

Original Research Article

Formononetin acts synergistically with a JAK2 inhibitor to suppress growth in myeloproliferative neoplasm by inhibiting JAK/STAT3 signaling pathway

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Abstract

Purpose: To determine the effect of formononetin (FMNT) in the proliferation, drug resistance, and DNA damage of myeloproliferative neoplasm (MPN), and to evaluate the potential of FMNT as a therapeutic target.

Methods: Cell viability curves and colony formation assays were used to characterize the proliferation of HEL or HEL/R cells. Flow cytometry was conducted to assess the apoptosis of HEL or HEL/R cells, while western blotting was performed to evaluate the expressions of DNA H2AX, DNA-PK, and Rad51, which are indicative of DNA damage, and the phosphorylation levels of JAK2 and STAT3 were determined.

Results: Formononetin (FMNT) suppressed cell proliferation of HEL cells in a dose-dependent manner. It significantly reduced colony formation and promoted apoptosis of HEL cells ($p < 0.05$). For HEL/R cells, FMNT treatment significantly reduced cell viability, and resistance, and promoted apoptosis. Moreover, FMNT elevated H2AX levels and significantly reduced the expressions of DNA-PK and Rad51 in TG101209 (TG)-induced JAK-TKI-resistant cells ($p < 0.05$). Furthermore, FMNT decreased JAK2 and STAT3 phosphorylation in JAK-TKI-resistant cells.

Conclusion: Treatment with FMNT represses proliferation, promotes apoptosis, weakens JAK-TKI resistance, and strengthens DNA damage in MPN cells by suppressing JAK/STAT3 pathway. This suggests that FMNT is a potential therapeutic candidate for the treatment of MPN.

Keywords: Drug resistance, Formononetin, Janus kinase 2, Myeloproliferative neoplasm

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INTRODUCTION

Myeloproliferative neoplasms (MPN) is a clonal hematopoietic stem cell disease that includes polycythemia vera (PV), essential

thrombocythemia (ET), and primary myelofibrosis (PMF) [1]. Mutation of JAK2-V617F is common in patients with PV, ET, and PMF. The JAK2 gene encodes a non-receptor tyrosine kinase that is critical for signaling downstream erythropoietin,

thrombopoietin, and related receptors that control the expansion of erythrocytes and megakaryocytes [1]. The JAK2-V617F mutation is closely related to signal transducers and activators of transcription 3/5 (STAT3 and STAT5), and phosphatidylinositol 3-kinase (PI3K) [1,2].

Preclinical studies showed that orally administered JAK2-selective tyrosine kinase inhibitors such as TG101209 (TG) and TG101348 (SAR302503), reduced JAK2 phosphorylation and inhibited JAK2-V617F-induced phosphorylation levels of STAT5 and STAT3 in primary human MPN cells [3,4]. The drug resistance of JAK2-TKI is the most important factor limiting its drug effect. Therefore, it is important to determine the mechanism of potential drug resistance against JAK2-TKI, and to develop other new JAK2-V617F targeting combinations for MPN cells.

Traditional Chinese medicines play an important role in treating tumors and improving drug resistance [5,6]. FMNT is an active ingredient isolated from *Astragalus membranaceus*, which has a variety of pharmacological effects [7]. Studies have shown that FMNT possesses antioxidant and anti-inflammation properties, and also inhibits tumor growth [8,9]. FMNT improves the multidrug resistance of triple-negative breast cancer cells [10], and its combination with metformin enhances cell growth inhibition and induces the apoptosis of breast cancer cells mediated by the ERK1/2 signaling pathway [11]. Similarly, it inhibits the JAK/STAT3 pathway, and weakens the malignant phenotype of tumor cells [12].

However, the effect of FMNT on MPN is still unclear. In this study, cell viability curves and colony formation assays were used to analyze FMNT function in HEL cells. Apoptosis and DNA damage in HEL and HEL/R cells treated with FMNT were also evaluated. Furthermore, the phosphorylation levels of JAK2 and STAT3 were assessed after treatment with FMNT.

