Association of PTPRT Mutations with Cancer Metastasis in Multiple Cancer Types

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Received 11 February 2022; Revised 21 May 2022; Accepted 30 May 2022; Published 25 June 2022

Academic Editor: Yingkun Xu

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Metastasis is one of the characteristics of advanced cancer and the primary cause of cancer-related deaths from cancer, but the mechanism underlying metastasis is unclear, and there is a lack of metastasis markers. PTPRT is a protein-coding gene involved in both signal transduction and cellular adhesion. It is also known as a tumor suppressor gene that inhibits cell malignant proliferation by inhibiting the STAT3 pathway. Recent studies have reported that PTPRT mutations may be associated with the tumor mutation burden (TMB) and could provide clinically predictive implications for immune checkpoint inhibitor (ICI) therapies [8, 9]. Hu et al. reported that PTPRT may be involved in the early metastatic seeding of colorectal cancer [10]. However, to the best of our knowledge, the association between PTPRT and cancer metastasis has not been investigated through a comprehensive analysis of large clinical datasets.

To address this question, we retrospectively analyzed the somatic mutations and cancer prognostic status from the previously published data [7–9]. The integration of somatic mutations and clinical prognostic information from multiple cohorts retrieved 16,182 metastatic and/or stage IV cancers and 26,480 early primary cancers. Subsequently, we found that PTPRT mutation was significantly associated with cancer metastasis in 6 common cancers, including breast cancer (BRCA), colorectal cancer (CRC), esophageal gastric cancer (EGC), non-small-cell lung cancer (NSCLC), skin cutaneous melanoma (SKCM), and skin cutaneous nonmelanoma (SKCNM). Furthermore, PTPRT mutation is associated with...
poor progression-free survival in pan-cancer and NSCLC. These results confirmed the effect of PTPRT mutation on tumor development and progression.

2. Materials and Methods

2.1. Genomic Data. All cancer samples and somatic mutation data were downloaded from cBioPortal (https://www.cbioportal.org) and GENIE databases (v6.1, http://synapse.org/genie) [11]. All nonsilent mutations, including missense, frameshift, nonsense, nonstop, splice site, and translation start site mutations, were considered. To ensure the consistency of data sources for finding potential metastasis markers, we screened the samples in the cBioPortal as follows: (1) the samples were sequenced on an MSK-impact panel; (2) the samples should be identified for whether they are primary tumors or metastasis tissues and the tumor stage; (3) because the mutation characteristics of MSI-H samples are different, we excluded the samples known to be MSI-H [12, 13]. The samples of unknown tissue origins in the GENIE database were excluded. Next, we obtained 16,182 metastatic and/or stage IV cancers (hereafter denoted as "metastatic cancer") and 26,480 early primary cancers (primary cancers with stages I–III). To remove noise from the analysis, PTPRT or other driver genes with nonsilent mutations that occurred in at least five metastatic cancers were selected, resulting in 6 types of cancers with 10,068 metastatic cancer samples and 13,487 early primary cancer samples, respectively. These 23,555 samples were used for further analysis (Table 1).

2.2. Gene Module Mutation Enrichment Analysis. The enrichment analysis pipeline is shown in Figure 1. After collecting the genomic mutation data from the database, we searched for the biomarkers of metastatic cancer by comparing the mutation frequency difference of a single driver gene (or "gene modules") between early primary cancer samples \(n = 13,487\) and metastatic cancer samples \(n = 10,068\). A

| Cancer type                        | Metastatic and/or stage IV (#) | Early primary cancer (#) |
|-----------------------------------|--------------------------------|--------------------------|
| Breast cancer (BRCA)              | 2587                           | 4814                     |
| Colorectal cancer (CRC)           | 2382                           | 2992                     |
| Esophagogastric cancer (EGC)      | 539                            | 849                      |
| Non-small-cell lung cancer (NSCLC)| 3298                           | 4012                     |
| Skin cancer, melanoma (SKCM)      | 1148                           | 669                      |
| Skin cancer, nonmelanoma (SKCNM)  | 114                            | 151                      |

Table 1: Distribution of cancer samples.

