XIV REUNIÓN GEAS
GRUPO DE ENFERMEDADES AUTOINMUNES SISTÉMICAS
21-22 OCTUBRE 2021 Madrid HOTEL MELIÁ AVENIDA AMÉRICA

Bloqueo-IL-1 en EAI

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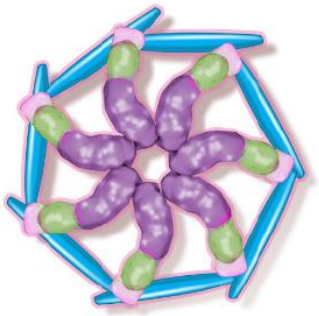


Inflammasome

IL-1β
IL-18

Pro-IL-1β
Pro-IL-18

Autoinduction:
IL-1 induces IL-1

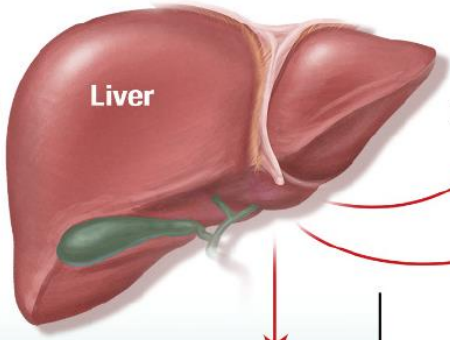
An amplification loop

IL-1 → IL-1

Further Amplification:
IL-1 induces IL-6

IL-6

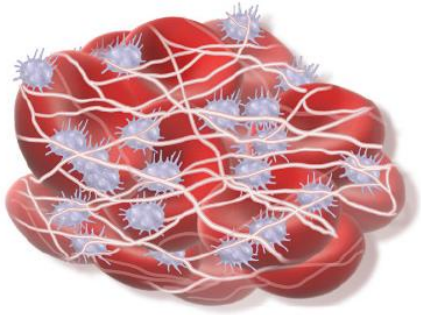
Acute phase response



Fibrinogen

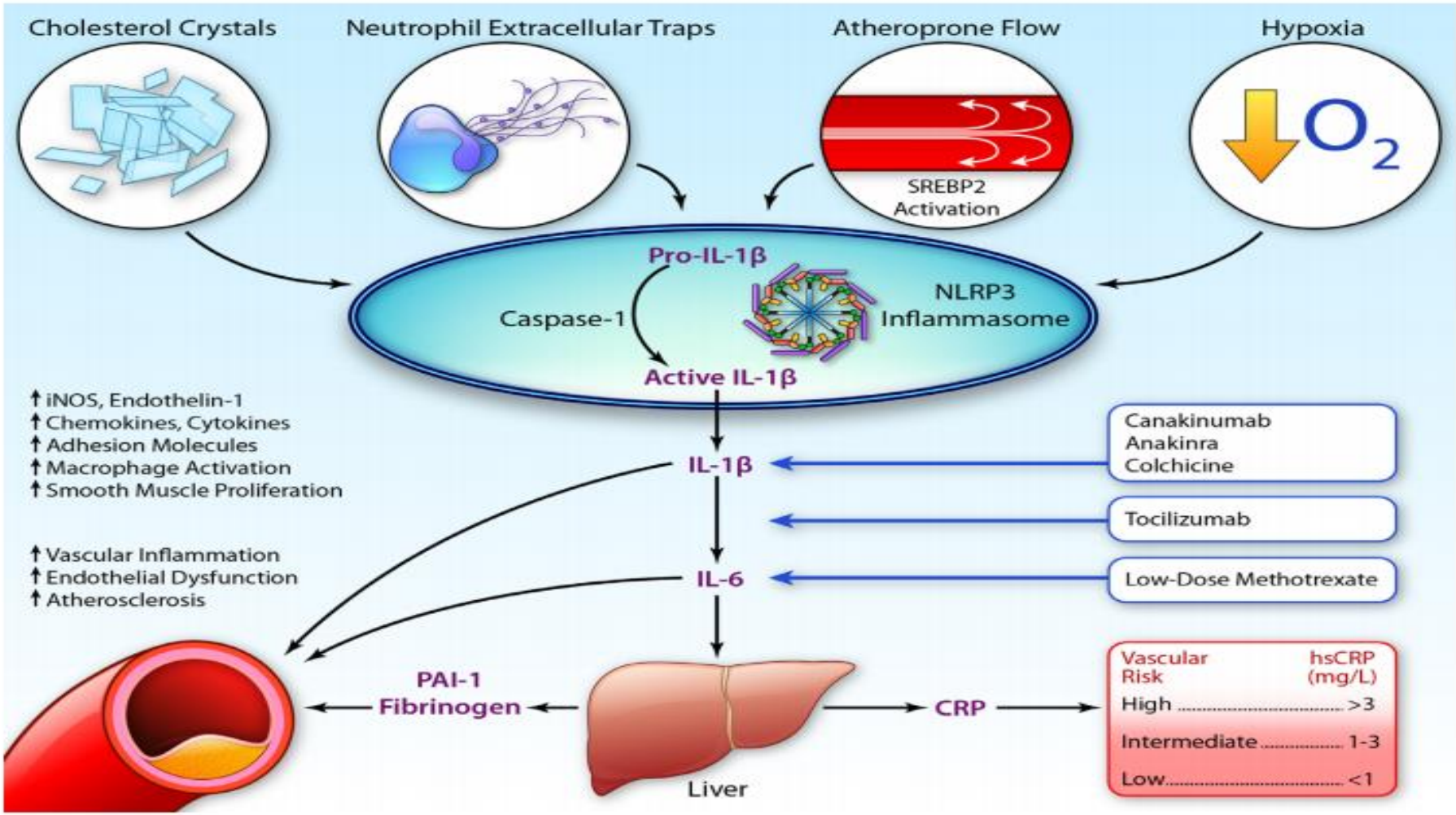
Plasminigen activator inhibitor-1

CRP, SAA

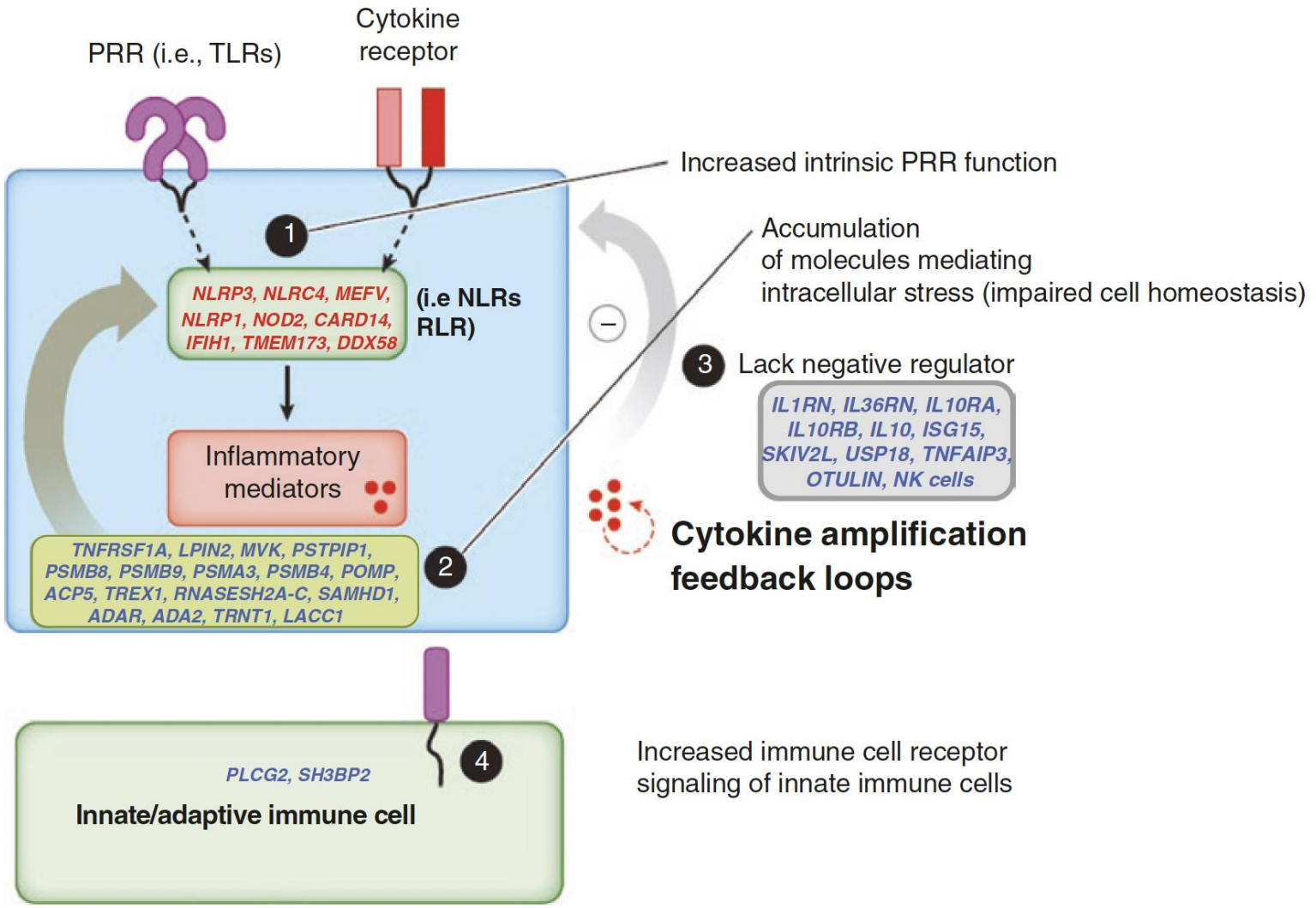


Thrombus formation and stability

Cells **2021**, *10*, 951.



