The Role of IL-1 in Autoinflammation

rare strength

NP-37093v3 07/25

IL-1 is a potent proinflammatory cytokine[1-3]

IL-1 was first reported in 1974 as an endogenous “pyrogen” (ie, it induces fever)

IL-1 is a powerful driver of inflammation

- IL-1 induces the **expression of other inflammatory mediators and cytokines** and promotes the **recruitment and activation of leukocytes** at sites of tissue damage, cellular stress, and/or infection
- IL-1 plays an important role in **protective immune responses**
- If not adequately regulated, IL-1 production and the resulting inflammation may lead to **tissue damage** and contribute to the pathogenesis of various **inflammatory diseases**

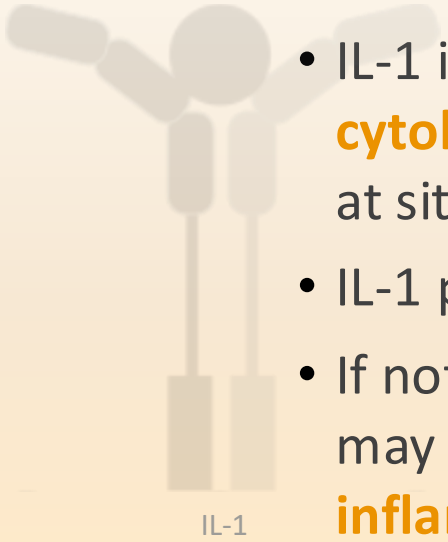
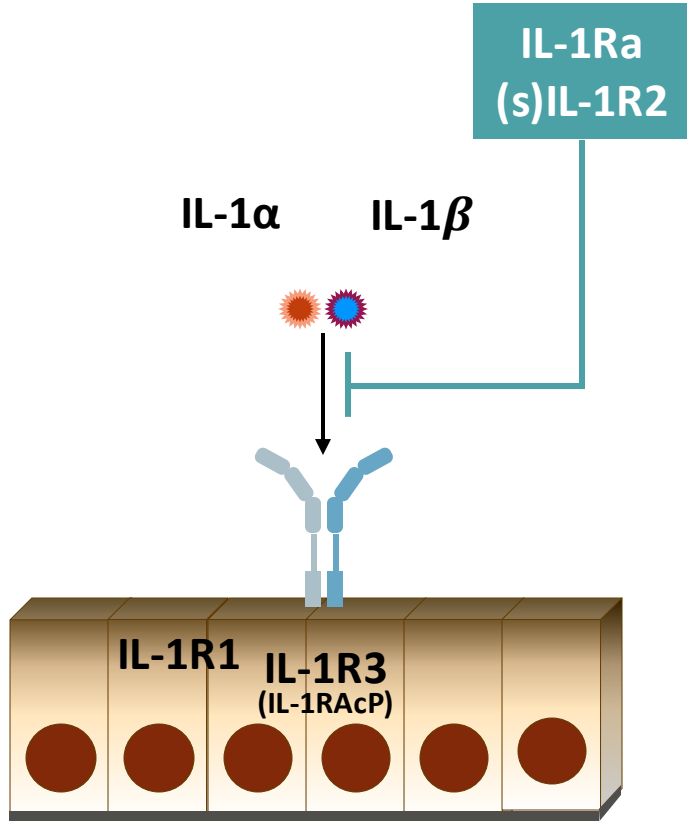


Figure adapted from Dinarello CA. *Nat Rev Rheumatol.* 2019;15:612–632.
IL-1R1, IL-1 receptor type 1; IL-1RAcP, IL-1 receptor accessory protein.
1. Dinarello CA. *Nat Rev Rheumatol.* 2019. 2. Schett G, et al. *Nat Rev Rheumatol.* 2016. 3. Broderick L and Hoffman HM. *Nat Rev Rheumatol.* 2022.

There are 2 distinct IL-1 proteins: IL-1α and IL-1β[1-3]

IL-1α and IL-1β bind to the same receptor, IL-1R1, which is present on most human cell types

- Due to the widespread expression of IL-1R1 and its co-receptor, IL-1RAcP, **IL-1 affects many cells and tissues** in the body



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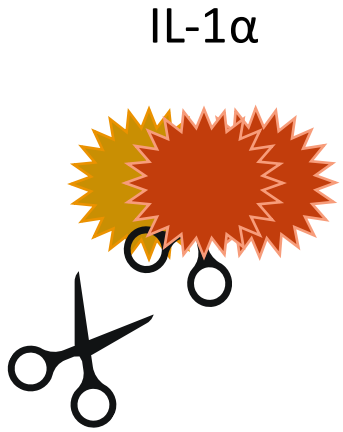
IL-1α protein

The IL-1α precursor, pro-IL-1α, is expressed on the cell surface or released from necrotic cells in response to stress, tissue damage, or infection[2,3]

IL-1α is constitutively expressed at low levels in numerous cell types, particularly epithelial cells, vascular endothelial cells, keratinocytes, and platelets[1,2]

- IL-1α expression is increased in response to stress and inflammatory signals, eg, PAMPs/DAMPs, IL-1 itself, or other cytokines[3,4]



