Commentary

Role of c-MYC/miRNA-548/HDAC6 axis in drug resistance and lymphoma survival

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The B cell lymphoproliferative malignancies (1) arise from B cells that require interaction with non-malignant cells and stromal cells during lymphomagenesis (2,3). There has been improvement in overall survival in these lymphomas (4), however, a significant proportion (30–40%) of cases relapse even with the introduction of rituximab in therapeutic regimens (3). Gene expression profiling studies reveal signatures originating from the microenvironment at diagnosis are significantly associated with response to therapy in follicular lymphoma (FL) and diffuse large B cell lymphomas (DLBCL) (5). Moreover, the diffuse distribution of follicular dendritic cells (FDCs) in mantle cell lymphoma (MCL) is associated with worse clinical outcome (5,6). These observations indicate that interaction between stroma and B cell lymphoma cells contributes to drug resistance and support neoplastic cell survival. A number of microRNAs (miRNAs) are dysregulated when lymphoma cells adhere to lymph node stromal cells in MCL and other B cell lymphomas (7). The dysregulated miRNAs critically influence the tumor development, progression and have been reported to be the important prognosticators in human cancers including lymphomas (8). Recently, prognostic miRNAs have identified in several NHL including DLBCL, MCL, FL and PTCL (8,9).

The interaction of FDC and B-cell plays an important role in survival and neoplastic progression in MCL and other non-Hodgkin lymphoma cells. This interaction is associated with the upregulation of miR-181a, which directly targets pro-apoptotic protein BIM, whereas miR-548m is down-regulated by stroma interaction (3). Knock down of miR-181a causes the upregulation of BIM and significantly increases apoptosis. Therefore, FDC protect B cell lymphoma cells against apoptosis through activation of miR-181a (6). The potential target of miR-548m through target Scan shows that 3'-UTR of HDAC6 contain sequence motif that perfectly matches with the "seed" sequence of miR-548m. Bone marrow stroma cells (HS-5) in *in-vitro* co-culture system induced the upregulation of HDAC6 expression and down regulation of miR-548m in HBL-2 and SUDHL-4 cells (3). These results indicate that stromal cells use the HDAC6 pathway to promote lymphoma cell survival (3). Interestingly, knockdown of HDAC6 distinctly nullified stroma-mediated lymphoma colony formation. Moreover, c-Myc activation has been observed in lymphoma cells co-cultured with stromal cells. Overexpression of miR-548m decreased c-Myc expression and its knockdown with anti-miR-548m transfection up-regulated c-Myc expression. In contrast, knock down of c-Myc subsequently blocked stroma-induced miR-548m downregulation. This clearly indicates that c-Myc/miR-548m forms a feed-forward loop which contributes to stroma-mediated c-Myc activation and miR-548m down-regulation in lymphoma microenvironment (3). In the current study (3), the authors have shown that adhesion of MCL and other B cell lymphoma cells to stroma contributes drug resistance, enhances lymphoma cell clonogenicity and cell survival through histone deacetylase 6 (HDAC6) upregulation.

