IJAE
Vol. 123, n. 1 (Supplement): 92, 2018
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Interactions between nuclear inositide signalling and leukemic bone marrow microenvironment

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Although hematopoietic stem cell studies led to the development of new targeted therapies for patients with acute myeloid leukemia (AML), the role of leukemic stem cells has to be clearly disclosed. Recent investigations showed that the perturbation of the bone marrow niche can initiate myeloid neoplasms, including AML and myelodysplastic syndromes (MDS), inducing leukemic stem cell proliferation and preventing drug-induced toxicity [1]. That is why several new therapies now target both leukemic stem cells and the bone marrow niche. Nuclear Phospholipase Cbeta1 (PI-PLCbeta1) is a key enzyme involved in hematopoietic regulation, and is particularly implicated in the progression of MDS to AML [2]. Here we studied the relationship between the bone marrow microenvironment and AML cells using in vitro co-culture experimental models. At first, we used hematopoietic cell lines, such as KG-1 (macrophage-like), THP-1 (monocytes) and HL-60 (promyeloblasts), then we switched to primary cells. We analyzed both the expression and topographic localization of inositide-dependent regulators (i.e. phospholipases and protein kinases) and hematopoietic differentiation markers, by means of Real-Time PCR, immunocytochemistry and flow cytometry. In addition, we are now performing experiments based on nuclear PI-PLCbeta1 overexpression or silencing in co-culture models. Our findings show that the presence of leukemic cells can perturb the bone marrow niche, inducing the gene expression of specific inositide players, such as PI-PLCbeta1, PI-PLCgamma1, PI-PLCgamma2 and protein kinase alpha. On the other hand, also specific hematopoietic proliferation and differentiation markers, like CD34, CD33, CD11b and CD14, are affected. All in all, our results not only show that nuclear inositides interact with the bone marrow niche, but also that their expression is altered during leukemic stem cell proliferation and is affected by nuclear PI-PLCbeta1 modulation, possibly paving the way to the development of innovative targeted therapies.

This work was supported by grants from MIUR PRIN-2015 and Almaidea Unibo.

References

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Key words

Nucleus, PI-PLCbeta1, Hematopoiesis.