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# Tyrosine kinase inhibitors modulate the expression of peroxiredoxins 1 and 2 in chronic myeloid leukemia cells

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ABSTRACT

Chronic myeloid leukemia (CML) is characterized by the presence of the BCR::ABL1 fusion protein with active tyrosine kinase activity. The BCR::ABL1 fusion protein induces the production of reactive oxygen species (ROS). DNA damage caused by ROS is involved in the mechanism of CML progression. Antioxidant systems include peroxiredoxins (PRDXs), which play various roles in hematological malignancies. Although tyrosine kinase inhibitors (TKIs) are known to affect ROS production, their effects on the expression of the antioxidants PRDX1 and PRDX2 remain unclear; thus, we aimed to evaluate the effects of TKIs on the expression of these PRDXs and ROS levels in CML cells. We found that TKIs, such as imatinib, nilotinib, and dasatinib, increased the gene expression of *PRDX2* in K562 cells; however, only dasatinib increased the cytoplasmic protein expression of PRDX2. Additionally, while TKIs reduced the gene expression of *PRDX1* in contrast to that of *PRDX2*, dasatinib increased the cytoplasmic protein expression of PRDX1. This discrepancy was linked to post-translational regulation through SUMOylation in cooperation with dasatinib. Our results suggest that the antioxidants PRDX1 and PRDX2 could serve as potential targets for TKIs in the treatment of CML.

## 1. Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder caused by the t(9;22) Philadelphia chromosome translocation, which fuses BCR to the c-ABL tyrosine kinase. The expression of the BCR::ABL1 fusion protein, which has high tyrosine kinase activity, induces genetic instability due to the production of reactive oxygen species (ROS) [1]. Mammals have developed antioxidant systems to protect cells from oxidative stress, but these systems are dysregulated in leukemia cells. Although the treatment of Philadelphia chromosome-positive leukemia has progressed dramatically, recurrence and treatment resistance caused by genomic instability are still major problems, and the increased production of ROS due to abnormalities in the expression of antioxidant enzymes is a therapeutic target [2]. Among the antioxidant enzymes, peroxiredoxins (PRDXs) belong to a family of thioredoxin-dependent peroxidases and are divided into two structural subgroups: typical 2-cysteine (PRDX1–5) and 1-cysteine (PRDX6) [2]. In addition to their role as antioxidants, PRDXs have various functions, including cell signaling, where ROS molecules act as second messengers [2].

One of the functions of PRDX1 is its interaction with the proto-oncogene ABL1, which inhibits tyrosine phosphorylation by interacting with the SH3 domain of the ABL1 protein. The BCR::ABL1 fusion protein retains the ABL1 SH3 domain, and the BCR moiety mediates binding to the ABL1 SH2 domain, which is required for the transforming activity of the BCR::ABL1 fusion protein. PRDX1 also inhibits the kinase activity of the BCR::ABL1 fusion protein and is thought to protect cells from oxidative stress caused by the BCR::ABL1 protein, acting as a tumor suppressor [3]. In contrast, a previous study showed that PRDX2 is overexpressed in neutrophils from patients with myelodysplastic syndrome, a clonal myeloid disorder that has the potential to progress to acute myeloid leukemia (AML). Additionally, there is an inverse relationship between neutrophil count, which reflects disease severity, and PRDX2 expression level [4]. Moreover, PRDX2 is epigenetically silenced in patients with AML, and low PRDX2 protein expression is associated with poor prognosis in patients with AML. These studies have shown that PRDX2 helps protect cells from oxidative stress in myelodysplastic syndrome, a preleukemic state, and that PRDX2 is suppressed when the disease progresses to AML, suggesting that PRDX2 functions as a tumor suppressor [5]. Notably, PRDX1 and PRDX2 are recognized as natural killer (NK) cell-enhancing factors (NKEF-A and -B) and play an important role as immunological activators; additionally, they can be secreted

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from some tumors and virus-infected CD8+ *T* cells [6]. Overall, these findings suggest that these peroxidases may be potential targets for leukemia therapy.

