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ORIGINAL PAPER

INCENP (Inner Centromere Protein) is Overexpressed in High Grade Non-Hodgkin B-cell Lymphomas

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Abstract Inner centromere protein (INCENP) is a member of the Chromosomal Passenger Complex (CPC), which is a four member protein complex essential for proper completion of mitosis and cell division (cytokinesis). Inappropriate chromosomal segregation and cytokinesis due to deregulated expression of chromosome passenger proteins may lead to aneuploidy and cancer including lymphomas. According to our knowledge this is the first study investigating immunohistochemical expression of INCENP in lymphoma cases and cancer tissues in general. Our purpose was to characterize the expression of INCENP in cases of non-Hodgkin B-cell lymphomas, to compare the immunoreactivity between low and high grades and to evaluate the correlation between INCENP and MIB-1 labeling indices. We examined INCENP and MIB-1 immunoreactivity in paraffin sections of 55 samples of non-Hodgkin B-cell lymphomas, obtained from 55 patients, 31 men and 24 women. Thirty were of high grade and 25 were of low grade. Our results showed significantly higher nuclear immunohistochemical expression of INCENP in high grade B-cell lymphomas versus low grade ones. Also INCENP expression was significantly correlated with MIB-1 labeling index. Taken together our results point to a possible association between increased INCENP immunostaining and B-cell lymphoma aggressiveness and also stress the need for further investigating the expression of INCENP and other mitotic regulatory proteins in lymphomas and other malignant neoplasms.

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Introduction

Inner centromere protein (INCENP) is a member of the chromosome passenger complex (CPC) which has recently received much attention as a key player in mitotic events, such as accurate chromosome segregation and completion of cytokinesis and exhibit dynamic localization during mitosis [1]. In mammalian cells CPC is a protein complex consisting of INCENP, Survivin, Aurora B kinase and Borealin (or Dasra-B). Aurora B is the enzymatic core of the complex, whereas Survivin, INCENP and Borealin (the non-enzymatic members of the complex) dictate the timing and localization of the kinase activity, thereby allowing it to act at the right place at the right time [1–3]. INCENP was the first protein identified in the chromosome passenger protein complex in 1985 [4]. The C-terminus (IN-Box) of this protein, which is highly conserved from yeast to humans, binds to Aurora-B and stimulates its kinase activity during mitosis [5, 6].

INCENP mRNA expression is particularly elevated in proliferative tissues such as the normal human colon and testis, which is consistent with its role in cell proliferation as an essential housekeeping gene required for mitosis [7]. Targeted deletion of INCENP gene in mice leads to polyploidization and early embryonic lethality [8]. The same defects are observed in mammalian cells in addition to the appearance of abnormal numbers of centrosomes when the dominant negative form of INCENP is overexpressed. Aberrant expression of INCENP also leads to abortive cytokinesis in yeast, Drosophila and mammalian cells [9–11]. These experimental findings show that strict

regulation of INCENP is essential for cell division. Deregulated expression of chromosome passenger proteins, such as Aurora kinases or Survivin is a hallmark of various cancers and experimentally induced changes in these regulators can promote tetraploidy or aneuploidy and loss of heterozygosity [9]. INCENP protein levels are increased in several colorectal cell lines [7]. There is also one recent study showing increased INCENP mRNA levels in cases of colorectal carcinoma [12]. How the overexpression of CPC proteins, individually or together, promotes aneuploidy and cancer remain an essential unanswered question and this is one of the reasons that studies of the CPC constitute one of the most dynamic areas of ongoing mitosis research.

Up to now only Survivin and to a lesser extend Aurora-B immunohistochemical expression has been adequately investigated in various human cancers tissues. According to our knowledge there are no reports concerning immunohistochemical detection of INCENP in human cancer tissues.

In our study we assessed the immunohistochemical expression of INCENP in cases of low and high grade non-Hodgkin B-cell lymphomas and reactive lymph nodes. Our results showed that INCENP is localized to the nuclei of lymphoma cells and also to the nuclei of proliferating cells (such as centroblasts) in normal germinal centers and paracortical areas. INCENP labeling index is significantly higher in cases of high grade B-cell lymphomas compared to low grade ones. Furthermore our results showed that INCENP expression is significantly correlated with MIB-1 labeling index. According to our knowledge this is the first report concerning immunohistochemical detection of INCENP in lymphoma cases and human cancer tissues in general.

