Characterization and clinical relevance of PDGFRA pathway copy number variation gains across human cancers

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Abstract
We investigated the copy number variation (CNV) of PDGFRA pathway across all common cancer types as well as its clinical relevance. This study included a total of 10,678 patients with pan-cancerous species involving 33 types of cancers and patient information was obtained from The Cancer Genome Atlas. According to the PDGFRA pathway CNV, all samples were divided into copy number gain (CN gain) group and No CN gain group. The analysis of loss of heterozygosity (LOH) fraction, CNV burden, tumor mutation burden (TMB), and the number of immunogenic mutations were performed, as well as the correlation analysis of PDGFRA pathway CN gain with tumor-related signaling pathways and tumor-infiltrating immune cell subpopulations. The results showed that CN gain of PDGFRA pathway in the cancer patients was associated with significantly shorter overall survival. The CN gain of PDGFRA pathway was identified as a prognostic risk factor for some tumors. CN gain was accompanied by an altered percentage of LOH, CNV burden, TMB, the number of immunogenic mutations were increased and tumor-infiltrating immune cell subpopulations were less. While certain tumor-related signaling pathways, such as hypoxia, cell cycle, DNA repair, and epithelial-mesenchymal transition were more enriched in the CN gain group, quiescence, and inflammation pathways were more enriched in the No CN gain group. In conclusion, PDGFRA pathway CNV gain may be a poor prognostic factor in cancer patients.

Keywords PDGFRA pathway · Copy number variation · Tumor-related signaling pathways · Tumor-infiltrating immune cells

Abbreviations
PDGFRA Platelet-derived growth factor receptor alpha
MSC Mesenchymal stromal cells
SPM Somatic point mutations
CNV Copy number variants
EMT Epithelial-mesenchymal transition
OS Overall survival
ACC Adrenocortical carcinoma
KIRC Kidney renal clear cell carcinoma
LUAD Lung adenocarcinoma
SARC Sarcoma
SKCM Skin Cutaneous Melanoma
UCEC Uterine Corpus Endometrial Carcinoma
LOH Loss of heterozygosity
TMB Tumor mutation burden
TNB Tumor neoantigen burden
ssGSEA single-sample gene set enrichment analysis
IQR Interquartile variance
KM Kaplan–Meier

Introduction
Platelet-derived growth factor receptor alpha (PDGFRA) gene encodes a tyrosine kinase receptor that activates tyrosine kinase (Ong et al. 2018). It has been shown that PDGFRA is involved in gene mutation, tumor cell proliferation, migration and invasion, maintenance of mesenchymal stromal cells (MSC), and immune infiltration, while it may serve as a potential biomarker and therapeutic target (Chang et al. 2018; Pantaleo et al. 2019; Wang et al. 2020a). Activation of

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PDGFRA signaling is sufficient to drive fibrosis in diverse organs. Targeting PDGFRA signaling can be an effective approach to treat fibrosis (Decker et al. 2017). However, the role of PDGFR signaling pathway in the pan-cancer context has yet to be investigated.

Somatic mutations are closely related to immunotherapy and clinical outcomes (e.g., survival), while these mutations can be classified as somatic point mutations (SPM) or somatic copy number variants (CNV). CNVs have been shown to be widely present in normal individuals (Hieronimus et al. 2018). As an important form of genetic structural variation, CNVs result from gains or losses of DNA segments larger than 1 kb in the human genome (Shao et al. 2019). Recently, Zheng et al. showed that CNV data had a higher validity in predicting cancer prognosis than SPM data (Zheng et al. 2020). Furthermore, the relationship between CNVs and gene expression is crucial for the prevention, diagnosis, and treatment of cancer (Shao et al. 2019). CNV-caused genetic mutations may lead to the development of immune escape (Chen et al. 2020). It has also been reported that copy number gains (CN gain) occur more frequently than copy number losses (CN loss) during epithelial-mesenchymal transition (EMT), and somatic CN gain activates gene expression by increasing gene dosage (Zhao et al. 2016). Interestingly, Anwar et al. identified frequent recurrence of CNVs in PDGFRA gene in a next-generation sequencing-based CNV study of invasive breast cancer patients (Anwar et al. 2020). PDGFRA CN gain was also detected in intractable epilepsy and high-grade astrocytoma and found to be significantly associated with the treatment and prognosis of the disease (Phillips et al. 2013; Vasudevaraja et al. 2021). While the importance of the tumor microenvironment has been increasingly recognized, the complexity of interaction between tumor cells and their microenvironment is becoming evident. However, characterization and clinical properties of PDGFRA CN gain in whole cancers have not been well documented.

