Protein Tyrosine Phosphatase Receptor Gamma as Potential Therapeutic Target for Chronic Myeloid Leukemia Patients

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Abstract
The worldwide CML incidence expects 100,000 patients every year thus representing a substantial health burden. A year 2000 is notable year, where Tyrosine kinase inhibitors (TKIs) had been introduced to the CML treatment plan. However, despite the dramatically reduce in mortality rate of CML patients due to TKIs, still over 25% of CML patients need to switch TKIs at least once during treatment timeline for many reasons. On the other hand, PTPRG behave as a tumor suppressor gene in different neoplasms and is strongly down-regulated in CML patients. We discussed briefly in series of articles the possible reasons of it is down regulation. Here, we discuss its role as potential therapeutic target in treatment plan.

Keywords
CML 2, PTPRG 3, leukemia, BCR::ABL1

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Introduction
The BCR::ABL1 alteration is the key to CML pathogenesis that leads to activation of different pathways. The global incidence rate of CML around one-two cases per 100,000 populations. Despite the fact the fusion gene BCR::ABL1 is the sole event to initiate the disease however, the presence of BCR::ABL1 only it’s not enough. Indeed, a mathematical modeling and other studies suggest more than one molecular pathway need to be affected for the full development of this hematological malignancy.1-4

On the other hand, the mainstream of CML management is targeting protein kinase (PK), leading to development of PK inhibitors, later known as tyrosine kinase inhibitors (TKIs). Currently, many TKIs approved by FDA of these, five TKIs: Imatinib Mesylate (IM), Nilotinib, Dasatinib, Ponatinib and Bosutinib are approved as first/second line of treatment5

The introduction of TKIs to the treatment plan has hugely transformed the life span of CML patients. Nonetheless, up to 25% of CML patients continue failing treatment due to activation/alteration of indirect pathways and more than 50% fail to achieve a deep molecular response (DMR) especially with IM treatment.6-8

Therefore, it is clear that not all CML patients will gain long-term benefits from TKIs. Therefore, it is important to investigate the negative regulatory mechanism that able to maintain the kinase in controlled balance, a role that can be defined as tumor suppressor.

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One of these regulatory mechanisms is represented by the activity of Protein Tyrosine Phosphatases (PTPs) that remove the phosphate groups derived from the activity of tyrosine kinases. As a result, the phosphorylation is reciprocally controlled by Protein Tyrosine Kinases (PTKs) and Phosphatases (PTPs) and maintained in equilibrium state in healthy individuals. Lately, there is growing body of evidence about the crosstalk between kinases and phosphatases in CML signaling pathways.

Among the latter, Protein Tyrosine Phosphatase Receptor Gamma (PTPRG) is a R5 member of the receptor-like family (RPTPs). It plays crucial role in intracellular signaling, thus controlling cell behavior such as proliferation and differentiation. PTPRG is well expressed in various isoforms in different tissues and considered a tumor-suppressor gene (TSG) mapped on chromosome 3p14.2. Structure of the human receptor tyrosine phosphatase gamma gene (PTPRG) and relation to the familial RCC 1 (3;8) chromosome translocation.9

One of the first direct evidence of a tumor suppressor role in cancer was described in CML, where a functional tumor suppressor role and its down regulation at diagnosis were observed.10

Later these findings were validated independently11 and extended in numerous studies.12-14 More specifically aberrant methylation of PTPRG genetic region was reported as one of possible mechanism of its down regulation. PTPRG has two CpG islands: one made of 25 CpGs sites in the promoter region and hypermethylation patterns were observed in CpG sites numbers 13 and 143. And one in intron 1 region with 26 CpGs interestingly, 23 out of 26 CpGs were hyper methylated when compared to healthy individuals.14

Other studies identified molecular mechanisms depending on PTPRG expression in a CML context,13 proposed that β-catenin, which has a key role in transcriptional regulator of stem cell renewal and is a BCR::ABL1 target is affected by PTPRG expression. PTPRG mediates both BCR::ABL1 and, probably, directly dephosphorylate β-Catenin. Promoting DNMT1 transcription causing PTPRG silencing through the hypermethylation of its promoter region, thus indicating a key role in the BCR::ABL1 activated pathway.13 More recently, our group had documented that PTPRG overexpression induce a global modification of gene expression and pinpoint the critical role of transcription factor in the reprogramming of CML cells.15

Ismail et al16 reported that the restoration of PTPRG protein expression on neutrophil-white blood cells following TKI-based therapy in CML patients was greater in optimal response patients when compared to those who failed treatment. Additionally, higher expression of PTPRG was observed with nilotinib treatment when compared to IM.11,16

We also proposed the influence of PTPRG single nucleotide polymorphisms (SNPs) and its ability to predict response of TKIs. In case-control study we reported three novel SNPs (c.1602_1603insC, c.85+ 14412delC, and c.2289-129delA) and two annotated SNPs (rs199917960) and c.1378-224A>G (rs2063204) were found to be significantly different in genotype and allele frequencies between the failed treatment cases compared to responders as well as healthy individuals, this correlation was noted with IM treatment.17,18

In the same context, the inhibitory concentration (IC50) of Nilotinib was documented to be more potent when compared to IM to inhibit of BCR::ABL1 activity but equipotent on progenitor cells,11 also reported that overexpression of PTPRG significantly improved IC50 for both treatments, while this effect was lost when PTPRG-CS (loss of function mutant) was expressed.12

The restoration of PTPRG levels was observed in CML patients in chronic and accelerated phases (fewer cases) however, due to low of incidence of CML in blast crisis further study is recommended to unveil the molecular details of PTPRG in advanced-phase disease.14,16,18

JAK2-STAT5 axis that is a relevant player in CML pathogenesis.19 A study documents interplay of PTPRG with JAK2-STAT5 pathway, with activation of PTPRG leading to dephosphorylation of JAK2-STAT5.20 Figure 1 summary the signaling integration of PTPRG with BCR::ABL1.