Tyrosine kinase inhibitors (TKIs) have made a significant contribution to the advancement of the treatment of CML; however, resistance to TKIs is still a major problem in CML management. Notably, the mechanisms of TKI resistance include chromosome instability caused by ROS production [7]. Research findings indicate that TKIs can regulate ROS production in the CML cell line K562 [8,9]. However, the effects and potential mechanisms of TKIs on the expression of the antioxidants PRDX1 and PRDX2 remain unclear. Therefore, this study aimed to investigate the effects of TKIs on ROS production and PRDX1 and PRDX2 expression in CML cells.

## 2. Materials and methods

The K562 and MOLT-4 cell lines were cultured in RPMI 1640 medium supplemented with 10 % fetal calf serum and antibiotics. TKIs and/or the small ubiquitin-like modifier (SUMO) inhibitor 2-D08 were added to the medium, and cells were cultured at 37 °C in 5 % $CO_2$ for 24 h. Intracellular ROS levels were determined by measuring the intensity of the fluorescent signal from a cell-permeable probe H2DCFDA. The gene and cytoplasmic protein expression levels of PRDX1 and PRDX2 were assessed using real-time PCR and western blotting. Quantitative PCR was based on the delta-delta method. Gene and protein expression levels were normalized to those of GAPDH. The sample for detection of SUMOylation was prepared by lysing the cells in the presence of N-ethylmaleimide. To detect SUMOylated PRDX1 protein, an immunoprecipitation assay was performed using the protein G-agarose. To assess the PRDX2 protein expression in the primary cells of CML patients, bone marrow mononuclear cells were separated and immunostained with anti-PRDX2 antibody. The statistical significance of the difference in mean values between the two groups was assessed using Student's *t*-test. Paired *t*-tests were used to compare the means between two related sample groups. Two-tailed *P*-values $<0.05$ were considered statistically significant. This study was approved by the institutional ethics committee of Tokyo Women's Medical University (No. 4601-R). Written informed consent was obtained from all patients before enrollment.

## 3. Results

### 3.1. PRDX1 expression and the effects of TKIs

First, we investigated the effects of TKIs on ROS production and the expression levels of PRDX1 under the following conditions: imatinib at 1 and 3 μM (Fig. 1A, left), nilotinib at 0.3 and 1 μM (Fig. 1A, middle), and dasatinib at 10 and 25 nM (Fig. 1A, right), and detected that each TKI reduced the intracellular ROS levels. Gene expression was evaluated in K562 cells treated with TKIs at the concentrations resulting in an effective decrease in ROS of 3 μM, 1 μM, and 10 nM for imatinib, nilotinib, and dasatinib, respectively. Importantly, these TKIs led to the downregulation of *PRDX1* gene expression in K562 cells (Fig. 1B, left); however, they did not induce downregulation in MOLT-4 cells, a non-CML T lymphoblast cell line (Fig. 1B, right). As PRDX1 is abundant in the cytosol, we evaluated its cytoplasmic protein expression. Contrary to the gene expression, the cytoplasmic protein levels of PRDX1 were increased in K562 cells treated with 10 nM dasatinib (Fig. 1C, left). Despite the discrepancy between the gene and cytoplasmic protein

