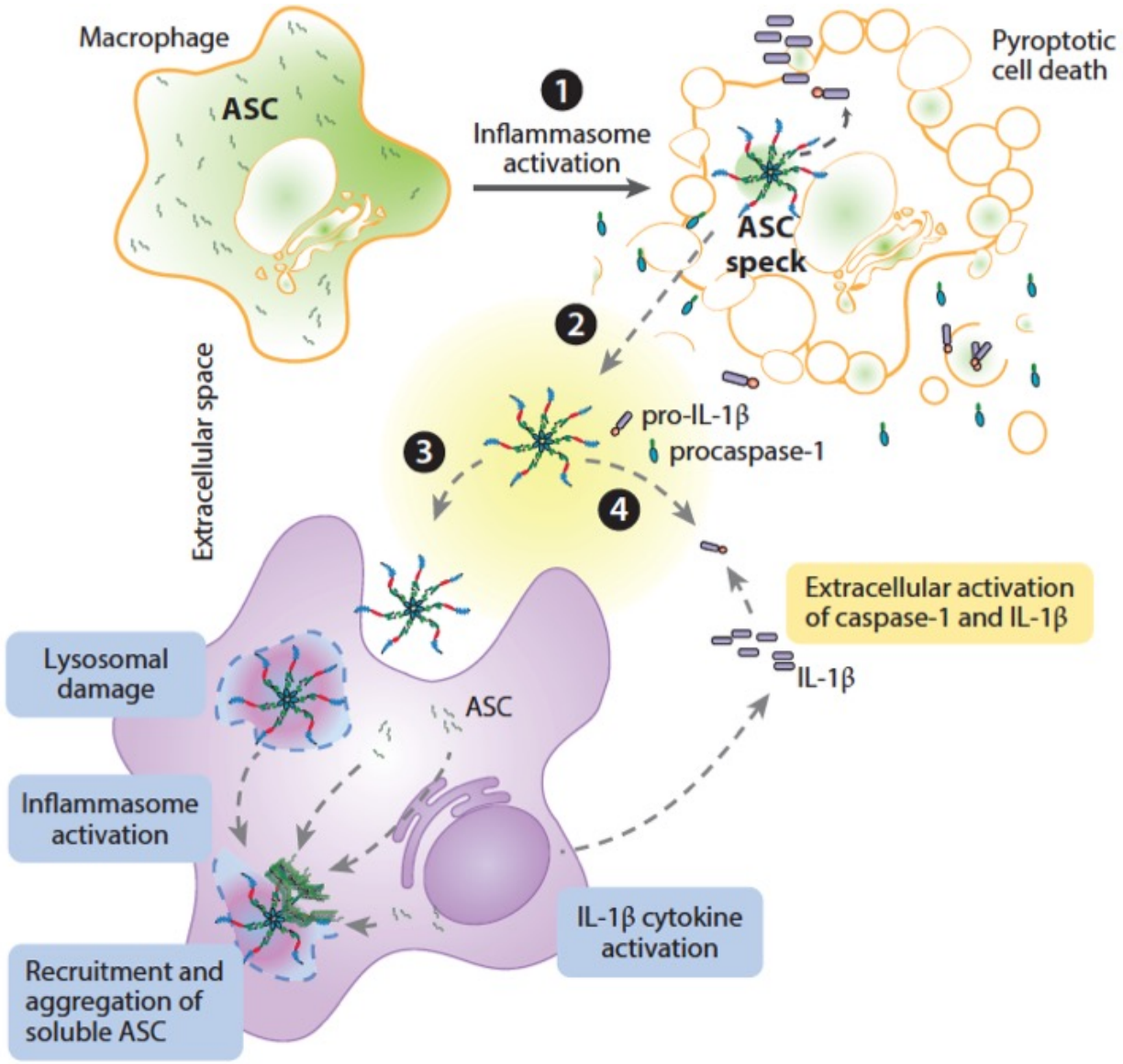
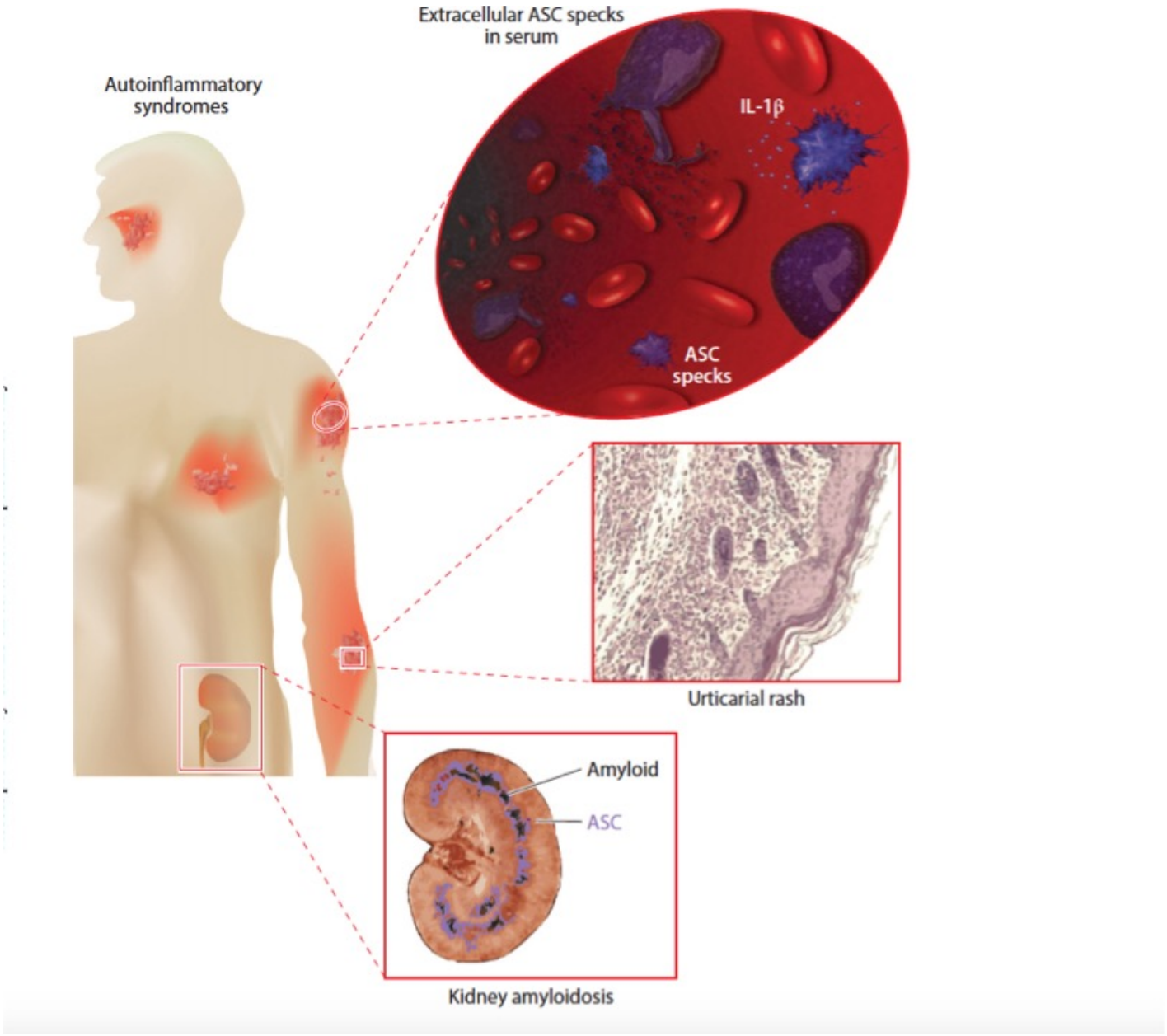


Figure 4

Partículas (Speck) contendo ASC acumulam no sangue de pacientes com AID.
Aparecem erupções cutaneas com infiltrado de PMN
ASC deposita-se nos rins próximos a depósitos de amilóide



Defeitos monogênicos dos inflamassomas

Febres periódicas hereditárias

CAPS (cryopyrin-associated periodic syndromes)

AIFEC/SCAN4 (autoinflammation with infantile enterocolitis)

FMF (familial Mediterranean fever)

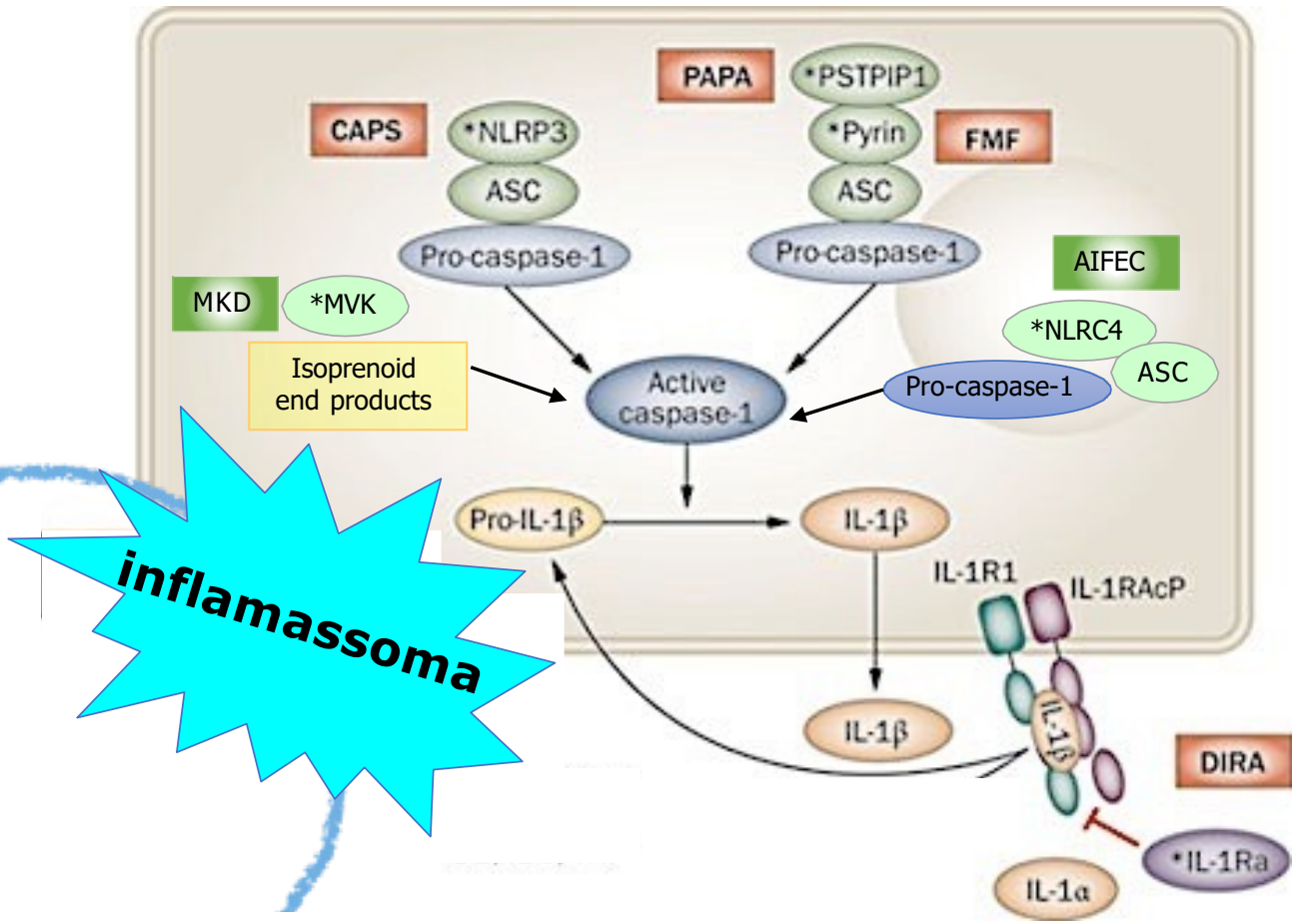
MKD (mevalonate kinase deficiency)

Síndromes piogênicas

PAPA (Pyogenic arthritis, pyoderma gangrenosum and acne) syndrome

DIRA (deficiency of IL-1RA)

Mutações genéticas raras



Modified from Aksentijevich , *2011*

Disregulação de IL-1ß (IL-18?)

Manifestações clínicas das síndromes autoinflamatórias

Mutações: Febre Familiar do Mediterrâneo
Familial Mediterranean Fever (FMF)

Mutações em PYRIN

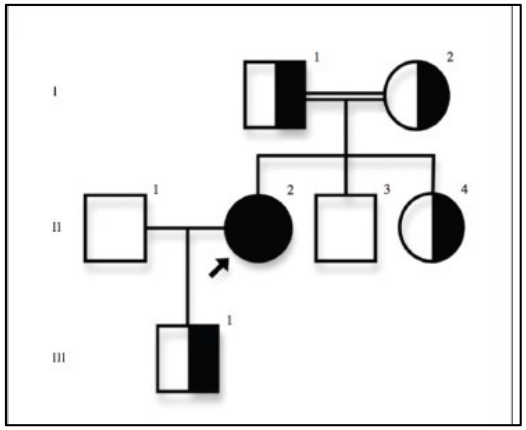
Domínio pyrin, presente em muitas prots

Permite a polimerização proteica

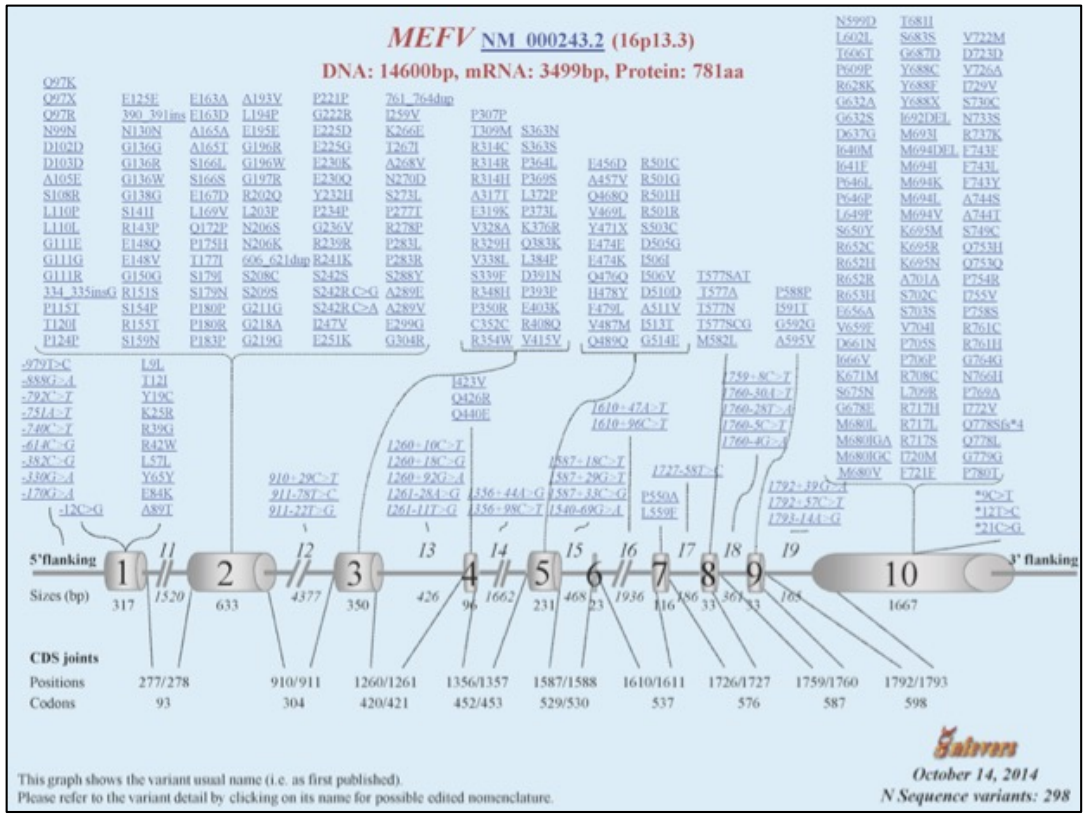
Todos os NLRP têm domínio pyrin

Funcionam tb como inibidores do inflamassoma

(Herança Autossômica Recessiva)



