Proceedings of Anticancer Research

Research Article

The Expression and Significance of CyclinD2, MPGES-1, Bcl2 in Diffuse Large B-cell Lymphoma

Qiushuang Ma[1#], Peng Lin[2#], Bingjuan Zhou[1], Yafei Zhao[3], Ling Li[4], Jinku Zhang[1*], Jirui Sun[1*]

[1]Department of Pathology, Baoding First Central Hospital, Baoding 071000, Hebei province, China;

[2]Department of Hematology, Baoding First Central Hospital, Baoding 071000, Hebei province, China;

[3]Department of Orthopedics, Baoding First Hospital of Traditional Chinese Medicine, Baoding 071000, Hebei province, China;

[4]Department of Dermatology, Baoding First Central Hospital, Baoding 071000, Hebei province, China

[#]Qiushuang Ma and Peng Lin both are the first authors and contributed equally to this work.

[*]Jinku Zhang and Jirui Sun are the corresponding authors and contributed equally to this work

Abstract: ***Objective:*** To study the expression and significance of cell cycle proteins CyclinD2, mPGES-1, Bcl2 in diffuse large B-cell lymphoma. ***Methods:*** Choose lymphoma and sexually hyperplastic lymphoid tissues as control. Immunohistochemical methods were used to detect the expression of CyclinD2, mPGES-1, and Bcl2, and to compare the positive expression rates of CyclinD2, MPGES-1 and Bcl2 in diffuse large B-cell lymphoma and reactive proliferative lymphoid tissues to compare their diffusion formation. B-cell lymphoma was analyzed for its clinicopathological features. ***Results:*** The positive expression rate of CyclinD2, mPGES-1 and Bcl2 in diffuse large B-cell lymphoma is higher than that in reactive proliferative lymphoid tissue, and the difference between the two is statistically significant. There was no statistical difference in CyclinD2, mPGES-1 and Bcl2 in diffuse large B-cell lymphoma between patients according to the age, sex, location, tissue type and degree of differentiation. ***Conclusion:*** CyclinD2, mPGES-1 and Bcl2 are highly expressed in patients with diffuse large B-cell lymphoma, and can be used as reference indicators for evaluating the malignant degree and efficacy of dysplasia.

Keywords: CyclinD2; mPGES-1; Bcl2; Diffuse large B-cell lymphoma; Clinicopathology

Publication date: November, 2020
Publication online: 30 November, 2020

[*]***Corresponding author:*** Jirui Sun, 15833867775a@sina.com; Jinku Zhang 843561234@qq.com

Diffuse large B-cell lymphoma is the most common type of adult lymphoma. Its histology, clinical manifestations and prognosis are highly heterogeneous. The disease progresses rapidly, and the median survival time of patients who are not treated in time is very low. Recent studies have confirmed that the occurrence of malignant tumors is often accompanied by abnormal expression of pro-proliferation factors and apoptosis inhibitors. This study aimed to explore the expression and significance of CyclinD2, MPGES-1, and Bcl2 in diffuse large B-cell lymphoma.

1 Materials and Methods

1.1 General Materials

89 cases of lymphoma tissue resected in hospital were collected, collection criteria as follow:

(1) All met the diagnostic criteria for diffuse large B-cell lymphoma: rapid swelling of lymph nodes, accompanied by systemic symptoms such as progressive weight loss, night sweats, and fever. Histopathology confirmed that the lymphocytes were large in size, rich in cytoplasm, and the nucleus was oval or round with prominent nucleoli. Diagnosed histopathologically.

(2) Received more than 3 courses of radiotherapy

and chemotherapy: blood coagulation and liver and kidney function are obviously abnormal; survival period is expected to be <3 months.

(3) Accompanied by other malignant tumors.