To comprehensively characterize PDGFRA CN gain, we collected the CNV data and clinical information of pan-cancer patients from the TCGA database, systematically analyzed functional status of the tumor cells, and quantified the components of immune cells in the tumor immune microenvironment. In this study, we identified PDGFRA CN gain as a prognostic risk factor for a significantly shorter overall survival (OS) in six cancer species, including adrenocortical carcinoma (ACC), kidney renal clear cell carcinoma (KIRC), lung adenocarcinoma (LUAD), sarcoma (SARC), skin cutaneous melanoma (SKCM), and uterine corpus endometrial carcinoma (UCEC). Moreover, the enrichment of related pathways that promote tumor development was higher in these six cancer types. Loss of heterozygosity (LOH), CNV burden was higher and effector immune cells all affect patient prognosis.

Materials and methods

Data collection and processing

The CNV data and clinical information for 10,678 patients with pan-cancerous species were downloaded from the TCGA database (https://gdc.cancer.gov/about-data/publications/panimmune). The reference data for gene sets contained in PDGFRA signaling pathway were obtained from the GSEA website (https://www.gsea-msigdb.org/gsea/msigdb/cards/PID_PDGFRA_PATHWAY.html) (Table 1).

We defined the tumor with CN gain in any of PDGFRA pathway genes as having PDGFRA pathway CN gain. Table S1 shows the number of cases for each cancer type and the number of cases with PDGFRA pathway CN gain variants in the TCGA cohort. The tumor mutation burden (TMB), the number of immunogenic mutations (TNB), CNV burden score, and LOH score were derived from the published studies (Thorsson et al. 2018).

Assessment of the functional status of tumor cells

To assess the functional status of tumor cells, 14 manually curated cancer-related signatures were calculated using the GSVA package in R software, including stemness, invasion,

| Table 1 Gene list in PDGFRA pathway |
|-------------------------------------|
| **Gene symbol** | **Ensembl Gene ID** | **Gene ID** |
| FOS | ENSG00000170345 | 2353 |
| IFNG | ENSG00000111537 | 3458 |
| JUN | ENSG00000177606 | 3725 |
| ITGA1 | ENSG00000138448 | 3685 |
| SRF | ENSG00000112658 | 6722 |
| PDGFRA | ENSG00000134853 | 5156 |
| PLCG1 | ENSG00000124181 | 5335 |
| ELK1 | ENSG00000126767 | 2002 |
| JAK1 | ENSG00000162434 | 3716 |
| PIK3R1 | ENSG00000145675 | 5295 |
| SHC1 | ENSG00000160691 | 6464 |
| PIK3CA | ENSG00000121879 | 5290 |
| CRK | ENSG00000167193 | 1398 |
| CRKL | ENSG00000199942 | 1399 |
| CAV3 | ENSG00000182533 | 859 |
| GRB2 | ENSG00000177885 | 2885 |
| CSNK2A1 | ENSG00000101266 | 1457 |
| CAV1 | ENSG00000105974 | 857 |
| SOS1 | ENSG00000115904 | 6654 |
| RAPGEF1 | ENSG00000107263 | 2889 |
| SHB | ENSG00000107338 | 6461 |
| SHF | ENSG00000138606 | 90,525 |
metastasis, proliferation, EMT, angiogenesis, apoptosis, cell cycle, differentiation, DNA damage, DNA repair, hypoxia, inflammation, and quiescence (Yuan et al. 2019).

**Quantitative analysis of tumor-infiltrating immune cell subpopulations**

To quantify the components of immune cells in the tumor microenvironment, the enrichment of 28 immune cell subpopulations was assessed using the single-sample gene set enrichment analysis (ssGSEA) method (Angelova et al. 2015).

