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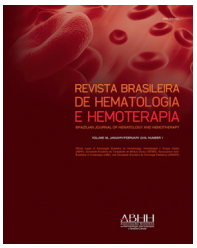

Scientific Comment

# Reactive oxygen species overload promotes apoptosis in JAK2V617F-positive cell lines☆

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Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), including essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF), are characterized by excessive myeloid proliferation, with predominant megakaryocytic, erythroid, and megakaryocytic/granulocytic expansion, respectively, and have a potential of transformation to acute myeloid leukemia.[1] From the molecular point of view, the Janus kinase 2 (JAK2)/signal transducer and activator of transcription (STAT) signaling pathway plays an important role in the pathogenesis of MPNs. A recurrent gain-of-function mutation, V617F in JAK2, has been reported in most PV cases and in more than half of ET and PMF cases.[2] In JAK2V617F-negative patients, other gain-of-function mutations in genes related to JAK2/STAT signaling activation, including *JAK2* exon 12,[3] *MPL*[4] and *Calreticulin* mutations,[5,6] have been identified.

The current therapies for MPN are limited and do not result in the elimination of the malignant clone. The only curative approach for these diseases is allogeneic stem cell transplantation.[7] Ruxolitinib is a selective JAK1/2 inhibitor approved by the Food and Drug Administration (FDA) of the United States for the treatment of intermediate and high-risk PMF and PV patients with inadequate response or intolerance to hydroxyurea. Results from phase III clinical trials demonstrated that ruxolitinib is well tolerated, reduces inflammatory cytokines and splenomegaly, and ameliorates constitutional symptoms in PMF patients.[8–10] Similarity, ruxolitinib controls the hematocrit levels, reduces the spleen volume, and improves symptoms in PV patients.[11] However, ruxolitinib treatment does not reverse bone marrow fibrosis, suggesting that additional therapeutic strategies are required.

Reactive oxygen species (ROS) play a singular role in MPN cell biology. Marty et al.[12] showed that hematopoietic cells from a JAK2V617F knock-in mice model present higher levels of ROS compared to those from normal mice, contributing to DNA damage and genomic instability, which promote disease progression. An increased basal level of ROS was also observed in primary hematopoietic cells from MPN patients compared to those from healthy donors.[13,14] Ahn et al.,[14] exploring the molecular mechanism of elevated JAK2V167F-induced ROS levels and cell survival under this stress condition, found that, due to DNA damage, B-cell lymphoma-extra large (BCL-XL) repression may be compromised.

In the current edition of the Revista Brasileira de Hematologia e Hemoterapia, Tavares et al.[15] report that L-amino acid oxidase (LAAO) derived from *Calloselasma rhosostoma* snake venom exhibits cytotoxicity and induces apoptosis in JAK2V617F-cell lines (HEL and SET2) in a ROS production-dependent manner. The anti-cancer effects of the LAAO isolated from the venom of other snake species has been

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described in solid tumors[16–18] and leukemia[19,20] cell lines. Notably, it has been reported that LAAO isolated from *C. rhosostoma*[20] and *Bothrops pirajai*[19] did not exert a prominent cytotoxic effect in peripheral blood mononuclear cells isolated from healthy donors and that rusvinoxidase, the LAAO isolated from *Daboia russelii russelii* was non-toxic in mice,[21] suggesting that cancer cells may be more susceptible to the cytotoxicity induced by these compounds. Recently, Mukherjee et al.[21] observed that treatment with rusvinoxidase induces ROS production and caspases activation, and also downregulates BCL-XL in the MCF-7 breast cancer cell line.

The work by Tavares et al.[15] is an important step to establishing the cellular functions of LAAO in MPN cell models and provides additional insights into the development of new therapies. However, it is still necessary to establish the specific effects of LAAO isolated from *C. rhosostoma* in normal hematopoietic progenitors, primary cells from MPN patients and JAK2V617F-driven murine models. The research conducted by Tavares et al.[15] also paves the way to an important frontier of knowledge: even though JAK2V617F-positive cells exhibit increased ROS levels compared to normal cells, the overload of ROS can elicit apoptosis in JAK2V617F-positive cells. The better understanding of the molecular mechanisms involved in the survival of JAK2V617F-positive cells under oxidative stress may be an interesting therapeutic opportunity.

Based on the data presented by Tavares et al. in MPN models and the findings from other research groups using solid tumor models, and taking into account that JAK2/STAT5 activation leads to aberrant expressions of BCL-XL,[22] future investigations verifying the effects of the combined treatment of JAK inhibitors and ROS inductors may be of interest.

## Conflicts of interest

The authors declare no conflicts of interest.

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