This stroma-mediated drug resistance can be reversed by

enforced expression of miR-548m as well as inhibition of c-Myc and HDAC6 *ex vivo* and *in vivo*. These findings define a novel mechanism by which the tumor microenvironment alters specific miRNA and HDAC6 levels, leading to drug resistance and lymphoma survival, with HDAC6 and c-Myc as potential therapeutic targets to overcome drug resistance in MCL and other B cell lymphomas. Histone deacetylase inhibitors (HDACi) showed promising activity against hematological malignancies in clinical trials (10). Various studies have determined the downstream molecular effector of HDAC6 in cell adhesion-mediated drug resistance (CAM-DR) by using HDAC6 pan inhibitors (3,10). These inhibitors show significant increase in the protein levels of Bim in acute myeloid leukemia (3). In addition, tubastatin A also abolished stromal cell-mediated tumor growth of NOD/SCID mice bearing HBL-2 and HK xenografts (3). When combined with mitoxantrone, tubastatin A enhanced mitoxantrone-induced lymphoma killing and disables stroma-mediated drug resistance *in vivo*. Collectively, stroma-mediated HDAC6 induction through unleashing of miR-548m repression is a novel therapeutic target for MCL and other B cell lymphomas (3). A novel small-molecule BET bromodomain inhibitor, JQ1, and the EZH2 inhibitor, DZNep, synergistically causes the MYC activation and upregulation of miR-26a expression. These inhibitors cooperatively suppressed lymphoma growth and clonogenicity in aggressive lymphoma cells. These findings signify a novel and promising approach for silencing MYC-miRNA-EZH2 amplification loop for combinatorial therapy of aggressive B-cell lymphomas (9). FDA has already approved Vorinostat (Zolinza) for the treatment of cutaneous T-cell lymphomas (10). Most of the studies have shown that vorinostat also down regulates the expression of Bcl-xl in B-cell lymphomas by inducing cell-cycle arrest, apoptosis and cooperate with the chemotherapy agents (10,11), however, phase I and II trial (12,13) did not find much success. Other HDAC inhibitors (LBH589 and MS-275) with good prognostic features may define the better role of HDAC inhibitors in B-cell lymphoma (13). In addition, combination of c-Myc inhibitor (JQ1) and cytotoxic drug may be a more ideal treatment for B cell malignancies. Targeting c-Myc overcomes stroma-mediated drug resistance, which cooperates with HDAC6 inhibition to synergistically suppress lymphoma survival and growth (3). The lymphoma-stroma interaction in lymphoma microenvironment directly affects the biology of lymphoma through genetic and epigenetic regulation (3), with HDAC6 and c-Myc as prospective therapeutic targets.

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Footnote

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References

1. Küppers R. Mechanisms of B-cell lymphoma pathogenesis. Nat Rev Cancer 2005;5:251-62.
2. Scott DW, Gascoyne RD. The tumour microenvironment in B cell lymphomas. Nat Rev Cancer 2014;14:517-34.
3. Molina A. A decade of rituximab: improving survival outcomes in non-Hodgkin's lymphoma. Annu Rev Med. 2008;59:237-50.
4. Lwin T, Zhao X, Cheng F, et al. A microenvironment-mediated c-Myc/miR-548m/HDAC6 amplification loop in non-Hodgkin B cell lymphomas. J Clin Invest 2013;123:4612-26.
5. Dave SS. Host factors for risk and survival in lymphoma.

Hematology Am Soc Hematol Educ Program 2010;2010:255-8.
6. Lwin T, Lin J, Choi YS, et al. Follicular dendritic cell-dependent drug resistance of non-Hodgkin lymphoma involves cell adhesion-mediated Bim down-regulation through induction of microRNA-181a. Blood 2010;116:5228-36.
7. Zheng RL, Jiang YJ, Wang X. Role of microRNAs on therapy resistance in Non-Hodgkin's lymphoma. Int J Clin Exp Med 2014;7:3818-32.
8. Iqbal J, Shen Y, Liu Y, et al. Genome-wide miRNA profiling of mantle cell lymphoma reveals a distinct subgroup with poor prognosis. Blood 2012;119:4939-48.
9. Iorio MV, Croce CM. Causes and consequences of microRNA dysregulation. Cancer J 2012;18:215-22.
10. Lindemann RK, Newbold A, Whitecross KF, et al. Analysis of the apoptotic and therapeutic activities of histone deacetylase inhibitors by using a mouse model of B cell lymphoma. Proc Natl Acad Sci U S A 2007;104:8071-6.
11. Bereshchenko OR, Gu W, Dalla-Favera R. Acetylation inactivates the transcriptional repressor BCL6. Nat Genet 2002;32:606-13.
12. Kadia TM, Yang H, Ferrajoli A, et al. A phase I study of vorinostat in combination with idarubicin in relapsed or refractory leukaemia. Br J Haematol 2010;150:72-82.
13. Hernandez-Ilizaliturri FJ, Czuczman MS. Therapeutic options in relapsed or refractory diffuse large B-cell lymphoma. Part 2. Novel therapeutic strategies. Oncology (Williston Park) 2009;23:610-5.

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