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Ghrelin induces gastric cancer cell proliferation, migration, and invasion through GHS-R/NF-κB signaling pathway

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Abstract This study aims to investigate the roles of ghrelin signaling in human gastric carcinoma cell lines AGS and SGC7901. Effects of ghrelin signaling on CDK6, P53, NF-κB/P65 and MMP2 mRNA and/or protein expression were determined by real-time PCR and western blot. MTT method and flow cytometry were performed to assess the gastric cancer cell proliferation. The SGC7901 cells overexpressing ghrelin were inoculated into nude mice to produce tumors which were measured later. The wound-healing assay and cell invasion assay were used to test the cell migration and invasive ability of gastric cancer. Ghrelin signaling promotes the oncogene CDK6 gene expression and represses the tumor suppressor gene P53 gene expression in gastric cancer. Ghrelin activates NF-κB/P65 signaling pathway through GHS-R in gastric cancer. Ghrelin upregulates the metastasis factor MMP2 expression via GHS-R/NF-κB signaling pathway in gastric cancer cells and promotes tumor cells migration and invasion, suggesting that ghrelin signaling is a critical pathway in cancer metastasis. Ghrelin induces cell proliferation, migration and invasion via GHS-R/NF-κB signaling pathway in gastric cancer cells. Ghrelin treatment must be avoided for gastric cancer patients.

Keywords Ghrelin · Proliferation · Invasion · GHS-R · NF-κB · Gastric cancer

Introduction

Ghrelin, a 28 amino acid peptide hormone with diverse physiological roles, is produced and secreted by gastrointestinal tract [1–3]. Ghrelin participates in many bio-process, including food intake [4], gastric motility [5], and acid secretion of the gastrointestinal tract [6]. Ghrelin is the endogenous ligand for the GH secretagogue receptor (GHS-R) [7]. GHS-Rs are considered as the unique receptors binding to ghrelin until now. Only acylated ghrelin can activate GHS-Rs and release growth hormone to regulate cell growth and proliferation [8]. GHS-Rs can activate several downstream pathways in cells, including calcium mobilization, protein kinase C (PKC) activation, matrix metalloproteinase-2 (MMP2) activity [9, 10]. Ghrelin and the GHS-Rs are expressed in a variety of normal and tumor tissues [11]. While the roles of ghrelin and the GHS-Rs in normal tissues are well studied, their roles in cancer are elusive.

Recent reports reveal that ghrelin is overexpressed in multiple malignant carcinoma cells [12, 13], and plays important roles in tumorigenesis [14]. High expression of ghrelin not only exists in endocrine system cancer like colon [14, 15] and pancreatic adenocarcinoma [16], but also in non-endocrine system cancer such as ovarian [17] and prostate cancer [18]. Nikolopoulos et al. [19] found that ghrelin is also overexpressed in gastrointestinal tract cancer. Even though Monjaraz and co-workers [20] reported that ghrelin inhibits the proliferation of prostate carcinoma cells, most convincing reports have shown that ghrelin is hyperactive in multiple cancers, and stimulates the proliferation of carcinoma cells. Jeffery et al. [21]

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