



Gastric Cancer and the Role of Hedgehog-Interacting Protein One as a Prognostic Marker: The New Paradigm



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Abstract

Hedgehog (Hh) signaling has been linked to foregut development since its initial discovery in *Drosophila*. The mammalian genome expresses three (3) Hh ligands, with sonic hedgehog (Shh) level of expression is highest in the mucosa of the embryonic and adult foregut. Hedgehog signaling aberrant activation is associated with pathological consequences in a range of human cancer. Hedgehog signaling is of pivotal role in homeostasis, neoplastic transformation, and gastrointestinal cancer development. The ability to track these cell types in tumor micro-environment broadens options for the more efficient screening of subjects predisposed to eventually developing gastric cancer as well as to expand opportunities for prophylactic therapy once atrophic gastritis develops. The Hedgehog-interacting protein (HHIP) gene is an essential homolog for multiple developmental processes. However, the expression and clinical correlation of HHIP in gastric cancer (GC) has not thoroughly been investigated. There is need to explore the expression of HHIP in gastric cancer (GC) and evaluate its clinicopathological and functional correlation.

Introduction

Although the incidence of gastric cancer (GC) is reducing worldwide, it is still relatively high in eastern Asia, especially in China [1]. In China, as the dominant types of cancer in the group ages 60 to 74 years, GC is the leading cause of death and is a major public health problem in the digestive system, with 0.50 million deaths and 0.68 million new cases in 2015 [2]. Although prevention efforts are critical to reducing the long-term burden of cancer, any effects will not be seen shortly. For this purpose, improving the access and availability of optimal prognostic and therapeutic biomarker may hold the most significant potential to provide active molecules for clinical management of GC patients, and provide the subdividing reference for clinical patients with different disease risk, as well as early intervention and individualized/precise treatment.

The Hedgehog-interacting protein (HHIP) gene is located on chromosome 4q31.21; it encodes a member of the hedgehog-interacting protein (HHIP) family. As an evolutionarily conserved protein, the hedgehog (HH) proteins are key mediators of many fundamental processes in embryonic development. HH signals can be transducing and regulating by multiple cell-surface receptors [3]. Abnormal activation of the hedgehog signaling pathway is one pivotal cause of the oncogenesis and development of human malignancies. By binding to all three hedgehog proteins, Sonic Hedgehog (SHH), Indian hedgehog (IHH) and Desert hedgehog (DHH), HHIP functions as negative regulators in the hedgehog

pathway and exhibits significant roles in human malignancies [4-7]. Cumulative evidence illustrated the role of HHIP in cancer. For example, down regulation of HHIP in stromal cells increased the proliferation of leukemic cell [4]; HHIP-over expressing attenuated the activation of HGF/MET and HH pathways and made lung adenocarcinoma cells more susceptible to stress conditions [5]. It has been shown that HHIP-over expressing inhibited GC cell proliferation, migration, and invasion [7].

Future Perspective

However, the relationship between HHIP expression and GC has never been illuminated. Prospective studies should be conducted to evaluate the dysregulation of HHIP mRNA and protein in The Human Protein Atlas (THPA) and The Cancer Genome Atlas (TCGA) GC database. We should validate the results in gastric cancer cohort and analyze the correlation of HHIP protein with clinicopathological characteristics and prognosis of GC patient [8]. Furthermore, the role of HHIP in GC cell migration and invasion in vitro should be evaluated.

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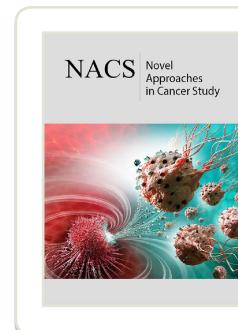
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