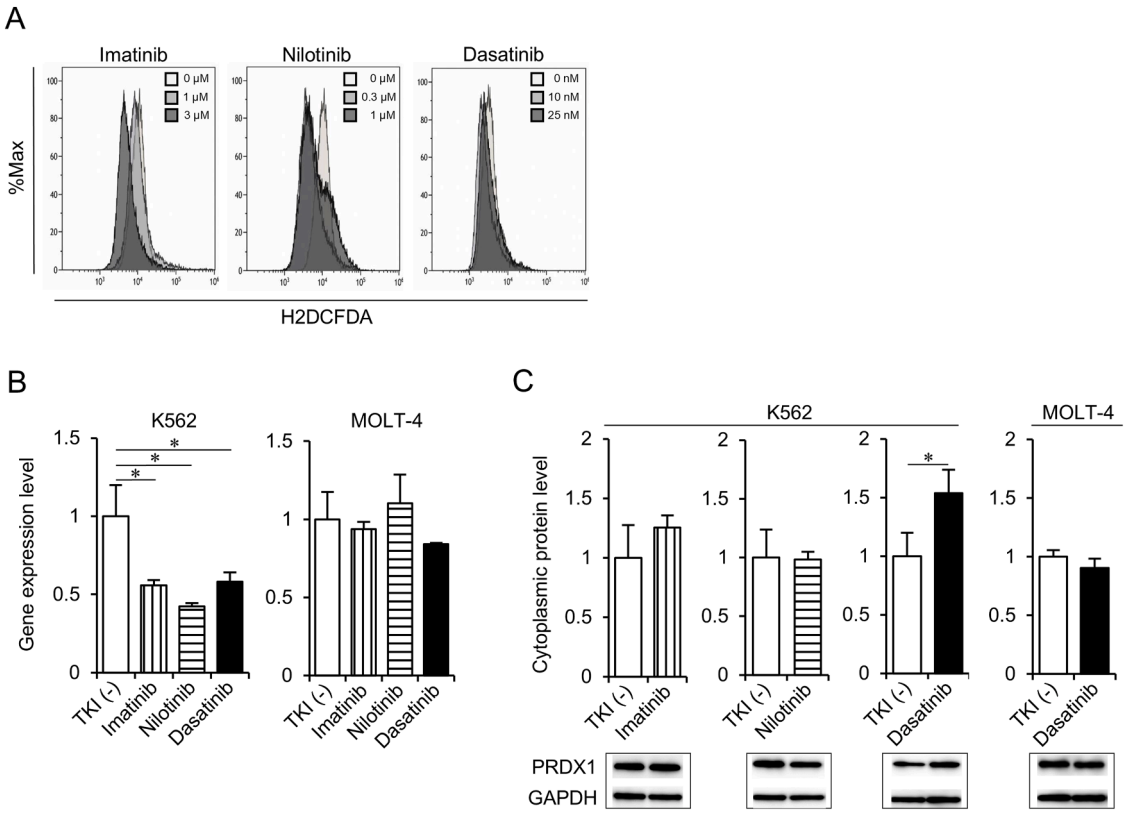


**Fig. 1.** Dasatinib modulates PRDX1 expression in K562 cells. (A) Intracellular levels of reactive oxygen species (ROS) were measured using a cell-permeable probe H2DCFDA (50 μM) and flow cytometry. K562 cells were treated with different tyrosine kinase inhibitors at indicated concentrations for 24 h. %Max: normalized histogram of counts. (B) Gene expression levels of *PRDX1* in K562 cells (left) and MOLT-4 cells (right). (C) Cytoplasmic expression levels of PRDX1 in K562 cells (left) and MOLT-4 cells (right). Cells were assessed following 24 h period treatment with 3 μM of imatinib (vertical stripes bar), 1 μM of nilotinib (horizontal stripes bar), and 10 nM of dasatinib (black bar). The densitometric analysis is shown in the upper panel, and representative western blot images are shown in the lower panel. Expression values relative to the control are shown as the mean ± standard deviation (SD) of values from triplicate experiments. *$p < 0.05$.

levels of PRDX1 in dasatinib-treated cells, imatinib and nilotinib were not associated with increased cytoplasmic expression of PRDX1 in K562 cells. This effect of dasatinib on the protein expression was not detected in MOLT-4 cells (Fig. 1C, right).

