Myelofibrosis

A Reference Guide for Journalists

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About Myelofibrosis

What Is Myelofibrosis?

Myelofibrosis (MF) is an uncommon blood cancer characterized by bone marrow scarring (fibrosis), enlarged spleen (splenomegaly), potential complications and symptoms including fatigue, fever, night sweats, itchy skin, bone pain, abdominal pain or discomfort and weight loss.[1] MF has a poor prognosis and limited treatment options.[1,2]

MF is a type of Philadelphia chromosome-negative "myeloproliferative neoplasm," a group of diseases in which specific types of blood cells are overproduced in the body and disrupt their normal functioning. Other Philadelphia chromosome-negative myeloproliferative neoplasms include essential thrombocythemia (ET) and polycythemia vera (PV). About 10% to 15% of MF cases begin with ET or PV and are called "secondary myelofibrosis;" the rest of cases develop on their own and are referred to as "primary myelofibrosis."[2,3]

How Many People Have Myelofibrosis?

The exact prevalence of MF is uncertain, and estimates vary widely. In the US, MF affects about 1.5 out of 100,000 people annually.[4] In the EU, the disease affects about 0.75 out of 100,000 people annually.[5,6] Others have reported incidence rates ranging from 0.5 to 1.5 per 100,000 in the population.[7] MF is typically diagnosed in people between 50 to 80 years old, but can occur at any age.[3] There are no known risk factors for the disease.[6]

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Causes

What Causes Myelofibrosis?

Bone marrow is a soft, blood-forming tissue that fills the cavities of bones and is the major source of red blood cells, white blood cells and platelets.[7] Normally, blood cell production is well regulated.

In MF, substances called cytokines – small proteins released by cells that affect how cells interact – increase in the marrow, stimulating blood cell production, inflammation and fibrosis. This is the basis for the name myelofibrosis: "myelo" (marrow) and "fibrosis" (accumulation of scar tissue).[3]

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The replacement of normal bone marrow cells with scar tissue results in decreased production of red and white blood cells and platelets, which in turn causes anemia, susceptibility to infections, and increased bruising and bleeding – hallmark symptoms of MF.[8] To compensate for this compromised process, the spleen and liver increase blood cell production and enlarge – called splenomegaly and hepatomegaly respectively.[7] Indeed, the spleen of MF patients can grow to ten times normal size – in some cases up to 10 kilograms in weight and 36 centimeters in length – and in many cases cause discomfort in the upper left abdomen or pain in the upper left shoulder.[2,3,9]

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Causes

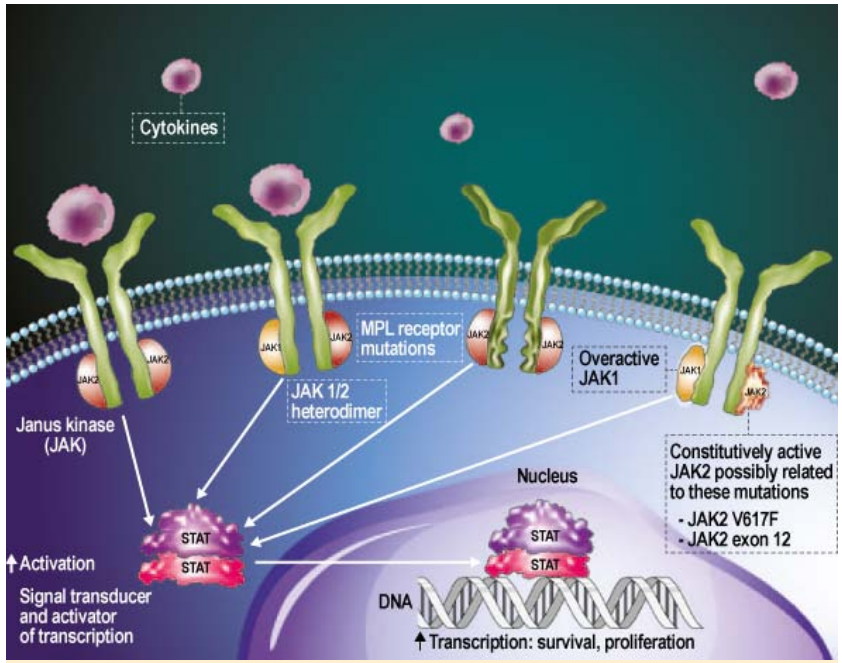

Figure 1: Potential routes to overactive JAK signaling.

