Title
A new therapeutic target for myelofibrosis is cause for Gli.

Journal
Science Translational Medicine, 9(392)

ISSN
1946-6234

Author
Jonas, Brian A

Publication Date
2017-05-31

DOI
10.1126/scitranslmed.aan4297

Peer reviewed

HHS Public Access

Author manuscript

Sci Transl Med. Author manuscript; available in PMC 2018 May 31.

Published in final edited form as:

Sci Transl Med. 2017 May 31; 9(392): . doi:10.1126/scitranslmed.aan4297.

A new therapeutic target for myelofibrosis is cause for Gli

Brian A. Jonas

Department of Internal Medicine, University of California Davis, Sacramento, CA 95817, USA

Abstract

Myeloproliferative neoplasm cells recruit Gli1 positive mesenchymal stromal cells to transdifferentiate into fibrosis-causing myofibroblasts, a process that can be inhibited by a Gli inhibitor.

Bone marrow fibrosis (BMF), characterized by deposition of reticulin and collagen fibers in the marrow, is a hallmark of primary myelofibrosis (PMF) and other myeloproliferative neoplasms (MPNs). PMF is characterized by mutations that activate JAK-STAT signaling and constitutional symptoms, splenomegaly, and reduced survival. Allogeneic hematopoietic stem cell transplantation is the only curative therapy but is limited by toxicity and donor availability. For most, PMF management focuses on inhibition of JAK-STAT signaling, which can lead to improvement in symptoms and splenomegaly but does not significantly affect the malignant clone or BMF. Recently, mesenchymal stromal cells (MSCs) and Hedgehog pathway signaling factors, including Gli1, have been implicated in the development of solid organ fibrosis, but the cellular origin of BMF remains unclear.

In a new study, Schneider *et al*. report that Gli1+ MSCs play a central role in BMF development and represent a new therapeutic target. After first confirming that murine and human BM Gli1+ cells are of MSC-origin, genetic fate-tracing in two murine PMF models showed that Gli1+ cells are mobilized from perivascular and endosteal niches by the malignant hematopoietic clone to become myofibroblasts. Genetic ablation of Gli1+ cells abrogated the myelofibrosis phenotype, confirming that Gli1+ cells are responsible for BMF and are a bona fide novel therapeutic target for PMF. Furthermore, the small-molecule Gli inhibitor GANT61 reversed the myelofibrosis phenotype by impairing the expansion of both the BMF-driving Gli1+ myofibroblasts and the malignant hematopoietic clone. Next, gene expression analyses identified the chemokine Cxcl4 as a primary effector of Gli1+ cell migration and transdifferentiation into myofibroblasts, which was confirmed in Cxcl4 knockout mice. In bone marrow biopsies and cultured MSC from patients with MPNs, Gli1+ MSCs were similarly increased in human BMF and sensitive to GANT61 inhibition.

This study shows that Gli1+ MSC play a critical role in the pathogenesis of myelofibrosis through recruitment and transdifferentiation into fibrosis-causing myofibroblasts, and

Highlighted Article

R. K. Schneider, A. Mullally, A. Dugourd, F. Peisker, R. Hoogenboezem, P. M. H. Van Strien, E. M. Bindels, D. Heckl, G. Büsche, D. Fleck, G. Müller-Newen, J. Wongboonsin, M. Ventura Ferreira, V. G. Puelles, J. Saez-Rodriguez, B. L. Ebert, B. D. Humphreys, R. Kramann, Gli1+ mesenchymal stromal cells are a key driver of bone marrow fibrosis and an important cellular therapeutic target. *Cell Stem Cell* 10.1016/j.stem.2017.03.008 (2017). Google Scholar

targeting Gli1+ cells with a Gli-inhibitor reversed the myelofibrosis phenotype. Given the limitations of current therapies, targeting Gli1+ cells alone or in combination with other agents, such as JAK inhibitors, represents a promising new approach for treating patients with PMF and other MPNs.