Crosstalk between microRNA and DNA Methylation Offers Potential Biomarkers and Targeted Therapies in ALK-Positive Lymphomas

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Purpose:
ALK-positive Anaplastic large-cell lymphoma (ALK(+) ALCL) is a T cell neoplasm defined by the presence of a translocation leading to the expression of a driver oncogene: ALK, with NPM-ALK fusions being the most common. Polychemotherapy involving doxorubicin is the standard first-line treatment but for the 30% of patients who relapse and develop resistance the prognosis remains poor. Our work highlights the role of two specific microRNAs, miR-150 and miR-125b in NPM-ALK oncogenic signaling and ALCL lymphoma resistance to conventional chemotherapy and targeted therapy.

Experimental Design:
We measured both expression and DNA methylation of the MIR150 and MIR125B1 genes in human and murine ALCL models. We addressed the implication of NPM-ALK, STAT3, DNMT1 and Topoisomerase II in the MIR150 and MIR125B repression. Using a microRNA-biotin pull down assay we identified the mRNA targets of miR-125b.

Results:
We showed that miR-150 is a tumor suppressor repressed by a NPM-ALK/STAT3-dependent DNA methylation. Thanks to the use decitabine, a hypomethylating drug, we could restore the expression of miR150 and block the growth of ALCL cells resistant to crizotinib (targeted therapy against ALK). We proposed that the modulation of DNA methylation could have potential therapeutic applications for ALK-positive malignancies. Lately, we showed that the expression of another microRNA, miR-125b, is also repressed in NPM-ALK(+) ALCL samples because of the abnormal hypermethylation of its promoter.Interestingly, we showed that the level of miR-125b is different when compared patients who do not relapse to those relapsing early after doxorubicin-containing chemotherapy. In ALCL cells, miR-125b has the capacity to induce chemoresistance, by blocking the expression of BAK1. We demonstrated that the expression of miR-125b is induced upon doxorubicin treatment because of topoisomerase II and DNMT1 loss on the miR-125b promoter. Thus, we proposed that the miR-125b-increase upon doxorubicin treatment leads to tumoral escape at the origin of early relapse of ALCL lymphoma. Our results showed that miR-125b, could be used as a biomarker to predict the outcome.

Conclusion:
In conclusion, the DNA methylation of specific miRNA genes offers potentially useful biomarkers for detecting cancer and predicting its outcome. Our results suggest that a hypomethylating therapeutic strategy, either alone or in combination with other agents, may benefit ALK(+) patients.

References:

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