doi: http://dx.doi.org/10.11606/issn.1679-9836.v102i1(ed.esp.)e-204653 Rev Med (São Paulo). 2023 Jan-Feb;102(1 ed. esp.):e-204653.

Letter to the Editor

Inhibition of BRD4 and mTOR pathway can modulate HVEM and GAL-9 in AML cells

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Dear Editor,

In the last decades, the development of new therapies has changed the scenario for hematologic neoplasia. However, for Acute Myeloid Leukemia (AML) there are still few options of treatments approved, which raises major concerns for the patients carrying this disease. AML affects mostly people over 65 years old and a significant part of these patients does not have good response to current chemotherapy treatment (cytarabine and daunorubicin) as well as for stem cell transplantation[1,2]. Recent studies have suggested BRD4 protein as a promising AML treatment target, however, resistance to BRD4 inhibitor treatment is reported in AML cells[3,4]. When overactivated, mTOR pathway is a signaling pathway linked to AML pathogenesis and the maintenance of malignant characteristics[5]. Our research group has previously shown that combining BDR4 inhibitor and mTOR pathway inhibitor can overcome resistance in AML cell lines by inducing cell cycle arrest, apoptosis, and DNA damage. This previous result follows literature about mantle cell lymphoma resistance to inhibitions of mTOR pathway[6]. Since immune checkpoint receptors are gaining importance in cancer research and showing promising results, it would be relevant to unravel the impact of BRD4 and mTOR inhibition in these receptors. Therefore, our objective was to investigate if this combined inhibitory treatment could modulate the expression of immune checkpoint receptors in AML cell lines.

We evaluated basal gene expression of immune checkpoints in AML cell lines by quantitative polymerase chain reaction (qPCR). We observed that HVEM and GAL-9 were expressed in these cell lines. After that, we treated cell lines with BRD4 inhibitor (JQ1), mTOR pathway inhibitor (Rapamycin), both inhibitors (Combo) and DMSO (vehicle). We observed modulation of the co-receptors HVEM and GAL-9 in some of the treated cells. We have also performed a killing assay with AML cell line treated and challenged to NK cells killing. This experiment showed increase death rate in Combo treatment when compared to all other treatments, suggesting a relevant role of the combined treatment in the modulation of checkpoint immune receptors.

In conclusion, our data confirm the direct anti-leukemic effect of the JQ1 and Rapamycin combined treatment and indicate that this treatment could downregulate immune checkpoint receptors, such as HVEM and GAL-9 in AML cells, reinforcing the possible future use of this combined therapy in AML patients.

Best regard,

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Received: 2022, Nov 19
Accepted: 2022, Nov 22