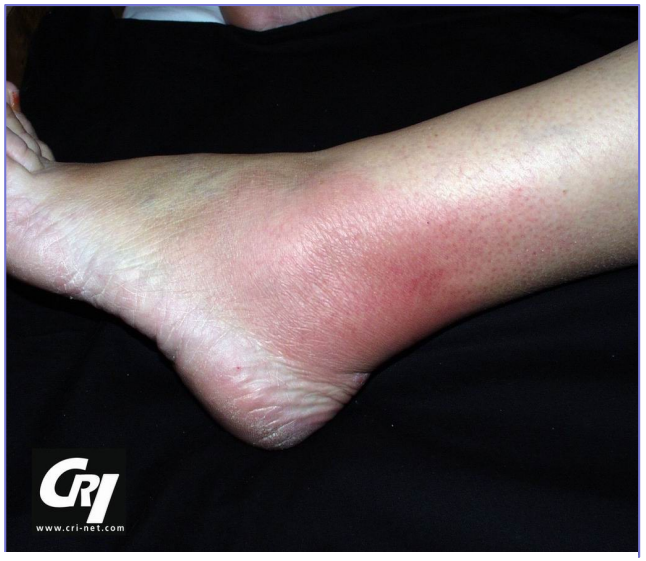
GENE: MEFV (16p13)



(Chae et al., 2009)

Febre Familiar do Mediterrâneo

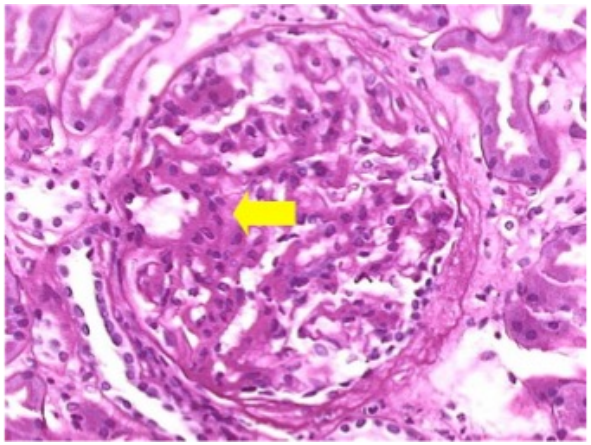
- Herança autossômica recessiva
- Mais comum em Judeus (1:135-1:500), Arabes, turcos, Armênios, mas também em outras populações mediterrâneas
- Episódios duram 1-3 dias com frequência variável
- Crises recorrentes de febre, poliserosite, eritema erisipeliode (perna, articulações), artrite



Erysipelas-like rash on legs

Simon et al 2005

- Dor abdominal (95%) – peritonite aguda estéril
- Pleurite 25-80% + periocardite (0.5%)
- Mono artrite (75%)
- Amiloidose sistêmica (13%)
- Mínima resposta a corticosteroides



Síndromes Auto-Inflamatórias associadas a NLPR3

CAPS (Cryopyrin-Associated Periodic Syndromes)- Inflamação associada a mutações em NLRP3)

Mutações em NLRP3 - três doenças:

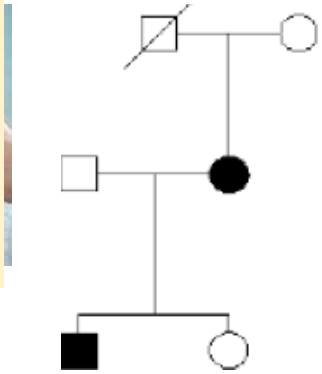
1 Familial Cold Autoinflammatory Sindrome (**FCAS**),
2 Muckle -Wells Syndrome (**MWS**)
3 Chronic Infantile Neurological Cutaneous and Arthritis (**CINCA**) ou Neonatal-Onset Multi-System Inflammatory Disease (**NOMID**)

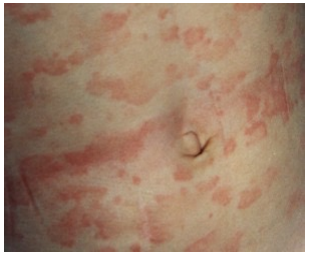
CAPS: Cryopyrin Associated Periodic Syndromes (NALP3)

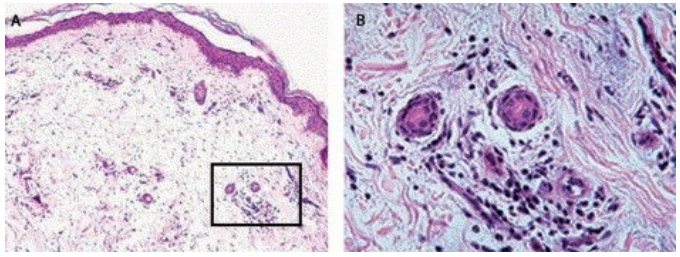
mild — severe

Familial cold autoinflammatory syndrome/FCAS

Quadro precipitado por exposição ao frio e tende a ter menor dimensão sistêmica

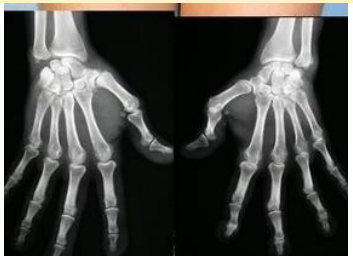






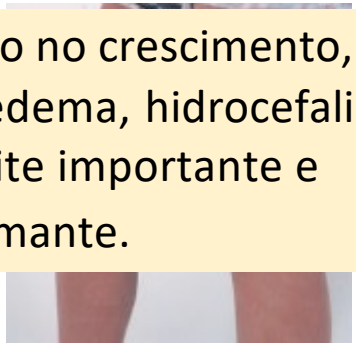
Muckle-Wells Syndrome /MWS

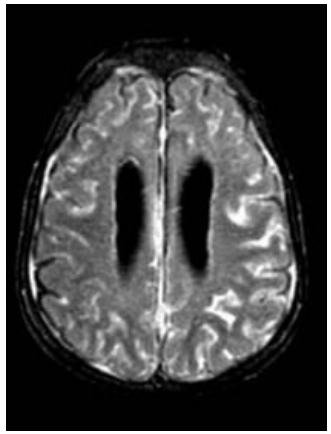
Não tem relação com frio
Surdez neurosensorial (20%)
Artrite



Neonatal-onset multisystemic inflammatory disease/NOMID

Atraso no crescimento, papiledema, hidrocefalia e artrite importante e deformante.

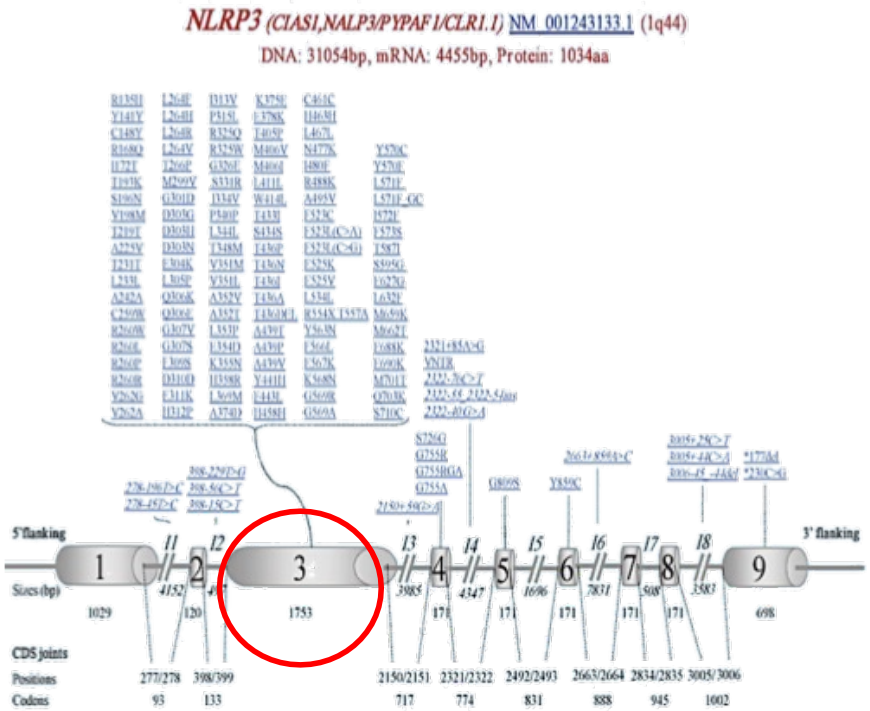




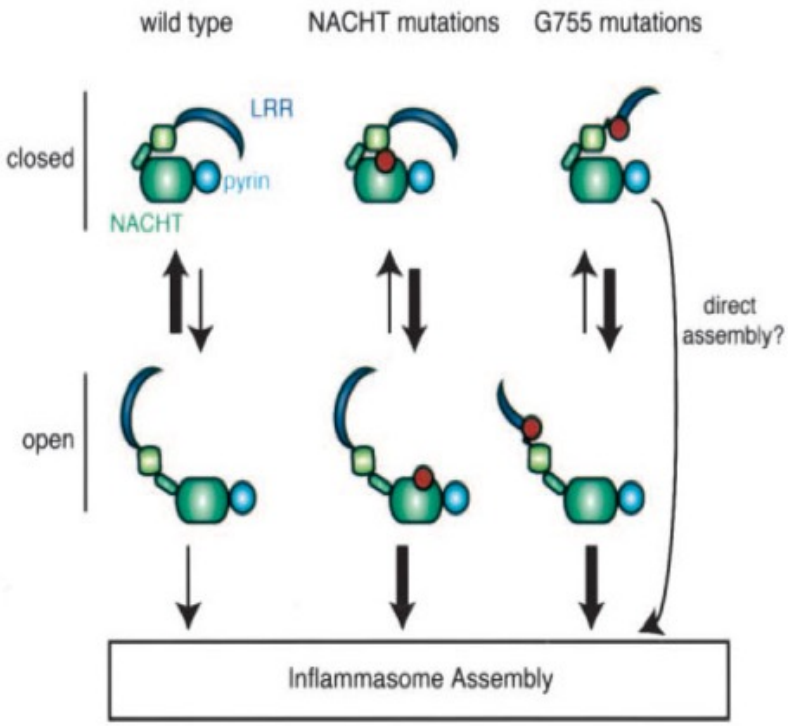
Febre recorrente, manifestações articulares (artralgia a artrite deformante) e rash cutâneo, em sua maioria semelhante à urticária. Também: conjuntivite não infecciosa, uveíte, vasculite, osteopenia

CAPS (Síndromes periódicas assoadas a criopirina)

1q44 CIAS1/NLRP3/cryopyrin (Hoffman, 2001)



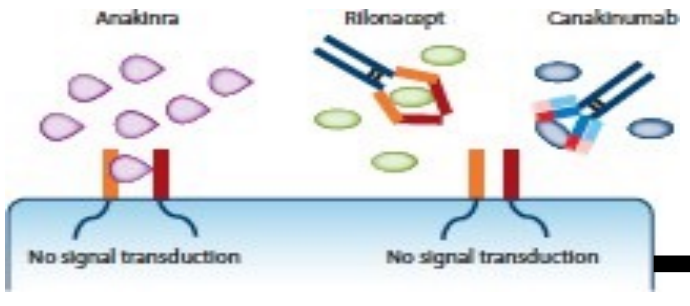
NACHT/NBD



From Aksentijevich, 2007

Ativação Constitutiva

Blocking of IL-1ß



↑↑IL-1ß

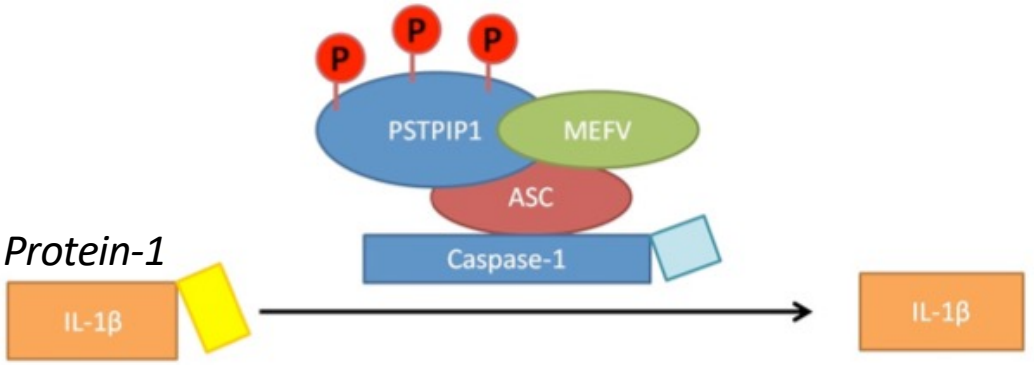
ANAKIRA=interleukin 1 receptor antagonista
Rilonacept= IL-1 Receotor Fusion Protein
Canakinumab= mAb anti-IL-1 beta

Síndrome PAPA (Pyogenic Arthritis Pyoderma grangrenosum and Acne)

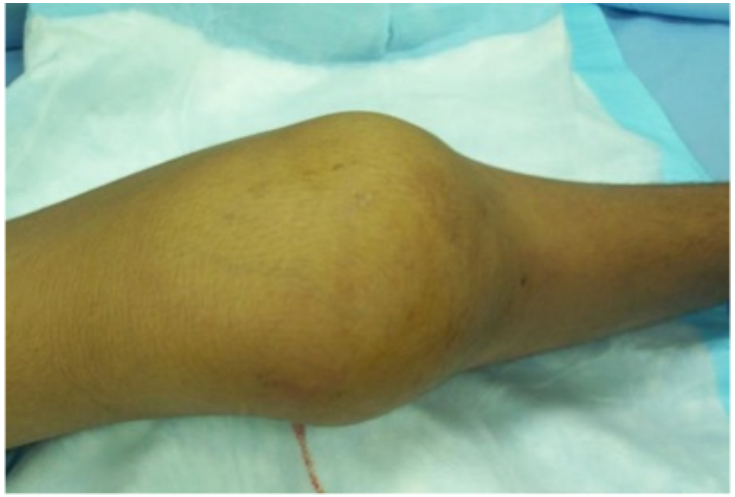
Artrite Estéril Piogênica, Pioderma Gangrenoso e Acn

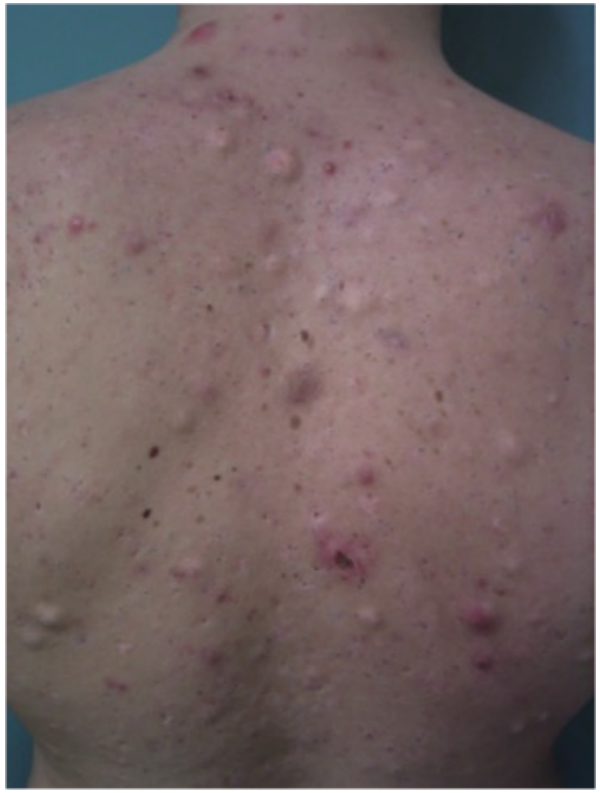
Mutações em PSTPIP1 (Chr 15)

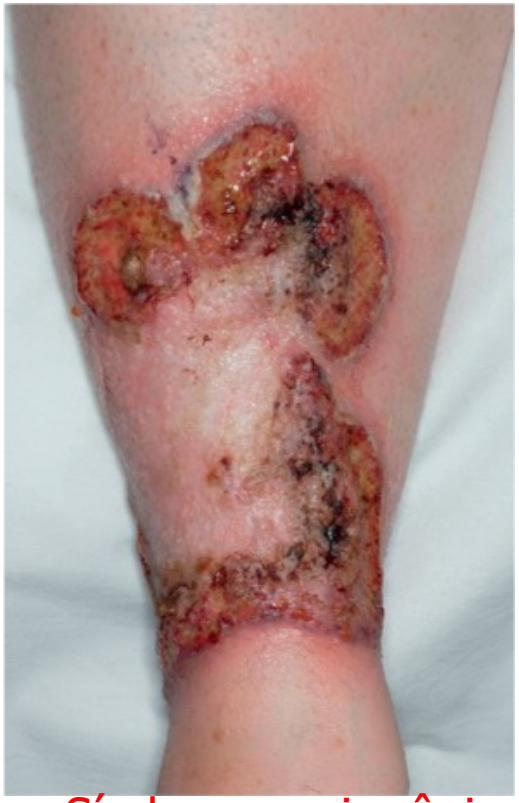
Prolina, Serina, Threonina Phosphatase Interacting Protein-1
Liga a Pyrin (MEFV). Interage com inflamassoma, forma piroxissomas.



