Pathophysiology of IL-1–Triggered Diseases

July 2025

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IL, interleukin.

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Contents

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Autoinflammatory vs. autoimmune disease

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Autoinflammation and autoimmunity[1–3]

Autoinflammation

- Abnormal **activation of an innate inflammatory response**[1,2]
- Characterized by fever, rash and chronic or recurrent systemic/tissue inflammation[1,2]
- Key immune cells:[1,2]

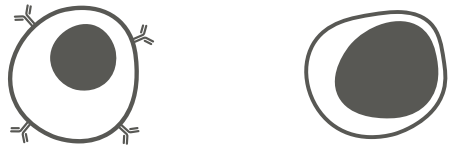
Neutrophil | Monocyte | Macrophage

- Key cytokines:[1]

IL-1α | IL-1β | IL-18

Autoimmunity

- Loss of tolerance to self-antigens, leading to an **adaptive immune response against self**[2]
- Characterized by the presence of auto-antibodies and tissue damage driven by autoreactive lymphocytes[2]
- Key immune cells:[2]



B cell | T cell

- Key cytokines:[3]

TNF | IL-6 | IL-17

IL, interleukin; TNF, tumor necrosis factor.

1. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 2. El-Shebiny EM, et al. *Egypt J Intern Med* 2021;33:11; 3. Chetaille Nézondet A, et al. *J Leukoc Biol* 2020;108:647–657.

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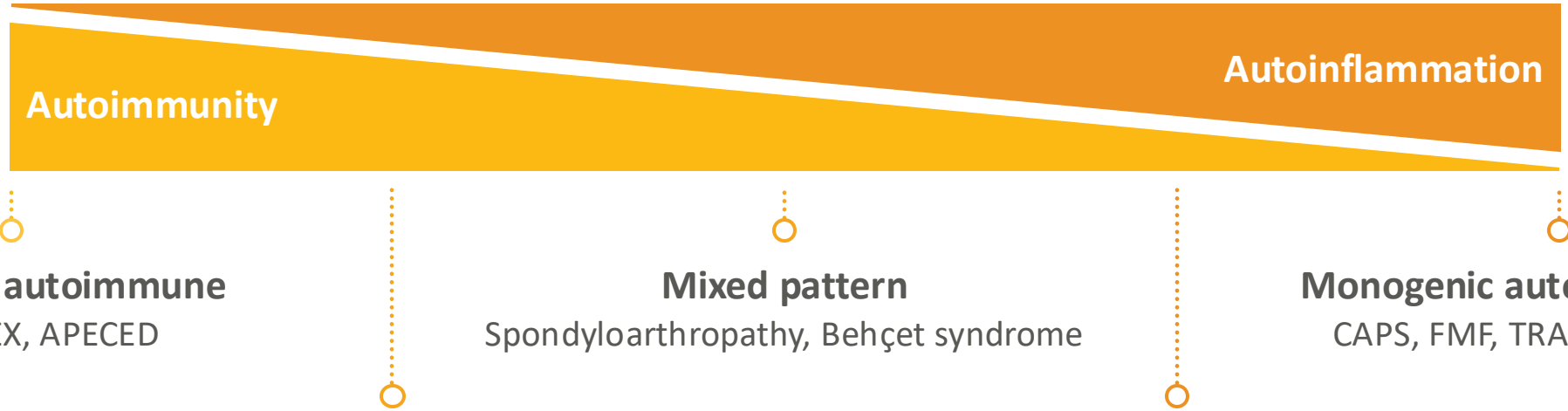
Autoinflammatory and autoimmune diseases fall on a spectrum[1–5]



Monogenic autoimmune
ALPS, IPEX, APECED

Polygenic autoimmune
T1DM, SLE, Celiac disease

Mixed pattern
Spondyloarthropathy, Behçet syndrome

Polygenic autoinflammatory
IBD, GCA, Still's disease

Monogenic autoinflammatory
CAPS, FMF, TRAPS, MKD, DIRA

Heterogeneity in affected tissues/systems and clinical phenotypes[2]

Mechanisms of initiation are poorly understood[2]

ALPS, autoimmune lymphoproliferative syndrome; APECED, autoimmune polyendocrinopathy candidiasis ecto-dermal dystrophy; CAPS, cryopyrin-associated autoinflammatory syndrome; DIRA, deficiency of the interleukin-1 receptor antagonist; FMF, familial Mediterranean fever; GCA, giant cell arteritis; IBD, inflammatory bowel disease; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; MKD, mevalonate kinase deficiency; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes mellitus; TRAPS, tumor necrosis factor receptor-associated periodic syndrome.

1. McGonagle D, et al. *PLoS Med* 2006;3:e297; 2. El-Shebiny EM, et al. *Egypt J Intern Med* 2021;33:11; 3. Szekanecz Z, et al. *Nat Rev Rheumatol* 2021;17:585–595; 4. Hedrich CM. *Clin Immunol* 2016;165:21–28; 5. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463.

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IL-1 and its role in autoinflammatory disease

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The IL-1 family comprises pro- and anti-inflammatory cytokines[1–5]

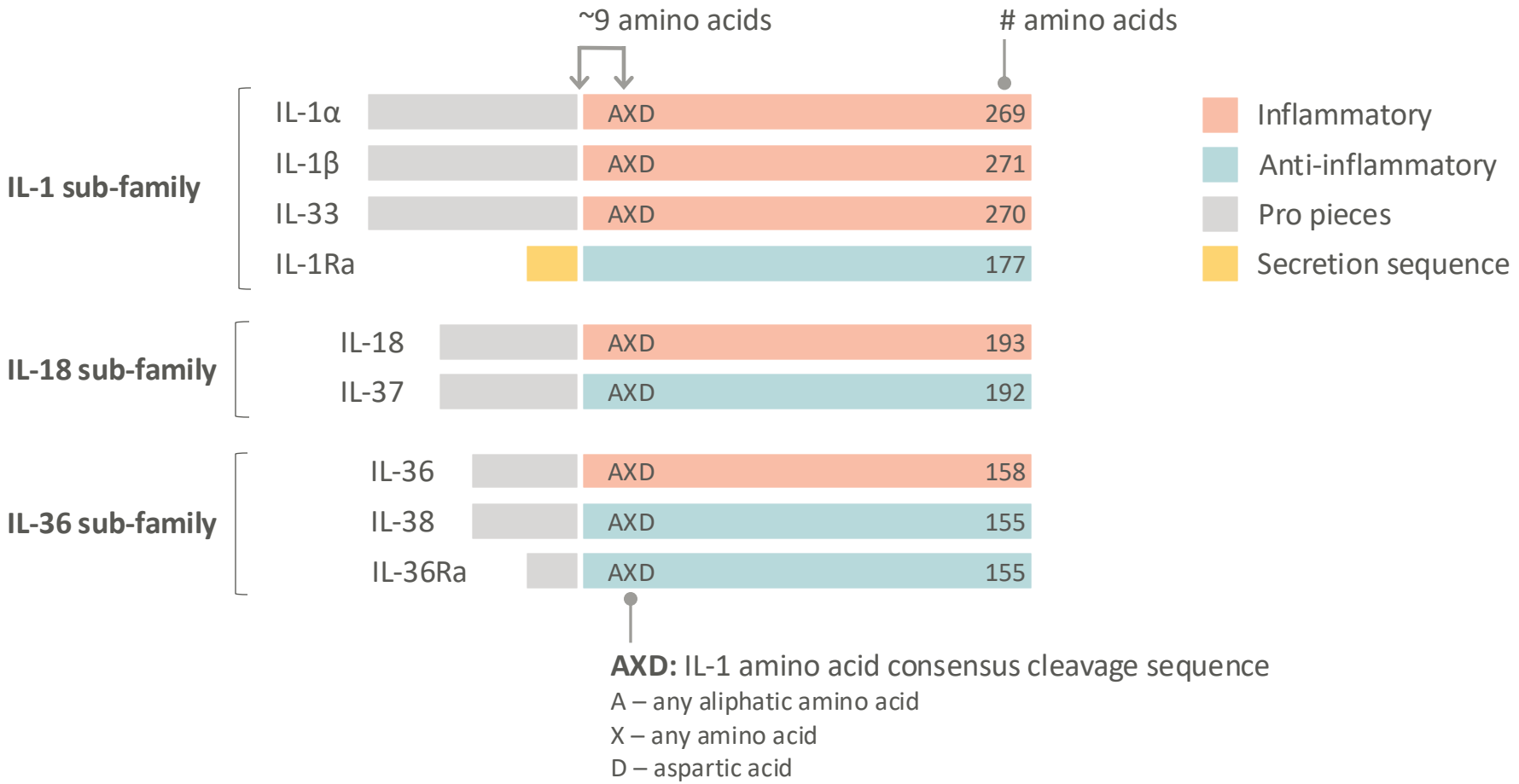

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Figure adapted from Garlanda C, et al. *Immunity* 2013;39:1003–1018.
IL, interleukin; IL-XRa, interleukin-X receptor antagonist.

1. Garlanda C, et al. *Immunity* 2013;39:1003–1018; 2. Adkis M, et al. *J Allergy Clin Immunol* 2016;138:984–1010; 3. Dinarello C. *Immunol Rev* 2018;281:8–27; 4. van de Veerdonk FL, et al. *Front Immunol* 2013:8;4:167; 5. Eisenberg SP, et al. *Proc Natl Acad Sci USA* 1991;88:5232–5236.

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IL-1 plays an important role in innate inflammation[1,2]

	IL-1α	IL-1β ("classical" IL-1)
Produced by	• Numerous cell types, particularly epithelial cells, endothelial cells, keratinocytes, and platelets[2–6]	• Activated myeloid cells (e.g., monocytes, macrophages, dendritic cells)[2–4,6]
Release	• Pro-IL-1α is released from necrotic cells in response to stress, tissue damage, or infection[1–6]	• Released following inflammasome activation and pyroptosis[1,2,4–6]
Function	• Local inflammation[3,4] • Signals tissue injury induced by non-infectious cellular stress (sterile inflammation)[3–6]	• Local and systemic inflammation[4] • Produced in response to infection or inflammation (induces acute phase proteins; recruits and activates lymphocytes)[2,3]
Expression	• Constitutively expressed[2–6] – Expression increases in response to triggers[4,5] • Membrane-bound or secreted cytokine[2–4,6] • Induced by cytokines, including IL-1[5]	• Induced in response to triggers[3,4,6] • Secreted cytokine[1,2,4] • Induced by cytokines, including IL-1[2,6]
Cleavage	• Pro-IL-1α (uncleaved) and IL-1α (cleaved) are functionally active[3–6]	• Only cleaved form (IL-1β) is active[1,2,4,6] – Pro-IL-1β is cleaved through inflammasome/ caspase 1 activation[1,2,4,6]
Circulatory levels	• Generally none[4,6]	• pg/mL range[1]

IL, interleukin.

1. Kaneko N, et al. *Inflamm Regener* 2019;13; 2. Dinarello CA. *Immunol Rev* 2018;281:8–27; 3. Boraschi D. *Front Immunol* 2022;13:872155; 4. Cavalli G, et al. *Autoimmun Rev* 2021;20:102763; 5. Di Paolo NC, et al. *Nat Immunol* 2016;17:906–913; 6. Garlanda C, et al. *Immunity* 2013;39:1003–1018.