While the exact sequence of molecular events leading to MF is not fully understood, researchers do know that the condition results from dysregulation of a cell signaling pathway called the JAK pathway that may be caused by a number of genetic mutations. The most common mutations identified to date – occurring in about half of all MF patients (and a significant percentage with other myeloproliferative neoplasms) – are those that cause abnormal function of a JAK protein.[3]

The JAK pathway involves a number of JAK (for "Janus kinase") proteins: JAK1, JAK2, JAK3 and tyrosine kinase 2. These proteins are key players in many important biological processes, including the regulation of immune function and the formation and development of blood cells.[10,11,12] As shown in Figure 1, JAK signaling involves the following sequence:[13]

1. A cytokine or blood cell growth factor binds to a receptor on the outside of a bone marrow stem cell
2. The two "legs" of the receptor close together and activate the JAK protein inside the cell
3. The JAK protein activates another protein called STAT (signal transducer and activator of transcription)
4. STAT goes into the nucleus where it activates a gene that promotes blood cell production or inflammatory responses

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Normally, the JAK pathway is tightly controlled to ensure normal blood cell production and function. However, in many patients with MF, the JAK pathway is overactive as a result of mutation(s) affecting JAK or other proteins in the signaling chain.[14] Generally, blood cell growth factors work through JAK2 and pro-inflammatory cytokines work though JAK1.[10,15] Since overactive JAK signaling can affect both JAK1 and JAK2, it is associated with both overproduction of blood cells and inflammation.

While not all MF patients have one of the mutations currently known to lead to overactive JAK signaling, it is believed that the JAK pathway is nonetheless overactive in all patients with MF as well as the other myeloproliferative neoplasms.[15,16,17] As such, the JAK pathway has been a primary area of research in exploring ways to treat myelofibrosis and other myeloproliferative neoplasms.[18]

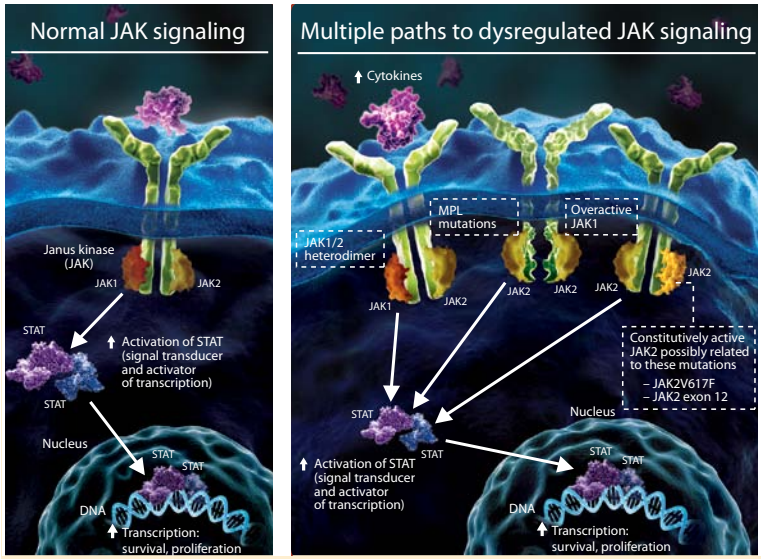

Figure 2: Normal vs. dysregulated JAK signaling.

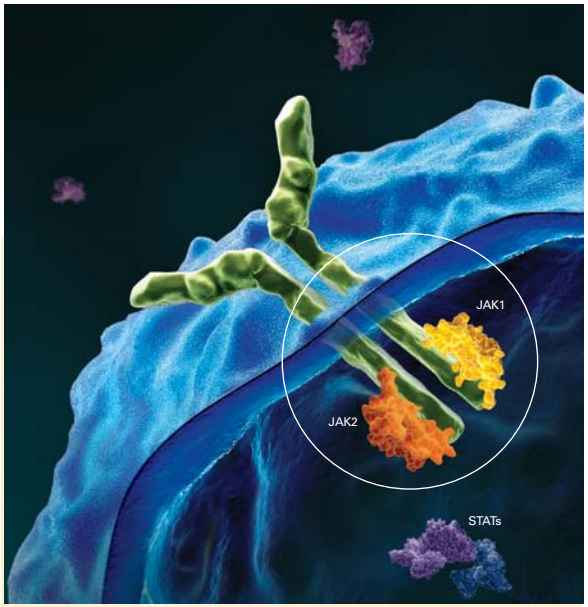

Figure 3: A closer look at JAK1 and JAK2.