EXPERIMENTAL

Cell culture

Human erythroleukemia HEL92.1.7 (HEL) cells with JAK2-V617F were cultured in RPMI-1640 medium plus 10 % fetal bovine serum (Gibco, Grand Island, NY, USA) and 1 % non-essential amino acids.—Human erythroleukemia cells in logarithmic growth phase were treated with the designated concentrations of TG (S2692; Selleck Chemicals, Houston, TX, USA), which is a small

molecule JAK2-selective kinase inhibitor. Subsequently, the cells were washed and cultured in doses of TG starting from 0.1 μ M to obtain a population of cells capable of sustained growth in 1.0 μ M TG101209 (HEL/R), designated as JAK2-TKI-resistant HEL (HEL/R) cells [13].

Cell viability assay

Human erythroleukemia or HEL/R cells cultured in increasing concentrations of TG (0.1 to 100 μ M) were seeded into 96-well plates and treated with FMNT, TG, or FMNT + TG. The supernatant was then replaced with a new medium supplemented with 10 μ L CCK-8 (Dojindo Molecular Technologies, Kumamoto, Japan) in each well, and the cells were cultured in an incubator with 5 % CO₂ at 37 °C for 48 h. Absorbance was determined at 450 nm, and the cell viability ratios were calculated.

Colony formation assay

Single cells of HEL or HEL/R were suspended and seeded in separate 6-well plates. Each well was treated with 0, 2.5, 5, 10, and 20 μ M of FMNT, TG, or FMNT + TG. When the ocular cell clusters were formed, they were fixed with 4 % paraformaldehyde, followed by 0.1 % Crystal Violet staining (548-62-9; Sigma-Aldrich, Shanghai, China). The number of visible colonies was then counted.

Flow cytometry

Apoptosis was measured using an apoptosis detection kit (BD Biosciences, Franklin Lakes, NJ, USA) based on Annexin V-fluorescein isothiocyanate (FITC)/propidium iodide (PI), according to the manufacturer's manual. Human erythroleukemia HEL or HEL/R cells were cultured in lipopolysaccharide to induce cell injury, and then they were treated with 0, 2.5, 5, 10, and 20 μ M of FMNT, TG, or FMNT + TG. Then, the cells stained with FITC and PI were analyzed via cell sorting which utilized a FACS Calibur (BD Biosciences, San Jose, CA, USA). The data were further analyzed using FlowJo software (BD Biosciences).

Western blotting

Total cellular protein was extracted using RIPA lysis buffer (Thermo Fisher Scientific, Carlsbad, CA, USA). The protein concentration of the lysates was measured by A280 using Nanodrop 2000 (Thermo, Electron, Massachusetts, US). The samples with the same total protein were processed for immunoblots using the primary antibodies listed in Table 1, followed by

incubation with HRP-conjugated goat anti-rabbit IgG (B900210; 1:5,000; ProteinTech Group, **Table 1:** Antibodies used

Protein	Cat. no.	Manufacturer	Dilution
γH2AX	ab11174	Abcam, Cambridge, MA, USA	1:5,000
p-DNA-PK	PA5-105789	Thermo Fisher Scientific, Carlsbad, CA, USA	1:3,000
Rad51	14961-1-AP	Proteintech Group, Rosemont, IL, USA	1:3,000
p-JAK2	ab32101	Abcam, Cambridge, MA, USA	1:2,000
JAK2	ab108596	Abcam, Cambridge, MA, USA	1:5,000
p-STAT3	ab267373	Abcam, Cambridge, MA, USA	1:3,000
STAT3	10253-2-AP	Proteintech Group, Rosemont, IL, USA	1:4,000
β-actin	20536-1-AP	Proteintech Group, Rosemont, IL, USA	1:5,000

Rosemont, IL, USA). Finally, the target bands were visualized with ECL reagents (Solarbio Life Sciences, Beijing, China). For quantification of the western blot signals, the relative intensities of each band were measured using ImageJ software (National Institutes of Health, Bethesda, MD, USA), and the relative expression of the target proteins was normalized to β-actin.

Quantification and statistical analysis

Data were presented as mean ± standard error of the mean (SE) from three biological replicates, and differences between the two groups were compared using unpaired *t*-tests. Multiple group comparison was done using analysis of variance.