Materials and Methods

Patients and Surgical Specimens

We assessed the immunostaining of INCENP and MIB-1 in 55 cases of non-Hodgkin B-cell lymphomas. The material was archival, formalin fixed, paraffin embedded, lymphoma tissues retrieved from the files of the Pathology department of the University Hospital of Thessalia. Of the 55 patients, 31 were men and 24 women, with mean age of 65. There were no cases with a history of previous treatment. The tumors were classified according to the current (2001) World Health Organization classification of lymphoid tissue tumors [13].

The high grade tumor group consisted of twenty-three diffuse large B-cell lymphomas (DLBCL), one Burkitt lymphoma, two Burkitt-like lymphomas, three follicular lymphomas (grade 3) and one MALT-type lymphoma with areas of transformation to diffuse large B-cell lymphoma.

The low grade tumor group consisted of eight B-chronic lymphocytic leukaemias/small lymphocytic lymphomas (B-CLL/SLL), five marginal zone B-cell lymphomas, five follicular lymphomas (grade 1), one lymphoplasmacytic lymphoma and six B-cell lymphomas of the MALT-type. Five lymph nodal samples with reactive B-cell hyperplasia were included in the study.

Immunohistochemical Procedures

Four-micrometer sections from selected paraffin blocks of each case were prepared. After deparaffinization, sections were rehydrated through decreasing alcohols. Antigen unmasking was achieved by treating sections in a 5-mM citrate buffer (pH 6) for a total of 20 min in a microwave oven at 600 W. After quenching of endogenous peroxidase with 3% hydrogen peroxide solution for 10 min, slides were incubated overnight at 4°C with a rabbit polyclonal antibody (1:500) against the C-terminal 350 amino acids of human INCENP (Abcam, Cambridge, MA). Adjacent sections were incubated for 30 min at room temperature with a monoclonal antibody (1:80) against the MIB-1 clone of Ki-67 (Dako, Denmark). The staining was developed with substrate chromogen solution (Envision, Dako, Denmark) and diaminobenzidine for 10 min. The slides were counterstained with Harris hematoxylin for 2 min, dehydrated, and mounted with DPX solution. As negative control for the staining procedure, the primary antibody was omitted.

Assessment of Immunohistochemical Staining

Representative images with the highest positive nuclear staining for INCENP and MIB-1 (hot spots) from all cases were photographed, using the Nikon DS-5M-L1 Digital Sight Camera System mounted on a Nikon optical microscope (Eclipse 50i model). Image analysis for estimation of positively stained nuclei was performed utilizing the public domain software for image analysis "ImageJ for microscopy" (Rasband, W.S., ImageJ, U.S. National Institutes of Health, Bethesda, Maryland, USA, http://rsb.info.nih.gov/ij/, 1997–2007) [14]. Segmentation of the color images was achieved after setting a threshold using the "Color functions/Threshold color" plugin. Threshold value was set after selecting an area of interest with one of the selection tools and activating the sample button that removes the pixels in the image that do not have the same color as those in the selection. Once the color images were segmented, they were converted to binary images and the menu command "Analyze/Analyze particles" was used to estimate the cell number in each image. Minimum size of particles was set on occasion to exclude objects that clearly were of no interest. The "Show:

outlines" option was selected to display an image of the selected objects. After automatic particle counting of positively and negatively stained nuclei, a percentage of the positive staining nuclei (labeling index) for INCENP and MIB-1were estimated in each case.

Statistical Analysis

Data were expressed as mean ± SEM (in all cases n = number of patients) and were analyzed statistically using the SPSS program package, version 9.0. Groups were inspected for normality and pairwise comparisons were performed with the non-parametric Mann–Whitney test. Differences were considered significant at p value<0.05. Correlation between INCENP and MIB-1 labeling index in the two groups of high grade and low grade B-cell lymphomas was assessed using the Pearson correlation test. Correlation was considered significant at the 0.01 level.