**Statistical analysis**

All statistical analyses were performed using R software (version 3.4.2). Data were presented as median and interquartile variance (IQR). The Student’s *t* test and Wilcoxon rank-sum test were used to analyze the differences between the two groups for normally distributed data and non-normally distributed data, respectively. Survival data were analyzed using Kaplan–Meier (KM) survival curves and log-rank test. The relationship between PDGFRA pathway CN gain in pan-cancer species and OS was examined using univariate COX regression. Bilateral *P* values < 0.05 were considered statistically significant.

**Results**

**The CNVs of PDGFRA pathway in pan-cancerous species**

We analyzed the CNVs of each PDGFRA pathway gene in TCGA database for each cancer type and found that the frequency of CN gain or CN loss in PDGFRA pathway varied from one cancer type to another (Fig S1). As illustrated in Fig. 1A, the frequency of CN gains in PDGFRA pathway ranged from 1 to 45% among various cancer types. Moreover, survival analysis showed that patients with CN gain in PDGFRA pathway had significantly shorter OS and worse prognosis (*P* < 0.0001) than the No CN gain group (Fig. 1B), whereas no significant correlation between CN loss in PDGFRA pathway and OS was found (Fig. 1C). Notably, univariate analysis identified PDGFRA pathway CN gain as a risk factor for poor OS in the following six cancer types: ACC (*P* < 0.05), KIRC (*P* < 0.01), LUAD (*P* < 0.05), SARC (*P* < 0.05), SKCM (*P* < 0.05), and UCEC (*P* < 0.001) (Fig. 1D).

We next performed KM survival analysis and log-rank test to verify the relationships between the CN gain and survival rates of the above-mentioned six cancer types. As shown in Fig. 2, OS was significantly shorter in patients with the CN gain of PDGFRA pathway for all six cancer types compared with the No CN gain group (*P* < 0.05).

**Analysis of PDGFRA pathway CN gain in relation to LOH fraction, CNV burden, TMB, and TNB**

Based on whether a CN gain in PDGFRA pathway was identified, patients in this study were divided into two groups: CN gain and No CN gain. We further analyzed the differences in LOH fraction, CNV burden, TMB, and TNB between the two groups of patients, and found that the differences were significant (*P* < 0.05) (Fig S2 and Table S2). Moreover, we observed that the CN gain of PDGFRA pathway was associated with a higher proportion of LOH alterations and higher CNV burden in most cancers such as KIRC, LUAD, SKCM, and UCEC, while the association was in the opposite direction in ACC (Fig. 3A, B). Likewise, while association of the CN gain in PDGFRA pathway with higher TMB and TNB values was identified in ACC, LUAD and some other types of cancers, the association was in the opposite direction in UCEC (Fig. 3C, D).

**Relationships between the CN gain of PDGFRA pathway and tumor-related signaling pathways**

Next, we examined the relationships between the CN gain of PDGFRA pathway and 14 tumor-related signaling pathways in the pan-cancer species (Fig S3). As depicted in Fig. 4A–D, F, in ACC, KIRC, LUAD, SARC, and UCEC, pathways related to tumorigenic progression, including hypoxia, cell cycle, DNA repair, and EMT, were more enriched in the CN gain group as compared to No CN gain group. On the contrary, in SKCM, pathways such as quiescence and inflammation were more enriched in the No CN gain group (Fig. 4E).

**Relationships between the CN gain of PDGFRA pathway and tumor-infiltrating immune cell subsets**

Furthermore, we investigated the relationships between the CN gain of PDGFRA pathway and tumor-infiltrating immune cell subpopulations in pan-cancerous species (Fig S4). Compared with the CN gain group, tumor-infiltrating immune cell subpopulations were more abundant in the No CN gain group among many cancer types. Thereafter, we analyzed the difference in the enrichment of tumor-infiltrating immune cell subpopulations between the CN gain and No CN gain groups among the six cancer species in which the CN gain of PDGFRA pathway was significantly associated with OS. The analysis revealed that in ACC, three immune cell subsets, Neutrophil, Eosinophil, and Natural killer cell, were significantly more abundant in the CN gain group (Fig. 5A), while in SARC, MDSC, Macrophage,
Central memory CD8 T cell, Regulatory T cell, Activated CD8 T cell and other immune cell subsets were significantly more enriched in the CN gain group (Fig. 5D). Conversely, in KIRC and SKCM, several immune cell subsets such as Immature B cell, Activated B cell, Effector memory CD8 T cell, and Type I T helper cell were significantly more abundant in the No CN gain group (Fig. 5B, E). Notably, we observed that in LUAD and UCEC, there were significant differences in the enrichment of certain immune cell subsets such as Eosinophil between the CN gain and No CN gain groups (Fig. 5C, F).