Autossômica Dominante



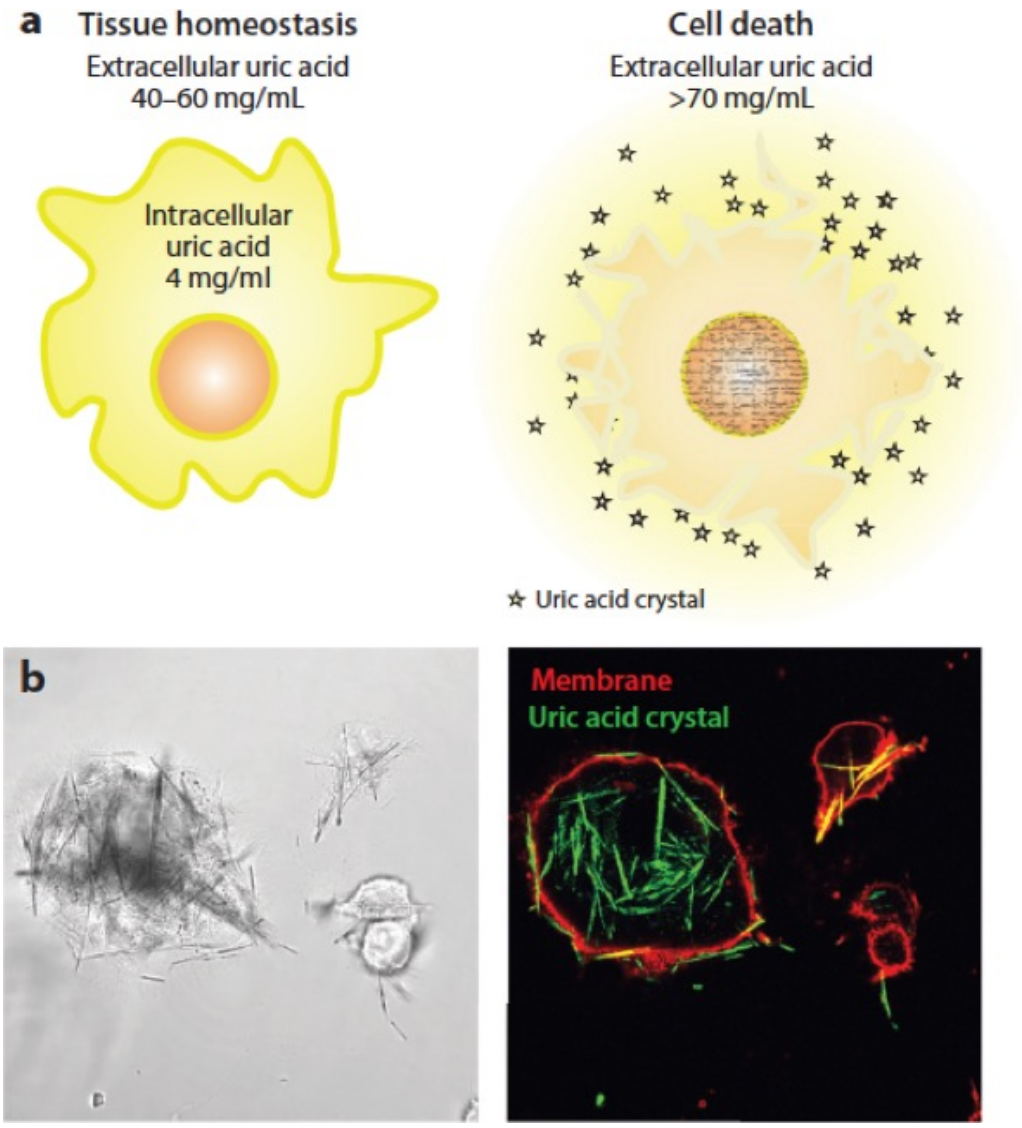


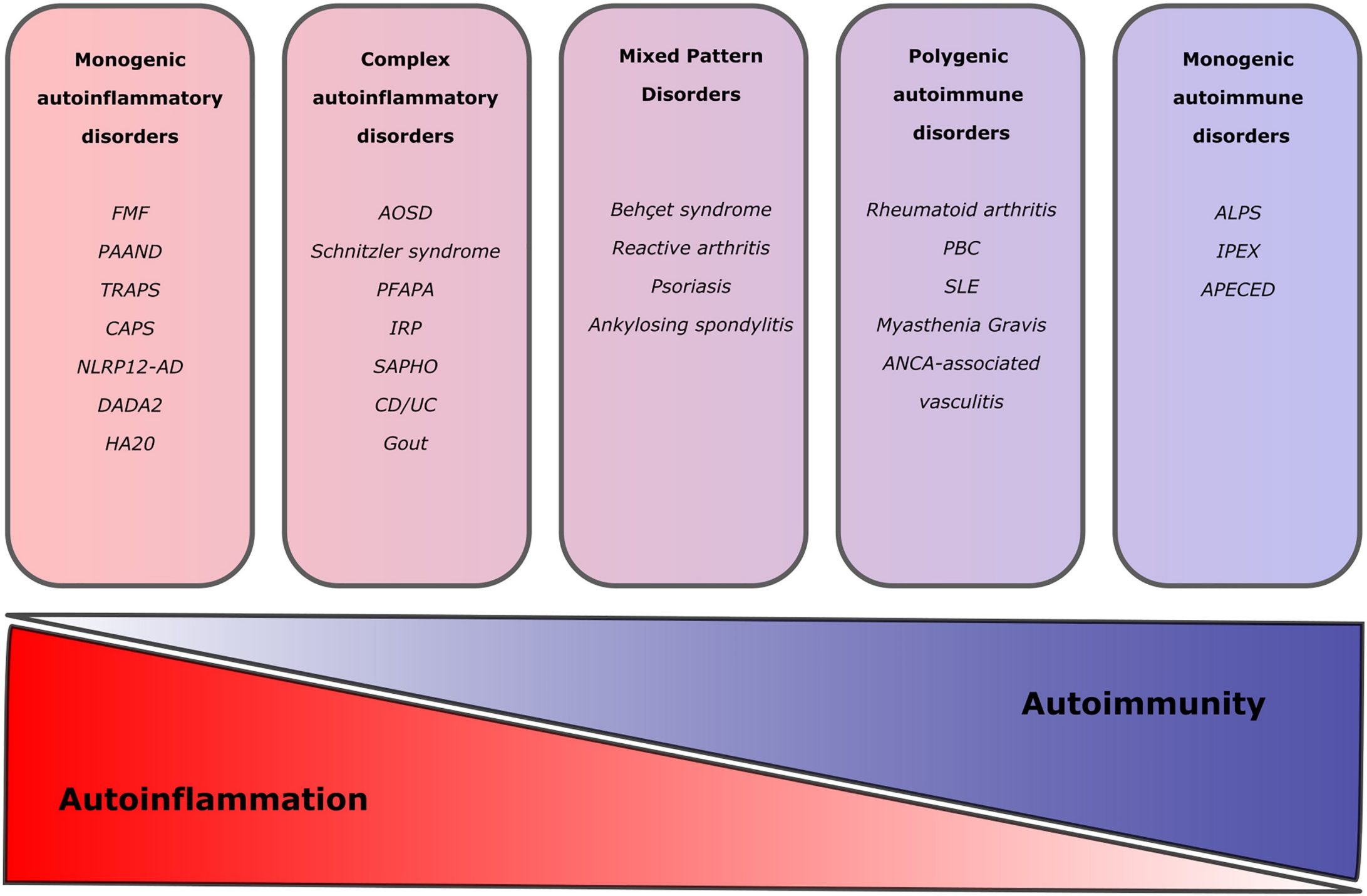


Síndromes piogênicas

Cristais de ácido úrico na Homeostasia e na Gota

Macrófagos ingerem os cristais de ac. Úrico e ativa-se o inflamassoma




Monogenic autoinflammatory disorders
FMF
PAAND
TRAPS
CAPS
NLRP12-AD
DADA2
HA20
Complex autoinflammatory disorders
AOSD
Schnitzler syndrome
PFAPA
IRP
SAPHO
CD/UC
Gout
Mixed Pattern Disorders
Behçet syndrome
Reactive arthritis
Psoriasis
Ankylosing spondylitis
Polygenic autoimmune disorders
Rheumatoid arthritis
PBC
SLE
Myasthenia Gravis
ANCA-associated vasculitis
Monogenic autoimmune disorders
ALPS
IPEX
APECED
Autoimmunity
Autoinflammation

ER stress *
Defective post-tranlational modification or protein misfolding generates ER stress and results in ROS and IL-1beta production
TRAPS

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NF-kB pathway activation through ubiquitination disorders or dysregulated NOD2 signaling.
HA20, ORAS, LUBAC deficiency, CRIA

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FMF, PAAND, CAPS, NLRP12-AD, HIDS

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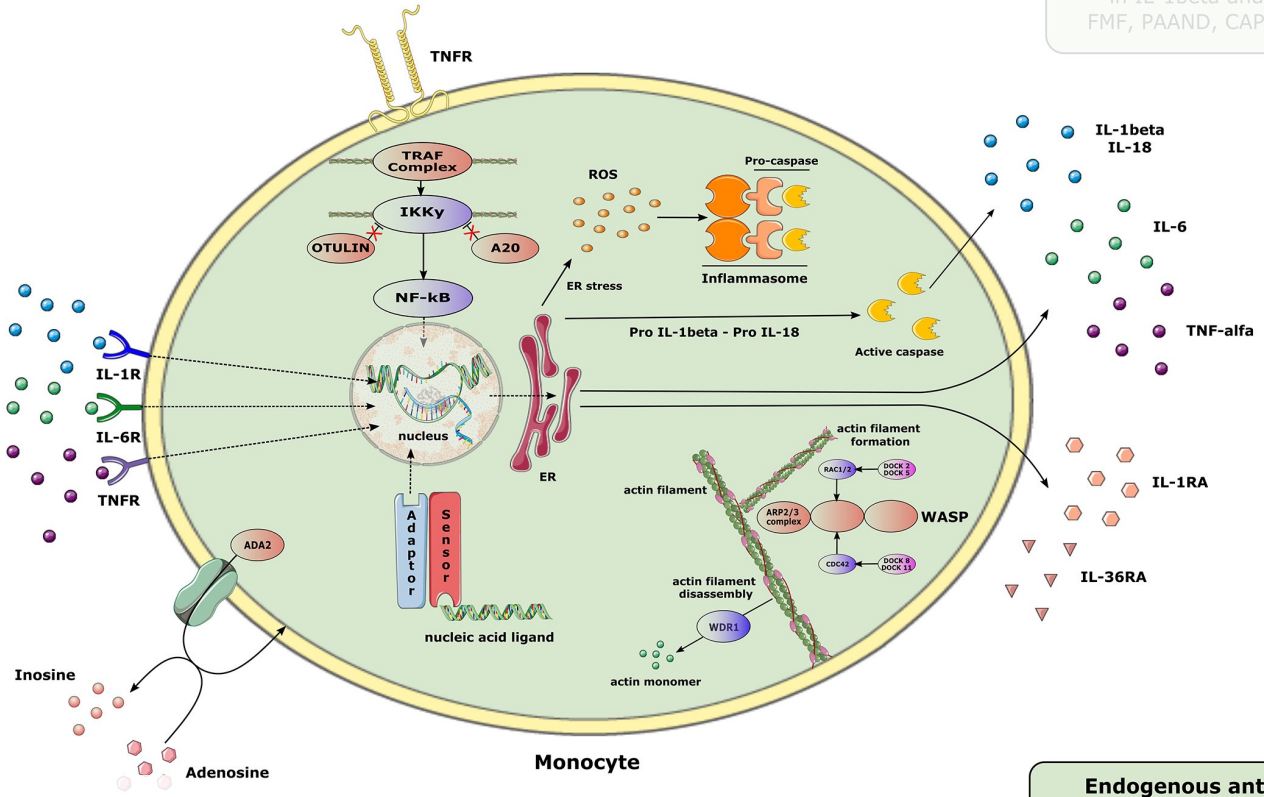
Reduced ADA2 enzymatic activity resulting in defective differentiation of M2 anti-inflammatory macrophages and impaired secretion of pro-inflammatory cytokines by neutrophils
DADA2



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Loss-of-function mutations in genes encoding endogenous cytokine antagonist impair the antagonization of proinflammatory signals
DIRA, DITRA

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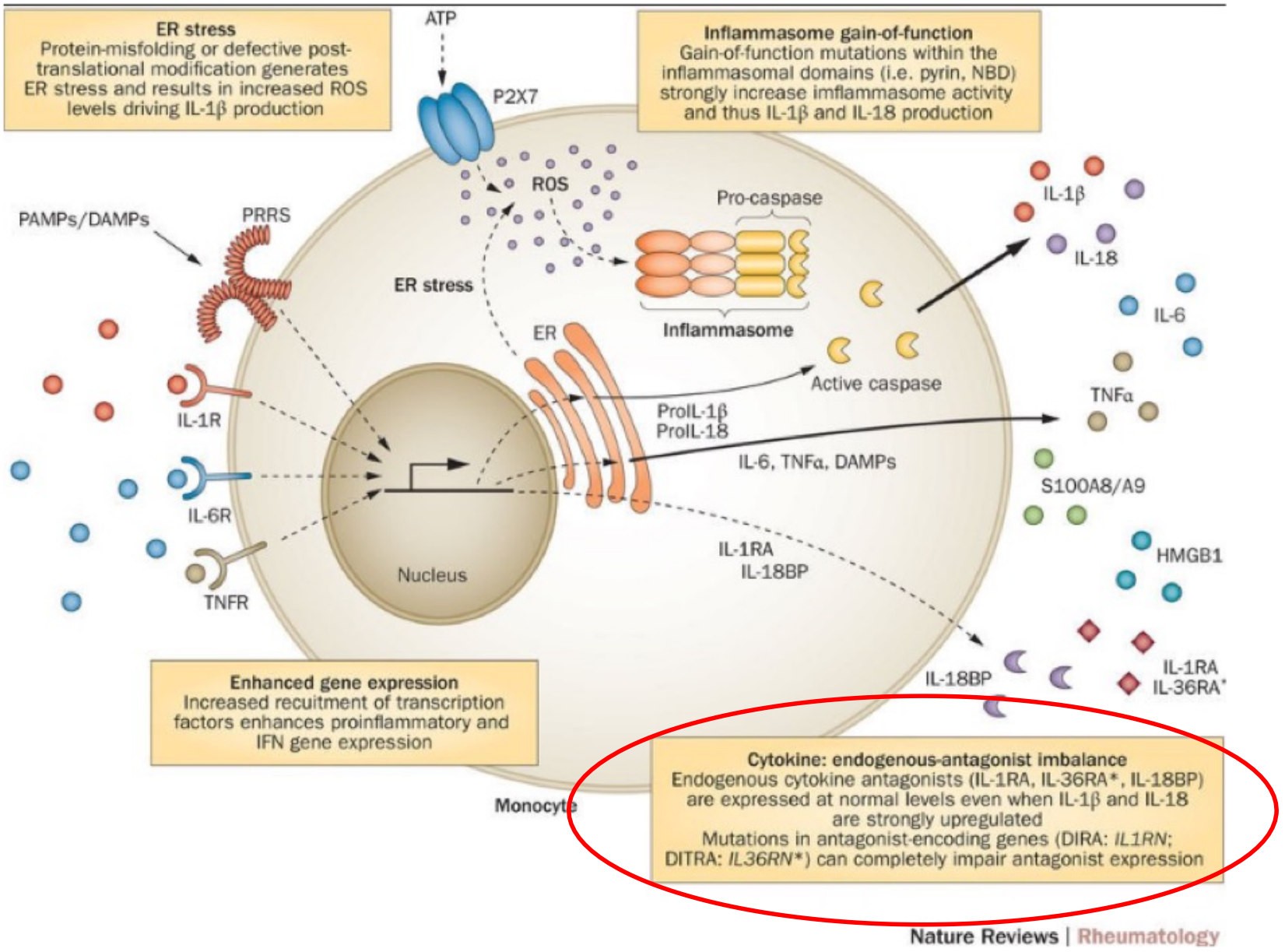
Actinopathies
Mutations in genes involved in the regulation of actin filament formation and disassembly
CDC42 deficiency, WDR1 deficiency, ARPC1B deficiency