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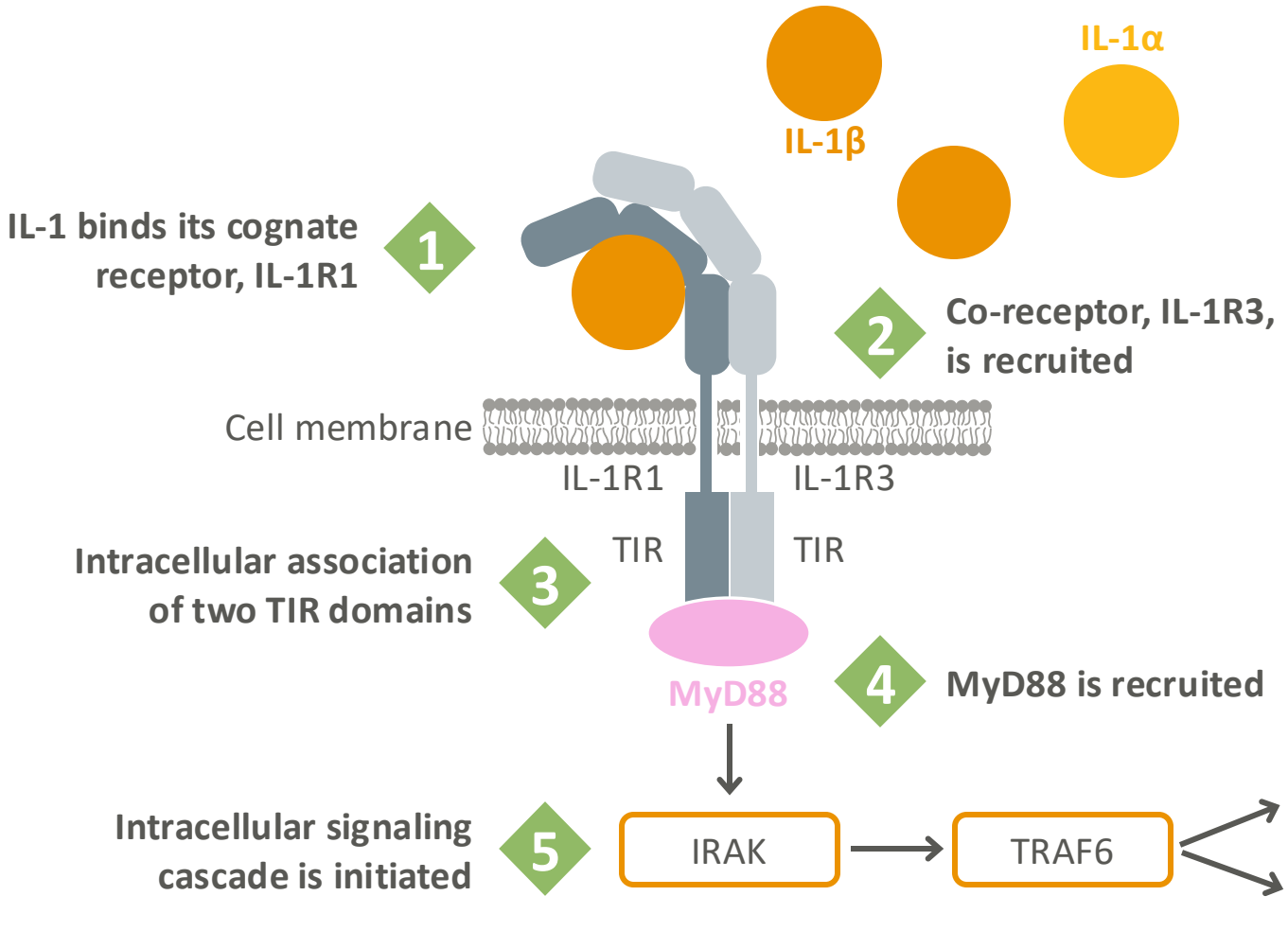
Pro-inflammatory signaling requires 5 steps:[1–4]



IL-1 receptors are part of the TIR domain superfamily, sharing a common sequence with TLRs and initiating the same intracellular signaling cascade to trigger inflammation[1]

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Figure adapted from Dinarello CA. *Nat Rev Rheumatol* 2019;15:612–632.
IL, interleukin; IL-1R1/3, interleukin-1 receptor 1/3; IRAK, interleukin-1 receptor-associated kinase; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa B; TIR, Toll-interleukin receptor; TLR, toll-like receptor; TRAF, tumor necrosis factor receptor-associated factor.

1. O'Neill L, et al. *Nat Rev Immunol* 2007;7:353–364; 2. Dinarello CA. *Blood* 2011;117:3720–3732; 3. Hernandez-Santana YE, et al. *Eur J Immunol* 2019;49:1306–1320; 4. Dinarello CA. *Nat Rev Rheumatol* 2019;15:612–632.

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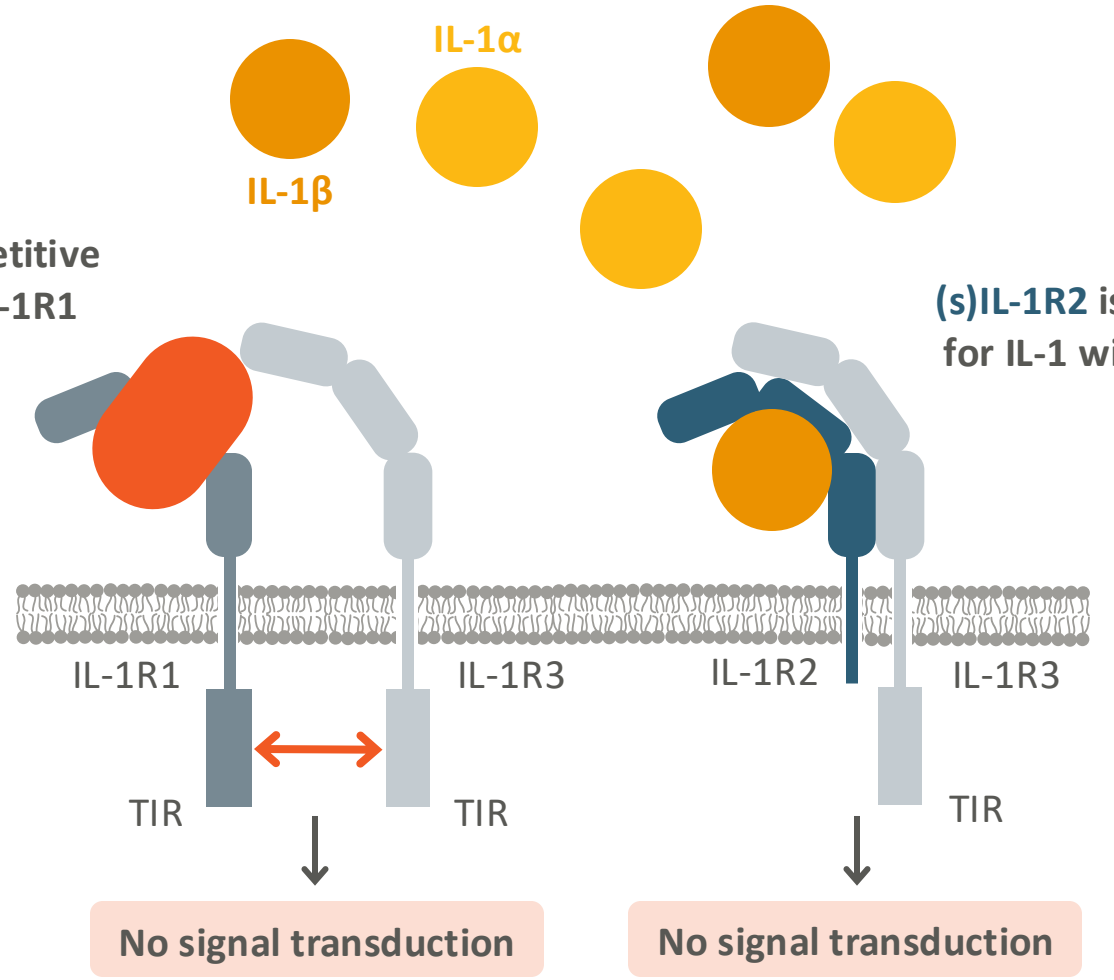
IL-1 signaling and regulation modulates inflammation[1–7]



Normal serum levels

IL-1α	n/a[2,6]
IL-1β	<1 pg/mL[3]
IL-1Ra	100–300 ng/mL[3]
IL-1R2	5–10 ng/mL[4]
IL-1R3	~300 ng/mL[4]

Due to its potency and extensive functions, IL-1 activity is tightly regulated at multiple levels: transcription, translation, processing, secretion and post-secretion[2,4]

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Figure adapted from Dinarello CA. *Nat Rev Rheumatol* 2019;15:612–632.
IL, interleukin; IL-1R1/2/3, interleukin-1 receptor 1/2/3; IL-1Ra, interleukin-1 receptor antagonist; (s)IL-1R2, (soluble) interleukin-1 receptor 2; n/a, no applicable; TIR, toll-interleukin receptor.
1. O'Neill L, et al. *Nat Rev Immunol* 2007;7:353–364; 2. Mantovani A, et al. *Immunity* 2019;50:778–795; 3. Dinarello CA. *Blood* 2011;117:3720–3732; 4. Garlanda C, et al. *Immunity* 2013;39:1003–1018; 5. Hernandez-Santana YE, et al. *Eur J Immunol* 2019;49:1306–1320; 6. Dinarello CA. *Nat Rev Rheumatol* 2019;15:612–632; 7. Schett G, et al. *Nat Rev Rheumatol* 2016;12:14–24.

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Effects of raising systemic IL-1β levels[1,2]

Metabolic	Hematologic	Immunologic	Inflammation	Physiologic
↑ ACTH	↑ CRP	T cell activation	↑ COX2	Fever
↑ cortisol	↑ ESR	Th17 differentiation	↑ NO	Rash
↓ insulin	↑ IL-6	DC maturation	↑ VEGF	Fatigue
↑ fibrinogen	↑ neutrophilia	NK cell activation	↑ chemokines	Muscle pain
↓ albumin	↑ phagocytosis	B cell activation	↑ IL-1	Shock
↑ iron stores	↓ erythropoiesis		↑ TNF	↓ appetite
			↑ IL-1Ra	↑ sodium excretion

ACTH, adrenocorticotropic hormone; COX2, prostaglandin-endoperoxide synthase 2; CRP, C-reactive protein; DC, dendritic cell; ESR, erythrocyte sedimentation rate; IL, interleukin; IL-1Ra, interleukin-1 receptor agonist; NK, natural killer; NO, nitric oxide; Th17, T-helper 17; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

1. Dinarello CA. *N Engl J Med* 1984;311:1413–1418; 2. Dinarello CA. *Eur J Immunol* 2011;41:1203–1217.

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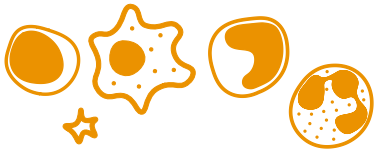
Pathophysiological effects of IL-1

Immunological



Immune cell recruitment and activation
Production of inflammatory mediators

Inflammation, tissue damage[1,2,9,11]

Liver

Induction of IL-6
Production of acute-phase reactants

Elevated acute-phase reactants, e.g., CRP, SAA[1,2,14]

CNS

Induction of PGE_2
Activation of the HPA axis

Fever, fatigue, loss of appetite, pain, production of cortisol[1,2,4–7]

Endothelium

Endothelial permeability
Vascular smooth muscle modulation

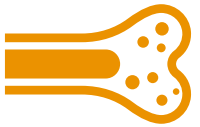
Skin rash, vasodilation, hypotension[1,3,15]

Musculoskeletal

Activation of synovial fibroblasts, chondrocytes, and osteoclasts; amino acid release from muscle

Cartilage degradation/ bone erosion,[8–10] muscle pain[16]

Bone marrow



Neutrophilia, thrombocytosis, anemia

Hematological abnormalities, hypercoagulation[1,11–13]

1. Rösen-Wolff A, et al. Cytokines in Autoinflammation In: Hashkes PJ, et al (Eds). Te… mic–pituitary–a… A.
3. Dinarello CA. Interleukin-1-Induced Hypotension and the Effect of an Interleuk… unction in Traun… ; 2. Garlanda C,
575;
4. Roerink ME, et al. *J Neuroinflammation* 2017;14:16; 5. Burfeind KG, et al. *Semin Cell Dev Biol* 2016;54:42–52; 6. Dinarello CA. *Eur J Immunol* 2011;41:1203–1217; 7. Ren K, et al. *Brain Res Rev* 2009;60:57–64;
8. Gabay C, et al. *Nat Rev Rheumatol* 2010;6:232–241; 9. Schett G, et al. *Nat Rev Rheumatol* 2016;12:14–24; 10. Schiff MH. *Ann Rheum Dis* 2000;59(Suppl 1):i103–i108; 11. Mantovani A, et al. *Immunity* 2019;50:778–795;
12. Nishmura S, et al. *J Cell Biol* 2015;209:453–466; 13. Vora SM, et al. *Nat Rev Immunol* 2021;21:694–703; 14. Sack GH. *Mol Med* 2018;24:46; 15. Fahey E, Doyle SL. *Front Immunol* 2019;10:1426;
16. Li W, et al. *Am J Physiol Cell Physiol* 2009;297:C706–C714.

