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OBJECTIVE:
Infiltration of neutrophils into the joints plays an important role in bone erosion and articular destruction in rheumatoid arthritis (RA). Neutrophil trafficking during inflammation is a process that involves activation of chemotactic receptors. Recent findings suggest that changes in chemotactic receptor patterns could occur in neutrophils under certain inflammatory conditions. The aim of this study was to evaluate the gain of responsiveness of neutrophils to CCL2 in RA patients and to assess the role of CCL2 in driving neutrophil infiltration into the joints.
METHODS:
Neutrophils were purified from the peripheral blood of patients with RA or from mice with antigen-induced arthritis (AIA). Expression of CCR2 was evaluated using polymerase chain reaction, flow cytometry, and immunofluorescence analyses. In vitro chemotaxis to CCL2 was assayed to evaluate the functional significance of de novo CCR2 expression. The murine AIA model was used to evaluate the in vivo role of CCR2 in neutrophil infiltration into the joints.
RESULTS:
High CCR2 expression and responsiveness to CCL2 were observed in neutrophils from the blood of patients with early RA and in neutrophils from the blood and bone marrow of mice with AIA. Genetic deficiency or pharmacologic inhibition of CCR2 protected against the infiltration of neutrophils into the joints. This protection was not associated with an impairment of the neutrophil chemotactic ability or CXC chemokine production in the joints. Moreover, adoptive transfer of wild-type mouse neutrophils to CCR2-deficient mice restored neutrophil infiltration and the articular mechanical hyperalgesia associated with joint inflammation.
CONCLUSION:
These findings suggest that CCR2 is directly involved in the detrimental infiltration of neutrophils into the joints in patients with RA, showing a new inflammatory role of CCR2 during RA flares or active disease.