STEM CELL INDEX IN THE PROGRESSION OF CERVICAL INTRAEPITHELIAL NEOPLASIA

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Cervical cancer represents the fourth most common type of gynaecological malignancy worldwide. Cervical cancer is characterised with high mortality rate, especially in developing countries, such as Georgia [1]. The high risk human papillomaviruses (HR-HPV), represent the major etiologic factor for cervical cancer [2]. However, it has been noted that stem cells are also playing one of the major roles in the development and progression of cervical cancer [3]. There are many different markers of stem cells including CD44 [4]. CD44 represents the primary adhesion molecule, which is involved in many different biological processes [5]. Some, studies indicate that, CD44 expression is relatively higher in cervical cancer tissues, compared to normal, non-tumorous tissues [5]. In vitro studies indicate that, cervical cancer cells, which are positive for CD44, show higher proliferation and self-renewal properties [6]. CK17 is also considered as another potential marker for cervical cancer stem cells. In vitro studies show that after TGF-β stimulation of CK17 significantly increases the stem cell like properties in cervical cancer cells [7]. Despite the ample of in vitro data, there is the lack of studies, investigating stem cell markers in patient cervical cancer tissues. In addition, little is known with regards to the association of the presence of CD44/CK17 positive stem cell population with the progression of cervical intraepithelial neoplasia (CIN) into cancer, as well as their association with epithelial-mesenchymal markers and proliferation and apoptotic characteristics in CIN and cancer specimens. In our previous studies, we have shown that epithelial-mesenchymal transition, as well as a certain proliferation and apoptotic characteristics are significantly associated with the progression of CIN. In our current study, we decided to extend previous studies and investigate the role of stem cells in the progression of CIN. In addition, we have investigated the correlation between stem cell markers, such as CD44 and CK17 with epithelial-mesenchymal transition and proliferation and apoptotic characteristics in CIN and cervical carcinoma specimens.

Material and methods. Formalin fixed and paraffin embedded tissue material was retrieved from the Research, Diagnostic and Teaching Laboratory of Tbilisi State Medical University, Georgia. Study included altogether 140 tissue samples, divided into two major groups: cases without co-infections (n=54) and cases with co-infections (n=86). Co-infections included bacterial vaginosis, chlamydia trachomatis and candida albicans. Cases without co-infections were divided into following subgroups: normal cervix (10 cases), CINI (18 cases), CINII (14 cases), CINIII (7 cases), invasive carcinoma (5 cases); Cases with co-infections were divided into following subgroups: cervix with only infections (15 cases), CINI (29 cases), CINII (19 cases), CINIII (15 cases), invasive carcinoma (8 cases).

Immunohistochemistry. 4μ FFPE tissue sections were deparaffinized in xylene, rehydrated by using serial dilutions of ethanol (96%, 80%, 70%) and heat mediated antigen retrieval has been performed. Ready to use antibodies against the following antigens were used: Ki67 (K2), Cyclin D1 (polyclonal) and phosphohistone-H3 (pHH3), E-cadherin(36B5), p63 (7JUL), β-catenin (17C2), vimentin (V9) Cas3 (cleaved), BAX (E63) and ER (6f11) (Leica). Staining and visualisation has been performed using Bond polymer refine detection system. The expression of all markers was evaluated as the percentage of marker positive cells.

mRNA analysis from The Cancer Genome Atlas (TCGA). The raw gene expression (mRNA) data for ovarian cancer was downloaded from the www.firebrowse.org, the cohort included altogether 309 patients with different grades of ovarian carcinoma. The study relevant genes, including CD44, CK17, Ki67, ER, CAS3, BAX, P63, E-Cadherin, β-catenin have been identified with the search function. Cyclin D1 was excluded from the study due to the lack of significant correlations with any other marker on immunohistochemistry level. In addition to standard statistical analysis (below), the two step clustering of the data have been performed.

Comparisons between groups were made using Mann-Whitney U test and Kruskal-Wallis test. The Kruskal-Wallis test is a nonparametric (distribution free) test, and is used when the assumptions of one-way ANOVA are not met. The Kruskal-Wallis test can be used for both continuous and ordinal-level dependent variables. Correlations were assessed using Spearman's rank correlation. The Spearman's rank correlation is also used when data is non-parametrically distributed. P values <0.05 were considered as significant. All statistical tests were performed using SPSS software V20.00.