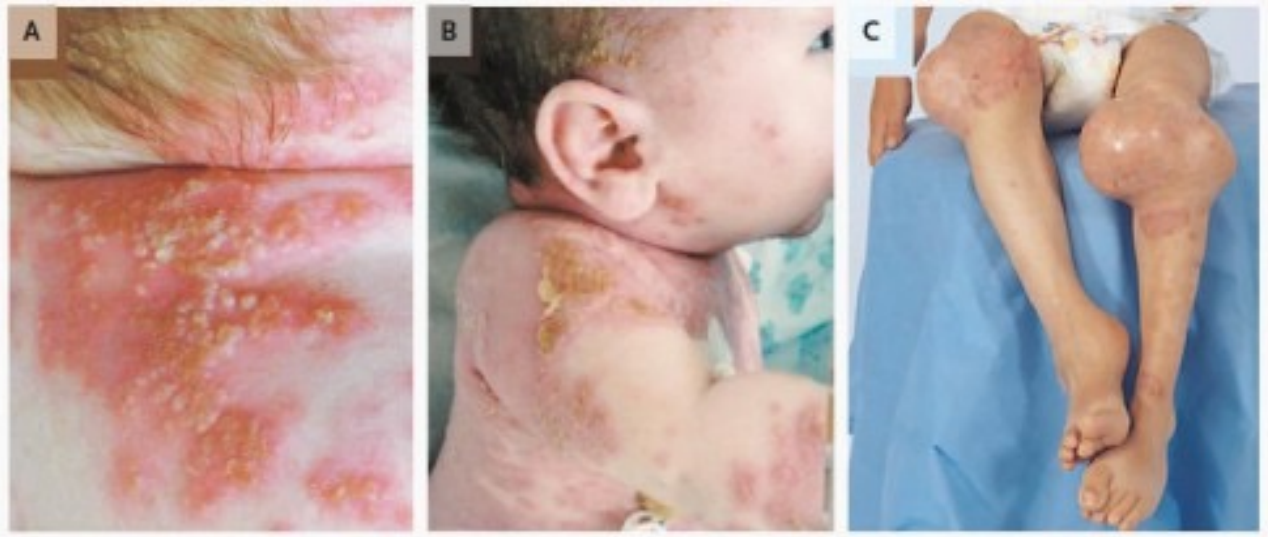
https://www.sciencedirect.com/science/article/pii/S1568997221000379

Síndromes Autoinflamatórias: Mecanismos



Síndrome DIRA (Deficient IL-1 Receptor Antagonist Gene)

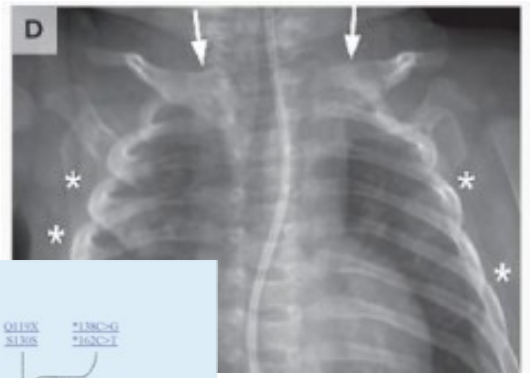
- Dermatite pustular
- Deformidades ósseas
- Osteomielite multifocal
- Vasculte
- Doença óssea inflamatória

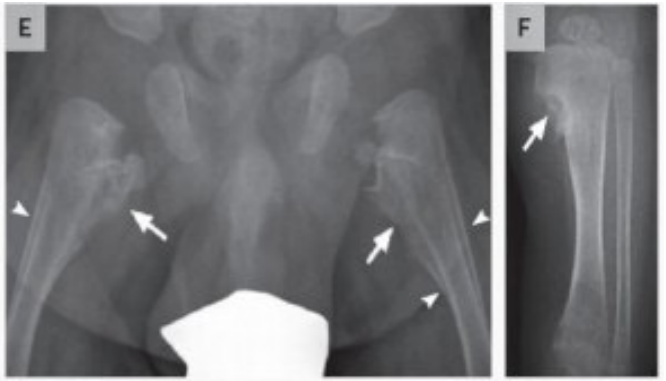


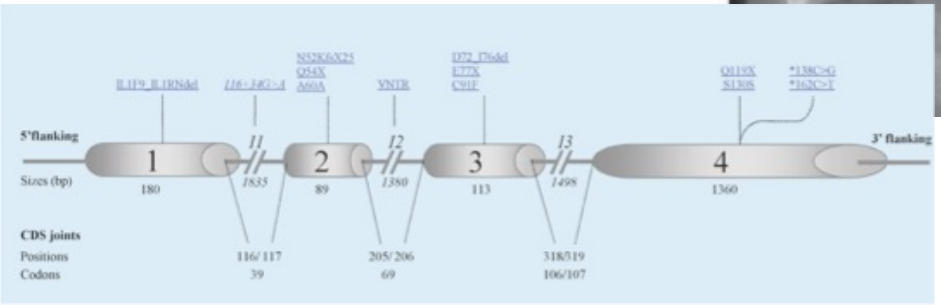
Responde ao tratamento com IL-1Ra

Mutação em *IL-1RN (2q14.2)*
(autossomica recessiva)

Se não tratada, pode levar . insuficiência respiratória e morte por tempestade de citocinas







Síndromes piogênicas

Doença piogênica cutânea (Deficiência no IL-36R e psoríase do tipo 2)

- Este grupo de doenças caracteriza-se por distúrbios cutâneos do tipo psoríaase com mutação nos genes CARD14 e IL36RN67

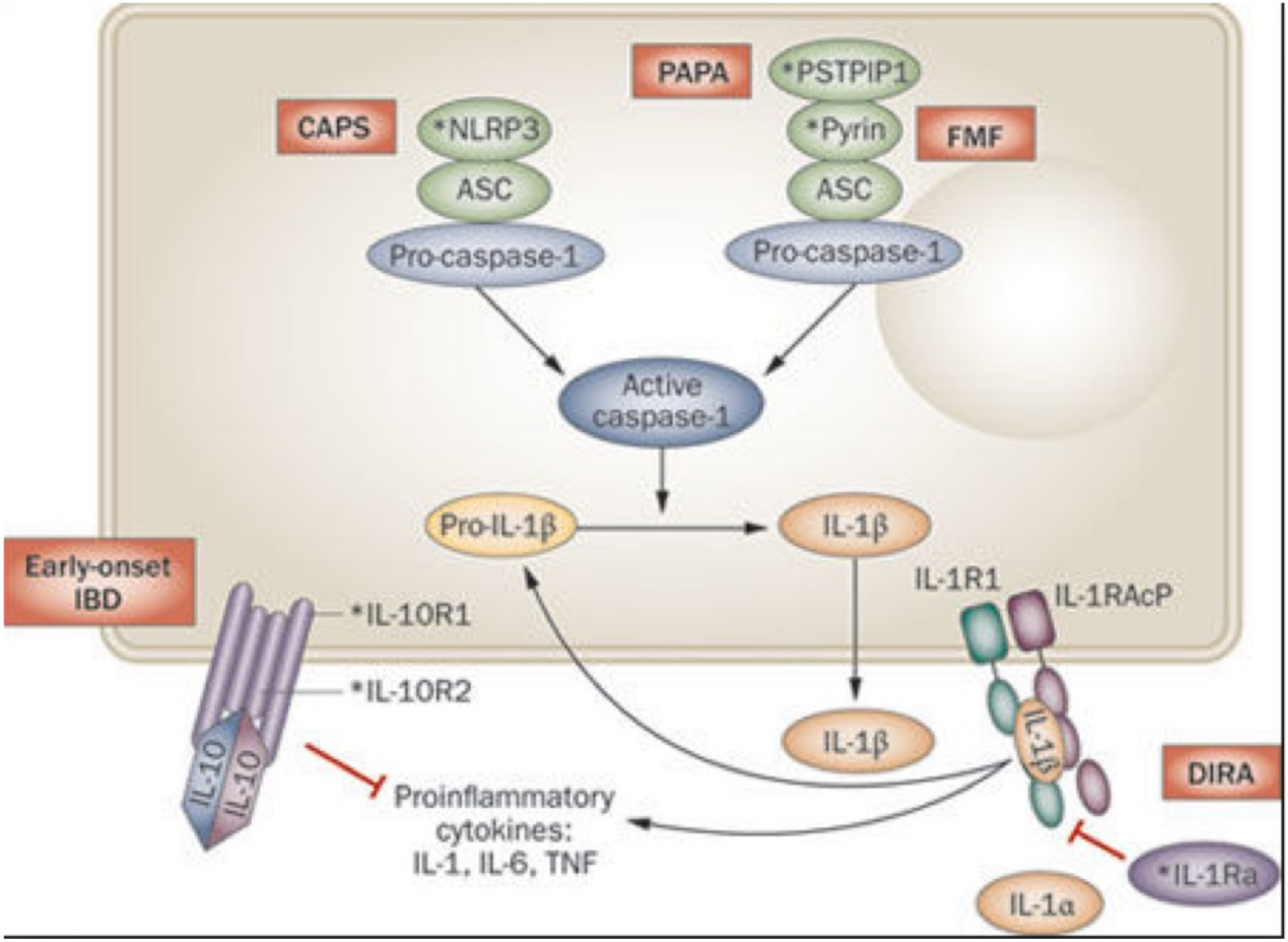
- Sutos recorrentes

- Quadro inicia-se de forma abrupta com febre baixa, artrite e pústulas cutâneas generalizadas, com elevação de provas inflamatórias que podem evoluir para infecção cutânea e morte por sepse

- A psoríase do tipo 2 tem comportamento de lesões psoriaseformes clássicas, mas com tendência familiar, início precoce e tendem a formar placas grandes

– Nenhuma das duas tem acometimento articular

Doença inflamatória intestinal e defeito no receptor da IL-10



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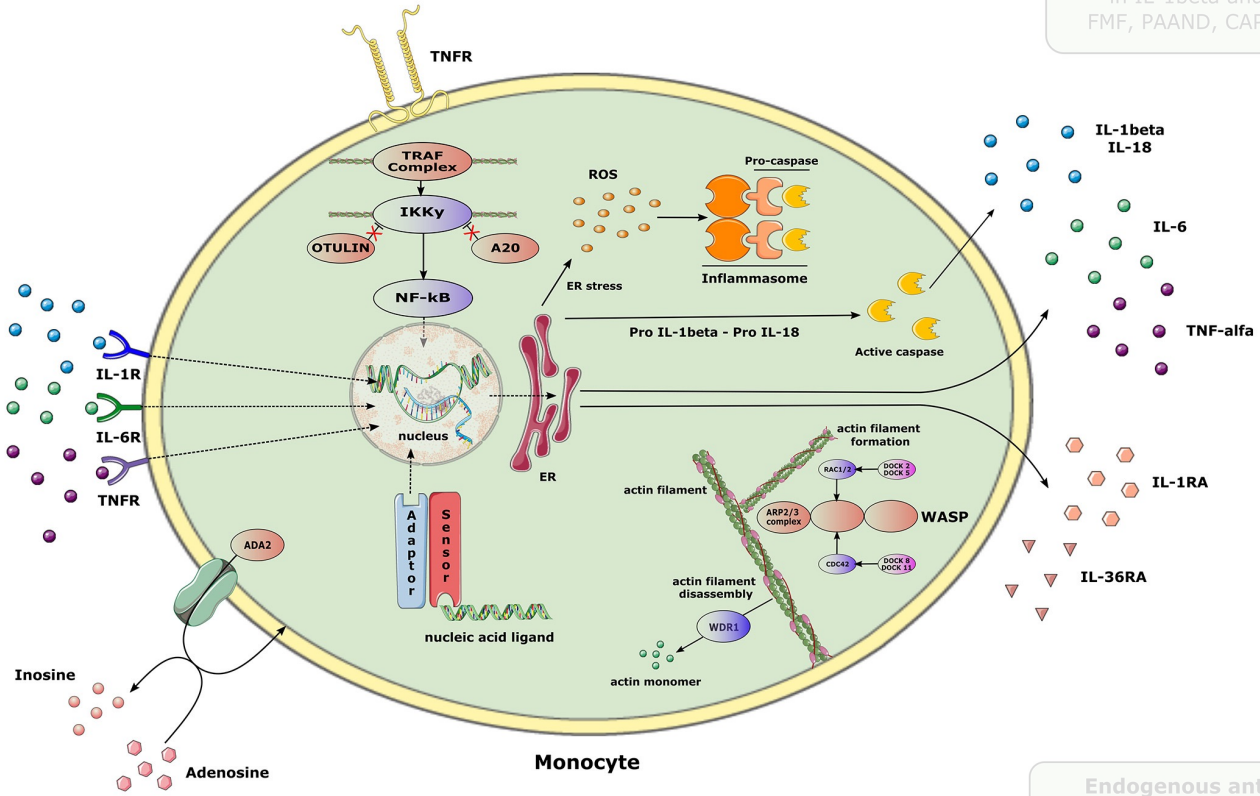

