Review Article
New insights into MicroRNAs involves in drug resistance in diffuse large B cell lymphoma

Xin Yu[1*], Zheng Li[2*]

*Departments of [1]Dermatology, [2]Orthopedics Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100042, China. *Equal contributors.*

Abstract: Diffuse large B cell lymphoma (DLBCL) accounts for nearly 40% of non-Hodgkin's lymphoma cases. The combined chemotherapy of rituximab, cyclophosphamide, Adriamycin, vincristine, and prednisone (R-CHOP) is considered as the standard therapy for DLBCL; however, nearly half of the patients become refractory to the R-CHOP regimen. Early identification of drug resistance and therapeutic failures are crucial for the identification of high-risk patients. MicroRNAs (miRNAs) are a group of small and non-coding RNAs negatively regulating gene expression through binding to their target mRNAs. Recent studies demonstrated that miRNAs are involved in chemotherapeutic drug resistance in tumor. In our review, we summarize the current evidence on the role of miRNAs in the prediction and modulation of cellular response to rituximab, cyclophosphamide, Adriamycin, vincristine, and prednisone in DLBCL.

Introduction

Diffuse large B cell lymphoma (DLBCL) accounts for nearly 40% of non-Hodgkin's lymphoma cases [1-4]. It includes a heterogeneous group of disorders with variable clinical and pathological features, response to treatment, and prognosis [5-7]. The combined chemotherapy of rituximab, cyclophosphamide, Adriamycin, vincristine, and prednisone (R-CHOP) is considered as the standard therapy for DLBCL, with complete remission in approximately ~80% cases [8-11]. However, nearly half of the patients become refractory to the R-CHOP regimen [12-14]. Early identification of drug resistance and therapeutic failures are crucial for the identification of high-risk patients [15-18]. Accumulating studies have investigated the molecular mechanisms underlying resistance to the R-CHOP regimen in DLBCL, which is key to improving the treatment response [19, 20].

MicroRNAs (miRNAs) are a group of small (19 to 25-nucleotides), non-coding RNAs negatively regulating gene expression through binding to their target mRNAs [21-23]. They are involved in various biological and pathophysiological pro-

cesses, including development, host defense, aging and tumorigenesis [24-26]. Increasing evidence has suggested aberrant expressed miRNAs in many human tumors, including DLBCL [27-30]. Through interactions with intracellular signaling pathways, miRNAs modulate many tumor-pertinent cellular processes, including cell proliferation, apoptosis, migration, invasion, stemness and chemoresistance [31-33]. In particular, miRNAs are involved in chemotherapeutic drug resistance in tumor cells [34, 35]. With development of RNA delivery technology, novel miRNA-based therapeutics will emerge.

In our review, we summarize the publications on the role of miRNAs in the prediction and modification of response to R-CHOP regimen in DLBCL. We also discuss the possible involved molecular targets and intracellular pathways.

R-CHOP

Anthracyclin-based chemotherapy with CHOP was introduced and proved to be effective for DLBCL in the late seventies [36, 37]. Immuno-chemotherapy adding rituximab (R) to CHOP

further improved the chemotherapy responses of DLBCL and become the standard for front-line treatment for DLBCL [18, 37].

Response prediction

The standard first line treatment R-CHOP is highly effective for DLBCL with more than 80% respond to this treatment [18, 38]. Patients with a relapse after R-CHOP have a substantially worse prognosis. A major problem for DLBCL treatment is the lack of predictors of response to the R-CHOP [39]. Identification of molecular biomarkers can improve risk stratification and enable comparisons among clinical trials [11]. Moreover, predictive markers contribute to understanding pathogenesis and the development of therapeutic agents in DLBCL [40]. The International Prognostic Index (IPI) is most often used for outcome prediction of patients with DLBCL [41]. MiRNA microarray technology is widely used in the comparison of differential expressed miRNAs between diseases and normal controls [23, 24]. Many studies have found that miRNAs are deregulated after anticancer treatment with R-CHOP in DLBCL [42, 43]. It was proved that a miRNA-based predictor could help to choose the optimal second line treatment and increase survival in patients treated by R-CHOP [43].

