FGFR1 expression defines clinically distinct subtypes in pancreatic cancer

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Abstract
Background: The clinical significance of fibroblast growth factor receptor 1 (FGFR1) protein expression in pancreatic cancer is largely unknown. In this study, we aimed to investigate the clinical significance of FGFR1 expression in pancreatic cancer.

Methods: First, we investigated the relationship between FGFR pathway gene expression and clinicopathological data in three pancreatic cancer cohorts containing 313 cases. Subsequently, to confirm the findings from the discovery cohorts, we performed immunohistochemistry (IHC) of FGFR1 protein in a validation cohort of 205 pancreatic cancer cases.

Results: In discovery cohort 1, FGFR1 and Klotho beta (KLB) overexpression was associated with low tumor stage (P < 0.05), low tumor grade (P < 0.05), and better overall survival. Multivariate analysis predicted FGFR1 (P < 0.05) as a prognostic factor for better overall survival. In discovery cohorts 2 and 3, only FGFR1 overexpression was associated with better overall survival (P < 0.05). In the validation cohort, there were 15.7% and 61% strong and weak/moderate FGFR1-positive cases, respectively. FGFR1-positive cases showed better overall survival than FGFR1-negative cases (P < 0.05). Furthermore, multivariate analysis revealed FGFR1 positivity as an independent prognostic factor for better overall survival in pancreatic cancer patients (hazard ratio 0.677, 95% confidence interval 0.471–0.972, P = 0.035).

Conclusions: FGFR1 expression, as estimated by IHC, may be used to define clinically distinct subtypes in pancreatic cancer. Moreover, FGFR1-based subclassification of pancreatic cancer may lead to new therapeutic approaches for the FGFR1-positive subtype.

Keywords: FGFR1, Classification, Prognosis, Pancreatic cancer, Anti-FGFR1 therapy

Background
The fibroblast growth factor receptor (FGFR) pathway is one of the major carcinogenic pathways in cancer [1–5]. Genetic deregulation of fibroblast growth factors and their receptors plays an important role in the initiation and progression of different types of cancer [6–9].

Helsten and colleagues [10] reported that the FGFR pathway is the third most frequently altered pathway in cancer, after the p53 and KRAS pathways. Accordingly, cancer drugs targeting the FGFR pathway have been tested in multiple cancers [1, 11]. Currently, phase I and phase II clinical trials of dovitinib, lucitanib, ponatinib, nintedanib, and pazopanib are underway in different solid tumors to block FGFR pathway activation [12–16].

In pancreatic cancer, aberrations in the FGFR pathway, particularly FGFR1 overexpression, have been reported. According to The Cancer Genome Atlas (TCGA) study on pancreatic cancer [17], FGFR1 is upregulated in approximately 5% of pancreatic cancers. Lehnen and colleagues [18] reported that FGFR1 was expressed in 4% (5/125) of pancreatic cancer cases, and
Expression of FGF19, cancers were analyzed (Additional file 1: Figure S1). The discovery cohort 3, RNA-seq data of 179 pancreatic and merck-NM_175737_a_at) was analyzed. In was estimated using RNA-seq data with a z-score > 2.0. KLB NM_002011_at), and merck2-NM_001174063.1), merck-NM_000604_at, merck-NM_023110_a_at, and FGFR1 (probe ID: merck-NM_019113_at), (probe IDs: merck-NM_005117_at), FGF19 (the FGFR4 ligand), and FGFR2 (the FGFR1 ligand), were selected for the analysis. Data from discovery cohort 1, consisting of 65 pancreatic cancer patients, were downloaded from the Gene Expression Omnibus database (Accession # GSE62452). Clinical features of discovery cohort 1, including stage, grade, and overall survival information, can be found in Additional file 1: Table S1. LogR expression values of data from the discovery cohort were generated from the Affymetrix Human Gene 1.0 ST array. In discovery cohort 1, the expression status of FGF19 (probe ID: 7950023), FGF21 (probe ID: 8030105), FGFR1 (probe ID: 8150318), FGFR4 (probe ID: 8110265), and KLB (probe ID: 8094679) were screened for the analysis. In discovery cohort 1, the expression status of FGF19 (probe ID: 7950023), FGF21 (probe ID: 8030105), FGFR1 (probe ID: 8150318), FGFR4 (probe ID: 8110265), and KLB (probe ID: 8094679) were screened for the analysis. In discovery cohort 2, the expression status of FGF19 (probe ID: 7950023), FGF21 (probe ID: 8030105), FGFR1 (probe ID: 8150318), FGFR4 (probe ID: 8110265), and KLB (probe ID: 8094679) were screened for the analysis. In discovery cohort 2, LogR expression values were generated using the gene expression and clinicopathological data from three pancreatic cancer cohorts containing 313 cases. Then, to confirm the findings from the discovery cohorts, we performed immunohistochemistry (IHC) targeting FGFR1 protein in a validation cohort of 205 pancreatic cancer cases.