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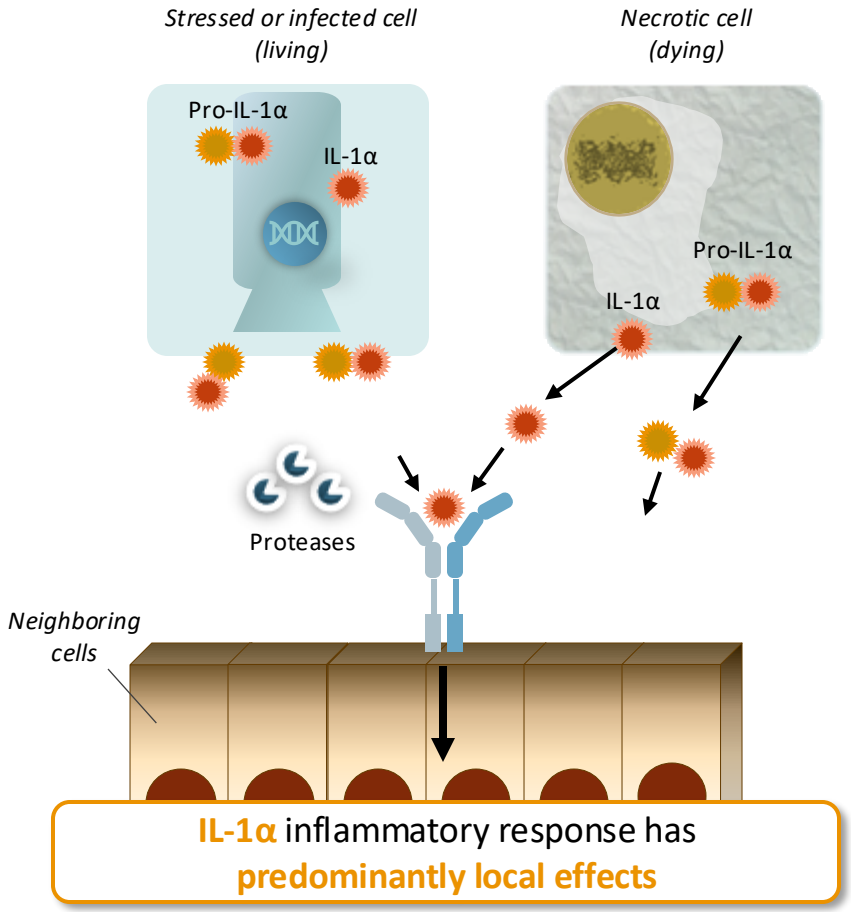
IL-1α activation

Both IL-1α and its precursor, pro-IL-1α, are functionally active[2,3,5]

- Pro-IL-1α can be cleaved into mature IL-1α by various proteases both inside and outside the cell

IL-1α activity[3,6]



IL-1α inflammatory response has predominantly local effects

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There are 2 distinct IL-1 proteins: IL-1α and IL-1β[1-3]

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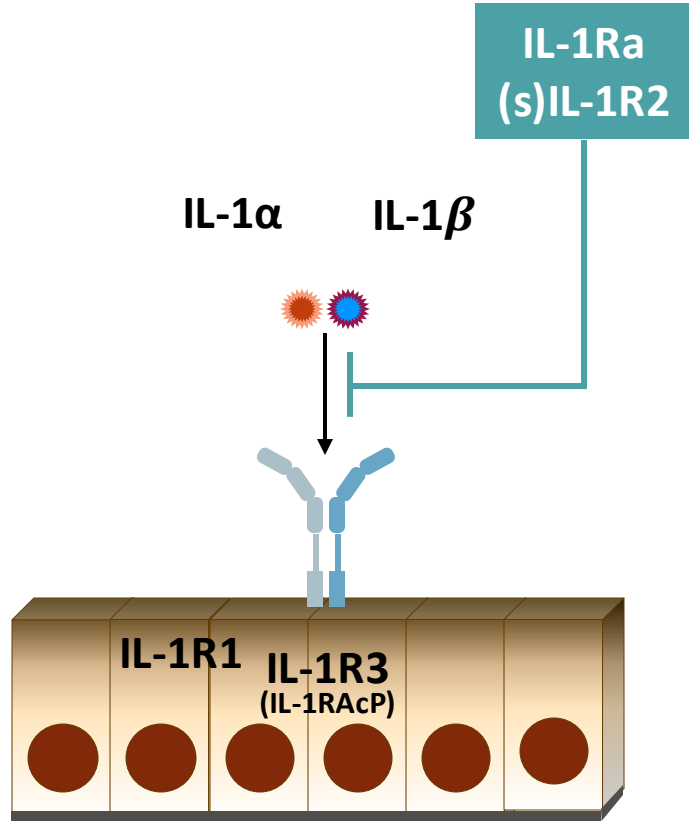
- Due to the widespread expression of IL-1R1 and its co-receptor, IL-1RAcP, **IL-1 affects many cells and tissues** in the body



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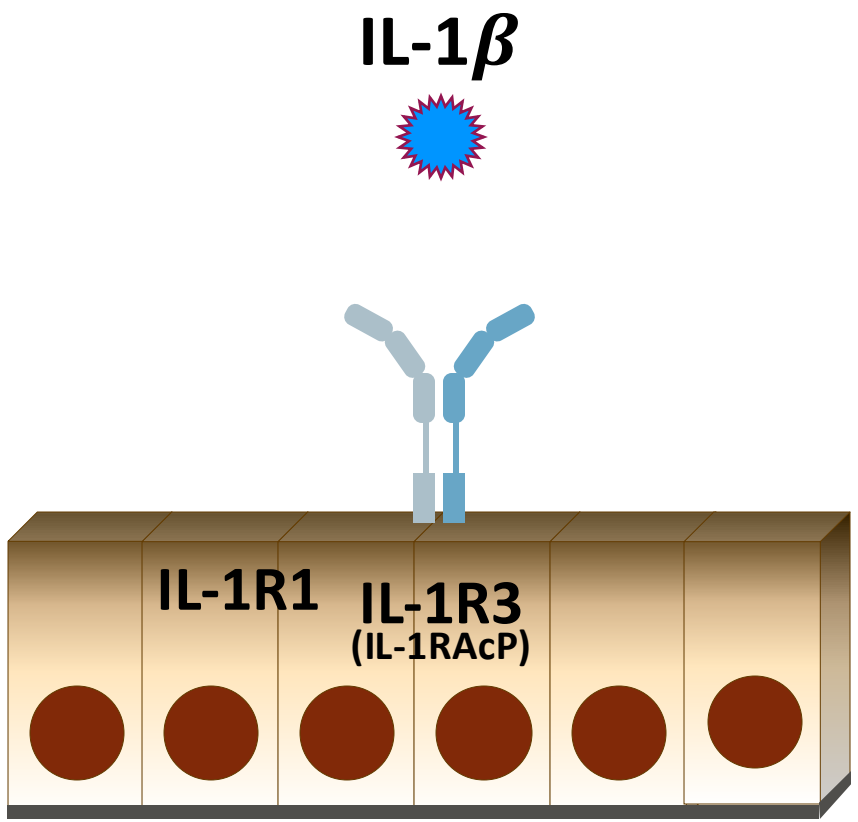
IL-1β protein