Results

Our results showed that INCENP is localized to the nuclei of neoplastic lymphocytes and also to the nuclei of proliferating cells in normal germinal centers and paracortical areas. There was strong immunopositivity for INCENP in all phases of mitosis as well as in all atypical forms of mitosis (Fig. 1). Cytoplasmic staining was not detected. INCENP immunostaining was higher in cases of high grade compared to low grade B-cell lymphomas (Fig. 2). The findings are presented in Table 1. The labeling indices graph for INCENP and MIB-1 and representative digitized images of INCENP immunostaining of low versus high grade cases are presented in Fig. 3.

The following interesting observations were also made: (1) In cases of B-CLL/SLL lymphomas INCENP immunopositivity was more common in areas of prolymphocytes and paraimmunoblasts, highlighting the characteristic for this type of lymphoma proliferation centers. (2) In follicular lymphomas INCENP expression was increased in high grade versus low grade tumors, reflecting possibly tumor progression. (3) In a case of a transformed MALT-lymphoma (case 30 in Table 1), INCENP was overexpressed in high grade areas highlighting the transformation of this low grade lymphoma to a high grade diffuse large B cell lymphoma (Fig. 4).

After calculating the percentage of immunostained nuclei, a statistically significant difference was observed in INCENP labeling indices between the high grade and the low grade group (High grade 57.7±3.6%, n=30; Low-grade 6.12±0.76%, n=25; $p<0.001$). This difference was in accordance with the statistically significant difference in

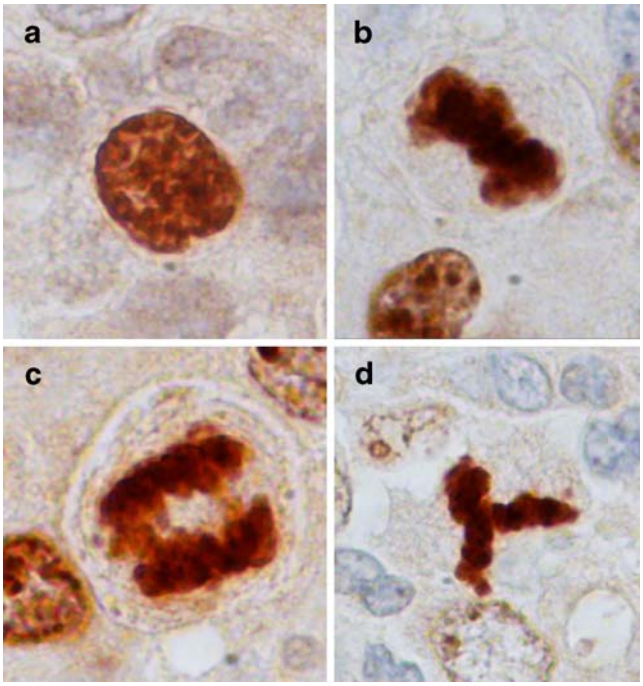

Fig. 1 Detection of INCENP in all stages of normal and abnormal mitoses from a case of diffuse large B-cell lymphoma (DLBCL). **a** prophase, **b** metaphase, **c** anaphase, **d** abnormal-tripolar mitotic figure. Original magnification ×1,000

MIB-1 labeling indices between these two groups of B-cell lymphomas (High grade 73.1±2.99%, n=30; Low-grade 9.2±1.12%, n=25; $p<0.001$).

High grade B-cell lymphomas exhibited also a significant degree of positive correlation between INCENP and MIB-1 labeling indices (r=0.897, $p<0.001$). Similarly, a positive correlation was also observed between INCENP and MIB-1 labeling indices in low grade B-cell lymphomas (r=0.875, $p<0.001$).