RESULTS

FMNT inhibited proliferation and enhanced apoptosis of MPN cells

The results showed that FMNT suppressed cell proliferation of HEL cells, which was dependent on FMNT concentration, with an IC₅₀ of approximately 11.95 μM (Figure 1 A). Moreover, colony formation assays were conducted on HEL cells treated with 2.5, 5, 10, or 20 μM FMNT, which showed that FMNT at doses above 2.5 μM significantly reduced colony formation (Figure 1 B and B'). Flow cytometry was also conducted to characterize the apoptosis of HEL cells treated with FMNT, and this showed that FMNT at concentrations of 5, 10, or 20 μM, significantly promoted the apoptosis of HEL cells (Figures 1 C and C'). The overall results showed that FMNT repressed the proliferation and promoted the apoptosis of MPN cells.

FMNT increases the sensitivity of JAK-TKI-resistant MPN cells

JAK2-TKI-resistant HEL (HEL/R) cells and HEL cells were cultured in increasing concentrations of TG, which showed that HEL/R had higher cell viability than HEL, and thus more resistant to TG (Figure 2 A). Furthermore, FMNT treatment

reduced the cell viability of HEL/R cells, indicating that FMNT attenuated the resistance of HEL/R (Figure 2 B). The cell viability was also determined using HEL/R cells treated with FMNT, TG, or FMNT + TG. Compared with the control group, there was a decline in cell viability after FMNT or TG treatment. Importantly, HEL/R cells treated with FMNT + TG showed a significant reduction in cell viability, when compared with FMNT or TG treatment alone (Figure 2 C).

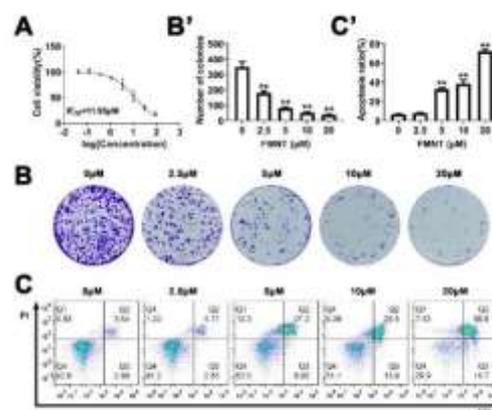


Figure 1: FMNT inhibited the proliferation and enhanced the apoptosis of MPN cells. (A) Viability of HEL cells after treatment with FMNT using doses of 0 to 20 μM; (B and B') The colony formation of HEL cells treated with FMNT; (C and C') Apoptosis of HEL treated with FMNT. ***P* < 0.01

Colony formation assays were then conducted on HEL/R cells treated with FMNT, TG, or FMNT + TG, and they showed that FMNT significantly reduced the colony formation of HEL/R, even after TG treatment (Figure 2 D and D'). Flow cytometry was also conducted to determine apoptosis of HEL/R cells, and it showed that FMNT treatment promoted cell apoptosis of HEL/R, along with those treated with TG (Figure 2 E and E'). Therefore, FMNT treatment weakened the JAK-TKI resistance of MPN cells.

FMNT increases DNA damage in JAK-TKI-resistant MPN cells

Western blotting was used to evaluate the expressions of these three molecules. Specifically, a single treatment with FMNT or TG promoted H2AX levels when compared with the control group. When treated with FMNT and TG together, H2AX levels were drastically elevated, showing that FMNT enhanced DNA damage in TG-induced JAK-TKI-resistant cells. For DNA-PK and Rad51, their expressions increased after a single treatment with FMNT or TG. However, FMNT significantly reduced the expressions of DNA-PK and Rad51 in TG-induced JAK-TKI-resistant cells, when compared with FMNT or TG separately treated cells (Figure 3). Together, the results showed that FMNT increased DNA damage in JAK-TKI-resistant-MPN cells.