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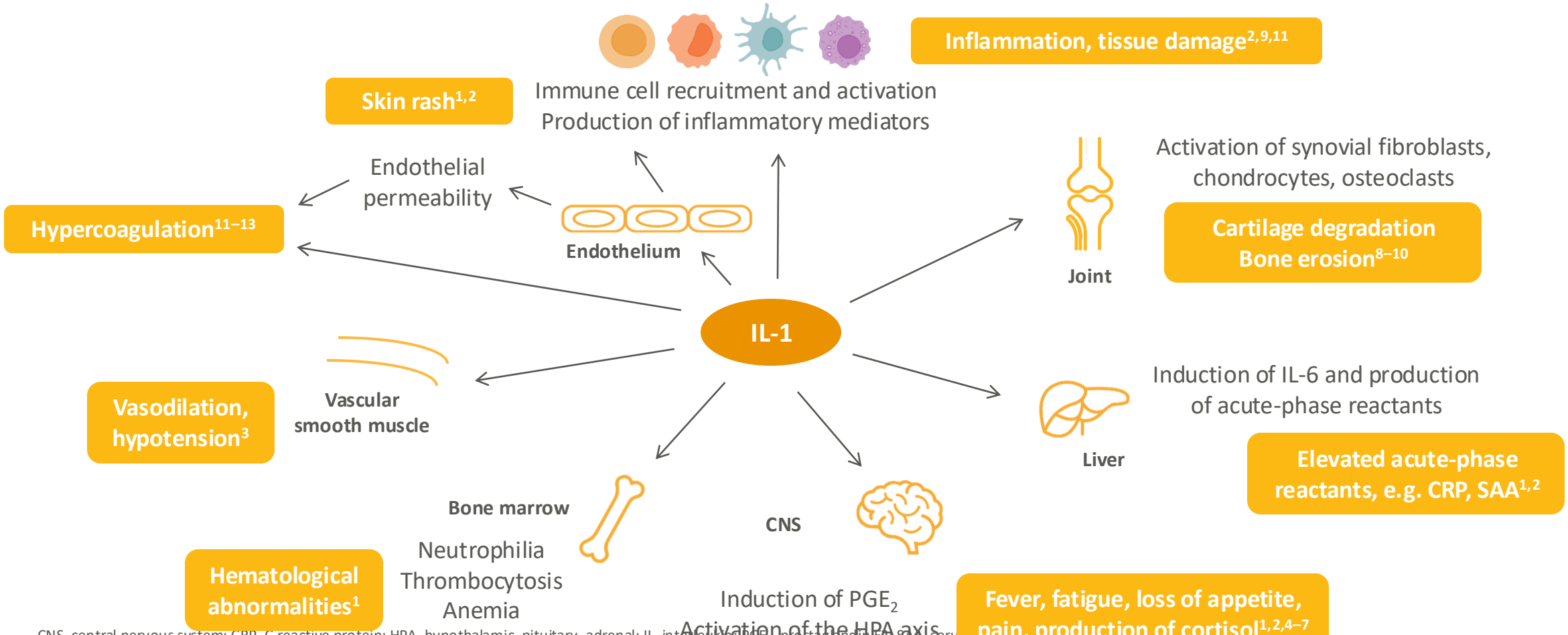
Pathophysiological effects of IL-1



CNS, central nervous system; CRP, C-reactive protein; HPA, hypothalamic–pituitary–adrenal; IL, interleukin; PGE_2, prostaglandin E2; SAA, seru

1. Rösen-Wolff A, et al. Cytokines in Autoinflammation In: Hashkes PJ, et al (Eds). Textbook of Autoinflammation. Switzerland. Springer; 2019:111–122; 2. Ganesan C, et al. *Immunity* 2013;39:1003–1018; 3. Dinarello CA. Interleukin-1-Induced Hypotension and the Effect of an Interleukin-1 Receptor Antagonist. In: Faist A, et al (Eds). Host Defense Dysfunction in Trauma, Shock and Sepsis. Berlin: Springer-Verlag; 1993:571–575; 4. Roerink ME, et al. *J Neuroinflammation* 2017;14:16; 5. Burfeind KG, et al. *Semin Cell Dev Biol* 2016;54:42–52; 6. Dinarello CA. *Eur J Immunol* 2011;41:1203–1217; 7. Ren K, et al. *Brain Res Rev* 2009;60:57–64; 8. Gabay C, et al. *Nat Rev Rheumatol* 2010;6:232–241; 9. Schett G, et al. *Nat Rev Rheumatol* 2016;12:14–24; 10. Schiff MH. *Ann Rheum Dis* 2000;59(Suppl 1):i103–108; 11. Mantovani A, et al. *Immunity* 2019;50:778–795; 12. Nishmura S, et al. *J Cell Biol* 2015;209:453–466; 13. Vora SM, et al. *Nat Rev Immunol* 2021;21:694–703.

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Summary

The IL-1 family is a group of structurally and functionally related cytokines[1]

The expression, release, and functional consequences of IL-1β, IL-1α, and IL-1Ra are intertwined and highly regulated at multiple levels[2]

IL-1 biology is complex; it exerts pathophysiological effects on a wide range of organ systems and tissue types, and is a key mediator of autoinflammation[3,4]

IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist.

1. Boraschi D. *Front Immunol* 2022;13:872155; 2. Garlanda C, et al. *Immunity* 2013;39:1003–1018; 3. Dinarello CA. *Eur J Immunol* 2011;41:1203–1217; 4. Kaneko N, et al. *Inflamm Regen* 2019;39:12.

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IL-1β production and the role of the inflammasome

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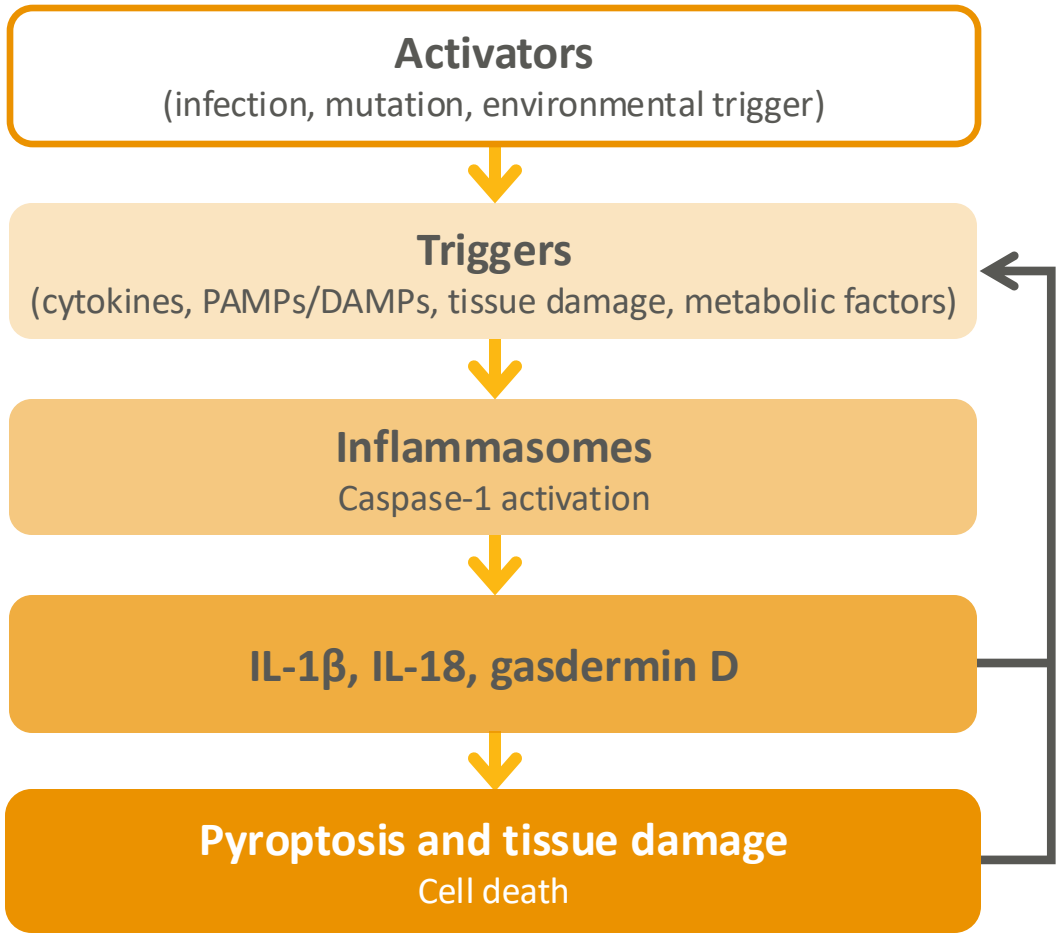
IL-1β production: A key function of the inflammasome

- Inflammasomes are intracellular protein complexes that assemble when a danger signal (PAMP/DAMP) stimulates a sensor molecule[1]
- Expressed most prominently by APCs, but also by other non-immune cell types[3]
- Produce IL-1β and IL-18, initiating an inflammatory cascade that can result in cell death[1,2]
- Normally closely regulated[2]
- Inappropriate or chronic activation:
  - Raises systemic IL-1β and IL-18 levels
  - Is the basis of many autoinflammatory diseases[2]



APC, antigen-presenting cell; DAMP, damage-associated molecular pattern; IL, interleukin; PAMP, pathogen-associated molecular pattern.

1. Davis BK, et al. *Annu Rev Immunol* 2011;29:707–35; 2. Zheng D, et al. *Cell Discov* 2020;6:36; 3. de Zoete MR, et al. *Cold Spring Harb Perspect Biol* 2014;6:a016287.

