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CTGF induces monocyte chemoattractant protein-1 expression to enhance monocyte migration in human synovial fibroblasts

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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). Migration and infiltration of mononuclear cells to inflammatory sites are plays important role during OA pathogenesis. Monocyte chemoattractant protein-1 (MCP-1/CCL2) is the key chemokine that regulates migration and infiltration of monocytes. However, the effect of CTGF on MCP-1 expression and monocyte migration are largely unknown. 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.