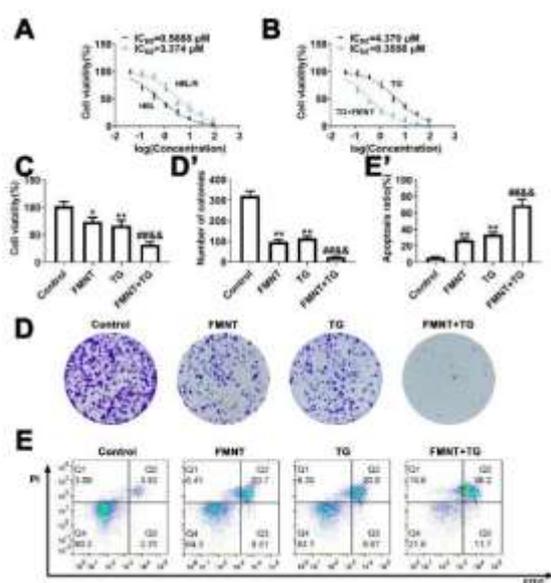


Figure 2: FMNT increased the sensitivity of JAK-TKI-resistant MPN cells. (A) Viability of JAK2-TKI resistant HEL (HEL/R) cells and HEL cells; (B) FMNT reduced the viability of HEL/R cells treated with TG or TG + FMNT; (C) Viability of HEL/R cells treated with FMNT, TG, or FMNT + TG; (D and D') The colony formation assay conducted on HEL/R cells treated with FMNT, TG, or FMNT + TG; (E and E') Apoptosis of HEL/R cells. (**) FMNT or TG vs. Control; (##) FMNT + TG vs. FMNT; (&&) FMNT + TG vs. TG. * $P < 0.05$, **/##/&& $p < 0.01$

FMNT inhibits the JAK/STAT3 pathway.

The phosphorylation levels of JAK2 and STAT3 proteins were measured by western blotting, and it showed that JAK2 and STAT3 phosphorylation was significantly reduced in FMNT- or TG-treated cells when compared with the control group. In the FMNT + TG group, JAK2 and STAT3 phosphorylation significantly reduced when compared with a single treatment with FMNT or TG, indicating that FMNT further decreased JAK2 and STAT3 phosphorylation in TG-treated

cells (Figure 4). These results showed that FMNT treatment suppressed the JAK/STAT3 pathway in JAK-TKI-resistant MPN cells.

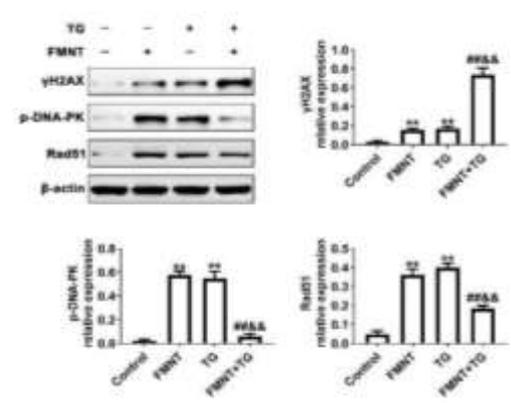


Figure 3: FMNT increases DNA damage in JAK-TKI-resistant MPN cells. Western blotting was conducted to evaluate the expressions of γ -H2AX, DNA-PK, and Rad51 involved in DNA damage. **FMNT or TG vs. Control; (##) FMNT + TG vs. FMNT; (&&) FMNT + TG vs. TG (**/##/&&) FMNT or TG vs. Control; (##) FMNT + TG vs. FMNT; (&&) FMNT + TG vs. TG. **/##/&& $P < 0.01$

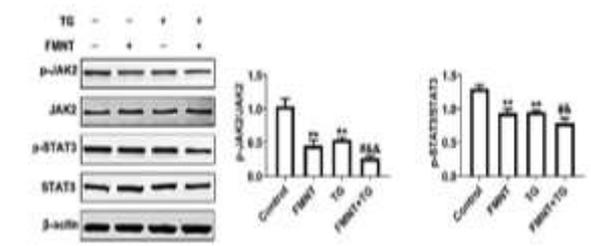


Figure 4: FMNT inhibits the JAK/STAT3 pathway. The protein expression and phosphorylation levels of JAK2 and STAT3. ** FMNT or TG vs. Control; # FMNT + TG vs. FMNT; & (&&) FMNT + TG vs. TG. #/##/&& $p < 0.05$, **/##/&& $p < 0.01$