Figure 1: The pipeline for gene module mutation enrichment analysis. Samples in GENIE (v6.1) were downloaded from https://www.synapse.org/genie. Samples in cBioPortal were downloaded from https://www.cbioportal.org. Early primary cancer: primary cancer samples of stages I–III; metastatic samples: primary cancer samples of stage IV or metastasis cancers.
were selected for neoantigen prediction using NetMHC [17], for candidate gene models [14]. The di of each cancer type predicted by Matthew et al. were selected driver genes mutated in the same sample. The driver genes gene module is defined as a combination of two or more driver genes mutated in the same sample. The driver genes of each cancer type predicted by Matthew et al. were selected for candidate gene models [14]. The differential analysis used the two-sided Fisher’s exact test, followed by Bonferroni’s multiple hypothesis tests.

2.3. The Neoantigen Prediction for Recurrent Mutations in PTPRT. The human leukocyte antigen (HLA) alleles of patients were downloaded from TCGA database [15], the mutations of patients in TCGA pan-cancer cohort (N = 10967) were downloaded from the cBioPortal database [16], and the recurrent mutations (frequency ≥ 2) of PTPRT were selected for neoantigen prediction using NetMHCpan [18], PickPocket [19], PSSMHCpan [20], and SMM [21]. The peptides with a length of 8–11 mers and an affinity (IC50) < 500 nM in at least two tools were regarded neoantigens.

2.4. Statistical Analysis. Statistical analyses were carried out using R studio (R 4.0.2), and the differential significance of mutation frequency between primary cancer and metastatic samples was determined by Fisher’s exact test. The P value was adjusted to q value by Bonferroni’s multiple hypothesis tests. For survival analysis, we used survival (v3.1-12) and survminer (v0.4.9), and the difference in survival was analyzed using the log-rank test, and the survival data were downloaded from cBioPortal. The different gene expressions

Figure 2: Expression level of PTPRT across different organs and in TCGA database. (a) PTPRT RNA expression level in different organs and colors refer to the various origins of tissue types. (b) PTPRT protein level in different organs. (c) PTPRT level in tumor and normal samples in TCGA cohort. A total of 17 cancer types with paired expression data; PTPRT was significantly downregulated in 12/17 cancer types (*P < 0.05; **P < 0.01; ***P < 0.001).
of PTPRT were analyzed in tumor and normal samples using online tools (https://www.proteinatlas.org and https://cistrome.shinyapps.io/timer), and the significance of differential expression was evaluated using the Wilcoxon test (*P < 0.05; **P < 0.01; ***P < 0.001).

3. Results

3.1. PTPRT Is Downregulated in Multiple Cancer Types. Since PTPRT is a tumor suppressor in cancer, we elucidated the expression landscape of PTPRT in tumorigenesis. PTPRT is mainly expressed in the brain tissues, and that in the other tissues is lower (Figure 2(a)). However, the protein level of PTPRT was medium in multiple organs (Figure 2(b)). The analysis of the expression data of samples in TCGA database revealed that PTPRT is downregulated in tumors compared to the paired normal samples. As shown in Figure 2(c), a total of 17 cancer types had significantly downregulated PTPRT levels in cancer tissues compared to normal tissue in most cancer types (the expression of PTPRT in 12/17 cancer types was downregulated, Figure 2(c)). In addition, some studies reported that the downregulation of PTPRT expression is associated with poor prognosis [22, 23].

3.2. The Mutation Landscape of PTPRT across Different Cancer Types. PTPRT is mutated in various cancers, such as melanoma and gastric cancer. To comprehensively depict the mutation landscape of PTPRT in different cancers, the mutation datasets from TCGA pan-cancer cohort (10967 samples), containing 32 cancer types, were collected. PTPRT mutations were detected in 24 cancer types, including SKCM, gastric adenocarcinoma, uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and lung adenocarcinoma (Figure 3(a)).

