Venereau E, Casalgrandi M, Schiraldi M, Antoine DJ, Cattaneo A, De Marchis F, Liu J, Antonelli A, Preti A, Raeli L, Shams SS, Yang H, Varani L, Andersson U, Tracey KJ, Bachi A, Uguccioni M, Bianchi ME. (2012). Mutually exclusive redox forms of HMGB1 promote cell recruitment or proinflammatory cytokine release. *J Exp Med*. 209:1519-1528.

Tissue damage causes inflammation, by recruiting leukocytes and activating them to release proinflammatory mediators. We show that high-mobility group box 1 protein (HMGB1) orchestrates both processes by switching among mutually exclusive redox states. Reduced cysteines make HMGB1 a chemoattractant, whereas a disulfide bond makes it a proinflammatory cytokine and further cysteine oxidation to sulfonates by reactive oxygen species abrogates both activities. We show that leukocyte recruitment and activation can be separated. A nonoxidizable HMGB1 mutant in which serines replace all cysteines (3S-HMGB1) does not promote cytokine production, but is more effective than wild-type HMGB1 in recruiting leukocytes in vivo. BoxA, a HMGB1 inhibitor, interferes with leukocyte recruitment but not with activation. We detected the different redox forms of HMGB1 ex vivo within injured muscle. HMGB1 is completely reduced at first and disulfide-bonded later. Thus, HMGB1 orchestrates both key events in sterile inflammation, leukocyte recruitment and their induction to secrete inflammatory cytokines, by adopting mutually exclusive redox states.