Discussion

Most known oncogenes and tumor suppressor genes involved in lymphomas and other human malignant neoplasms are key regulators of the cell cycle, such as cyclins, cyclin-dependent kinases (CDKs), CDK inhibitors (mainly p16, p15, p21 and p27) and CDK substrates (mainly Rb protein) that regulate the G1 progression and G1/S transition [15]. Mutations in these genes lead to dysregulation of the pathways controlling entry and progression into the cell cycle and are essential to allow uncontrolled proliferation of cancer cells. However in the last few years, various genetic alterations have been identified that do not provoke a direct increase in cell proliferation but rather target specific molecules that act as mitotic regulators involved in the progression through mitosis and cytokinesis,

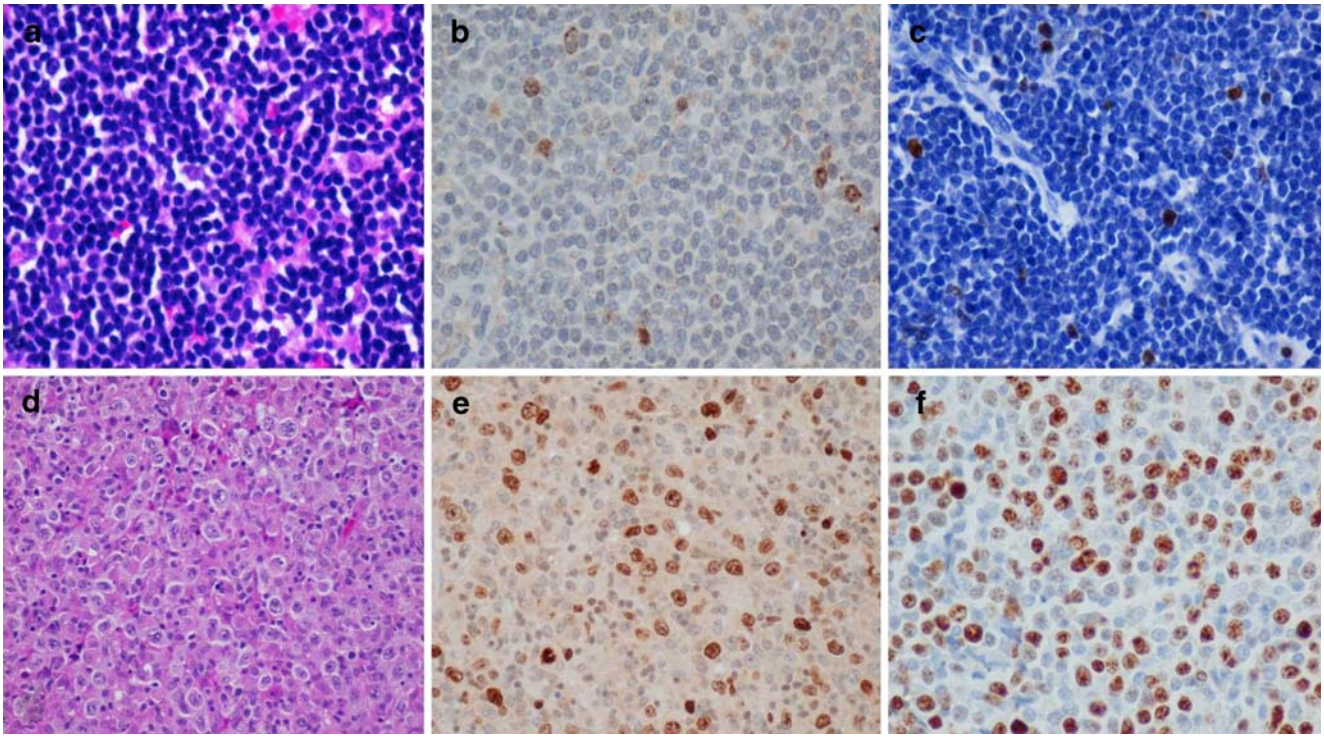

Fig. 2 Low labeling indices of INCENP and MIB-1 in a case of B-CLL/SLL. **a** H/E, **b** INCENP, **c** MIB-1. Original magnification ×400. High labeling indices of INCENP and MIB-1 in a case of diffuse large B-cell lymphoma (DLBCL). **d** H/E, **e** INCENP, **f** MIB-1. Original magnification ×200

such as the chromosomal passenger complex proteins (CPC). Although these alterations do not directly promote uncontrolled proliferation, they induce chromosomal aberrations and aneuploidy which may represent a primary event leading to unbalanced expression of a cluster of crucial genes, cellular transformation and cancer [16, 17]. Thus, carcinogenesis may not necessarily require key mutations in cancer-related genes but a genetic imbalance caused by chromosomal gains or losses due to the disruption of the mitotic spindle or to molecular alterations of proteins conducting mitosis. In the present study we have evaluated the immunohistochemical expression of such a protein named Inner Centromere Protein (INCENP) in paraffin sections from non-Hodgkin B-cell lymphoma cases and from reactive lymph nodes.