Methodology
Data collection and screening
The overall study design is described in Additional file 1: Figure S1. Five FGFR pathway genes that are frequently dysregulated in multiple cancers, namely FGFR1, FGFR4, KLB (an FGFR co-receptor), FGF19 (the FGFR4 ligand), and FGFR2 (the FGFR1 ligand), were selected for the analysis. Data from discovery cohort 1, consisting of 65 pancreatic cancer patients, were downloaded from the Gene Expression Omnibus database (Accession # GSE62452). Clinical features of discovery cohort 1, including stage, grade, and overall survival information, can be found in Additional file 1: Table S1. LogR expression values of data from the discovery cohort were generated from the Affymetrix Human Gene 1.0 ST array. In discovery cohort 1, the expression status of FGF19 (probe ID: 7950023), FGF21 (probe ID: 8030105), FGFR1 (probe ID: 8150318), FGFR4 (probe ID: 8110265), and KLB (probe ID: 8094679) were screened for the analysis. In discovery cohort 2, LogR expression values were generated using the RSTA Custom Affymetrix 2.0 array (Additional file 1: Figure S1). The expression status of FGF19 (probe ID: merck-NM_005117_at), FGF21 (probe ID: merck-NM_019113_at), FGFR1 (probe IDs: merck-NM_000604_at, merck-NM_023110_a_at, and merck2-NM_001174063.1), FGFR4 (probe ID: merck-NM_0020111_at), and KLB (probe IDs: merck-BC033021_at and merck-NM_175737_a_at) was analyzed. In discovery cohort 3, RNA-seq data of 179 pancreatic cancers were analyzed (Additional file 1: Figure S1). The expression of FGF19, FGF21, FGFR1, FGFR4, and KLB was estimated using RNA-seq data with a z-score > 2.0. All detailed information from the pancreatic cancer dataset is available in the public cBioPortal database (Pancreatic Adenocarcinoma, TCGA, provisional).

Statistical analysis
The associations of FGE19, FGF21, FGFR1, FGFR4, and KLB expression with clinical features, including stage, grade, and survival, were calculated using χ² and Fisher exact tests for the three discovery cohorts. Survival analysis was performed using Kaplan–Meier curves with log-rank (Mantel–Cox) P values. Cox proportional hazard regression and univariate and multivariable analyses were used to evaluate the association between gene expression and survival. Since the sample sizes of the discovery cohorts were small, the multivariable Cox regression model may have led to the overfitting of the data. Therefore, each gene was analyzed separately in combination with the clinical features in multivariable analysis. The hazard ratio (HR) and 95% confidence interval (CI) were also calculated for each factor. P values were two-sided, and P < 0.05 was considered to be statistically significant. All statistical analyses were performed with SPSS 21.0 software (IBM, Armonk, NY, USA).

Validation in 205 patients using IHC
Immunohistochemical labeling was performed in a validation cohort of 205 pancreatic cancer patients at the immunohistochemistry laboratory of the Department of Pathology, Asan Medical Center. In brief, 4-μm-thick sections were deparaffinized with xylene and hydrated in an ethanol series. Endogenous peroxidase activity was blocked by incubation in 3% H₂O₂ for 10 min, and then heat-induced antigen retrieval was performed. Primary antibodies were used with a Benchmark autostainer (Ventana Medical Systems, Tucson, AZ, USA) in accordance with the manufacturer’s protocol. Sections were incubated at room temperature for 32 min in primary antibody for FGFR1 (rabbit polyclonal, 1:100; Abnova, Taipei, Taiwan). The sections were then labeled with an automated immunostaining system and processed with an iView DAB detection kit (Benchmark XT, Ventana Medical Systems). Immunostained sections were lightly counterstained with hematoxylin, dehydrated in ethanol, and cleared in xylene. Immunoreactivity was interpreted by light microscopic examination and independently evaluated by two pathologists, coauthors of this study (Y.N.S. and S.M.H.), who were blind to the clinicopathologic information. Cases were categorized as positive, weak positive, and negative.