IL-1β is mainly produced by activated myeloid cells (eg, monocytes, macrophages, dendritic cells, neutrophils, and microglia)[1-3]



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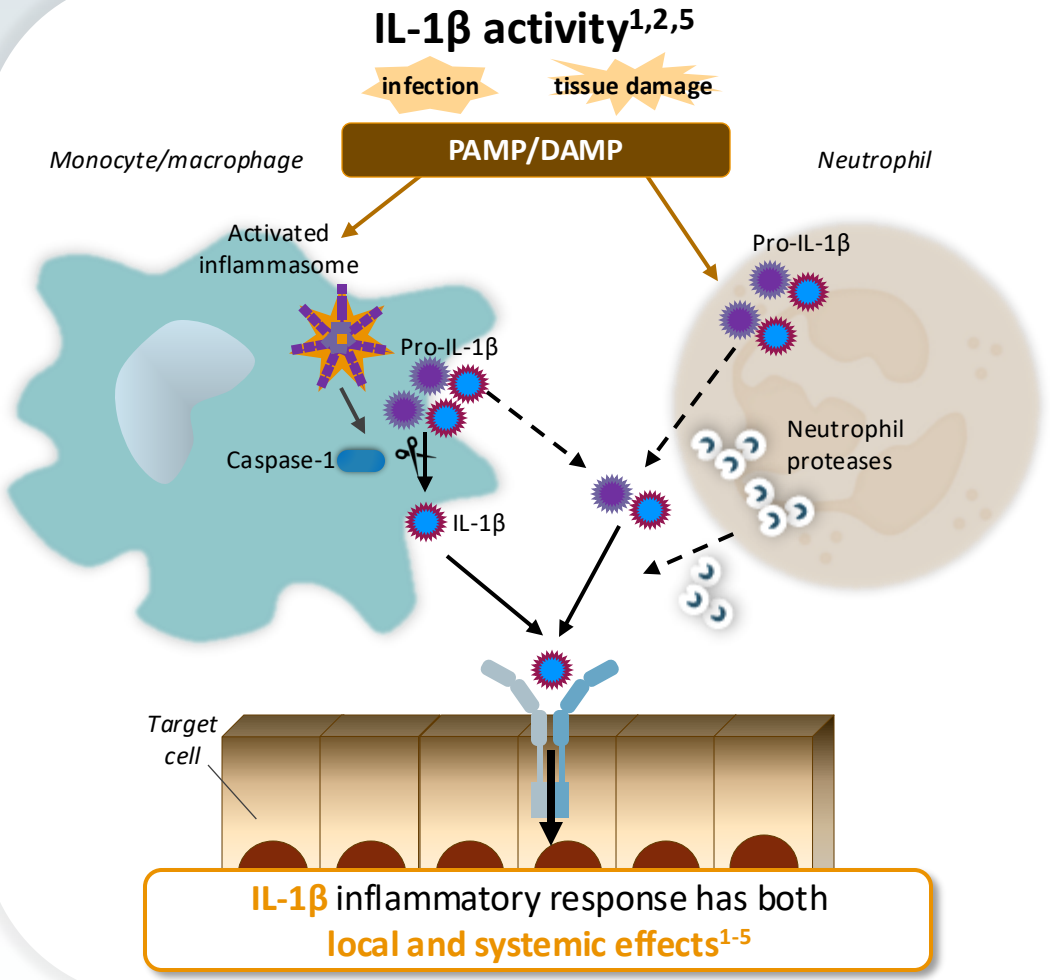
IL-1β activation

IL-1β is not constitutively expressed but is induced in response to infection or tissue injury[2,4]

Unlike IL-1α, IL-1β is not active in its precursor form (pro-IL-1β)[1-3]

- Cleavage of pro-IL-1β into active IL-1β by caspase-1 requires activation of the **inflammasome**, a multiprotein complex that forms in the cytosol in response to various stimuli during the innate immune response



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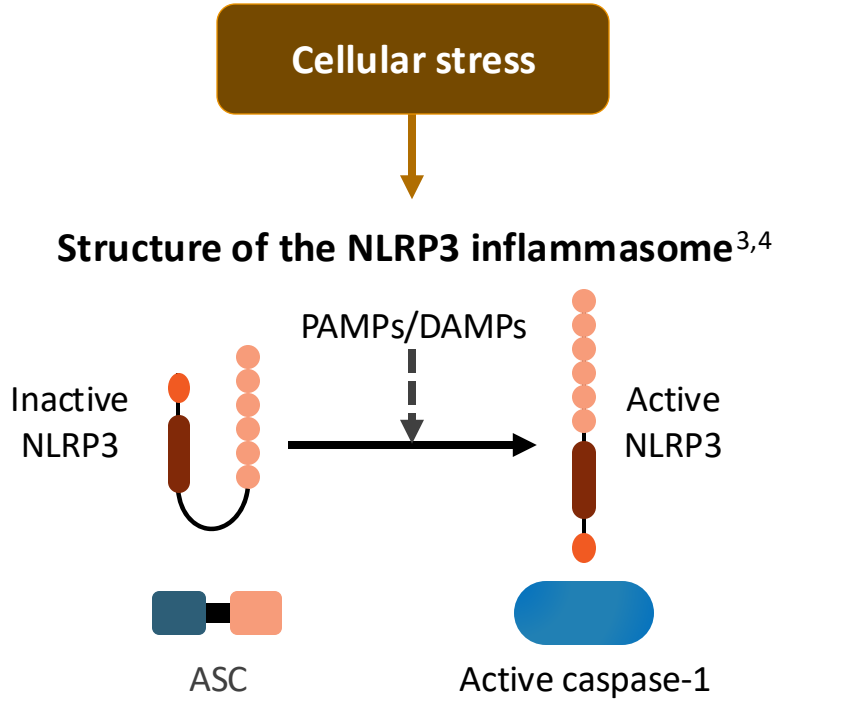
Role of inflammasomes in IL-1β production