Circ Res. 2016;118:145-156



Goldbach-Mansky R., de Jesus A.A. (2019) Classification of Genetically Defined Autoinflammatory

			Group No	Gene (chromosome region)	Clinical Findings	
					Mucocutaneous	Other / Specific features
Autoinflammatory diseases caused by excessive interleukin (IL)-1 signaling, production and secretion						
Intrinsic PRR activation	**CAPS**	**NOMID**	Group 2b	*NLRP3* (1q44)	Neutrophilic urticaria	Sensorineural hearing loss, bony overgrowth, cognitive impairment, hydrocephalus and brain atrophy, visual nerve atrophy and blindness
		MWS	Group 2b	*NLRP3* (1q44)	Neutrophilic urticaria	Sensorineural hearing loss
		FCAS	Group 2a	*NLRP3* (1q44)	Neutrophilic urticaria	Sensorineural hearing loss (very rare)
	FMF		Group 1a	*MEFV* (16p13.3)	Erysipelas-like erythema	Serositis and abdominal adhesions, pericarditis, epididymitis
	PAAND		Group 3f	*MEFV* (16p13.3)	Severe acne, pyoderma gangrenosum, neutrophilic small vessel vasculitis	Pyoderma gangrenosum without pyogenic arthritis
Extrinsic PRR activation	**HIDS/MKD**		Group 1a	*MVK* (12q24.11)	Maculopapular or purpuric exanthema	Abdominal pain, recurrent and or severe infections in up to 30% of the patients
	TRAPS		Group 1b	*TNFRSF1A* (12p13.31)	Erysipelas-like erythema	Pericarditis, scrotal pain, prolonged fever episodes
	Majeed syndrome		Group 3a	*LPIN2* (18p11.31)	Pustular dermatitis	Sterile osteomyelitis, dyserythropoietic anemia
Loss of negative regulation	**DIRA**		Group 3a	*IL1RN* (2q13)	Pustular dermatitis	Osteomyelitis and periostitis, bone deformities, absence of odontoid process, venous thrombosis, vasculitis (rare)

Goldbach-Mansky R., de Jesus A.A. (2019) Classification of Genetically Defined Autoinflammatory

Interferon mediated autoinflammatory diseases					
Intrinsic PRR or adaptor molecule activation	**SAVI**	Group 5a	*TMEM173* (5q31.2)	Erythematous-purpuric lesions, ischemic ulcerative skin disease, necrosis of extremities, loss of tissue	Acral and cold sensitive area vasculitis (chilblain distribution), nasal septum perforation, anemia, lymphopenia, hypergammaglobulinemia
	AGS7	Group 5b	*IFIH1* (2q24.2)	Chilblain lesions, livedo reticularis	Variable severity of CNS disease, thrombocytopenia
Extrinsic PRR activation	**AGS1**	Group 5b	*TREX1* (3p21.31)	Chilblain lesions, livedo reticularis	Thrombocytopenia, neonatal-onset, higher mortality
	AGS2	Group 5b	*RNASEH2B* (13q14.3)	Chilblain lesions, livedo reticularis	Later onset, lower morbidity and mortality
	AGS3	Group 5b	*RNASEH2C* (11q13.1)	Chilblain lesions, livedo reticularis	Thrombocytopenia, neonatal-onset, higher mortality
	AGS4	Group 5b	*RNASEH2A* (19p13.2)	Chilblain lesions, livedo reticularis	Thrombocytopenia, neonatal-onset, higher mortality
	AGS5	Group 5b	*SAMHD1* (20q11.23)	Chilblain lesions, livedo reticularis	Later onset, lower morbidity and mortality, inflammatory intracranial large-vessel vasculitis
	AGS6	Group 5b	*ADAR* (1q21.3)	Chilblain lesions, livedo reticularis	Later onset, lower morbidity and mortality
	CANDLE	Group 4a	*PSMB8* and other genes (6p21.32)	Nodular exanthema, panniculitis, lipodystrophy	Myositis, arthritis, dyslipidemia, growth delay, anemia, cytopenias
	SPENCD	Group 5c	*ACP5* (19p13.2)	Hyperpigmentation, vitiligo, hemangioma	Recurrent infections (pneumonia and URI), spondylometaphyseal dysplasia, short stature, autoimmunity (AIHA, AITP, positive ANA, thyroiditis)
Loss of negative regulation	**USP18 deficiency**	Group 5b	*USP18* (22q11.21)	Petechiae with thrombocytopenia	Thrombocytopenia, early mortality (1 week-22 days of life)

Goldbach-Mansky R., de Jesus A.A. (2019) Classification of Genetically Defined Autoinflammatory

Autoinflammatory diseases caused by nuclear factor kappa B (NF-κB) dysregulation in keratocytes					
Intrinsic PRR or adaptor molecule activation	**CAMPS**	Group 3d	*CARD14* (17q25.3)	Plaque or pustular psoriasis	Rare systemic manifestations
Extrinsic PRR activation	**AMPS**	Group 3d	*AP1S3* (2q36.1)	Generalized or palmo-plantar pustular psoriasis, nail dystrophy	Severe nail dystrophy and digit tapering may be observed
Loss of negative regulation	**DITRA**	Group 3d	*IL36RN* (2q13)	Generalized pustular psoriasis	Fever of elevated temperature, secondary skin infections
Autoinflammatory diseases caused by nuclear factor kappa B (NF-κB) also affecting interferon (IFN) signaling					
Loss of negative regulation	**ORAS**	Group 4b	*OTULIN* (5p15.2)	Nodular panniculitis and lipodystrophy, pustular and scarring rash (n=1)	Failure to thrive, early age of onset (1-4.5 months-old)
	NDAS	Group 4b	*IKBKG* (Xq28)	Lymphohistiocytic panniculitis, lipodystrophy	Non-caseating granulomas in skin, lymph nodes and liver, conical teeth (n=1), hypogammaglobulinemia, thrombocytopenia
Loss of negative regulation	**HA20**	Group 3c	*TNFAIP3* (6q23.3)	Oral ulcers, genital ulcers, erythematous papules, folliculitis, pathergy	Hemolytic anemia, thrombocytopenia, positive ANA
Autoinflammatory diseases caused by nuclear factor kappa B (NF-κB) dysregulation and granulomatous diseases					
Intrinsic PRR or adaptor molecule dysregulation	**Blau syndrome/PGA**	Group 6a	*NOD2/CARD15* (16q12.1)	Ichthyosis-like exanthema	Granulomatous arthritis, parotitis, pericarditis (rare)
Extrinsic PRR dysregulation	**LACC1**	Group 7a	*LACC1* (13q14.11)	Erythematous maculopapular rash	Quotidian fever, arthritis

Goldbach-Mansky R., de Jesus A.A. (2019) Classification of Genetically Defined Autoinflammatory

Autoinflammatory diseases caused by systemic macrophage activation (with and without high IL-18 levels)						
Intrinsic PRR or adaptor molecule activation (high IL-18 levels)	NLRC4-MAS		Group 7a	*NLRC4* (2p22.3)	Rare dermographism / urticarial rash	Coagulopathy, pancytopenia, ↑ferritin, ↑triglycerides
	XLP2-MAS		Group 7a	*XIAP* (Xq25)	Uncommon	Coagulopathy, pancytopenia, ↑ferritin, ↑triglycerides
Impaired cytotoxicity	Without albinism	FHL2	Group 7b	*PRF1* (10q22.1)	Uncommon	Coagulopathy, pancytopenia, ↑ferritin, ↑triglycerides
		FHL3	Group 7b	*UNC13D* (17q25.1)	Uncommon	Coagulopathy, pancytopenia, ↑ferritin, ↑triglycerides
		FHL4	Group 7b	*STX11* (6q24.2)	Uncommon	Coagulopathy, pancytopenia, ↑ferritin, ↑triglycerides
		FHL5	Group 7b	*STXBP2* (19p13.2)	Uncommon	Coagulopathy, pancytopenia, ↑ferritin, ↑triglycerides
	With albinism	CHS	Group 7b	*LYST* (1q42.3)	Skin and hair hypopigmentation, photosensitivity	Coagulopathy, pancytopenia, ↑ferritin, ↑triglycerides
		GS2	Group 7b	*RAB27A* (15q21.3)	Skin and hair hypopigmentation, photosensitivity	Coagulopathy, pancytopenia, ↑ferritin, ↑triglycerides

