

Evaluation of PTPRT Mutations as Biomarkers for Cancer Metastasis Across Multiple Cancer Types

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Research article

Keywords:

Posted Date: March 9th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-16367/v1>

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Abstract

Cancer metastasis is the main cause of cancer-related death, but the mechanism of metastasis is still unclear, and there is lack of metastasis markers. *PTPRT* is a protein coding gene which may be 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[1-3]. Recent studies have reported that *PTPRT* may be involved in the early metastasis of colorectal cancer, but to our knowledge, no comprehensive study has yet revealed a link between *PTPRT* and metastasis in other types of cancer[4, 5]. In this study, we found that mutations in *PTPRT* were a potential biomarker of cancer metastasis in multiple cancers through a combined analysis using a large data set.

Introduction

Cancer metastasis is the main cause of cancer-related death, but the mechanism of metastasis is still unclear, and there is lack of metastasis markers. *PTPRT* is a protein coding gene which may be 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[1-3]. Recent studies have reported that *PTPRT* may be involved in the early metastasis of colorectal cancer, but to our knowledge, no comprehensive study has yet revealed a link between *PTPRT* and metastasis in other types of cancer[4, 5]. In this study, we found that mutations in *PTPRT* were a potential biomarker of cancer metastasis in multiple cancers through a combined analysis using a large data set.

Results

In all 16,182 metastatic cancers and 26,480 early primary cancers, *PTPRT* non-silent mutations occurred in at least five metastatic cancers in six type of cancers, corresponding to 10,068 of metastatic cancer samples and 13,487 early primary cancer samples, respectively. These 23,555 samples were used for further differential analysis (Table 1). Among the six types of cancer, *PTPRT* mutations were significantly enriched in metastatic cancer (Figure 1, A-F, $p < 0.05$, $q < 0.05$), except that q -value was not significant in melanoma due to the small number of primary cancer tissue samples (Figure 1E, 14 / 1148 vs 0 / 669, $q = 0.156$, $p = 0.00097$). In breast cancer, the combined mutation of *PTPRT* and *PIK3CA* in metastatic breast cancer was significantly higher than in primary tissue (Figure 1A, $q = 0.025$). In colorectal cancer, as previously reported[4], the combined mutation of *APC-PTPRT*, *APC-PTPRT-TP53* and *PTPRT-TP53* were significantly higher in metastatic colorectal cancer than in primary tissue (Figure 1B, $q = 3.4E-05$, $q = 0.0006$ and $q = 2.6E-06$, respectively). In Esophagogastric cancer, the combination of *PTPRT* and *TP53* in metastatic cancer is significantly higher than that in primary tumor tissue (Figure 1C, $q = 0.023$). In NSCLC, the combined mutation of *KEAP1-PTPRT*, *PTPRD-PTPRT-TP53* and *PTPRT-TP53* were significantly higher in metastatic NSCLC than in primary tissue (Figure 1D, $q = 0.02$, $q = 0.0097$ and $q = 1.68E-07$, respectively).

In summary, by analyzing the mutation data of all 42662 cases from GENIE and cBioPortal databases, we found that *PTPRT* was not only enriched in metastatic cancer tissues of colorectal cancer, but also in

other cancer types, such as esophageal cancer, breast cancer, non-small cell lung cancer and melanoma. This finding suggests that *PTPRT* mutation may be a molecular marker of cancer metastasis in a variety of cancers, and that simultaneous mutations in *PTPRT* and other driver genes may be responsible for different cancer metastases. Of course, since we do not have the clinical tracking information of these samples, especially GENIE database has not provided the tumor stage and prognosis information, so all primary cancer samples are counted as non-metastasis, which may make our results tend to be conservative. In general, these data suggest that *PTPRT* may be closely related to metastasis in multiple cancers, so it is necessary to carry out postoperative adjuvant treatment measures, such as chemotherapy, for tumor patients with *PTPRT* mutations.

Methods

All samples and mutation data were downloaded from the cBioPortal database (<https://www.cbioportal.org>) and GENIE database (v6.1, <http://synapse.org/genie>). All nonsynonymous mutations including missense, frameshift, nonsense, nonstop, splice site and translation start site mutations were considered. In order to obtain potential metastasis markers, we screened the samples in cBioPortal as follows: (1) the samples were sequenced by MSK-impact panel; (2) the samples should be clear about whether they are primary tumor tissues or metastasis tissues, and tumor stage. (3) because the mutation characteristics of MSI-H samples are obviously different, we exclude the samples that are known to be MSI-H. For samples in the GENIE database, we excluded samples of unknown tissue types. Totally, we obtained 16,182 metastatic and / or stage IV cancers and 26,480 early primary cancers. We search for the molecular markers of metastatic cancer by comparing the mutation difference of a single driver gene (or gene modules) between early cancer and metastatic cancer. The difference analysis uses the two-sided Fisher exact test and Bonferroni's multiple hypothesis test. Driver genes of each cancer type and *PTPRT* were selected as candidate gene models for comparison[6]. This study was approved by the Ethical Committee of the Union Medical College Hospital Affiliated of Fujian Medical University. Since the data used in this study are all from the public database, the traditional informed consent was waived, and the participants in the original genome research provided informed consent.

