Molecular Mechanism on Healing Process of Peptic Ulcer

Ari Fahrial Syam*, Mohammad Sadikin**, Septelia Inawati Wanandi**, Abdul Aziz Rani*

* Department of Internal Medicine, Faculty of Medicine, University of Indonesia-dr. Cipto Mangunkusumo. Jl. Diponegoro no. 71, Jakarta Pusat 10430, Indonesia. ** Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Indonesia.

Correspondence mail to: ari_syam@hotmail.com.

INTRODUCTION

Peptic ulcer is defined as integrity disturbance of gastric and/or duodenum mucosa which causes local defect or excavation due to active inflammation. Nowadays, it has been widely known that the aggressive and defensive factors play a role in the development of peptic ulcer. With this knowledge, the focus of treatment is primarily to protect the gastroduodenal mucosa and to suppress gastric acid production.

Various things may bring disturbance to aggressive and defensive factors in the stomach. The aggressive factors are gastric acid, pepsin, bile reflux, non-steroidal anti inflammatory drugs (NSAID), Helicobacter pylori bacteria and alcohol; while the defensive factors are mucosal blood flow, surface epithelial cells, prostaglandin, phospholipids or surfactant, mucus, bicarbonate secretion, gastric motility, mucosa impermeability against H+ ion, heat shock protein, and others.1

The common causes of peptic ulcer frequently found in daily practice are infection of Helicobacter pylori, NSAID consumption and stress ulcer. Peptic ulcer, as a result of stress ulcer, is associated with hypoxia that occurs in gastrroduodenal mucosa.

HOW CAN HYPOXIA CAUSE LESIONS ON GASTRIC MUCOSA?

Hypoxia causes reduced mucosal blood flow that consequently decreases the heat shock protein (HSP) and eventually causes defensive factor diminution. This will disturb the balance of aggressive and defensive factors, and in the end will induce lesions formation in gastric mucosa.

Tissue hypoxia will cause several clinical manifestations, varying from erosion to ulcer, when such lesion occurs in the stomach. One of the most frequent manifestations is peptic ulcer.
In condition of extreme stress, such as major surgery or 24 hours after various organ failures, gastroduodenal mucosa damage will occur, i.e. in the form of erosion and small ulcers. If such physiological stress factor continues, bleeding will occur, and lesions will become more apparent in the form of ulcer.²

**AGGRESSIVE AND DEFENSIVE FACTORS OF GASTRIC MUCOSA**

Several cells of gastric mucosa contribute to gastric acid production. The G cells at the antrum of stomach release gastrin hormone. The hormone acts in enterochromaffin-like cells at the corpus of stomach, commanding it to release histamine. Histamine consequently will stimulate parietal cells to secrete acid. Gastrin hormone also directly stimulates parietal cells and increases the performance of enterochromaffin-like cells and parietal cells. G cells, enterechromaffin-like cells and parietal cells are regulated through release of somatostatin peptide inhibitor from somatostatin cells, which reside in the entire gastric area.³

As it has been mentioned previously, prostaglandin is one of important defensive factors for protecting gastric mucosa. Synthesis of prostaglandin depends on activity of cyclooxygenase (COX) enzyme. Two forms of COX can be identified in various cells, i.e. COX-1 and COX-2. COX-1 is responsible for producing prostaglandin, which physiologically has important role to maintain homeostasis functions, such as preserving the integrity of mucosa and mucosal blood flow. NSAID suppresses COX-1 activity, thus forming lesions in gastric mucosa.⁴ ⁵

Aspirin, one of NSAID that has been widely used for several clinical indications, causes damage of gastrointestinal mucosa, induces stress ulcer and exacerbates the previous gastric ulcer. Interaction process between NSAID and stress that may cause lesion of stomach mucosa is shown on figure 4.⁴

**MOLECULAR PROCESS OF ULCER HEALING**

Histologically, an ulcer consists of 2 main structures, which are the margin and the base. The margin has distinctive edge and it is formed by non-necrotizing mucosa which has epithelial component. The base is formed by granulation tissue, consisting of fibroblast, macrophage and proliferative endothelial cells which forms micro vessels.⁶ (Figure 5)

Epithelial cells, layered by glands from the margin of ulcer, produce differentiation, express epidermal growth factor receptor (EGF-R) and actively proliferate. Proliferation is important for ulcer healing because this
Process supplies essential epithelial cells for re-epithelization of mucosa surface and reconstruction of gastric gland.² (Figure 5)

Epithelial cells migrate from the margin of ulcer to granulation tissue inducing re-epithelization of ulcer base. Growth factors, such as epidermal growth factor, hepatocyte growth factor, vascular endothelial growth factor and platelet derived growth factor are major stimulators for cells to go through proliferation, mitosis, migration, and re-epithelization. Re-epithelization is a migration process of epithelial cells from the margin of ulcer, to preserve cells epithelization. It is an important process of ulcer healing, either gastric ulcer or skin ulcer. Cell migration depends on transcription factors and cytoskeleton rearrangement. Cytoskeleton consists of actins filament, microtubules, intermediate filament, focal adhesion and other related proteins. Cytoskeleton plays an important role in cell structure and mobility.³

The process of granulation tissue formation in the base of ulcer takes place in 48-72 hours after ulceration process occurs. Granulation tissue consists of proliferation of connective tissue cells, such as macrophage, fibroblast and proliferative endothelial cells which form micro vessels through angiogenesis process.⁶ The migration from fibroblast to granulation tissue and its proliferation process are induced by growth factor (TGFβ, PDGF, EGF, FGF) and cytokines (TNFα and IL-1), which are descended from inflammation cells, activated endothelial cell and macrophages. Granulation tissue supplies connective tissue cells in order to develop lamina propria and micro vessels, consequently forming micro vascular in the ulcer scar tissue. This angiogenesis process is an important process in peptic ulcer healing. VEGF is an essential regulator of such angiogenesis process.

The ulcer healing process including cell growth, differentiation and migration is regulated by the interaction between extracellular matrix, epithelial cells and endothelial cells, through integration of multiple signals. It is also initiated by growth factor and cytokines, growth inhibitor and extracellular matrix component descendants, as well as transmitted through integrin. Cross talk process among various pathways and signaling systems demonstrates the cell integration to matrix interaction.

CONCLUSION

The ulcer healing process addressed from molecular basis, which has been elucidated in this
article, shows that various genes are involved in the ulcer healing process. Through sequential analysis of gene expression throughout ulcer healing process, these genes are divided into three phases of response genes. These three phases are initial, intermediate and late responses. Initial response genes are activated in 30 minutes to 2 hours, e.g. EGF-R, c-fos, c-jun, egr-1, Sp-1, TFF-2/SP. Intermediate response genes are activated for 6 hours to 2 days, e.g. EGF, bFGF, PDGF and VEGF. Late response genes are activated for 14 days, e.g HGF, ITF, c-met/HGF-R. It is also important to be noticed that several growth factors are produced by epithelial cells, such as EGF, TGFβ; while others, such as PDGF, VEGF, HGF, bFGF and KGF are produced by mesenchymal cells.

REFERENCES