Goldbach-Mansky R., de Jesus A.A. (2019) Classification of Genetically Defined Autoinflammatory

Autoinflammatory diseases caused by enzymatic defects in innate and adaptive immune cell signaling pathways					
PLAID		Group 6b	*PLCG2* (16q23.3)	Cold-induced urticaria and/or granulomatous skin rash	Positive autoantibodies and autoimmune manifestations, recurrent and/or severe infections, allergic disease
APLAID		Group 6b	*PLCG2* (16q23.3)	Erythematous plaques and vesico-pustular lesions, cellulitis	Mild immunodeficiency
Cherubism		NA	*SH3BP2* (4p16.3)	No rash reported	Oligodontia, agenesis of teeth, displaced teeth
Unclassifiable autoinflammatory diseases based on pivotal inflammatory mediators					
Accumulation of intracellular stress	**PAPA**	Group 3b	*PSTPIP1* (15q24.3)	Pyoderma gangrenosum, severe acne	Thrombocytopenia and neutropenia (rare) deforming aseptic pyogenic arthritis
	PFIT	Group 3f	*WDR1* (4p16.1)	Severe recurrent oral ulcers with scarring and microstomia, recurrent perianal ulceration	Hyperferritinemia, thrombocytopenia, neutropenia, recurrent infections
	DADA2	Group 5d	*ADA2* (22q11.1)	Livedo reticularis, purpuric lesions and ischemic and necrotic skin disease	Testicular pain, portal hypertension, lymphopenia, low IgM, recurrent infections
Loss of negative regulator	**IBD28**	Group 3e	*IL10RA* (11q23.3)	Folliculitis	Colitis, recurrent infections
	IBD25	Group 3e	*IL10RB* (21q22.11)	Folliculitis	Colitis, recurrent infections
	IBD with IL-10 deficiency	Group 3e	*IL10* (1q32.1)	Folliculitis	Colitis, recurrent infections
	NISBD	Group 3e	*ADAM17* (2p25.1)	Perioral and perianal erythema and generalized pustular rash	Cardiomyopathy, secondary skin infections, paronychia, increased IgE

Goldbach-Mansky R., de Jesus A.A. (2019) Classification of Genetically Defined Autoinflammatory

"PATRÓN de AUTOINFLAMACIÓN"

- Recurrencia
  - Fiebre
  - Serositis
  - Piel/mucosas (Urticarias, aftas, uveítis,..)…
- Procesos inflamatorio "multifoco" sin autoanticuerpos
- PCR elevada /SAA / S100
- Monocito-Macrófago / Neutrófilo
- Autofagia
- Rasgo familiar

REEVALUAR

Recurrent fever episodes and characteristic inflammatory findings
(inflammation of joints, eyes, skin or/and serous membranes, headaches, musculoskeletal complaints, abdominal pain, fatigue, lymphadenopathy, irritability)

History and physical exam	Laboratory markers	Additional testing	Differential diagnoses
Patients/family history, ethnicity, clinical findings	WBC, CRP, ESR, SAA, Liver/kidney function, urine	Eye exam, HF-PTA, x-rays, MRI, CSF, ultrasound, echo	Infections, neoplasms, PID, metabolic/autoimmune diseases

⇩

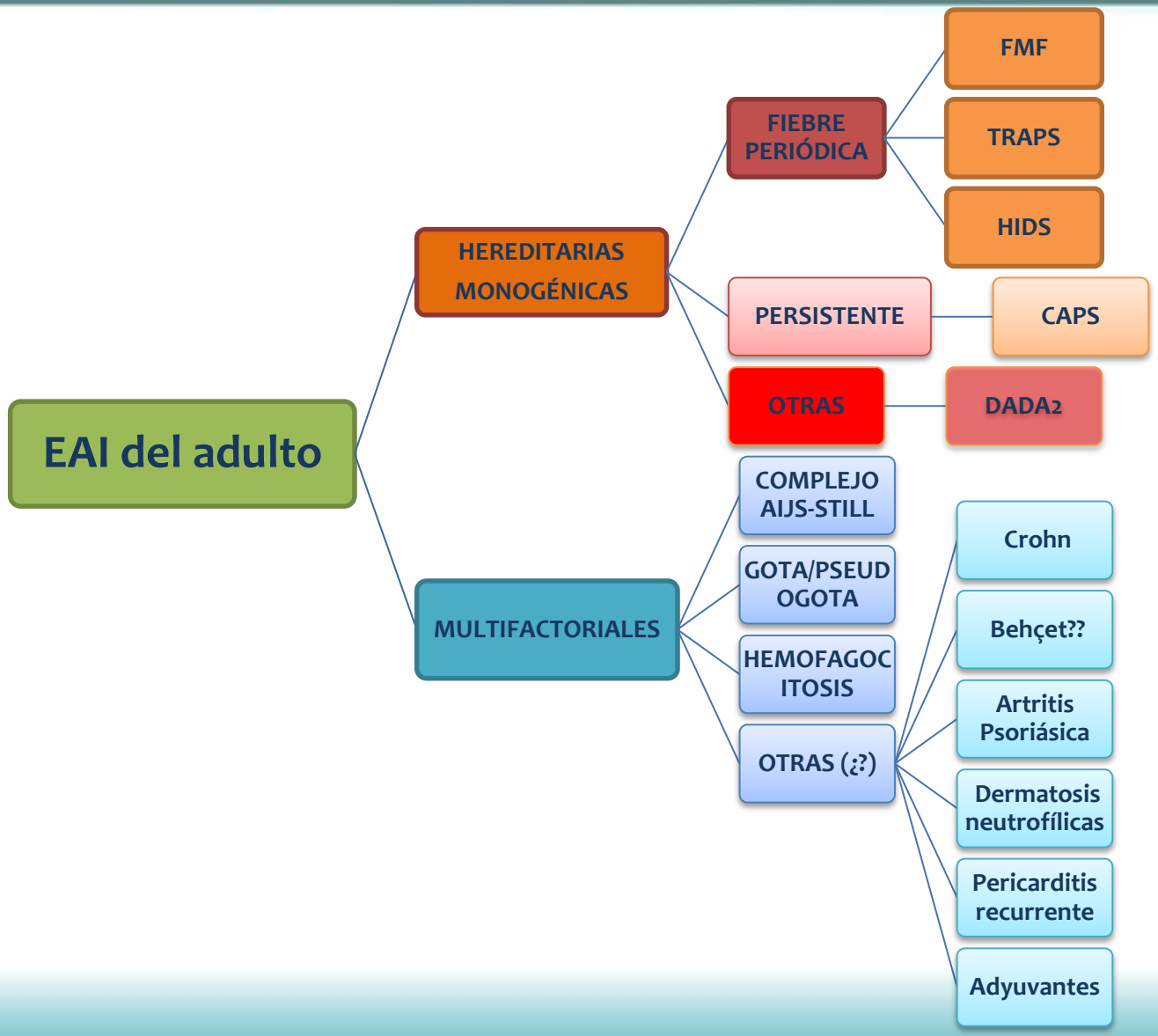
Suspicion of IL-1 mediated AID

Pattern of clinical symptoms	Pattern of inflammatory markers	Genetic testing
AIDAI, symptom diary	SAA, CRP (S100) during flares and in between	AID gene panel

⇩

Diagnosis of IL-1 mediated AID

Classic AID phenotype + Inflammatory makers + Pathogenic mutation	**Classic AID phenotype + Inflammatory makers + No pathogenic mutation** Consider WES/WGS, SM	**Atypical AID phenotype + Inflammatory makers + Pathogenic mutation**	**Atypical AID phenotype + Inflammatory makers + No pathogenic mutation** Consider WES/WGS, SM
Confirmation of classic IL-1 mediated AID			**Unclassified AID**

