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Original article

Immunohistochemical expression of galectin-3 is significantly associated with grade, stage and differentiation of endometrial carcinomas

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ABSTRACT

This study describes galectin-3 immunohistochemical phenotype and its association with clinicopathological factors in the carcinoma of endometrium. Seventy one cases of endometrial carcinoma and 30 cases of benign and normal endometrium were employed for the detection of galectin-3 protein using tissue microarrays and immunohistochemistry staining. Thirty nine (55%) cases, including 54.2% of endometrioid adenocarcinomas and 55.5% serous carcinomas, were positively stained for galectin-3. Brown granular expression of this glycoprotein was detected in transformed epithelial cells of 36 cases including 28 cases with membranous and cytoplasmic staining and 8 cases with only cytoplasmic staining; nuclear expression was present in stromal cells of the remaining 3 cases. Twenty-four (80%) control cases showed granular cytoplasmic and membranous expression, and six control cases were negative. Tumor grade, stage and differentiation were significantly associated with galectin-3 immunoreactivity (p-values are 0.043, 0.016, and 0.044 respectively), cases with membranous and cytoplasmic staining is significantly associated with grade I and stage II, while cases with loss of staining are more frequent in grade II, III and poorly differentiated tumors. No significant association of galectin-3 staining was observed with age, diagnosis, recurrence and alive status. The current study supports the tumor suppression role of galectin-3 in endometrial carcinoma. Greater galectin-3 immunostaining has been found in control endometrial tissues compared to endometrial tumors. Loss or decreased galectin-3 immunoexpression gives a sign for poor prognoses in endometrial carcinoma patients.

1. Introduction

Galectin-3 is a part of protein group called lectins, which have been recognized by their ligand binding specificity for carbohydrate residues (β-galactoside). This protein has 31-kDa molecular weight, and is encrypted by the LGALS3 gene which mapped on chromosome 14q21–q22 [1,2]. Galectin-3 is expressed by different human tissues, including malignant ones, and exerts its functions intracellularly at the level of cytoplasm, nucleus, or at cell membranes and/or extracellularly mediating interactions between cells and the matrix components [3–6]. It is a multifunctional glycoprotein due to its expression location and capacity to bind a wide panel of ligands [3,4,7–9]. This glycoprotein has a significant role in carcinogenesis and selection of tumor-related physiological and pathological activities, including proliferation, adhesion, differentiation, migration, malignant transformation, tumor invasion and metastasis, angiogenesis, as well as apoptosis [5–11].

Many reports have described the phenotype of galectin-3 in different neoplasms and tried to evaluate its diagnostic value and its efficacy as a prognostic factor of tumor behavior and possible metastatic potential in relation to clinicopathological parameters of different cancers. Nevertheless, the results revealed a serious debate, galectin-3 was either upregulated or downregulated in cancer tissues comparative to their normal counterpart, exclusive of consistent association with clinicopathological characteristics, and in addition several reports proposed that elevated galectin-3 sug-

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gests a bad prognosis, whereas other studies reported otherwise [12]. The phenotype of galectin-3 has been noted to be upregulated in breast cancer [13], gastric cancer [14], hepatocellular carcinoma [15], melanoma [16], cervical cancer [17], tongue carcinoma [18], and thyroid tumors [19]. In other studies, galectin-3 expression was found to be downregulated in different tumors including head and neck [20], prostate [21], breast [22], stomach [23], colorectal [24], and cervical cancers [25]. This inconsistency proposes that the involvement of galectin-3 phenotype in malignancy is tumor-specific.

Nevertheless, insufficient data is available about the clinical value of galectin-3 immunophenotype in endometrial carcinomas. Therefore, this research will describe galectin-3 immunoexpression and its relationship with the clinicopathological findings of endometrial carcinomas. Furthermore, this study will evaluate galectin-3 phenotype as a marker for the diagnosis and prognoses of endometrial carcinomas.

2. Material and methods

The pathology archives at the Teaching Hospital of King Abdulaziz University was the source for paraffin blocks of seventy-one cases of endometrial carcinomas and 30 samples of benign endometrial conditions (control group) which were utilized in the present study. All recruited cases (benign and malignant) were sectioned and H&E stained for histopathological reevaluations. All the necessary clinical data were obtained from the unit of medical records. Control group samples (4 endometrial polyps, 10 secretory endometrium and 16 proliferative endometrium) were collected from subjects who were curetted for non-malignant disorders. Thirty six years was the average age of control group subjects (ranged 22–50). Blocks of all cases were utilized in tissue microarray production. Ethically, the current study has been approved by a King Abdulaziz University specialized committee.