Results and discussion. The results of the study in specimens without co-infections showed the following distribution of CD44 and CK17 in study groups: the mean positivity of CD44 in normal cervix was 7±2.1, in CINI it was 15±5.3, in CINII it was 28±6.1, in CINIII it was 41±9.3 and in invasive carcinoma the mean positivity for CD44 was 57±8.6. With regards to CK17, in normal cervix the mean positivity was 68±9.1, in CINI the mean positivity was 32±3.6, in CINII the mean positivity was 43±6.8, in CINIII the mean positivity was 47±7.7 and in invasive carcinoma, the mean positivity for CK17 was 36±4.7.

The results of the study in specimens with co-infections showed the following distribution of CD44 and CK17 in study groups: the mean positivity of CD44 in normal cervix was 9±3.3, in CINI it was 16±6.2, in CINII it was 31±4.8, in CINIII it was 48±9.9 and in invasive carcinoma the mean positivity for CD44 was 63±13.3. With regards to CK17, in normal cervix the mean positivity was 71±7.1, in CINI the mean positivity was 36±4.8, in CINII the mean positivity was 47±9.7, in CINIII the mean positivity was 52±6.7 and in invasive carcinoma, the mean positivity for CK17 was 32±6.1.

The correlation analysis in specimens without co-infections, between CD44 and other markers showed the following results: There was significant positive correlation between CD44 and vimentin ($r=.894$, $p<0.001$), Ki67 ($r=.867$, $p<0.0001$), phosphohistone-H3 ($r=.821$, $p<0.0001$) and Bax1 ($r=.867$, $p<0.0001$), whilst there was a negative correlation between CD44 and Cas3 ($r=-.942$, $p<0.0001$), E-cadherin ($r=-.851$, $p<0.0001$) and β-catenin ($r=-.923$, $p<0.0001$). The correlation analysis between CK17 and other markers did not show any significant correlation on immunohistochemistry level.

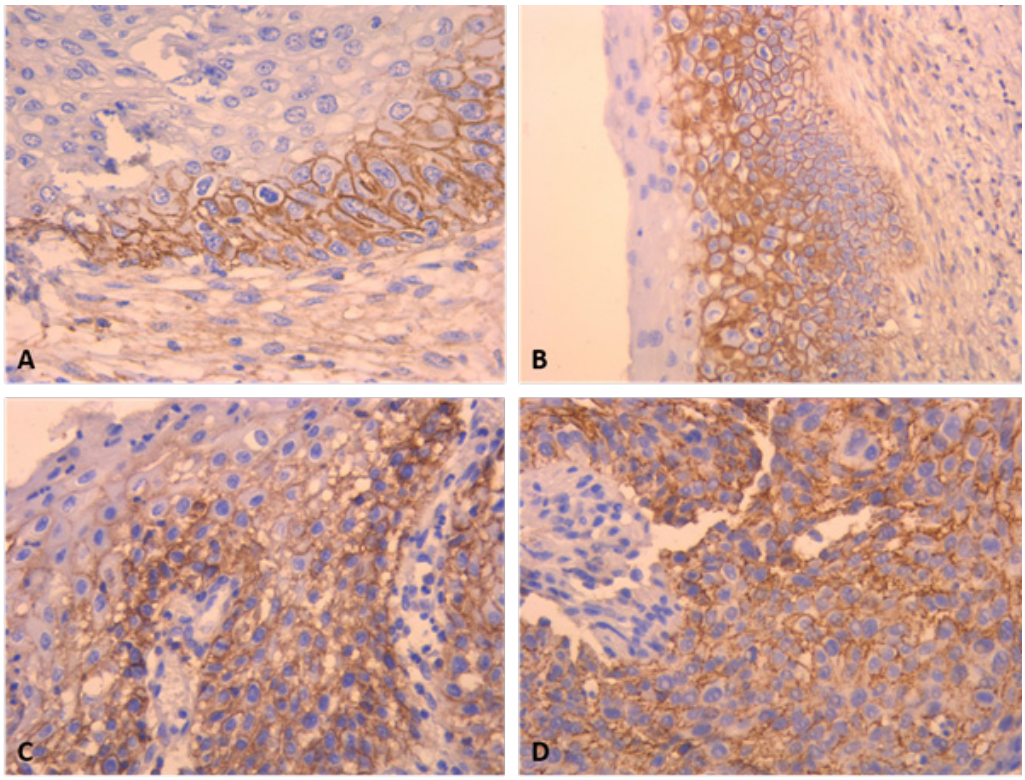


Fig. 1. The expression of CD44 in A. CINI, B. CINII, C. CINIII, D. Cervical Carcinoma, IHC, x200