The main roles of inflammasomes are the production of active IL-1β and IL-18 and the induction of cell death by pyroptosis in response to pathogens, danger signals, or cellular stress[1,2]

The basic structure of an inflammasome consists of a

- **sensor molecule** (eg, NLRP3)
- **adaptor protein** (most commonly ASC)
- **effector protease** (commonly caspase-1)[1,3]

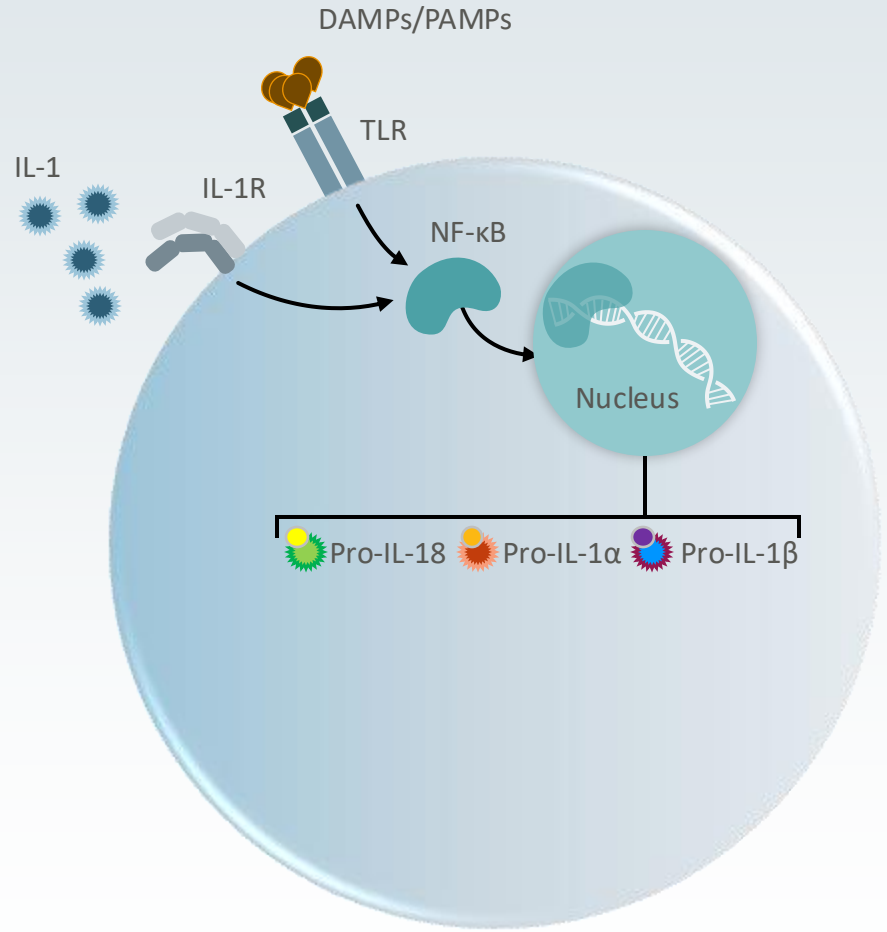


The inflammasome and its role in the production of active IL-1β were discovered in the early 2000s[5]

ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase recruitment domain; DAMP, damage-associated molecular pattern; LRR, leucine-rich repeat; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NOD, nucleotide-binding oligomerization domain; PAMP, pathogen-associated molecular pattern.

1. Broderick L. Inflammasomes and autoinflammation. In: *Textbook of Autoinflammation*. Springer; 2019. 2. Guo H, et al. *Nat Med.* 2015. 3. Putnam CD, et al. *Immunol Rev.* 2024. 4. Mangan MSJ, et al. *Nat Rev Drug Discov.* 2018. 5. Martinon F, et al. *Mol Cell.* 2002.

A deeper dive into NLRP3 inflammasome[1,2]



