Expression of Alpha-type Platelet-derived Growth Factor Receptor–influenced Genes Predicts Clinical Outcome in Glioma

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Abstract

BACKGROUND: Alpha-type platelet-derived growth factor receptor (PDGFRα) is a cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family. PDGFRα plays an important role in the regulation of several biological processes and contributes to the pathophysiology of a broad range of human cancers, including glioma. Here, we hypothesize that the genes directly or indirectly influenced by PDGFRα might be useful for prognosis in glioma. METHODS: By comparing the genome-wide gene expression pattern between PDGFRα+ and PDGFRα−/− cells from human oligodendrocyte progenitor, we defined the genes potentially influenced by PDGFRα. RESULTS: The PDGFRα-influenced genes are strongly associated with cancer-related pathways. We subsequently developed a prognostic gene signature derived from the PDGFRα-influenced genes. This gene signature is able to predict clinical outcome of glioma. This signature is also independent of traditional prognostic factors of glioma. Resampling tests indicate that the prognostic power of this gene signature outperforms random gene sets selected from human genome. More importantly, this signature is superior to the random gene signatures selected from glioma related genes. CONCLUSIONS: Despite the absence of clear elucidation of molecular mechanisms, this study suggests the vital role of PDGFRα in carcinogenesis. Furthermore, the PDGFRα-based gene signature provides a promising prognostic tool for glioma and validates PDGFRα as a novel and effective therapeutic target in human cancers.

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Introduction

Alpha-type platelet-derived growth factor receptor (PDGFRα) is a cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family, which is encoded by the gene PDGFRA. Platelet-derived growth factor receptors (PDGFRs) are a family of catalytic receptors that play important roles in the regulation of several biological processes including embryonic development [1], angiogen-
WHO grade III, such as anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, and anaplastic ependymoma, and WHO grade IV, such as glioblastoma. Amplification of PDGFRα has been observed in both low-grade [7] and high-grade [8,9] gliomas. In addition, overexpression of the gene PDGFRα in glioma at the time of the first diagnosis was found to be associated with poor overall survival [10]. Inhibition of PDGFRs has been shown to slow down glioma cell growth in experimental models [1]. Therefore, inhibition of PDGFR signaling has become one of the targeted therapeutic strategies for glioma [11].

Although the pathological function of PDGFRs in gliomas remains controversial, coexpression module based on the gene PDGFRα has been developed to enable the molecular classification of glioma for clinical diagnosis [12]. It is also reasonable to hypothesize that the genes directly or indirectly influenced by PDGFRα might be useful for prognostic purpose in glioma. Here, we utilized high-throughput gene expression data to identify the genes potentially influenced by PDGFRα in glioma. We compared the genome-wide gene expression pattern between PDGFRα⁺ and PDGFRα⁻ cells from human oligodendrocyte progenitor [13]. The genes deregulated in PDGFRα⁺ cells were considered as PDGFRα influenced genes. Gene ontology analysis indicates that the PDGFRα-influenced genes are strongly associated with cancer-related pathways. We subsequently developed a prognostic gene signature derived from the PDGFRα influenced genes. This gene signature is able to predict clinical outcome in two independent glioma cohorts. This signature is also independent of traditional prognostic factors in glioma. Our study suggests that the PDGFRα-influenced genes potentially serve as biomarkers and therapeutic targets in clinical and pharmacological contexts, respectively.

