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Antiproliferative activity of 6-(imidazo [1, 2-a] pyridine-3-yl)-N-(4-piperidinyl)-2-pyridinamine on diffuse large B-cell lymphoma through IRAK4 inhibition

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Potent interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitors have been explored as a blockade of toll-like receptor/interleukin-1 receptor (TLR/ILR) signaling pathway to alleviate autoimmune-related diseases including rheumatoid arthritis and multiple sclerosis. Additionally, some cancers have been reported to show an increase in IRAK4 activity or to bear L265P mutation in MyD88, adaptor protein of TLR/IL1R, resulting in constitutive activation of a cascade of downstream signaling pathway. A hit 6- (imidazo [1, 2-a] pyridine-3-yl)-N-(4-piperidinyl)-2-pyridinamine, which was originally discovered from JNK kinase screening project at UCB, had considerable potency in an enzyme assay with IC50 of 216 nM. To delineate the underlying mechanism of IRAK4 target-based inhibition of lymphoma proliferation, in this study, this compound was further evaluated in cell-based assays. Use of an IRAK4 inhibitor potently down-regulated the LPS-induced NFκB transcriptional activity in NFκB-luciferase/A549 stable cell line and NO production in RAW264.7 stimulated with LPS. Moreover, a subgroup of DLBCL, OCI-Ly3, has a mutation in MyD88 and can aggressively proliferate in clumps even though not being stimulated. Treatment of OCI with IRAK4 inhibitor induced change of cell aggregates into either small fragmented aggregates or single cell, altering morphologically cells with low viability, as determined in a MTS assay. Furthermore, cells exposed to IRAK4 inhibitor were subjected to flow cytometer analyses in order to examine cell death modality. When cells were treated with a hit compound, there was an increase in population of cells undergoing early apoptosis and late apoptosis with treatment times. Cell death was executed through activation of caspase 3/7, as demonstrated by the fact that use of a pan-caspase inhibitor zVAD could rescue IRAK4 inhibitor-induced cell death. Therefore, IRAK4 targeting is proposed to be a promising strategy in controlling the proliferation of MyD88-defective lymphoma in addition to treatment of autoimmune-related diseases.

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