Table 1. Distribution of CD44 and CK17 in specimens without co-infections

	Without co-infection		
	CD44 (%)	**CK17 (%)**	**Total N**
Normal cervix	7	68	10
CINI	15	32	18
CINII	28	43	14
CINIII	41	47	7
Invasive CA	57	36	5

Table 2. Distribution of CD44 and CK17 in specimens with co-infections

	With co-infection		
	CD44 (%)	**CK17 (%)**	**Total N**
Cervix with Infection	9	71	15
CINI	16	36	29
CINII	31	47	19
CINIII	48	52	15
Invasive CA	63	32	8

The correlation analysis in specimens with co-infections, between CD44 and other markers showed the following results: There was significant positive correlation between CD44 and vimentin (r=.914, p=0.041), Ki67 (r=.897, p<0.0001), phospho-histone-H3 (r=.873, p<0.0001) and Bax1 (r=.930, p<0.0001), whilst there was a negative correlation between CD44 and Cas3 (r=-.972, p<0.0001), E-cadherin (r=-.871, p<0.0001) and β-catenin (r=-.943, p<0.0001).

Table 3. Results of correlation analysis in specimens without co-infections

Spearman's rho		CK17	p63	E-cadherin	β-catenin	vimentin	Cas3	Bax1	Ki67	Cyclin D1	Phosphohiston-H3	ER
CD44	Correlation Coefficient	-0,300	0,000	-0,851	-0,923	0.894*	-0,942	0.890**	0.867**	0,000	0.8210**	-0,600
	Sig. (2-tailed)	0,624	1,000	0,000	0,000	0,041	0,000	0,000	0,000	1,000	0,000	0,285
	N	54	54	54	54	54	54	54	54	54	54	54
CK17	Correlation Coefficient		,200	,300	,300	-,112	,300	-,300	-,300	-,200	-,300	-,100
	Sig. (2-tailed)		,747	,624	,624	,858	,624	,624	,624	,747	,624	,873
	N		54	54	54	54	54	54	54	54	54	54
p63	Correlation Coefficient			0,000	0,000	-,224	0,000	0,000	0,000	-1.000**	0,000	,400
	Sig. (2-tailed)			1,000	1,000	,718	1,000	1,000	1,000		1,000	,505
	N			54	54	54	54	54	54	54	54	54
E-cadherin	Correlation Coefficient				0.956**	-.894*	0.820**	-0,861	-0,971	0,000	-1.000**	,600
	Sig. (2-tailed)				0,000	,041	0,000	0,000	0,000	1,000		0,285
	N				54	54	54	54	54	54	54	54
β-catenin	Correlation Coefficient					-.894*	0.870**	-0,93	-0,89	0,000	-0,84	,600
	Sig. (2-tailed)					,041	0,000	0,000	0,000	1,000	0,000	0,285
	N					54	54	54	54	54	54	54
vimentin	Correlation Coefficient						-.894*	.894*	.894*	,224	.894*	-.894*
	Sig. (2-tailed)						,041	,041	,041	,718	,041	,041
	N						54	54	54	54	54	54
Cas3	Correlation Coefficient							-0,91	-0,932	0,000	-0,862	,600
	Sig. (2-tailed)							0,000	0,000	1,000	0,000	0,285
	N							54	54	54	54	54
Bax1	Correlation Coefficient								0.970**	0,000	0.990**	-,600
	Sig. (2-tailed)								0,000	1,000	0,000	,285
	N								54	54	54	54
Ki67	Correlation Coefficient									0,000	0.844**	-,600
	Sig. (2-tailed)									1,000	0,000	,285
	N									54	54	54
Cyclin D1	Correlation Coefficient										0,000	-,400
	Sig. (2-tailed)										1,000	,505
	N										54	54
Phosphohiston-H3	Correlation Coefficient											-,600
	Sig. (2-tailed)											,285
	N											54