**Discussion**

**PDGFRA** is of critical importance in mesenchymal development, homeostasis and pathogenesis. Aberrant **PDGFRA** activities have been linked to a variety of diseases, including
fibrosis, cancer, and pediatric diseases (Mueller et al. 2016; Decker et al. 2017). In this study, we analyzed the distribution of PDGFRA pathway CN gain in pan-cancer patients based on information from the TCGA database and investigated the association of PDGFRA pathway CN gain with tumorigenesis-related pathways, immune cell subpopulations, and survival rates.

First, we showed that the frequency of CN gain or CN loss in PDGFRA pathway varied among different cancer types. Notably, the CN gain of PDGFRA pathway was significantly associated with shorter OS in six cancer types including ACC, KIRC, LUAD, SARC, SKCM, and UCEC, thus serving as a prognostic risk factor for poor OS. It has been shown that CN gain at the PDGFRA locus can influence the relative frequency of tumor malignant cells and promote the tumor growth, whereas high expression of PDGFRA in glioblastoma can markedly improve the prognosis of patients (Moon et al. 2017). Given that both PDGFRA CNVs and dysregulation of tumor-related pathways are usually present in cancer, we propose that the CN gain of PDGFRA pathway could be a potential target for analyzing cancer-related mechanisms in ACC, KIRC, LUAD, SARC, and UCEC.

Moreover, we found that in most cancers, tumor-infiltrating immune cell subsets, especially the effector immune cell subsets such as Activated CD8 T cell, Effector memory CD8 T cell, Activated B cell, and Immature B cell are less abundant in the group of PDGFRA pathway CN gain (Seo et al. 2018; Han et al. 2020; Bian et al. 2021). This observation may underlie the worse prognosis linked to the CN gain in PDGFRA pathway. On the contrary, in ACC and SARC, more tumor-infiltrating immune cell subsets were enriched in the CN gain group; among them, the dominant ones were pro-tumor growth cell subsets such as Neutrophil, Eosinophil, MDSC, and Macrophage. It has been shown that PDGFRA induces proliferation and differentiation of eosinophils and neutrophils, while CN gain can cause dysregulation of the two immune cell subsets (Buitenhuys et al. 2007; Wang et al. 2020b). In contrast, the effector immune cell subpopulations including Immature B cells and Activated B cells were more enriched in No CN gain group of PDGFRA pathway, particularly in KIRC and SKCM. Taken together, these data indicate that the tumor immune microenvironment varies among the cancer types and is related to CNV.

Next, we examined the relationships between the CN gain of PDGFRA pathway and 14 tumor-related signaling pathways in each cancer type, especially the above-mentioned six cancer types with poor OS. The study revealed that there was a significant enrichment of pathways related to tumorigenic progression, such as Hypoxia, cell cycle, DNA repair, and EMT in the group of PDGFRA pathway CN gain. Hypoxia pathway is critical for the function of cells, organs and organisms. Liu et al. showed that both Hypoxia and PDGFRA amplification were associated with tumor localization and could serve as potential targets for specific therapies (Liu et al. 2016). While cell cycle plays an important regulatory role in diseases, small molecule inhibitors regulating the cell cycle can cause PDGFRA overexpression and CNV imbalance (Paugh et al. 2011). DNA repair is a key system for identifying and repairing structural or sequence abnormalities in DNA. The combination of PDGFR pathway, CNV, and DNA repair analysis can identify potential therapeutic targets (Zarghooni et al. 2010). Activation of EMT provides cancer cells with increased plasticity that is required for their invasion and metastasis. Studies have shown that PDGFRA activates the EMT pathway and decreases the expression of genes that favor epithelial integrity, enhancing metastatic diseases (Lopez-Campistrous et al. 2020).