**Materials and Methods**

**Gene Expression Data Sets**

We obtained the gene expression data for both PDGFRα⁺ and PDGFRα⁻ oligodendrocyte progenitor cells from the Gene Expression Omnibus (GEO) database [14] (GEO accession: GSE29368), which was based on the Affymetrix Human Genome U133 Plus 2.0 Array [13]. In the original study, the PDGFRα⁺ cells were defined based on expression of the PDGFRα epitope CD140a, which were sorted from the fetal human forebrain using FACs [13]. The gene expression data from University Hospital of Coimbra (UHC), Portugal (GEO accession: GSE43289) [15] and Henry Ford Hospital (HFH), USA (GEO accession: GSE4290) [16] were used to identify the glioma related genes, in which the gene expression level was significantly correlated with WHO glioma grade. Both the UHC and HFH data sets were based on the Affymetrix Human Genome U133 Plus 2.0 Array. The gene expression data from Shanghai Changzheng Hospital (SCH), China (GEO accession: GSE19728) [17], was used to validate the relationship between glioma grade and our PDGFRα-influenced gene signature (PIGS), which was also based on the Affymetrix Human Genome U133 Plus 2.0 Array. To validate the prognostic power of the gene signature, we collected two independent cohorts with available clinical outcome information: the EORTC (European Organisation for Research and Treatment of Cancer) cohort (GEO accession: GSE43107) [18] and the UCLA (University of California at Los Angeles) cohort (GEO accession: GSE4412) [19], which were based on Affymetrix Human Exon 1.0 ST Array and Affymetrix Human Genome U133A/B Array, respectively. Figure 1 indicates the working scheme of how all these transcriptomic data sets were implicated in this study.

**Microarray Data Processing**

We applied the robust multiaarray average (RMA) function in the “affy” package of bioconductor [20] to summarize the expression level of each probe set for the data sets generated by Affymetrix Human Genome U133 Plus 2.0 Array and Affymetrix Human Genome U133A/B Array. For the data set based on Affymetrix Human Exon 1.0 ST Array, the gene expression values were summarized using the Affymetrix Power Tools Version 1.15.0. The function “mas5calls” in the “affy” package [21] was used to compute probe set present/absent call for the progenitor cell, UHC, and HFH data sets. For the progenitor cell data set, only the probe sets that were present in all replicates of at least one group were used for further analysis. For the

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**Figure 1. The working scheme of the study.** We first compared the transcriptomic pattern between PDGFRα⁺ and PDGFRα⁻ cells from human oligodendrocyte progenitor, which yielded a list of PDGFRα-influenced genes. Next, the UHC and HFH cohorts were analyzed to infer the glioma-related genes, which were either positively or negatively correlated with glioma grade. We developed a gene signature based on the intersection between the upregulated genes in high-grade glioma and the overexpressed genes in PDGFRα⁺ cells and the intersection between the downregulated genes in high-grade glioma and the underexpressed genes in PDGFRα⁻ cells. We validated the power of this gene signature in grade prediction in the SCH cohort. We further validated the predictive power of the gene signature in differentiating glioma patients with distinct survivals in the EORTC and UCLA cohorts.
the same library of the R Statistical Package, was used to compare expression values. The formula is shown below:

\[ Wi = \frac{\sum_{i=1}^{n} W_i (e_i - \mu_i)}{\tau_i} \]

Here, \( S \) is the risk score of the patient; \( n \) is the number of genes in PIGS; \( W_i \) denotes the weight of gene \( i \) (as shown in Table 1); \( e_i \) denotes the expression level of gene \( i \) and \( \mu_i \) and \( \tau_i \) are the mean and standard deviation of the expression values for gene \( i \) across all subjects, respectively. A higher risk score implies a poorer clinical outcome.

**Results**

**Genes Influenced by PDGFRα**

We compared the gene expression pattern between PDGFRα+ and PDGFRα− cells from human oligodendrocyte progenitor. One PDGFRα+ cells microarray data set containing gene information for both PDGFRα+ and PDGFRα− cells was collected from the GEO database [14] (GEO accession: GSE29368) [13], which was based on the Affymetrix Human Genome U133 Plus 2.0 Array. At the specified significance level of FDR < 5% and fold change (FC) > 2 (see Materials and Methods for details), 1445 probesets encoding 1076 genes were found to be overexpressed in PDGFRα+ cells (Supplementary Table S1 and Figure S1), while 741 probesets encoding 541 genes were underexpressed in PDGFRα+ cells (Supplementary Table S2 and Figure S1). We considered these deregulated genes as PDGFRα+-influenced genes. We next searched the enriched Kyoto Encyclopedia of Genes and Genomes (KEGG) [28] pathways among the PDGFRα+-influenced genes. We found that the PDGFRα+-influenced genes are significantly associated with several cancer-related KEGG terms, such as “colorectal cancer,” “pathways in cancer,” “melanoma,” “prostate cancer,” and “glioma” (Figure 2). These findings suggest that the PDGFRα+-influenced genes are involved in human cancer pathogenesis.