Table 4. Results of correlation analysis in specimens with co-infections

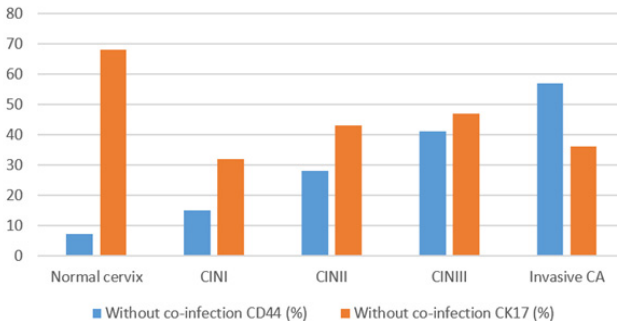
Spearman's rho		**CK17**	**p63**	**E-cad-herin**	**β-cate-nin**	**vi-men-tin**	**Cas3**	**Bax1**	**Ki67**	**Cyclin D1**	**Phos-pho-his-ton-H3**	**ER**
CD44	Correlation Coefficient	-0,400	0,000	-0,871	-0,943	0.914*	-0,972	0.930**	0.897**	0,000	0.873**	-0,700
	Sig. (2-tailed)	0,523	1,000	0,000	0,000	0,041	0,000	0,000	0,000	1,000	0,000	0,369
	N	86	86	86	86	86	86	86	86	86	86	86
CK17	Correlation Coefficient		,100	,200	,200	-,222	,500	-,200	-,200	-,200	-,600	-,900
	Sig. (2-tailed)		,642	,716	,716	,716	,716	,716	,716	,642	,716	,624
	N		86	86	86	86	86	86	86	86	86	86
p63	Correlation Coefficient			0,000	0,000	-,339	0,000	0,000	0,000	-1.000**	0,000	,700
	Sig. (2-tailed)			1,000	1,000	,621	1,000	1,000	1,000		1,000	,809
	N			86	86	86	86	86	86	86	86	86
E-cad-herin	Correlation Coefficient				0.978**	-0,924	0.864**	-0,893	-0,991	0,000	-1.000**	,300
	Sig. (2-tailed)				0,000	,041	0,000	0,000	0,000	1,000		0,385
	N				86	86	86	86	86	86	86	86
β-cate-nin	Correlation Coefficient					-0,934	0.880**	-0,96	-0,91	0,000	-0,85	,800
	Sig. (2-tailed)					,041	0,000	0,000	0,000	1,000	0,000	0,485
	N					86	86	86	86	86	86	86
vime-ntin	Correlation Coefficient						-0,994	-0,994	-0,994	,224	-0,994	-0,994
	Sig. (2-tailed)						,031	,031	,031	,718	,031	,031
	N						86	86	86	86	86	86
Cas3	Correlation Coefficient							-0,94	-0,952	0,000	-0,882	,500
	Sig. (2-tailed)							0,000	0,000	1,000	0,000	0,285
	N							86	86	86	86	86
Bax1	Correlation Coefficient								0.990**	0,000	0.990**	-,800
	Sig. (2-tailed)								0,000	1,000	0,000	,225
	N								86	86	86	86
Ki67	Correlation Coefficient									0,000	0.944**	-,700
	Sig. (2-tailed)									1,000	0,000	,215
	N									86	86	86
Cyclin D1	Correlation Coefficient										0,000	-,300
	Sig. (2-tailed)										1,000	,805
	N										86	86
Phos-pho-histon-H3	Correlation Coefficient											-,900
	Sig. (2-tailed)											,315
	N											86