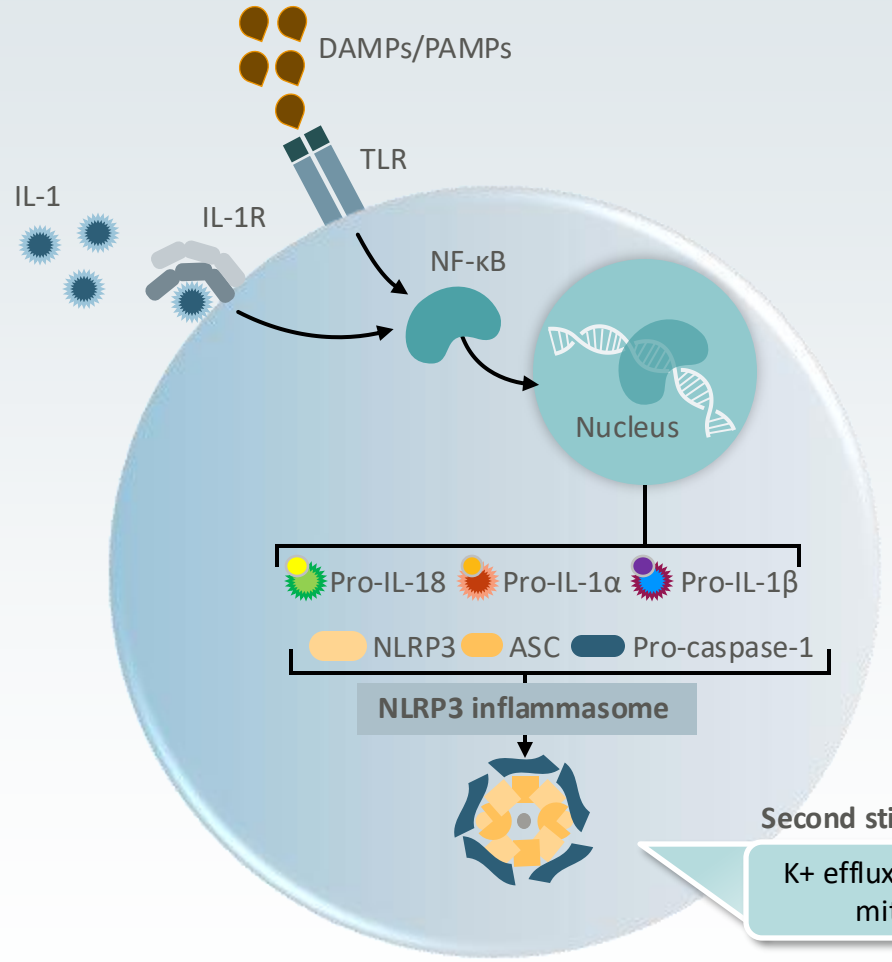
Signal 1: Priming

- DAMPs/PAMPs or proinflammatory 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 proinflammatory 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.

A deeper dive into NLRP3 inflammasome[1,2]

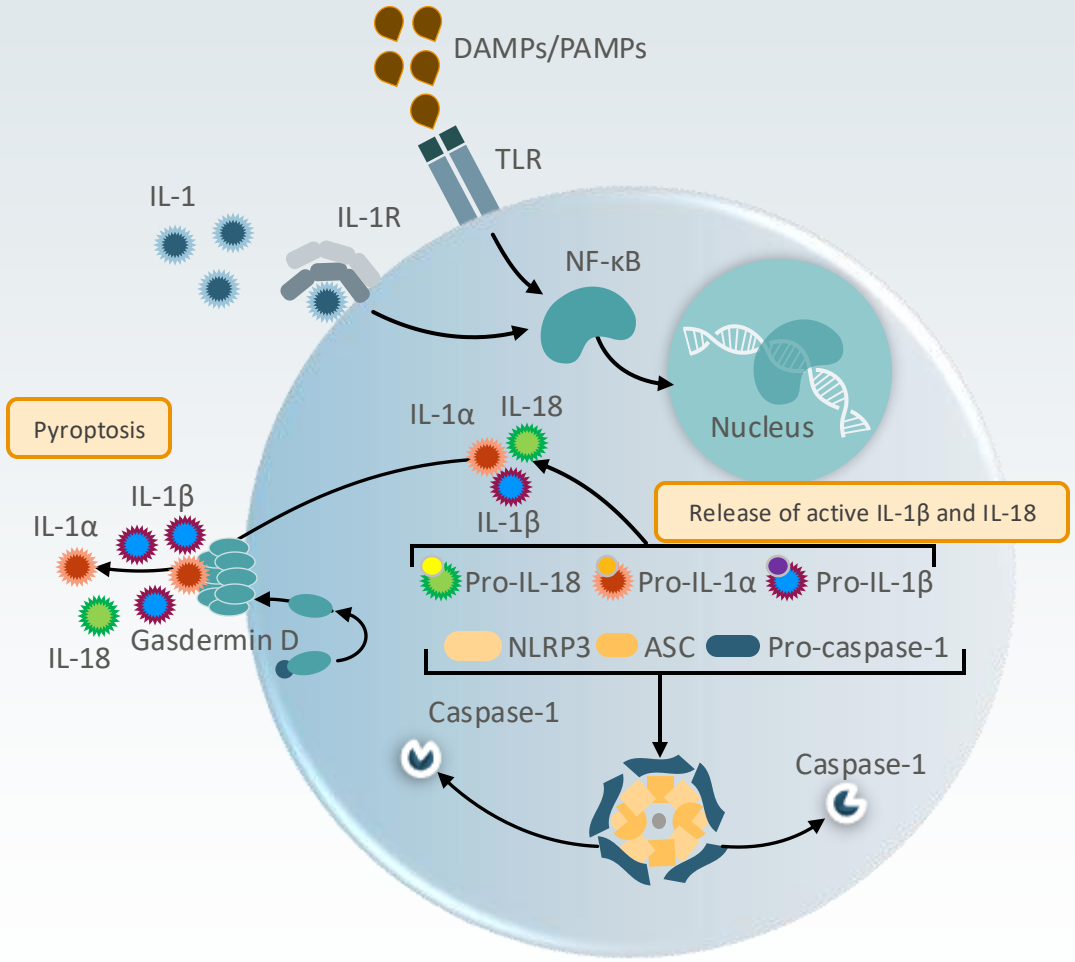


Signal 2: Activation[1]

- The pattern recognition receptor NLRP3 senses a second stimulus, which triggers formation of the inflammasome complex
- 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.

