

# The Role of The Megakaryocyte in Primary Myelofibrosis



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Primary myelofibrosis is an insidiously progressive disease that leads ultimately to scarring and failure of the bone marrow. Of the myeloproliferative disorders, it has the worst overall prognosis and morbidity. Despite many significant advances in the treatment of this disease, many aspects of its origin and progression remain poorly understood.

Although fundamentally a neoplasm of the hematopoietic stem cell, there is more to this disease than simple uncontrolled growth of cells. The malignant cells and their progeny are able to alter the environment of the bone marrow by influencing other normal cells (collectively referred to as stromal cells) that form the intricate architecture vital for normal bone marrow function. The eventual result of this interaction between the malignant clone and the stromal cells is marrow fibrosis—a process in which normal “spongy” marrow is replaced by hard scar tissue formed mostly

by excessive deposition of collagen and other connective tissue. The malignant stem cells and their progeny also leave the confines of the bone marrow as the disease progresses, and establish residence in other hematopoietic organs, most notably the spleen. This leads to the enlargement of the spleen and liver that is so characteristic of this disease, causing significant morbidity.

The hematopoietic cell thought to contribute most to the fibrotic process is the megakaryocyte. Megakaryocytes are very large cells (50- 150 micrometers in diameter) whose normal function is platelet production. Platelets are in fact remnants of megakaryocyte cell bodies which are shed into the blood stream as these large cells die inside the bone marrow. This normal process of controlled megakaryocyte suicide (called apoptosis) is very complex, and has been elucidated in remarkable detail through the work of many researchers. It is vital that this process occurs adjacent to the marrow blood

vessels, so that platelets are released into flowing blood and not static marrow tissue, as the latter may have grave consequences, including marrow fibrosis.

Megakaryocytes are very rich in compounds called cytokines. A number of these, such as transforming growth factor-beta (TGF-beta), platelet derived growth factor (PDGF), and fibroblast growth factor (FGF), are known to cause tissue fibrosis by stimulating stromal cells to produce collagen and other connective tissue. Normally, these cytokines are neatly packaged inside platelets shed from megakaryocytes, and only released when platelets are activated at sites of tissue injury, resulting in local fibrosis and scarring which repairs and heals the injury. However, if the contents of megakaryocytes are improperly released into the marrow environment as a result of their premature death away from the marrow blood vessels, it is conceivable that an uncontrolled and disseminated fibrotic reaction can follow. In fact, upon

microscopic examination of the bone marrows of patients with primary myelofibrosis, one sees tight clusters of immature megakaryocytes and necrotic (dead) megakaryocytes surrounded by fibrotic areas, often distanced from the vasculature.

To test the idea that normal megakaryocyte localization and movement is impaired in primary myelofibrosis, we are using cell culture techniques and studying the migratory properties of these very important cells. By comparing the behavior of megakaryocytes from patients with primary myelofibrosis to that of normal controls, we hope to uncover a key element of the fibrotic process.

The process of marrow fibrosis is not a feature exclusive to primary myelofibrosis, but is in fact seen in other cancers that involve the marrow including acute leukemia and solid malignancies that metastasize to bone. Therefore, interruption of normal megakaryocyte life cycle and motility may be a general feature of cancer involving the bone marrow.