Low expression of Mda-7/IL-24 and high expression of C-myb in tumour tissues are predictors of poor prognosis for Burkitt lymphoma patients

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ABSTRACT

Objectives: Burkitt lymphoma is one of the most common types of haematopoietic malignancy in children and adolescents. Mda-7/IL-24 had been identified as a differentiation inducer of Burkitt lymphoma cells. Previous studies have revealed that knockdown of C-myb can also lead to the terminal differentiation of Burkitt lymphoma cells. The aim of the present study was to investigate the correlation between the expression of Mda-7/IL-24 and C-myb, as well as their prognostic significance, for Burkitt lymphoma patients.

Methods: The tumour tissues were collected from 59 cases of Burkitt lymphoma patients and detected with Western blotting and immunohistochemistry.

Results: The results showed that the expression of Mda-7/IL-24 was lower, whereas the expression of C-myb was higher in Burkitt lymphoma tissues compared to specimens of normal lymph node tissues. Furthermore, C-myb expression was negatively correlated with Mda-7/IL-24 expression at the protein level in Burkitt lymphoma tissues and cell lines. Both the expression of Mda-7/IL-24 and C-myb in Burkitt lymphoma tissues was associated with some clinicopathological parameters, such as clinical stage, infiltration in the bone marrow, Ki67 and overall survival rates.

Conclusion: These results indicated that low expression of Mda-7/IL-24 along with high expression of C-myb are predictors for poor prognosis of Burkitt lymphoma patients; this outcome suggests that Mda-7/IL-24 and C-myb might be potential targets for clinical treatment of Burkitt lymphoma.

Abbreviations: Mda-7/IL-24: melanoma differentiation associated gene7/interleukin 24; FCM: flow cytometry; Ecog: Eastern Cooperative Oncology Group; IPI: International lymphoma prognosis index

KEYWORDS

Mda-7/IL-24; C-myb; Burkitt lymphoma; prognosis

Introduction

Burkitt lymphoma is one of the most common subtypes of paediatric haematopoietic malignancy and accounts for approximately 40% of newly diagnosed non-Hodgkin's lymphoma in children and adolescents [1]. Although high-dose combination chemotherapy is an effective strategy for the treatment of Burkitt lymphoma, a poor prognosis is inevitable for the patients due to recurrence, invasion of bone marrow tissue and development of chemotherapy resistance [2,3]. However, the exact mechanisms involved in occurrence and progression of Burkitt lymphoma remain unclear. Haemopoietic tumours, including Burkitt lymphoma, are characterized by a block in terminal differentiation. Therefore, acquiring more knowledge of the key molecules involved in affecting cell differentiation may provide new therapeutic targets for treatment of Burkitt lymphoma and further improve the survival rates of patients.

Interleukin-24 (IL-24), which is also known as melanoma differentiation associated gene 7 (Mda-7), was first identified in human melanoma cells [4,5]. Although its physiological role is poorly understood, overexpression of Mda-7/IL-24 exerts a tumour suppressing effect through several mechanisms, such as suppressing tumour cell invasion, arresting the cell cycle, inducing apoptosis and improving terminal differentiation in multiple malignant carcinomas [6–8]. In our previous study, overexpression of Mda-7/IL-24 resulted in mature differentiation of Raji and Daudi cells (the two types of Burkitt lymphoma cell lines) via upregulating the expression of Blimp1 in vitro [7]. Involvement of Mda-7/IL-24 in regulation of the cell growth and differentiation made it a novel target in tumour investigations and provided novel insight into understanding the mechanisms involved in the progression of Burkitt lymphoma.
C-myb acts as an important transcription factor involved in regulating the terminal differentiation of B lymphocytes [9–14]. Overexpression of C-myb is observed in a broad spectrum of lymphoid malignancies, including Burkitt lymphoma. More recently, C-myb has been shown to inhibit terminal differentiation of B phenotype lymphoma [9]. It has been shown that knockdown of C-myb by RNA interference will lead to plasma cell differentiation of Burkitt cell lines and recapitulate partial characteristics similar to characteristics caused by stable transfection of Mda-7/IL-24, which indicates that there may be an inverse correlation between Mda-7/IL-24 and C-myb. Furthermore, the expression of Mda-7/IL-24 and C-myb in tumour tissues may be associated with the clinicopathological characteristics and prognosis of Burkitt lymphoma patients.