### 3.2. Dasatinib regulated PRDX1 expression via SUMOylation in K562 cells

As this discrepancy in the expression of PRDX1 suggested that dasatinib regulated the cytoplasmic protein levels of PRDX1 post-transcriptionally, we evaluated the SUMOylation of PRDX1 with a co-immunoprecipitation assay. As illustrated, when the anti-PRDX1 antibody was used to precipitate PRDX1-interacting cytoplasmic proteins, SUMO1 was detected as the theoretical band. This was in contrast to the findings with the negative control antibody (Fig. 2A, left). Conversely, when the anti-SUMO1 antibody was used, the PRDX1 band was also detected (Fig. 2A, right). Then, we confirmed that SUMO inhibitor 2-D08 did not affect the gene expression levels of *PRDX1* (Fig. 2B, left), but 2-D08 alone decreased the cytoplasmic PRDX1 expression levels (Fig. 2B, right). Moreover, the effect of dasatinib was diminished by co-culturing with 2-D08 (Fig. 2B, right).

### 3.3. Effects of TKIs on PRDX2 expression

Next, we evaluated the effects of TKIs on *PRDX2* gene expression levels in K562 cells. Unlike *PRDX1* gene expression, *PRDX2* gene expression significantly increased in K562 cells (Fig. 3A, left). Notably, no changes in gene expression were observed in MOLT-4 cells (Fig. 3A, right). Moreover, as shown in Fig. 3B, dasatinib significantly increased the cytoplasmic protein levels of PRDX2, whereas imatinib and nilotinib had no such effect in K562 cells. These effects were also not observed in MOLT-4 cells. We then investigated the impact of dasatinib treatment on primary bone marrow mononuclear cells from patients with CML. All patients had chronic-phase (CP) CML, and their characteristics are shown in Table 1. Dasatinib tended to increase the gene expression levels of *PRDX2* in primary cells, although the differences were not significant ($P = 0.0854$). Notably, one of the five patients with CP-CML (Patient number 2) exhibited a marked increase in *PRDX2* gene expression (Fig. 3C), and an immunocytochemistry assay of the bone marrow mononuclear cells from Patient number 2 showed an increase in PRDX2 protein levels (Fig. 3D).

## 4. Discussion

The activation of tyrosine kinase by the BCR::ABL1 fusion protein induces ROS production. We investigated the effects of TKIs on ROS production and the expression of PRDX1 and PRDX2, which act as tumor suppressors and antioxidants, in CML cells. Previous studies have demonstrated that TKIs can modulate ROS levels in K562 cells; treatment with 1.0 μM imatinib or 0.1 μM nilotinib for 16 h reduced ROS levels [8]. However, higher concentrations of nilotinib were shown to increase ROS production (IC50 8.4 ± 0.09 μM) for 24 h [9]. Similarly, dasatinib (IC50 5.8 ± 0.07 μM) increased ROS production over a 24 h period [9]. In our study, treatment of K562 cells with 1 and 3 μM imatinib, 0.3 and 1 μM nilotinib, and 10 and 25 nM dasatinib for 24 h resulted in reduced ROS levels. When gene expression was evaluated at concentrations resulting in an effective decrease in ROS production (3 μM, 1 μM, and 10 nM for imatinib, nilotinib, and dasatinib, respectively), TKIs decreased *PRDX1* gene expression but increased *PRDX2* expression. Notably, dasatinib treatment also increased the cytoplasmic protein expression of both antioxidants.