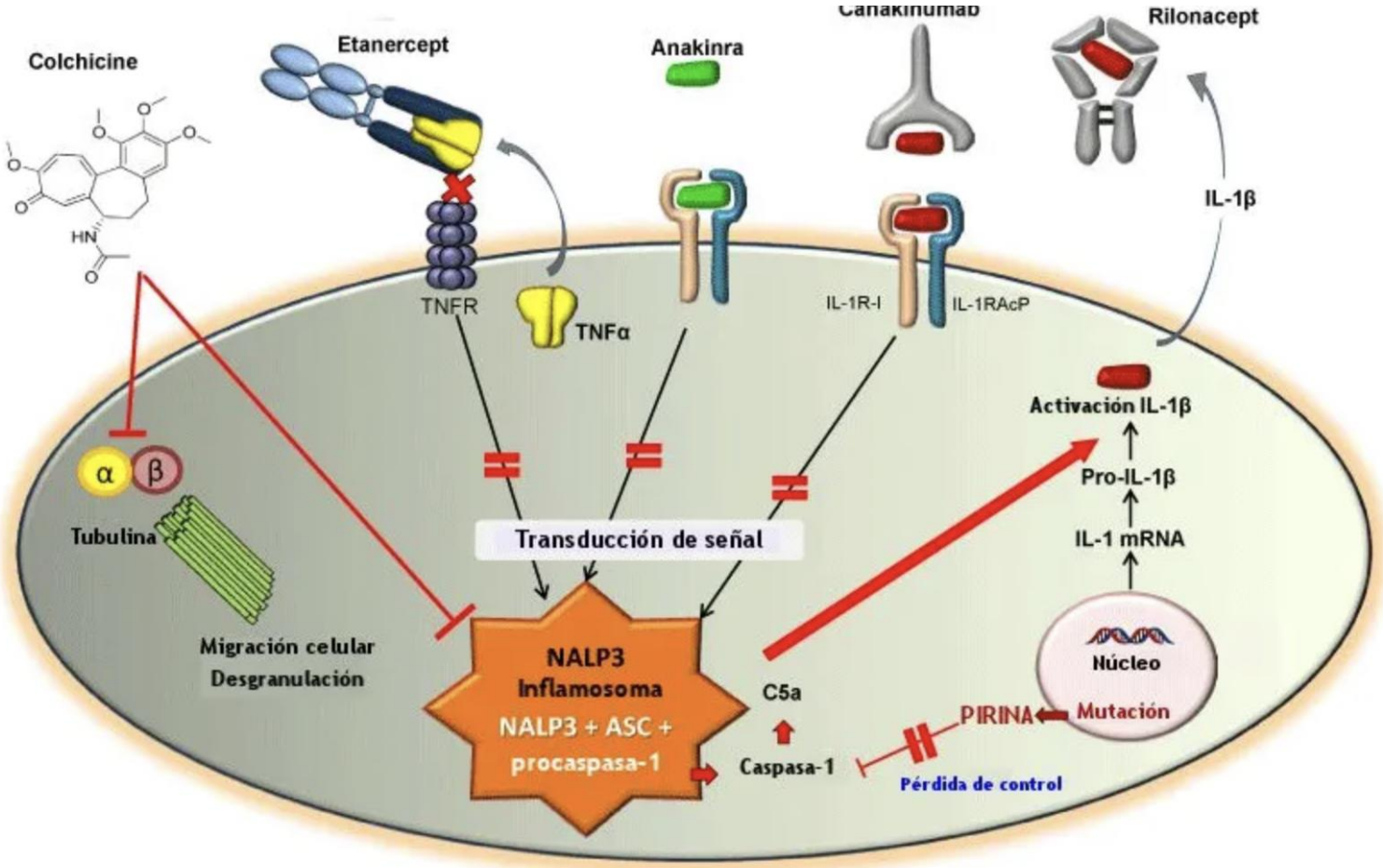

EAI del adulto
HEREDITARIAS MONOGÉNICAS
FIEBRE PERIÓDICA
FMF
TRAPS
HIDS
PERSISTENTE
CAPS
OTRAS
DADA2
MULTIFACTORIALES
COMPLEJO AIJS-STILL
GOTA/PSEUDOGOTA
HEMOFAGOCITOSIS
OTRAS (¿?)
Crohn
Behçet??
Artritis Psoriásica
Dermatosis neutrofílicas
Pericarditis recurrente
Adyuvantes

Características distintivas de los síndromes febriles periódicos más comunes: PFS y CAPS

	FMF	HIDS/MKD	TRAPS	FCAS	MWS	CINCA/ NOMID
Tipo de herencia	Autosómica recesiva	Autosómica recesiva	Autosómica dominante	Autosómica dominante	Autosómica dominante	Autosómica dominante
Edad al debut (años)	<20	<2	Variable, la mayoría <10	<1	<20	Neonatal
Distribución étnica predominante	Turcos, árabes, judíos, armenios	Europeos	Todas las etnias	Europeos	Europeos	Europeos
Gen implicado	*MEFV*	*MVK*	*TNFRSF1A*	*NLRP3*	*NLRP3*	*NLRP3*
Duración de un ataque típico	12 h–3 d	3–6 d	3 d–3 sem	<24 h	1–2 d	Persistente
Síntomas característicos	Derrame pleural, lesiones cutáneas similares a erisipela	Linfadenopatías	Dolor muscular severo, edema periorbitario	Inducción por exposición al frío	Sordera neurosensorial	Lesiones óseas epifisarias, rasgos dismórficos
Respuesta a colchicina	Sí	No	No	No	No	No

Curr Rheumatol Rep. 2010;12:101-7.

fiebre mediterránea familiar



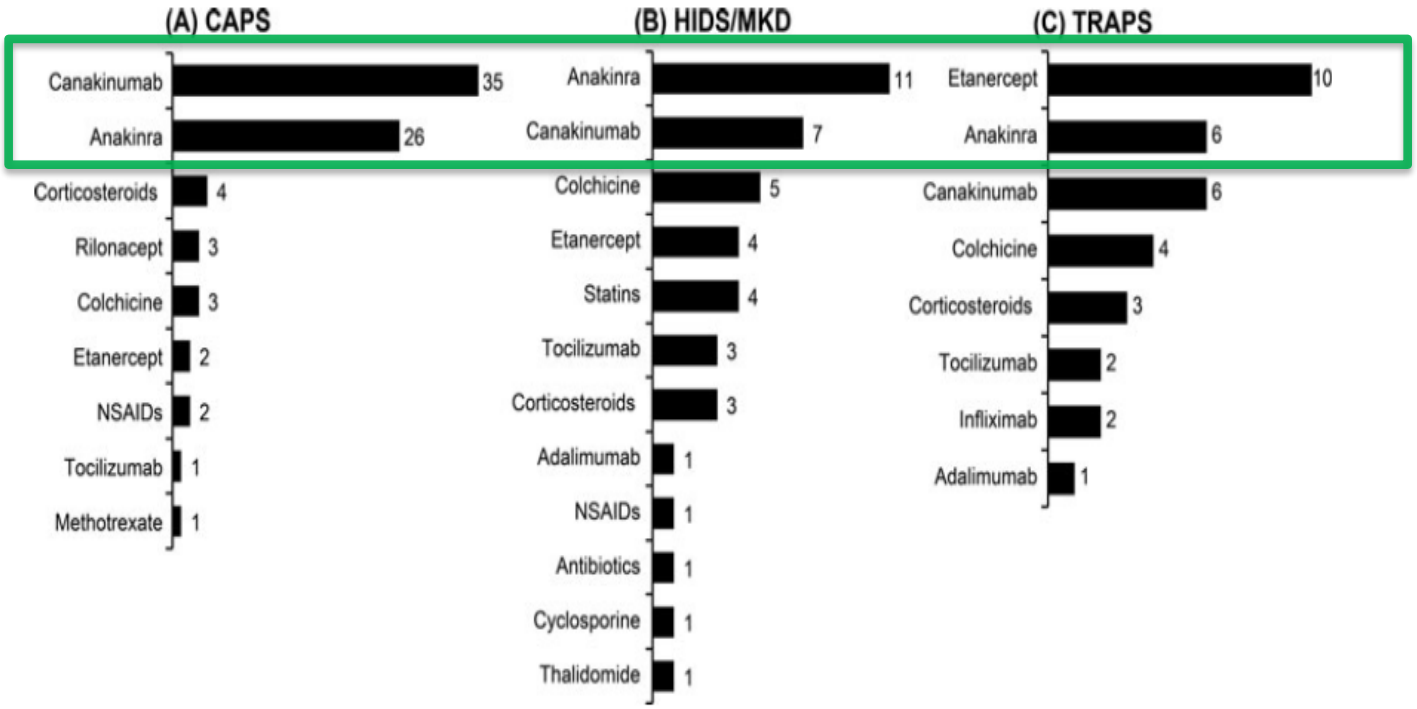
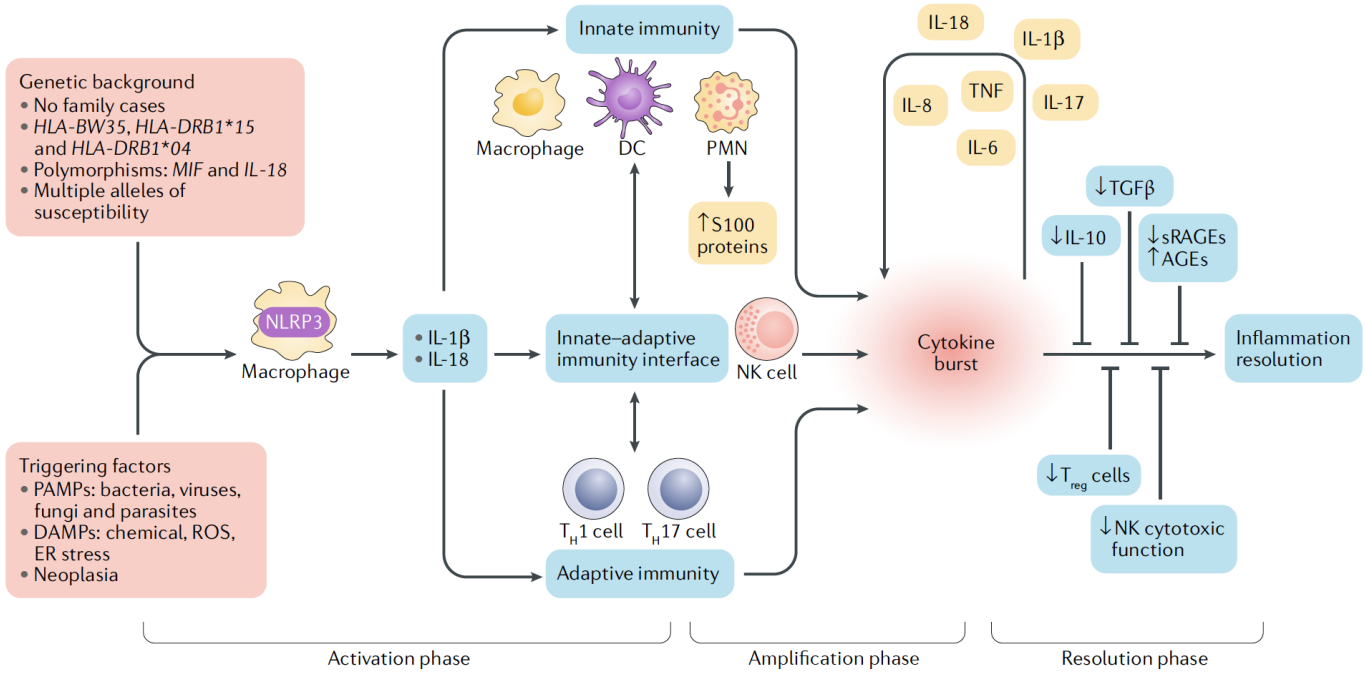
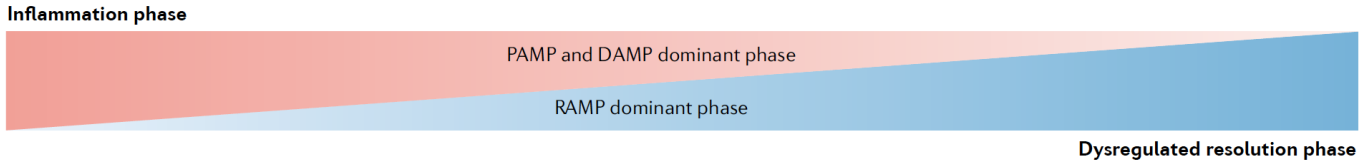