To study the clinical significance of Mda-7/IL-24 and C-myb expression, we analysed their correlations with clinicopathological parameters of patients with Burkitt lymphoma. Additionally, the effect of overexpressing Mda-7/IL-24 on the expression of C-myb in Burkitt lymphoma cells in vitro was also investigated with the goal of clarifying a potential molecular correlation between Mda-7/IL-24 and C-myb. We found that Mda-7/IL-24 was attenuated and C-myb increased in Burkitt lymphoma tissues along with low expression of Mda-7/IL-24 and high expression of C-myb, which could be a predictor for a worsening clinical condition and prognosis for Burkitt lymphoma patients. This study also shows that transfection with exogenous Mda-7/IL-24 inhibited the expression of C-myb in Burkitt lymphoma cells in vitro, which suggests that C-myb may have the potential to function as a target of Mda-7/IL-24 in Burkitt lymphoma cells. These results revealed that Mda-7/IL-24 and C-myb might be potential targets in differentiation therapy that could be applied in patients with Burkitt lymphoma.

Materials and methods

Patients

The specimens for Burkitt lymphoma tissues and normal lymph node tissues were collected from 59 cases of Burkitt lymphoma patients and 28 cases of patients without carcinomas who underwent a lymph node biopsy at the Fourth Hospital of Hebei Medical University (Shijiazhuang, China) between January 2010 and January 2017. This research was approved by the ethics committee of the Fourth Hospital of Hebei Medical University and informed consent was provided by all of the patients. The median age of Burkitt lymphoma patients at the time of surgery was 8 years (range: 1–18 years), and the median age of patients in the control group was 7 years (range: 1–17 years). The median serum LDH activity of the patients with Burkitt lymphoma was 496.8 (108.2–2879.5) U/L. The median Ki67 positive rate of patients with Burkitt lymphoma was 95% (80–100%). None of the Burkitt lymphoma tissue patients received preoperative radiotherapy and chemotherapy. The patients were treated with modified CODOX-M/IVAC (CODOX-M: Cyclophosphamide, Vincristine, Doxorubicin, high-dose methotrexate; IVAC: ifosfamide, Etoposide and high-dose Cytarabine) combined with a rituximab regimen. The clinical stage, Eastern Cooperative Oncology Group (EcoG) scores, International lymphoma prognosis index (IPI) and histological type were determined according to the Ann Arbor classification and the WHO classification of 2008 [12,13]. Patient clinical information was collected and stored in a database. The specimens were collected and fixed in 10% formalin promptly after surgery.

Cell lines and reagents

The human Burkitt lymphoma cell lines Raji and Daudi were obtained from the research centre of the Fourth Hospital of Hebei Medical University (Hebei, China) and cultured in a RPMI-1640 medium (Sigma, St. Louis, MA, U.S.A.) supplemented with 10% foetal calf serum (FCS, Gibco, Grand Island, NY, U.S.A.) in a 5% CO₂ humidified incubator at 37°C. Antibodies against Mda-7/IL-24, C-myb and β-actin were purchased from Abcam (Cambridge, MA, U.S.A.). LipofectamineTM2000 and the pPACKHTM Lentivector Packaging kit were supplied by System Biosciences (Palo Alto, CA, U.S.A.).

Immunohistochemistry

An immunohistochemical assay was performed to analyse the Mda-7/IL-24 and C-myb expression in Burkitt lymphoma tissues and their relevance to the clinicopathological characteristics of patients. Briefly, the lymphoma tissue sections were de-waxed with xylene and ethanol. After antigen retrieval in a pressure kettle in Tris-EDTA buffer (pH 9.0), the sections were incubated with anti-Mda-7/IL-24 and anti-C-myb monoclonal antibodies for 3 hours at 37°C, and then the samples were incubated with a horseradish peroxidase-conjugated anti-mouse secondary antibody. The protein expression level was measured based on the percentage of positive cells and the intensity of staining. High expression samples were cases with >50% of cells staining for Mda-7/IL-24 or C-myb.

Western blot analysis

To further analyse the Mda-7/IL-24 and C-myb expression in Burkitt lymphoma tissues and their correlation, Burkitt lymphoma tissues were lysed with 500 μl of lysis buffer. The lysates were then subjected to Western blot analysis to determine the amount of Mda-7/IL-24 and C-myb. Briefly, the proteins were
subjected to agarose gel electrophoresis and were electrotransferred onto a polyvinylidene difluoride membrane. The membranes were incubated with primary antibodies at different dilutions, including antibodies against Mda-7/IL-24 (1:1000), C-myb (1:5000) and β-actin (1:5000) Ab for 8 hours at 4°C. The level of Mda-7/IL-24 and C-myb in each sample was calculated as the ratio of the intensity of protein to the intensity of β-actin using Odyssey V3.0 software (LI-COR Biosciences).

