Analyses of the expression and prognosis of ILDR1 in human gastric cancer

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ABSTRACT

The worldwide mortality rate of gastric cancer worldwide remains high. Immunoglobulin-like domain containing receptor 1 (ILDR1) belongs to an evolutionarily conserved protein family, and little is known about this gene in gastric cancer. In this paper, we analyzed the expression of ILDR1 and its relationship with clinical outcomes in gastric cancer using publicly available databases. ONCOMINE, GEPIA2, UALCAN, Kaplan–Meier Plotter, cBioPortal, GeneMANIA and LinkedOmics databases were used to analyze the expression, prognostic values, mutations and functional networks of ILDR1 in gastric cancer. We observed that ILDR1 was overexpressed in gastric cancer than in normal tissues. ILDR1 expression was significantly higher in patients with gastric cancer than in normal controls during subgroup analysis based on cancer stage, patient’s race, sex, age, tumor grade, H. pylori infection, histological subtype, and nodal metastasis status. Survival analysis showed that upregulation of ILDR1 expression was significantly associated with poor prognosis. Genomic alterations in ILDR1 were analyzed using cBioPortal, protein–protein interaction (PPI) networks were constructed using GeneMANIA and the co-expressed genes, gene ontology, and pathways of ILDR1 were determined using the LinkedOmics web tool. ILDR1 showed significant differences in expression between gastric cancer and normal tissues and, thus, may be a promising prognostic biomarker for gastric cancer.

1. Introduction

While the incidence and mortality rate of gastric cancer have been observed to be declined consistently on a global scale, the disease remains one of the most commonly malignancy worldwide. Indeed, estimates indicate that over 1 million new cases of gastric cancer were diagnosed in 2018 [1]. Unfortunately, because the disease is often diagnosed only when it has reached advanced stages, gastric cancer is characterized by excess mortality and the third leading cause of cancer-related deaths, with approximately 800,000 deaths globally [1]. With significant progress in the mechanism research and treatment of gastric cancer, emerging treatment options are applied in the clinic, including targeted and immune-based therapies, but the current emerging treatments are not effective for all patients [2]. Hence, it is important to further identify novel diagnostic and prognostic biomarkers that can address the biological complexity, poor prognosis and high recurrence rate of gastric cancer [3].

Immunoglobulin (Ig)-like domain containing receptor 1 (ILDR1) is a putative type I transmembrane protein, which contains an Ig-like extracellular N-terminal domain [4]. This gene encodes three different splice variants; of these variants, two are membrane-spanning and one is cytoplasmic [4]. ILDR1 protein shows tissue-specific expression and is highly expressed in prostate, testes, pancreas, and kidney tissues. IDLR1 has been reported to function as a barrier for cellular tight junctions [5]. Kim NK reported that mutations in ILDR1 disrupt tricellulin, thereby prohibiting the formation of tricellular tight junctions [6]. Most available studies suggest that mutations of the ILDR1 gene are the cause of autosomal recessive hearing impairment and hearing loss [7, 8, 9]. In addition, ILDR1 can mediate the secretion of cholecystokinin secretion through a mechanism that is dependent on fatty acids and lipoproteins [10]. The gene has been shown to be overexpressed in some tumor diseases and may be involved in the formation and development of tumors [11, 12]. These previous studies indicate that ILDR1 may function as a multimeric receptor on the cell surface and that the expression of this gene may be a diagnostic marker for cancer progression. Nevertheless, the role of ILDR1 in cancer, especially in gastric cancer, is largely unknown.

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In this study, we investigated the expression pattern of ILDR1 and its mutations by using data obtained from patients with gastric cancer in various public databases. We also estimated the relationship between ILDR1 gene expression and clinical outcomes in patients with gastric cancer using various online platforms.

2. Material and methods

2.1. Analysis of ILDR1 expression in cancer

We analyzed the mRNA expression levels of ILDR1 in multiple cancers and their corresponding normal tissues using the Oncomine database (https://www.oncomine.org/resource/login.html) [13], Gene Expression Profiling Interactive Analysis 2 (GEPIA2) (http://gepia2.cancer-pku.cn/index) [14], and the UALCAN web tool (http://ualcan.path.uab.edu/index.html) [15]. In GEPIA2, we compared the expression of ILDR1 in tumor samples from The Cancer Genome Atlas (TCGA) with the combined expression data of normal adjacent mucosa in TCGA and normal healthy stomach tissues in Genotype-Tissue Expression (GTEX) [16]. ILDR1 were queried using default settings to get the corresponding results in all analyses. We used the following parameters in the Oncomine database to compare fold-changes in mRNA expression in gastric cancer tissue with that in normal tissue: p-value < 1E-4, fold-change > 2, and gene ranking in the top 10%.

