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Acute myeloid leukemia (AML) is characterized by the accumulation of clonal or oligoclonal undifferentiated leukemic blasts in the bone marrow (BM) and/or blood that exhibit uncontrolled growth, differentiation block, and impaired apoptosis. Despite high rates of remission obtained with conventional chemotherapy, disease relapse remains a major clinical challenge. Increasing evidence indicates that the BM microenvironment plays a key role in leukemic cell survival, promoting drug resistance and influencing outcome. Therefore, the identification of molecules involved in protection of AML cells mediated by BM niche may leads to the design of novel therapeutic strategies.

CD157 glycoprotein is expressed by myeloid cells, bone marrow stromal cells (BMSCs) where it supports pre-B cell growth, and by vascular endothelial cells where it is involved in the control of leukocyte diapedesis.

In this study we investigated the functional role of CD157 in AML blasts and in the interplay between leukemic cells and BMSCs.

We analyzed the expression of CD157 in 45 BM blood samples from AML patients at diagnosis. CD157 was heterogeneously expressed by all AML samples, with higher expression in M4 and M5 AML subtypes. CD157 ligation by an agonistic antibody both in fresh AML and OCI-AML3 cell line, activated the phosphatidylinositol 3-kinase (PI3K)/AKT/Bcl-2 signaling pathway leading to increased cell survival and adhesion, and influencing tumor cell resistance to apoptotic signals and sensitivity to cytarabine (AraC) treatment. To confirm these findings, the expression of CD157 was knocked down by means of a short hairpin RNA in THP1 and U937 AML cells. Loss of CD157 expression caused increased cell sensitivity to nutrient deprivation and to AraC cytotoxic effect and altered cell apoptosis. Indeed, CD157-negative cells showed lower levels of Mcl1 anti-apoptotic and higher levels of Bax pro-apoptotic Bcl-2 family members, than CD157-positive cells.

CD157 was also expressed by fresh BMSCs isolated from AML patients. In vitro, forced expression of CD157 in HS5 human BMSCs strengthened the protection mediated by BMSCs on AraC-induced cell death driving leukemia cells toward quiescence.

Collectively, these results suggest that CD157 has a functional role both in AML cells and BM niche and is involved in the stroma-mediated protection of AML cells against cytotoxic drugs, hinting to the potential clinical utility of CD157 as therapeutic target.