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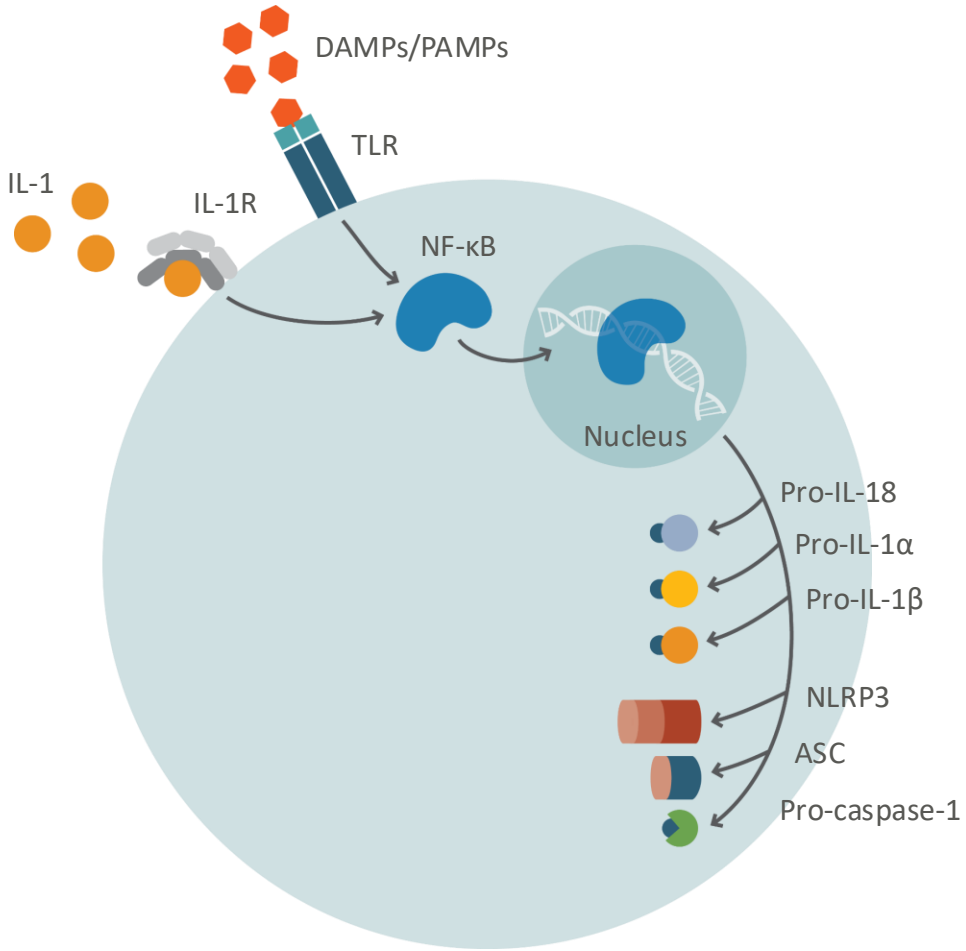
The NLRP3 inflammasome[1,2]



- The NLRP3 inflammasome is expressed by many cell types, but primarily by innate immune cells such as macrophages, monocytes, and DCs[1,3]
- Like other inflammasomes, the NLRP3 inflammasome complex consists of:[1]
  - A sensor (NLRP3)
  - An adaptor (ASC)
  - An effector (caspase-1)

Signal 1: Priming

- DAMPs/PAMPs or pro-inflammatory cytokines stimulate the transcriptional upregulation of pro-IL-1 and pro-IL-18 via NF-κB, as well as each component of the inflammasome complex[1]

Monocytes are constitutively primed, and only require Signal 2 (activation) to trigger a pro-inflammatory response[4]

Figure adapted from Mulay SR. *Kidney Int* 2019;96:58–66.
ASC, adaptor protein; DAMP, damage-associated molecular pattern; DC, dendritic cell; IL, interleukin; IL-1R, interleukin-1 receptor; NF-κB, nuclear factor kappa B; NLRP3, nucleotide-binding and leucine-rich repeat family pyric domain containing 3; PAMP, pathogen-associated molecular pattern; TLR, Toll-like receptor.
1. Blevins HM, et al. *Front Aging Neurosci* 2022;14:879021; 2. Mulay SR. *Kidney Int* 2019;96:58–66; 3. Jo E, et al. *Cell Mol Immunol* 2016;13:148–159; 4. Gritsenko A, et al. *Front Immunol* 2020;11:565924.
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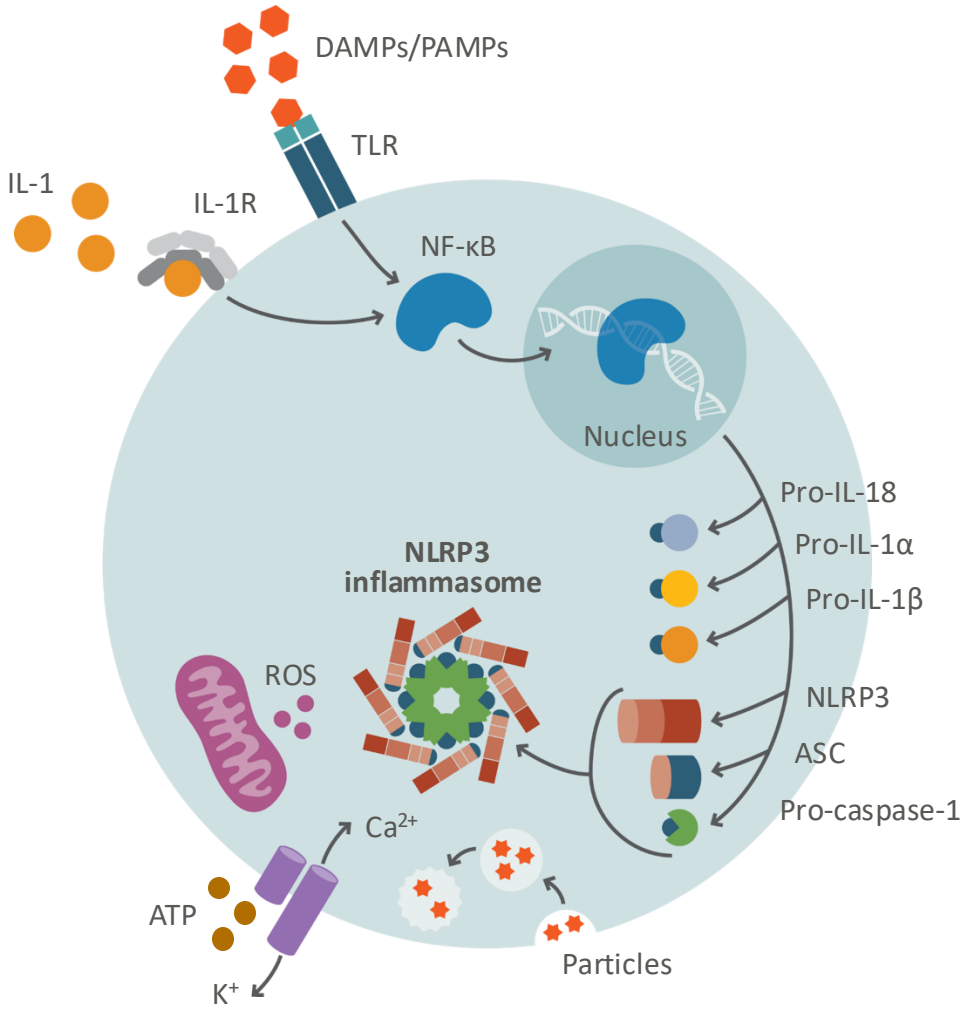
The NLRP3 inflammasome[1,2]



Signal 2: Activation[1]

- The pattern recognition receptor NLRP3 senses a second stimulus, which triggers formation of the inflammasome complex
- NLRP3 is activated by many different stimuli, such as:
  - Particulate matter (e.g., uric acid crystals)
  - Ion fluxes (e.g., K^+, Ca^{2+})
  - Lysosomal damage
  - Most pathogens
  - Extracellular ATP
  - Mitochondrial ROS
- The NLRP3 inflammasome assembles through:
  - PYD/PYD interactions between NLRP3 and ASC, forming a “speck”
  - CARD/CARD interactions between ASC and pro-caspase-1
- Pro-caspase-1 is converted into active caspase-1

Figure adapted from Mulay SR. *Kidney Int* 2019;96:58–66.
ASC, adaptor protein; ATP, adenosine triphosphate; CARD, caspase activation and recruitment domain; DAMP, damage-associated molecular pattern; IL, interleukin; IL-1R, interleukin-1 receptor; NF-κB, nuclear factor kappa B; NLRP3, nucleotide-binding and leucine-rich repeat family pyric domain containing 3; PAMP, pathogen-associated molecular pattern; PYD, pyrin domain; ROS, reactive oxygen species; TLR, Toll-like receptor.
1. Blevins HM, et al. *Front Aging Neurosci* 2022;14:879021; 2. Mulay SR. *Kidney Int* 2019;96:58–66.

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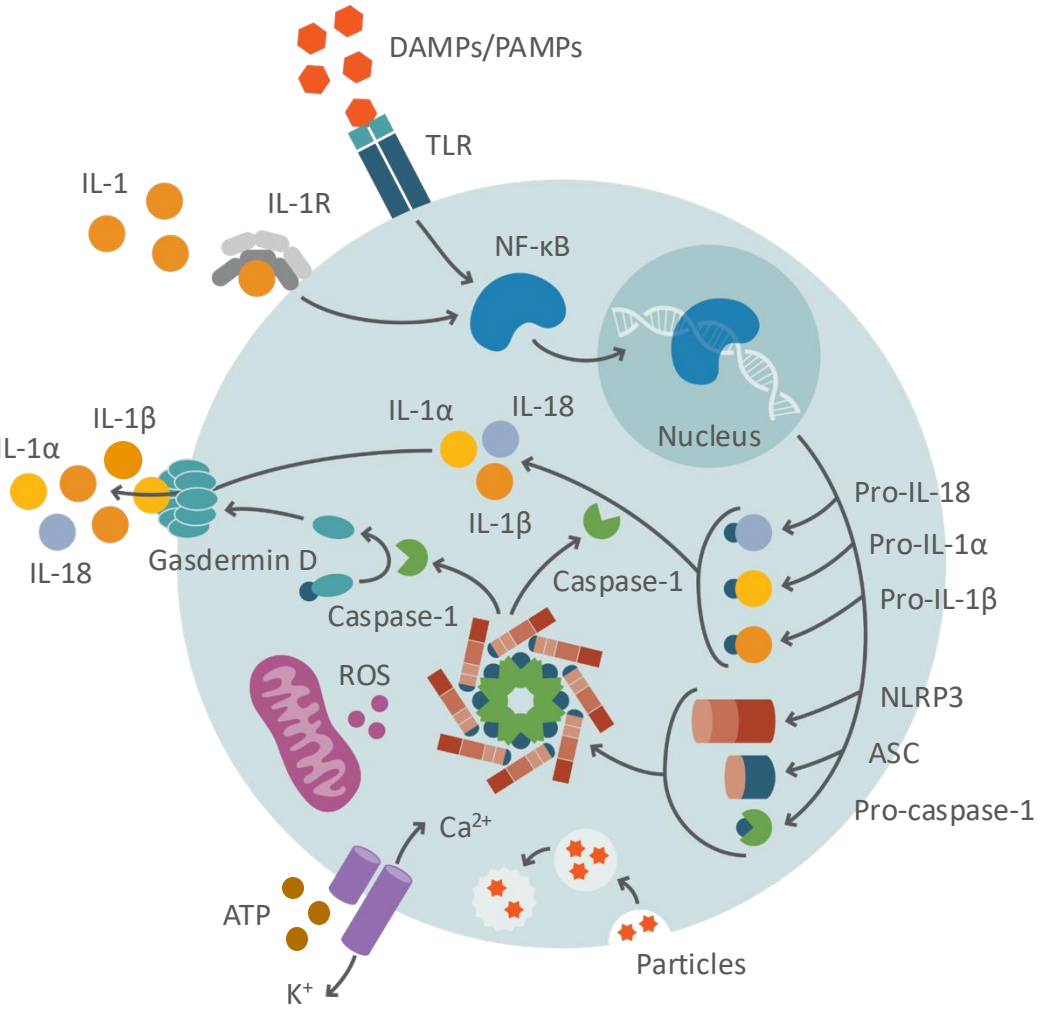
The NLRP3 inflammasome[1,2]



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Production of inflammatory mediators

- Caspase-1 cleaves the biologically inactive pro-IL-1 and pro-IL-18 into their active forms, IL-1 and IL-18
- Caspase-1 also cleaves and activates gasdermin D, a protein involved in inflammatory cell death
  - Gasdermin D forms pores in the cell membrane, disrupting the cell's osmotic potential and initiating pyroptosis
  - Pyroptosis results in the release of intracellular contents, including IL-1 and IL-18

Mutations in *NLRP3* can cause constitutive activation of the inflammasome or a reduced threshold for its activation, leading to the subsequent activation of caspase-1, release of IL-1, and autoinflammation[3,4]

Figure adapted from Mulay SR. *Kidney Int* 2019;96:58–66.
ASC, adaptor protein; ATP, adenosine triphosphate; DAMP, damage-associated molecular pattern; IL, interleukin; IL-1R, interleukin-1 receptor; NF-κB, nuclear factor kappa B; NLRP3, nucleotide-binding and leucine-rich repeat family pyric domain containing 3; PAMP, pathogen-associated molecular pattern; ROS, reactive oxygen species; TLR, Toll-like receptor.
1. Blevins HM, et al. *Front Aging Neurosci* 2022;14:879021; 2. Mulay SR. *Kidney Int* 2019;96:58–66; 3. Moltrasio C, et al. *Front Immunol* 2022;13:1007705; 4. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463.