2.2. ILDR1 gene expression and clinicopathological features of gastric cancer

The relationships between the expression of ILDR1 and different gastric cancer characteristics in the TCGA dataset were examined using the UALCAN web tool with default settings [16]. The characteristics of gastric cancer in this study included individual cancer stage, age, histological subtype, race, sex, Helicobacter pylori infection status, and tumor grade. We compared the expression of ILDR1 among different subgroups and normal group.

2.3. The prognostic value of ILDR1 in gastric cancer

The prognostic value of ILDR1 mRNA expression was evaluated using the Kaplan–Meier Plotter (http://kmplot.com/analysis/) [17], which contains gene expression data and survival information of patients with gastric cancer. To analyze the overall survival (OS), first progression survival (FPS), and post-progression survival (PPS) of patients with gastric cancer, we categorized the patients into two groups according to median expression (high expression vs. low expression) and assessed differences by using a Kaplan–Meier survival plot with hazard ratios, 95% confidence intervals, and log rank P values.

2.4. Evaluation of genomic alterations in the ILDR1 gene in gastric cancer

We analyzed genomic alterations in the ILDR1 gene using the cBioPortal web tool (http://www.cbioportal.org/) [18, 19]. The cBioPortal was used to assess the location and frequency of mutations of ILDR1 in TCGA stomach adenocarcinoma. GeneMANIA can construct PPI networks on the basis of physical interaction, coexpression, predicted, colocalization, common pathway, genetic interaction, and shared protein domains. To generate and analyze the gene co-expression network, GeneMANIA was used in this study [20].

2.5. Co-expressed genes, signaling pathways, and gene ontology analyses of ILDR1

LinkedOmics (http://www.linkedomics.org/login.php) is a publicly available portal containing multi-omics data from 32 TCGA cancer types [21]. Co-expression of ILDR1 was analyzed statistically using Pearson’s correlation coefficients, and the results were presented as volcano plots, heat maps, or scatter plots as appropriate. We analyzed gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment using LinkedOmics. The rank criterion was FDR < 0.05, and 500 simulations were performed.

3. Results

3.1. Elevated expression of ILDR1 in gastric cancer and other cancers

We initially evaluated the transcription level of ILDR1 in cancer compared with that in normal samples using the Oncomine database and GEPIA2, which contains information expression data on 33 human cancers from TCGA and GTEX data. In the Oncomine database, upregulation of ILDR1 was observed in gastric cancer and lung cancer, whereas downregulation was observed in colorectal cancer (Figure 1A). GEPIA2 analysis suggested that ILDR1 is highly expressed in 12 types of cancers and lowly expressed in only one type of cancer (Figure 1B).

The mRNA expression level of ILDR1 in the Oncomine analysis was significantly upregulated in patients with gastric cancer in 4 analyses out of 20/2 datasets out of 6. Cho gastric statistics of Oncomine database indicated that ILDR1 is overexpressed in genetic intestinal adenocarcinoma compared with gastric normal tissue with a fold change of 3.229 (Figure 2A), diffuse gastric adenocarcinoma with a fold change of 2.965 (Figure 2B), and gastric mixed adenocarcinoma with a fold change of 3.599 (Figure 2C). DErrico gastric analysis of Oncomine database revealed that ILDR1 was upregulated in gastric intestinal type adenocarcinoma with a fold change of 3.475 (Figure 2D). GEPIA2 analysis also revealed a significant increase in ILDR1 mRNA expression in TCGA gastric cancer compared to that in normal tissues in TCGA and GTEX (Figure 2E). Over-expression of ILDR1 was also verified in the TCGA gastric cancer dataset using the UALCAN tool (Figure 3A).