INCENP is a member of the Chromosomal Passenger Complex and together with the other members of the complex (Survivin, Borealin and Aurora B) orchestrates highly different processes, such as proper chromosome alignment, histone modification and cytokinesis [1–3]. INCENP, the first identified protein of the complex [4], acts as a scaffold for borealin and survivin and binds through its C-terminus to Aurora-B (the enzymatic core of the complex) stimulating its kinase activity during mitosis [5, 6]. In early mitosis the complex corrects misattachments between kinetochores and the mitotic spindle, promoting correct chromosome alignment at the metaphase plate. Furthermore Aurora B promotes histone modification by phosphorylating Histone 3. Finally at the end of mitosis CPC regulates the proper execution of cytokinesis [1].

Deregulated expression of chromosome passenger proteins, such as Aurora kinases or Survivin, is a hallmark of various cancers, and experimentally induced changes in these regulators can promote tetraploidy or aneuploidy and loss of heterozygosity [9]. Up to now only Survivin and to a lesser extend Aurora-B immunohistochemical expression has been adequately investigated in various human cancers tissues. Overexpression of Survivin in a wide range of malignant tumor tissues, including lymphomas, leukaemia (ALL, AML), colorectal cancer, astrocytic gliomas and breast cancer has been consistently reported in the literature [18–22]. Similarly, correlative data from fewer studies showing overexpression of Aurora-B Kinase in solid tumors and tumor cell lines have been reported [23–26]. On the contrary there is only one study investigating Borealin immunohistochemical expression in cancer tissues, showing a positive relationship between its nuclear accumulation and poor prognosis in cases of gastric adenocarcinoma [27]. According to our knowledge there are no reports concerning immunohistochemical detection of INCENP in human cancer tissues.

Table 1 INCENP and MIB-1 labeling indices (L.I) in non Hodgkin B-cell lymphoma cases

n	High grade B-cell lymphomas	INCENP (%)	MIB-1 (%)	*n*	Low grade B-cell lymphomas	INCENP (%)	MIB-1 (%)
1	DLBCL	55	60	1	B-CLL/SLL	7	10
2	DLBCL	60	85	2	B-CLL/SLL	8	8
3	DLBCL	55	60	3	B-CLL/SLL	10	10
4	DLBCL	70	85	4	B-CLL/SLL	6	12
5	DLBCL	80	90	5	B-CLL/SLL	5	12
6	DLBCL	65	90	6	B-CLL/SLL	3	4
7	DLBCL	40	75	7	B-CLL/SLL	5	7
8	DLBCL	90	95	8	B-CLL/SLL	8	10
9	DLBCL	40	60	9	Nodal marginal zone l.	5	6
10	DLBCL	65	70	10	Nodal marginal zone l.	20	30
11	DLBCL	30	60	11	Nodal marginal zone l.	8	10
12	DLBCL	40	60	12	Splenic marginal zone l.	8	8
13	DLBCL	35	60	13	Splenic marginal zone l.	4	4
14	DLBCL	80	95	14	Follicular l. (grade I)	5	15
15	DLBCL	60	85	15	Follicular l. (grade I)	8	15
16	DLBCL	50	60	16	Follicular l. (grade I)	5	10
17	DLBCL	55	65	17	Follicular l. (grade I)	7	12
18	DLBCL	60	70	18	Follicular l. (grade I)	5	8
19	DLBCL	45	60	19	Lymphoplasmacytic l. (nodal)	3	5
20	DLBCL	65	70	20	MALT lymphoma	1	2
21	DLBCL	80	90	21	MALT lymphoma	5	6
22	DLBCL	60	85	22	MALT lymphoma	10	12
23	DLBCL	35	60	23	MALT lymphoma	2	5
24	Burkitt lymphoma	95	99	24	MALT lymphoma	1	3
25	Burkitt-like lymphoma	90	99	25	MALT lymphoma	4	6
26	Burkitt-like lymphoma	85	95				
27	Follicular l. (grade III)	35	60				
28	Follicular l. (grade III)	40	50				
29	Follicular l. (grade III)	45	60				
30	MALT l. with areas of transformation to DLBCL	25[a]	40[a]				