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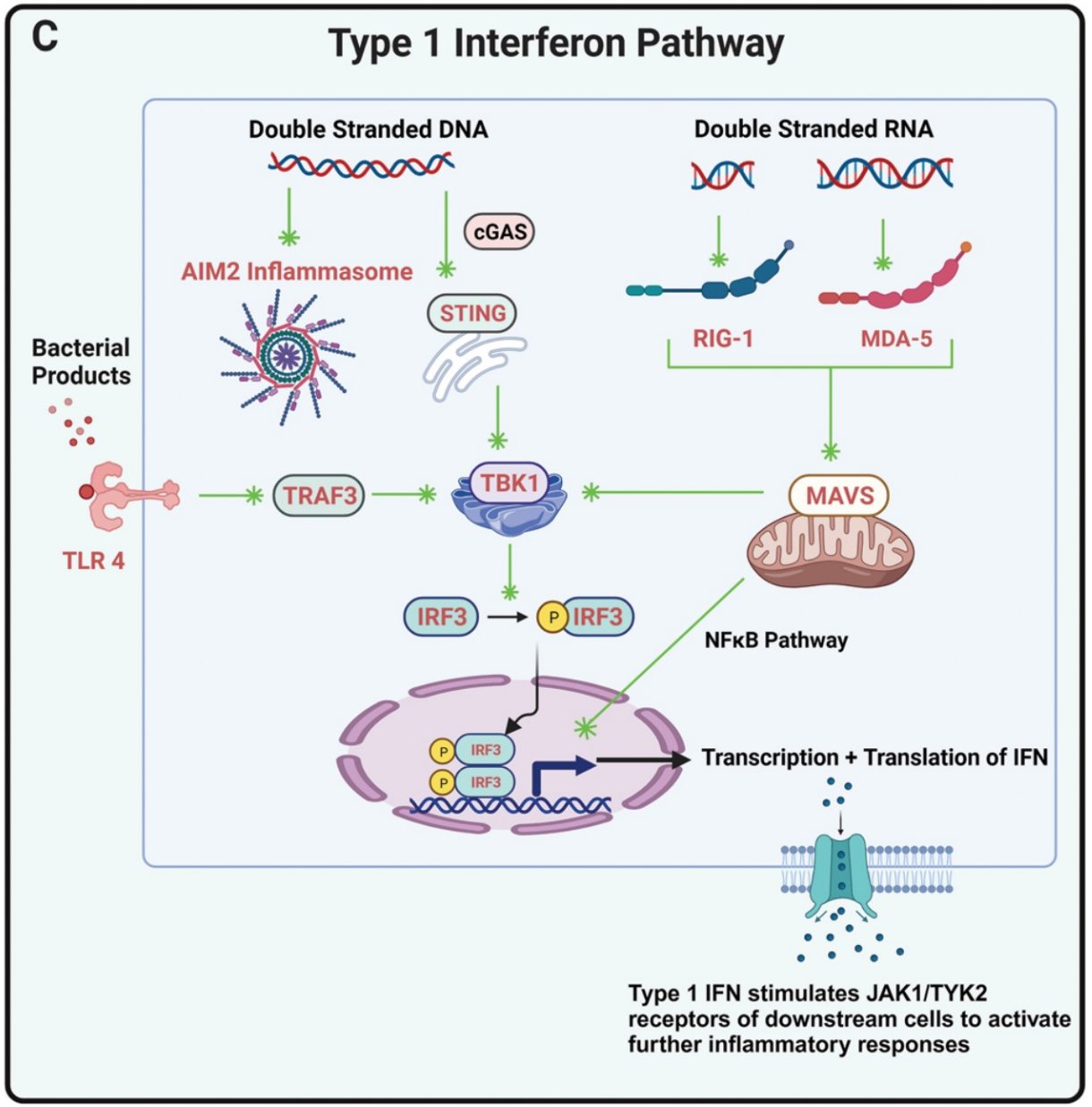
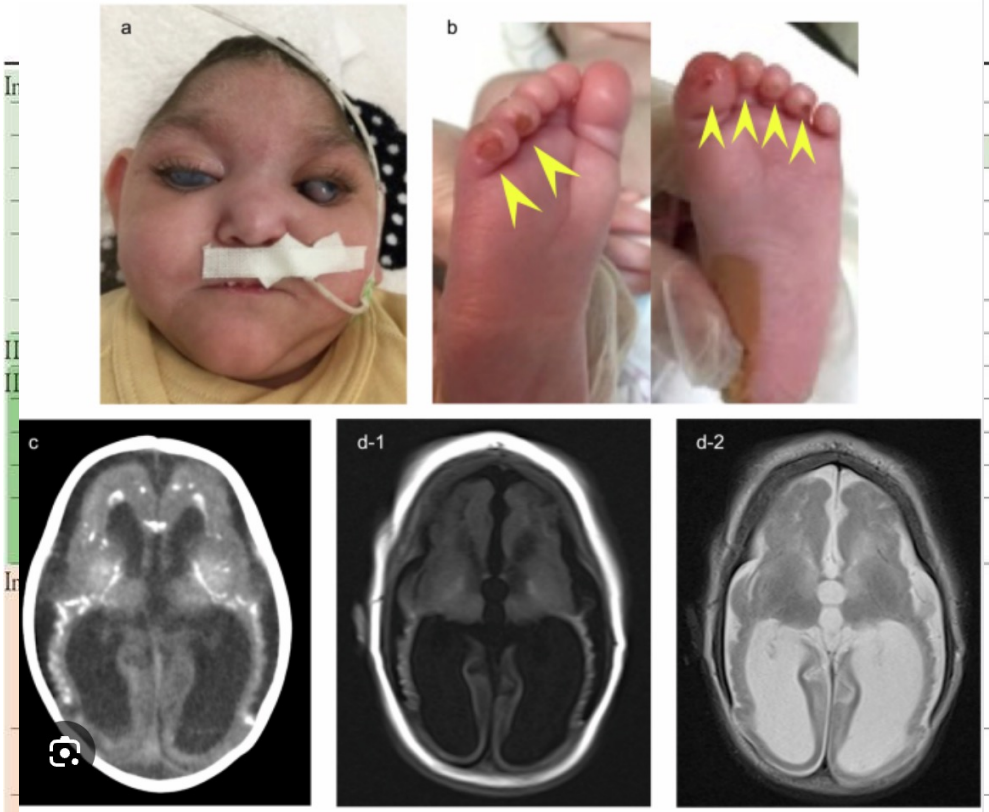


Figure 2C: The interferon pathway is activated by the accumulation of nucleic acid in the cytosol. Double stranded DNA is sensed by cGAS which generates cGAMP and stimulates downstream STING (endoplasmic reticulum). STING activates TBK1 (golgi) which phosphorylates IRF3 leading to its nuclear translocation to drive expression and release of type 1 interferon. This subsequently stimulates JAK1/TYK2 receptors of downstream cells to signal through the JAK/STAT pathway (not shown) to promote further inflammatory gene expression. In addition to RIG-1, MDA-5, AIM2, and cGAS, there are numerous other sensors of nucleic acid such as endosomal TLRs, IFI-16, ZBP1 (not shown).

Table 1. Heat map of autoinflammatory syndromes discussed in the main text.

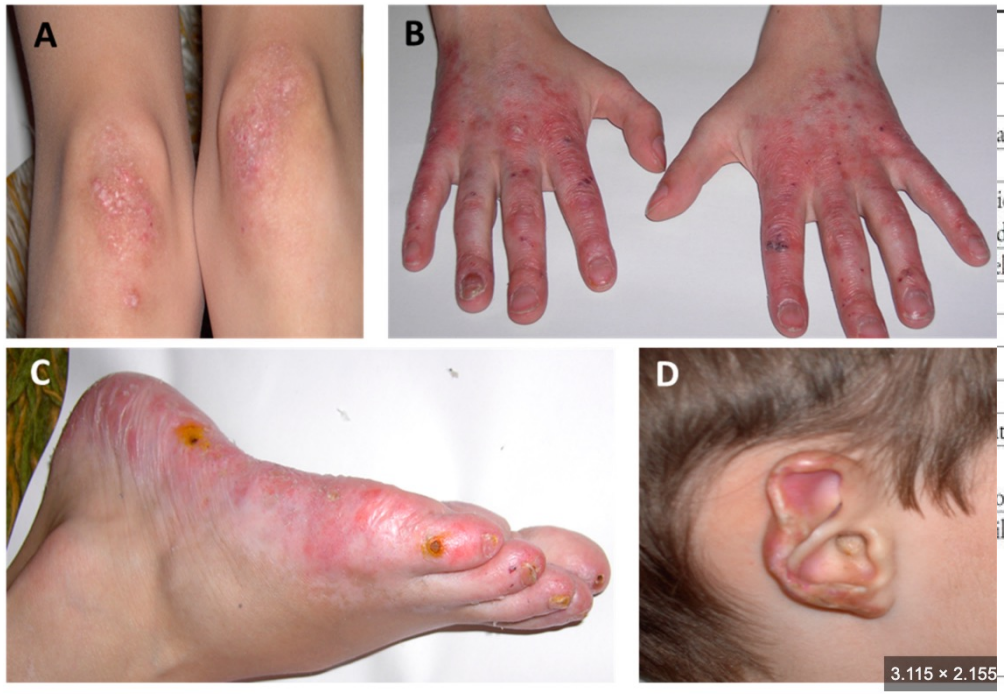
Nature



A case of severe Aicardi–Goutières syndrome with a homozygous RNASEH2B intronic variant | Human...

Visitar ›

MDPI



STING-Associated Vasculopathy with Onset in Infancy: A Review Focusing on Pathophysiology and...

Visitar ›

PRAAS	*PSMB4, PSMA3, POMP, PSMG, PSMB8, PSMB9*[a], *PSMB10*	Dental dysplasia, aortic calcification
COPA syndrome	*COPA*	Kidney dysfunction
OPAID[a]	*OAS1*	FTT
ATAD3A deficiency[a]	*ATAD3A*	Dystonia, thyroiditis, calcifications, HCM
ZNFX1 deficiency[a]	*ZNFX1*	Renal disease

AGS: Aicardi-Goutières Syndrome (Imita infecção viral)
SAVI: **S**timulator of **I**nterferon **G**enes (**STING**)–**A**ssociated **V**asculopathy with **I**nfantile onset
SMS: **S**TM245–**M**ediated **S**yndrome (também chamada de **SINE syndrome** – *STING-Independent Nuclease-related autoinflammatory disease*)
PRASS: Proteasome-Associated Autoinflammatory Syndrome
COPA: **C**oatomer subunit alpha (**COPA**) **Syndrome (**Transporte retrogrado RE-CG)

Sigla / Nome	Mecanismo principal	Manifestação típica	Idade de início	Órgão-alvo principal	Genética / Mutação
AGS (Aicardi-Goutières Syndrome)	Defeitos em enzimas que degradam DNA/RNA	Encefalopatia, calcificações cerebrais, lesões tipo chilblains	Neonatal ou primeiros meses	Cérebro, pele, fígado	TREX1, RNASEH2A/B/C, SAMHD1, ADAR, IFIH1
SAVI (STING-Associated Vasculopathy with Infantile onset)	Ativação constitutiva do STING	Vasculite, úlceras, pneumonia intersticial	Primeiros meses de vida	Pulmão, pele, vasos	TMEM173 (STING)
SMS (STING-Independent Nuclease-related autoinflammatory disease)	Mutação em RNASET2 (STM245), ativação independente do STING	Encefalopatia, lesões cutâneas, calcificações cerebrais	Infância	Cérebro, pele	STM245 / RNASET2
PRASS (Proteasome-Associated Autoinflammatory Syndrome)	Defeito na degradação de proteínas → ativação crônica de IFN	Lipoatrofia, febre, inflamação sistêmica	Infância	Pele, fígado, imune	PSMB8, PSMB4, etc.
COPA Syndrome	Defeito no transporte retrógrado Golgi → RE, ativa STING	Pneumonite, glomerulonefrite, artrite	Infância / adolescência	Pulmão, rim, articulações	COPA

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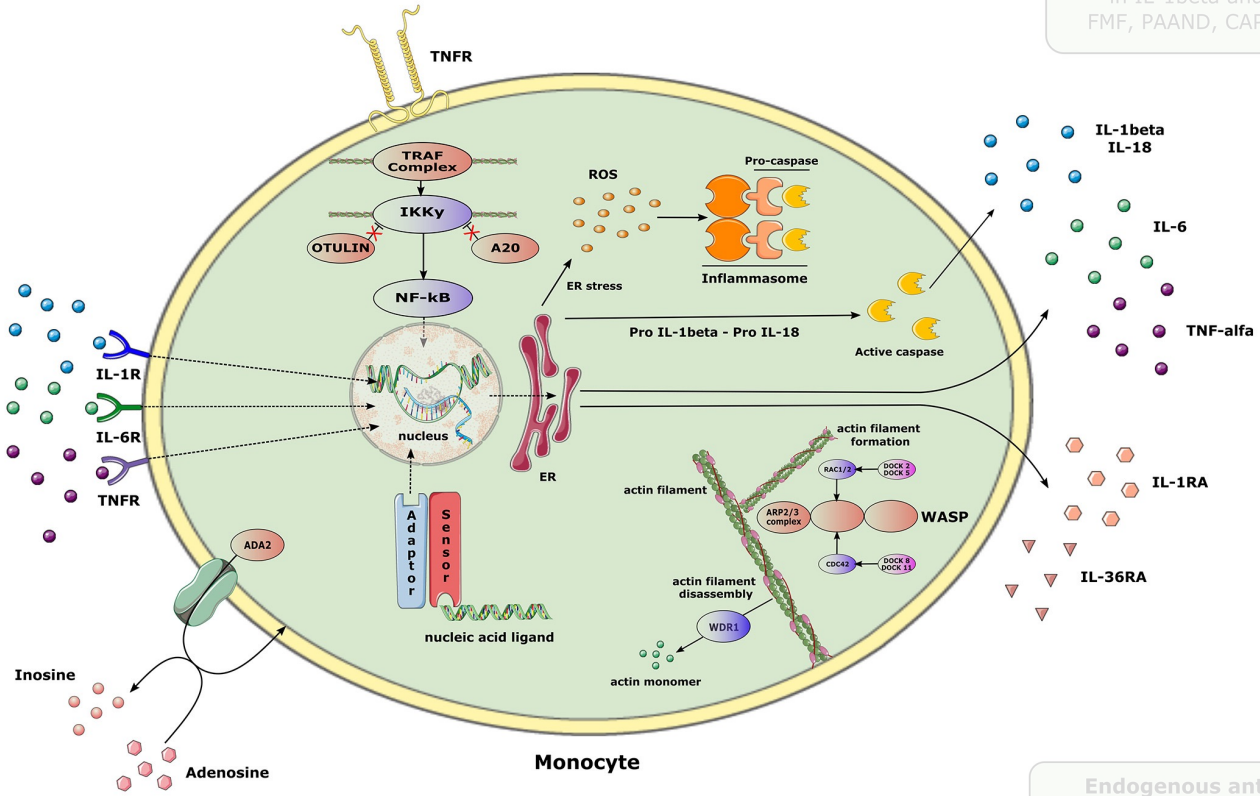

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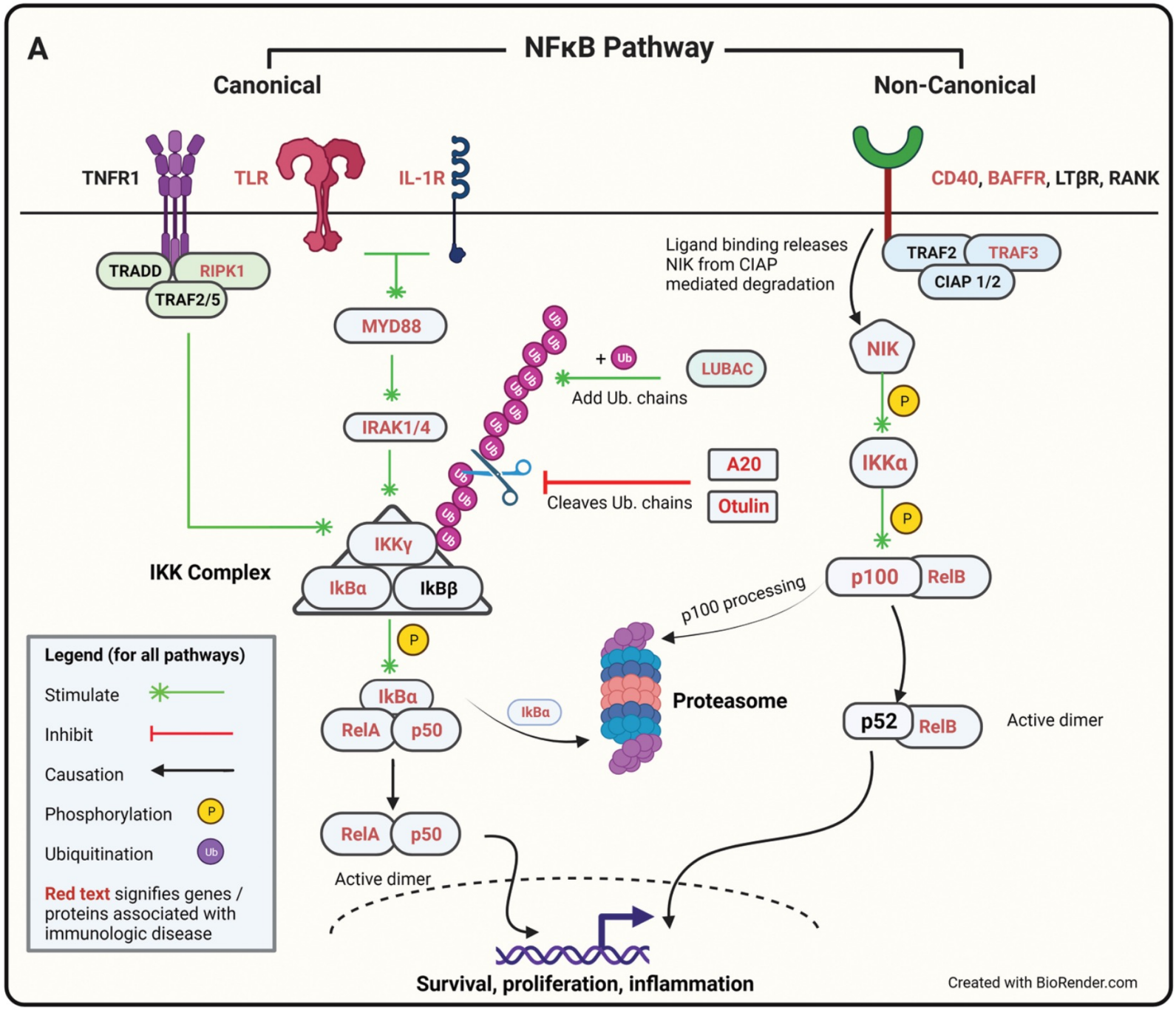


Figure 2A: The NFκB pathway is important in regulating immunity and inflammation, but also cell survival, growth and development. It is mediated by five major components: RelA (p65), RelB, c-Rel, NFκB1 (p105/50), and NFκB (p100/52).