**Transfection of Burkitt lymphoma cell lines**

To investigate the effects of overexpressing Mda-7/IL-24 on expression of C-myb in Burkitt lymphoma cells, Raji and Daudi cells were stably transfected with the lentiviral vector encoding the human Mda-7/IL-24 gene using LipofectamineTM2000 and the pPACKH1TM Lentivector Packaging kit (pPACKH1-REV, pPACKH1-GAG and pVS-G) as previously described [2].

**Statistical analysis**

All statistical analyses were performed using the SPSS 13.0 software (SPSS Inc., Chicago, IL, U.S.A.). A Chi-square test was used to test for significance in clinical relevance of expression of Mda-7/IL-24 and C-myb. Differences were assessed by the one-way analysis of variance along with Student’s t-tests to compare two independent samples. p < .05 was considered statistically significant. All data are expressed as the mean ± standard deviation. The results shown in the figures are representative of at least three independent experiments.

**Results**

**Associations of Mda-7/IL-24 and C-myb expression in Burkitt lymphoma tissues and cell lines**

As shown in **Figure 1(A)**, the Burkitt lymphoma tissues showed significantly decreased expression of Mda-7/IL-24 and increased expression of C-myb proteins compared to normal lymph node tissues. As overexpression of Mda-7/IL-24 or knockdown of C-myb was reported to be able to induce the terminal differentiation of Burkitt lymphoma cells, the correlation between the expression of Mda-7/IL-24 and C-myb was analysed in Burkitt lymphoma patients. At the protein level, the relative optical densities of Mda-7/IL-24 and C-myb were 0.47 ± 0.19 and 0.54 ± 0.18, respectively, and the expression of C-myb was negatively correlated with Mda-7/IL-24 in Burkitt lymphoma tissues (**Figure 1(B)**, r = −0.4885, p < .01), which indicated that there may be a negative regulatory relationship between Mda-7/IL-24 and C-myb.

Additionally, the expression of Mda-7/IL-24 protein was significantly lower, whereas the expression of C-myb protein was significantly higher in parent and empty vector-transfected Raji and Daudi cells compared to normal lymphocytes. In contrast, Mda-7/IL-24 overexpressing cell lines showed significantly decreased expression of C-myb protein (**Figure 1(C)**), which suggested that the loss of Mda-7/IL-24 expression might be the key factor that is upregulating C-myb expression in Burkitt lymphoma cells.

**Associations of Mda-7/IL-24 and C-myb expression with Burkitt lymphoma clinicopathological parameters**

In Burkitt lymphoma tissues, the staining of Mda-7/IL-24 was found on the cytoplasm of most tumour cells and the nuclei of only a few cells, while C-myb was detected in the nuclei of tumour cells (**Figure 2**).

Of the 59 lymphoma tissues, high expression of the Mda-7/IL-24 and C-myb proteins was found in 26 and 31 cases of Burkitt lymphoma tissues, respectively, whereas high expression of Mda-7/IL-24 and low expression of C-myb were detected in all of the normal lymph node tissues. These results agreed with the previous findings that attenuated Mda-7/IL-24 expression and increased expression of C-myb that were observed in a variety of tumours [16,17].

To characterize the clinical role of Mda-7/IL-24 in Burkitt cell lymphoma, we analysed the relationship between the Mda-7/IL-24 or C-myb expression in tumour tissues and clinicopathological parameters of children Burkitt lymphoma patients. As shown in **Tables 1 and 2**, the expression of Mda-7/IL-24 and C-myb protein was significantly related to the clinical stage, bone marrow metastasis status, Ki67 and IPI index, whereas it was not related to gender, age and ECOG scores. Burkitt lymphoma patients with an early clinical stage (stage I and II), low Ki67 positive rate (≤90%), low IPI index (≤2), and negative bone marrow infiltration had significantly higher expression of Mda-7/IL-24 and lower expression of C-myb compared to patients with an advanced clinical stage (stage III and IV), high Ki67 positive rate (>90%), positive bone marrow infiltration and high IPI index (>2), which indicates there is a correlation between Mda-7/IL-24 or C-myb expression and the bioactivities, progression and prognosis of Burkitt lymphoma. Taken together, the low expression of Mda-7/IL-24 and high expression of C-myb could be predictors for a worse clinical condition and prognosis of patients with Burkitt lymphoma.

**Correlation of Mda-7/IL-24 and C-myb expression with tumour-specific survival for Burkitt lymphoma patients**

The overall three-year survival rate for patients with Burkitt lymphoma was 52.54%. The causes of death were lymphoma progression/relapse (25 patients,
and treatment-related death (3 cases of patients, 10.71%). The primary causes of treatment-related death included secondary infection after bone marrow suppression (2 patients, 7.14%) and tumour dissolution syndrome (1 patient, 3.57%). Kaplan–Meier survival curves showed that lower Mda-7/IL-24 or higher C-myb expression were associated with worse overall survival (log-rank test: \( p < .01 \); Figure 3).