1.2 Methods

Lymphatic tissue was collected, put in liquid nitrogen, and transferred to -80 ℃ low temperature box for use. Detection done by immunohistochemical staining. The thickness of the paraffin slice is 4, and it was baked in an oven at 70°C for 1.5 hours. The sections were deparaffinized with xylene and hydrated with 100%, 90%, 80% and 70% ethanol gradients. They were then rinsed with distilled water for 3 minutes, followed by rinsing with phosphate buffered saline (PBS) 3 times. The sections were incubated with 3% H_2O_2 in deionized water for 10 minutes to inhibit endogenous peroxidase activity. After washing 3 times with PBS, corresponding hot antigen retrieval was performed according to the requirements of each antibody, and washed 3 times with PBS. The diluted monoclonal antibody was added to the slices and placed in a refrigerator at 4°C overnight. It was washed 3 times with PBS, added with antibody antibody polymer, and left at room temperature for 30 minutes. Washed 3 times with PBS. The color was changed by adding 2 drops of 3,3-diaminobenzidine (DAB) concentrated solution to each section. The color development time was adjusted under the microscope until the positive substance has a brownish yellow reaction, and then rinsed with tap water to stop the color reaction. After dyeing with hematoxylin, it turned blue again with tap water, then dehydrated with ethanol gradients, and sealed with neutral resin.

1.3 Observation Indicators

(1) The proportion of positive cells. Five fields (400 times) were randomly selected under a high-power microscope, and more than 200 cells were observed in a single field. CyclinD2 is positive in the nucleus, while BCL2 and mPGES-1 are expressed in the nucleus and cytoplasm, showing yellow or brown particles.

(2) Follow-up through outpatient and telephone for five years, and statistics of the five-year survival rate.

2 Results

2.1 CyclinD2, mPGES-1 and Bcl2 and Differences in Reactive Hyperplastic Lymphoid Tissues

The positive expression rate of CyclinD2, Bcl2 and mPGES-1 in diffuse large B-cell lymphoma is higher than that in reactive hyperplastic lymphoid tissues, as shown in Table (2.1-1).

Table 2.1-1. Comparison of the expression of CyclinD2、Bcl2、mPGES-1 between the two groups *n*(%)

Group	*n*	CyclinD2	Bcl2	mPGES-1
Diffuse Large B-cell Lymphoma group	89	31 (34.83)	56 (62.92)	69 (77.53)
Reactive Hyperplastic Lymphoid Tissue group	25	1 (4.00)	2 (8.00)	3 (12.00)

2.2 Clinicopathological Features

There are significant differences in the expression of CyclinD2, mPGES-1, Bcl2 in diffuse large B-cell lymphoma in different age, gender, location, histological type and degree of differentiation. It is related to immunophenotyping, IPI index, and first treatment efficacy, as shown in table (2.2-2).

Table 2.2-2. Expression of CyclinD2, mPGES-1, Bcl2 in diffuse large B-cell lymphoma and its relationship with clinicopathological features (*n*)

Indicators		*n*	CyclinD2		χ^2	*P*	Bcl2		χ^2	*P*	mPGES-1		χ^2	*P*
			Positive	Negative			Positive	Negative			Positive	Negative		
Age (y.o.)	>40	55	18	37	0.025	0.874	36	19	0.396	0.529	42	13	0.112	0.738
	<40	35	13	21			20	14			27	7		
Gender	Male	40	11	29	1.720	0.189	33	16	0.915	0.339	37	12	0.738	0.614
	Female	49	20	29			23	17			32	8		
Site	Extranodal	50	18	32	0.069	0.793	32	18	0.057	0.812	40	10	3.064	0.080
	Intranodal	39	13	26			24	15			29	10		
Tissue Type	Immunoblast	15	5	10	0.018	0.894	11	4	0.838	0.359	9	6	3.181	0.075
	Central blast	74	26	48			45	29			60	14		
Degree of Differentiation	High	50	17	33	0.035	0.852	30	20	0.417	0.518	38	12	0.1523	0.696
	Low	39	14	25			26	13			31	8		
Stage	Ⅰ – Ⅱ	52	9	43	16.921	0.000	24	28	15.073	0.000	35	17	7.499	0.006
	Ⅲ – Ⅳ	37	22	15			32	5			34	3		
Immunophen-otyping	Non-CCB Type	46	6	40	19.912	0.000	18	28	23.098	0.000	29	17	11.466	0.001
	CCB Type	43	25	18			38	5			40	3		
IPI Index	Low	40	8	32	7.041	0.008	18	22	10.002	0.002	25	15	9.418	0.002
	High	49	23	26			38	11			44	5		
First Treatment Efficacy	Complete Remission	54	13	40	4.299	0.038	25	29	16.268	0.000	35	19	12.739	0.000
	Incomplete Remission	35	18	22			31	4			34	1		