Figure 2 An overview of treatments used in the included studies of CAPS, HIDS/MKD and TRAPS. CAPS, cryopyrin-associated periodic syndromes; HIDS, hyperimmunoglobulin D syndrome; MKD, mevalonate kinase deficiency; NSAIDs, non-steroidal anti-inflammatory drugs; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

RMD Open 2020;**6**:e001227.

adult-onset Still's disease





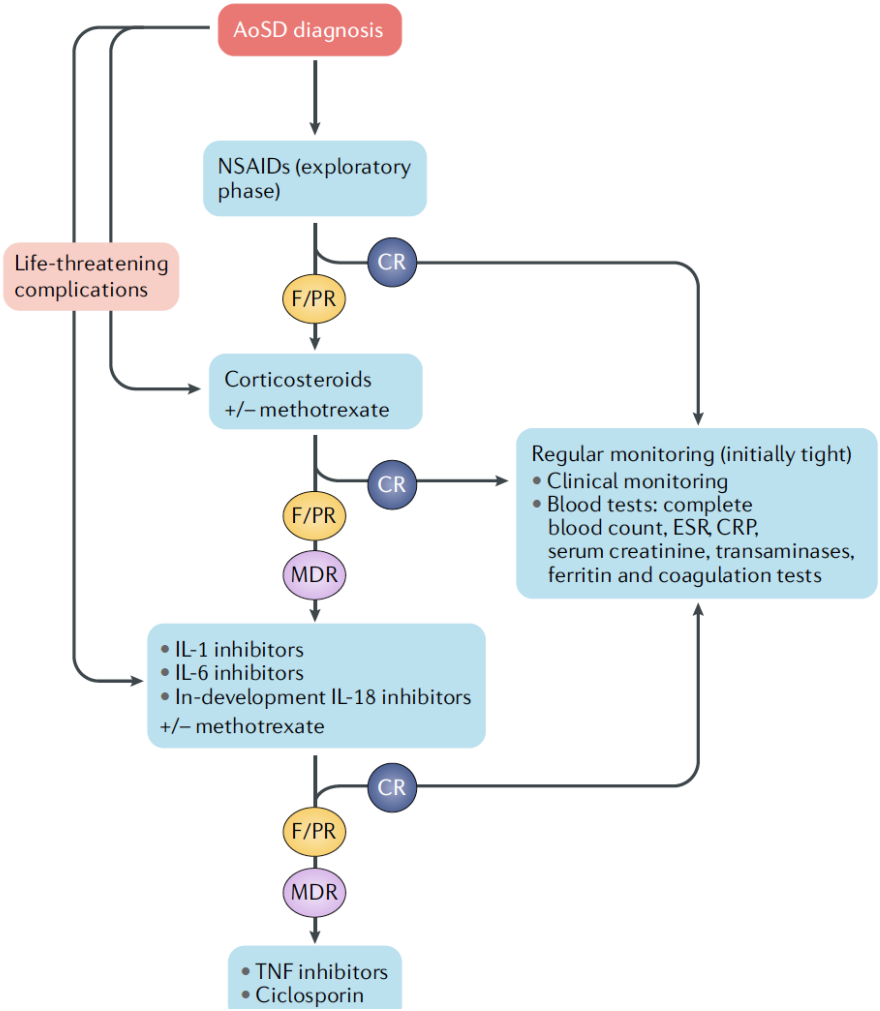

AoSD diagnosis
NSAIDs (exploratory phase)
CR
F/PR
Life-threatening complications
Corticosteroids +/– methotrexate
CR
F/PR
MDR
Regular monitoring (initially tight)
• Clinical monitoring
• Blood tests: complete blood count, ESR, CRP, serum creatinine, transaminases, ferritin and coagulation tests
• IL-1 inhibitors
• IL-6 inhibitors
• In-development IL-18 inhibitors
+/– methotrexate
CR
F/PR
MDR
• TNF inhibitors
• Ciclosporin

Table 13
AOSD treatment options (24,112,115–119).

Line of treatment	Treatment	Pros	Cons
First line	NSAIDs and corticosteroids	• Monocyclic pattern • Systemic corticosteroids achieve remission in 65% of patients • Corticosteroids are the first line of treatment for AOSD	• Polycyclic systemic pattern or chronic arthritis • NSAIDs do not achieve remission in >80% of patients • Steroid dependency occurs in approximately 45% of cases • Steroid dependence was associated with splenomegaly, low glycosylated ferritin, an elevated ESR, and young age at onset of AOSD
First line	Methotrexate	• First-line steroid-sparing treatment in AOSD • Systemic and chronic articular AOSD, especially steroid dependent	• Slow to induce remission, especially of systemic symptoms • Can cause severe adverse events, including liver toxicity and pneumonitis • Blood count, renal function, and liver enzymes should be monitored
Second line	IL-1 inhibitors* including anakinra and canakinumab	• Patients refractory to conventional corticosteroid and DMARD therapy • Polycyclic or chronic AOSD • Canakinumab and anakinra are the only approved biologics** • Are relatively safe	• Patients receiving anakinra are more likely to relapse as soon as treatment is stopped compared with those receiving canakinumab due to a shorter half-life (4–6 h vs 26 days) • Injection site reactions are more frequent with anakinra

* Rilonacept is currently not approved.
** Canakinumab is the only approved biologic for AOSD in the US, while in Europe, both canakinumab and anakinra are approved for AOSD.
Abbreviations: AOSD: adult-onset Still's disease; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; IL: interleukin; NSAID: nonsteroidal anti-inflammatory drug.