DLBCL Diffuse large B-cell lymphoma, *B-CLL/SLL* B-chronic lymphocytic leukaemia/small lymphocytic lymphoma
[a] In areas of large cell transformation

Using a polyclonal antibody raised against the C-terminal 350 amino acids of human INCENP we assessed for the first time the immunohistochemical expression of INCENP in paraffin sections of B-cell lymphomas. Our results showed that INCENP is localized to the nuclei of lymphoma cells. INCENP labeling index is significantly higher in cases of high grade B-cell lymphomas (such as diffuse large B-cell lymphomas and grade 3 folicullar lymphomas) compared to low grade ones (such as B-CLL/SLL, marginal zone and grade 1 follicular lymphomas). Furthermore, our results showed that INCENP expression is significantly correlated with MIB-1 labeling index, an important correlation since Ki-67 expression rate has been associated with survival mainly in some series of high grade B-cell lymphomas [28] and to a lesser extent in some series of low grade B-cell lymphomas [29]. This positive correlation between INCENP and MIB-1 immunostaining as well as the strong immunopositivity for INCENP in all phases of mitosis is compatible with the close relationship of INCENP and the other CPC members with the mitotic apparatus. Moreover, the strong expression of INCENP in all atypical mitotic figures points to the known relationship of overexpressed CPC members and aneuploidy [9].

INCENP expression was increased in high grade follicular lymphomas versus low grade ones, reflecting possibly tumor progression. INCENP was also overexpressed in high grade areas in a case of a transformed MALT-lymphoma, highlighting the transformation of this low grade lymphoma to a high grade diffuse large B cell lymphoma. The above observations point to the possibility that INCENP could be used as an auxiliary progression/transformation immunohistochemical marker in B-cell lymphomas.

All the above findings are in accordance with a recent report showing that other mitotic regulatory proteins such as securin, aurora A kinase and polo-like kinase 1 (all of which are substrates of the anaphase promoting complex or

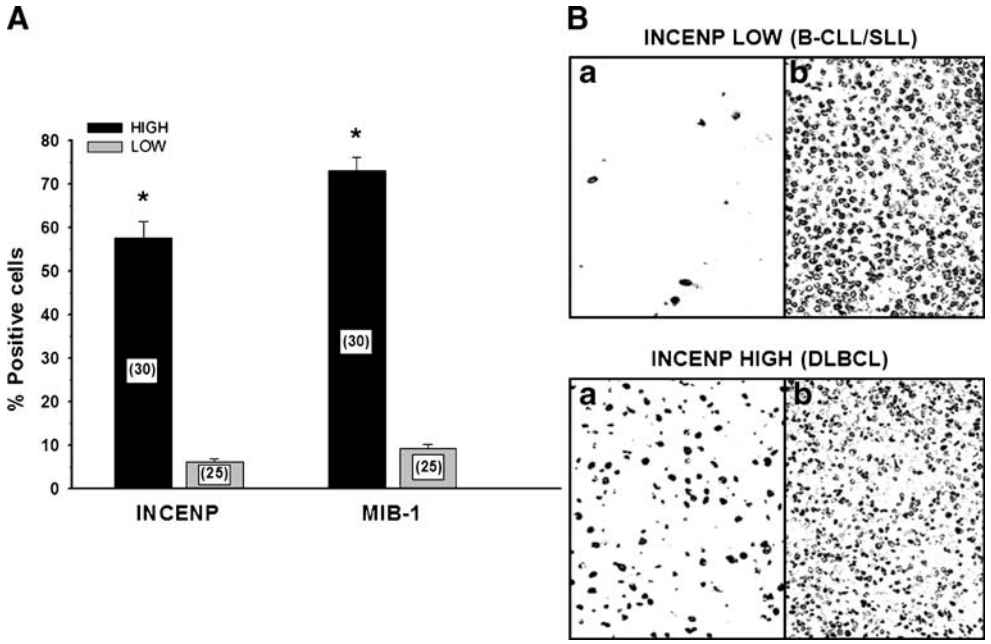

Fig. 3 **A** Graph of INCENP and MIB-1 nuclear labeling indices, calculated as discussed on "Materials and Methods" section, from all B-cell lymphoma cases (vertical axis: percentage of neoplastic cells showing nuclear positivity). **B** Representative digitized images of INCENP immunostaining from low and high grade B-cell lymphoma cases (*a* positive INCENP nuclei, *b* background negative nuclei digitized from hematoxylin staining)