3 Discussion

Diffuse large B-cell lymphoma (DLBCL) is one of the common subtypes of non-Hodgkin's lymphoma. It often happens to the elderly. The clinical manifestation is "rapidly increasing painless mass". It can also cause different degrees of nose bleeding and dysphagia. The prognosis is not ideal. In recent years, the biological research of diffuse large B-cell lymphoma has shown certain clinical value, which is not only conducive to the diagnosis of the disease, but also useful for predicting the treatment effect and prognosis assessment. CyclinD2 is a common subtype of cyclin, which is the ultimate receptor for inducing oncogenic signals and mitosis. It plays a key role in cell-cycle regulation. CyclinD2 can activate cyclin-dependent kinases to form complexes, induce phosphorylation inactivation of RB, promote the up-regulation of E2F gene expression, and participate in DNA synthesis. Many carcinogenic factors can lead to abnormal regulation of CyclinD2 gene and products, leading to uncontrolled cell-cycle, promoting unlimited cell proliferation, and conducive to malignant transformation and tumor formation. CyclinD2 can be abnormally expressed in a variety of malignant tumors and participates in the pathogenesis of tumors. The results of this study have shown that the positive expression rate of CyclinD2 in diffuse large B-cell lymphoma is higher than that in reactive lymphoid tissues, but the positive expression rate is only 34.83%. Considering that the methylation of the promoter region of CyclinD2 gene affects protein expression, further analysis of the relationship between CyclinD2 and clinicopathological features shows that there are significant differences in CyclinD2 in different Ann Arbor stages, immunotypes, immune function classifications, IPI index and first treatment efficacy. This indicates that the detection of the AOR expression can not only identify benign and malignant diseases, but also reflect the biological behavior of the tumor, thereby evaluating the efficacy.

BCL2 is an apoptosis suppressor gene, mainly expressed in the mitochondrial nuclear membrane, outer membrane and rough endoplasmic reticulum. Its overexpression can inhibit cell apoptosis caused by many factors, prolong cell lifespan, and promote cell biochemistry. It was found that the expression of apoptotic cells was significantly reduced. Studies have shown that overexpression of BCL-2 can significantly inhibit cell-line and tissue cell apoptosis. It should also be pointed out that it can control and induce cell apoptosis, and unbalanced proliferation can lead to diseases.

Acknowledgement

Key Laboratory of Molecular Pathology and Early

Diagnosis of Tumor in Hebei Province

References

[1] Cui YX, Wang XH, Chen X. Analysis on the value of using flow cytometry to detect CyclinD1 and BCL-2 in patients with B-cell lymphoma[J]. Journal of Experimental Hematology, 2016, 24(1): 98-101. DOI:10.7534/j.issn.1009-2137.2016.01.019.

[2] Wang LH, Zhao YP, Jin SS, et al. Effects of MicroRNA-96 on the proliferation and migration of human retinal pigment epithelial cells[J]. Chinese Journal of Optometry & Ophthalmology and Visual Science, 2020(3): 184-185-186-187-188-189-190.

[3] Qin Y. Correlation between abnormal expression of HK-II and TNFAIP3 and malignant characteristics of tumor cells in diffuse large B-cell lymphoma [J]. Journal of Hainan Medical University, 2018, 24(22): 2015-2018+2022.

[4] Huang WT, Zhang HZ, Zhou XY, et al. The expression of CyclinD2 in diffuse large B-cell lymphoma and its clinical significance [J]. Chinese Journal of Clinical and Experimental Pathology,2018,34(01):27-31.

[5] Chen J. The regulatory role of nuclear receptor NR2E1 in the compensatory proliferation of pancreatic β-cells [D]. Wuhan University,2017.

[6] Cheng Y. The effect and mechanism of miRNA-493 targeting E2F1 and RhoC in inhibiting lung cancer cell proliferation and metastasis [D]. Central South University, 2013.