A deeper dive into NLRP3 inflammasome[1,2]



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;
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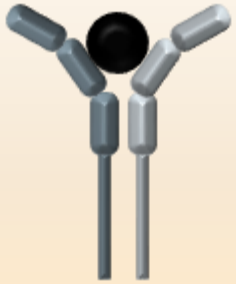
IL-1–driven inflammation[1]



IL-1 is a potent proinflammatory cytokine produced early in the innate inflammatory response

As the IL-1 receptor is expressed on many different cell types, the effects of IL-1 are wide and varied, and IL-1 is involved in many aspects of inflammation

As a result, IL-1 is important in the fight against infections but also contributes to various inflammatory diseases

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1. Rösen-Wolff A & Rubartelli A. Cytokines in autoinflammation. In: *Textbook of Autoinflammation*. Springer; 2019.

Pathophysiological effects of increasing IL-1

CNS

Fever, fatigue, loss of appetite, pain, production of cortisol[1–6]

Induction of PGE_2

Activation of the HPA axis

Liver

Elevated acute-phase reactants, eg, CRP, SAA[1,2,9]

Induction of IL-6

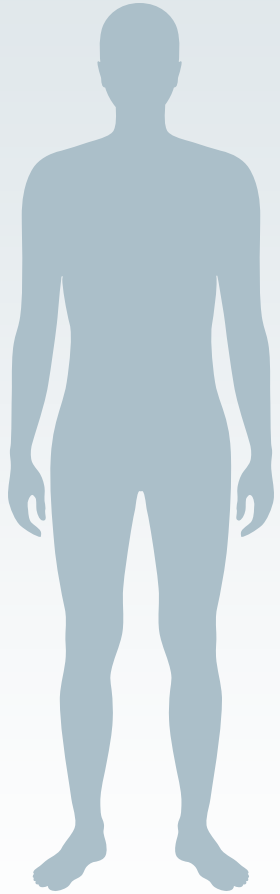
Production of acute-phase reactants

Immunological

Inflammation, tissue damage[1,2,10,13]

Immune cell recruitment and activation

Production of inflammatory mediators



Endothelium

Skin rash, vasodilation, hypotension[1,7–8]

Endothelial permeability

Vascular smooth muscle modulation

Bone marrow

Hematological abnormalities, hypercoagulation[1,10–12]

Neutrophilia, thrombocytosis, anemia

Musculoskeletal

Cartilage degradation/ bone erosion,[13–15] muscle pain[16]

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

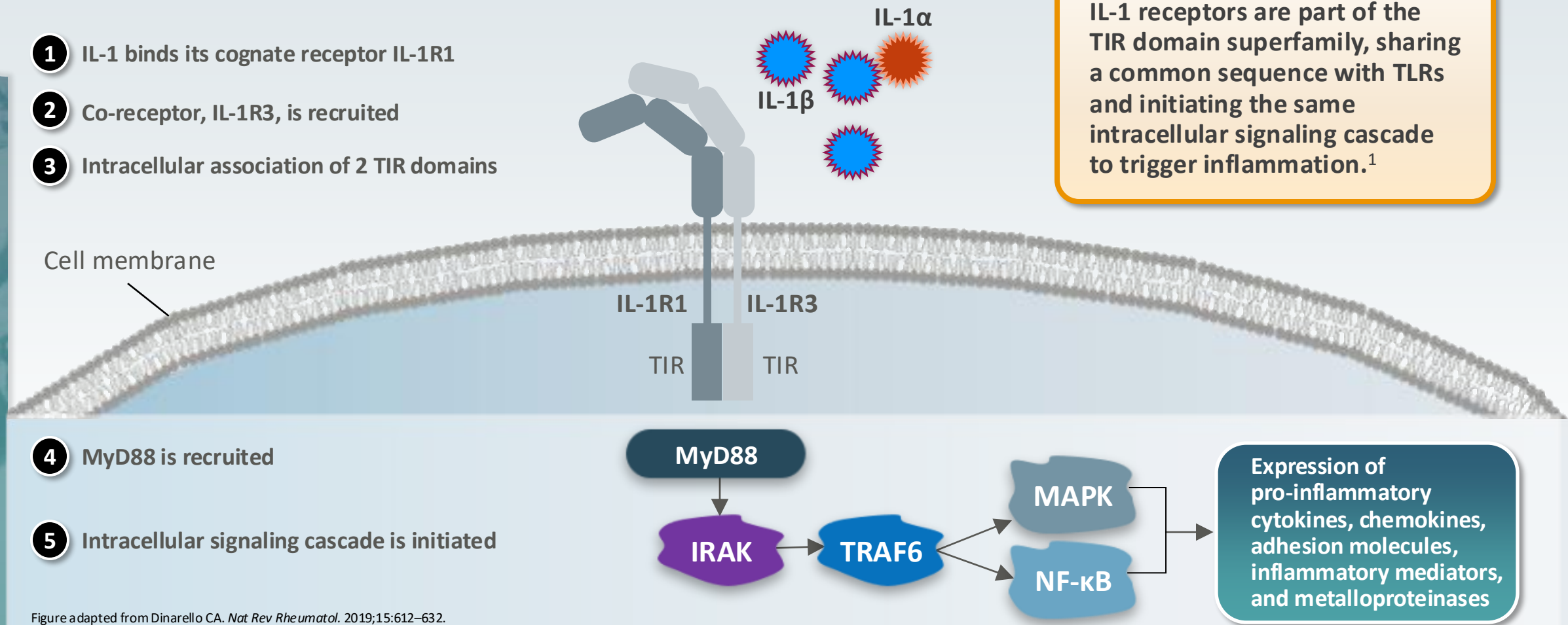
CNS, central nervous system; CRP, C-reactive protein; HPA, hypothalamic–pituitary–adrenal; IL, interleukin; PGE_2, prostaglandin E2; SAA, serum amyloid A.

