CD157 contributes to the environment-mediated chemoresistance in acute myeloid leukemia

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saydin@cittadellasalute.to.it

S. Augeri[1], S. Morone[1], S. D'Ardia[2], S. Aydin[2], C. Dal Secco[1], E. Ortolan[1] and A. Funaro[1].
[1]Dipartimento di Scienze Mediche, Università di Torino; [2]Dipartimento di Ematologia ed Oncologia, A.O.U Città della Salute e della Scienza, Torino, Italy

Background

Acute myeloid leukemia (AML), the most common acute leukemia in adults, has a poor long-term prognosis due to development of chemoresistance and eventual tumor relapse. Increasing evidence suggests that the interaction between leukemic cells and bone marrow (BM) microenvironment contributes to tumor survival and exerts protective effects from chemotherapy-induced tumor cytotoxicity.

CD157 is an adhesion molecule expressed in AML blasts (especially in M4 and M5 subtypes), by BM stromal cells and by selected epithelial cancers, where it protects cells from apoptosis and chemotherapy. In this study we explored the role of CD157 in the cross-talk between myeloid blasts and BM niche.

Materials and Methods

The functional role of CD157 was analysed in U937 and THP1cell lines engineered for the expression of CD157 and in fresh AML samples by means of specific agonist antibodies. The HS5 human BM stromal cells were used as an in vitro model to investigate the crosstalk between leukemic blasts and stromal cells. The viability of leukemic cells treated with Cytarabine (AraC) was evaluated by PrestoBlue assays and Annexin-FITC/PI staining. The CD157-mediated signalling pathway was analysed by western blot and flow cytometry.

Results

CD157 ligation by an agonistic antibody both in fresh AML and cell lines, activated the phosphatidylinositol 3-kinase (PI3K)/AKT/Bcl-2 signaling pathway and inactivated BAD and GSK3β, leading to increased cell survival and adhesion, and influencing tumor cell resistance to apoptotic signals and sensitivity to AraC treatment. Furthermore, genetic loss of CD157 in AML cells i) reduced survival and increased sensitivity to AraC, ii) reduced the number of cells in G0/G1 phases, iii) enhanced sensitivity to nutrient deprivation, and iv) attenuated the protective effect exerted by BMSCs against AraC-induced cell death. On the other side, forced expression of CD157 in HS5 stromal cells strengthened the protection mediated by BMSCs on AraC-induced cell death driving leukemia cells toward quiescence.

Conclusion

Collectively, these results suggest that CD157 expressed both by tumor cells or by the surrounding BM stromal cells takes part to the dialogue between AML cells and microenvironment and has a role in the protective effect exerted by BMSCs against cytotoxic drugs.