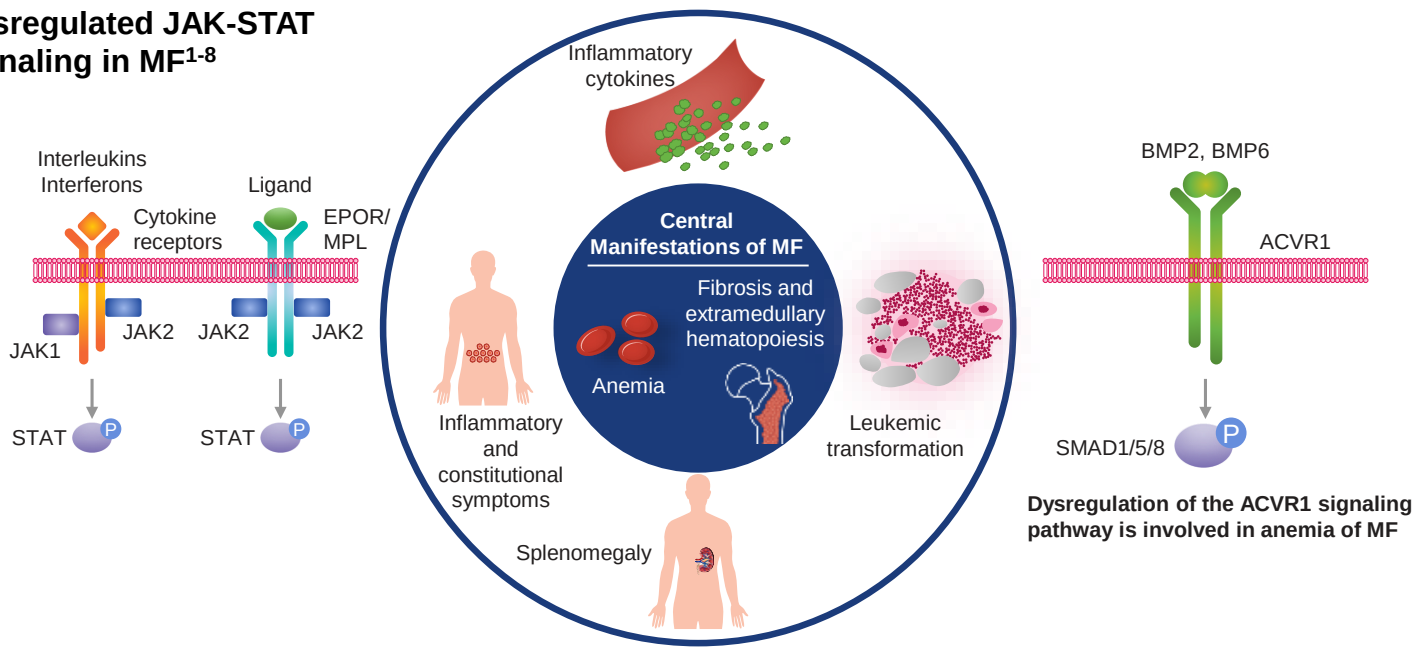
Myelofibrosis Pathophysiology

MF, a rare, fatal BM cancer, is a progressive, Philadelphia chromosome–negative MPN with significant heterogeneity in natural history, mortality, and morbidity. Constitutive activation of the JAK-STAT signaling pathway is a key component in the pathogenesis and clinical manifestations of the disease, regardless of genotype, including *JAK2* mutational status.[1-4]

Drivers of Disease in MF: Aberrant JAK1, JAK2, and ACVR1 Signaling[1-8]

- Dysregulated JAK-STAT signaling in MF drives the production of inflammatory cytokines and clonal proliferation, leading to bone marrow fibrosis, extramedullary hematopoiesis, burdensome splenomegaly, and constitutional symptoms.[1-4]
- Chronic inflammation also drives hyperactivation of ACVR1, elevated hepcidin, dysregulated iron metabolism, and anemia of MF.[5-8]