Results
Expression analysis of FGFR genes in discovery cohort 1
The logR expression values of five FGFR-related genes were dichotomized according to their median expressions (Additional file 1: Figure S2). FGFR1 had the
highest expression, with a median enrichment of 5.922, whereas FGFR21 had the lowest expression, with a median enrichment of 2.884. The expression level of FGFR4 was significantly correlated with those of FGF19 (Pearson Correlation = 0.30, P = 0.014), KLB (Pearson Correlation = 0.41, P = 0.001), and FGFR1 (Pearson Correlation = 0.29, P = 0.02). Notably, a strong correlation was observed between FGFR1 and KLB expression (Pearson’s correlation = 0.60, P < 0.001). FGFR21 expression was not correlated with that of any of the other four genes.

Association between FGFR genes and clinical features in discovery cohort 1
According to Fisher’s exact test results, overexpression of FGFR4 (P < 0.001) and KLB (P = 0.005) were significantly associated with a low tumor grade. Overexpression of FGFR1 was significantly associated with both low tumor grade (P = 0.023) and low tumor stage (P = 0.023). FGF19 and FGFR21 overexpression did not show any association with clinical features.

Next, the association between FGFR1, FGF21, FGFR1, FGFR4, and KLB overexpression and the overall survival of pancreatic cancer patients was evaluated. According to univariate analysis, FGFR1 overexpression (HR 0.475, 95% CI 0.277–0.817, P = 0.007) and KLB overexpression (HR 0.536, 95% CI 0.318–0.903, P = 0.019) were significantly associated with better overall survival. In addition, FGFR4 overexpression showed a trend toward better overall survival, but it did not reach statistical significance (HR 0.610, 95% CI 0.370–1.008, P = 0.054) (Table 1). Kaplan–Meier curves also showed a clear separation between patients with high and low expression of FGFR1 (Fig. 1a), KLB (Fig. 1b), and FGFR4 (Fig. 1c). Furthermore, multivariable analysis was performed along with the prognostic factors (tumor stage and tumor grade) associated with pancreatic cancer. FGFR1 expression was the only prognostic factor for better overall survival (HR = 0.524, 95% CI 0.281–0.977, P = 0.042) (Table 2).

Table 1 Univariate analysis of FGFR-related genes for overall survival in cohort 1

| Gene name | Hazard ratio (95% CI) | P value |
|-----------|-----------------------|---------|
| FGFR1     | 0.475 (0.277–0.817)    | 0.007   |
| FGFR4     | 0.610 (0.370–1.008)    | 0.054   |
| FGF19     | 1.029 (0.630–1.682)    | 0.908   |
| FGFR21    | 0.853 (0.515–1.413)    | 0.537   |
| KLB       | 0.536 (0.318–0.903)    | 0.019   |

Expression and survival analysis of FGFR genes in discovery cohort 2
The potential significance of the FGFR-pathway genes was further evaluated in cohort 2. Similarly, logR expression values of the five FGFR-related genes were dichotomized according to their medians (Additional file 1: Figure S3). Consistent with the results in cohort 1, the highest median expression was observed for FGFR1. Of note, of all five genes, only patients with FGFR1 expression had significantly better overall survival by Kaplan–Meier analysis (Fig. 1d).

Expression and survival analysis of FGFR genes in discovery cohort 3
The TCGA pancreatic cancer dataset, which includes data from 179 pancreatic cancer patients, was selected as cohort 3. Overexpression of FGFR1, KLB, FGF19, FGFR4, and FGFR21 was identified in 7 (4%), 7 (4%), 6 (3%), 5 (2.8%), and 2 (1.1%) patients, respectively (Additional file 1: Figure S4A). Notably, only FGFR1 overexpression was significantly associated with better overall (P = 0.0158) and disease-free survival (P = 0.006) (Additional file 1: Figure S4B).

FGFR1 immunolabeling in the validation cohort
Representative IHC images of FGFR1-positive and -negative cases from the validation cohort are depicted in Fig. 2a, b, respectively. Thirty (15.7%) cases were strongly FGFR1-positive, and 118 (61%) were moderately/weakly positive. Forty-three cases (22.5%) were negative for FGFR1 expression.

