Ruprecht-Karls-Universität Heidelberg

Medizinische Fakultät Mannheim

Dissertations-Kurzfassung

Interleukin (IL)-13 induces connective tissue growth factor via TGF-beta independent Smad signaling in rat hepatic stellate cells

Autor: Yan Liu
Institut / Klinik: II. Medizinische Klinik
Doktorvater: Prof. Dr. S. Dooley

The Th2 cytokine Interleukin (IL)-13 is pro-fibrotic in many chronic infectious and autoimmune diseases, including liver fibrosis. The fibrogenic activity of IL-13 is well studied in murine models, especially in schistosomiasis associated liver fibrosis, whereas the underlying cellular and molecular mechanism still remains unclear. It was recently suggested that IL-13 mediates its fibrogenic effects through TGF-β dependent and independent routes.

In liver, connective tissue growth factor (CTGF) facilitates excessive extracellular matrix (ECM) production and hepatic stellate cell (HSC) activation, and is considered a critical downstream mediator of fibroproliferative TGF-β effects. HSCs are known as the major source of CTGF in the liver. The current study reveals for the first time that IL-13 represents the major inducer of CTGF expression in HSCs.

To dissect the molecular mechanism underlying IL-13 dependent liver fibrogenesis, its downstream signaling leading to CTGF induction in HSCs was thoroughly investigated. It came out that IL-13 time- and dosage- dependently induces CTGF in HSCs via a TGF-β independent pathway, although participation and collaboration of Smad1 and Smad2 transcription factors and their upstream receptor kinases (Activin receptor-like kinases, ALKs) were required. As expected, IL-13 induced canonical Stat6 phosphorylation in HSCs, which however was not involved in CTGF induction. Instead, Erk-MAPK pathway was found to be responsible for IL-13 induced early Smad phosphorylation and CTGF production.

Taken together, the present study demonstrates that IL-13 induces CTGF expression in HSCs through activating TGF-β independent ALK/Smad signaling via an Erk-MAPK dependent mechanism rather than via its canonical JAK/Stat6 pathway. These results provide further insight into the molecular mechanism of pro-fibrotic IL-13 activity in liver.