Table 4 | **AoSD treatments**

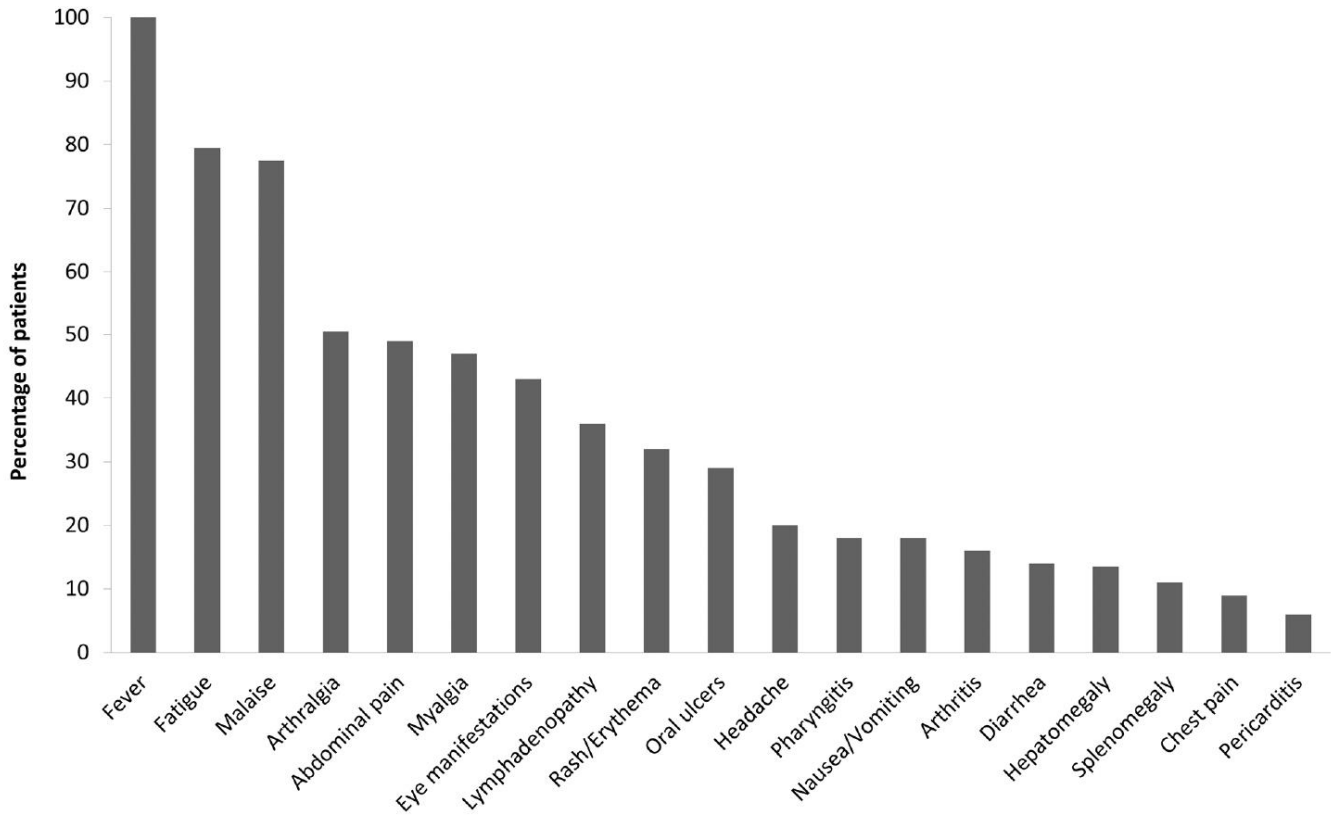
Targeted therapy	International nonproprietary name and usual dose	Reported number of patients	Preferential AoSD pattern	Follow-up duration (months)	Complete remission (%)	Steroid dose reduction	Refs
IL-1 receptor antagonists	Anakinra (100 mg, sometimes 200 mg, daily subcutaneously)	>250	Systemic and articular	>12	80	Yes	20,85–91,94
Anti-IL-1ß	Canakinumab (4 mg/kg up to max. 300 mg per month subcutaneously)	10	Systemic and articular	>12	100	Yes	98–108
IL-1 trap	Rilonacept (loading dose 100–320 mg and then 100–320 mg per week)	11	Systemic and articular	>12	100	Yes	84,96
TNF blockers	• Infliximab (3.0–7.5 mg/kg weeks 0, 2 and 6 and then every 6–8 weeks intravenously) • Etanercept (50 mg per week subcutaneously)	<100	Articular	>12	0–100	NA	78–83
IL-6 receptor antagonists	Tocilizumab (8 mg/kg per month intravenously or 162 mg per week subcutaneously)	<150	Systemic and articular	>12	60–85	Yes	104–107,109–112
Anti-IL-18	Tadekinig alpha (80 mg per week subcutaneously or 160 mg per week subcutaneously)	<25	NA	4	NA	NA	113
B cell-directed	Rituximab (1 g intravenous at day 1 and day 15, next cycle after 6 months)	1	NA	12	NA	NA	171
T cell-directed	Abatacept (500–1,000 mg per month intravenously[a] or 125 mg per week subcutaneously)	2	NA	>12	NA	NA	172,173

AoSD, adult-onset Still's disease; NA, not available. [a]Abatacept dose depends on patient weight: <60 kg = 500 mg, 60–100 kg = 750 mg and ≥100 kg = 1,000 mg.

Journal of
Clinical Medicine

Review

Syndrome of Undifferentiated Recurrent Fever (SURF): An Emerging Group of Autoinflammatory Recurrent Fevers



J. Clin. Med. 2021, 10, 1963

Review

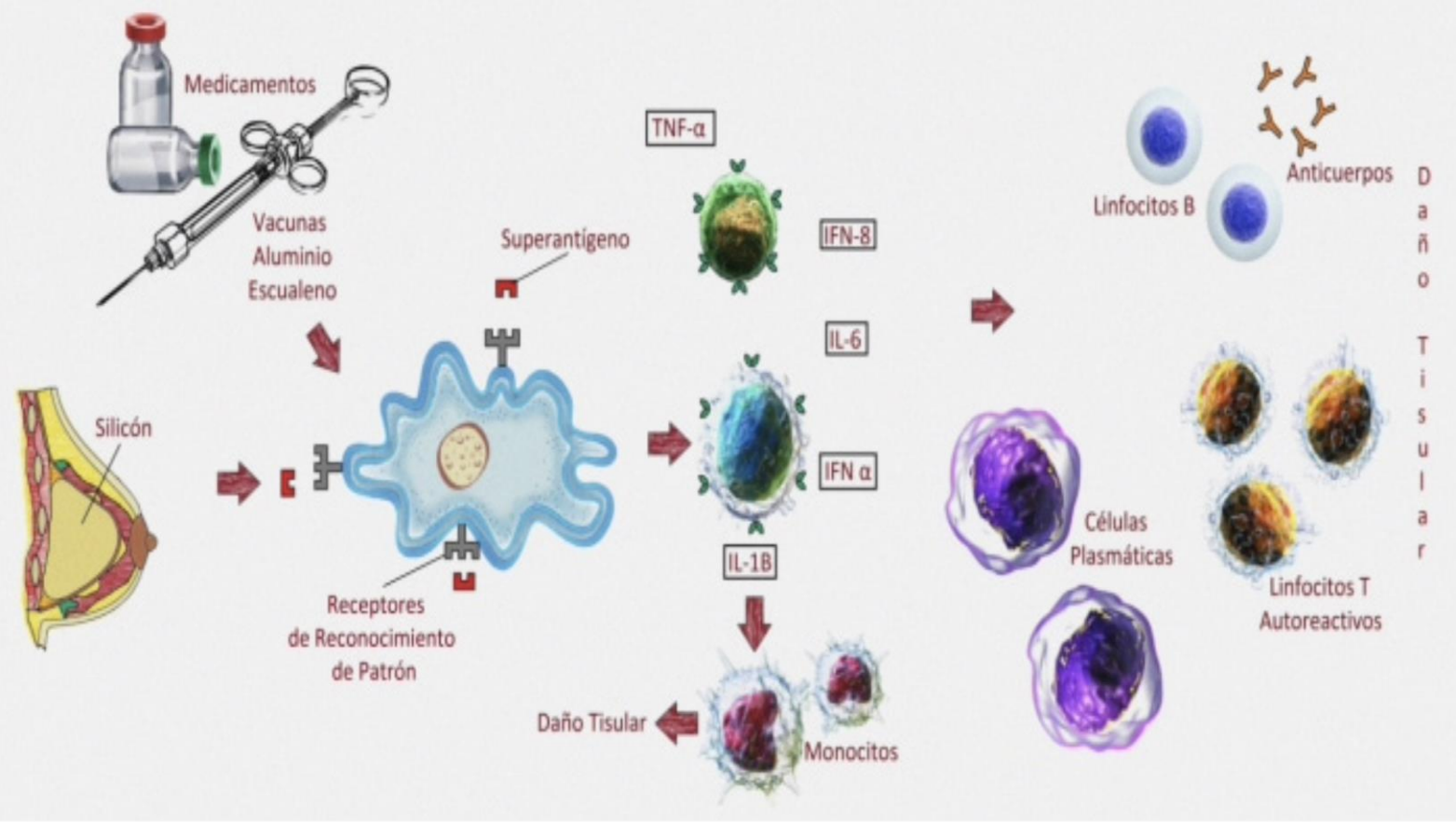
Syndrome of Undifferentiated Recurrent Fever (SURF): An Emerging Group of Autoinflammatory Recurrent Fevers

Table 3. Proposed empirical indications for the clinical suspicion of SURF.