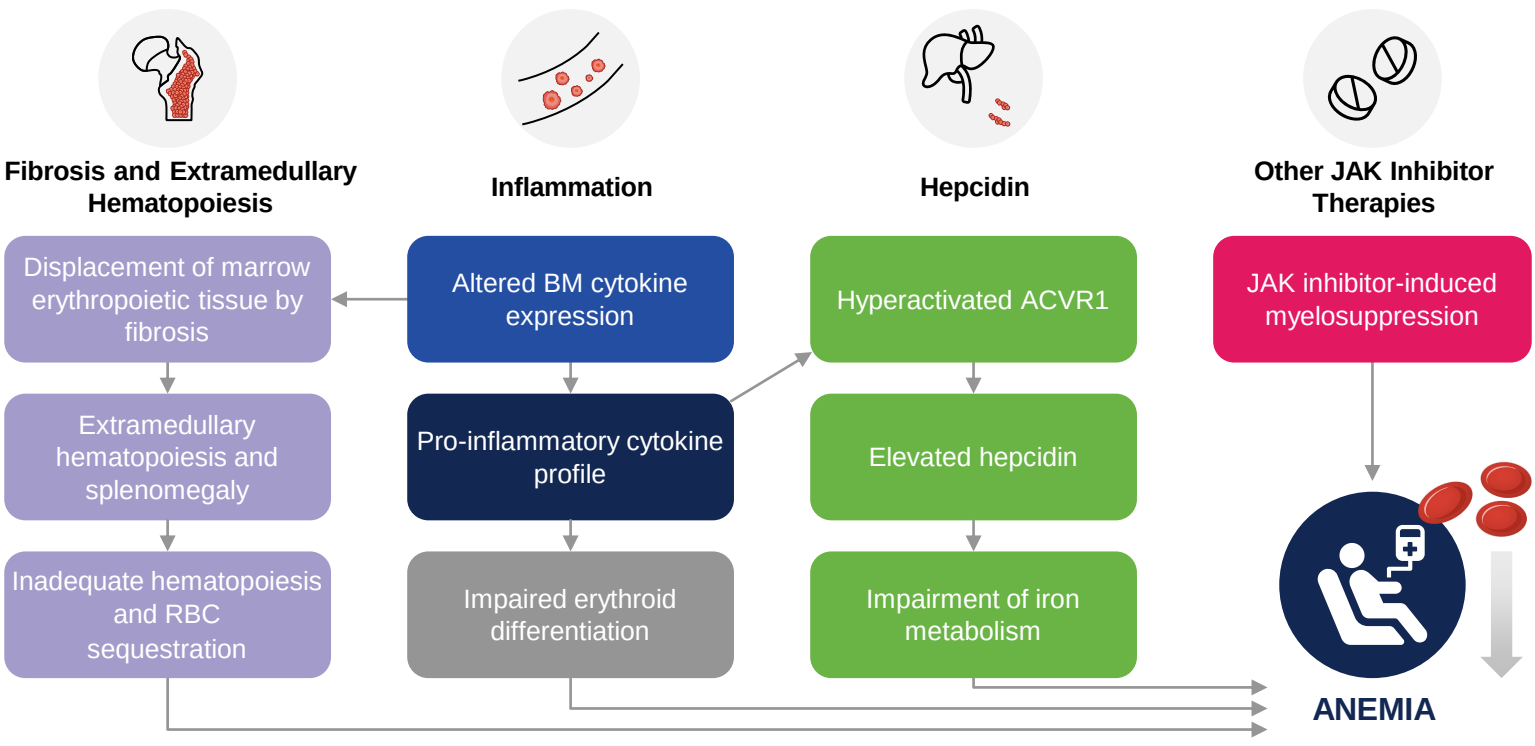
Dysregulated JAK-STAT signaling in MF[1-8]



Dysregulation of the ACVR1 signaling pathway is involved in anemia of MF

Drivers of Anemia in MF[7]

- Anemia in MF is multi-factorial and includes BM fibrosis, anemia of chronic inflammation, splenic sequestration of red blood cells, myelosuppression by some currently available JAK inhibitors, and other factors.



