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, TNFalpha, 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.