1. Rösen-Wolff A, et al. Cytokines in autoinflammation In: Hashkes PJ, et al (Eds). *Textbook of Autoinflammation*. Switzerland. Springer; 2019:111–122. 2. Garlanda C, et al. *Immunity*. 2013;39:1003–1018. 3. Roerink ME, et al. *J Neuroinflammation*. 2017;14:16. 4. Burfeind KG, et al. *Semin Cell Dev Biol*. 2016;54:42–52. 5. Dinarello CA. *Eur J Immunol*. 2011;41:1203–1217. 6. Ren K, et al. *Brain Res Rev*. 2009;60:57–64. 7. 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. 8. Fahey E, Doyle SL. *Front Immunol*. 2019;10:1426. 9. Sack GH. *Mol Med*. 2018;24:46; 10. Mantovani A, et al. *Immunity*. 2019;50:778–795. 11. Nishmura S, et al. *J Cell Biol*. 2015;209:453–466. 12. Vora SM, et al. *Nat Rev Immunol*. 2021;21:694–703. 13. Schett G, et al. *Nat Rev Rheumatol*. 2016;12:14–24. 14. Gabay C, et al. *Nat Rev Rheumatol*. 2010;6:232–241. 15. Schiff MH. *Ann Rheum Dis*. 2000;59(Suppl 1):i103–i108. 16. Li W, et al. *Am J Physiol Cell Physiol*. 2009;297:C706–C714.

IL-1 and its role in autoinflammatory disease

Proinflammatory signaling requires 5 steps[1–4]:

1. IL-1 binds its cognate receptor IL-1R1
2. Co-receptor, IL-1R3, is recruited
3. Intracellular association of 2 TIR domains
4. MyD88 is recruited
5. Intracellular signaling cascade is initiated



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]

Expression of pro-inflammatory cytokines, chemokines, adhesion molecules, inflammatory mediators, and metalloproteinases

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.

Pathogenic consequences of IL-1–driven inflammation

The role of IL-1 as a master cytokine in inflammation is evidenced by the pathogenic consequences of

genetic mutations that lead to **uncontrolled IL-1 production** or signaling[1]

DIRA (deficiency of IL-1 receptor antagonist)

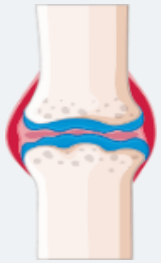
Infants born with loss-of-function mutations in *IL1RN* **lack endogenous IL-1Ra** and develop life-threatening, overwhelming **sterile inflammation of the skin, joints, and bones**[1,2]

NOMID (neonatal-onset multisystem inflammatory disease)

Gain-of-function mutations in *NLRP3* lead to a **hyperactive inflammasome**, **overproduction of IL-1β**, and **systemic inflammation** (eg, fever, rash, uveitis, arthritis, hearing loss, and aseptic meningitis) in children with NOMID[1,3,4]

excessive or prolonged IL-1 signaling that contribute to the pathogenesis and clinical manifestations of various other inflammatory and autoimmune diseases[1,5,6]

Rheumatoid arthritis



IL-1 and other cytokines such as TNFα, IL-6, and IL-17 promote joint inflammation and damage[5]

IL-1Ra, IL-1 receptor antagonist; *IL1RN*, IL-1 receptor antagonist gene; LRR, leucine-rich repeat; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NOD, nucleotide-binding oligomerization domain.

1. Dinarello CA, et al. *Nat Rev Drug Discov.* 2012. 2. Aksentijevich et al. *N Engl J Med.* 2009. 3. Hoffman HM et al. Cryopyrin-associated periodic syndromes (CAPS). In: *Textbook of Autoinflammation*. Springer; 2019.
4. Goldbach-Mansky et al. *N Engl J Med.* 2006. 5. Smolen et al. *Nat Rev Dis Primers.* 2018. 6. Nigrovic. *Arthritis Rheumatol.* 2014.

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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

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.

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]

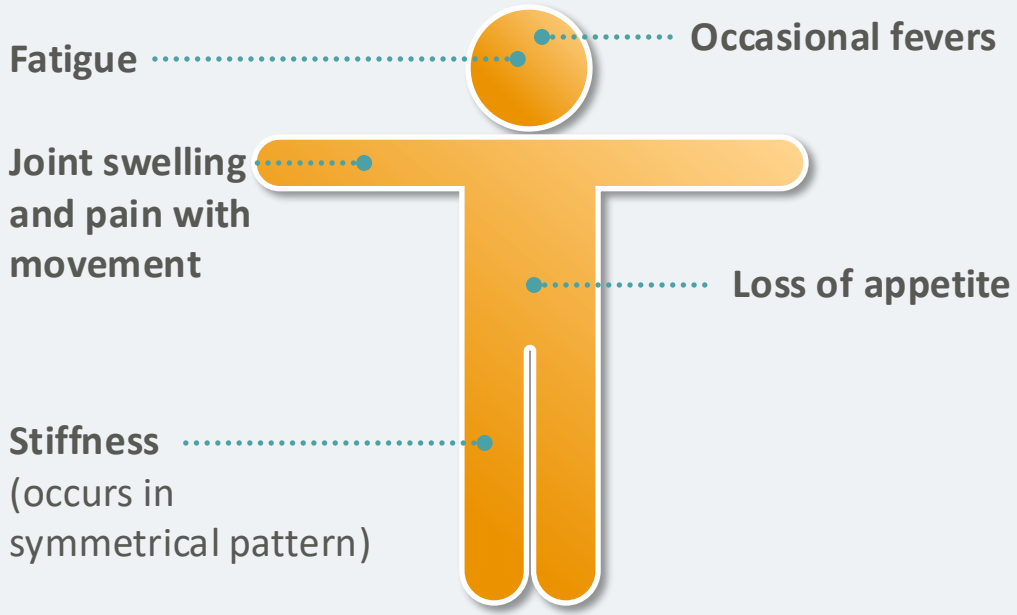
Increasing severity[3]

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.