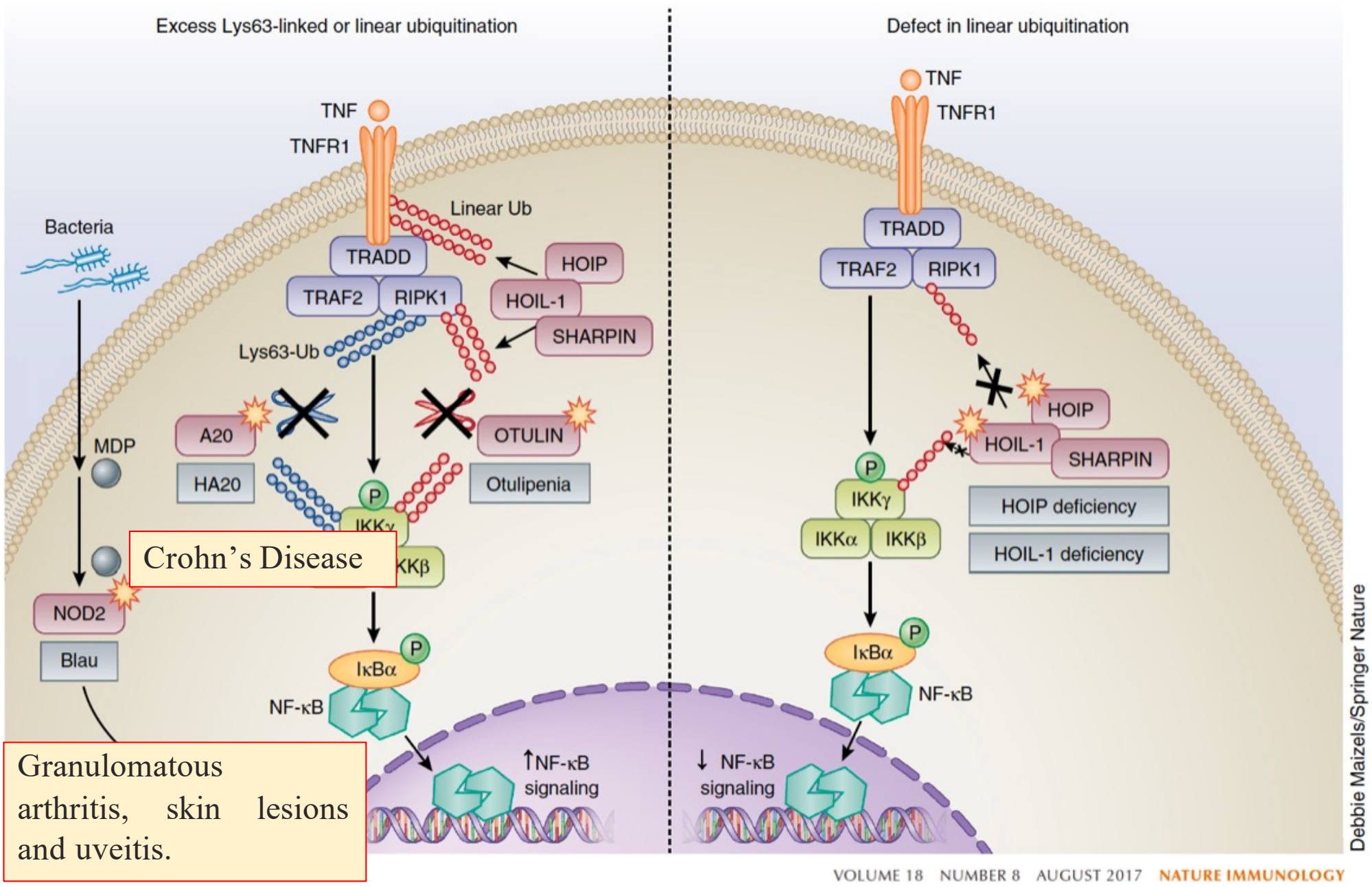
The **canonical** pathway is activated by diverse stimuli such as TNF receptor superfamily members, pattern recognition and cytokine receptors, and B and T cell receptors (not shown). Signaling converges onto the IKK complex which phosphorylates IκBα leading to ubiquitin mediated destruction in the proteasome. This releases the active RelA/p50 dimer to translocate into the nucleus and bind the κB enhancer, driving inflammatory gene expression.

Throughout, receptor signaling complexes (such as IKK) are stabilized by long chains of Met-1 linked ubiquitin generated by LUBAC. This is countered by deubiquitinases such as A20 and Otulin, which cleave ubiquitin chains, destabilizing receptor signaling complexes and dampening pathway activation.

The **non-canonical** pathway differs in that signalling does not converge on the IKK complex. It is activated in response to a more selective set of stimuli namely CD40, BAFFR, LTβR, and RANK. Without stimulation, the central component NIK is tagged for ubiquitin mediated destruction by the TRAF2-3/CIAP1-2 complex. Upon stimulation, this complex is recruited to the membrane, releasing NIK to phosphorylate and activate downstream components leading to the translocation of RelB/p52 active dimers into the nucleus to drive gene expression.

https://www.jrheum.org/content/jrheum/51/9/848.full.pdf

Síndromes Autoinflamatórias mediadas pela via NFkB



Síndromes Autoinflamatórias mediadas pela via NFkB

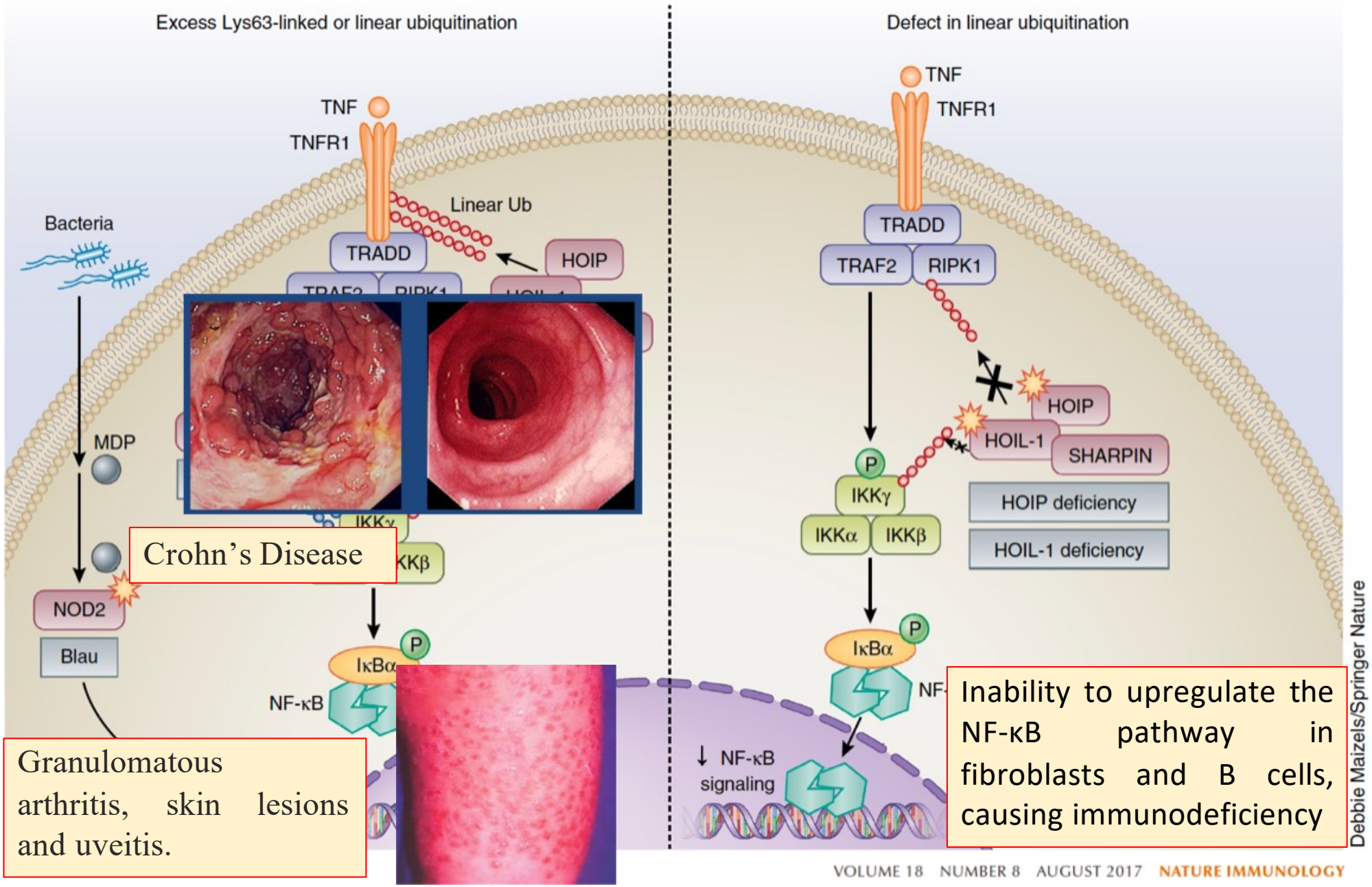


Table 1. Heat map of autoinflammatory syndromes discussed in the main text.

Category	Autoinflammatory Condition	Gene	Clinical Features														
			Fever	Joint	Rash	Ulcer	Eye	GI	CNS	Vasculitis	Lung	Bone	HLH	Infection	Lipodystrophy	Thrombocytopenia	DD	Other
NF-κB–opathies	Haploinsufficiency of A20	*TNFAIP3*																
	RAID	*RELA*																
	RIPK1 deficiency	*RIPK1*																
	RIPK1 gain-of-function	*RIPK1*																
	Otulipenia	*FAM105B*																Lymphadenopathy
	Blau syndrome	*NOD2*																Sarcoidosis
	CARD14-mediated pustular psoriasis	*CARD14*																
	SYK-associated AID[a]	*SYK*																Lymphoma
	TBK1 deficiency[a]	*TBK1*																Short stature
	DEX[a]	*ELF4*																Perianal abscesses
	ROSAH[a]	*ALPK1*																Splenomegaly, anhidrosis
	NDAS[a]	*IKBKG*																Panniculitis

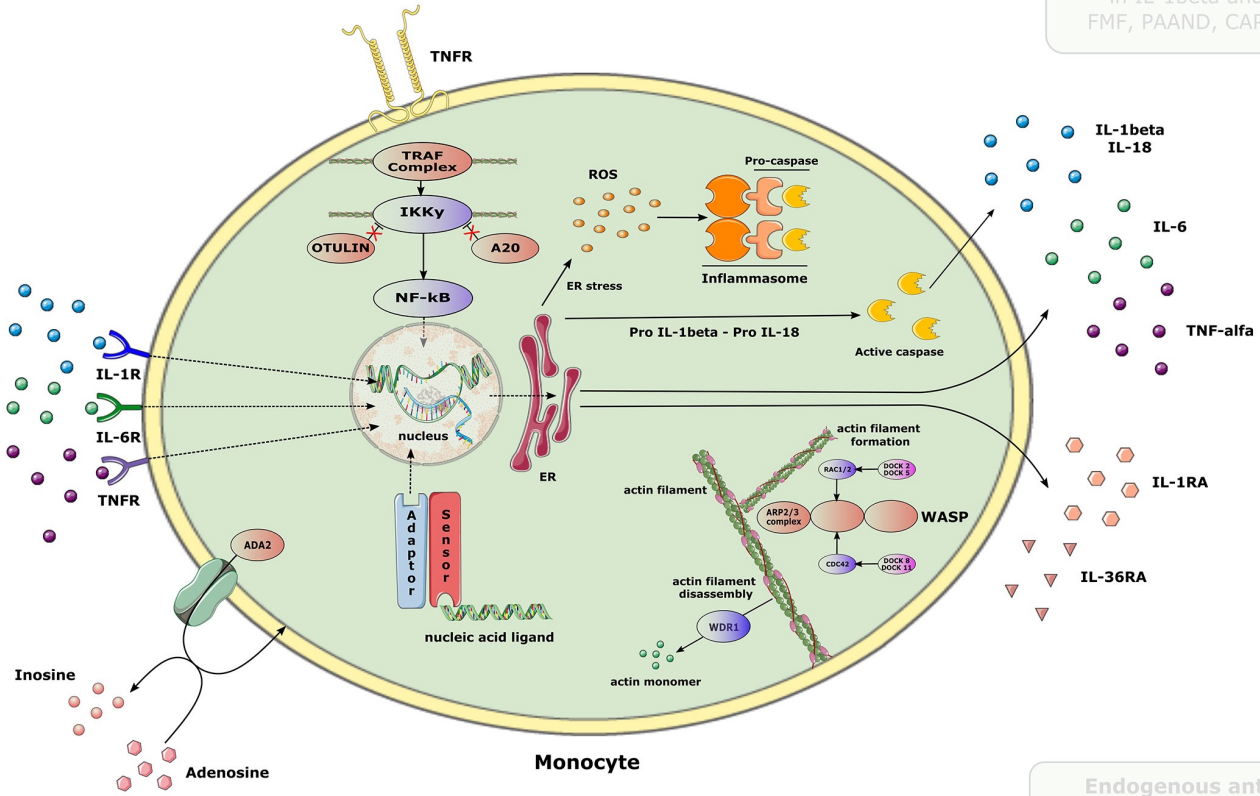
RAID: RelA-Associated Inflammatory Disease

ER stress *
Defective post-tranlational modification or protein misfolding generates ER stress and results in ROS and IL-1beta production
TRAPS

NF-kB-related disorders *
NF-kB pathway activation through ubiquitination disorders or dysregulated NOD2 signaling.
HA20, ORAS, LUBAC deficiency, CRIA

Inflammasomopathies *
Gain-of-function mutations in the inflammasome (pyrin, NACHT) generates increased inflammasome activity and results in IL-1beta and IL-18 production
FMF, PAAND, CAPS, NLRP12-AD, HIDS

ADA2 deficiency *
Reduced ADA2 enzymatic activity resulting in defective differentiation of M2 anti-inflammatory macrophages and impaired secretion of pro-inflammatory cytokines by neutrophils
DADA2



Endogenous antagonist mutations
Loss-of-function mutations in genes encoding endogenous cytokine antagonist impair the antagonization of proinflammatory signals
DIRA, DITRA

Type I interferonopathies *
Enhanced IFN gene expression due to accumulation of endogenous nucleic acids (TREX1), enhanced sensitivity or constitutive activation of a nucleic acid (IFIH1) or non-nucleic (TMEM173) acid receptor of the IFN signaling pathway
AGS, CANDLE, SAVI, RVCL