In the present study, we observed that in SKCM, quiescence and inflammation pathways were more enriched in the No CN gain group. This observation was consistent with the previous reports (Moon et al. 2017). Given that both PDGFRA CNVs and dysregulation of tumor-related pathways are usually present in cancer, we propose that the CN gain of PDGFRA pathway could be a potential target for analyzing cancer-related mechanisms in ACC, KIRC, LUAD, SARC, and UCEC.
Fig. 2 Relationship between the CN gain of PDGFRA pathway and prognosis of the six cancer types. KM survival curves showing the relationship between the CN gain of PDGFRA pathway and OS in six cancer types including ACC (A), KIRC (B), LUAD (C), SARC (D), SKCM (E), and UCEC (F)
Fig. 3 Relationships of PDGF-FRA pathway CN gain with LOH fraction, CNV burden, TMB, and TNB in pan-cancerous species. Comparison of LOH fraction (A), CNV burden (B), TMB (non-silence per MB) (C), and TNB (number of immunogenic mutation) (D) in different cancer species between the pathway CN gain and No CN gain groups.
disorders in the PDGFRA pathway, which may require attention in subsequent immunotherapy choices.

In sum, in ACC, PDGFRA pathway CN gain promoted tumorigenesis, leading to a poor survival, which was found to be significantly associated with ACC in our study for the first time. The CN gain of PDGFRA pathway in KIRC, LUAD and UCEC leaded to a higher proportion of LOH occurrence and enrichment of CNV burden, with less abundant effector immune cells, promoting tumorigenesis related to worse survival. Previous studies have shown that PDGFRA is associated with KIRC protein expression, gene mutations and brain metastasis, while affecting the survival of patients (Terada 2012; Schiefer et al. 2015). PDGFRA mutations have also been detected in LUAD (Seo et al. 2012). In addition, Wang et al. reported that CNV has a significant negative impact on the survival rate of UCEC patients (Wang et al. 2020c). However, the specific mechanisms underlying the CN gain of PDGFRA pathway and the above three cancer types remain to be further investigated. In SARC, the CN gain of PDGFRA pathway promoted tumorigenesis. The tumor-related pathways and immune cell subpopulations were relatively enriched, but the immune cells had weaker effects, resulting in worse survival rate. CNV is an important event in the development of SARC and is associated with dysregulation of PDGFRA, indicating a poor prognosis (Helbig et al. 2017). This observation was consistent with the OS data obtained in the present study. Similarly, we showed that in SKCM, the CN gain of PDGFRA pathway caused a lower enrichment of multiple immune cell subpopulations, resulting in worse survival. It has been demonstrated that while the immune microenvironment is critical to the treatment of SKCM patients, CNV has the potential of being a biomarker for active melanoma disease and
survival (Silva et al. 2018; Pozniak et al. 2019). Overall, the present study not only prove the previous observations, but also provide new insights into mechanisms underlying the effects of PDGFRA pathway CN gain on the immune microenvironment.

In conclusion, the CN gain of PDGFRA pathway was identified as a prognostic risk factor for six cancer types: ACC, KIRC, LUAD, SARC, SKCM, and UCEC. The presence of PDGFRA pathway CN gain in the tumors was associated with significantly shorter OS of patients. This study suggested that the impact of tumor characteristics and immune characteristics on the survival of patients may vary from one tumor type to another. The presence of PDGFRA pathway CN gain in tumors with enriched pathways favoring tumorigenic progression. Patients with LOH for immune escape, high enrichment of CNV burden, and few abundant effector immune cells have poorer prognosis. The underlying mechanisms remain to be further investigated.

Fig. 5 Relationships between the CN gain of PDGFRA pathway and tumor-infiltrating immune cell subpopulations in pan-cancerous species. The relationships between the CN gain of PDGFRA pathway and tumor-infiltrating immune cell subpopulations in six cancer species with significant survival, including ACC (A), KIRC (B), LUAD (C), SARC (D), SKCM (E), and UCEC (F). The upper part and lower part of the horizontal divider indicate $P < 0.05$ and $P > 0.05$, respectively. The left blue dot and right red dot of the vertical divider represent CN gain/No CN gain < 1 and CN gain/No CN gain > 1, respectively.

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Code availability Not applicable.

Declarations

Conflict of interest The authors declare that they are no conflict of interests.
Ethics approval  Not applicable.

Consent to participate  Not applicable.

Consent for publication  Not applicable.

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