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HDACIs and the inhibition of invasive potential

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Commentary to: Ierano C, Basseville A, To KK, Zhan Z, Robey RW, Wilkerson J, Bates SE, Scala S. Histone deacetylase inhibitors induce CXCR4 mRNA but antagonize CXCR4 migration. Cancer Biol Ther 2013; 14:175-83; PMID:23192271; http://dx.doi.org/10.4161/cbt.22957

A major problem in the treatment of cancer and prolongation of patient survival is the dissemination of cells from a defined tumor site into a loco-regional disease and ultimately to full metastatic spread into distant organs. In the manuscript by Ierano et al. multiple chemically diverse histone deacetylase inhibitors (HDACIs) in tumor cell types of many diverse origins were shown to increase expression of the receptor CXCR4; a receptor whose expression promotes metastatic spread of tumor cells and that is correlated with a stage independent poor prognosis.[1,2] The ligand of CXCR4, CXCL12, also called stromal cell-derived factor (SDF1), stimulates signaling through multiple pathways downstream of the CXCR4 receptor including SRC kinases, ERK1/2, and STAT3. Inhibition of SRC, ERK or STAT3 can all suppress tumor cell migration and reduce the threshold at which tumor cells undergo apoptosis.[3-8] The authors noted that despite increased CXCR4 expression following HDACI treatment, exogenous CXCL12 ligand had a reduced ability to stimulate cell signaling processes, with the phosphorylation of both SRC and STAT3 at activating sites declining. This resulted in less induced migration of HDACI-treated tumor cells. No studies were undertaken to determine whether HDACI-treated cells transduced to express activated forms of SRC or STAT3 or retained their invasive phenotype; however a loss of SRC and STAT3 signaling would predict for a less invasive phenotype.

Precisely how and why signaling by CXCR4 was being altered by HDACIs was not investigated in the manuscript. Of particular interest would be whether cell surface levels of CXCR4 are altered despite an overall increase in receptor protein levels. Another possibility is that the CXCR4 receptors or other docking proteins who function to mediate CXCR4 function have had their expression and/or acetylation changed by HDACI treatment such that transduction of signals does not take place to SRC/STAT3. It is also possible that HDACIs, drugs known to increase reactive oxygen species levels and the basal level of ERK1/2 activity, may have also caused some form of uncoupling of the CXCR4 receptor from some of its downstream signaling intermediates. As protein tyrosine phosphatases are highly ROS-sensitive and the activity of SRC and STAT3 are both regulated by tyrosine phosphorylation, the HDACI effect on ROS/PTPase function may also be mechanistically involved in this process.

The data in the present manuscript also draw attention to the use of clinically relevant small molecule inhibitor drugs that could be used to suppress the invasive phenotype and simultaneously promote tumor cell killing. For example, there are a number of FDA-approved or late Phase II/III trial clinically relevant SRC inhibitors, e.g., dasatinib, AZD0530; a JAK-STAT inhibitor e.g., Xeljanz; and MEK1/2 inhibitors, e.g., AZD6244, trametinib. The rational combination of such agents would likely both reduce the invasive potential of tumor cells as well as increase the levels of apoptosis or, in addition, cell radio-/chemo-sensitivity. Other groups are also attempting to block invasion using novel approaches, e.g., inhibition of *mda-9*.[9] At present, whether the combination of HDACIs with such signal modulators

result in a less invasive phenotype will require additional experimentation.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

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