Identified the role of CTGF in Osteoarthritis synovial fibroblast (OASF) inflammation

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Connective tissue growth factor (CTGF; also known as CCN2) is an inflammatory mediator, and shows elevated levels in regions of severe injury and inflammatory diseases. CTGF is abundantly expressed in osteoarthritis (OA). OASFs showed significant expression of CTGF, and expression was higher than in normal SFs. OASFs stimulation with CTGF induced concentration-dependent increases in IL-6 expression. CTGF mediated IL-6 production was attenuated by αvβ5 integrin neutralized antibody and apoptosis signal-regulating kinase 1 (ASK1) shRNA. Pretreatment with p38 inhibitor (SB203580), JNK inhibitor (SP600125), AP-1 inhibitors (Curcumin and Tanshinone IIA), and NF-κB inhibitors (PDTC and TPCK) also inhibited the potentiating action of CTGF. CTGF-mediated increase of NF-κB and AP-1 luciferase activity was inhibited by SB203580 and SP600125 or ASK1 shRNA or p38 and JNK mutant. Our results suggest that CTGF increased IL-6 production in OASFs via the αvβ5 integrin, ASK1, p38/JNK, and AP-1/NF-κB signaling pathways. Migration and infiltration of mononuclear cells to inflammatory sites are also playing important role during OA pathogenesis. Monocyte chemoattractant protein-1 (MCP-1/CCL2) is the key chemokine that regulates migration and infiltration of monocytes. Our results showed that MCP-1 was highly expressed in OA synovial fibroblasts (OASFs) as compared to normal SFs. Directly apply OASFs with CTGF increased MCP-1 expression by concentration and time-dependent manner. CTGF mediated MCP-1 production was attenuated by αvβ5 integrin neutralized antibody. Pretreatment with focal adhesion kinase (FAK), MEK, AP-1, and NF-κB inhibitors also inhibited the potentiating action of CTGF. CTGF-mediated increase of NF-κB and AP-1 luciferase activity was inhibited by FAK, MEK, and ERK inhibitors or mutants. In vitro chemotaxis assay showed that OA synovial fluid and supernatants from CTGF treated OASFs increased migration of monocyte. In addition, CTGF-mediated migration was inhibited by the FAK and MEK inhibitor. Taken together, our results indicated that CTGF enhances the migration of monocyte cells by increasing MCP-1 expression through the αvβ5 integrin, FAK, MEK, ERK, and NF-κB/AP-1 signal transduction pathway.