肾福康胶囊通过STAT3/YAP通路调控细胞串扰改善肾间质纤维化的机制Δ

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摘　要　目的　探讨肾福康胶囊（SFK）通过信号转导及转录活化因子3（STAT3）/Yes相关蛋白（YAP）通路调控巨噬细胞-成纤维细胞串扰改善肾间质纤维化（RIF）的作用机制。**方法**　用转化生长因子β$_1$（TGF-β$_1$）诱导巨噬细胞RAW264.7极化，再建立巨噬细胞与肾成纤维细胞NRK-49F的非接触共培养体系，以及巨噬细胞与YAP敲低肾成纤维细胞非接触共培养体系，给予低、中、高浓度（4、8、16 μg/mL）SFK，以及STAT3抑制剂（STAT3-I，1.64 μg/mL）、氯沙坦钾片（阳性对照，0.28 μg/mL），干预48 h。检测巨噬细胞中CD86、CD163、STAT3蛋白和CD86、F4/80、STAT3 mRNA表达水平，共培养肾成纤维细胞中α平滑肌肌动蛋白（α-SMA）、波形蛋白（Vimentin）、Ⅰ型胶原（Col-Ⅰ）、基质金属蛋白酶1（MMP-1）、YAP蛋白及mRNA表达水平，以及共培养YAP敲低肾成纤维细胞中α-SMA、Vimentin、MMP-1蛋白及mRNA表达水平。**结果**　TGF-β$_1$诱导后巨噬细胞中CD86、CD163、STAT3蛋白表达水平和CD86、F4/80、STAT3 mRNA表达水平均显著升高（$P<0.05$）；极化的巨噬细胞的培养液可激活肾成纤维细胞，使肾成纤维细胞中α-SMA、Vimentin、Col-Ⅰ、YAP蛋白及mRNA表达水平均显著升高，MMP-1蛋白及mRNA表达水平显著降低（$P<0.05$）；SFK、STAT3-I可逆转以上指标的变化，其中SFK中浓度组部分指标效果强于SFK低、高浓度组。在巨噬细胞与YAP敲低肾成纤维细胞非接触共培养实验中，各组细胞中α-SMA、Vimentin、MMP-1蛋白及mRNA表达差异均无统计学意义。**结论**　SFK可通过阻断STAT3/YAP通路，抑制巨噬细胞-肾成纤维细胞串扰，从而延缓RIF进展。

关键词　肾福康胶囊；肾间质纤维化；巨噬细胞；成纤维细胞；细胞串扰；STAT3/YAP通路

Mechanism of Shenfukang capsule in ameliorating renal interstitial fibrosis by regulating cellular crosstalk via the STAT3/YAP pathway

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ABSTRACT　OBJECTIVE To investigate the mechanism by which Shenfukang capsule (SFK) ameliorates renal interstitial fibrosis (RIF) by regulating macrophage-fibroblast crosstalk via the signal transducer and activator of transcription 3 (STAT3)/Yes-associated protein (YAP) pathway. **METHODS** RAW264.7 macrophages were induced to polarize with transforming growth factor-β$_1$ (TGF-β$_1$). Subsequently, a non-contact co-culture system of macrophages with renal fibroblasts NRK-49F, as well as a non-contact co-culture system of macrophages with YAP-knockdown renal fibroblasts, were established. Cells were treated with low, medium, and high concentrations (4, 8, 16 μg/mL) of SFK, as well as a STAT3 inhibitor (STAT3-I, 1.64 μg/mL) and losartan potassium tablets (positive control, 0.28 μg/mL), for 48 h. After intervention, the protein and mRNA expression levels of CD86, CD163, and STAT3 in macrophages, as well as CD86, F4/80, and STAT3 mRNA, were detected. In co-cultured renal fibroblasts, the protein and mRNA expression levels of α-smooth muscle actin (α-SMA), Vimentin, collagen type Ⅰ (Col-Ⅰ), matrix metalloproteinase-1 (MMP-1), and YAP were detected. In co-cultured YAP-knockdown renal fibroblasts, the protein and mRNA expression levels of α-SMA, Vimentin, and MMP-1 were also detected. **RESULTS** Following TGF-β$_1$ induction, the protein expression levels of CD86, CD163, and STAT3, as well as the mRNA expression levels of CD86, F4/80, and STAT3 in macrophages were significantly increased ($P<0.05$). The conditioned medium from polarized macrophages activated renal fibroblasts, as evidenced by significantly increased protein and mRNA expression levels of α-SMA, Vimentin,

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