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LIPS

Elucidating the Role of sFRP2 in Modulating Organ Fibrosis

Background

Fibrosis is the typical response to injury, which leads to distorted architecture, pathologic signaling and ultimately organ dysfunction. In cardiac tissue specifically, a fibrotic response to injury can lead to a decrease in the heart's ability to function and plays a significant role in the pathogenesis of most heart diseases. Secreted frizzled-related protein (sFRP2) is upregulated following cardiac ischemic injury in fibroblasts. sFRP2 has been identified as a mesenchyme derived factor that augments post-myocardial infarction (MI) repair, in part by down-regulating fibrosis. Yet, the molecular mechanism that regulates sFRP2's effect on fibroblasts in modulating tissue fibrosis is incompletely understood. We have generated a transgenic mouse model in which we can temporally and spatially regulate the expression of sFRP2 in injury-induced activated fibroblasts. In three different injury models (heart, kidney, and skin) sFRP2 induction exerted an anti-fibrotic effect in comparison to control Cre mice. sFRP2 overexpression in heart following MI resulted in reduced scar size, improved function, and reduced adverse cardiac remodeling. Based on our preliminary observation, we hypothesize that sFRP2 inhibits fibrosis by modulating the pro-fibrotic signaling pathways in post-injury activated myofibroblasts. To test this hypothesis, we analyzed the pro-fibrotic pathways activated in response to injury in sFRP2 and Cre mice at multiple time points following injury. These pro-fibrotic pathways: TGFb, Wnt, and MAP kinase signaling, were analyzed via semi-quantitative RT-PCR and Western Blot Analysis.

Methodological Approach

sFRP2 expression was induced post-infarct following tamoxifen treatment in mice expressing sFRP2 under FSP1 promoter. Following Cre activation by tamoxifen, sFRP2 gets expressed in FSP1+ cells instead of GFP. BMT animals were generated to ensure sFRP2 expression in fibroblasts since FSP1 is also expressed in hematopoietic cells. The animals were treated with tamoxifen for five consecutive days prior to injury.

Findings

Transient induction of sFRP2 expression following MI in sFRP2 mice modulates profibrotic signaling pathways. Moreover, transgenic activation of sFRP2 in mice downregulates profibrotic pathways. Post-injury activation of sFRP2 expression was also shown to decrease fibrosis following skin injuries. Post excisional skin injury was shown to induce sFRP2 expression in FSP1+ fibroblasts leading to a reduction in fibrosis.