Alencar et al. proved that miRNAs were independent predictors of outcome in DLBCL patients treated with R-CHOP by quantitative real-time PCR analyses [44]. The expression of miR-18a correlated with overall survival (OS), whereas the expression of miR-181a and miR-222 correlated with progression-free survival (PFS). Furthermore, expression of the miR-18a, miR-181a, and miR-222 were independent predictors of survival except the expression of miR-222 for OS and the expression of miR-18a for PFS. In summary, miRNAs may be useful for survival prediction of patients with DLBCL and their role in DLBCL should be investigated further.

Lawrie et al. found that the 21-microRNA signatures resulted in correct prediction of clinical outcome for 31/38 (82%) in patients treated with R-CHOP [45]. In addition, eight microRNAs (miR-302, miR-330, miR-425, miR-27a, miR-199b, miR-142 miR-519 and miR-222) were significantly correlated with event-free survival (EFS) EFS times in patients treated with

R-CHOP. These eight microRNAs could correctly predict clinical outcome in 32/38 (84%) of cases by SVM analysis.

Another study investigated the response predictor of 20 microRNAs treated with R-CHOP or R-CHOEP as first line treatment in a cohort of 116 de novo DLBCL patients [42]. The prediction compared the results of formalin-fixed paraffin embedded (FFPE) samples and the matched the clinical response. When the standard International Prognostic Index (IPI) was included to separate responders and non-responders, the predictions improved. Patients predicted sensitive to their second and third line treatment survived longer than patients predicted not sensitive (90% CI: 485 days versus 227 days). These results suggested miRNA based predictor contributed to the selection of the second line treatment treated by R-CHOP regimen.

Berglund et al. investigated expression of miR-NA-200c from a cohort of 61 DLBCL patients treated with CHOP or R-CHOP [46]. They showed that the expression of microRNA-200c affected the clinical outcome of DLBCL patients. High miRNA-200c expression predicted shorter overall survival. The median survival of patients with high miRNA-200c expression was 20.3 months while patients with low miRNA-200c were 35.8 months. In addition, time from initial diagnosis to the first relapse was significantly shorter in patients with high microRNA-200c expression than patients with low microRNA-200c expression. In summary, miRNA-200c is involved in the pathogenesis of DLBCL with further studies required to confirm its roles.

Through analysis of miRNA-129-5p expression from DLBCL patients treated with CHOP or R-CHOP, Hedstro et al. showed that patients with low miRNA-129-5p expression had a significantly shorter overall survival than patients with high miRNA-129-5p expression [47]. The median survival of patients with low miRNA-129-5p expression was 23 months while patients with high miRNA-129-5p expression were 58 months. However, the expression of miRNA-129-5p showed no significant difference between tumor tissue and the tissue surrounding the tumor, as well as the normal controls. To conclude, miRNA-129-5p affected the overall survival and clinical outcome of DLBCL patients treated with CHOP or R-CHOP. MiRNA-

129-5p may contribute to DLBCL pathogenesis, which needed larger studies and further investigations to elucidate and confirm its roles in DLBCL.

Another report showed that expression of miR-146b-5p and miR-320d was correlated with clinical outcomes of DLBCL patients treated with the CHOP regimen through analysis of a retrospective cohort of 106 primary nodal DLBCL samples [48]. Lower levels of miR-146b-5p and miR-320d were found in DLBCLs with poor prognosis when the median survival period (40.8 months) was used as the cutoff point. Low expression level of miR-146b-5p was associated with decreased progression-free survival. In addition, low expression level of miR-320d was correlated with reduced progression-free survival and overall survival. Taken together, these results suggest that low expression of miR-146b-5p and miR-320d may be predictive of compromised responses of a subset of DLBCL patients to treatment with the CHOP regimen and that restoration of these miRs may be useful to improve the therapeutic efficacy of CHOP.

The stable expression of miRNAs in serum suggests their potential in prognostic biomarkers in diseases, especially in many tumors. Song et al. investigated the role of serum miRNA in predicting response to R-CHOP regimen in DLBCL patients using real-time PCR-based miRNA profiling [49]. A total of 15 serum miRNAs were altered more than 10-fold in DLBCL patients between the complete remission and primary refractory groups. In addition, the expression levels of 5 miRNAs (miR-224, miR-455-3p, miR-1236, miR-33a, and miR-520d-3p) were associated with response to R-CHOP treatment in DLBCL patients and were significantly predicted treatment responses independent from the IPI score. In conclusion, these 5 serum miRNAs may serve as novel prognostic biomarkers of DLBCL patients with R-CHOP treatment.