To determine how deeply the PDGFRα+-influenced genes are involved in glioma, we explored the genes that are associated with the severity of glioma. We obtained two gene expression data sets of glioma patients from the GEO database: the UHC cohort (GEO accession: GSE43289) [15] and the HFH cohort (GEO accession: GSE4290) [16]. Both data sets were based on the Affymetrix Human Genome U133 Plus 2.0 Array. There were 40 subjects in the UHC cohort, which included 3 grade I, 3 grade II, 6 grade III, and 28 grade IV patients. For the HFH cohort, there were in total 176 samples including 23 nontumor, 45 grade II, 31 grade III, and 77 grade IV subjects. Spearman's rank correlation test was used to identify the glioma related genes, in which the gene expression level was significantly correlated with glioma grade. Only the genes differentially expressed with glioma grade (Spearman’s rank correlation test: adjusted \( P < 0.005 \) after Benjamini–Hochberg correction) in the both cohorts were retained for further analysis. In total, we found that...
81 probesets encoding 67 genes were upregulated in high-grade glioma (Figure 3A and Supplementary Table S3) while 340 probesets encoding 275 genes were downregulated in high-grade glioma (Figure 3A and Supplementary Table S3) while 340 probesets encoding 67 genes were upregulated in high-grade glioma (Figure 3A and Supplementary Table S3). Interestingly, the genes that were upregulated in high-grade glioma were more likely to be overexpressed in PDGFRα+ cells, compared with the downregulated genes (Figure 3B). Among the upregulated genes in high-grade glioma, 10 genes were found to overlap with the overexpressed genes in PDGFRα+ cells, which is statistically significant (cumulative hypergeometric test: P = 5.0 \times 10^{-3}). For the downregulated genes in high-grade glioma, 18 genes significantly overlapped with the underexpressed genes in PDGFRα+ cells (cumulative hypergeometric test: P = 2.7 \times 10^{-2}). All these results suggest that the PDGFRα+-influenced genes are significantly enriched among the glioma associated gene set.

**PDGFRα+-influenced Gene Signature**

Above, we identified 10 genes within the intersection between the upregulated genes in high-grade glioma and the overexpressed genes in PDGFRα+ cells. In addition, 18 downregulated genes in high-grade glioma were found to overlap with the underexpressed genes in PDGFRα+ cells. We designated all these 28 genes as PIGS (Table 1 and Supplementary Figures S2 and S3). Based on the PIGS, we constructed a scoring system to assign each subject a risk score, representing a linear combination of the PIGS expression values weighted by the direction of differential expression: 1 for the upregulated and −1 for the downregulated genes in PDGFRα+ cells (see Materials and Methods for details). A higher risk score suggests a poorer clinical outcome.

We first tested whether the PIGS based risk score was able to predict glioma grade. For this purpose, we obtained an independent gene expression data sets, the SCH cohort, from the GEO database including 17 glioma patients (GEO accession: GSE19728) [17]. As we expected, there was a significant positive correlation (Spearman’s rank correlation test: P = 1.7 \times 10^{-3}) between glioma grade and PIGS-based risk score (Figure 3C).

**PIGS Predicts Survival in Glioma**

We next tested whether the PIGS-based risk score can be used to predict survival in glioma. From the GEO database, we downloaded two independent gene expression data sets: the EORTC cohort including 95 high-grade glioma patients (GEO accession: GSE43107) [18] and the UCLA cohort composed of 85 high-grade glioma patients (GEO accession: GSE4412) [19]. These data sets were chosen based on two criteria: (i) the large number of samples (sample size ≥ 80) and (ii) the availability of clinical outcome data. We defined PIGS positive (PIGS+) patients as those having a risk score > 0, while the other patients were assigned as PIGS negative (PIGS−), as the median of risk score was approximately equal to zero in each validation cohort (Supplementary Figure S4). Univariate Cox proportional hazard regression of survival indicates that the PIGS+ patients have a 2.91- and 2.46-increased risk of death in the EORTC and UCLA cohorts, respectively (Table 2). Kaplan–Meier survival curves demonstrate a significant difference in survival between the PIGS+ and PIGS− glioma patients in the two validation cohorts (log-rank test: P = 2.2 \times 10^{-6} for the EORTC cohort and P = 8.1 \times 10^{-4} for the UCLA cohort) (Figure 4A).