Example: Inflammasome-associated diseases[1–4]

- Single inflammasome (somatic or germline) mutations can cause disease[1]
  - Occur in all known inflammasomes
  - Somatic mutations are challenging to detect
- Usually gain-of-function mutations[2]
  - Lead to abnormal caspase-1 activation
  - Excessive IL-1β and IL-18 release
  - Pyroptotic tissue damage
- Largely, but not exclusively, characterized by excessive IL-1β and IL-18 signaling[3,4]
  - Details not always well understood

Gene	Disease	Proposed mechanism
NLRP1	Vitiligo	Variants linked to susceptibility
NLRP3	CAPS	Mutations constitutively activate caspase-1
NLRP12	FCAS2	Aberrant NF-κB activation
NLRC4	MAS	Mutations constitutively activate caspase-1
MEFV	FMF	Mutations constitutively activate caspase-1
PSTPIP1	PAPA syndrome	Mutations in *PSTPIP1* constitutively activate the pyrin inflammasome, which activates caspase-1

Single mutations can be harmful

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CAPS, cryopyrin-associated autoinflammatory syndromes; FCAS2, familial cold autoinflammatory syndrome 2; FMF, familial Mediterranean fever; IL, interleukin; MAS, macrophage activation syndrome; NF-κB, nuclear factor kappa B; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne.

1. Masters S, et al. *Ann Rev Immunol* 2009;27:621–68; 2. Stoffels M, Kastner DL. *Annu Rev Genomics Hum Genet* 2016;17:245-72; 3. Netea MG, et al. *Nat Immunol* 2017;18:826–831; 4. Cordero MD, et al. *J Autoimmun* 2018;91:13–22.

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Mechanism of autoinflammatory disease: Multiple possibilities for dysregulation

Autoinflammatory disease can originate from:

1. Abnormal sensitivity to cytokine or PRR stimulation
2. Excessive stress response, such as elevated production of ROS
3. Inadequate negative regulation of the inflammatory response, such as low inhibitory cytokine production
4. Excessive downstream signaling

…and many other factors

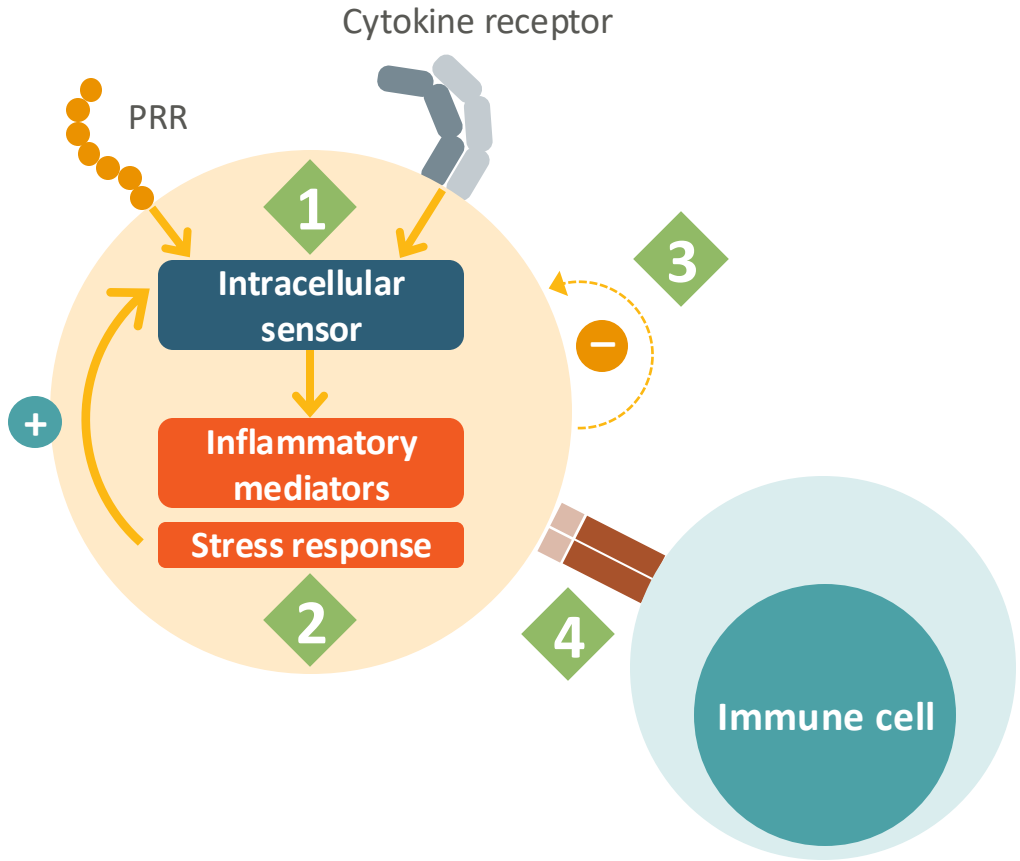

Figure adapted from de Jesus AA, et al. *Ann Rev Immunol* 2015;33:823–74.
PRR, pattern recognition receptor; ROS, reactive oxygen species.
de Jesus AA, et al. *Ann Rev Immunol* 2015;33:823–74.
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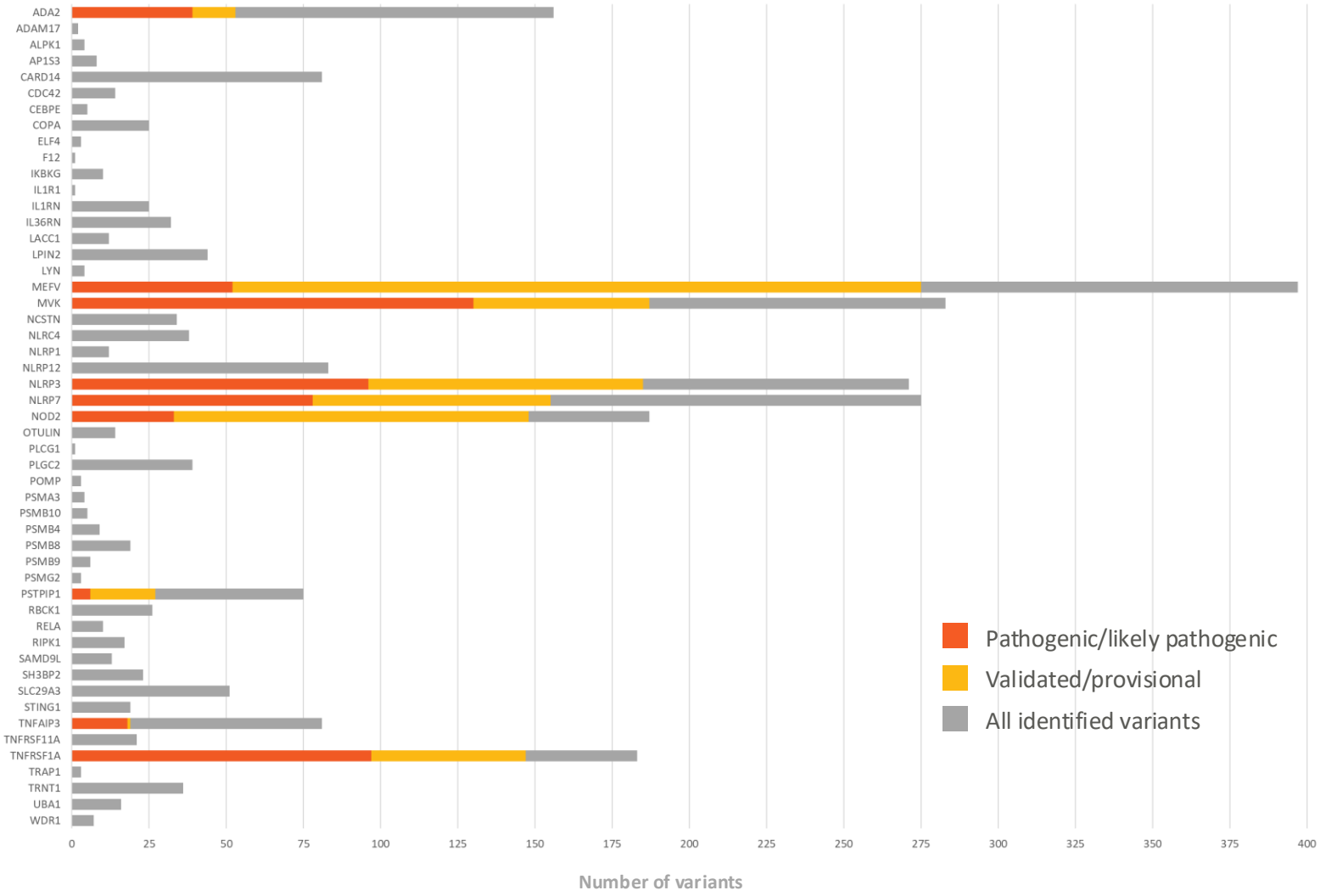
There are many autoinflammatory gene variants



There are multiple sequence variants of genes responsible for autoinflammatory diseases

These may be germline or somatic, and vary in penetrance, expressivity, and presentation

Infevers is an online registry of hereditary autoinflammatory disorder mutations.[1–5] This graph represents all identified genes and their variants as of 28 January 2024.

1. Infevers: an online database for autoinflammatory mutations©. Available at: https://infevers.umai-montpellier.fr/web/index.php. Accessed February 2024; 2. Van Gijn ME, et al. *J Med Genet* 2018;55:530–537; 3. Milhavet F, et al. *Hum Mutat* 2008;29:803–808; 4. Touitou I, et al. *Hum Mutat* 2004;24:194–198; 5. Sarrauste de Menthière C, et al. *Nucleic Acids Res* 2003;31:282–285.

