In Silico Analysis of miR-181a and miR-155 and Their Target Genes in the Pathogenesis of Acute Lymphoblastic Leukaemia

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Abstract

Acute lymphoblastic leukaemia (ALL) represents 80% of acute leukaemia in children and 20% in adults. In most cases, the cause remains unknown; however, genetic predisposition is found in most patients. Clinically, a patient is diagnosed with ALL when peripheral blood smear or bone marrow aspirate is overpopulated with lymphoblasts. Although the 5-year overall survival rate exceeds 90% using available treatments, the life-threatening effects still affect some patients [1]. Therefore, further improvement in clinical outcomes and reduction of adverse effects require novel therapeutic approaches such as microRNAs (miRNAs) biomarkers. In addition, miRNAs have demonstrated distinct expression profiles in classifying the ALL subtypes and involved in various cancers [2].

Previously, miR-181a and miR-155 have been discussed, either acting as oncogenic or tumour suppressive miRNAs in carcinogenesis. The study aims to investigate the role of miR-181a and miR-155 and their predicted target genes in the pathogenesis of ALL. Hence, in silico analysis was conducted using miRDB 6.0 software to identify the predicted target genes and GeneCodis 4.0 software to identify signalling pathways regulated by miR-181a and miR-155. As presented in Table 1, miR-181a was found to be downregulated whereas miR-155 was significantly upregulated in ALL groups as compared to control groups [3].

Table 1. Selected candidate miRNAs for predicted target genes

<table>
<thead>
<tr>
<th>miRNAs</th>
<th>miRBase ID</th>
<th>NCBI Gene ID</th>
<th>Genomic Location</th>
<th>Expression Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-181a</td>
<td>MIMAT0000256</td>
<td>406995</td>
<td>chr1:198859044-198859153 (-)</td>
<td>Downregulated</td>
</tr>
<tr>
<td>miR-155</td>
<td>MIMAT0000646</td>
<td>406947</td>
<td>chr21:25573980-25574044 (+)</td>
<td>Upregulated</td>
</tr>
</tbody>
</table>

Analysis of target expression was conducted to identify predicted target genes in ALL cell line, DND-41. In this study, the predicted target genes are regulated by miR-181a and miR-155 (with target score ≥ 80 and target expression ≥ 20) revealed 57 genes and 29 genes, respectively. The most significant genes regulated by miR-181a and miR-155 were DUSP6 and H3F3A, respectively. DUSP6 is a regulator for
hyperactivation of the extracellular signal-regulated kinase (ERK) in relapsed pre-B ALL patients. Thus, this reaction caused lesions in the RAS pathway and oncogenic tyrosine kinases (e.g., BCR-ABL1).

Additionally, a complete transformation of pre-B ALL clones was done by BCR-ABL1 and correlated with the activity of other MAPKs such as MAPK14 and MAP2K1. Therefore, ERK was identified as a negative feedback regulator of the RAS-ERK pathway [4].

H3F3A was reported to be involved in the pathogenesis of paediatric leukaemia caused by mutated genes that encoded proteins during epigenetic regulation. The mutation in H3F3A led to the inability of this residue to undergo periodic regulatory post-translational modifications and blocked trimethylation of all H3 during T-ALL pathogenesis. Specifically, the recurrent T-ALL patients found the lysine-to-arginine mutations at H3K27 and H3K36. Hence, the reduced expression of H3 proteins was associated with unfavourable prognosis [5].

The functional enrichment analysis of KEGG pathway was conducted by using GeneCodis 4.0 software. The most significant pathway targeted by miR-181a and miR-155 was p53 signalling pathway and MAPK pathway, respectively.

SESN3 was mainly responsive to p53 protein by inducing its expression upon oxidative stress and strictly associated with the antioxidant response during p53 signalling pathway. Hence, SESN3 could be a potential therapeutic drug for anticancer therapy, such as decreased mTORC1 mechanism in leukaemia patients [6]. Besides that, FOS was disrupted the MAPK pathway components, specifically MEK1 and MEK2 which could increase sensitivity to chemotherapy in relapsed ALL patients. These components were involved in ERK phosphorylation that critically drives chemoresistance during MAPK/ERK signalling pathway [7].

In conclusion, differentially expressed miRNAs have promising roles and can be used as effective biomarkers for diagnostic, prognostic, predictive and therapeutic effects in ALL patients.

Keywords

MicroRNAs, Acute Lymphoblastic Leukaemia, In silico analysis

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negative feedback control enables pre-B cell transformation and represents a therapeutic target in acute lymphoblastic leukemia. *Cancer Cell.* 2015;28;114–128. https://doi.org/10.1016/j.ccell.2015.05.008