**Table 2. Univariate Cox proportional hazards regression of survival by PIGS status.**

| Cohort | N   | HR   | 95% CI of HR | P-value |
|--------|-----|------|-------------|---------|
| EORTC  | 95  | 2.91 | (1.84, 4.61) | 5.5 \times 10^{-6} |
| UCLA   | 85  | 2.46 | (1.43, 4.23) | 1.2 \times 10^{-3} |

N: patient number; HR: hazard ratio; CI: confidence interval.
Nonrandom Prognostic Power of PIGS

Venet et al. suggested that most published prognostic gene signatures were not significantly better than random gene sets of identical size that were randomly picked up from human genome [29]. Here, resampling tests were used to address this issue. We generated 1000 random gene signatures by randomly selecting 28 genes from human genome (the same size as PIGS). For each random gene signature, we calculated the risk score for each glioma patient. By each round of randomization (i.e., each randomly generated 28-gene list), we calculated the Wald statistic (Z), the ratio of Cox regression coefficient to its standard error, which stands for the prognostic power of the 28 random genes. Our alternative hypothesis was that the Z of PIGS should be more positive than expected by chance if the prognostic power of PIGS was significantly better than the random gene signatures. Figure 4B demonstrates that the Z of PIGS is significantly larger than that of the random gene sets in the two validation cohorts (right-tailed: P = 0.003 for the EORTC cohort and P = 0.015 for the UCLA cohort).

PIGS is Better than the Random Gene Signatures Selected from Glioma-related Genes

Here, we address why we focused on the PDGFRα-influenced genes to develop prognostic signature. To answer this question, we compared the performance of PIGS against the gene set associated with glioma by a second resampling test. We limited the resampling pool to the genes that were differentially expressed with glioma grade (Supplementary Tables S3 and S4) and defined these genes as glioma related. We then randomly selected 28 genes from the glioma-related gene pool and tested the predictive power of the random gene set. The performance of the random gene signature was also quantified by the Z-value computed by univariate Cox proportional hazard regression of survival. We found that the prognostic power of PIGS is significantly better than that of 1000 random glioma-related gene signatures selected from the glioma-related genes. The black triangle stands for the Z-value of PIGS. Right-tailed P-values of the sampling distributions were calculated.

PIGS is Independent of Standard Prognostic Covariates

To confirm the role of PIGS as an independent prognostic factor, we investigated the performance of PIGS in comparison with the traditional prognostic variables in glioma. Because of the limited clinical and pathological information, we did not consider the UCLA cohort. Only the EORTC cohort was investigated by multivariate model.

Firstly, we only considered the prognostic variables including age, gender, type of surgery (biopsy, partial, or total resection), Eastern Cooperative Oncology Group (ECOG) performance score [30], loss of heterozygosity (LOH) on chromosome 1p and 19q [31], and histological status (anaplastic oligoastrocytoma or anaplastic oligodendroglioma). There were 89 patients without missing data. Multivariate Cox proportional hazards regression of survival indicates that PIGS is the most significant covariate compared with the other clinical and pathological factors (Table 3).

Secondly, we took more molecular factors into account, including epidermal growth factor receptor (EGFR) amplification [32], isocitrate dehydrogenase 1 (IDHI) mutation [32], and O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation [33]. Because of missing observations, only 53 patients were included in this round. Multivariate Cox proportional hazards regression reveals that PIGS is still the most significant covariate in the new multivariate model (Table 4).