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Infevers: *NLRP3* sequence variants[a]

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Exon 4

Y141=	C148Y	E150=	R168Q	R170S	I313V	P315L	R325W	R325Q	G326E	L467=	N477K	I480F	R488K	A495V
I172T	K173E	T193K	T193M	S196N	S331R	S332N	I334V	P340=	L344=	M521T	F523Y	F523C	F523L	F523L
V198M	D211N	H213R	T219=	A225V	T348M	T348=	V351L	V351M	A352T	E525K	E525V	L534=	T542M	R554*
G227=	T231=	L233=	A242=	C259W	A352V	L353P	E354D	K355T	K355N	T557A	Y563N	F566L	E567K	E567A
R260W	R260P	R260L	R260=	V262A	H358R	L369M	A374D	K375E	E378K	K568N	G569R	G569A	Y570N	Y570F
V262G	L264F	L264V	L264R	L264H	T405P	M406V	M406I	L411V	L411=	Y570C	L571F	L571F	I572F	F573S
L264P	T266P	D280N	I288M	M299V	L411=	W414L	I415=	T433I	S434=	T587I	S595G	I598F	E627G	E627D
D303H	D303N	D303A	D303G	E304K	K435E	T436P	T436A	T438del	T436N	L632F	D646Y	M659K	M662T	L677P
L305P	Q306E	Q306K	G307S	G307V	T436I	A439P	A439T	A439V	Y441H	S678=	E688K	M701T	Q703K	S710C
F309Y	F309S	D310=	E311K	H312P	Y441=	F443L	H458=	C461=	H463=	H711H	A712S			

Infevers

***NLRP3* - NM_001243133.2**

2024-01-28

Exon 8 S896P

Exon 9 T952M

3' UTR c.*177delC

5' UTR c.-40G>T

Exon 2 H49R A69= A75V

Exon 5 S726G G755R G755R G755A

Exon 6 G809S

Exon 7 Y859H Y859C V860= G866R

Intron 2 c.278-196T>C c.278-45T>C

Intron 3 c.397+7G>A c.398-229T>G c.398-56C>T c.398-15C>T

Intron 4 c.2150+59G>A

Intron 5 c.2321+85A>G c.2322-225T>C c.2322-224G>A c.2322-197T>G c.2322-194T>C c.2322-76C>T c.2322-40G>A

Intron 7 c.2492+82delG c.2493-133G>C c.2493-40G>A c.2663+71T>C c.2663+859A>C

Intron 9 c.3005+25C>T c.3005+44C>A c.3006-45_3006-44del

- Pathogenic/likely pathogenic variant
- Flanking region
- UTR
- Exonic region
- Intronic region

[a]Includes 185/271 identified variants with either validated or provisional status as of 28 January 2024.
UTR, untranslated region.
Infevers is an online registry of hereditary autoinflammatory disorder mutations.[1–5]

1. Infevers: an online database for autoinflammatory mutations©. Available at: https://infevers.umai-montpellier.fr/web/index.php. Accessed February 2024; 2. Van Gijn ME, et al. *J Med Genet* 2018;55:530–537; 3. Milhavet F, et al. *Hum Mutat* 2008;29:803–808; 4. Touitou I, et al. *Hum Mutat* 2004;24:194–198; 5. Sarrauste de Menthière C, et al. *Nucleic Acids Res* 2003;31:282–285.

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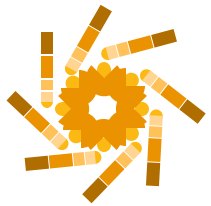
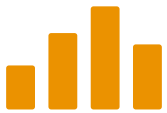
Summary

IL-1β is expressed primarily in myeloid cells as an inactive precursor, and requires protease cleavage to become active[1,2]



Caspase-1–dependent cleavage of pro-IL-1β is driven primarily by the activation of inflammasomes in response to a danger signal, such as the NLRP3 inflammasome[2]

Single mutations in genes associated with the inflammasome often cause persistent activation and lead to IL-1–driven autoinflammatory disorders[3]



Monogenic mutations in genes that lead to IL-1 activation through pathways other than direct inflammasome activation or with variable penetrance/expressivity result in a spectrum of disease presentation[4]

IL, interleukin; NLRP3, nucleotide-binding and leucine-rich repeat family pyric domain containing 3.

1. Blevins HM, et al. *Front Aging Neurosci* 2022;14:879021; 2. Jo E, et al. *Cell Mol Immunol* 2016;13:148–159; 3. Masters S, et al. *Ann Rev Immunol* 2009;27:621–668; 4. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463.

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Diagnosing autoinflammatory disease

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Diagnosis of autoinflammatory diseases[1–3]

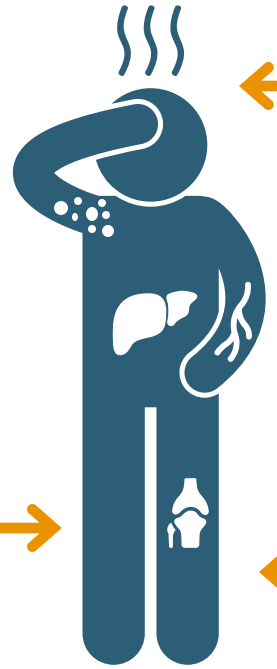
Clinical exam[3]

Recurrent/persistent inflammatory manifestations, including **fever in the absence of infection**, particularly in children or young adults

Common manifestations:

- Skin (rash)
- Musculoskeletal
- Hematopoietic
- Gastrointestinal
- Respiratory
- Nervous system

Suspected autoinflammatory disease



Genetic testing[2]

Next-generation sequencing:

- Whole exome/genome sequencing
- Targeted gene panel

Specific tests/biomarkers[3]

Examples include:

- Serum 100 protein
- Immunoglobulin D
- Serum amyloid A
- Urinary mevalonic acid

Routine laboratory parameters[3]

Elevation in:

- ESR
- CRP
- Ferritin
- WBCs (possible)[4]

Functional analysis[1,3]

Examples include:

- Inflammasome analyses
- Cytokine profile
- IFN gene signature assay
- ADA2 enzyme activity
- Proteasome assays

- **Autoinflammatory diseases present with complex pathobiological features;** the ultimate diagnosis will depend on the differential analysis of the outcomes of each assessment[1,2]
- **Direct measurement of IL-1 is not a reliable diagnostic biomarker** because circulating IL-1β levels are typically low, and IL-1α levels are below the level of detection even in patients with severe autoinflammatory disease[5–8]

ADA2, adenosine deaminase 2; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IFN, interferon; IL, interleukin; WBC, white blood cell.

1. Kul Cinar O, et al. *Front Pediatr* 2022;10:867679; 2. Nigrovic PA, et al. *J Allergy Clin Immunol* 2020;146:925–937; 3. Zen M, et al. *Clin Rev Allergy Immunol* 2013;45:227–235; 4. Bonnekoh H, Krause K. *Curr Treat Options Allergy* 2015;2:235–245; 5. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 6. Lachmann HJ, et al. *J Exp Med* 2009;206:1029–1036; 7. Mantovani A, et al. *Immunity* 2019;50:778–795; 8. Monastero RN, et al. *Int J Inflam* 2017;2017:4309485.

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Diagnosis: Clinical signs and symptoms

Autoinflammatory disease should be suspected in those who present with:[2,3]

- **Fever**, **rash**, or recurrent **unexplained inflammation** in the absence of infection
- **Early age** of onset
- A **family history** of autoinflammatory disease

One size does not fit all

Clinical signs of autoinflammatory disease[1–3]

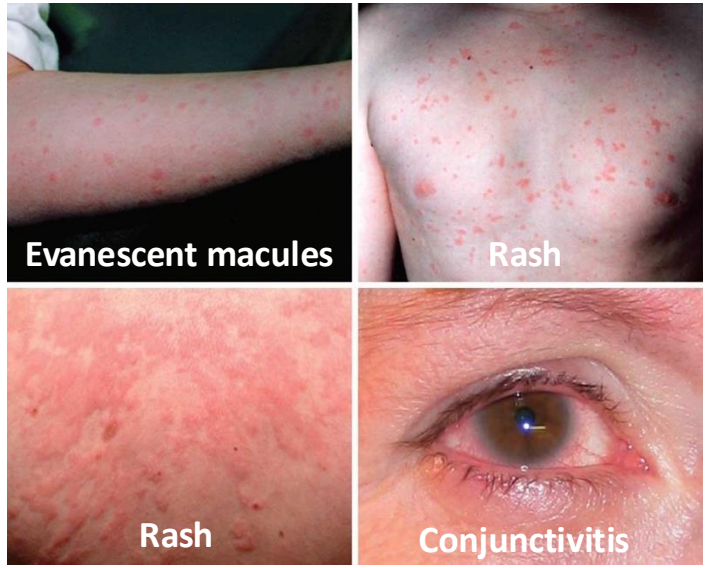
- Recurrent episodes of fever lasting a few hours to several weeks[2]
- Elevated inflammatory markers (e.g., CRP and ESR)[1,2]
- Skin rashes[2]
- Musculoskeletal, gastric, hematopoietic, ear, eye, and CNS symptoms[2]

Signs of multiorgan inflammation[2]:

- Myalgia/arthralgia
- Lymphadenopathy/splenomegaly
- Weight loss
- Fatigue
- Malaise
- Flu-like symptoms

Symptoms tend to recover with defervescence[2]

Typical symptoms of autoinflammatory disease[4]



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CNS, central nervous system; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

1. Nigrovic PA, et al. *J Allergy Clin Immunol* 2020;146:925–937; 2. Zen M, et al. *Clin Rev Allergy Immunol* 2013;45:227–235; 3. Gutierrez M, et al. *Rheum Dis Clin North Am* 2022;48:371–395;
4. Leslie KS, et al. *Arch Dermatol* 2006;142:1591–1597.

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Diagnosis: Laboratory testing

Laboratory tests for a clinical workup of a patient with suspected IL-1–mediated autoinflammatory disease include:[1]

CRP **ESR** **SAA** **Ferritin** **S100**

Acute phase reactants

IL-1–induced biomarkers of systemic inflammation that correlate with disease activity in most patients[2–4,10]

CBC
(with differential)

Blood cell counts

An increase in WBCs associated with inflammation may correlate with disease flares[5]

Establishing the extent of inflammatory organ involvement or damage requires laboratory tests for markers of renal/hepatic/neurological function where clinically indicated[1]

Direct measurement of IL-1 is not a reliable diagnostic biomarker because circulating IL-1β levels are typically low, and IL-1α levels are below the level of detection even in patients with severe autoinflammatory disease[6–9]

CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; S100, serum 100 protein; SAA, serum amyloid A; WBC, white blood cell.

1. Romano M, et al. *Ann Rheum Dis* 2022;81:907–921; 2. Gattorno M, et al. *Ann Rheum Dis* 2019;78:1025–1032; 3. Chuamanochan M, et al. *World Allergy Organ J* 2019;12:100019; 4. Kuemmerle-Deschner JB, et al. *Ann Rheum Dis* 2017;76:942–947; 5. Gutierrez MJ, et al. *Rheum Dis Clin North Am* 2022;48:371–395; 6. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 7. Lachmann HJ, et al. *J Exp Med* 2009;206:1029–36; 8. Mantovani A, et al. *Immunity* 2019;50:778–795; 9. Monastero RN, et al. *Int J Inflam* 2017;2017:4309485; 10. Nirmala N, et al. *Curr Opin Rheumatol* 2014;26:543–552.