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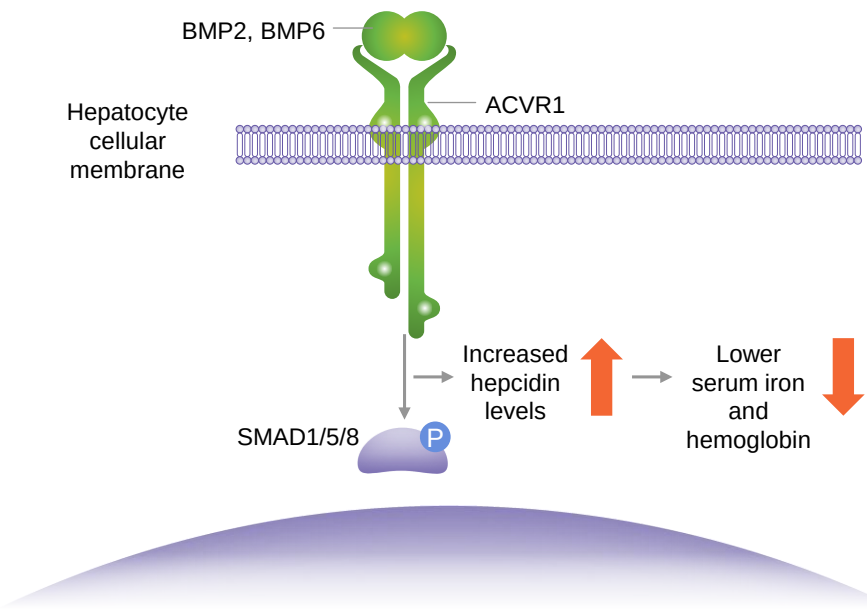
Inflammation, Hepcidin, and Anemia in MF[5-8]

- Anemia of chronic inflammation, a contributor to anemia of MF, is a dynamic and complex process characterized by dysregulated ACVR1 signaling, increased hepcidin levels, decreased serum iron, and an iron-restricted anemia.
- Elevated hepcidin, the master iron regulatory hormone, reduces iron uptake from the gut, increases iron sequestration in monocytes and macrophages, reduces iron availability for erythropoiesis, and shortens the erythrocyte lifespan.
- Aberrant cytokine signaling in MF increases the synthesis of hepcidin:
  - Hyperactivation of ACVR1 increases SMAD1/5/8-dependent transcription of hepcidin, upregulating hepcidin production in chronic inflammation.

Dysregulated ACVR1 Signaling in MF[5-8]



- Hepcidin is elevated in chronic inflammation.
- Elevated hepcidin causes iron restricted anemia.
- Elevated hepcidin predicts lower survival in MF.

Adapted from Verstovsek S, et al. *Future Oncol*. 2021;17(12):1449-1458. Copyright © 2021 Future Medicine Ltd.

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Abbreviations:
ACVR1 = activin A receptor type 1; BM = bone marrow; BMP = bone morphogenetic protein; EPOR = erythropoietin receptor; JAK = Janus kinase; JAK-STAT = Janus kinase-signal transducer and activator of transcription; MF = myelofibrosis; MI = medical information; MPL = myeloproliferative leukemia protein; MPN = myeloproliferative neoplasm; P = phosphorylation; RBC = red blood cell; SMAD1/5/8 = small mothers against decapentaplegic homolog 1/5/8; STAT = signal transducer and activator of transcription.

References:
1. Garmezy B, et al. *Blood Rev.* 2021;45:100691; **2.** Masselli E, et al. *Cells.* 2020;9(9):2136; **3.** Rampal R, et al. *Blood.* 2014;123(22):e123-e133; **4.** Guijarro-Hernández A, et al. *Cancers (Basel).* 2021;13(5):984; **5.** Pardanani A, et al. *Am J Hematol.* 2013;88(4):312-316; **6.** Ganz T. *N Engl J Med.* 2019;381(12):1148-1157; **7.** Naymagon L, Mascarenhas J. *Hemasphere.* 2017;1(1):e1; **8.** Chifotides HT, et al. *J Hematol Oncol.* 2022;15(1):7.

MED--US-10280 | November-25