Table 5. Results of correlation analysis from the TCGA dataset

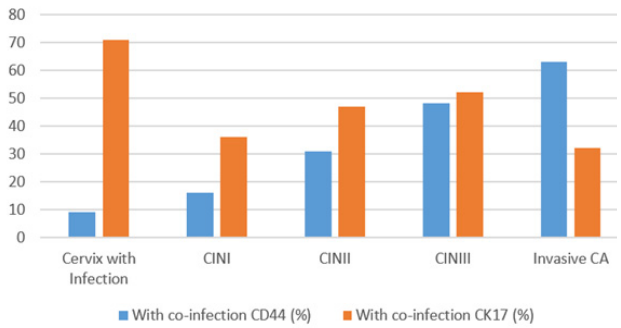
Spearman's rho		CK17	Ki67	ER	CAS3	BAX	P63	E-Cadherin	β-catenin	Vimentin
CD44	Correlation Coefficient	.370**	.112*	-.184**	-,019	-.172**	.569**	,087	-.115*	,008
	Sig. (2-tailed)	,000	,049	,001	,739	,002	,000	,129	,044	,882
	N	309	309	309	309	309	309	309	309	309
CK17	Correlation Coefficient		-.183**	-.270**	-,059	,023	.371**	,022	-,076	-,088
	Sig. (2-tailed)		,001	,000	,300	,686	,000	,702	,180	,124
	N		309	309	309	309	309	309	309	309
Ki67	Correlation Coefficient			,103	,077	-.383**	.152**	.141*	.277**	.136*
	Sig. (2-tailed)			,069	,175	,000	,008	,013	,000	,017
	N			309	309	309	309	309	309	309
ER	Correlation Coefficient				,033	-.162**	-.178**	-,065	,034	.196**
	Sig. (2-tailed)				,559	,004	,002	,253	,555	,001
	N				309	309	309	309	309	309
CAS3	Correlation Coefficient					.147**	.181**	-,007	-,089	-,002
	Sig. (2-tailed)					,010	,001	,904	,118	,972
	N					309	309	309	309	309
BAX	Correlation Coefficient						-.130*	-,085	-.220**	,112
	Sig. (2-tailed)						,022	,134	,000	,050
	N						309	309	309	309
P63	Correlation Coefficient							.120*	-.143*	-.156**
	Sig. (2-tailed)							,035	,012	,006
	N							309	309	309
E-Cadherin	Correlation Coefficient								,098	-,106
	Sig. (2-tailed)								,086	,063
	N								309	309
β-catenin	Correlation Coefficient									.175**
	Sig. (2-tailed)									,002
	N									309

Table 6. Distribution of different markers in CD44 low and high groups. Mann-Whitney U test. Data analysis results from TCGA

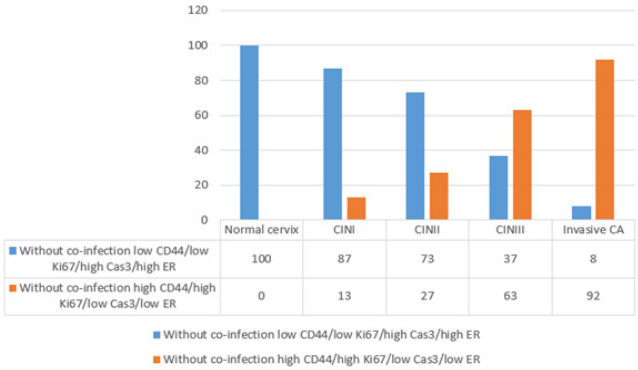
CD44	N	Mean Rank	*P*	Markers
Low	154	130.79	<0.0001	CK17
High	155	179.05		
Low	154	140.68	0.005	Ki67
High	155	169.23		
Low	154	170.23	0.003	ER
High	155	139.86		
Low	154	156.69	0.74	Cas3
High	155	153.32		
Low	154	172.19	0.001	BAX
High	155	137.92		
Low	154	110.93	< 0.0001	p63
High	155	198.79		
Low	154	144.81	0.046	E-cadherin
High	155	165.12		
Low	154	160.78	0.057	β-caenin
High	155	149.26		
Low	154	152.22	0.586	Vimentin
High	155	157.76		



Graph 1. Distribution of CD44 and CK17 in groups without co-infections



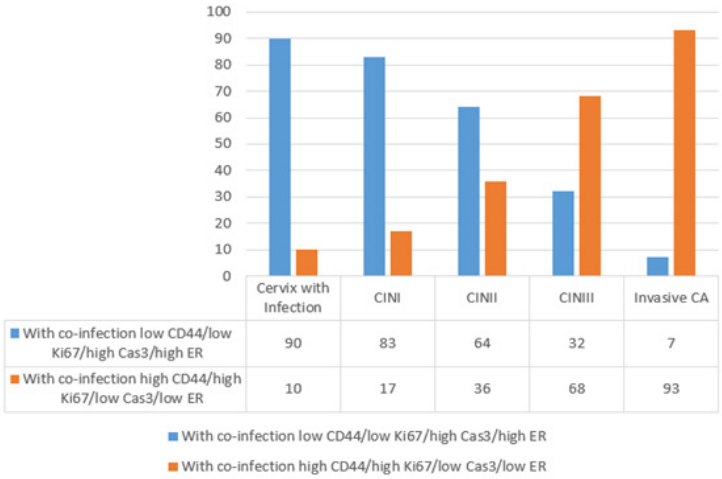
Graph 2. Distribution of CD44 and CK17 in groups with co-infections



Graph 3. The distribution of cervical lesions in two phenotypic groups, in specimens without co-infections

The mRNA expression data analysis showed the following significant correlations: CD44 was significantly, positively correlated with CK17 (r=.317, p<0.0001), Ki67 (r=.112, p=0.049) and p63 (r=.569, p<0.0001), whilst it was negatively correlated with ER (r=-.184, p<0.001), Bax (r=-.172, p=0.002) and β-catenin (r=-.115, p=0.044).