cyclosome) are overexpressed in high grade lymphomas and in other high grade tumors, promoting chromosomal aberrations and aneuploidy [30]. The notion that failure of normal chromosome segregation leading to subsequent mitotic catastrophe is a central mechanism among events leading to chromosome or genomic instability and aneuploidy

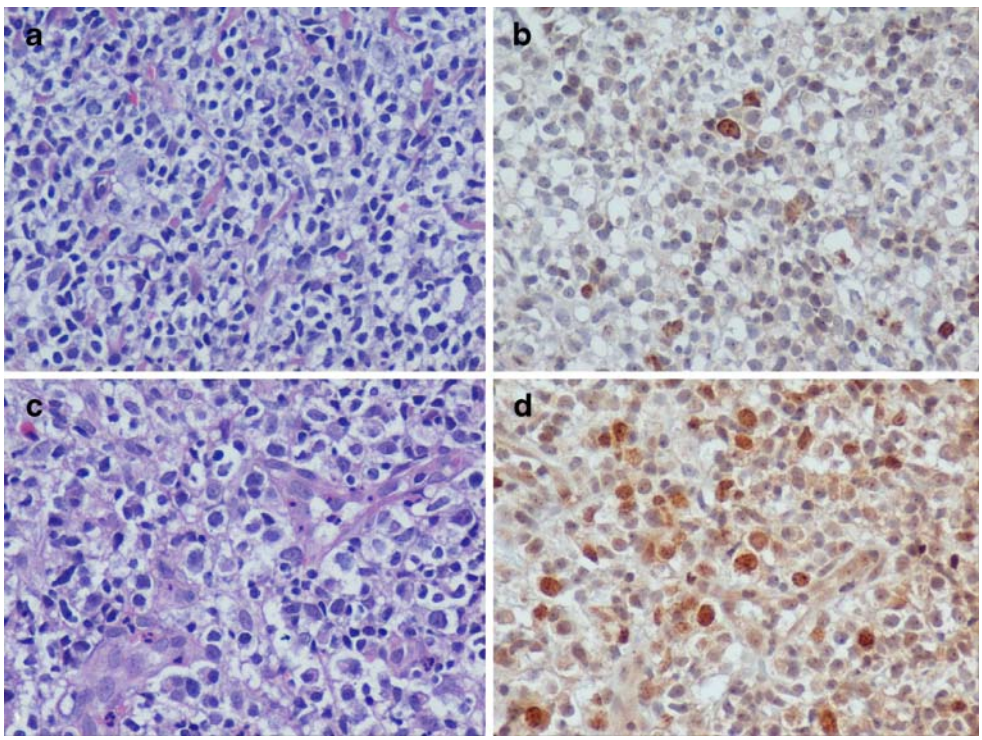

Fig. 4 Low INCENP labeling index in a case of MALT-lymphoma (**a** H/E, **b** INCENP) with areas of transformation to DLBCL showing overexpression of INCENP (**c** H/E, **d** INCENP). Original magnification ×400

(typically seen in malignant tumors) is supported by such recent studies and stresses the need for further investigating the expression of mitotic regulatory proteins such as CPC and spindle checkpoint proteins.

In conclusion, this is the first immunohistochemical study of INCENP expression in B-cell lymphoma cases and reactive lymph nodes showing nuclear localization of the protein and point to a possible association between increased INCENP immunostaining and B-cell lymphoma aggressiveness. Despite the limited knowledge on the molecular mechanisms that relate aberrant expression of INCENP and the other CPC members to aneuploidy and cancer, the clinical success of mitotic poisons such as vincristine for lymphoma treatment and taxanes for various solid tumors reinforces the interest in these proteins, their roles in human cancer and the therapeutic opportunities to modulate their function in lymphoma and cancer treatment in general.

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