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Symptoms & Diagnosis

Myelofibrosis Symptoms and Diagnosis

A physician may consider a diagnosis of MF when a routine medical examination shows an enlarged spleen (found in almost all patients) and abnormal blood counts. Detailed criteria for diagnosing primary and secondary MF have been developed.[19,20]

Patients who are symptomatic may also report the following:[3,8]

- Weakness, fatigue, shortness of breath on exertion (e.g., exercise)
- Weight loss
- Night sweats
- Pallor (paleness)
- Unexplained bruising, easy bleeding
- Increased likelihood of getting an infection
- An enlarged liver, detectable in two-thirds of patients
- Severe upper left shoulder pain (reflecting referred pain from the spleen, sometimes due to inadequate blood flow)
- Bone pain, especially in the lower extremities (uncommon)

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Symptoms & Diagnosis

Findings from a complete blood count (CBC) that suggest a diagnosis of MF often include below-normal levels of red blood cells (anemia), above-normal levels of white blood cells (due to increased inflammation), above- or below-normal levels of platelets, abnormally shaped red blood cells and immature red and white blood cells. Blood tests may also show abnormal levels of other substances.[3,8]

Diagnosis is usually completed by a bone marrow aspiration and biopsy.[3]

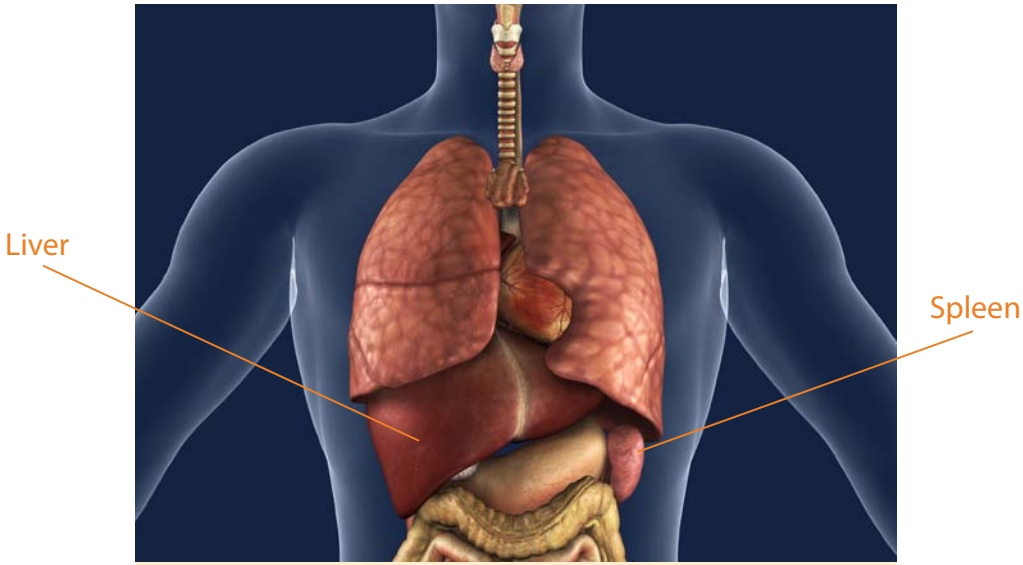

Figure 4: Locations of the spleen and liver. Almost all MF patients have an enlarged spleen, and two-thirds have an enlarged liver.

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Treatment

How is Myelofibrosis Treated?

Patients who are symptom free usually are not treated, and most remain stable for years without requiring treatment. In patients with symptoms, the goal of therapy is to reduce spleen size, relieve symptoms, improve quality of life and reduce the risk of complications.

Approved treatment options for MF are limited. In November 2011, the first JAK1 and JAK2 inhibitor studied and developed to treat patients with intermediate or high-risk MF was approved by the U.S. Food and Drug Administration (FDA). MF therapies that target the uncontrolled signaling in the JAK pathway aim to manage overactive JAK signaling in order to reduce spleen volume, control clinical symptoms and improve quality of life. JAK inhibitors' side effects can generally be regulated and can include reversible grade 3 or 4 hematological toxicity; gastrointestinal symptoms; nausea; vomiting and diarrhoea.[21] Additional research is underway on a number of treatment approaches for MF.[3,22]

Other treatments that are currently being used are associated with side effects such as transformation to leukemia, enlarged liver (hepatomegaly), drowsiness, constipation, fatigue, burning or prickling sensation (paresthesias) and low white blood cell count (neutropenia).[16] Some of the treatments aimed at relieving symptoms and reducing the risk of complications include:[3]