Univariate and multivariate analysis for overall survival
According to the statistical analysis, no significant associations were observed between FGFR1 positivity and poor clinicopathological features, including bile duct invasion, duodenal invasion, perineural invasion, lymphovascular invasion, and lymph node metastasis. However, in univariate analysis, overall survival was significantly associated with age (HR 1.451, 95% CI 1.073–1.961, P = 0.016), bile duct invasion (HR 1.469, 95% CI 1.099–1.963, P = 0.009), lymphovascular invasion (HR 1.455, 95% CI 1.088–1.944, P = 0.011), lymph node metastasis (HR 2.495, 95% CI 1.811–3.436, P < 0.001), and FGFR1 expression (HR 0.590, 95% CI 0.415–0.839, P = 0.003) (Table 3). Furthermore, in the multivariate analysis, age (HR = 1.587, 95% CI 1.130–2.230, P = 0.008), bile duct invasion (HR 1.657, 95% CI 1.211–2.269, P = 0.002), lymph node metastasis (HR 2.360, 95% CI 1.665–3.344, P < 0.001), and FGFR1 expression (HR 0.677, 95% CI 0.471–0.972, P = 0.035) were predicted as significant prognostic biomarkers for
overall survival in pancreatic cancer. Notably, FGFR1 expression was the only prognostic biomarker for better overall survival (i.e., HR < 1) (Table 3).

**Discussion**

The main finding of this study is that FGFR1 protein expression defines clinically distinct subtypes of pancreatic cancer. FGFR1-positive cases showed better overall survival than FGFR1-negative cases. To the best of our knowledge, this study is the first to demonstrate the clinical significance of FGFR1 overexpression in pancreatic cancer.

The clinical significance of FGFR1 overexpression has not been thoroughly investigated in pancreatic cancer for two reasons: (1) KRAS mutation, which does not have any targeted solution, is almost universal in pancreatic cancer; (2) FGFR1 overexpression is not exclusive with KRAS mutation [17, 20]. Although, recent genomic and transcriptomic studies identified new subtypes of PADC, but prognostic role of FGFR1 is not highlighted. For instance, Bailey and colleagues demonstrated that Kras\textsuperscript{G12D/+};Trp53\textsuperscript{R172H} mutant subtype (containing group of genes with FGFR1 expression) showed less aggressive clinical outcome compared to Kras\textsuperscript{G12D/+};Trp53\textsuperscript{R172H};TAp63\textsuperscript{R110H} mutant.

![Kaplan–Meier survival analyses of FGFR1, FGFR4, and KLB in pancreatic cancer cohorts 1 and 2. Green represents expression ≥ the median, while blue represents expression < the median. Overall survival by expression of FGFR1 (a), KLB (b), and FGFR4 (c) in cohort 1. Overall survival by expression of FGFR1 (d) in cohort 2. FGFR fibroblast growth factor receptor, KLB klotho beta](image)
subtype (containing group of genes without FGFR1 expression) in pancreatic cancer [21]. Furthermore, another transcriptomic profiling study classified PADC patients into L1–L6 subtypes. Interestingly, the L5 subtype which showed most favorable clinical outcome from the rest of the molecular subtypes was also enriched with FGFR1 pathway related genes [22].

Our finding can have immediate clinical ramifications. In pancreatic cancer, FGFR1 is the most frequently altered receptor of the four FGFR receptors, and, using readily applicable immunohistochemistry methods, FGFR1 can be used to classify pancreatic cancer into FGFR1-positive and -negative subtypes. As FGFR1-positive pancreatic cancer has better prognosis, FGFR1 can be used as an independent predictor of better overall survival in pancreatic cancer patients. Moreover, FGFR1-based subclassification of pancreatic cancer may lead to new therapeutic approaches for the FGFR1-positive subtype. For example, it may be possible to target FGFR1 using antibody in strongly FGFR1-positive pancreatic cancer, in the same manner in which HER2 is targeted using anti-HER2 antibodies in HER2-positive breast cancer.

Only a few previous studies have examined FGFR1 expression in pancreas cancers, and they reported a wide range of FGFR1 positivity (4–57%) [18, 19, 23]. Lehnen and colleagues observed that 4% (5/125) of pancreatic cancer patients showed FGFR1 expression, and amplification was noted in 2.6% of the cases (4/155) [18]. In contrast, Kornmann et al. reported that 57% (4/7) of pancreas cancers showed immunoreactivity for FGFR1 IIIc [19]. Our study is unique in that we evaluated FGFR1 expression based on the intensity of FGFR1 labeling, and we observed strong FGFR1 positivity in 15.7% (30 cases) and moderate/weak FGFR1 positivity in 61.8% (118 cases) in a cohort of Korean pancreatic cancer patients.

