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Two distinct types of cell responses upon down-regulation of Notch1 signalling by a γ-secretase inhibitor in T-ALL cell lines

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Notch1 signalling plays an important role in the pathogenesis of T-cell lymphoblastic leukemia (T-ALL). In Notch1 signal transduction, the γ-secretase proteolytic complex is indispensable for the cleavage and activation of Notch1 protein. Therefore, in T-ALL, the treatment with γ-secretase inhibitors (GSI) blocking the Notch1 signalling pathway, is thought to be a potential therapeutic approach. Furthermore, it has been proposed that GSI combined with chemotherapy drugs could be more effective than GSI or chemo-therapy alone.

In this study, I investigated cell responses to compound E, a potent γ-secretase inhibitor, and to combination treatment of compound E plus chemotherapeutic agents commonly used in the treatment of T-ALL. I identified two distinct ways of GSI affecting cells. (1) Type 1, represented by cell lines TALL1 and HSB2: compound E alone resulted in cell

apoptosis followed cell cycle arrest. Moreover, GSI alone achieved similar or even better effects than a combination therapy with chemotherapy drugs. The combined strategy appeared to be unnecessary in this subtype of cells. (2) Type 2, represented by cell lines CEM and Jurkat J6: GSI alone caused neither cell cycle block nor cell death. Conversely, in the combination protocol, it rendered the cells resistant to chemotherapy drugs and decreased cell apoptosis induced by drugs. The combined strategy was not beneficial but detrimental to the treatment response of cells to chemotherapy. In this type of cells, an increased expression of anti-apoptotic gene Bcl-xl upon GSI treatment was correlated with the inhibition of apoptosis.

In conclusion, this work provides new insights into the effects of GSI treatment in T-ALL: in a subset of T-ALL cell lines, down-regulation of Notch1 signalling by GSI did not repress cell proliferation, but prevented drug-induced apoptosis, most probably via upregulation of Bcl-xl gene expression.