Mandatory features
Recurrent fever with elevated inflammatory markers [1]
Negative criteria for PFAPA [2]
Negative genotype for HRF [3]
Additional supporting features
Monthly attacks
Attacks duration of 3–5 days
Fatigue/malaise
Arthralgia/myalgia
Abdominal pain
Eye manifestations [4]
Continuous colchicine/anti-IL1 response [5]

[1] at least 3 similar episodes of fever of unknown origin in 6 months; [2] according to the modified Marshall's and/or Eurofever criteria. [3] not conclusive NGS and/or Sanger sequencing of at least the most commonly associated genes (MEFV, MVK, TNFRSF1A, NLRP3). [4] periorbital edema and/or corneal erythema. [5] amelioration of symptoms and/or acute phase reactants. PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenopathy; HRF, hereditary recurrent fever; IL, interleukin.

Sindrome Autoinflamatorio por Adyuvante



profesionales
Guías de urgencias
Fuentes/ Procedimientos

Pericarditis recurrente idiopática

Aportaciones

Definición de la enfermedad

La pericarditis recurrente idiopática, es un síndrome autoinflamatorio poco frecuente que se define en base a la presencia de inflamación pericárdica recurrente de origen desconocido después de un primer episodio de pericarditis aguda y un intervalo asintomático de 4 a 6 semanas o más. Los episodios recurrentes de dolor torácico pueden ser el único signo de presentación, aunque el dolor torácico puede ir acompañado de roce pericárdico, cambios electro- o ecocardiográficos, derrame pericárdico e incremento de la proteína C reactiva. El taponamiento cardíaco es una complicación poco frecuente potencialmente mortal.

ORPHA:251307

Nivel de clasificación: Trastorno

Sinónimos: -

Prevalencia: **Desconocido**

Herencia: **No aplicable**

Edad de inicio o aparición: **Cualquier edad**

CIE-10: **I09.2**

OMIM: -

UMLS: -

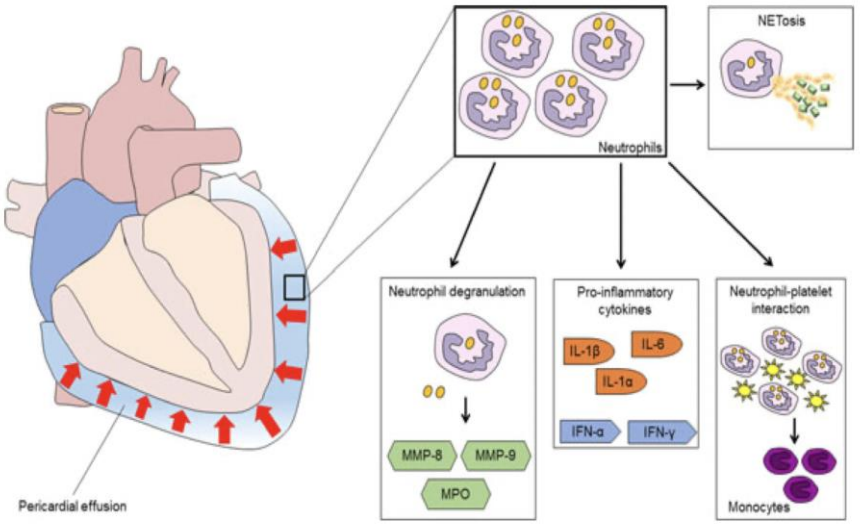
MeSH: -

GARD: -

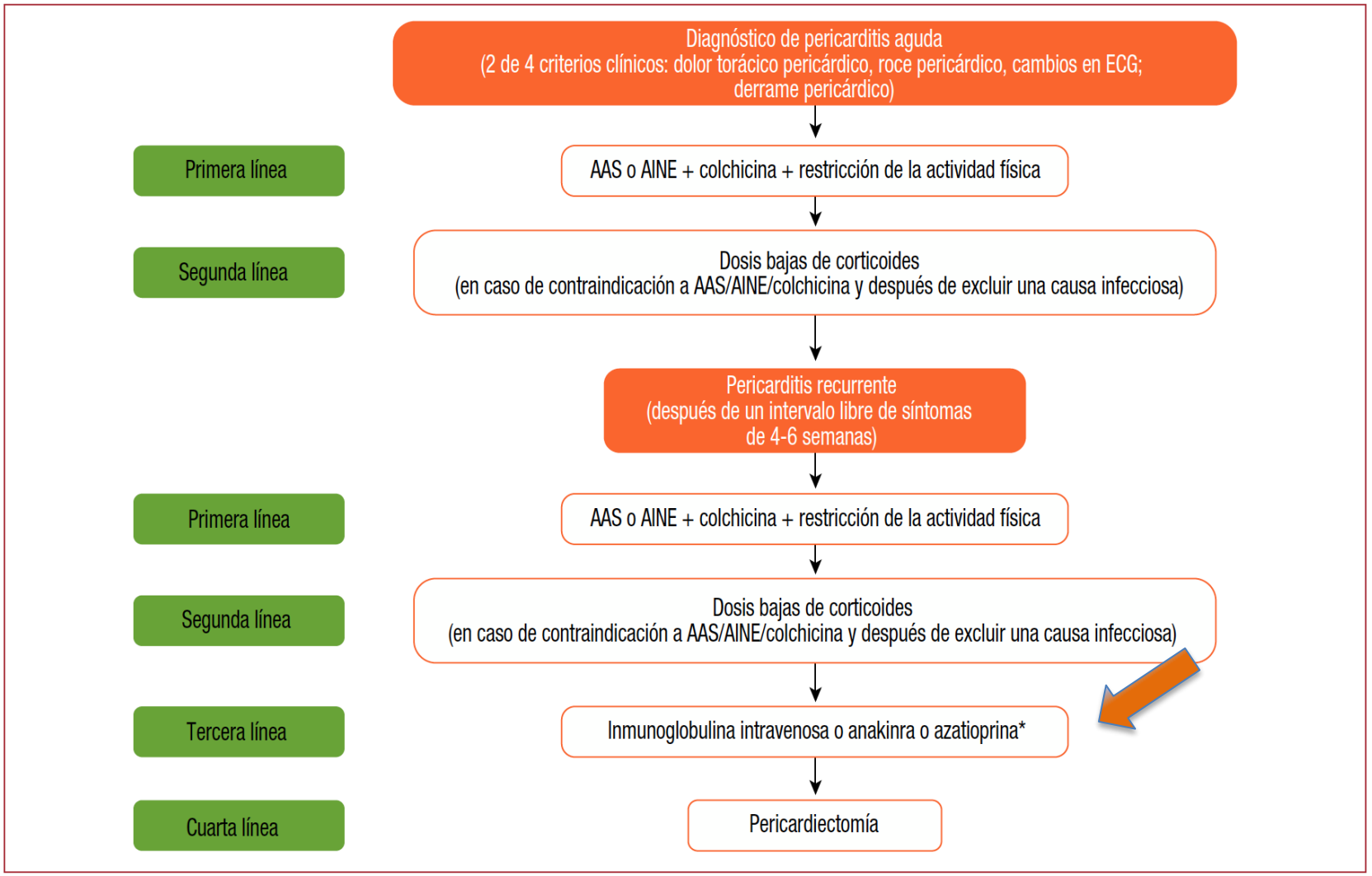
MedDRA: -

PERICARDITIS RECURRENTE AGUDA AUTOINFLAMATORIA

- Enfermedad Autoinflamatoria POLIGÉNICA
- NLRP3
- IL-1
- NETOSIS
- Tratamiento
  - COLCHICINA
  - BLOQUEO IL-1



J Cell Physiol. 2019;234:5390–5398.