PRDXs are an antioxidant enzyme family involved in several functions, such as cell differentiation, cell growth, and carcinoma development. Gao et al. identified abnormal expression of PRDX1–6 in several types of cancer compared with normal tissues based on a comprehensive database analysis. Increased expression levels of PRDX1, PRDX4, and PRDX6 were associated with poor survival, whereas those of PRDX2 and PRDX3 were associated with favorable survival [10]. Notably, PRDX1 and PRDX2 have several functions wherein peroxide molecules serve as second messengers, in addition to their antioxidant roles. Moreover, they were first known as NKEF-A and NKEF-B, first identified as cytosolic proteins from red blood cells, and have been shown to augment NK cell activity. PRDX1 and PRDX2 may act through Toll-like receptor 4 in NK cells, enhancing their cytotoxic activity. Additionally, PRDX1 inhibits macrophage migration inhibitory factor, which is known to suppress NK cell activity. These findings are consistent with the observation that PRDX1 activates NK cells more strongly than PRDX2 as an NKEF [6]. As we develop a better understanding of leukemia treatment and the relationship between cancer and immunity, there have been both clinical and basic interests in the significance of NK cells for immunotherapy in patients with hematological malignancies [11]. The first-generation TKI imatinib significantly improved outcomes in patients with Philadelphia chromosome-positive leukemia. Alternative inhibitors, such as the second-generation TKIs dasatinib and nilotinib, have exhibited faster and deeper responses compared to imatinib. Moreover, dasatinib has been reported to increase NK cell numbers during treatment, enhancing

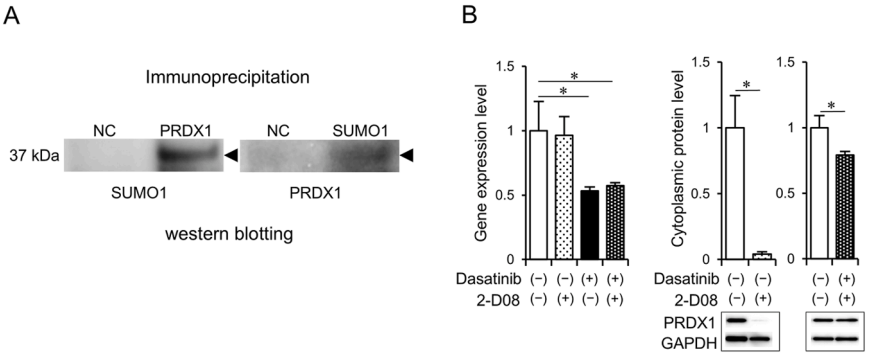


**Fig. 2.** Dasatinib and SUMOylation cooperatively regulated the cytoplasmic expression of PRDX1 independent of the effects on gene expression in K562 cells. (A) Cytoplasmic fractions of K562 cells were subjected to immunoprecipitation with anti-PRDX1 or anti-SUMO1 antibodies, followed by western blotting with anti-SUMO1 (left) and anti-PRDX1 (right) to detect SUMOylated PRDX1. Arrowheads (◂) indicate the theoretical band of SUMOylated PRDX1. NC: IP negative control. (B) Gene expression levels of *PRDX1* following treatment with 2-D08 alone (dotted bar), 10 nM of dasatinib without (black bar) or with 20 μM of 2-D08 (white dotted bar) (left panel). Right panels show the cytoplasmic protein levels. The densitometric analysis is shown in the upper panel, and representative western blot images are shown in the lower panel. Expression values relative to the control are shown as the mean ± standard deviation (SD) of values from triplicate experiments. $^*p < 0.05$.