2.1. Tissue microarray production (TMA)

TMA has been assembled and produced using the recruited 101 endometrial carcinomas and control samples as mentioned in our previous study [26]. TMA blocks were sectioned and placed on coated slides for immunohistochemistry staining.

2.2. Immunohistochemistry method

Ventana Automatic immunostainer (Ventana Medical Systems Inc. Arizona, USA) was used for galectin-3 automated immunohistochemical staining using multimer technology. Mouse monoclonal anti- galectin-3 antibody (product code: 760–4256, Cell Marque, CA, USA), was applied to all sections including endometrial carcinomas and control samples. A compatible visualizing system (UltraViewTM DAB) was applied according to the instructions of manufacturer (Ventana).

A negative control slide was included in addition to a positive internal control section from human tonsil tissue. Slides were regarded as positive once brown granular cytoplasmic, membranous or nuclear immunostaining was detected in tumor cells.

The intensity of galectin-3 immunostaining and the percent of positively stained cells were scored by two independent pathologists.

Immunohistochemical staining has been evaluated semi quantitatively in three 40× fields. In the present study, cases were considered positive when they showed brown immunostaining in

Table 1
Distribution of various clinicopathological variables of bladder cancer with galectin-3 immunostaining levels.

		Pattern of stain								P-Value[a]
		Positive epithelial cells				Positive stromal cells		Negative		
		Cytoplasmic		Membranous and cytoplasmic		Nuclear		Negative		
		n	%	n	%	n	%	n	%	
Age in Years	40–49	2	8.0%	13	52.0%	1	4.0%	9	36.0%	0.197
	50–59	4	16.7%	7	29.2%	1	4.2%	12	50.0%	
	60–69	1	6.7%	8	53.3%	0	0.0%	6	40.0%	
	≧70	1	14.3%	0	0.0%	1	14.3%	5	71.4%	
	Clear cell carcinoma	0	0.0%	0	0.0%	0	0.0%	1	100.0%	0.146
Final Diagnosis	Endometrioid adenocarcinoma	4	6.8%	25	42.4%	3	5.1%	27	45.8%	
	MMMT	1	50.0%	1	50.0%	0	0.0%	0	0.0%	
	Serous carcinoma	3	33.3%	2	22.2%	0	0.0%	4	44.4%	
	I	2	5.0%	21	52.5%	2	5.0%	15	37.5%	0.043
Grade	II	5	21.7%	4	17.4%	1	4.3%	13	56.5%	
	III	0	0.0%	2	33.3%	0	0.0%	4	66.7%	
	Ungraded	1	50.0%	1	50.0%	0	0.0%	0	0.0%	
	I	1	2.6%	15	38.5%	2	5.1%	21	53.8%	0.016
Stage	II	2	40.0%	3	60.0%	0	0.0%	0	0.0%	
	III	2	22.2%	2	22.2%	0	0.0%	5	55.6%	
	IV	1	33.3%	0	0.0%	1	33.3%	1	33.3%	
	Unstaged	2	13.3%	8	53.3%	0	0.0%	5	33.3%	
	Well differentiated tumors	2	4.9%	21	51.2%	2	4.9%	16	39.0%	0.044
Differentiation	Moderately differentiated tumors	5	25.0%	4	20.0%	1	5.0%	10	50.0%	
	Poorly differentiated tumors	0	0.0%	2	25.0%	0	0.0%	6	75.0%	
	NA	1	50.0%	1	50.0%	0	0.0%	0	0.0%	
	No	5	8.9%	23	41.1%	3	5.4%	25	44.6%	0.585
Recurrence	Yes	3	20.0%	5	33.3%	0	0.0%	7	46.7%	
	No	4	23.5%	4	23.5%	1	5.9%	8	47.1%	0.161
Alive	Yes	4	7.4%	24	44.4%	2	3.7%	24	44.4%	

[a] Fisher's Exact Test: Exact Sig. (2-sided).