DISCUSSION

MPN is a group of rare blood cancers, in which excessive white blood cells, red blood cells, or platelets are produced in the bone marrow. Studies have shown that FMNT possesses pharmacological functions that aid the inhibition of tumor growth, as well as the activities involved in anti-oxidation and anti-inflammation [8,9]. Moreover, it has a synergistic effect with temozolamide in promoting apoptosis and inhibiting the migration of tumor cells [15]. The combination of FMNT and metformin enhances cell growth inhibition and induces apoptosis of breast cancer cells [11]. Studies have shown that in triple-negative breast cancer, FMNT improved tumor cell resistance to paclitaxel by inhibiting autophagy [6]. The results of the present study showed that FMNT treatment decreased cell viability, weakened colony formation ability, and accelerated the apoptosis of HEL cells. Thus, it is

reasonable to conclude that FMNT repressed the proliferation and promoted the apoptosis of MPN cells.

Myeloproliferative neoplasm is a clonal hematopoietic stem cell disease with a common mutation of JAK2-V617F. Several JAK2-TKIs including TG101209 and TG101348, reduce JAK2 phosphorylation and JAK2-V617F-induced phosphorylation of STAT5 and STAT3 in primary human MPN cells [3,4]. The drug resistance of JAK2-TKI is the most important factor limiting its therapeutic effect. Therefore, the potential drug resistance mechanism against JAK2-TKI and the development of other new JAK2-V617F targeting combinations for MPN cells are currently the intense focus of research. Furthermore, FMNT plays an important role in treating tumors and improving drug resistance. For example, FMNT improved multiple drug resistance of tumor cells in triple-negative breast cancer cells [10]. Thus, it is necessary to evaluate the efficacy of FMNT in JAK-TKI-resistant MPN cells. Importantly, the results of this study showed that FMNT weakened the JAK-TKI resistance of MPN cells, which suggests that FMNT may be a novel therapeutic candidate for MPN treatment.

Accumulating evidence shows that the activation of the DNA damage response is closely related to resistance to genotoxic anti-tumor therapeutics. Elucidation of how FMNT causes DNA damage would help to identify how it improves drug resistance. In the present study, western blotting was used to analyze three typical biomarkers of DNA damage. The γ H2AX, which is a histone variant H2AX with Ser-139 phosphorylation, is an early cellular response marker in the induction of DNA double-strand breaks. Detection of this phosphorylation has been considered a specific marker for the initiation of DNA damage [16]. The Rad51, a eukaryotic RecA homolog, plays a critical role in repairing DNA double-strand breaks via homologous recombination. It is recruited to the fork to promote DNA damage tolerance [17]. The DNA-PK functions in DNA double-strand break repair, and in triggering apoptosis at critically shortened telomeres. In addition, DNA-PK is involved in the secretion of pro-metastatic proteins by modifying the tumor microenvironment. For example, DNA-PK acts as a metastatic driver by stimulating angiogenesis and tumor migration in melanomas [14]. Therefore, it is reasonable to suggest that FMNT regulates JAK-TKI resistance by promoting DNA damage. It has been reported that FMNT inhibited the JAK/STAT3 pathway, thereby repressing the malignant phenotype of tumor cells [12]. Furthermore, the JAK2-V617F

mutation is mediated by STAT5 and STAT3 [1,2]. It has been reported that JAK2-TKI-resistant HEL/R cells exhibited significantly higher IC₅₀ values for JAK2-TKI, which was associated with higher phosphorylation levels of JAK2, STAT5, and AKT [13]. The JAK/STAT3 pathway is repressed by Taxifolin in a dose-dependent manner [18].

CONCLUSION

Formononetin reduces JAK2 and STAT3 phosphorylation, thus inhibiting JAK/STAT3 pathway. It also plays an important role in repressing the proliferation and promoting the apoptosis of MPN cells, decreases JAK-TKI resistance and strengthens DNA damage by suppressing JAK/STAT3 pathway in MPN cells. Therefore, FMNT is a promising therapeutic candidate for the management of MPN.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities relating to claims relating to the content of this article will be borne by the authors. Huijun Jiang and Xiaoqun Zheng designed and conducted the study; Huijun Jiang, Zaijing Fan, and Jiashan Li supervised data collection analyzed and interpreted the data; Huijun Jiang and Xiaoqun Zheng prepared the manuscript for publication and reviewed the draft of the manuscript. All authors read and approved the manuscript for publication.

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