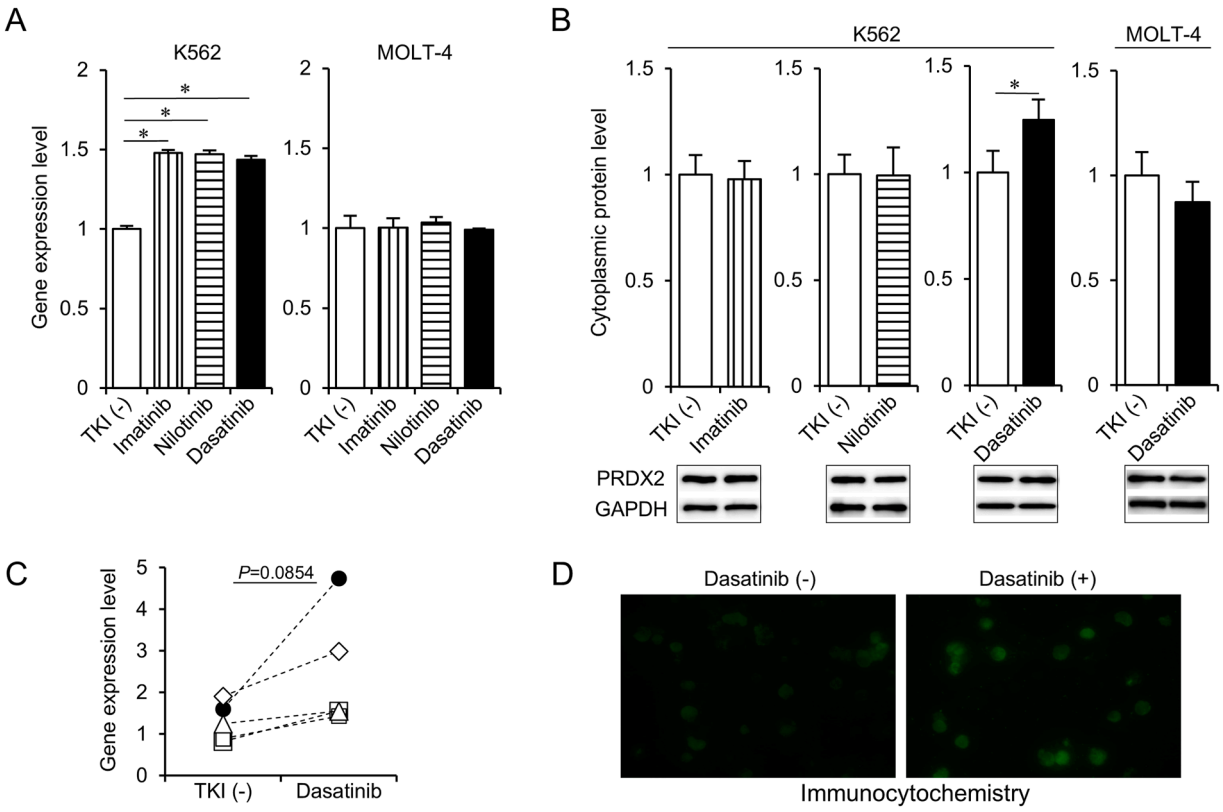


**Fig. 3.** Dasatinib induces PRDX2 expression in chronic myeloid leukemia (CML) cells. (A) Gene expression levels of *PRDX2* in K562 cells (left) and MOLT-4 cells (right). (B) Cytoplasmic expression levels of PRDX2 in K562 cells (left) and MOLT-4 cells (right). Cells were assessed following 24 h period treatment with 3 μM of imatinib (vertical stripes bar), 1 μM of nilotinib (horizontal stripes bar), and 10 nM of dasatinib (black bar). The densitometric analysis is shown in the upper panel, and representative western blot images are shown in the lower panel. Expression values relative to the control are shown as the mean ± standard deviation (SD) of values from triplicate experiments. (C) The line graph shows changes in *PRDX2* mRNA expression in primary bone marrow mononuclear cells from five patients with CML after 24-h period treatment without or with 10 nM of dasatinib (Patient no 2 indiated as ●). (D) Immunocytochemical staining of PRDX2 in primary bone marrow mononuclear cells from Patient number 2 with CML. Cells were treated without or with 10 nM of dasatinib for 24 h. *$p < 0.05$.

