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CHANGES IN RELATIVE EXPRESSION LEVELS OF STAT TRANSCRIPTION FACTORS IN B-LYMPHOCYTES AT CHRONIC LYMPHOCYTIC LEUKEMIA

Background/Aim. Chronic lymphocytic leukemia (CLL) is characterized by progressive accumulation of long-lived transformed B-lymphocytes with impaired cell survival and apoptosis control. This is driven (in part) by microenvironmental cytokines, acting through the JAK/STAT pathway. The aim of the present study was to characterize the IL-2-mediated STAT signaling in B-lymphocytes of the CLL patients. **Methods.** Blood samples from twenty nine CLL patients and twelve conditionally healthy donors were stimulated with IL-2 (10 ng/mL) in the culture medium. Relative mRNA expression of the STAT3, STAT4, STAT5A, STAT5B and STAT6 was assessed by RT-qPCR (calculated by $\Delta\Delta C_t$ method with TBP as a reference gene); the protein signals were evaluated by immunofluorescence. **Results.** IL-2 stimulation induced significant changes in STAT3, STAT4, and STAT6 at the mRNA level in both groups with differing kinetics. Relative mRNA expression of STAT3 in CLL B-cells was significantly higher than in healthy donors at baseline (0 min) and 5 min (8-fold and 7.9-fold increase, respectively; $p < 0.05$), peaking early at 5 min before declining, whereas healthy donors showed a delayed rise reaching a maximum by 60 min. STAT4 expression demonstrated an earlier, hypersensitive peak in CLL at 5 min (>15 -fold higher vs. healthy donors; $p < 0.05$). STAT6 showed distinct kinetic shifts: baseline and 10-min post-stimulation levels were higher in healthy donors (2.5-fold and 19-fold higher, respectively; $p < 0.05$), whereas at 5 min, CLL cells exhibited a transient overshoot (2.7-fold higher vs. healthy donors; $p < 0.05$). Baseline STAT5A mRNA level in CLL cells was markedly depressed (17-fold lower vs. healthy donors; $p < 0.05$); after stimulation, it transiently increased in CLL but steadily declined in healthy donors. STAT5B mRNA levels showed no statistically significant differences between the groups across all time points. Immunofluorescent microscopy showed the absence of nuclear STAT5/ppSTAT5 signals in CLL cells before and after stimulation, versus clear nuclear translocation in healthy donor cells. **Conclusions.** The obtained results indicate systemic dysregulation of the JAK/STAT signaling in CLL B-lymphocytes. STAT5 proteins, key mediators of canonical IL-2 signaling, are neither transcriptionally induced nor functionally activated, pointing to a post-receptor blockade, while atypical STAT6 activation suggests compensatory pathway switching. Thus, the JAK/STAT cascade may represent a potential target for CLL-directed therapy. **Grants/Fundings.** Supported by NRFU grant No. 0124U003787, "Activation of signaling cascades for elimination of transformed B-cells in chronic lymphocytic leukemia."

Keywords: chronic lymphocytic leukemia, STAT transcription factors, IL-2 signaling, JAK/STAT pathway, B-lymphocytes.

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