Re-Evaluation of Microcirculatory Endothelial Cell as an Endocrine System of Leptin: Its Significance During Ulcer Healing and *Helicobacter pylori* Infection


**Key words.** Leptin, *Helicobacter pylori*, Acetic acid-induced ulcer, Endothelial cell, Myofibroblast

**Introduction**

The myofibroblast, i.e., activated or modified fibroblast, has been shown to have growth-promoting effects on endothelial cells and be closely associated to angiogenesis [1]. Our recent histochemical studies have revealed a marked increase in the number and size of myofibroblasts in the *Helicobacter pylori* (Hp)-infected human and Mongolian gerbil fundic mucosa [2,3]. On the other hand, the mediators which stimulate the conversion of undifferentiated mesenchymal cells or fibroblasts to the myofibroblasts remain to be clarified. Recently, leptin, a protein product of obese gene expressed primarily by adipocytes, has been shown to be related to angiogenesis [4], and the relation of leptin and myofibroblast is an interesting point, because myofibroblast derives from fat-storing or Ito cells. In this chapter, we discuss the immunohistochemical changes of leptin and its Ob receptors during the healing of

---

1 Department of Clinical Pharmacy and Clinical Sciences, School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan
2 Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
3 Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan
4 Department of Internal Medicine, Kitasato Institute Hospital, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan
acetic acid-induced ulcer in rats and Hp-induced gastric mucosal damage in Mongolian gerbils.

**Alteration of Leptin and Ob Receptors During Healing of Acetic Acid-Induced Ulcer**

Stomach tissues were treated with Zamboni’s fixative, and the indirect immunofluorescence method using monoclonal antibodies against leptin (YC-040, Yanaihara Institute, Shizuoka, Japan) was performed, counterstained with Alexa Fluor 594 phalloidin (Molecular Probes, Leiden, the Netherlands), and observed by confocal laser microscopy (Leica TCS NT). In the control group, leptin immunoreactivity was recognized in the mesenchymal cells in the lamina propria mucosa, i.e., endothelial cells of the microcirculatory network and fibroblasts showing weak alexa phalloidin reactivity. Some of the surface epithelial cells showed very weak leptin immunoreactivity (Fig. 1). Ob-R immunoreactivity was recognized in the mesenchymal cells surrounding the microvascular network as well as in the endothelial cells.

In the acetic acid-treated group, 100% acetic acid was attached to the serosal surface of the stomach for 30 s 7 days before the experiments. One week after the acetic acid-induced gastric ulcer formation, leptin receptor immunoreactivity significantly increased in the endothelial cells and surrounding fibroblasts. In addition, Ob-R immunoreactivity was shown to accumulate in the tip portion of the regenerated fundic glandular mesenchymal cells.

As to the leptin localization in the microcirculation, a relationship to angiogenesis has recently been pointed out, because leptin administration has been reported to bring about new fenestrated blood vessels [4]. Leptin has also been shown to synergistically stimulate angiogenesis with basic fibroblast growth factor and vascular endothelial growth factor, the two most potent and commonly expressed angiogenic factors. As a whole, leptin has been suggested to be closely linked to the regeneration of the gastric mucosa after acetic acid-induced gastric mucosal injury.

**Alteration of Leptin and Ob Receptors in Hp-Induced Gastric Mucosal Damage**

*Helicobacter pylori* infection was evoked in Mongolian gerbils by the oral administration of CagA- and VacA-positive Hp strain (ATCC 43504) 12 months before the experiments. In this group leptin was markedly recognized in the mesenchymal cells including myofibroblasts which showed strong