- Hydroxyurea – to decrease very high platelet counts, decrease size and associated complications of an enlarged spleen and to help treat other symptoms
- Thalidomide/lenalidomide – to improve anemia, platelet count, enlarged spleen and other constitutional symptoms
- Interferon alfa – to treat an enlarged spleen, bone pain and high platelet counts
- Androgens – to promote red cell production and relieve the symptoms of severe anemia
- Recombinant erythropoietin – to treat anemia

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- Glucocorticoids (e.g., prednisone) – to treat anemia
- Bisphosphonates – to relieve bone pain and improve blood counts
- Anagrelide – to treat a very high platelet count
- Radiation therapy – to treat an enlarged spleen, bone pain and tumors outside the marrow
- Splenectomy – performed if the spleen is very large and causes a very low platelet count or other clinical problems

Stem cell transplantation is performed in some patients (usually those under age 55) and may cure MF, but it involves potentially life-threatening risks. In the procedure, high-dose radiation and chemotherapy are first given to a patient to destroy their dysfunctional marrow stem cells. Then stem cells – usually from a close immunological match to the patient (e.g., a sibling) – are transplanted to the patient's marrow, where they grow and, hopefully, restore normal marrow function. Transplantation can be difficult if fibrosis is extensive. Further, there is a high risk of toxicity from the pre-transplantation chemotherapy and radiation and of graft-versus-host disease resulting from the donated stem cells attacking the recipient's tissues.[3] The five-year survival rate after transplantation is approximately 30%.[23]

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Prognosis

What is the Prognosis for a Person with Myelofibrosis?

The average survival of people with primary MF is about 5-6 years. Some people may survive for decades, but patients classified as high risk have an average survival of 1.3 years.[24] Researchers have developed scoring systems that can predict a patient's prognosis, based on factors such as age (e.g., over vs. under 65 years), blood counts, and symptoms.[24,25,26]

Studies show that within 10 years of MF diagnosis, up to approximately 20% of MF patients (and different proportions of patients with ET and PV) progress to a form of leukemia called secondary acute myelogenous leukemia, which is virtually untreatable and has a very poor prognosis.[27,28]

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Cytokine
A protein that is made by cells of the immune system and serves to regulate it.[29] Cytokines provide signals to regulate immunological aspects of cell growth and function during both inflammation and specific immune responses.[30]

Essential thrombocythemia
A disease in which the number of thrombocytes (platelets) in the blood is above normal, without known cause.[29]

Growth factor
A protein that functions to regulate cell division and cell survival.[29]

JAK1
A tyrosine kinase protein essential for signaling for certain cytokines.[12]

JAK2
A tyrosine kinase protein essential for the growth and differentiation of hematopoietic (blood-forming) stem cells.[12]

JAK3
A tyrosine kinase protein essential for the growth and differentiation of white blood cells.[12]

JAK/STAT signaling pathway
A key signal transduction pathway used by cytokines and growth factors to regulate gene expression. In this pathway, a cytokine or growth factor binds to its receptor to activate a protein of the JAK (Janus kinase) family, which then stimulates a STAT (signal transducer and activator of transcription) protein to travel to the nucleus and start transcription of a specific gene.[12]

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Myelofibrosis
A blood cancer in which the bone marrow is replaced by fibrous tissue and is no longer able to produce adequate numbers of normal blood cells.[29]

Myeloproliferative neoplasms
A group of blood cancers – including myelofibrosis, polycythemia vera and essential thrombocythemia – in which large numbers of abnormal red blood cells, white blood cells or platelets grow and spread in the bone marrow and the blood.[31]

Philadelphia chromosome
An abnormal chromosome present in bone marrow cells that is responsible for the constant production of abnormal white blood cells and is the hallmark of chronic myeloid leukemia. Specifically, an abnormality of chromosome 22 in which part of chromosome 9 is transferred to it.[29]

Platelet
A small piece of cell in the blood that forms blood clots. Also called a thrombocyte.[29]

Polycythemia vera
A disease in which the number of red blood cells in the bone marrow and blood is above normal.[29]

Receptor
A molecule inside or on the surface of a cell that binds to a specific protein.[29]

Signal transduction
The transfer of information between and within cells through a signaling pathway.[32]

Splenomegaly
An enlargement of the spleen beyond its normal size with symptoms including fatigue, the inability to eat a large meal and pain on the upper left side of the abdomen.[7]

Tyrosine kinase
A protein involved in communication between and within cells.[30]

Tyrosine kinase 2
A tyrosine kinase protein essential for signaling for certain cytokines.[12]

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Glossary & Resources

The Association of Cancer Online Resources

European Leukemia Network

The Leukemia & Lymphoma Society

The MPD Foundation

MPD Voice

The National Cancer Institute

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