Table 3. Multivariate Cox proportional hazards regression conducted on 89 patients from the EORTC cohort.

| Covariate                     | HR     | 95% CI of HR | P-value |
|-------------------------------|--------|--------------|---------|
| PIGS, + vs. −                 | 3.46   | (2.04, 5.84) | 3.7 × 10⁻³ |
| Age (per year)                | 1.03   | (1.00, 1.06) | 6.7 × 10⁻² |
| Gender male vs. female        | 0.94   | (0.55, 1.61) | 8.4 × 10⁻¹ |
| Type of surgery (biopsy, partial, or total resection) | 0.65   | (0.43, 0.97) | 3.7 × 10⁻² |
| ECOG performance score (0, 1, or 2) | 1.51   | (1.08, 2.10) | 1.7 × 10⁻² |
| 1p/19q LOH, + vs. −           | 0.87   | (0.43, 1.75) | 6.9 × 10⁻¹ |
| Histology AOA vs. AOD         | 1.78   | (0.95, 3.04) | 7.4 × 10⁻¹ |

HR: hazard ratio; CI: confidence interval; AOA: anaplastic oligoastrocytoma; AOD: anaplastic oligodendroglioma.
From Tables 3 and 4, we can notice that patient age, type of surgery, ECOG performance score, and MGMT methylation status are also significant variables in multivariate model. Therefore, we further stratified the patients in the EORTC cohort according to respective significant factors and redid Cox proportional hazards regression. For patients with age $\leq 45$, $45 < \text{age} \leq 55$, and age $\geq 55$, PIGS$^+$ patients had $2.78$-fold ($P = 1.2 \times 10^{-2}$), $3.04$-fold ($P = 7.7 \times 10^{-3}$), and $3.09$-fold ($P = 1.4 \times 10^{-2}$) increased risk for death, respectively. For patients with biopsy, partial resection, and total resection, PIGS$^+$ patients had $9.15$-fold ($P = 4.2 \times 10^{-2}$), $3.18$-fold ($P = 3.9 \times 10^{-4}$), and $2.73$-fold ($P = 1.7 \times 10^{-2}$) increased risk for death, respectively. For patients with ECOG performance score 0, 1, and 2, PIGS$^+$ patients had $2.24$-fold ($P = 4.2 \times 10^{-2}$), $3.99$-fold ($P = 2.8 \times 10^{-3}$), and $4.69$-fold ($P = 1.7 \times 10^{-2}$) increased risk for death, respectively. For patients with methylated MGMT promoter, PIGS$^+$ patients had $3.52$-fold ($P = 3.2 \times 10^{-4}$) increased risk for death. Kaplan–Meier survival curves also demonstrate significantly reduced survival for PIGS$^+$ patients in each subset grouped by age, type of surgery, ECOG performance score, and MGMT methylation status (Figure 5). Taken together, these results suggest that PIGS is an independent prognostic variable and enhances the identification of glioma patients at greater risk for death.

**Discussion**

PDGFRα plays a role in organ development, wound healing, and tumor progression. Mutations in the gene PDGFRA have been

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**Table 4.** Multivariate Cox proportional hazards regression conducted on 53 patients from the EORTC cohort.

| Covariate                          | HR    | 95% CI of HR | $P$-value |
|------------------------------------|-------|--------------|-----------|
| PIGS, $+$ vs. $-$                  | 6.10  | (2.48, 15.00)| 8.2 x 10^{-3} |
| Age (per year)                     | 1.05  | (1.00, 1.10) | 4.5 x 10^{-2} |
| Gender male vs. female             | 1.75  | (0.76, 4.05) | 1.9 x 10^{-1} |
| Type of surgery (biopsy, partial, or total resection) | 0.31  | (0.16, 0.58) | 3.2 x 10^{-4} |
| ECOG performance status (0, 1, or 2) | 1.01  | (0.59, 1.72) | 9.7 x 10^{-1} |
| 1p/19q LOH, $+$ vs. $-$            | 0.07  | (0.15, 2.10) | 3.9 x 10^{-1} |
| EGFR amplification, $+$ vs. $-$    | 1.37  | (0.58, 3.25) | 4.8 x 10^{-1} |
| IDH1 mutation, $+$ vs. $-$         | 0.40  | (0.16, 1.01) | 5.2 x 10^{-2} |
| MGMT methylation, $+$ vs. $-$      | 1.73  | (1.19, 10.53)| 2.4 x 10^{-2} |
| Histology AOA vs. AOD              | 1.18  | (0.49, 2.86) | 7.1 x 10^{-1} |

HR: hazard ratio; CI: confidence interval; AOA: anaplastic oligoastrocytoma; AOD: anaplastic oligodendroglioma.