Next, we analyzed the distribution of mutations in PTPRT. The lollipop plot showed that the missense and truncating mutations (nonsense, nonstop, frameshift deletion, and frameshift) were randomly distributed in the various functional regions of the gene (Figure 3(b)) without hotspot mutations.

3.3. Mutation Enrichment of PTPRT and the Associated Gene Modules in Metastatic Cancers. As mentioned in Figure 1, we obtained the mutation data of PTPRT and other gene modules in early primary and metastatic tumors from 6 cancer types. Among these, PTPRT mutations were significantly mutated in metastatic cancers (Figures 4(a)–4(f)).
In melanoma, the $q$ value is $>0.05$, which could be attributed to the small number of primary cancer samples (Figure 4(f), 14/1148 vs. 0/669, $q = 0.156$, $P = 0.00097$).

Additionally, many gene modules involved in PTPRT were significantly enriched in metastatic cancers. In breast cancer, the combined mutation frequency of PTPRT and PIK3CA in metastatic breast cancer was significantly higher than in primary cancer (Figure 4(a); $q = 0.025$). In colorectal cancer, the combined mutation frequency of APC-PTPRT, APC-PTPRT-TP53, and PTPRT-TP53 was significantly higher in metastatic colorectal cancer than in primary cancer (Figure 4(b); $q = 3.4E − 05$, $q = 0.0006$, and $q = 2.6E − 06$, respectively). In esophagogastric cancer, the combination mutation frequency of PTPRT and TP53 in metastatic cancer is significantly higher than that in primary cancer (Figure 4(c), $q = 0.023$). The combined alteration of KEAP1-PTPRT, PTPRD-PTPRT-TP53, and PTPRT-TP53 was significantly higher in metastatic NSCLC than in primary cancer (Figure 4(d), $q = 0.02$, $q = 0.0097$, and $q = 1.68E − 07$, respectively).

Conversely, the mutation frequency of other cancer driver genes or gene modules (such as TP53, PIK3CA, ARID1A, and BRAF) was not significantly different between the two groups ($q > 0.05$) or had a slightly higher mutation frequency in primary cancer than in metastatic cancer samples (Supplementary Table S1–6). This demonstrated the specificity of PTPRT mutation as a candidate biomarker for cancer metastasis across multiple cancer types.
3.4. The Association of PTPRT Mutation and the Prognosis of Cancer. Next, we explored the effect of PTPRT mutation on tumor prognosis. In TCGA pan-cancer cohort (n = 10967), the PTPRT mutations were associated with poor prognosis of cancers (log-rank test, P = 0.016; Figure 5(a)). Similarly, in TCGA NSCLC cohort (TCGA LUAD and LSCC, n = 1053), the PTPRT mutations were associated with poor progression-free survival in NSCLC (log-rank test, P = 0.012; Figure 5(b)). We further analyzed PTPRT mutation in another combined pan-cancer cohort conducted by ICGC/TCGA and MSK (validation cohort, n = 3418) with similar observations that PTPRT-altered groups tend to have poor progression-free survival and overall survival (log-rank test, P = 0.1 and P = 0.016, respectively, Figures 5(c) and 5(d)).

3.5. The Neoantigens Derived from Recurrent PTPRT Mutations as Potential Drug Targets. Tumor suppressor genes are difficult to target by conventional drug modalities and are commonly regarded as “undruggable.” Deniger et al. found that some neoantigens derived from hotspot mutations in TP53 (p.Y220C and p.G245S) had strong immunogenicity, and the transfer of TP53 “hotspot” mutation-reactive T cell receptors into peripheral blood T cells could be evaluated as a potential therapy for various cancer types [24, 25]. Similarly, we investigated the potential neoantigens from the recurrent mutations of PTPRT. Some recurrent mutations (p.G826R and p.R1117C) of PTPRT were predicted to generate high-affinity neoantigens in pan-cancer that could be used as potential targets for immunotherapies in the future (Table 2).

