Talk

Molecular basis of liver fibrosis

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Keywords: liver fibrosis; gata4; hif2α; hepatic stellate cells

ABSTRACT

Motivation: Liver fibrosis is the result of an exacerbated scarring response after continuing damage of the tissue. (1). Hepatic stellate cells (HSCs) have been described as a key factor for this process. In the normal liver, HSCs remain quiescent and are only activated by an injury trigger (2). Previously, our group reported that GATA4 is a crucial factor for the maintenance of HSCs quiescence and the inhibition of fibrosis. Therefore, unraveling the molecular pathways mediated by GATA4 could be useful for promoting fibrosis regression (3). In this project, we perform a lineage tracing assay in order to explore GATA4 expression during regeneration after inducing fibrosis with tetrachloride (CCl4) in mice. In addition, we study the potential transcriptional repression of Hif2α by GATA4, a mechanism that could explain, at least in part, the role of GATA4 in the inhibition of liver fibrosis.

Methods: CCl4 injections were used to induce liver fibrosis in a mouse model with constitutive GFP expression in HSCs. Livers were extracted and analyzed by immunofluorescence right at the end of the treatment and after 4 weeks of recovery. A conserved Hif2α intronic region, which contains two putative GATA sites were cloned into the pGL3 luciferase reporter plasmid. Transient transfections experiments were performed using pGl3-Hif2α plasmid and a plasmid for Gata4 constitutive expression to study the potential transcriptional repression of Hif2 by GATA4. Dual-Luciferase ® Reporter Assay System (Promega) was used for luciferase measurement.

Results: Preliminary results showed that reversion of activated HSCs to a quiescent state is accompanied by reactivation of GATA4 expression in mice recovering from CCl4 treatment. These results pointed to a crucial role of GATA4 for reversion of HSCs phenotype. On the other hand, 293T cells transfected with GATA4 expression plasmids showed reduced luciferase activity, which likely indicates a repression of Hif2α by GATA4 via the conserved GATA binding sites in the HIF2α enhancer region.

Conclusions: There is growing evidence that GATA4 not only orchestrates the preservation of normal tissue organization, but also actively contributes to fibrosis regression. Moreover, our work proposes genetical regulation of Hif2α by GATA4 could be decisive for this process.

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