Actinopathies
Mutations in genes involved in the regulation of actin filament formation and disassembly
CDC42 deficiency, WDR1 deficiency, ARPC1B deficiency

https://www.sciencedirect.com/science/article/pii/S1568997221000379

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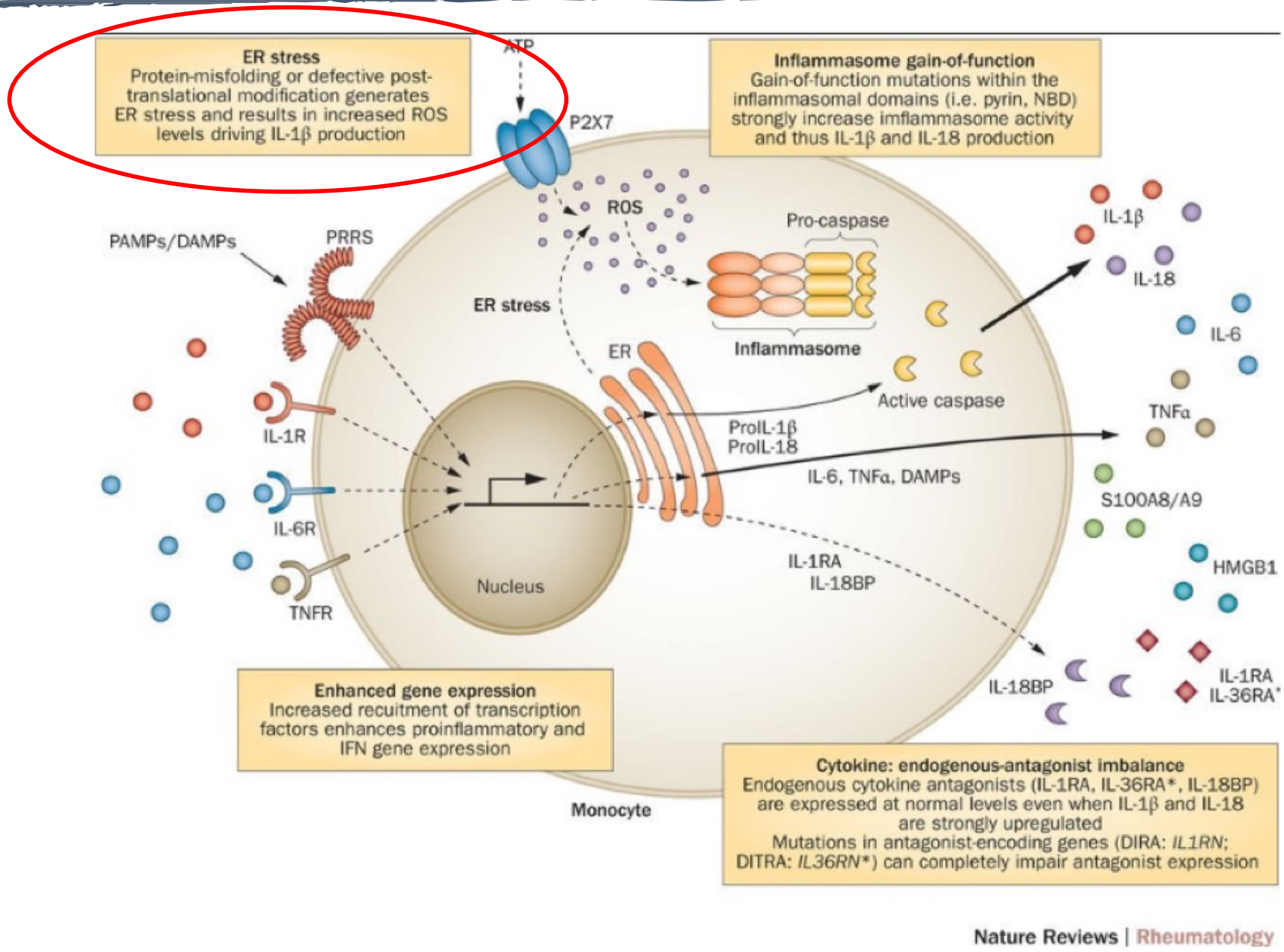
	DEX[a]	*ELF4*																Perianal abscesses
	ROSAH[a]	*ALPK1*																Splenomegaly, anhidrosis
	NDAS[a]	*IKBKG*																Panniculitis
Cytoskelopathies	NOCARH	*CDC42*																
	ARPC1B deficiency	*ARPC1B*																
	NCKAP1 deficiency	*NCKAP1*																
	PFIT	*WDR1*																
Enzymatic deficiencies	MKD	*MVK*																Elevated IgD
	DADA2	*CECR1*																
	SIFD	*TRNT1*																Sideroblastic anemia
	PLAID	*PLCG2*																
	APLAID	*PLCG2*																
Other	TRAPS	*TNFRSF1A*																
	VEXAS	*UBA1*																Deep vein thrombosis
	C2orf69 deficiency[a]	*C2orf69*																Hypomyelination, microcephaly, DWS, FTT
	HCK-associated AID[a]	*HCK*																Hepatosplenomegaly
	IL-33 gain-of-function[a]	*IL33*																Eosinophilic dermatitis, IgE
	STAT6 gain-of-function[a]	*STAT6*																IgE, allergy
	DPM[a]	*STAT4*																Poor wound healing, hypogammaglobulinemia
	LAVLI[a]	LYN																Hepatosplenomegaly

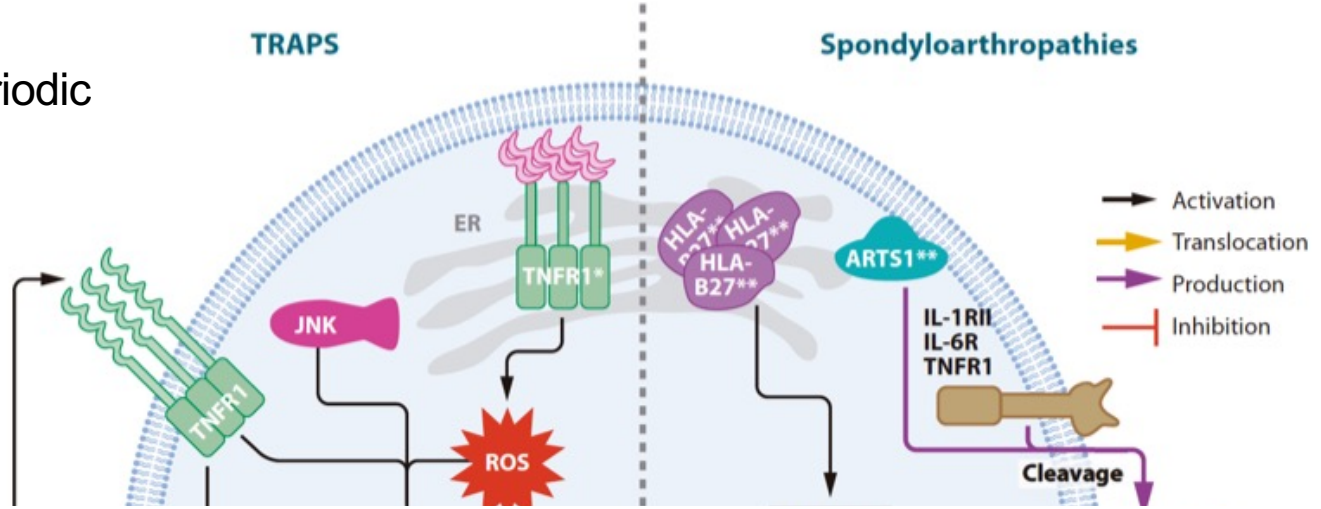
RAID: RelA-Associated Inflammatory Disease

Síndromes Autoinflamatórias: Mecanismos



Síndromes Autoinflamatórias mediadas por falhas no dobramento de proteínas

TNF-receptor associated periodic syndrome



Aspecto	TRAPS	Espondilite Anquilosante
Proteína mal dobrada	TNFR1 (mutado)	HLA-B27 (misfolded homodimers)
Local de acúmulo	Retículo endoplasmático	Retículo endoplasmático
Resposta celular ativada	ER stress, UPR, NF-κB, MAPK	ER stress, UPR, IL-23/IL-17 axis
Citocinas centrais	IL-1β, TNF	TNF, IL-17, IL-23
Tipo de imunidade envolvida	Inata (inflamassoma)	Inata + adaptativa (Th17, células NK)
Consequência clínica	Febre periódica, artrite migratória	Sacroileíte, espondilite axial crônica

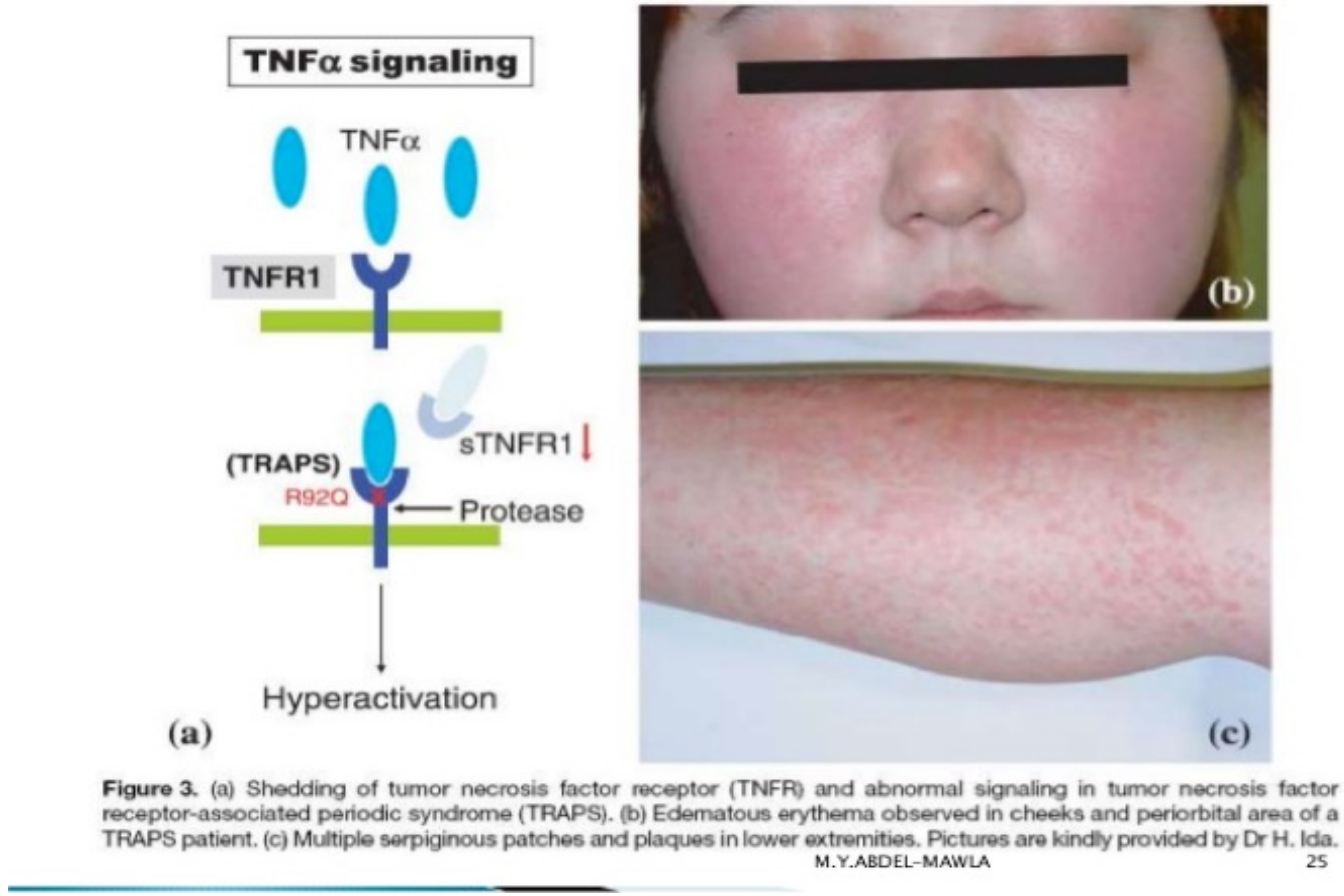


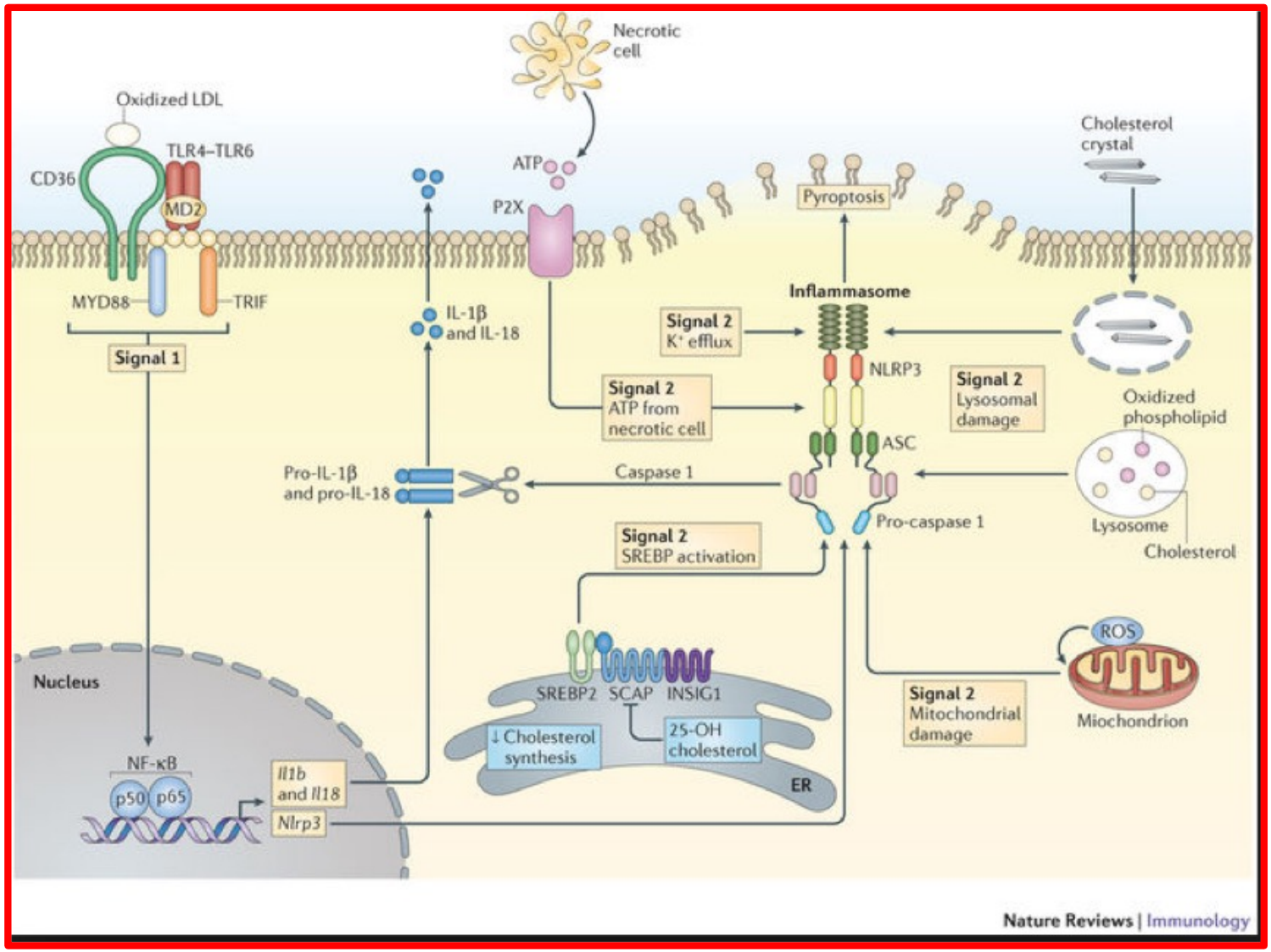
Figure 3. (a) Shedding of tumor necrosis factor receptor (TNFR) and abnormal signaling in tumor necrosis factor receptor-associated periodic syndrome (TRAPS). (b) Edematous erythema observed in cheeks and periorbital area of a TRAPS patient. (c) Multiple serpiginous patches and plaques in lower extremities. Pictures are kindly provided by Dr H. Ida.

