**CD157 reduces acutemyeloid leukemia cell sensitivity tocytarabine through upregulation of MCL-1 anti-apoptotic protein**

# CD157 reduces acute myeloid leukemia cell sensitivity to Cytarabine through upregulation of Mcl-1 anti-apoptotic oncoprotein

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**Background**

Acute myeloid leukemia (AML) is a heterogeneous malignancy characterized by the expansion of immature myeloid cells. Patient survival is low due to the occurrence of chemoresistance and tumor relapse. However, mechanisms underlying drug resistance in AML patients remain largely unknown. Therefore, to clarify the molecular basis of drug resistance and to identify novel markers with potential clinical utility represent an urgent need.

CD157, an adhesion molecule expressed by myelomonocytic cells, bone marrow stromal cells and selected epithelial cancers, was found expressed in more than 90% of AML both at diagnosis and after relapse, although at variable levels.

In this study we investigated i) the role of CD157 in drug response, and ii) explored the intracellular pathways underlying the functional properties of CD157 in AML cells.

**Materials and Methods**

U937, THP-1 and OCI-AML3 AML cell lines engineered for the expression of CD157 as well as fresh AML blasts were used as in vitro models for functional studies. The viability of cells treated with Cytarabine (AraC) alone or in combination with S63845 (a specific inhibitor of Mcl-1 anti-apoptotic protein) was assessed by PrestoBlue and Annexin V/PI assays. Intracellular signaling pathways were analysed by Western Blot and Flow Cytometry.

**Results**

Ligation of CD157 by SY11B5 agonistic mAb elicited a time- and dose-dependent pro-survival effect, compared to the isotype-matched control mAb, both in fresh AML blasts and cell lines. This effect was accompanied by activation of the PI3K/Akt/Bcl-2 pathway leading to reduced sensitivity to apoptotic signals and AraC treatment. Consistent with these results, knockdown of CD157 enhanced AML cell sensitivity to nutrient deprivation and to AraC cytotoxicity. Furthermore, CD157-positive cells treated with AraC showed a remarkable increase of Akt phosphorylation, decreased cleavage of the pro-apoptotic Bax protein and reduced degradation of the anti-apoptotic Mcl-1 protein, compared to CD157-negative cells. These findings suggested that the modulation of these intracellular pathways could be implicated in the pro-survival effect mediated by CD157. Indeed, treatment of CD157-positive cells with the S63845 Mcl-1 inhibitor in combination with AraC dampened the activity of Mcl-1 anti-apoptotic protein and rescued AML cell sensitivity to chemotherapy.

**Conclusion**

Overall, these results demonstrate an essential role of CD157 as a regulator of survival, stress resistance and drug sensitivity in AML blasts, and suggest a potential clinical utility of CD157 as biomarker to guide treatment with new combinatorial therapeutic strategies to overcome drug resistance.