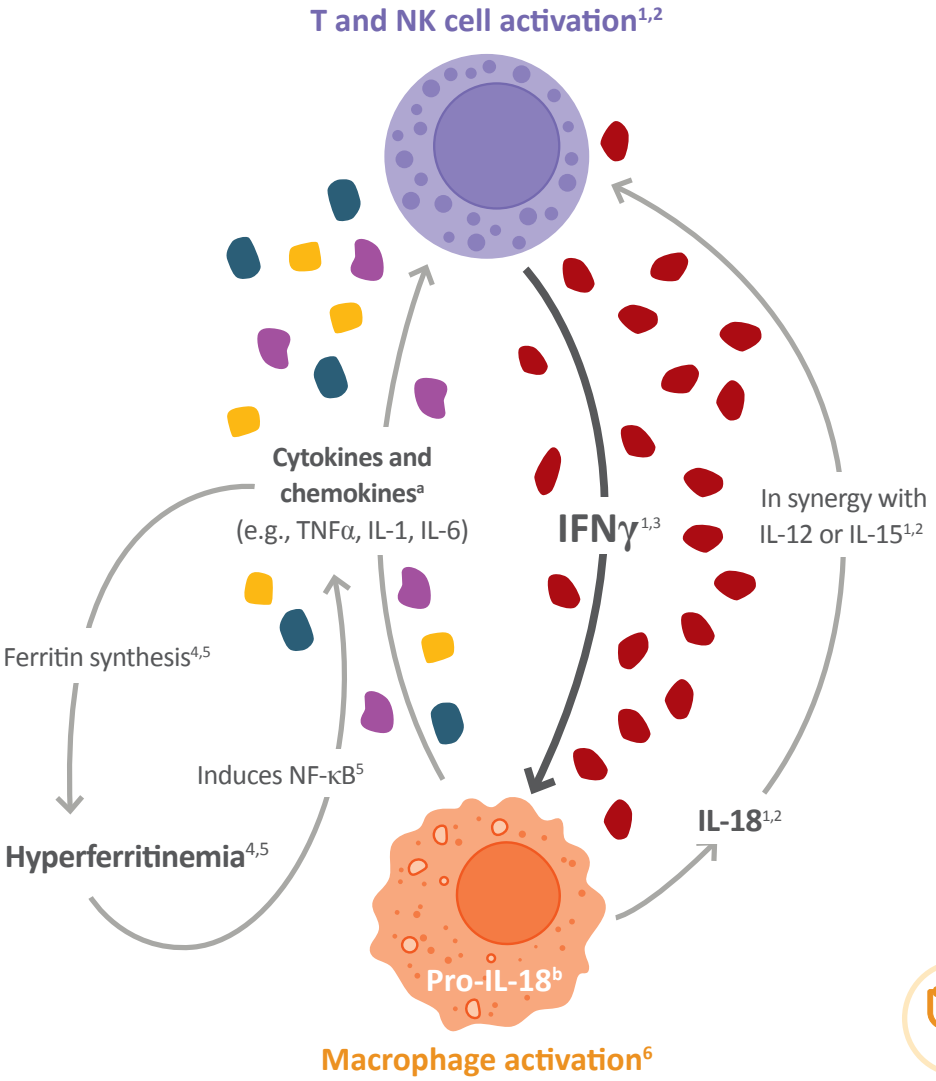
IFNγ plays a pivotal pathogenic role in MAS[1]



IFNγ hyperactivates macrophages[1]

- IFNγ is primarily released by activated T and NK cells[1,3]
- IFNγ activates macrophages to release cytokines, creating a positive feedback loop[1,3,8]
- Elevated levels of IFNγ causes macrophage hyperactivation[1]

IL-18 promotes IFNγ secretion[1,2]
GOF mutations in inflammasomes (which activate IL-18) are common in people with MAS[2,3,7]

Increasing levels of cytokines in MAS lead to hyperferritinemia[4,5]

- Ferritin is upregulated by cytokines[4,5]
- Hyperferritinemia further promotes a pro-inflammatory state by creating a positive feedback loop in cytokine production[4,5,9]

Systemic hyperinflammation drives:[6]

Immune dysregulation | Tissue damage | Multiple organ failure

- **IFNγ activity and ferritin levels are elevated in MAS[3,7,10,11]**
- **Elevated IL-18 levels are also characteristic of patients with MAS in Still's disease[1,10]**

[a]Including IFNγ, IL-1β, IL-2, IL-6, IL-18, and TNFα[2,9]. [b]IL-18 requires inflammasome activation to be secreted.[1,2,12]

GOF, gain of function; IFNγ, interferon gamma; IL, interleukin; MAS, macrophage activation syndrome; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer; TNFα, tumor necrosis factor alpha.

