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After tissue damage, inflammatory cells infiltrate the tissue and release proinflammatory cytokines. HMGB1 (high mobility group box 1), a nuclear protein released by necrotic and severely stressed cells, promotes cytokine release via its interaction with the TLR4 (Toll-like receptor 4) receptor and cell migration via an unknown mechanism. We show that HMGB1-induced recruitment of inflammatory cells depends on CXCL12. HMGB1 and CXCL12 form a heterocomplex, which we characterized by nuclear magnetic resonance and surface plasmon resonance, that acts exclusively through CXCR4 and not through other HMGB1 receptors. Fluorescence resonance energy transfer data show that the HMGB1-CXCL12 heterocomplex promotes different conformational rearrangements of CXCR4 from that of CXCL12 alone. Mononuclear cell recruitment in vivo into air pouches and injured muscles depends on the heterocomplex and is inhibited by AMD3100 and glycyrrhizin. Thus, inflammatory cell recruitment and activation both depend on HMGB1 via different mechanisms.