

MicroRNAs and lymphomas

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MicroRNAs (miRNAs) are small non-coding RNAs which regulate the expression of target mRNAs through base pairing to partially (in mammals) or perfectly (in plants) complementary sites, mainly, but not exclusively, in the 3'-untranslated region (3'-UTR) of their targets [1]. Should a perfect complementarity occur, the mRNA is cleaved and degraded, whereas a translational silencing is the main miRNA regulatory mechanism in the case of imperfect base pairing [1].

MiRNAs have important regulatory functions, including cell cycle, apoptosis and differentiation [2]. Systematic miRNA expression profiling has revealed widespread aberrant miRNA expression in cancer with respect to the normal tissues, including lymphomas [3–6].

Earlier studies have shown that miR-155 is up-regulated in pediatric Burkitt's lymphoma [4], diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBL) and Hodgkin's lymphoma [5–6] (Table 1). This miRNA is encoded by the final portion of the BIC (B-cell integration cluster) gene, which was originally identified as a common retroviral integration site in avian leukosis virus-induced B-cell lymphomas [7]. Our group demonstrated that mice overexpressing miR-155 in B lymphocytes develop polyclonal pre-leukemic pre-B-cell proliferation followed by full-blown B-cell malignancy [8]. More recently two knock-out mice models have demonstrated a critical role of miR-155 in immunity by showing that BIC/miR-155^{-/-} have defective dendritic cell functions, impaired cytokine secretion and T_H cells intrinsically biased toward T_H2 differentiation [9–10]. Moreover miR-155 could represent the connection between inflammation, immunity and cancer since its expression can be induced by mediators of the flogosis and is involved in the response to endotoxin shock [11].

He et al. [12] reported that the miR-17~92 polycistron, which is located in 13q31–32, a region commonly amplified in B-cell lymphoma, was up-regulated in 65% of the B-cell

lymphoma patients. The authors overexpressed the miR-17~92 cluster in HPCs from mice that carry the MYC transgene and reported that the miR-17~92 cluster acted, together with MYC expression, to accelerate tumor development [12]. A different group recently generated mice with high miR-17~92 expression in lymphocytes and found that these mice developed a lymphoproliferative disease and autoimmunity and died prematurely (Table 1) [13]. The transgenic lymphocytes exhibited enhanced proliferation and survival due to the down-regulation of PTEN and the pro-apoptotic Bim (which controls B-lymphocyte apoptosis) by the miR-17~92 cluster [13].

Insights about the regulation of this cluster in lymphoma was provided by O'Donnell et al. [14]. Using an inducible system of MYC expression and Chip assays, the authors showed that MYC binds and activates the expression of the miR-17~92 cluster at chromosome 13q31. Furthermore, they indicated that E2F transcription factor 1 (E2F1) is down-regulated by two miRNAs of the cluster, miR-17-5p and miR-20a. E2F1 is a direct target of MYC that promotes cell-cycle progression [15]. Thus, MYC simultaneously activates E2F1 and limits its translation through a miRNA-based mechanism, enabling a tightly controlled proliferative signal [14].

references

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Table 1.

| MicroRNA | Genomic location | Expression in patients | Experimental data | Refs |
|-------------------|------------------|---|--|-----------|
| miR-155 | 21q21 | Up-regulated in DLBCL, Hodgkin, pediatric Burkitt's | Induces lymphoproliferation, pre-B lymphoma/leukemia in mice | 28, 41–44 |
| miR-17~92 cluster | 13q14 | Up-regulated in lymphomas | Cooperates with MYC; targets E2F1, Bim and PTEN | 45–47 |

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