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Autophagy in chronic lymphocytic leukaemia, molecular regulation and crosstalk with deregulated apoptosis

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Background: Promotion of cell survival is vital for cancer development. The course of tumorigenesis involves many genetic alterations that collectively lead to cellular transformation and tumour growth. Intensive studies over the years delineated the contribution of loss of apoptotic (also named type I) cell death, responses to tumour formation.

One of the cellular processes critical for cell survival under metabolic stress and energy starvation is autophagy (also known as type II cell death), a catabolic process involved in capture and delivery of cytoplasmic components to lysosomes for degradation. The orchestrated interplay between these two machineries greatly affects the cell fate.

The role of the Bcl-2 family of pro- and antiapoptotic proteins as key regulators of the apoptosis cascade and the mitochondrial-mediated pathway of caspase activation has been greatly emphasised over years. Of this family, Bcl-2 was the first identified and remains the best characterized.

Beclin 1 sits at the core of autophagy regulation. Beclin 1, the mammalian orthologue of the yeast *Atg6* gene, is a major determinant in the initiation of autophagy. It was originally discovered as a Bcl-2-interacting protein and was the first human protein shown to be indispensable for autophagy.

The interaction between Bcl-2 family proteins and Beclin 1, can mediate crosstalk between autophagy and apoptosis

Chronic Lymphocytic Leukaemia (CLL) is a mature B cell neoplasm; presently an incurable disease representing the most common form of leukaemia, CLL typifies how dysregulation of the cell death pathways leads to malignancy. During the past decade, deregulated apoptosis has been greatly characterized as a hallmark of CLL. Aberrant expressionof Bcl-2 is common in CLL and is associated with poorresponse to chemotherapy and decreased overall survival. Therefore, targeting Bcl-2 family members becomes an important and attractive approach towards cancer therapy and is currently a very rapidly evolving area of research.

By emphasizing the role of autophagy and the cross talk between autophagy and apoptosis in CLL pathogenesis, novel therapeutic intervention points may be revealed.Because autophagy-modulating agents have already been used clinically to treat cancer. It is conceivable that targeting autophagic pathways may provide a new opportunity for discovery and development of more novel cancer therapeutics.

Methods: Peripheral blood samples from 30 newly diagnosed CLL patients were used, beclin 1 and bcl2 genes expression were evaluated using QRT-PCR.

Results: The expression of beclin1 mRNA was found to be higher in the peripheral white blood cells of the CLL patients in relation to normal controls ($p=0.004$) with a significant correlation between the gene expression and positive ZAP 70, CD38 expression, Similarly, the expression of bcl2 mRNA was found elevated in CLL patients versus the controls, elevated Beclin 1 expression was directly correlated with elevated Bcl2expression ($p=0.026$).

Conclusion: Overexpression of the autophagy related gene "beclin 1" and its association with increased Bcl2 expression in the vicinity of CLL, suggests a role of autophagy in keeping a survival advantage to CLL cells. The study points to the role of autophagy in the pathogenesis of CLL and the crosstalk between the autophagic and apoptotic machineries in controlling the survival of the CLL cells, which could open new avenues in targeted chemotherapy.

Keywords: Chronic lymphocytic leukaemia, Beclin1, Bcl-2

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