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HMGB1 is a nuclear protein that is released or secreted following trauma or severe cellular stress. Extracellular HMGB1 triggers inflammation and recruits leukocytes to the site of tissue damage. We review recent evidence that the ability of HMGB1 to recruit leukocytes may be entirely due to the formation of a heterocomplex with the homeostatic chemokine CXCL12. The HMGB1-CXCL12 heterocomplex acts on the CXCR4 receptor more potently than CXCL12 alone. Notably, only one of the redox forms of HMGB1, the one where all cysteines are reduced (all-thiol), can bind CXCL12. Both HMGB1 containing a disulfide bond between C23 and C45, which induces chemokine and cytokine release by activating TLR4, and HMGB1 terminally oxidized to contain a cysteine sulfonate are inactive in recruiting leukocytes. Thus, the chemoattractant and cytokine-inducing activities of HMGB1 are separable, and we propose that they appear sequentially during the development of inflammation and its resolution. The HMGB1-CXCL12 heterocomplex constitutes a specific target that may hold promise for the treatment of several pathologies.