Declarations

Author Contributions

Dr Chao Chen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Dr C.Chen and XQ.Zhang. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Dr C.Chen and XQ.Zhang.

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Competing interests

The authors declare that they have no competing interests.

Funding

This work is supported by the National Natural Science Foundation of China (No.81702826), the Science, Technology and Innovation Commission of Shenzhen Municipality under grant No. JSGG20170824152728492, the Science, Technology and Innovation Commission of Shenzhen Municipality under grant No. JCYJ20170303151334808.

Availability of data and materials

The datasets generated and analyzed during the current study can be obtained by contacting corresponding author.

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Table 1

Table 1 Distribution of cancer samples

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
Melanoma (SKCM)	1148	669
Skin Cancer, Non-Melanoma (SKCNM)	114	151

Figures

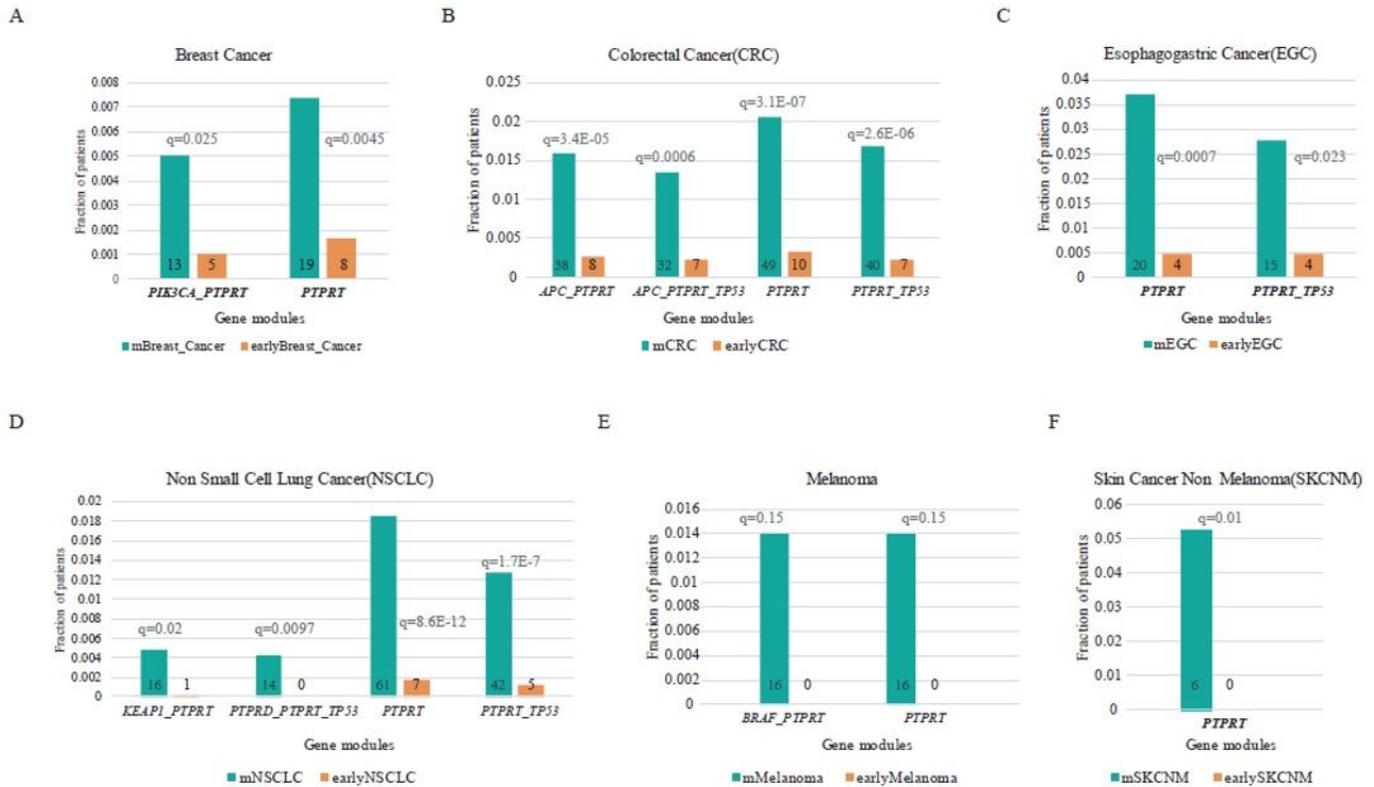


Figure 1

Comparison of mutations in different gene modules between early and metastatic cancers. A, Breast cancer (BRCA). B, Colorectal Cancer (CRC). C, Esophagogastric Cancer (EGC). D, Non-Small Cell Lung Cancer (NSCLC). E, Melanoma (SKCM). F, Skin Cancer, Non-Melanoma (SKCNM).