Rheumatoid arthritis (RA): Clinical presentation[1]

Characteristic symptoms



Factors associated with RA

Genes

- Genetics may determine who gets the disease and the severity of the symptoms

Environment

- Inhalants, bacteria, viruses, gum disease, and lung disease play a role in the development of RA

Sex Hormones

- Women are more likely than men to develop RA
- Symptoms may improve during pregnancy and return after

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1. Rheumatoid Arthritis. NIAMS. https://www.niams.nih.gov/health-topics/rheumatoid-arthritis

IL-1 and inflammation: Summary

IL-1 is a potent **proinflammatory cytokine** with pleiotropic effects

There are 2 distinct IL-1 proteins**, IL-1α and IL-1β. IL-1α** is constitutively expressed and has **mainly local effects. IL-1β** is inactive in its precursor form and exerts **both local and systemic effects**

The role of IL-1 as a master cytokine in inflammation is evidenced by the **pathogenic consequences of excess IL-1 production or signaling**

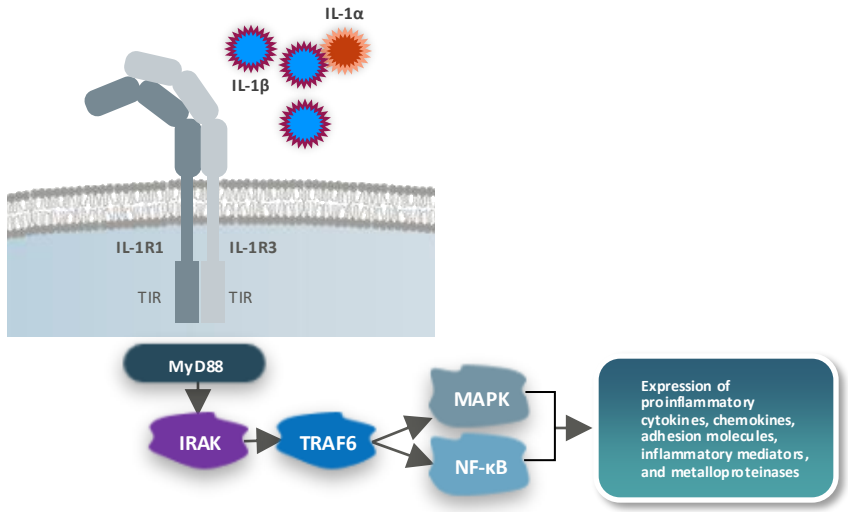
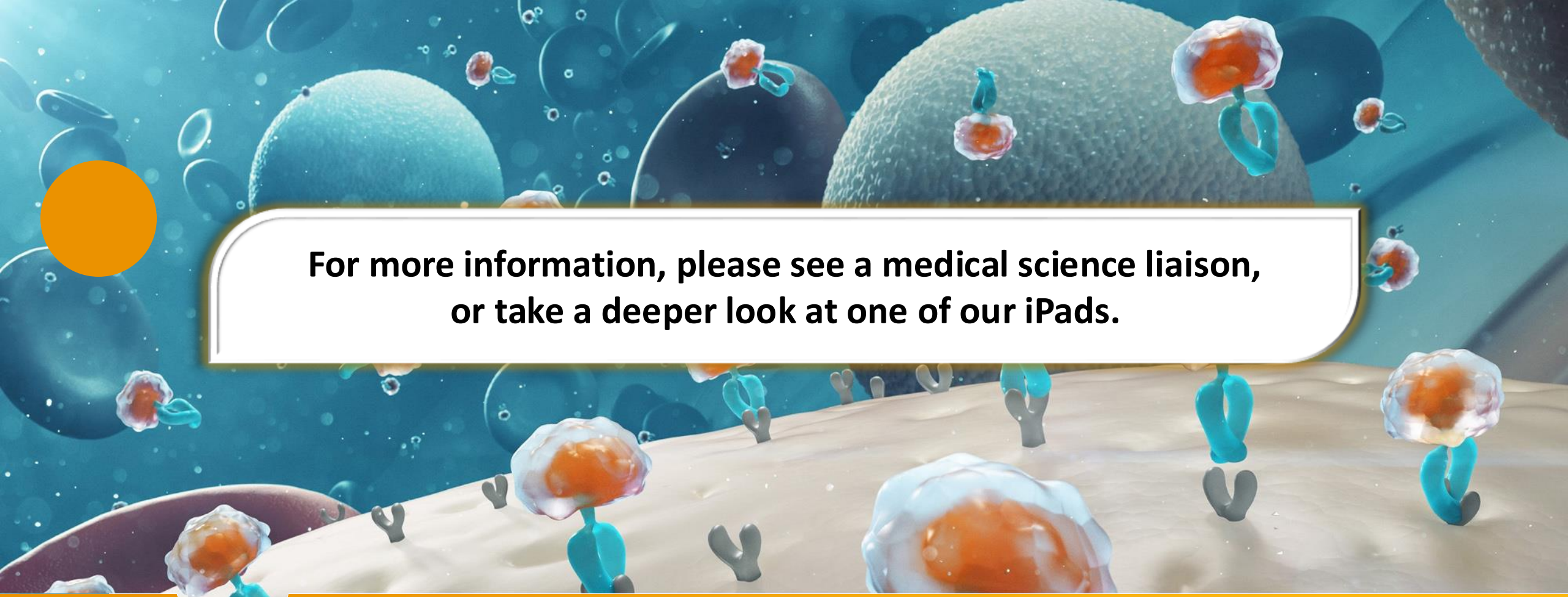


Figure adapted from Dinarello CA. *Nat Rev Rheumatol.* 2019;15:612–632.
IL-1R1/3, interleukin-1 receptor 1/3; IRAK, interleukin-1 receptor-associated kinase; LRR, leucine-rich repeat; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor-κB; TIR, toll-interleukin receptor; TRAF6, tumor necrosis factor receptor-associated factor.



For more information, please see a medical science liaison, or take a deeper look at one of our iPads.

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