Patients with 7q gain display distinct biologic and clinical characteristics with higher complete response rate and better overall survival in DLBCL patients treated with R-CHOP. Chigrinova et al. showed that expression s of miR-96, miR-182, miR-589, miR-25 were increased in samples with 7q gain [50]. A similar trend was also observed for miR-339 (hsa-miR-339-5p), miR-489, miR-106B and miR-

29A. In summary, 7q gains delineate a group of DLBCL with higher rate of CR after R-CHOP and better outcome, possibly regulated by miRNAs.

The expression of miR-224 was decreased in DLBCL compared with normal B-cell [51]. In additions, miR-224 directly inhibited CD59 expression by binding to its 3'-untranslated region. Furthermore, the expression levels of miR-224 and CD59 can predict the response and prognosis of DLBCL patients treated with R-CHOP regimen. To conclude, miR-224 may play significant roles in the development of DLBCL.

Response modification

Numerous studies have demonstrated that miRNA-21 was upregulated in various cancers, serving as a well-established oncogenic miRNA [52-54]. In addition, it is involved in the development of many tumors as well as the sensitivity of tumor cells to chemotherapeutic drugs. Recently, Bai et al. investigated the role of miR-21 in the regulation of the sensitivity of the DLBCL cell line CRL2631 to the CHOP regimen [55]. They found that knockdown of miR-21 significantly sensitized CRL2631 cells to CHOP treatment, increasing the cytotoxic effects of the CHOP regimen. In addition, PTEN was proved to be a target gene of miR-21 in CRL2631 cells. Moreover, miR-21 affected cellular sensitivity to the CHOP regimen through the PI3K/AKT signaling pathway. Furthermore, NF-KB was proved to be a key upstream signal of miR-21 since knockdown of NF-KB reduced miR-21 expression level and increased the cytotoxic effects of CRL2631 cells to the CHOP regimen. These results provide evidence that it may be possible to overcome microRNA-based DLBCL drug resistance.

As mentioned above, low expression of miRNA-146b-5p and miRNA-320d predicts poor outcome of DLBCL treated with CHOP regimen. Moreover, functional studies showed that overexpression of miR-146b-5p or miR-320d decreased proliferation of DLBCL cells, whereas knockdown of miR-146b-5p or miR-320d increased DLBCL cell proliferation [48].

Summary and future expectations

MiRNAs are a class of small, non-coding RNA molecules involved in the regulation of gene

expression through targeting various genes [33, 56]. Aberrant expressed miRNAs are found in many diseases, especially in various human tumors, including DLBCL [24, 25, 31]. In recent years, accumulating studies have suggested the roles of miRNAs in the prediction of clinical outcomes and the modulation of the efficiency in anticancer treatments [57-59]. In the present review, the alterations in miRNA expression profiles can help to predict the responses to R-CHOP chemotherapy regimen and clinical outcome in DLBCL, which can help to design new treatment strategies. However, larger cohort studies are required to confirm these results and establish the optimal cut-off values.

Furthermore, miRNAs can regulate DLBCL cancer cells sensitivity to R-CHOP. Therefore, combination of miRNAs with existing chemotherapeutic strategies might increase the cytotoxic of R-CHOP regimen, thereby improving the clinical outcomes of DLBCL patients. The most promising miRNA targets include miR-21, miR-NA-146b-5p and miRNA-320d. However, the detailed mechanisms and intracellular pathways in the miRNA and R-CHOP effects are largely uninvestigated. Larger studies and further investigations are warranted to reveal the roles of miRNAs in modulation of R-CHOP treatment. Further studies are required to investigate the prognostic impact of individual miRNAs in independent cohorts of DLBCL patients. In addition, current reports were mainly conducted in DLBCL cells in vitros. There is no study on the safety and efficiency of miRNA treatment in xenograft mice model and in humans.

Address correspondence to: Zheng Li, Department of Orthopedics Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100042, China. Tel: 86-010-69152812; Fax: 86-010-69152812; E-mail: kleeo@163.com

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