Inhibition of the Healing of Gastric Ulcer by Glucocorticoid and Its Relation to Proinflammatory Cytokines

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Gastric ulcer is one of the most common gastrointestinal tract diseases, and has affected humans for centuries. *Helicobactor pylori* infection, use of drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), and stress are some of the known factors that can cause gastric ulcers.

Current treatment of gastric ulcer has 2 main approaches. One is to eliminate the *H. pylori* bacterium using antibiotics. The other approach is to use antacids and/or acid blockers to reduce the level of acid in order to relieve pain and promote healing of inflammatory injuries. Proton pump inhibitors such as omeprazole and cytoprotective drugs including sucralfate and bismuth subcitrate are commonly used to treat gastric ulcer with good results. However, elucidating the detailed mechanisms of gastric ulcer healing remains a major focus for researchers.

Since gastric ulcer is considered to be an inflammatory injury and the healing process involves cell proliferation, epithelial and fibroblast cell-cell interaction, angiogenesis, tissue remodeling and regeneration, many effectors involved in the ulcer healing process have been studied using both *in vivo* and *in vitro* models.[1–3] At present, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, cyclooxygenases (COX), prostaglandins (PGE) and proteases are key players in the control of the healing processes. The dynamic and complicated interactions among these effectors are under extensive investigation. However, the interaction between the glucocorticoids that are used frequently in the management of inflammatory diseases and these effectors is not clear.

Working to dissect the molecular mechanism of gastric protection by modulation of transcription factors and their relation to proinflammatory cytokines, Lahiri et al found that treatment of rats with acetic acid-induced chronic gastric ulcer with pioglitazone, a peroxisome proliferator-activated receptor-γ (PPAR-γ) ligand, resulted in attenuation of gastric injury.[4] The expression of TNF-α and IL-1β in ulcer tissue was increased, while that of PPAR-γ was decreased. After treatment with pioglitazone, the expression of TNF-α and IL-1β was reduced and PPAR-γ was increased in gastric mucosa. These results confirmed the findings of Brzozowski et al, who had observed that pioglitazone not only decreased the gene expression of TNF-α and IL-1β in ulcer tissue, but also reduced the plasma level of TNF-α and IL-1β in rats with acetic acid-induced ulcers.[5] However, an interesting finding by Lahiri et al is that pioglitazone treatment significantly upregulated the level of glucocorticoid receptors and a glucocorticoid receptor antagonist, RU486, inhibited the effect of pioglitazone on TNF-α and IL-1β during the ulcer healing process. This interaction between glucocorticoid receptor and PPAR-γ showed that glucocorticoid and its receptors played important roles in the regulation of expression of proinflammatory cytokines and the consequent healing process of gastric ulcers.

During the gastric ulcer healing process, the proliferation and migration of gastric epithelial cells are regulated by cytokines and hormones. Using human gastric ulcer mucosa biopsy samples for analysis of gene expression of COX-2 and local cytokines, Wu et al found that *H. pylori* infection did not affect the expression of COX-2 and local cytokines in gastric mucosa while patients taking NSAID had decreased COX-2 levels and delayed healing of gastric ulcer.[6] NSAID-induced inflammatory injury in gastric mucosa is

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known to be mediated by the inhibition of COX and PGE2. Endogenously generated PGE2 from upregulated COX-2 at the ulcer margin plays an important role in ulcer healing by various gastric protection factors such as proton pump inhibitor, growth factors and melatonin.[7] The inhibition of PGE2 production by NSAIDs blocks the gastric protection effect and delays healing. It is clear that PGE2 plays a critical role in gastric ulcer healing.

In the October 2009 issue of the *Journal of the Chinese Medical Association*, Luo et al examined the effects of dexamethasone on TNF-α-stimulated epithelial cell migration. Their results clearly showed that TNF-α treatment of RGM-1 rat normal gastric epithelial cells resulted in increased cell migration that was dependent on COX-2 protein expression and the secretion of PGE2 in a time-dependent manner. This TNF-α-stimulated migration was blocked by dexamethasone treatment, with concomitant decreased levels of COX-2 and PGE2.[8] In addition, Luo et al had previously shown that angiogenesis and the expression of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) and PGE2 were increased in gastric ulcer margin tissues using an acetic acid-induced rat gastric ulcer model. Dexamethasone treatment reduced angiogenesis and delayed ulcer healing together with reducing levels of VEGF and PGE2.[1] Moreover, Luo et al showed that dexamethasone treatment resulted in inhibition of ERK1/ERK2 and COX-2 signaling pathways and inhibited the epidermal growth factor-stimulated proliferation of RGM-1 rat gastric epithelial cells.[9] A recent study by Martin et al found that glucocorticoid-inducible protein annexin-1 was significantly increased in gastric margins in the ulcer healing process. Annexin-1 knockout mice had impaired healing response to indomethacin-induced gastric damage.[10] These results together suggest that glucocorticoids may have both positive and negative regulatory functions in the ulcer healing process.

Interaction of epithelial, fibroblast and immune cells and their intercommunication is another important aspect in gastric ulcer healing. At the same time, NSAIDs and cytokines also modulate factors that are involved in tissue remodeling. Iwamoto et al showed clearly that TNF-α, IL-1β and PGE2 treatment significantly increased the expression of urokinase-type plasminogen activator and its receptor in gastric fibroblasts. The IL-1β-induced increase in urokinase-type plasminogen activator and its receptor was dose-dependently inhibited by indomethacin.[2] Luo et al further showed that bFGF stimulated the growth of RGM-1 gastric epithelial cells and dexamethasone blocked this bFGF-stimulated signal transduction and COX-2 expression.[3] These results clearly demonstrate that inhibition of COX-2 by either NSAIDs or glucocorticoids can result in reduced levels of PGE2 in the ulcer area and hinder tissue remodeling and delay ulcer healing.

In conclusion, gastric ulcer healing is a complicated process that is regulated by multiple factors. The balance between ulcer healing promoting factors such as TNF-α, IL-1β, VEGF and PGE2, and ulcer inhibiting drugs such as NSAIDs and glucocorticoids will determine the progression or healing of gastric ulcer. Luo et al's results[8] add to the direct evidence that glucocorticoids have a negative impact not only on the proliferation but also on the migration of gastric epithelial cells. The potential of using glucocorticoid antagonists in combination with ulcer healing drugs is worthy of further investigation.

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