### Table 2 Multivariate analysis of FGFR-related genes for overall survival in cohort 1

| Factors       | Hazard ratio (95% CI) | P value |
|---------------|-----------------------|---------|
| **FGFR1**     |                       |         |
| FGFR1 (high vs. low) | 0.524 (0.281–0.977)  | 0.042   |
| Tumor grade (1, 2 vs. 3, 4) | 0.585 (0.337–1.016)  | 0.057   |
| Tumor stage (1, 2 vs. 3, 4) | 0.814 (0.427–1.548)  | 0.530   |
| **FGFR4**     |                       |         |
| FGFR4 (high vs. low) | 0.975 (0.516–1.842)  | 0.937   |
| Tumor grade (1, 2 vs. 3, 4) | 0.514 (0.263–1.002)  | 0.051   |
| Tumor stage (1, 2 vs. 3, 4) | 1.109 (0.614–2.001)  | 0.732   |
| **KLB**       |                       |         |
| KLB (high vs. low) | 0.640 (0.375–1.093)  | 0.102   |
| Tumor grade (1, 2 vs. 3, 4) | 0.547 (0.316–0.945)  | 0.031   |
| Tumor stage (1, 2 vs. 3, 4) | 1.082 (0.606–1.931)  | 0.791   |

*Fig. 2* Immunohistochemistry and Kaplan–Meier survival analysis of FGFR1 in the validation cohort of 205 pancreatic cancer patients. a, b Represent immunohistochemistry results of FGFR1-positive and -negative cases, respectively. c Overall survival of pancreatic cancer patients in the discovery cohort with high and low FGFR1 (c). FGFR: fibroblast growth factor receptor.
Using only the strong FGFR1 expression group, the frequency of FGFR1 labeling was higher than the results of Lehnen and colleagues’ study. However, if we include moderate/weak FGFR1 labeling, the frequency was similar to that of Kornmann’s study. This wide range of FGFR1 labeling results may be plausibly explained by different FGFR1 expression rates based on different ethnic groups (Korean and Western populations), use of different antibody clones, or different cutoffs for FGFR1 labeling.

**Conclusion**

In summary, FGFR1 overexpression, evaluated by IHC, may be used as a prognostic biomarker for overall survival in pancreatic cancer patients. Moreover, FGFR1 overexpression may define a subset of pancreatic cancer, leading to new therapeutic approaches.

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**Table 3** Cox regression analysis for overall survival in 205 pancreatic cancer patients

|                           | P value | HR    | 95.0% CI for HR | P value | HR    | 95.0% CI for HR |
|---------------------------|---------|-------|-----------------|---------|-------|-----------------|
| Age, years (≥ 60 vs. < 60) | 0.016   | 1.451 | 1.073 1.961     | 0.008   | 1.587 | 1.130 2.230     |
| Gender                    | 0.235   | 1.191 | 0.892 1.591     |         |       |                 |
| Tumor size, cm (≥ 2 vs. < 2) | 0.241 | 1.534 | 0.751 3.135     |         |       |                 |
| Differentiation (well/moderate vs. poor) | 0.076 | 1.428 | 0.964 2.115     |         |       |                 |
| Extension (confined vs. peripancreatic soft tissue) | 0.061 | 1.898 | 0.970 3.714     |         |       |                 |
| Bile duct invasion (absent vs. present) | 0.009 | 1.469 | 1.099 1.963     | 0.002   | 1.657 | 1.211 2.269     |
| Duodenum invasion (absent vs. present) | 0.074 | 1.303 | 0.975 1.742     |         |       |                 |
| Lymphovascular invasion (absent vs. present) | 0.011 | 1.455 | 1.088 1.944     | 0.098   | 1.320 | 0.950 1.834     |
| Perineural invasion (absent vs. present) | 0.086 | 1.403 | 0.953 2.064     |         |       |                 |
| Lymph node metastasis (absent vs. present) | < 0.001 | 2.495 | 1.811 3.436     | < 0.0001 | 2.360 | 1.665 3.344     |
| Tumor stage<sup>a</sup> | 0.059   | 1.382 | 0.988 1.933     |         |       |                 |
| FGFR1 (positive vs. negative) | 0.003   | 0.590 | 0.415 0.839     | 0.035   | 0.677 | 0.471 0.972     |

* Tumor stage was not included for multivariate analysis because tumor size, in addition to bile duct and duodenal invasion and extension (confined vs peripancreatic soft tissue extension), are components of T stage

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**Acknowledgements**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Availability of data and materials**

The links of data are mentioned in “Methodology” section.

**Consent for publication**

Not applicable.

**Ethics approval and consent to participate**

Not applicable.

**Funding**

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare (HI16C1985) and by a grant from Gachon University Gil Medical Center (FRD2016-20).

**Publisher’s Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 21 September 2018   Accepted: 12 December 2018

**Published online** 28 December 2018

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