A recent review summarizes the current knowledge regarding the role of this gene in cancer, and there is no doubt that still more investigations need to be done to unveil the molecular details of gene product and it’s widely network with other signaling pathways. This will lead to exploit potential clinical application of PTPRG in solid and blood cancer21,22

In the limelight of achieving treatment-free remission (TFR), there is a trending approach of combining more than one TKIs or one of TKIs along with non-TKI drugs during treatment cycles to overcome any kind of PK domain resistance. Another noticeable trend is using multikinase Inhibitors that can overcome mutated wild-type BCR::ABL1, however, these drugs are still at different clinical trial phases.23,24

The mentioned approaches focused on one arm which is protein kinase, while the other arm protein tyrosine phosphatases are yet to be sufficiently explored.

PTPRG as an Attractive Therapeutic Strategy in CML

Tumor suppressors play a vital role in preventing tumorigenesis, several studies had briefly discussed effective of developing anticancer regimens targeting tumor suppressor pathway.25,26

TKI is known to be a lifelong treatment, based on the fact that CML patients are likely to develop Adverse Effects (AEs) of different grades, many of which lead to cardiovascular events. These may include, but not limited to, hypertension, left ventricular systolic dysfunction and eventually heart failure. These potential adverse events will eventually affect quality of life. In the same context also lies the dilemma of discontinuing TKIs. This will open the door to possible alternative ways to minimize AEs by promoting natural inhibitory mechanism.

Another important element may also affect treatment plan is CML Leukemic Stem Cells (LSCs). LSCs represent a low frequency subpopulation of leukemia cells that have ability of
self-renewal and drug resistance. Due to these unique proprieties, LSCs are the main reason of disease burden relapse. β-catenin is active regulator of LSCs, and as mentioned earlier, PTPRG has a vital role in β-catenin phosphorylation leaving less chances of escaping LSCs from treatment protocol.

Altogether a body of evidence support the interest in extending the analysis the predicting role of PTPRG expression in the outcome of CML treatment to a large cohort of CML patients particularly in the view that both mRNA as well as protein expression can be monitored using standard analytic procedures. These studies would pave the way to the justification of studies aiming to the specific modulation of PTPRG expression targeting either methylases or with the aid of demethylating agents that were tested without a clinically validated marker of efficacy to correlate with.27 The extension of studies aimed at exploring the possibility to exploit PTPRG as a monitoring tool and possible therapeutic target will help to establish a scientific and objective correlation between Health-Related Quality of Life (HR QoL) of CML patients and PTPRG role in the disease. A possibility exists that individual carrying very low level of this PTPRG might be at increased risk of developing CML, a condition that require the evaluation of PTPRG protein and mRNA expression levels in patient in remission phase of the disease compared with the general population, a study that has not be performed as yet.

Combination therapy targeting independent molecular pathways leaves less opportunity for escaping any kind of resistance to PK domain and is a well-established strategy in oncology. Targeting PTPRG in CML management is still hypothetical but might represent an interesting achievable target of small molecules that enhance PTPRG activity,28 possibly contributing to achieve a deeper molecular response in shorter time and reducing the chance of relapse in the long-term. This will significantly improve quality of life of CML patients. Furthermore, this is will open the door to adopt this approach to other cancers, such as chronic lymphocytic leukemia or solid tumors where PTPRG also plays an established tumor suppressor role.

**Conclusions**

Drug personalization is a future aim for physician’s experience, this could be done by tailor patient therapy to optimize efficacy and decrease toxicity of TKIs. This approach needs to open the spectrum of treatment plan via introducing/developing treatment options that increase durable DMR rates. Therapeutic targeting of TSGs is still available option however, much work is still be done to unveil the details of the molecular pathways involved.

In this article, we discuss the recent advances of PTPRG and its important role as tumor suppressor in CML disease,
and briefly discussed perspective of preclinical modeling of PTPRG as supportive therapy along with TKIs. However, further international collaboration studies are warranted to study larger and different cohorts in order to fully support PTPRG as therapeutic target or as prognostic and predictive values for the response to therapy of CML patients.

**Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| CML          | Chronic Myeloid Leukemia |
| PTPRG        | protein tyrosine phosphatase receptor gamma |
| BCR::ABL1    | A fusion gene formed when translocation between chromosomes 9 and 22 occurs |
| TKIs         | Tyrosine kinase inhibitors |
| PK           | protein kinase |
| FDA          | The Food and Drug Administration |
| IM           | Imatinib Mesylate |
| RPTPs        | Receptor-like family |
| TSG          | A tumor-suppressor gene |
| DNMT1        | DNA (cytosine-5)-methyltransferase 1 |
| IC50         | The inhibitory concentration |
| JAK2-STAT5   | The Janus kinase 2/signal transducer and activator of transcription 5 |
| AEs          | Adverse Effects |
| LSCs         | CML Leukemic Stem Cells |
| mRNA         | Messenger RNA |
| HR QoL       | Quality of Life |

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