PERSPECTIVE

MiR 155a and miR 181a function in chronic lymphocytic leukemia

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EDITORIAL

Chronic Lymphocytic Leukaemia (CLL) is the most common type of adult leukaemia in the Western world, but it is less common in the Eastern world. Despite the fact that the Chinese population is ageing and that most CLL patients live for many years, the number of people affected by CLL is increasing year after year. This disease has been cited as a prime example of a tumour with low cell turnover, in which an intrinsic resistance to apoptosis is responsible for the gradual accumulation of neoplastic CD5+ B cells. CLL cells express high levels of the anti-apoptotic BCL-2 family member proteins, BCL-2 and MCL-1, which have been linked to resistance to chemotherapy, lending credence to this theory, making this disease extremely heterogeneous.

CLL is the most common type of adult leukaemia in the Western world, accounting for approximately 30% of all leukemias in Caucasians. Contrary to its earlier description as a relatively homogeneous disease, CLL is now viewed as a heterogeneous disease with variable clinical course that correlates with several biologic prognostic markers. Cytogenetics determined by Fluorescence *In Situ* Hybridization (FISH) and IgVH are the most clinically significant prognostic markers, followed by ZAP70 status. Patients with CLL who have deletions of 11q or 17p, high expression of ZAP70 or CD38, or a lack of V region somatic hypermutation have markers that indicate a more aggressive disease.

Chronic Lymphocytic Leukaemia (CLL) is the most common type of human leukaemia; approximately 10,000 new cases are diagnosed each year in the United States. This disease is distinguished by an accumulation of small, mature B cells that express the CD5/CD19/CD23 markers. The clinical course of CLL is highly variable, and several prognostic markers have been identified to aid in the clinical management of CLL patients, including immunoglobulin heavy chain variable-region (IGHV) gene mutation status, -associated protein 70 (ZAP-70) expression levels, and cytogenetic abnormalities.

MCL-1 is a protein that is found in the intestines. Furthermore, the X-linked Inhibitor of Apoptosis Protein (XIAP) is increased in CLL cells, contributing to apoptotic resistance. These findings suggest that increased levels of anti-apoptotic proteins MCL-1, BCL-2, and XIAP contribute to CLL cells' apoptotic resistance to chemotherapeutic agents and monoclonal antibodies. The precise mechanisms underlying their upregulation however, are unknown.

CLL is a mature B cell disease. CLL cells frequently express an anergic B Cell Receptor (BCR) and exhibit dysregulated apoptotic programmes. CLL has been classified using mRNA expression profiling. Though CLL is not generally thought to be an activated B cell disease, mRNA expression profiling in one study characterised CLL cells as similar to activated B cells and memory B cells. NF-B nuclear translocation is linked to B cell activation in normal B cells. CLL cells are distinguished by constitutive nuclear localization of NF-AT (nuclear factor of activated T cells) and NF-B2/p52, indicating an activated B cell state.

Normal B lymphocytes do not express ZAP-70, but detectable levels are found in leukemic cells. Several studies have shown that high expression of this protein is usually correlated with IGHV unmutated status, implying that ZAP-70 is a useful surrogate marker for IGHV mutation status. More than 80% of CLL patients have genomic abnormalities, with the most common chromosomal abnormalities being deletions at 13q (> 50%), 11q (18%), trisomy 12 (15%-18%), and 17p (7%-10%). As a result, 5 prognostic categories have been defined in a statistical model, with poor survival in patients with 17p deletion, 11q deletion, or trisomy 12 and better survival in patients with normal karyotype and 13q deletion as the sole abnormality.

Despite the fact that CLL cells are sensitive to the chemotherapies commonly used to treat the disease, CLL is still incurable. As a result, the role of miRNAs in enhancing chemotherapy-induced apoptosis is critical. The miRNA expression profile in malignant B cells isolated from Chinese patients with CLL was investigated in this study. MiR-181a and miR-181b levels were measured in 156 CLL patients with well-defined disease. We also looked at how changing miRNA levels in primary CLL cells affected them. The findings suggest that miRNA deregulation is common in CLL and that miR-181s may act as endogenous regulators of multiple oncogene expression, inducing apoptosis.

The abnormal expression of miRNAs may play important roles in the occurrence, development, and prognosis of Chronic Lymphocytic Leukaemia (CLL), with potential ethnic differences. p53 and immunoglobulin heavy chain variable region gene (IGVH) mutations were tracked, and miRNA profile screening of CD19+ cells from Uygur CLL patients was carried out, analysed using miRNA arrays, and confirmed using real-time PCR. In CD19+B lymphocytes from six Uygur CLL patients, there were 68 differentially expressed miRNAs, with miR-1295, miR-29b, miR-34a, miR-21, and miR-29c being the five most upregulated and miR-181a, miR-126, miR-181b, miR-125a-5p, and miR199b being the five most downregulated. Profile screening did not eliminate miR-15a/miR-16-1, which is thought to be important disease drivers.

New evidence supports the idea that Chronic Lymphocytic Leukaemia (CLL) is a genetic disease with the main changes occurring in a new class of genes known as microRNAs (miRNAs). MiRNA down-regulation of the genes miR-15a and miR-16-1, which are located at 13q14.3, is characteristic of cases with a good prognosis. Both microRNAs have a negative post-transcriptional regulation of BCL2. TCL1 levels are elevated in CLL patients who use unmutated immunoglobulin heavy-chain variable-region genes (IgVH) or have high levels of the 70-kD Zeta-Associated Protein (ZAP-70) due to low levels of miR-29 and miR-181, both of which directly target this oncogene. These miRNAs have the potential to be used for disease therapy by targeting BCL2 or TCL1.

There were no differences in miR-15a/miR-16-1 expression levels between CLL patients and healthy donors, but miR-15a/miR-16-1 expression levels were lower in CLL patients with a 13q deletion. Furthermore, there was no difference in the expression levels of the seven miRNAs listed above between 44 Han and 40 Uygur CLL patients. In 84 Uygur and Han CLL patients, miR-29b, miR-181a, and miR-181b expression levels were associated with IGVH mutations, while miR-34a, miR-29b, and miR-181b expression levels were associated with a p53 abnormality.

We discovered a miRNA signature in untransformed B cells induced shortly after activation using miRNA expression profiling. This activated B cell miRNA signature is also present in CLL cells, indicating that CLL has an activated B cell phenotype. Our findings suggest that individual miRNAs involved in B cell activation may play a role in B cell transformation and could be targets for therapeutic gene silencing in CLL.

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