



<b>Title</b>	<b>Specific inhibition of cyclooxygenase-2 down-regulates NF-kappaB activation in gastric cancer cells by blocking its nuclear translocation</b>
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## S-GH-1

### Macrophage Migration Inhibitory Factor is an Important Mediator in Gastric Inflammatory Disease

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**Background:** Macrophage migration inhibitory factor (MIF) is an important pro-inflammatory mediator that plays a pivotal role in inflammatory and immune-mediated diseases. However, its pathogenic role in gastric inflammation remains unknown. This study investigates whether MIF plays a role in gastric inflammatory disease.

**Methods:** Expression of MIF was examined in a rat gastric ulcer model induced by acetic acid and the functional role of MIF in acute gastric ulceration was investigated by administration of the anti-MIF antibody.

**Results:** MIF mRNA and protein was markedly upregulated during acute gastric ulcer, which correlated highly with accumulation of macrophages ( $p < 0.001$ ), and, to a lesser extent, of neutrophils ( $p < 0.05$ ) to the site of inflammation. Macrophages, like neutrophils, were a major cell type of the inflammatory cells infiltrating the ulcer base and highly expressed iNOS. Of importance, macrophages, but not neutrophils, were a rich source of MIF during acute gastric ulceration. Blockade of MIF with a neutralizing anti-MIF antibody significantly inhibited the marked upregulation of MIF, TNF $\alpha$ , iNOS, and ICAM-1, and largely reduced macrophage and neutrophil accumulation and activation, thus, reduced ulcer sizes or prevented ulceration.

**Conclusions:** This study has demonstrated that MIF was markedly upregulated during acute gastric ulceration. Results from the functional blocking study indicate that MIF is a key inflammatory mediator and plays a regulatory role in the pathogenesis of gastric inflammation.

## S-GH-2

### Specific Inhibition of Cyclooxygenase-2 Down-Regulates NF-kappaB Activation in Gastric Cancer Cells by Blocking Its Nuclear Translocation

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**Background:** Specific cyclooxygenase-2 (COX-2) inhibitor is known to have anti-inflammatory, and anti-tumor effect. The molecular mechanism for these diverse properties is not known. Since NF-kappaB has been documented to regulate the expression of various genes involved in inflammation and carcinogenesis, we investigate the effect of a specific COX-2 inhibitor SC236 on NF-kappaB activation induced by PMA.

**Methods:** AGS and MKN28 cells were stimulated with PMA with or without SC236 or aspirin. NF-kappaB transcriptional activity was measured with a transiently transfected NF-kappaB luciferase reporter gene. The cytoplasmic and nuclear pool of p65 and of IkappaB-alpha proteins were examined by Western blot analysis.

**Results:** Our results show that SC236 inhibits PMA-induced NF-kappaB activation in gastric cancer cells. SC236 also suppressed PMA-induced nuclear translocation of the p65 subunit of NF-kappaB, and NF-kappaB-directed reporter gene transcription. Unlike aspirin and sulindac, SC236 had no significant effect on PMA-induced IkappaB-alpha phosphorylation and degradation.

**Conclusion:** We have demonstrated a new mechanism in regulation of NF-kappaB by the specific COX-2 inhibitor. The results suggest that inhibition of NF-kappaB activation by SC-236 contribute to its anti-inflammatory and anti-tumor effects.