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Diagnosis: Genetic testing

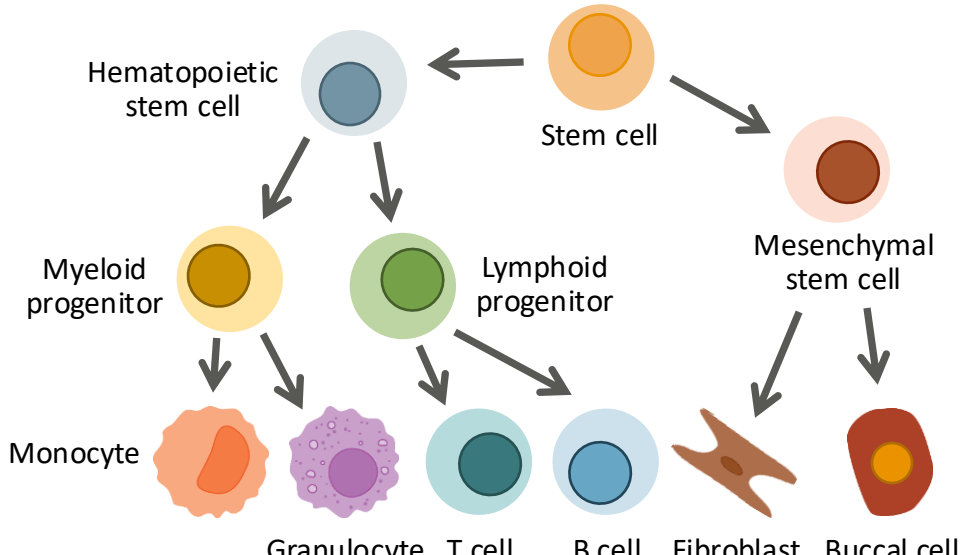
Genetic testing is a crucial component of an accurate diagnosis for **monogenic** autoinflammatory diseases[1,2]

- Monogenic autoinflammatory diseases can be familial or caused by *de novo* somatic mutations
- Somatic mutations may be difficult to detect by standard-coverage NGS and require deeper sequencing

~60% of patients with systemic autoinflammatory disease have no known pathogenic mutations[3–6]

Functional analyses (e.g., inflammasome analysis, cytokine assays, etc.)[7–9] to probe the pathogenicity of genetic VUS are becoming increasingly necessary in clinical practice[10]

Example: A myeloid-restricted somatic mutation manifesting as adult-onset CAPS



	Granulocyte	T cell	B cell	Fibroblast	Buccal cell
Subcloning	15.2%	0%	4.3%	0%	0.5%
Targeted sequencing	18.0%	0.9%	5.6%	0.1%	1.9%

Conventional sequencing was negative for *NLRP3* mutations; however, exome and deep sequencing revealed a mutation in monocytes (13.3–16.8%) and granulocytes (15.2–18.0%)[11]

Figure adapted from Zhou Q, et al. *Arthritis Rheumatol* 2015;67:2482–2486.
CAPS, cryopyrin-associated periodic syndrome; NGS, next-generation sequencing; VUS, variants of unknown significance.

1. Romano M, et al. *Ann Rheum Dis* 2022;81:907–921; 2. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 3. Harrison SR, et al. *JCI Insight* 2016;1:e86336;
4. Schnappauf O, et al. *Rheumatology (Oxford)* 2019;58(Suppl 6):vi44–vi55; 5. Papa R, et al. *Rheumatology (Oxford)* 2020;59:344–360; 6. Hoffman HM, Broderick L. *Arthritis Rheumatol* 2017;69:253–256;
7. Chirita D, et al. *Methods Mol Biol* 2022;2523:179–195; 8. Kuemmerle-Deschner JB, et al. *Rheumatology (Oxford)* 2020;59:3259–3263; 9. Tsuji S, et al. *Clin Exp Immunol* 2019;198:416–429;
10. Kul Cinar O, et al. *Front Pediatr* 2022;10:867679; 11. Zhou Q, et al. *Arthritis Rheumatol* 2015;67:2482–2486.

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The autoinflammatory disease patient journey can be lengthy and frustrating

Given the rarity of autoinflammatory diseases, median time to diagnosis is often delayed by:[1,2]

5 years for patients with **monogenic** autoinflammatory diseases

1 year for patients with **polygenic** autoinflammatory diseases

Diagnostic delays lead to insufficient treatment/disease progression, quality of life impairment, and higher morbidity/mortality for patients with autoinflammatory disease[1,3,4]

HCPs report that the key challenges in diagnosing autoinflammatory conditions include:[1]

- Atypical or no clinical symptoms at presentation
- Symptom overlap with other diseases or mosaicism
- Access to specialized testing

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HCP, healthcare professional.

1. Chuamanochan M, et al. *World Allergy Organ J* 2019;12:100019; 2. Ozen S, et al. *Arthritis Care Res (Hoboken)* 2017;69:578–586; 3. Obici L, et al. *Autoimmun Rev* 2012;12:14–17; 4. Romano M, et al. *Ann Rheum Dis* 2022;81:907–921.

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Summary

Patients with evidence of systemic inflammation who present without persistent infection or autoantibodies should raise suspicion of and be tested for IL-1–mediated autoinflammatory disorders[1,2]

Genetic testing may confirm an IL-1–driven autoinflammatory disorder diagnosis, but new disease phenotype–genotype correlations continue to be identified[3]

Rare monogenic and common polygenic diseases with neutrophilia and inflammation may respond to treatments targeting the IL-1 pathway, leading to diagnostic insights[3]

IL, interleukin.

1. Nigrovic PA, et al. *J Allergy Clin Immunol* 2020;146:925–937; 2. Zen M, et al. *Clin Rev Allergy Immunol* 2013;45:227–235; 3. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–4

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IL-1–mediated inflammatory diseases

IL, interleukin.

CAPS: Clinical presentation[1–3]

CAPS is a spectrum of rare **monogenic** autoinflammatory disorders characterized by **fever, urticarial rash, joint pain, conjunctivitis,** and **elevation of acute phase reactants**[1–3]

	FCAS	MWS	NOMID
Characteristic manifestations	Urticaria, chills, conjunctivitis, myalgia/arthralgia, fever[1]	Sensorineural hearing loss, urticarial rash, conjunctivitis, myalgia/arthralgia, fever, amyloidosis[1,2]	CNS inflammation (chronic aseptic meningitis, vision loss, hearing loss, cognitive impairment), knee arthropathy, urticarial rash, fever[1]
Age at onset	Usually ≤6 months[3]	Usually during childhood[3]	Perinatal[3]
Episode duration	Brief episodes (<24 hours) **triggered by cold exposure**[1,3]	Longer lasting episodes (2–3 days)[1,3]	Persistent chronic inflammation[1,3]

Increasing severity[3]

CAPS, cryopyrin-associated autoinflammatory syndrome; CNS, central nervous system; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome; NOMID, neonatal-onset multisystem autoinflammatory disease.

1. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 2. Yu JR, et al. *Curr Allergy Asthma Rep* 2011;11:12–20. 3. Welzel T, et al. *J Clin Med* 2021;10:128.

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CAPS: Pathophysiology[1,2]

Autosomal dominant, gain-of-function mutations in the ***NLRP3*** gene[1,2]

NLRP3 protein activity is augmented, leading to the **overproduction and release of IL-1β[2]**

Increased systemic inflammation and a spectrum of phenotypic manifestations[1,2]

The spectrum of known genetic variants for CAPS continues to grow—VUS are common, leading to atypical clinical symptoms and disease courses[3]

Estimated global prevalence: 2.7–5.5 in 1 million[*3]

Caucasians are more often affected; no gender differences have been observed[3]

The proportion of somatic mosaicism in CAPS-like patients has been estimated to be 0.5–19%[4]

Treatment with IL-1 inhibitors can control symptoms and prevent the development of further sequelae[5]

[*]True prevalence is likely to be higher than estimated due to lack of awareness and misdiagnosis.[6]

CAPS, cryopyrin-associated autoinflammatory syndrome; IL, interleukin; NLRP3, nucleotide-binding and leucine-rich repeat family pyric domain containing 3; VUS, variants of unknown significance.

1. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 2. Welzel T, et al. *Front Immunol* 2021;12:516427; 3. Welzel T, et al. *J Clin Med* 2021;10:128; 4. Labrousse M, et al. *Crit Rev Clin Lab Sci* 2018;55:432–442; 5. Yu JR, Leslie KS. *Curr Allergy Asthma Rep* 2011;11:12–20; 6. Williams R, et al. *Br J Nursing* 2019;28:1180–1186.

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DIRA: Clinical presentation[1–5]

DIRA is a rare, **monogenic** autoinflammatory syndrome characterized by persistent, **systemic inflammation** presenting in the **perinatal** period[1–5]

Characteristic symptoms[1,2,5]

- Fetal distress
- Pustular rashes (may be triggered by mechanical stress)
- Oral mucosal lesions
- Joint swelling and pain with movement

DIRA is often misdiagnosed as infectious osteomyelitis with pustulosis and systemic inflammation, leading to ineffective treatment with antibiotics[2,3]

Clinical findings

- Elevated acute phase reactants[2–5]
- Fever is usually absent[2,4]
- Skin biopsies may show[5]:
  - Neutrophilic infiltration of the dermis/epidermis
  - Pustule formation along hair follicles
  - Acanthosis and hyperkeratosis
- Radiography may show[3]:
  - Balloon-like widening of rib ends/clavicle
  - Periosteal elevation along long bones
  - Multifocal osteolytic lesions

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DIRA, deficiency of the interleukin-1 receptor antagonist.

1. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 2. Aksentijevich I, et al. *N Engl J Med* 2009;360:2426–2437; 3. Mendonca LO, et al. *J Clin Immunol* 2017;37:445–451; 4. Goldbach-Mansky R. *Clin Exp Immunol* 2012;167:391–404; 5. Li Y, et al. *Pediatr Rheumatol Online J* 2022;20:90.

DIRA: Pathophysiology[1–5]

Autosomal recessive, loss-of-function mutations in the ***IL1RN*** gene[1–5]

IL-1Ra is absent or non-functional, and unable to bind to IL-1R1 to act as an antagonist[3]

More **IL-1α** and **IL-1β** can bind and signal through IL-1R1, leading to **increased systemic inflammation**[5]

The mortality of untreated DIRA is estimated to be approximately 30% in early infancy[3]

Treatment with IL-1 inhibitors that inhibit **both** IL-1α and IL-1β can control disease activity and prevent long-term complications[6]

Estimated global prevalence: only 20 patients have been reported[5]

Founder mutations have been identified in patients from Puerto Rico, the Netherlands, Newfoundland, Palestine/Lebanon, and Brazil[4]

DIRA, deficiency of interleukin-1 receptor antagonist; IL, interleukin; IL-1R, interleukin receptor; IL-1Ra, interleukin-1 receptor antagonist.

1. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 2. Aksentijevich I, et al. *N Engl J Med* 2009;360:2426–2437; 3. Mendonca LO, et al. *J Clin Immunol* 2017;37:445–451; 4. Goldbach-Mansky R. *Clin Exp Immunol* 2012;167:391–404; 5. Li Y, et al. *Pediatr Rheumatol Online J* 2022;20:90; 6. Romano M, et al. *Ann Rheum Dis* 2022;81:907–921.

Monogenic autoinflammatory diseases driven by IL-1[1,2]

Disease	Main clinical features	
Familial cold autoinflammatory syndrome (FCAS)	Cold urticaria, chills, conjunctivitis, myalgia/arthralgia, fever	*NLRP3*
Muckle–Wells syndrome (MWS)	Sensorineural hearing loss, urticarial rash, conjunctivitis, myalgia/arthralgia, fever	*NLRP3*
Neonatal-onset multisystem inflammatory disease (NOMID)	CNS inflammation (chronic aseptic meningitis, vision loss, hearing loss), knee arthropathy, urticarial rash, fever	*NLRP3*
Familial Mediterranean fever (FMF)	Serosal pain (abdominal, chest), arthralgia, erysipeloid rash, fever	*MEFV*
Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)	Sterile skin abscesses, myalgia, myositis, rash, fever	*MEFV*
Hyper IgD syndrome (HIDS)	Triggered by vaccination, abdominal pain, vomiting, rash, myalgia/arthralgia, aphthous ulcers, fever	*MVK*
Mevalonic aciduria (MA)	Developmental delay, failure to thrive, dysmorphic features, recurrent fever	*MVK*
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)	Painful centrifugal rash, periorbital edema, prolonged fever, abdominal pain, headache, conjunctivitis, myalgia/arthralgia	*TNFRSF1A*
Deficiency of IL-1 receptor antagonist (DIRA)	Pustular rash, sterile osteomyelitis, periostitis, hepatosplenomegaly, fever	*IL1RN*
Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome	Pyoderma gangrenosum, arthritis, acne	*PSTPIP1*
Hyperzincemia/hypercalprotectinemia (Hz/Hc)	Rash, failure to thrive, hepatosplenomegaly, neutropenia	*PSTPIP1*
Neonatal-onset cytopenia with dyshematopoiesis, autoinflammation, rash, and HLH (NOCARH)	Pancytopenia, neurodevelopmental defects, facial dysmorphism, recurrent infection, rash, macrophage activation syndrome/HLH, fever	*CDC42*
Majeed syndrome	Osteomyelitis, dyserythropoietic anemia, rash, fever	*LPIN2*

CNS, central nervous system; HLH, hemophagocytic lymphohistiocytosis; IgD, immunoglobulin D; IL, interleukin.

1. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 2. Szekanecz Z, et al. *Nat Rev Rheumatol* 2021;17:585–595.

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Non-monogenic autoinflammatory diseases with a proposed pathogenic role for IL-1[1,2]

Disease	Main clinical features	Cytokine implicated
Systemic juvenile idiopathic arthritis (sJIA)/ adult-onset Still's disease (AOSD)	Fever, rash, arthritis/arthralgia	IL-1, IL-6, TNF, IL-18, IFNγ
Kawasaki disease	Fever, conjunctivitis, mucositis, rash, cervical lymphadenopathy, coronary artery dilatation	TNF, IL-1
Schnitzler syndrome	Chronic urticaria associated with monoclonal gammopathy, recurrent fever, bone pain, arthralgia	IL-1, TNF
Gout	Recurrent flares of inflammatory arthritis, chronic arthropathy, tophaceous deposits, uric acid nephrolithiasis	IL-1
Recurrent pericarditis	Pleuritic chest pain, pericardial rub, ECG changes, pericardial effusion	IL-1
Chronic recurrent multifocal osteomyelitis (CMRO)	Recurrent fever, arthritis, multifocal bone inflammation	IL-1, TNF
Hidradenitis suppurativa (HS)	Inflammatory nodules, sinus tracts and open comedones in intertriginous areas	TNF, IL-1
PASH, PASS, PAPASH	HS lesions, pyoderma gangrenosum, and acne (PASH) + ankylosing spondylitis (PASS), or + pyogenic sterile arthritis (PAPASH)	IL-1, IL-18 (PASH; PASS) IL-1, TNF, IL-17A, IL-18 (PAPASH)
Acute hemorrhagic leukoencephalitis (AHLE)	Fever, neurological dysfunction, seizures, CSF pleocytosis	IL-1
Periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA)	Recurrent fever with regular periodicity, aphthous stomatitis, exudative pharyngitis, cervical adenitis	IL-1
Behçet's disease	Oral and genital ulcers, uveitis	IL-1, TNF

CSF, cerebrospinal fluid; ECG, electrocardiogram; IL, interleukin; PASH, pyoderma gangrenosum, acne, suppurative hidradenitis; PASS, pyoderma gangrenosum, acne, suppurative hidradenitis, and ankylosing spondylitis; PAPASH, pyogenic arthritis, acne, pyoderma gangrenosum, and suppurative hidradenitis; TNF, tumor necrosis factor.

1. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 2. Szekanecz Z, et al. *Nat Rev Rheumatol* 2021;17:585–595.

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Summary

CAPS is a spectrum of rare monogenic autoinflammatory disorders caused by gain-of-function mutations in *NLRP3*[1]

DIRA is a rare, monogenic autoinflammatory syndrome caused by loss-of-function mutations in *IL1RN*[2]

Mutations in genes involved in the IL-1 signaling pathway can cause severe disease[1]

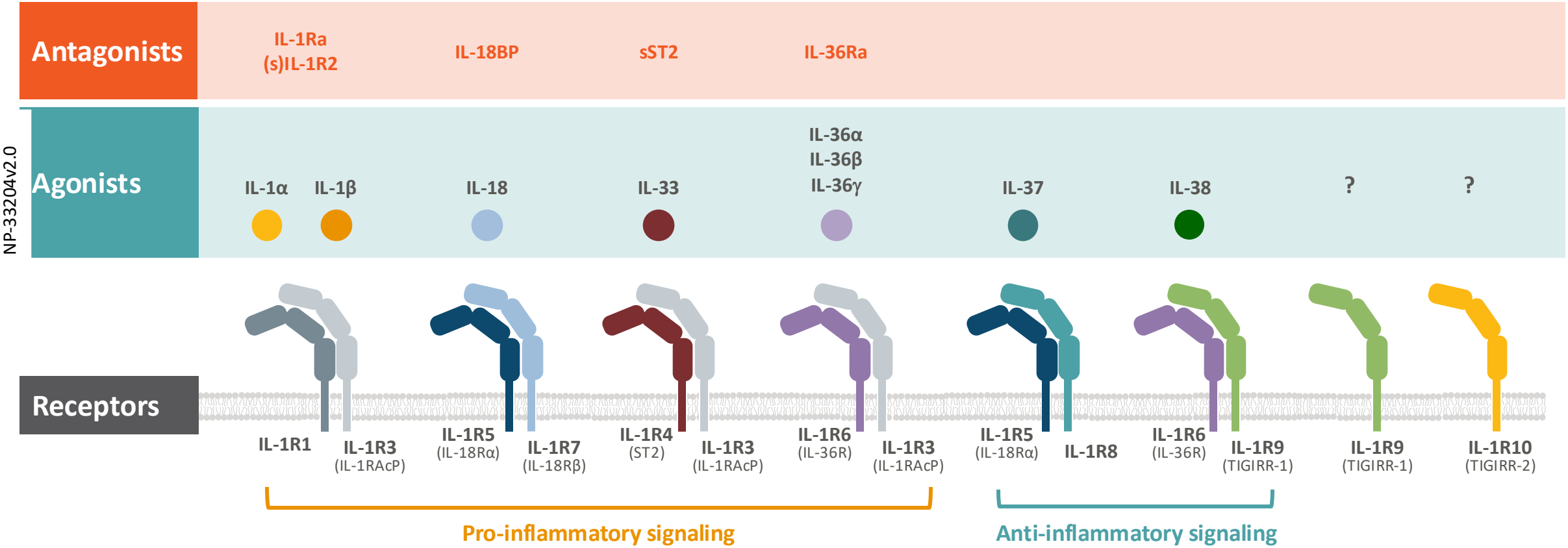
CAPS, cryopyrin-associated autoinflammatory syndrome; COVID-19, coronavirus disease 2019; DIRA, deficiency of interleukin-1 receptor antagonist; IL, interleukin.

1. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 2. Potere N, et al. *EBioMedicine* 2022;85:104299; 2. Mendonca LO, et al. *J Clin Immunol* 2017;37:445–451.

Appendix

The IL-1 superfamily modulates innate immune responses and inflammation[1–3]

IL-1 is not a single molecule, but rather a superfamily of structurally and functionally related cytokines[4]



NP-33204v2.0

Figure adapted from Dinarello CA. *Nat Rev Rheumatol* 2019;15:612–632.
IL, interleukin; IL-1R, intrleukin-1 receptor; (s), soluble.

1. Dinarello CA. *Nat Rev Rheumatol* 2019;15:612–632; 2. Hernandez-Santana YE, et al. *Eur J Immunol* 2019;49:1306–1320; 3. Mantovani A, et al. *Immunity* 2019;50:778–795; 4. Boraschi D. *Front Immunol* 2022;13:8721

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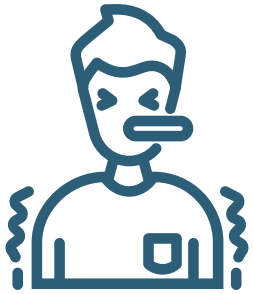
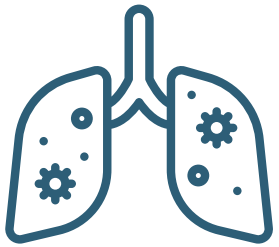
Severe COVID-19: IL-1–mediated pathophysiology[1–6]



Excessive activation of inflammatory pathways in a subset of patients with COVID-19 may lead to severe disease[1,2]

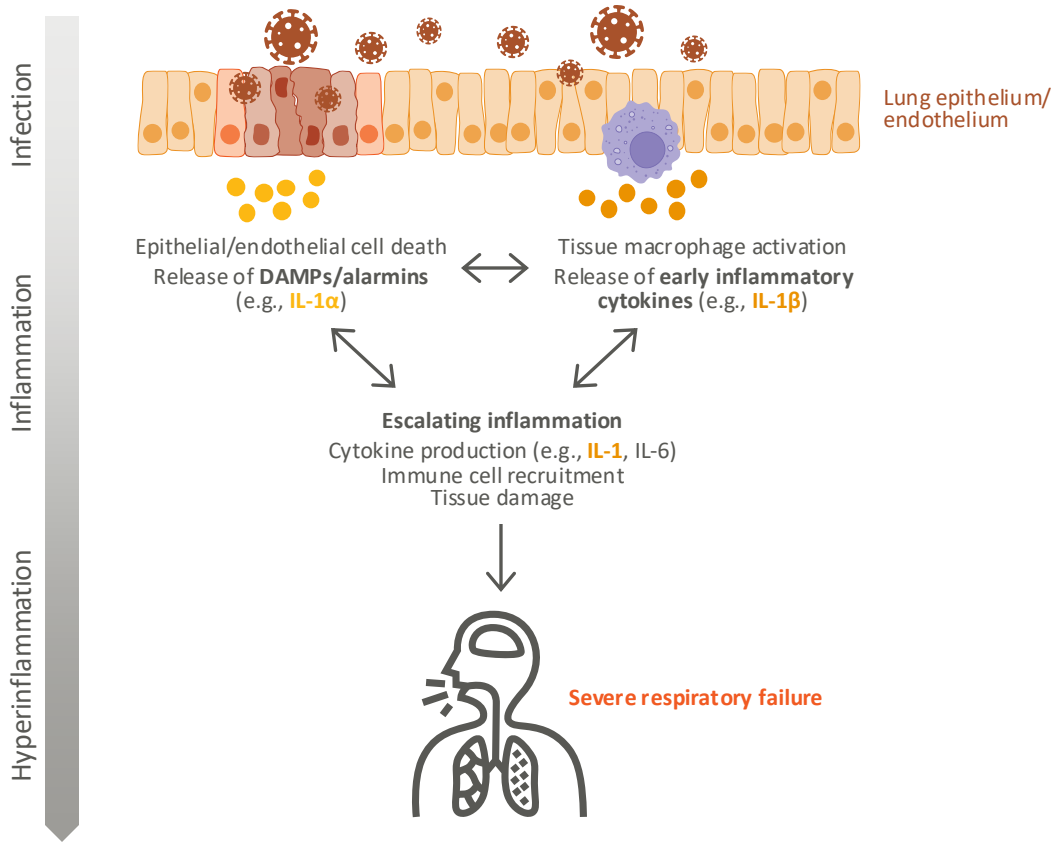
- The SARS-CoV-2 viral protein ORF3a has been shown to directly activate the NLRP3 inflammasome[7]



Characterized by[1,2]:

- Hyperinflammation
- Elevated levels of multiple cytokines
- Severe respiratory failure

Proposed role of IL-1 in the development of severe respiratory failure in patients with COVID-19[3-6]



COVID-19, coronavirus disease 2019; DAMP, damage-associated molecular pattern; EU, European Union; IL, interleukin; NLRP3, nucleotide-binding and leucine-rich repeat family pyric domain containing 3; SARS-CoV-2, severe acute respiratory syndrome-related coronavirus 2.

1. Bhaskar S, et al. *Front Immunol* 2020;11:1648; 2. Henderson LA, et al. *Arthritis Rheumatol* 2020;72:1791–1805; 3. van de Veerdonk FL, Netea MG. *Crit Care* 2020;24:445; 4. Calabrese LH, Calabrese C. *Cleve Clin J Med* 2020;doi: 10.3949/ccjm.87a.ccc044; 5. Kyriazopoulou E, et al. *Elife* 2021;10:e66125; 6. Kyriazopoulou E, et al. *Nat Med* 2021;27:1752–1760; 7. Bertoni A, et al. *J Allergy Clin Immunol* 2022;150:796–805.

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Thank you

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