IL10-inhibits Fibroblast Progenitor Cell-mediated Cardiac Fibrosis in Pressure-overloaded Myocardium

Suresh K Verma, Venkata N Garikipati, Ctr for Transnational Med, Temple Univ, Philadelphia, PA; Prasanna Krishnamurthy, Houston Methodist Res Inst, Houston, TX; Cindy Benedict, Emily Nickoloff, Raj Kishore, Ctr for Transnational Med, Temple Univ, Philadelphia, PA

Background: Activated fibroblasts (myoFBs) play critical role in cardiac fibrosis, however, their origin in diseased heart remains uncertain. Recent studies suggest the contribution of bone marrow fibroblasts progenitor cells (BM-FPC) in pressure overload (PO)-induced cardiac fibrosis. Previously we have shown that interleukin-10 suppress PO-induced cardiac fibrosis, however, its role on inhibition of BM-FPC-mediated fibrosis is not known. Thus, we hypothesized that IL-10 inhibits PO-induced homing and transition of BM-FPC to myoFBs and therefore, attenuates cardiac fibrosis.
Methods and Results: Cardiac fibrosis was induced in Wild-type (WT) and IL-10-knockout (KO) mice by transverse aortic constriction (TAC). TAC-induced left ventricular (LV) dysfunction and fibrosis were further exaggerated in KO mice. Systemic recombinant IL-10 administration markedly improved LV function and inhibited PO-induced cardiac fibrosis. PO-enhanced FPC (Prominin1^{+} cells) mobilization and homing in IL-10 KO mice compared to WT mice. Furthermore, bone marrow transplantation (BMT) experiment was performed wherein WT marrow from GFP mice was repopulated in IL-10 KO mice. FPC mobilization was significantly reduced in BMT-IL10 KO mice compared to IL-10 KO mice after TAC. Furthermore, immunofluorescence result in BMT mice showed that subsets of myoFBs are derived from BM after TAC. To identify the molecular mechanism, wild type BM-FPC were treated with TGFβ_2 with or without IL10. IL10 treatment significantly inhibits TGFβ_2-induced FPC to myoFBs transition. As miRNAs are key players in cardiac fibrosis, next we performed fibrosis-associated miRNA profiling using miRNA array kit. TGFβ_2-induced miR-208, 155, 21 and 145 expression was markedly inhibited by IL-10.
Conclusion: Taken together, our findings suggest that both reduced homing to heart and transition of FPC to myofibroblasts mediate anti-fibrotic effect of IL10 during PO-induced heart failure. Ongoing investigations using molecular approaches will provide a better understanding on the mechanistic and therapeutic aspects of IL10 on PO-induced cardiac fibrosis and heart failure.

Disclosure Block:
S.K. Verma: None. **V.N.S. Garikipati:** None. **P. Krishnamurthy:** None. **C. Benedict:** None. **E. Nickoloff:** None. **R. Kishore:** None.