The three-year survival rate for patients with high Mda-7/IL-24 expression in tumour tissues was 65.38% and 42.42% for those with low expression, which indicated that Burkitt lymphoma patients with low Mda-7/IL-24 expression in tumour tissues had a poorer prognosis compared to patients with high expression (\( p < .01 \)). In addition, the three-year survival rate for patients with high C-myb expression in tumour tissues was 38.71%
and 67.86% for patients with low expression, which suggested that Burkitt lymphoma patients with high C-myb expression in tumour tissue also had a poorer prognosis than patients with low expression \((p < .01)\).

Additionally, the three-year cumulative relapse rate for patients with high Mda-7/IL-24 expression in tumour tissues was 26.92% and 42.42% for patients with low expression, which indicated that Burkitt lymphoma patients with low Mda-7/IL-24 expression in tumour tissue had a higher recurrence tendency than patients with high expression \((p < .01)\). Additionally, the three-year cumulative relapse rate for patients with high C-myb expression in tumour tissues was 48.39% and 21.43% for patients with low expression;

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**Table 1.** Association between Mda-7/IL-24 expression and clinicopathological parameters of patients with Burkitt lymphoma.

| Parameters               | Mda-7/IL-24 expression | \(\chi^2\) | p-value |
|--------------------------|------------------------|-------------|---------|
| Gender                   | High       | Low       | \(\chi^2\) | p-value |
| Male                     | 15         | 20        | 0.051   | 0.821   |
| Female                   | 11         | 13        |          |         |
| Age (years)              |            |           |          |         |
| >10                      | 14         | 21        | 0.578   | 0.447   |
| \(\leq10\)               | 12         | 12        |          |         |
| Clinical stages          |            |           |          |         |
| I–II                     | 15         | 9         | 5.577   | 0.018   |
| III–IV                   | 11         | 24        |          |         |
| Infiltration in bone marrow |            |           |          |         |
| No infiltration          | 16         | 10        | 19.956  | <0.001  |
| Infiltration (<25%)      | 7          | 10        |          |         |
| Infiltration (≥25%)      | 3          | 13        |          |         |
| Ki67 positive rate (%)   |            |           |          |         |
| >90                      | 12         | 28        | 9.973   | 0.002   |
| \(\leq90\)               | 14         | 5         |          |         |
| Ecog scores              |            |           |          |         |
| >2                       | 14         | 20        | 1.145   | 0.285   |
| \(\leq2\)                | 12         | 13        |          |         |
| IPI index                |            |           |          |         |
| >2                       | 11         | 23        | 4.468   | 0.035   |
| \(\leq2\)                | 15         | 10        |          |         |

**Table 2.** Association between C-myb expression and clinicopathological parameters of patients with Burkitt lymphoma.

| Parameters               | C-myb expression | \(\chi^2\) | p-value |
|--------------------------|------------------|-------------|---------|
| Gender                   | High       | Low       | \(\chi^2\) | p-value |
| Male                     | 19         | 16        | 0.105   | 0.746   |
| Female                   | 12         | 12        |          |         |
| Age (years)              |            |           |          |         |
| >10                      | 18         | 17        | 0.043   | 0.836   |
| \(\leq10\)               | 13         | 11        |          |         |
| Clinical stages          |            |           |          |         |
| I–II                     | 7          | 17        | 8.866   | 0.003   |
| III–IV                   | 24         | 11        |          |         |
| Infiltration in bone marrow |            |           |          |         |
| No infiltration          | 8          | 18        | 27.087  | <0.001  |
| Infiltration (<25%)      | 9          | 8         |          |         |
| Infiltration (≥25%)      | 14         | 2         |          |         |
| Ki67 positive rate (%)   |            |           |          |         |
| >90                      | 26         | 14        | 7.731   | 0.005   |
| \(\leq90\)               | 5          | 14        |          |         |
| Ecog scores              |            |           |          |         |
| >2                       | 17         | 17        | 0.208   | 0.648   |
| \(\leq2\)                | 14         | 11        |          |         |
| IPI index                |            |           |          |         |
| >2                       | 22         | 12        | 4.761   | 0.029   |
| \(\leq2\)                | 9          | 16        |          |         |
this outcome further suggested that Burkitt lymphoma patients with high C-myb expression in tumour tissues had a poorer prognosis (p < .01).