3.2. Association between ILDR1 expression and the clinical characteristics of gastric cancer patients

The association between ILDR1 mRNA expression and the clinicopathological characteristics of TCGA gastric cancer data was investigated using UALCAN web. ILDR1 expression was significantly higher in gastric cancer patients than in normal controls during subgroup analysis based on cancer stage, patient’s race, sex, age, tumor grade, H. pylori infection, histological subtype, and nodal metastasis status (Figure 3 B-I). In terms of cancer stages, tumor grade and node metastasis, the expression of ILDR1 was higher in GC than that of normal tissue; interestingly, ILDR1 expression was most enhanced in cancer stage 1 of GC patients as compared to any other cancer stage group (Figure 3B, 3F, 3I). The expression of ILDR1 was overexpressed in contrast to normal tissue regardless of gender, age, race, histological subtype, and Helicobacter pylori infection.

3.3. Prognostic value of ILDR1 in gastric cancer

We used the Kaplan–Meier Plotter to assess the association between ILDR1 expression and survival outcomes of gastric cancer cohorts. The patients were separated into two groups according to the median ILDR1 expression level in each cohort. The Kaplan–Meier curve and log-rank test revealed that increased ILDR1 mRNA levels were significantly associated with the overall survival (OS), progression-free survival (FPS), and post-progression survival (PPS) (Figure 4 A–C) in all patients with gastric cancer. Patients with gastric cancer and high ILDR1 mRNA levels had poorer prognosis than those with low ILDR1 mRNA levels.

3.4. Genomic alterations in ILDR1 in gastric cancer

The types and frequencies of ILDR1 alterations were analyzed in a cohort of patients with gastric cancer using cBioPortal. Mutation and amplification of ILDR1 was only found in stomach adenocarcinoma and
tubular stomach adenocarcinoma (Figure 5A). ILDR1 was altered in 7 of 393 (2%) gastric cancer patients (Figure 5B). These alterations included amplification in two cases and mutation in five cases. Six mutations between amino acids 0 and 546 were identified in ILDR1 (Figure 5C). We constructed a network of ILDR1 and the 20 most frequently altered neighbor genes by using GeneMANIA, and results showed that ILDR2,
Figure 3. ILDR1 transcription in different subgroups of patients with gastric cancer (UALCAN). (A) Box plots showing the mRNA expression of ILDR1 in gastric cancer tumors (red plot) and the corresponding normal tissues (blue plot) (UALCAN). ILDR1 mRNA expression level according to individual cancer stage (B), race (C), gender (D), age (E), tumor grade (F), Helicobacter pylori infection (G), histological subtype (H), and nodal metastasis status (I).

Figure 4. Prognostic value of the mRNA expression level of ILDR1 in gastric cancer patients (Kaplan-Meier Plotter). (A) Overall survival (OS), (B) first progression survival (FPS), and (C) post-progression survival (PPS).
LSR, PDZD7, ANKK1, MAVS, RAX2, GGT7, ITCH, PRR11, WWWP1, NEDD4L, GU18235.2, NEDD4, NBPF9, KIR2DL2, PRAC1, CDH26, ZNF492, TP63 and TMEM141 are closely associated with ILDR1 (Figure 5D).

3.5. Analysis of genes co-expressed with ILDR1 in gastric cancer

Genes co-expressed with ILDR1 in gastric cancer were analyzed using LinkedOmics. We found that 2380 genes (dark red dots) were significantly positively correlated with ILDR1 whereas 1696 genes (dark green dots) were significantly negatively correlated with the gene (false discovery rate, FDR < 0.05) (Figure 6A). The top 50 genes that were significantly positively and negatively correlated with ILDR1 were illustrated using heat maps (Figure 6B, 6C). The most significantly co-expressed genes were ICA1, SCNN1A, GPR56, DDR1, PTK6, CLDN7, TTC22, PRR15, and CLDN3.

KEGG pathway analysis of co-altered genes showed enrichment in steroid hormone biosynthesis, tight junction, hematopoietic cell lineage, and ribosome, among others (Figure 6D). GO analysis was performed to categorize the functions into biological processes, molecular functions, and cellular components. ILDR1 and its positively related genes were mainly involved in the regulation of epidermal development and adaptive immune response linked with the top biological process (Figure 6E), apical part of cell and side of membrane in cellular component (Figure 6F), and cell adhesion mediator activity and structural constituent of ribosome in molecular function (Figure 6G).

