Hypoxic Macrophage Derived Oncostatin-M inhibits cardiac fibrosis

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[Introduction]
Hypoxia is a pathological condition in which the tissue is deprived of adequate oxygen supply, occurring in the cardiac tissue of heart disease patients. Each cell exerts its own responses to hypoxia, and most of them are mediated through a transcription factor, hypoxia inducible factor 1α (HIF-1α). Macrophages, a key mediator of inflammation, accumulate in such hypoxic areas, and hypoxic responses of macrophage strongly accelerate the pathological processes.
We reported that HIF-1α-induced metabolic reprogramming (active glycolysis) is required for hypoxic macrophage migratory capacity.
It is conceivable that HIF-1α-mediated macrophages play a crucial role in the progression of cardiovascular diseases, however, their precise functions still remain unclear.
[Method and Result]
Through macrophage transcriptome analysis and chromatin immunoprecipitation assay, we identified Oncostatin-M (OSM), a part of the interleukin 6 cytokine family, as a novel direct HIF-1α target gene.
Intriguingly, pathological analysis of human heart specimens obtained from heart failure patients revealed that the number of OSM-positive macrophages inversely correlated with the area of cardiac fibrosis ($r = -0.63$, $P = 0.0053$).
To test the effect of OSM on cardiac fibroblast in vivo, we generated fibroblast-specific OSM receptor knockout (fOSMR CKO) mice and performed Transverse Aortic Constriction (TAC) operation, a commonly used experimental model for pressure overload-induced cardiac remodeling. Interestingly, cardiac fibrosis was more prominent in fOSMR CKO mice than controls.
Moreover, we are currently investigating the expression of OSM in other type of human specimens, such as blood serum of heart failure patients and left atrial appendage of AF patients.
[Conclusion]
These results demonstrate an essential role of macrophage hypoxia signaling via OSM in regulating cardiac fibrosis.

Keywords : Macrophage,Hypoxia,Inflammation,Fibrosis,Heart disease
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