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Circ_0027599/PHDLA1 suppresses gastric cancer progression by sponging miR-101-3p.1

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Abstract

Background: Pleckstrin homology-like domain family A member 1 (PHLDA1) is a tumor suppressor gene in gastric cancer, but its role regulated by circular RNAs (circRNAs) is not known. CircRNAs are important regulators in cancer growth and progression, however, the molecular roles of circRNAs in gastric cancer are rarely known. The study was aimed to investigate the role of circRNAs in regulating PHLDA1 expression in gastric cancer.

Results: The circRNA expression profile in the gastric cancer tissues by circRNA microarray showed that hsa_circ_0027599 (circ_0027599) was significantly down-regulated in gastric cancer patients and cells when comparing with the controls. Circ_0027599 overexpression suppressed gastric cancer cell proliferation and metastasis. By using bioinformatics tools and luciferase reporter assays, circ_0027599 was verified as a sponge of miR-101-3p.1 (miR-101) and suppressed cancer cell survival and metastasis. It was also verified that PHLDA1 was regulated by circ_0027599 in gastric cancer cells.

Conclusions: The study uncovered that PHLDA1 was regulated by circ_0027599/miR-101, which suppressed gastric cancer survival and metastasis in gastric cancer.

Keywords: Circ_0027599, miR-101-3p.1, Gastric cancer, PHLDA1

Background

Gastric cancer is a common type of cancer from digestive system in the world and there are near one million new gastric cancer cases every year [1, 2]. There are great achievements in gastric cancer therapy and diagnosis, but the prognosis of gastric cancer is still poor and the 5-year survival rate of gastric cancer is below 30% [2]. Therefore, it is pivotal to identify or find new biomarkers and therapeutic targets for improving gastric cancer prognosis. Better elucidating the mechanisms of gastric tumorigenesis and aggressiveness is important for improving the therapeutic efficiency of gastric cancer [2].

Pleckstrin homology-like domain family A member 1 (PHLDA1) protein is encoded by the *PHLDA1* gene [3]. This gene encodes an evolutionarily conserved proline-histidine rich nuclear protein [3]. PHLDA1 could function as an oncogene or a tumor suppressor gene in cancers. In oral cancer, PHLDA1 was overexpressed, which acted as an apoptosis suppressor and was associated with advanced clinical stage of oral cancer [4]. However, in oral squamous cell carcinoma, the expression of PHLDA1 was very low and acted as a tumor suppressor [5]. In colon cancer, PHLDA1 was a putative epithelial stem cell marker in the human small and large intestine and contributes to cell migration and proliferation [6]. In estrogen receptor (ER) positive breast cancer, ER and NF-κB worked together to upregulate PHLDA1 expression directly through enhanced transcription and indirectly through repression of miR-181a and miR-181b [7]. Down-regulation of PHLDA1 protein was found in breast cancer and patients with low PHLDA1 protein levels had shorter disease-free survival and overall survival than patients with high PHLDA1 protein levels, which suggested that it was a strong predictor of poor prognosis for breast cancer patients [8–10]. PHLDA1 may be down-regulated in breast cancer with ER negative [11]. In gastric cancer, PHLDA1 is down-regulated and may be a tumor inhibitor [12]. So, PHLDA1 acts as an oncogene or a suppressor in tumor depending on their background.

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