4. Discussion

Gastric cancer patients are often diagnosed at advanced stages of the disease, which often results in poor treatment effects and high mortality. Because of the high heterogeneity of gastric cancer, current targeted therapy is only effective for a small percentage of these patients. Thus, the development of new therapeutic strategies to improve the survival rate of these patients is of great importance. To identify new biomarkers of gastric cancer, we performed bioinformatics analysis of ILDR1 by using public data to guide future research on gastric cancer.
Epithelial–mesenchymal transition (EMT) is a key process in cancer progression and is characterized by the loss of epithelial markers, including E-cadherin and tight junction proteins [22]. Tight junction proteins are a hallmark of intracellular signaling pathways and can promote EMT and tumorigenesis. Extensive research has shown that the expression pattern of tight junction proteins is correlated with the prognosis of cancer patients [23, 24]. Therefore, these proteins may serve as prognostic factors and therapeutic targets for gastric cancer [25].

ILDR1 belongs to an evolutionarily conserved protein family, namely, the angulin protein family, which is localized at tight junctions and...
includes immunoglobulin-like domain-containing receptor 2 and lipopolysis-stimulated lipopeptin receptor [26]. ILDR1 was first identified via a lymphoma-specific subtraction strategy and was localized to chromosome 3q21.1 [4]. Liu showed that ILDR1 binds to the splicing factors TRA2A, TRA2B, and SRSF1 and translocates to the nucleus in the presence of splicing factors to affect alternative splicing of tubulin delta 1, IQ motif containing B1, and proteocadherin 19 [27]. Wendy found that LSR changes its expression pattern in the colon and kidney of ILDR1 knockout mice and that this change in tissue localization compensates for the loss of ILDR1 and maintains the barrier function of the epithelia [28]. Most of the available literature suggests that ILDR1 plays a crucial role in epithelial barrier function in the ear and is associated with non-syndromic sensorineural hearing loss [7, 8, 9]. Relative to other genes, ILDR1 has been less investigated in other diseases, including cancers. Zagaria revealed that ILDR1 is overexpressed due to a rare recurrent chromosomal translocation (3;11)(q13;q14) in two patients with myelodysplastic syndromes [11]. Emami NC conducted an integrated study of prostate cancer genetic etiology and confirmed that ILDR1 is highly expressed in prostate tissue and related to the B7/CD28 family of T cell immune checkpoint markers [12].

The present systematic study used bioinformatics analyses of public datasets to demonstrate the prognostic value of ILDR1 in gastric cancer for the first time. Our data revealed a significant upregulation of ILDR1 in gastric cancer tissues, as well as a negative correlation of its expression levels with the OS, FPS, and PPS of gastric cancer patients. Significant associations were revealed between ILDR1 expression and various clinicopathological characteristics in TCGA gastric cancer cohort. In the future, further in-depth studies are required to explore the detailed molecular mechanisms of ILDR1 in gastric cancer patients. Changes in gene expression may result from genetic mutations, copy number alterations, and epigenetic control in cancer cells. Analysis of gastric datasets from TCGA revealed two cases of amplification and five cases of mutations. Based on these findings, we speculate that the mutation of this gene occurs in only a small number of gastric cancers.

Finally, we used the LinkedOmics web tool to determine the co-altered genes, pathways, and gene ontology associated with ILDR1 in gastric cancer. CLDN7 and CLDN3, which are members of the claudin family and are among the most significantly co-expressed genes, are integral membrane proteins and components of tight junction strands, and genes have been associated with multiple malignancies [29, 30, 31]. The most significantly positively correlated KEGG pathway was steroid hormone biosynthesis, a complex process in which cholesterol is converted into steroid hormones with the participation of various enzymes and cofactors [32]. The most significantly negatively correlated KEGG pathway was the hematopoietic cell lineage, which allows cells to undergo either self-renewal or differentiation into multiline age-committed progenitor cells [33]. GO analysis of biological processes revealed that the most enriched ontology terms were epidermis development, digestion, adaptive immune response, regulation of leukocyte activation, and ribonucleoprotein complex biogenesis. These results suggest the widespread impact of ILDR1 on physiological and pathological processes.

In this study, we systematically analyzed the expression and prognostic value of ILDR1 in gastric cancer. Our results indicate that the increased expression of ILDR1 in gastric cancer may play an important role in gastric tumorigenesis. Thus, ILDR1 may be a therapeutic target for gastric cancer.

Declarations

Author contribution statement

Li Wang: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Guodong Song and Yong Wang: Conceived and designed the experiments.

Rujun Zhai: Performed the experiments; Analyzed and interpreted the data.

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Data availability statement

Data included in article/ supp. material/ referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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