EDITORS' CHOICE | FIBROSIS

A scar-y movie, starring IL-11

Kevin R. King

+ See all authors and affiliations

Science Translational Medicine 29 Nov 2017:
Vol. 9, Issue 418, eaar2443
DOI: 10.1126/scitranslmed.aar2443

Article Info & Metrics eLetters

Abstract

IL-11 is found to be a critical mediator of TGFβ1-induced scarring and fibrosis in the heart and kidney.

Fibrosis is considered a largely irreversible process leading to functional decline in a wide range of tissues. In the heart, fibrosis impairs contractile function and electrical conduction causing progressive heart failure and fatal arrhythmias. It is also thought to impair cardiac regeneration. Transforming growth factor β1 (TGFβ1) is credited with fueling fibrosis; however, it also has many nonfibrotic roles that make it an unattractive target for direct inhibition. Therefore, Schafer and colleagues set out to identify fibrosis-selective targets downstream of TGFβ1 signaling and discovered a surprising role for interleukin-11 (IL-11), a cytokine best known for its role in hematopoiesis.

single cell RNA-seq analysis found the most common IL-11–expressing cell type to be ECM-producing fibroblasts. The authors also found that fibroblasts expressed the IL-11 receptor, IL-11RA, suggesting the possibility of an autocrine signaling loop. When stimulated with recombinant IL-11, fibroblasts increased ECM production, motility, contraction, and invasion. Moreover, IL-11 "ligand traps," IL-11RA–neutralizing antibodies, or siRNA each decreased TGFβ1-induced fibrosis in multiple assays.

Surprisingly, stimulation of fibroblasts with IL-11 increased ECM production without altering gene expression. The authors therefore designed a series of experiments that led them to propose a transcription-independent mechanism in which IL-11 interacts with IL-11RA shed from cellular surfaces and signals in trans to induce ECM production and fibrosis. Exploration of the intracellular mechanism revealed that TGFβ1 activated the ERK kinase in an IL-11–dependent fashion and that blocking ERK reduced IL-11-induced fibrotic phenotypes. In vivo, IL-11 was spontaneously increased in multiple preclinical models of cardiovascular and renal fibrosis including angiotensin II infusion, transverse aortic constriction in the heart, and folate-induced kidney damage. Administration of recombinant IL-11 or expression of IL-11 from a collagen promoter in vivo caused widespread fibroblast activation, increased histologic evidence of fibrosis, and end organ damage with cardiac and renal dysfunction. Meanwhile, mice deficient in the IL-11 receptor were protected from fibrosis in the same models, pointing to its potential as a target for therapeutic inhibition.

The mechanism by which IL-11 and its receptor signal in trans, and how this relates to ERK-dependent fibrosis, remains unclear. Nevertheless, this study provides many lines of evidence that bring IL-11 into focus as a potential therapeutic target to inhibit fibrosis; a fundamental pathophysiologic process afflicting nearly every tissue and underlying a wide range of clinically important diseases.

Highlighted Article

S. Schafer, S. Viswanathan, A. A. Widjaja, W.-W. Lim, A. Moreno-Moral, D. M. DeLaughter, B. Ng, G. Patone, K. Chow, E. Khin, J. Tan, S. P. Chothani, L. Ye, O. J. L. Rackham, N. S. J. Ko, N. E. Sahib, C. J. Pua, N. T. G. Zhen, C. Xie, M. Wang, H. Maatz, S. Lim, K. Saar, S. Blachut, E. Petretto, S. Schmidt, T. Putoczki, N. Guimarães-Camboa, H. Wakimoto, S. van Heesch, K. Sigmundsson, S. L. Lim, J. L. Soon, V. T. T. Chao, Y. L. Chua, T. E. Tan, S. M. Evans, Y. J. Loh, M. H. Jamal, K. K. Ong, K. C. Chua, B.-H. Ong, M. J. Chakaramakkil, J. G. Seidman, C. E. Seidman, N. Hubner, K. Y. K. Sin, S. A. Cook, IL11 is a crucial determinant of cardiovascular fibrosis. *Nature* 10.1038/nature24676 (2017).
Google Scholar

View Abstract

Science Translational Medicine
Vol 9, Issue 418
29 November 2017
Table of Contents