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**Figure 5.** Kaplan–Meier curves for glioma patients grouped by clinical and pathological factors. (A) Patients were stratified by age. (B) Patients were stratified by surgery type. (C) Patients were stratified by ECOG performance score. (D) Patients were stratified by MGMT promoter methylation status. The black curves are for the PIGS$^+$ patients, while the gray curves are for the PIGS$^-$ patients. $P$-values were calculated by log-rank test.
associated with a variety of human cancers [34–36]. In addition, elevated PDGFRα expression was found in several human tumors [4–6,35], particularly in glioma [1,7,10]. In this study, we investigated the prognostic power of PDGFRα-influenced genes in glioma. By comparing the genome-wide gene expression pattern between PDGFRα+ and PDGFRα− cells, we defined the genes potentially influenced by PDGFRα. These genes are strongly associated with cancer-related KEGG pathways. We subsequently developed a prognostic gene signature, PIGS, which was composed of 28 PDGFRα-influenced protein-coding genes. We indicate that PIGS-based risk score can be used to predict glioma grade. In addition, PIGS is able to predict clinical outcome in two independent glioma cohorts.

Multivariate Cox regression indicates that PIGS outperforms the traditional prognostic factors of glioma. Besides PIGS status, we considered nine clinical and pathological variables in the multivariate model, including age, gender, surgery type, ECOG performance score, 1p/19q LOH status, EGFR amplification status, IDH1 mutation status, MGMT promoter methylation status, and histological status. PIGS-based risk score is the most significant covariate compared with all the other factors. Even we stratified the data sets according to the other significant covariates, PIGS was still able to differentiate the patients with poor outcome from the long survival ones in each subgroup. These results confirm that PIGS is not dependent on specific values of the respective covariates. PIGS working cooperatively with traditional clinical and pathological factors may increase prognostic accuracy when identifying patients at higher risk of death in glioma.

A controversial computational study by Venet et al. suggested that the majority of published prognostic gene signatures of breast cancer were not significantly better than random gene sets of identical size that were randomly selected from human genome [29]. To address this issue in our study, we conducted a resampling test by randomly selecting 28 genes (the same size as PIGS) from human transcriptome and calculated the prognostic power for the random gene signature. The resampling test indicates that PIGS is superior to the random gene sets selected from human genome. However, it should also be noted that, in the EORTC cohort, the Z-value is larger than two (2.3% percentile in normal distribution) for almost half of the random gene signatures (Figure 4B). Therefore, the performance of a prognostic signature for glioma should not only be measured by the nominal P-values generated by Cox regression or log-rank test as many randomly generated gene signatures could also classify subjects with a fairly significant nominal P-value. Therefore, we suggest that resampling test should be a standard procedure when generating prognostic biomarkers for specific human disease. Nominal P-values only address the statistical question as to whether the given gene set is related to disease, but not the question whether the gene set is more related to disease than random gene sets [29]. Resampling test also demonstrates that the prognostic power of PIGS is even better than the random signatures selected from the gene pool that are differentially expressed in glioma. This result addressed the question why we only developed gene signature around PDGFRα instead of using unbiased screening.

**Conclusions**

Despite the absence of clear elucidation of molecular mechanisms, this study suggests the vital role of PDGFRα in carcinogenesis. Furthermore, the PDGFRα-based gene signature provides a promising prognostic tool for glioma and validates PDGFRα as a novel and effective therapeutic target in human cancers.

**Declarations of Interest**

None.

**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tranon.2019.10.002.

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