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Regulation of cell adhesion signaling in B-ALL immunotherapy

Adhesion molecules, such as integrins and selectins, serve as attachment points for the cell to adhere to the extracellular matrix, or other cells. We have previously studied their role in the interaction of myeloid leukemia cells with the extracellular matrix [1,2], as well as their regulation by Src family kinases [3].

Immunotherapeutic approaches we are studying now are based on effective interactions of cytotoxic T lymphocytes with malignant cells. Ideally, this leads to the elimination of the leukemia cells. A successful interaction of cytotoxic T cells and leukemia cells, and the formation of the immunological synapse between those cells, is mediated by cell adhesion molecules.

One of such immunotherapeutics used in B-cell acute lymphoblastic leukemia (B-ALL) treatment is blinatumomab. Blinatumomab is a bi-specific antibody, a T cell engager, which functions by physically connecting the CD19 surface marker of malignant B cells with a CD3 molecule on the surface of cytotoxic T cells. Blinatumomab, therefore, facilitates the elimination of malignant B cells by the patient's immune system, using his cytotoxic T cells.

It is becoming more and more clear, however, that B-ALL relapses after blinatumomab therapy are localized in extramedullary tissues more often than expected. This suggests that blinatumomab therapy can change the malignant cell adhesion properties, and those cells are then able to survive in tissues where they would not normally be able to attach. This subsequently leads to the formation of new tumors.

According to our hypothesis, blinatumomab can modify the adhesion properties of leukemia cells in two possible ways — either by the interaction with CD19 itself or by forming a non-cytotoxic immunological synapse. Both scenarios can lead to induced differences in cell adhesion molecule expression (and therefore lead to interaction with extramedullary tissues), or by changing the regulation of existing adhesion molecules.

More recently, blinatumomab therapy is supported by tyrosine kinase inhibitors (TKI), which are widely used in the therapy of chronic myeloid leukemia. The combination of TKI — mainly dasatinib and ponatinib — with blinatumomab, or with CAR-T cell therapy, leads to superior results in clinical settings.

Interestingly, one of the main targets of TKIs are previously mentioned Src family kinases. Some of them are involved in the regulation of cell adhesion processes, as we reported before [3]. Src kinases, therefore, represent a common denominator in the regulation of leukemia cell adhesion, and in cutting-edge leukemia immunotherapy approaches.

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[1] Obr, A.; Röselová, P.; Grebeňová, D.; Kuželová, K. Real-Time Analysis of Imatinib- and Dasatinib-Induced Effects on Chronic Myelogenous Leukemia Cell Interaction with Fibronectin. PLoS One **2014**, *9*, e107367.

[2] Kuželová, K.; Obr, A.; Marková, J.; Gašová, Z. Integrin Expression and Adhesivity to Fibronectin in Primary Acute Myeloid Leukemia Cells: Impact of NPM1 and FLT3 Mutations. Eur. J. Haematol. **2020**, *105*, 578-587.

[3] Röselová, P.; Obr, A.; Holoubek, A.; Grebeňová, D.; Kuželová, K. Adhesion Structures in Leukemia Cells and their Regulation by Src Family Kinases. Cell. Adh Migr. **2018**, *12*, 286-298.