

Novel mechanism of ghrelin therapy for cachexia

I read with great interest the recent article by Ji-an Chen *et al.*¹ Calorie intake is a major factor for the body composition including muscle mass.² So, increase of food intake by the ghrelin administration *in vivo* could be one of the mechanisms for improvement of muscle wasting. In addition to that, this article showed the novel mechanism, which suggested that ghrelin administration could improve the muscle wasting induced by cisplatin in the skeletal muscle locally.

Anamorelin HCl is a novel, orally active, ghrelin receptor agonist in clinical development for the treatment of cancer cachexia.³ Anamorelin enhanced body weight, tended to improve handgrip strength, increased appetite and quality of life, and decreased inflammatory markers from a phase 2 study.^{4,5} As patients were permitted to receive chemotherapy while on the study, therapeutic effect of anamorelin could be resulted from the effects on the tumor-induced and chemotherapy-induced muscle wasting. Judging from the aspect, the article suggests a novel mechanism that supports the clinical test partially.

Another clinical trial suggested that the adverse effects of cachexia induced by cancer and chemotherapy cannot be recovered by additional nutrition alone.⁶ The trial supports the hypothesis that the appetite regulation would not be enough for cachexia therapy. On the other hand, ghrelin is known to have multi-actions, including not only increase in food intake but also decrease in energy expenditure and inflammation, increase in growth hormone and direct anabolic effect in skeletal muscles and adipose tissue.^{1,7–10} In addition to the increased appetite, some of these effects were confirmed in anamorelin trial.^{4,5} In order to make a better understanding of cachexia pathophysiology and

therapeutic options for cachexia, it is important to understand the therapeutic mechanism of ghrelin and anamorelin in detail. For instance, it remains unclear whether ghrelin and anamorelin directly affected on the muscle cell *in vivo* and which action of ghrelin and anamorelin is the most important for the treatment of cachexia. Further advances are urgently needed.

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