**Table 1**
Patient characteristics.

| Patient (number) | Age (years) | Sex | Sokal score | Hasford score | EUTOS score |
|---|---|---|---|---|---|
| 1 | 71 | Female | intermediate | intermediate | low |
| 2 | 32 | Male | low | low | low |
| 3 | 30 | Male | low | low | low |
| 4 | 68 | Male | low | intermediate | high |
| 5 | 82 | Male | intermediate | intermediate | low |

immune reactivity and improving prognoses [12]. Up to half of the patients receiving dasatinib treatment demonstrate lymphocytosis of large granular lymphocytes, which includes cytotoxic cells (NK and CD8+ *T* cells) and is associated with an anti-leukemic effect. Moreover, patients treated with dasatinib possessed increased numbers of classical (CD3-CD56+) and matured NK cells (CD56+CD57+) compared to imatinib- or nilotinib-treated patients. These patients presented lower expression of NK-inhibitory markers, which was associated with treatment response [12]. Furthermore, the effect of PRDX1 on NK cells has been applied in the development of chimeric antigen receptor-NK (CAR-NK) cells. Klopotowska et al. reported that NK cells lacked PRDX1 and generated CAR-NK cells expressing PRDX1, which displayed potent antitumor activity against breast cancer under oxidative stress [13].

Our results showed that dasatinib, not imatinib or nilotinib, increased the cytoplasmic levels of antioxidants PRDX1 and PRDX2 in CML cells, despite these TKIs affecting the expression of *PRDX1* and *PRDX2* similarly. Furthermore, dasatinib and SUMOylation cooperatively regulated the cytoplasmic expression of PRDX1 independently of their effects on gene expression. SUMOylation is a post-translational modification present in almost all eukaryotes and is essential for maintaining genomic integrity, regulating transcription, controlling gene expression, and stabilizing proteins [14]. SUMOs are ubiquitin-like polypeptides that conjugate to target proteins via an ATP-dependent enzymatic cascade similar to ubiquitylation. Many proteins, including those related to oxidative stress, can be modified by SUMOs. PRDX1 has also previously been reported to be modified by SUMOylation in liver cells [15], and we confirmed this in K562 cells. When TKI treatment reduced ROS levels, the suppression of *PRDX1* gene expression could be explained by its role as an antioxidant. The increase in cytoplasmic PRDX1 protein may result from the stabilizing effect of SUMOylation. Unlike *PRDX1* gene expression, *PRDX2* gene expression was increased by TKIs; however, the mechanism underlying *PRDX2* gene regulation remains unknown. Our results were derived from experiments using cell lines and a limited number of CML cells, and further investigations with larger sample sizes are needed to confirm our findings. However, these preliminary results suggest that dasatinib increases the protein expression of PRDX1 and PRDX2 in K562 cells, which are potential anti-cancer drug targets.

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## Data statement

The data reported in this study are available from the corresponding author upon reasonable request.

## Glossary

**BCR::ABL1 Fusion Protein**: An abnormal protein produced by the fusion of the *BCR* and *ABL* genes, which has increased tyrosine kinase activity and is associated with CML.

**Chronic Myeloid Leukemia (CML):** A type of cancer that affects the blood and bone marrow, characterized by the overproduction of myeloid cells.

**Peroxiredoxins (PRDXs):** The peroxiredoxin-based antioxidant enzyme system is one of the major antioxidant systems in humans. PRDXs were initially identified as radical scavengers. Currently, the intracellular functions of PRDXs are known to include not only antioxidant activity but also regulation of Redox signaling, the cell cycle, tumor suppression, aging, damage-associated molecular patterns, and many other processes.

**Reactive Oxygen Species (ROS):** Chemically reactive molecules containing oxygen, which can cause oxidative damage to DNA, proteins, and lipids. They are involved in cancer progression.

**Tyrosine Kinase:** An enzyme that adds a phosphate group to a tyrosine residue in a protein, playing a crucial role in signaling pathways that regulate cell division and growth.

## CRediT authorship contribution statement

**Hiroshi Kazama:** Conceptualization, Data curation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Yan-Hua Wang:** Methodology, Software, Visualization, Writing – review & editing. **Junji Tanaka:** Conceptualization, Writing – review & editing.

## Declaration of competing interest

The authors declare no potential conflict of interest regarding the content of this manuscript.

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