The role of IL32 in the acute myeloblastic leukemia chemoprotection and leukocyte migration

Matheus Lopes[1]; João Kleber Novais Pereira[1]; Paula de Melo Campos[1]; João Agostinho Machado-Neto[1]; Irene Lorand-Metze[1]; Fabíola Traina[1,2]; Fernando Ferreira Costa[1]; Sara T. Olalla Saad[1]; Patrícia Favaro[1,3]

[1]Hematology and Hemotherapy Center-University of Campinas/Hemocentro-Unicamp, Instituto Nacional de Ciência e Tecnologia do Sangue, Campinas, São Paulo, Brazil.
[2] Department of Internal Medicine, University of São Paulo at Ribeirão Preto Medical School, Ribeirão Preto, São Paulo, Brazil.
[3] Department of Biological Sciences, Federal University of São Paulo, Diadema, São Paulo, Brazil.

Mesenchymal stromal cells are part of the bone marrow microenvironment, and can contribute to the survival of leukemia cells. IL32, a pleiotropic cytokine, has been reported to be an important mediator in several autoimmune and inflammatory disorders. Recently, IL32 was described as being dysregulated in myelodysplastic syndrome and in chronic myelomonocytic leukemia. Herein, we characterize the effects of IL32 silencing in HS5, a stromal phenotype cell line with the ability to secret cytokines and support hematopoiesis. IL32 silencing enhanced cell viability and proliferation of HS5 *($p<0.05$)* and resulted in a lower recruitment of T $CD4^+$ cells, mainly in a proinflammatory microenvironment *($p<0.01$)*. Compared with miControl cells, miIL32 showed a decreased cytokine expression, including IL1β, IL6, TNFα and CCL5. IL32 silencing was not capable of modifying the chemoprotection to AraC induced apoptosis conferred by HS5 to U937 cells. However, using a transwell system, a significant stronger chemoprotection was observed in U937 when co-cultured with miIL32 HS5 cells. Molecularly, we observed that IL32 inhibition downmodulated NFκB and MAPK pathways; there was a decreased phosphorylation of IKKα, IKKβ, JNK and p38. Our study provides evidence of the role of IL32 in the milieu of the microenvironment that interacts with the leukemia cells, providing signaling to the cell death and to the leukocyte recruitment to the niche.

Keywords: IL32; stromal cells; leukemia.