In summary, these analyses demonstrated that low Mda-7/IL-24 expression and high C-myb expression in Burkitt lymphoma tissues were associated with poor prognosis. These results could provide some evidence that simultaneous measurement of the expression of Mda-7/IL-24 and C-myb in tumour tissues might be more accurate for determining the prognosis of patients with Burkitt lymphoma.

**Discussion**

Burkitt lymphoma is one of the most common types of haematopoietic malignancy in children and adolescents [14,15]. In this study, we analysed the Mda-7/IL-24 and C-myb expression and their relevance to the clinicopathological characteristics of Burkitt lymphoma patients. Although Mda-7/IL-24 has been widely regarded as an anti-tumour molecule and has been shown to inhibit haematopoietic tumour proliferation [4], little is known about its clinical role in Burkitt lymphoma. Attenuated expression of Mda-7/IL-24 was found in various kinds of carcinomas, such as colon cancer, breast cancer, melanoma and acute myeloid leukaemia [4,16,17]. The decreased expression of Mda-7/IL-24 was thought to be associated with numerous tumour biological characteristics, such as growth, metastasis, recurrence and chemotherapy resistance [4,18–20]. Our previous studies have shown that transfection of endogenous Mda-7/IL-24 induced mature differentiation of Raji and Daudi lymphoma cells, which was
characterized by proliferation inhibition, cell cycle arrest, morphological and cell surface antigen changes and decreased expression of malignant markers [7]. Furthermore, C-myb is an innate regulatory transcription factor that contributes to differentiation blockage in a variety of haematopoietic malignancies. Chen et al. [14] had reported that knockdown of C-myb can induce terminal differentiation in Burkitt lymphoma cell lines. Thus, elucidating the correlations of expression of Mda-7/IL-24 and C-myb with clinico-pathological parameters is necessary for us to understand the novel functions of Mda-7/IL-24 and C-myb involved in the progression of Burkitt lymphoma.

Furthermore, overexpressing Mda-7/IL-24 or silencing C-myb will increase the expression of Blimp1 and induce terminal differentiation in Raji and Daudi cells [7,14]. Given the same target molecular in the downstream of overexpressing Mda-7/IL-24 and silencing C-myb, we hypothesize that there may be a negative regulatory relationship between Mda-7/IL-24 and C-myb, and the expression of Mda-7/IL-24 and C-myb in tumour tissues may be associated with the clinicopathological characteristics and prognosis of Burkitt lymphoma patients.

To verify this hypothesis, we analysed the significance of the expression of Mda-7/IL-24 and C-myb and demonstrated that aberrant low expression of Mda-7/IL-24 and high expression of C-myb were positively correlated with Ki67, malignant stage and bone marrow metastases. Moreover, Kaplan–Meier survival curves showed that lower Mda-7/IL-24 and higher C-myb expression were associated with a higher relapse rate and worse overall survival; this outcome suggests that low expression of Mda-7/IL-24 and high expression of C-myb in tumour tissue could be predictors for poor prognosis of Burkitt lymphoma. In addition, Mda-7/IL-24-overexpressing Burkitt lymphoma cell lines showed significantly decreased expression of C-myb protein, which suggested that loss of Mda-7/IL-24 expression may be the key factor upregulating C-myb expression in Burkitt lymphoma cells. In this study, we provided direct evidence that Mda-7/IL-24 exerted its roles in Burkitt lymphoma cells through inhibition of C-myb, and this hypothesis was also supported by the observed inverse expression pattern of Mda-7/IL-24 and C-myb in human normal lymph node and Burkitt lymphoma tissues as well as decreased expression of C-myb protein in the Raji and Daudi cells transfected with Mda-7/IL-24. Indeed, Mda-7/IL-24 deletion and C-myb overexpression may play an important role in carcinogenesis of Burkitt lymphoma.

In summary, although there have been investigations of Mda-7/IL-24 expression in a variety of tumours [21–23], this is the first study to analyse its association with C-myb in Burkitt patients to evaluate the prognostic significance. The present study revealed that low expression of Mda-7/IL-24 along with high expression of C-myb are associated with a worse clinical condition and outcomes in Burkitt lymphoma patients and further indicated the possible role of C-myb in Mda-7/IL-24-induced terminal differentiation of Burkitt lymphoma cells; this outcome suggested they could be potent targets to establish new therapeutic strategies for improving the prognosis of patients with Burkitt lymphoma.

Disclosure statement
No potential conflict of interest was reported by the authors.

Funding
This work was partially supported by the Natural Science Foundation of China (grant no. 81703073), the Natural Science Foundation of Hebei Province (grant no. H2015206376), and Health Department of Hebei Province (no. 20160171).

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