Type 3: Protein folding disorders of the innate immune system

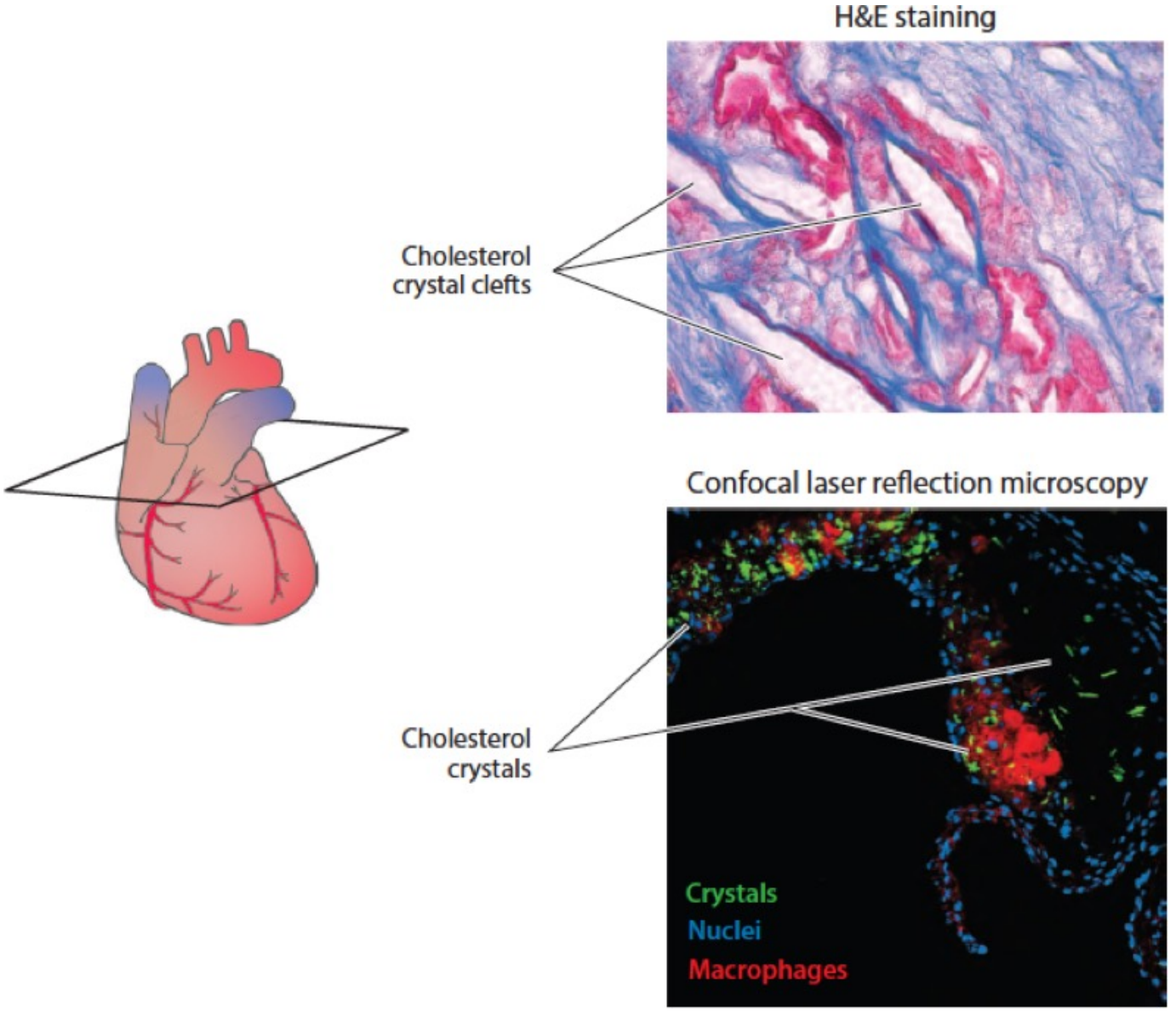
TRAPS[q]	*TNFRSF1A* (12p13)	TNFRSF1A[r] (TNFR1, p55, CD120a)
Spondyloarthropathies	Complex	
	HLA-B (6p21.3)	HLA-B27[s]
	ERAP1 (5q15)	ERAP1[t] (ARTS1)

TNF receptor associated periodic syndrome

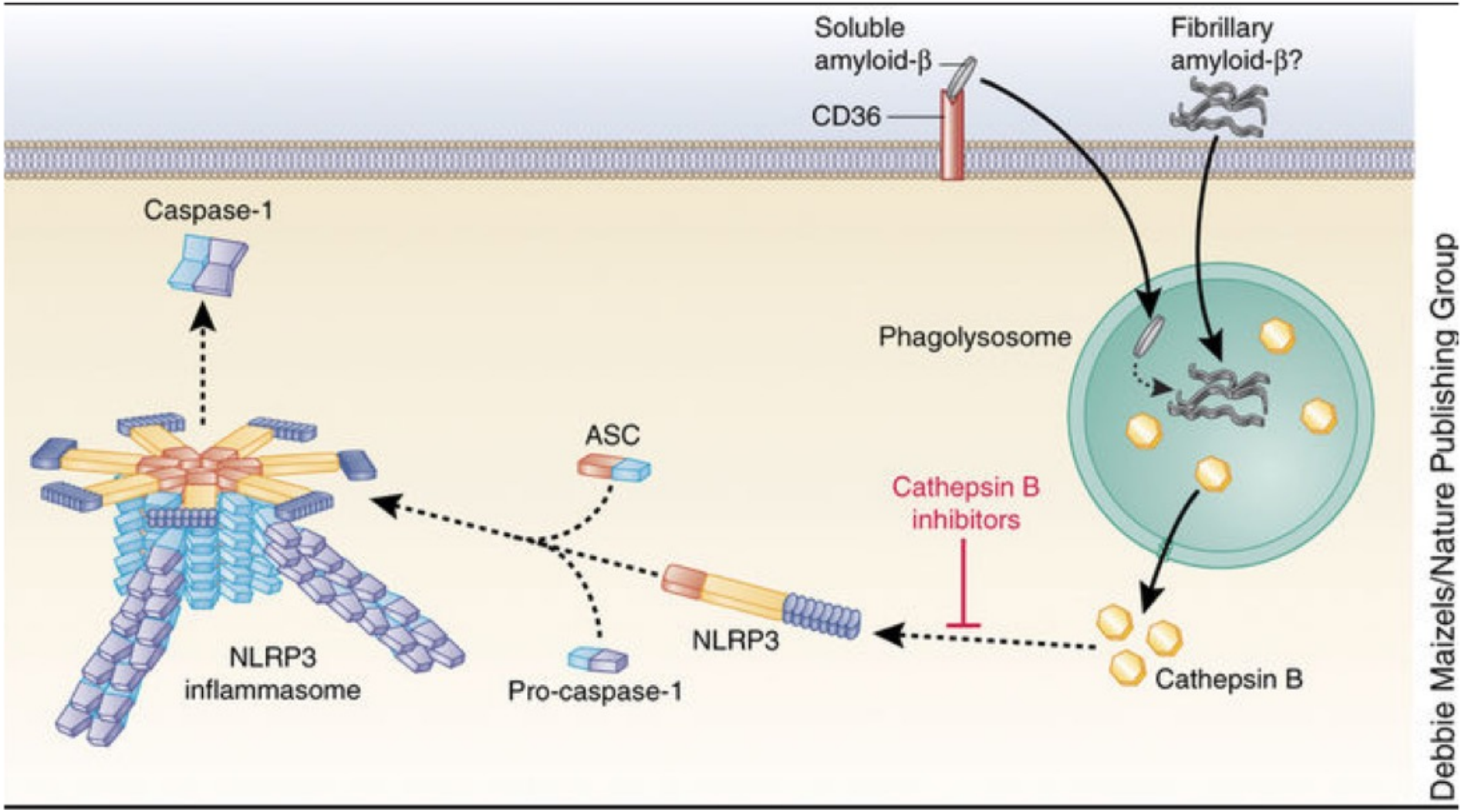
Aterosclerose como doença autoinflamatória



Placa de aterosclerose contém cristais de colesterol dentro de fendas das lesões .
Cristais se acumulam dentro e fora de macrófagos das lesões dos vasos



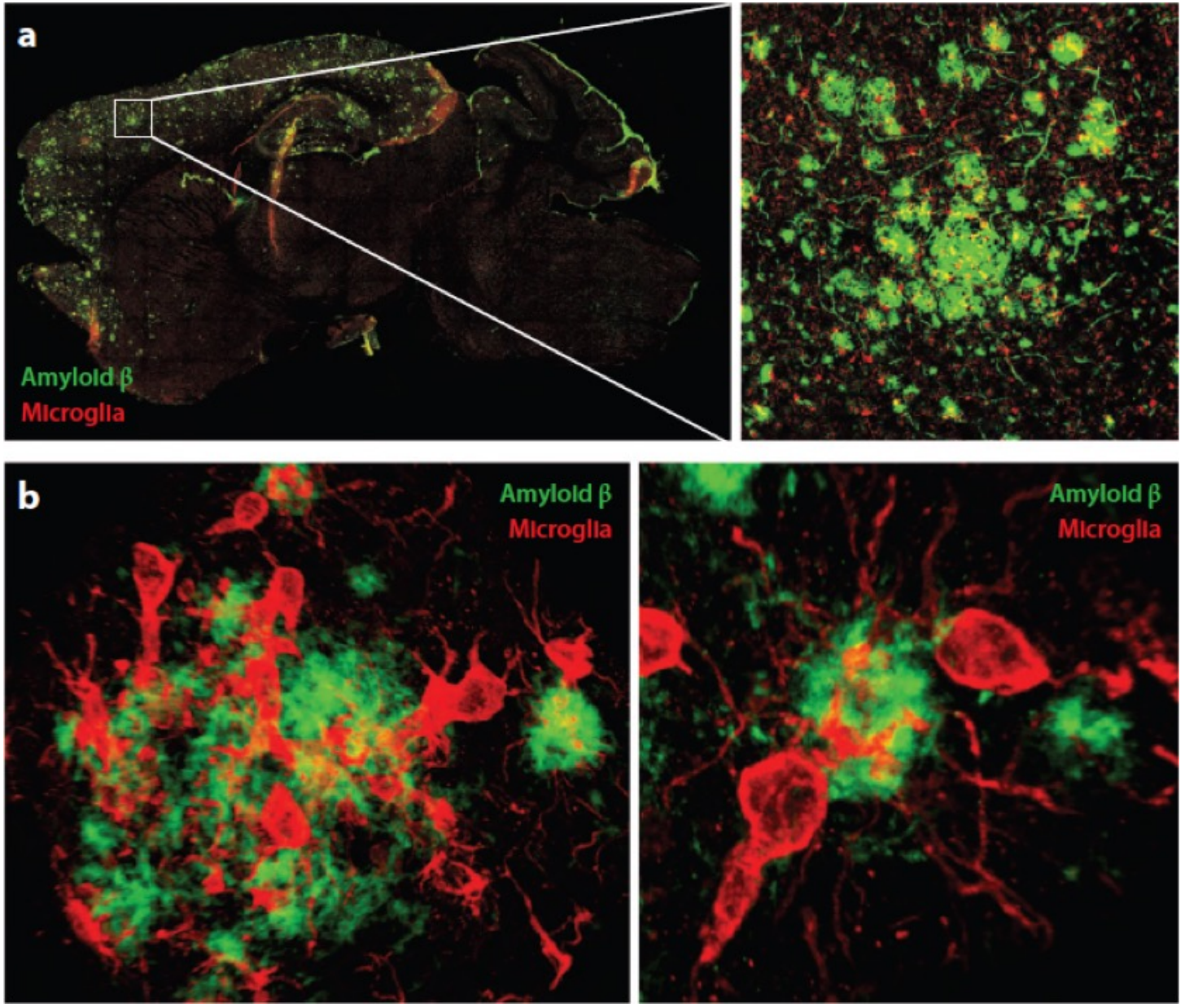
Doença de Alzheimer e Ativação do Inflamassoma NLRP3



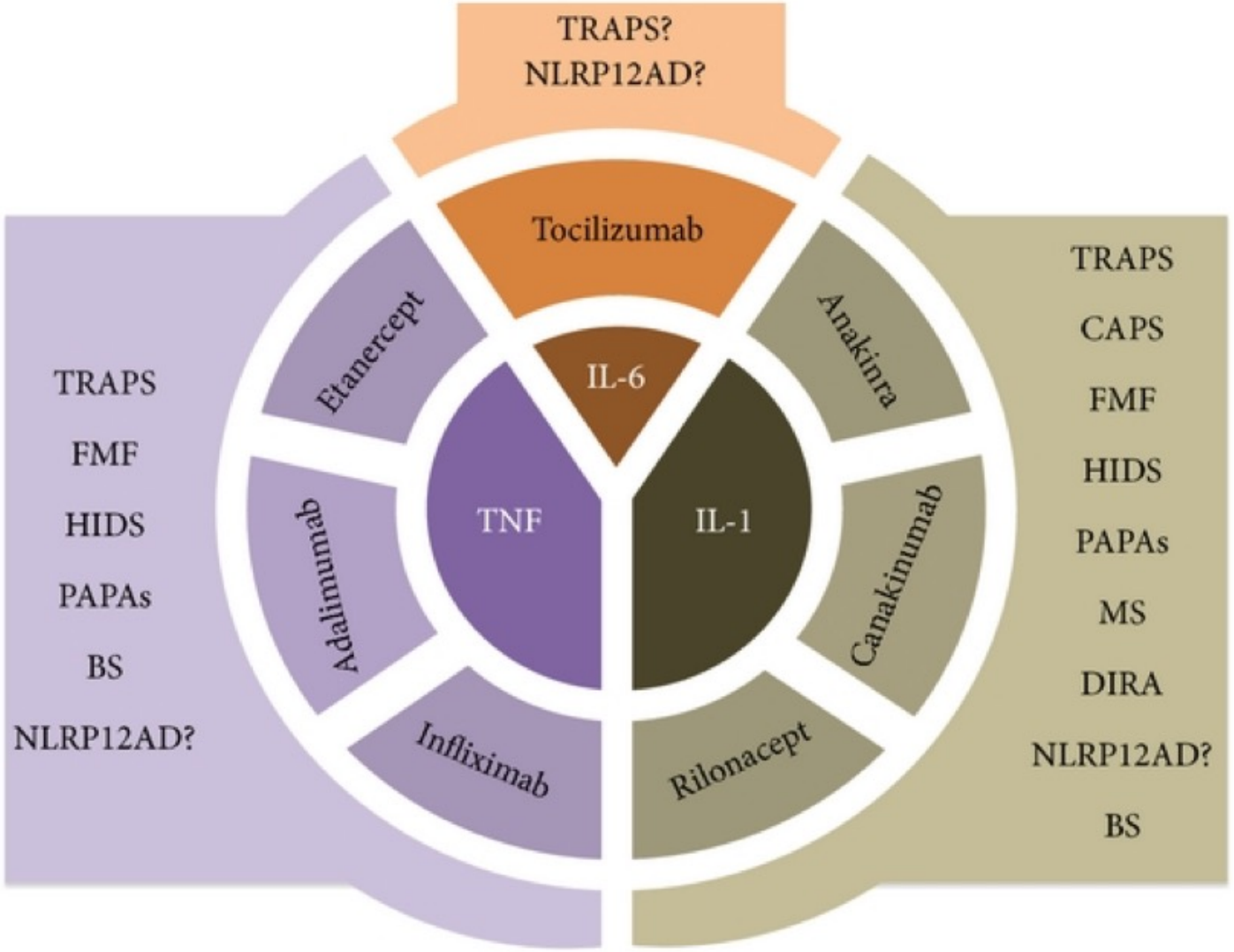
Doença de Alzheimer

Depósito de Beta-Amilóide no Cérebro Associado com Microglia

Placa amilóide



Terapia com anticorpos monoclonais



Doenças autoinflamatórias

Ativação descontrolada de mecanismos da Imunidade Inata

Ativação de receptores de conhecimento de padrões associados à microorganismos e associados ao perigo: **TLR e NOD (Inflamassoma).**

Alterações genéticas associadas com ganho de função:
NOD2: Síndrome de Bau
Inflamassomo (pirina): Febre Familiar do Mediterrâneo

Mutações poligênicas: Doença de Crohn

Inflamação inata induzida por sinais de perigo: Gota, Aterosclerose, Sarcoidose.

Inflamação estéril: pós-trauma, alterações de temperatura **citotóxicas**

Doenças Autoimunes x Autoinflamatórias

Table 2. A comparison of autoimmunity and autoinflammation.

		Autoinflammation	Autoimmunity
Etiology	Genetics	Mutations in germline encoded elements of innate immune system	Generation of self-reactive lymphocyte receptors by somatic recombination
		Monogenic > polygenic	Polygenic > monogenic
	Immunology	Failure of autoinhibitory mechanisms ± constitutive inflammatory cytokine signaling	Failure of immune tolerance and lymphocyte-driven tissue damage
			Self-reactive lymphocytes and autoantibodies
Demographics	Age of onset	Pediatric > adult	Adult > pediatric
	Family history	+++	+/–
Clinical features	Triggers	Stress, infections, cold, physical exertion or trauma, vaccination, menses, pregnancy	Stress, infections, pregnancy
	Recurrent fevers	+++	Usually not the presenting complaint
	Ocular	Conjunctivitis, periorbital edema	Episcleritis/scleritis, retinitis, iritis
	Oral/genital ulcers	+++	+
	Gastrointestinal	Colitis in children, peritonitis	IBD in adults
	Bone inflammation	++	–
	Other	Rashes, synovitis, neurologic and renal involvement	
Tests	Elevated inflammatory markers	During attacks	Low grade at baseline
	Autoantibodies	–	+++
	Yield of genetic testing	+++	–
Response to treatment	Colchicine, IL-1 blockers	+++	+
	Antimetabolites[a], HCQ, CSA, tacrolimus	–	+++
	JAKi/TNFi, steroids	+++	

https://www.jrheum.org/content/jrheum/51/9/848.full.pdf

Obrigada pela sua atenção !