4. Discussions and Conclusion

Previous studies have demonstrated the functional impact of PTPRT mutation in tumor progression and metastasis [6, 26–28]. Wang et al. first identified and confirmed that PTPRT functions as a tumor suppressor [29]. PTPRT mutations are often loss-of-function mutations that disrupt cell-cell adhesion, leading to tumor progression and metastasis [30]. Some studies showed that PTPRT regulates the STAT3 signaling pathway by dephosphorylation of pSTAT3 [7, 31, 32], thus promoting cell survival, proliferation, angiogenesis,
migration, invasion, and metastasis [31, 32]. In the present study, the comprehensive analysis of the mutation data from GENIE and cBioPortal databases revealed that PTPRT mutations are significantly enriched in metastatic samples across multiple cancer types, deeming the mutations as risk factors for cancer metastasis in various cancers. In addition to mutations, another factor that affects the function of PTPRT is hypermethylation of the promoter region [31], which also leads to the dysfunction of PTPRT. Based on the previous results and our analysis, we propose the potential mechanism of PTPRT dysfunction leading to tumor metastasis in Figure 6.
Since PTPRT acts as a tumor suppressor in cancer, direct targeting of PTPRT for cancer therapy has not been reported. Conversely, STAT3 represents a promising therapeutic target in clinical trials [32]. Peyser et al. reported that patients with frequent promoter hypermethylation or mutations of PTPRT are sensitive to STAT3 inhibitors [7, 31]. Thus, PTPRT functional status might have implications for the efficacy of therapies targeting STAT3.

Several studies suggested that PTPRT mutation is positively correlated with TMB, and patients with PTPRT mutation might benefit from ICI therapy, indicating that PTPRT is a potential biomarker in immunotherapy [8, 9]. Based on the prediction based on recurrent mutations in PTPRT, we identified potential PTPRT neoantigens (Table 2) that might have a therapeutic value in immunotherapies, for example, cancer vaccines or T cell therapies.

In conclusion, the integration of mutation data and clinical information from multiple cohorts suggested that PTPRT mutations have a significant influence on cancer prognosis and may serve as potential biomarkers for cancer metastasis. This finding emphasizes on PTPRT as a specific therapeutic target for advanced cancers.

**Data Availability**

The data reported in this study are available in the supplementary materials, and other data can be obtained by contacting the corresponding author. The code used for this manuscript is available at https://github.com/gkdsuperchan/PTPRT-analysis.

**Ethical Approval**

This study was approved by the Peking University Shenzhen Hospital Institutional Review Board, which waived additional informed consent because all data used in this study were obtained from public databases.

**Consent**

Participants in the original genomic studies provided informed consent.

**Disclosure**

The paper is published in a preprint at Research Square [33] (https://www.researchsquare.com/article/rs-16367/v1).

**Conflicts of Interest**

The authors declare that they have no competing interests.

**Authors’ Contributions**

C.C. and J-X.L. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. C.C., Q-M.X., X-Q.Z., and H-Z.L. analyzed and interpreted the data. C.C., Q-M.X., and F.M. revised the manuscript. All authors have read and approved the manuscript.

**Acknowledgments**

We sincerely thank the support provided by China National GeneBank. This research is supported by the UMHS-PUHSC Joint Institute Project (2019020(PUSH)-r1), the Science, Technology and Innovation Commission of Shenzhen Municipality under grant Nos. JSGG20180508152912700 and JCYJ20180228175531145, and the Open Fund Project of BGI-Shenzhen (BGIRSZ20200003).

**Supplementary Materials**

Supplementary Table S1: differences in the mutational frequency between genes (or gene modules) in early and metastatic breast cancer (BRCA). Supplementary Table S2: differences in the mutational frequency between genes (or gene modules) in early and metastatic colorectal cancer (CRC). Supplementary Table S3: differences in the mutational frequency between genes (or gene modules) in early and metastatic esophagogastric cancer (EGC). Supplementary Table S4: differences in the mutational frequency between genes (or gene modules) in early and metastatic non-small-cell lung cancer (NSCLC). Supplementary Table S5: differences in the mutational frequency between genes (or gene modules) in early and metastatic skin cancer nonmelanoma (SKCM). **(Supplementary Materials)**

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