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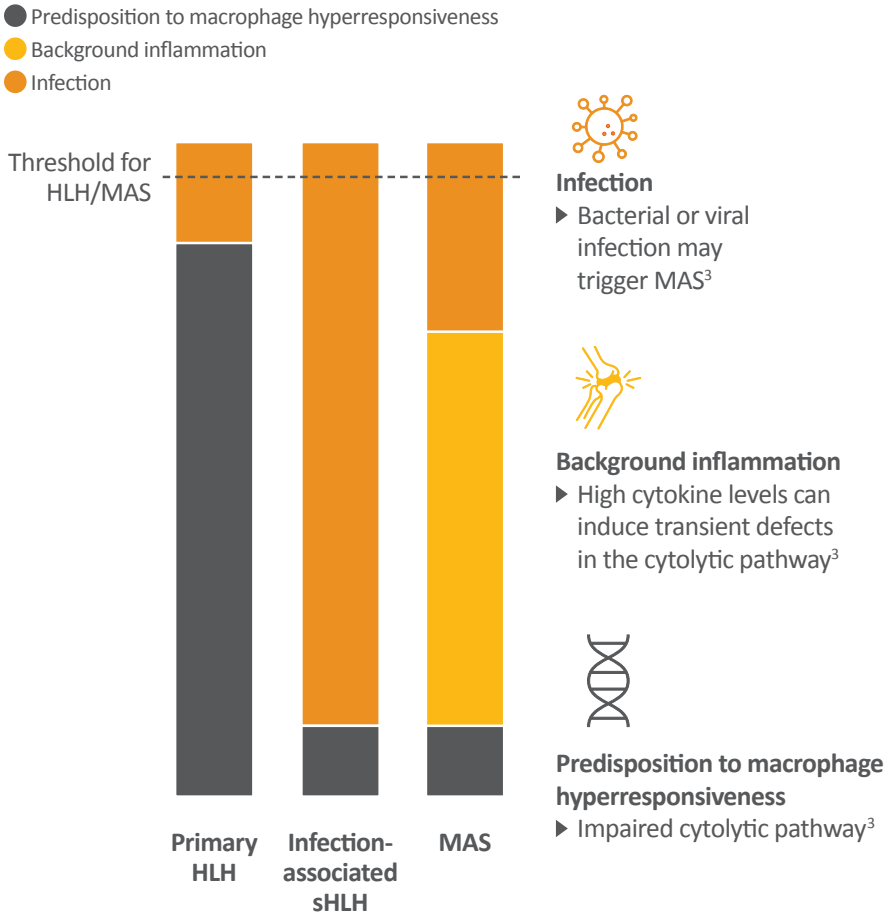
An interaction between host and environmental factors drives MAS in Still's disease[1–3]

Genetic predisposition, background inflammation and infectious triggers are superimposed until a certain threshold is reached, beyond which inflammation is no longer controlled and fulminant MAS develops



Downstream effects of elevated IFNγ activity

Fever: IL-6, IL-1, and TNFα are pyrogens[4]

Hepatosplenomegaly: IL-6 and TNFα cause an increase in acute inflammatory response, lymphocyte infiltration, and activation[4]

Hyperferritinemia: TNFα upregulates ferritin synthesis in hepatocytes and other macrophages[5]

Hypertriglyceridemia: Elevated TNFα decreases lipoprotein lipase activity, reducing triglyceride clearance, resulting in high triglyceride levels[6]

Hypofibrinogenemia: IFNγ-activated macrophages release plasminogen activator, which produces plasmin, driving fibrinolysis.[7] Macrophage infiltration of the liver also decreases fibrinogen production[8]

Hemophagocytosis: In the liver, spleen, and bone marrow caused by overactive macrophages[9]

Cytopenia: High IFNγ impairs multilineage differentiation, causing a reduction of hematopoietic stem and progenitor cells, ultimately resulting in pancytopenia and hypocellular marrow[10,11]

Elevated liver enzymes: IL-6, TNFα, and IL-1β drive acute-phase protein production. Activated hepatic macrophages can also cause liver damage[4]

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Figure adapted from Brisse E, et al. *Br J Haematol* 2016;174:203–217.

HLH, hemophagocytic lymphohistiocytosis; IFNγ, interferon gamma; IL, interleukin; MAS, macrophage activation syndrome; sHLH, secondary hemophagocytic lymphohistiocytosis; TNFα, tumor necrosis factor alpha.

1. Brisse E, et al. *Br J Haematol* 2016;174:203–217; 2. Strippoli R, et al. *J Rheumatol* 2013;40:761–767; 3. Grom AA, et al. *Nat Rev Rheumatol* 2016;12:259–268; 4. Duque GA, Descoteaux A. *Front Immunol* 2014;5:491; 5. Morimoto A, et al. *Pediatr Int* 2016;58:817–825; 6. George MR. *J Blood Med* 2014;5:69–86; 7. Valade S, et al. *PLoS One* 2021;16:e0251216; 8. Valade S, et al. *Medicine (Baltimore)* 2015;94:e1692; 9. Crayne CB, et al. *Front Immunol* 2019;10:119; 10. Lin F-C, et al. *Blood* 2014;124:3699–3708; 11. Morales-Mantilla DE, King KY. *Curr Stem Cell Rep* 2018;4:264–271.

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