QUANTITATIVE ANALYSIS OF APOPTOTIS RELATED GENES IN CHRONIC MYELOGENOUS LEUKEMIA (CML) CELLS AS THERAPEUTIC TARGETS

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Apoptosis is a tightly controlled mechanism and its deregulation has been shown to play a key role in a number of human diseases, including haematopoietic malignancies. Chronic myelogenous leukemia (CML) cells are highly resistant to apoptosis even induced by chemotherapeutic drugs. Although apoptotic pathways are complex, involving several interlocking proteins, the relative expression of pro- and anti-apoptotic proteins may influence the disease progression. Fas, a cell surface protein, can be triggered by its death-promoting ligand (FasL) to activate downstream caspases pivotal in the initiation of programmed cell death. Bcl-2 family member proteins and inhibitors of apoptosis proteins (IAPs) are two major negative regulators of apoptosis. By using a quantitative TaqMan reverse transcription-polymerase chain reaction, in this study we examined the Fas, Caspase-3, survivin and bcl-2 mRNA expression levels in peripheral blood mononuclear cells of 31 CML patients as well as of 25 normal healthy donors. We found no significant differences in Fas and Caspase-3 levels between CML patients and controls. On the other hand, we found aberrantly elevated levels of bcl-2 and survivin gene expression in CML patients (up to 5 log orders higher than controls). Our results indicate that antiapoptotic genes may play a role in leukemogenesis and could be a therapeutic target. Thus, monitoring the expression levels of these genes during the follow up could be an useful clinical tool. At the moment we are widening the patient pool in order to better correlate the above-named genes expression levels with the clinical stage and the pharmacological treatment. Western blot experiments are already in progress in order to study the survivin protein levels, and in other experiments, we are also treating the K562, that are BCR-ABL positive chronic myeloid leukaemia cells, with anti-survivin ODN. Moreover, we would like to demonstrate a hypothetical survivin involvement in the BCR-ABL pathway in imminent experiments in which we will treat the K562 cells with the BCR-ABL tyrosine kinase inhibitor STI571.