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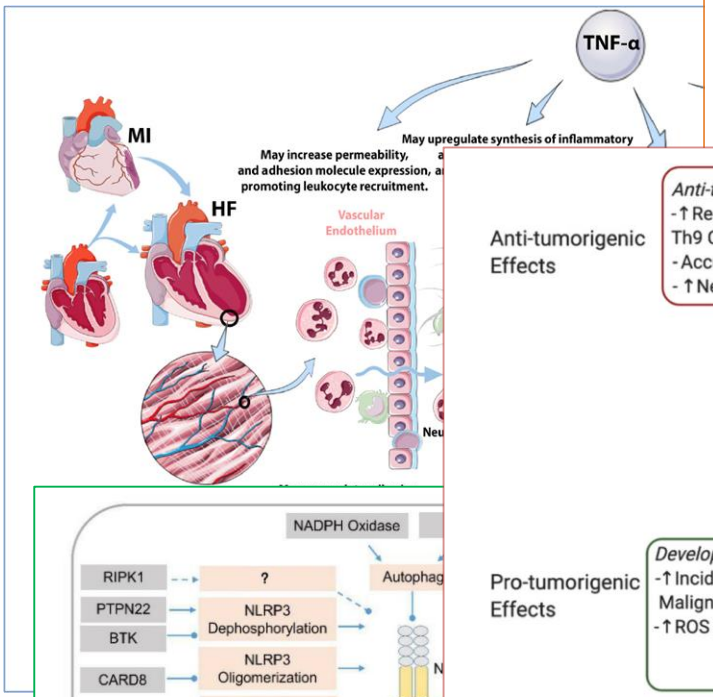

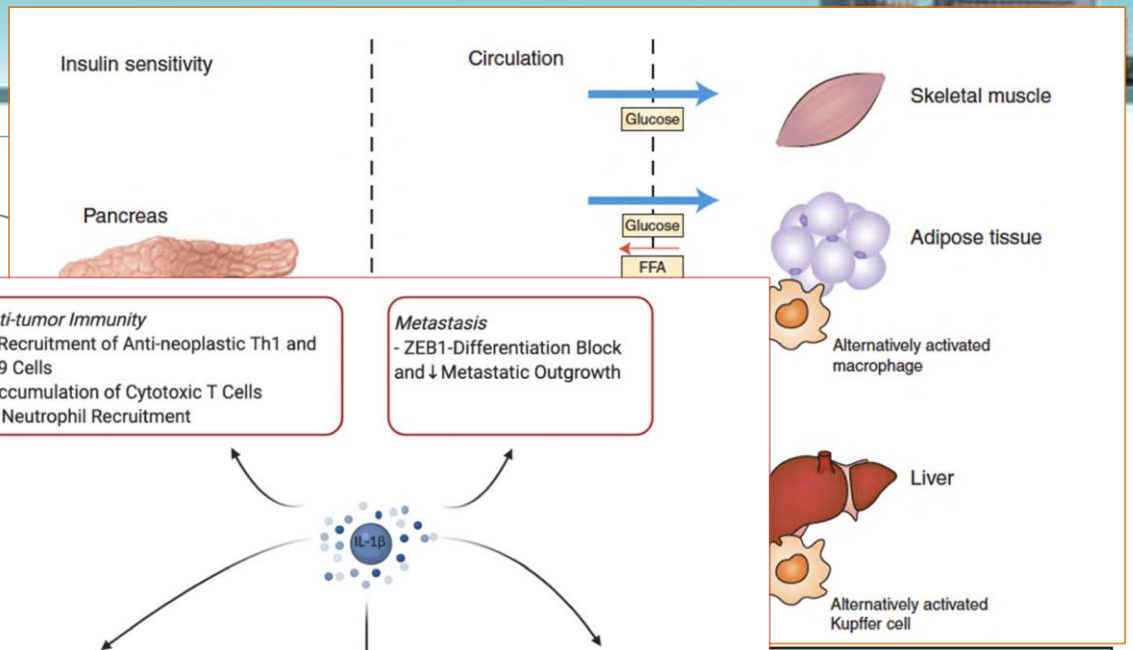

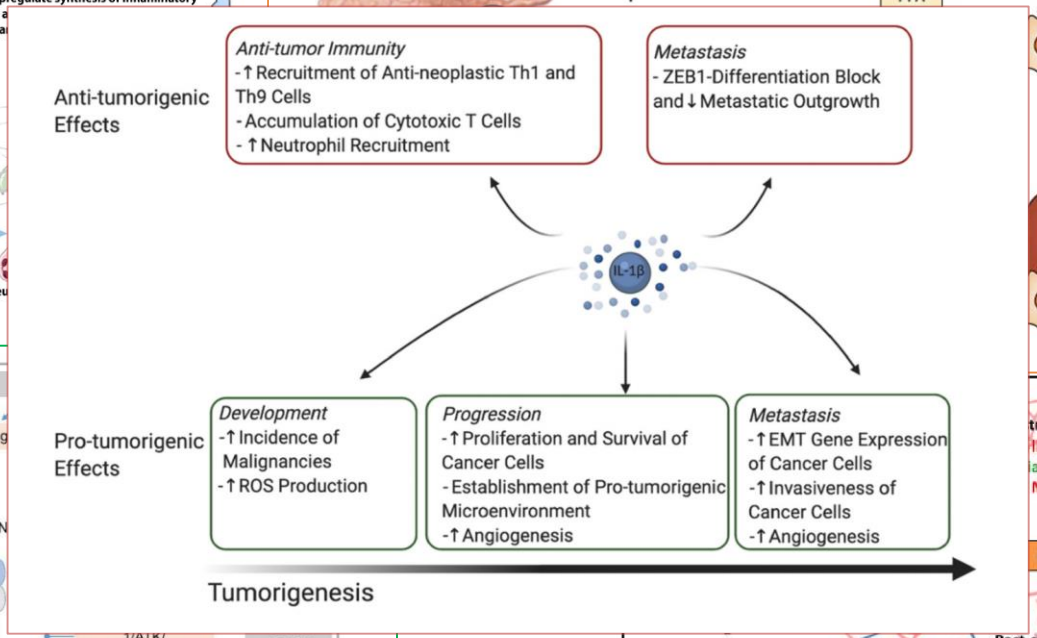

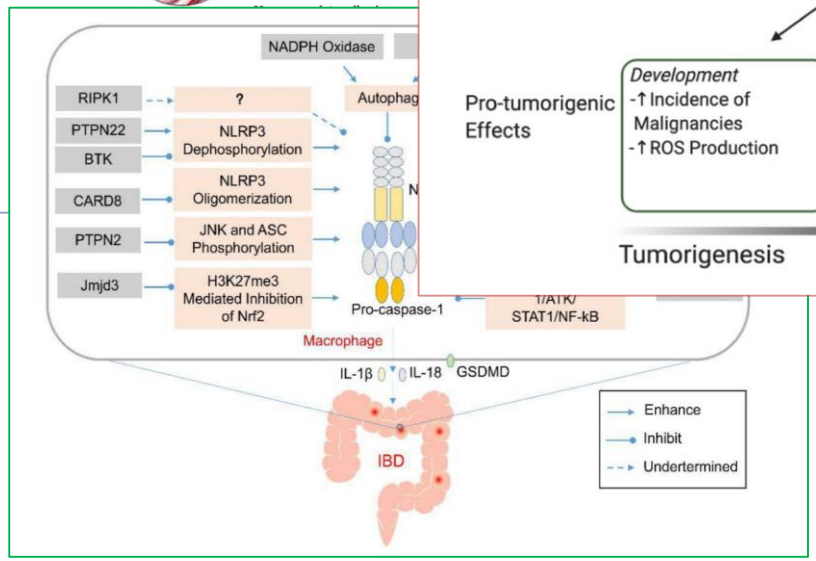

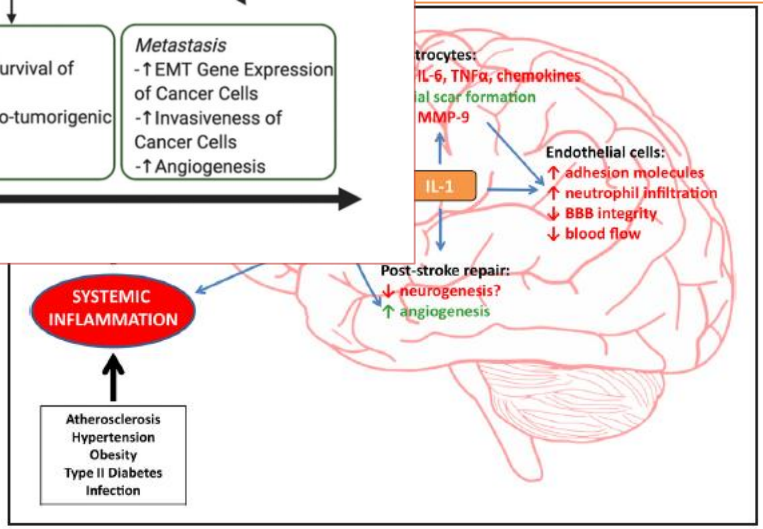

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