Inhibition of the Jagged-1/Notch pathway increases the hematopoiesis-supportive activity of mesenchymal stem cells

Alexandra Briquet, Marie Dolhet, Yves Beguin, André Gothot
GIGA-Research, Hematology Unit, University of Liège, Belgium

Objective

Mesenchymal stem cells (MSC) are able to support hematopoiesis ex vivo. The aim of this work consisted in determining the contribution of the Notch/Jagged-1 pathway in the ex vivo hematopoiesis-supportive activity of MSC.

Methods and Results

It is well known that Notch is expressed in CD34+ hematopoietic precursors. By Western blot and flow cytometric analysis, we confirmed the expression of Jagged 1 by MSC. Next, Dexter-type long term cultures were carried out with MSC and cord blood CD34+ cells in the presence of neutralising anti-human Jagged-1 antibody (anti-Jagged-1). After 3 weeks, absolute numbers of CD34+, CD10+, CD19+, CD11b+ and CD33+ cells grown in culture were determined by flow cytometric analysis using TruCount tubes. Compared to culture with irrelevant IgG, outgrowth of lymphoid and myeloid cells, as well as expansion of CD34+ cells, were not affected by Jagged-1 inhibition.

Repopulation assays in irradiated NOD/SCID mice were set with the expansion product of CD34+ cells co-cultured for one week in contact with MSC and in the presence of anti-Jagged-1 or non specific IgG. Compared to infusion of CD34+ cells cultured in the presence of control IgG, repopulating activity was increased by Jagged-1 neutralisation ($p=0.051$).

In further experiments, to determine whether this enhancement of repopulating activity was due to direct or indirect effects, the influence of anti-Jagged-1 on MSC was studied. The phenotype, adipogenic, chondrogenic and osteogenic differentiation capacity, as well as CFU-F content of MSC were not affected by Jagged-1 inhibition. However, we noted a 2-fold increase of IL-8 secretion ($p<0.001$) in the presence of anti-Jagged-1.

Conclusion

These data suggest that, in our conditions, the Jagged-1/Notch pathway inhibits the supportive activity of MSC toward NOD/SCID-repopulating cells. This is not paralleled by changes in the phenotype, differentiation potential or CFU-F capacity of MSC but may be related to inhibition of IL-8 secretion.