MYC translocation-negative classical Burkitt lymphoma cases: an alternative pathogenetic mechanism involving miRNA deregulation

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Abstract:

The molecular feature of Burkitt lymphoma (BL) is the translocation that places c-Myc under the control of immunoglobulin gene regulatory elements. However, there is accumulating evidence that some cases may lack an identifiable MYC translocation. In addition, during the EUROFISH project, aiming at the standardization of FISH procedures in lymphoma diagnosis, we found that five cases out of 35 classic endemic BLs were negative for MYC translocations by using a split-signal as well as a dual-fusion probe. Here we investigated the expression pattern of miRNAs predicted to target c-Myc, in BL cases, to clarify whether alternative pathogenetic mechanisms may be responsible for lymphomagenesis in cases lacking the MYC translocation. miRNAs are a class of small RNAs that are able to regulate gene expression at the post-transcriptional level. Several studies have reported their involvement in cancer and their association with fragile sites in the genome. They have also been shown to control cell growth, differentiation, and apoptosis, suggesting that these molecules could act as tumour suppressors or oncogenes. Our results demonstrated a modulation of specific miRNAs. In particular, down-regulation of hsa-let-7c was observed in BL cases, compared to normal controls. More interestingly, hsa-mir-34b was found to be down-regulated only in BL cases that were negative for MYC translocation, suggesting that this event might be responsible for c-Myc deregulation in such cases. This hypothesis was further confirmed by our in vitro experiments, which demonstrated that increasing doses of synthetic hsa-mir-34b were able to modulate c-Myc expression. These results indicate for the first time that hsa-mir-34b may influence c-Myc expression in Burkitt lymphoma as the more common aberrant control exercised by the immunoglobulin enhancer locus