In addition to Spearman's correlation analysis, Mann-Whitney U test showed the following results in CD44 low and high groups: CD44 high group was characterised with the higher expression of CK17 (p<0.0001), higher expression of Ki67 (p=0.005), lower expression of ER (p=0.003), lower expression of BAX (p=0.001), higher expression of p63 (p<0.0001) and



Graph 4. The distribution of cervical lesions in two phenotypic groups, in specimens with co-infections

higher expression of E-cadherin (p=0.046). The comparative analysis of CD44 expression in groups without co-infections showed that the expression of CD44 is lower in normal cervix and it is significantly increased during the progression of cervical intraepithelial neoplasia, showing the maximum expression in invasive carcinoma. Whilst CK17 showed more heterogeneous distribution pattern. Particularly, the highest expression of CK17 was seen in normal cervical epithelium and the lowest expression of CK17 was seen in CINI. However, the expression of CK17 was also gradually increasing from CINI to invasive carcinoma of the cervix. The comparative analysis of CD44 and CK17 expression in groups with co-infections showed the similar trends. However, when compared the expression of CD44 and CK17 was more pronounced in groups with co-infections, compared to the groups without co-infections.

The further analysis of immunohistochemical expression of the mentioned markers identified two major groups of cervical intraepithelial neoplasia and invasive carcinoma, based on the expression of stem cell marker CD44 and proliferation, apoptotic and hormonal characteristics. First group was characterised with I. low CD44/low Ki67/high Cas3/high ER phenotype, whilst the second group was characterised with II. high CD44/high Ki67/low Cas3/low ER phenotype. Particularly, the phenotype I was seen in 100% of normal cervical tissues, without co-infections. Phenotype II, which indicates more aggressive characteristics of the lesion, was seen in 13% of CINI without co-infections, in 27% of CINII without co-infections, in 63% of CINIII without co-infections and in 92% of invasive carcinoma without co-infections.

Similar trend has been seen in specimens with co-infections. Particularly, the phenotype I was seen in 90% of normal cervical tissues, with co-infections. Phenotype II, which indicates more aggressive characteristics of the lesion, was seen in 17% of CINI with co-infections, in 36% of CINII without co-infections, in 68% of CINIII with co-infections and in 93% of invasive carcinoma with co-infections.

In addition to immunohistochemical data, we have performed the in silico gene expression analysis from TCGA dataset of 309 ovarian cancers, which showed the similar results. Particularly, the two groups were also clustered separately based on the expression of above mentioned markers. Phenotype I represented 7.5% of invasive cervical carcinomas, whilst phenotype I was characteristic of 93.5% of invasive cervical carcinomas. To the best of our knowledge we are first who performed such a profound analysis of stem cell marker CD44 and epithelial-mesenchymal, proliferation, apoptosis and hormone receptor markers in tissue specimens from the patients with cervical intraepithelial neoplasia and invasive cervical carcinoma. The results of our study indicate that the detection of CD44 stem cell marker might be used as an important prognostic factor for cervical intraepithelial neoplasia progression, together with proliferation marker Ki67, apoptotic marker Cas3 and ER. It is known that CINI lesions progressing into advanced CIN disease and cervical carcinoma in about 8-12% of cases, whilst the progression rate of CINIII into carcinoma is about 60%. Our study results are in line with this previous observation, as we have shown that CIN lesions with more aggressive phenotype (II) represent about 13-17% of CINI lesions and 63-68% of CIN III lesions. Therefore, the mentioned phenotypic characteristics could be used for the early assessment of CIN patient prognosis and for the relevant clinical management.

Conclusions. The results of our study indicate that stem cell index based on the CD44 detection is significantly increased with the progression of cervical intraepithelial neoplasia. In addition, CD44 expression significantly correlates with the epithelial-mesenchymal transition, proliferation-apoptotic features and ER status in both protein and mRNA level. Two, low and high risk groups of cervical intraepithelial lesions as well as carcinoma can be identified based on the expression of CD44, Ki67, Cas3 and ER.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. //CA Cancer J Clin. - 2020 Jan;70(1):7-30. doi: 10.3322/caac.21590. Epub 2020 Jan 8. PMID: 31912902.
2. Chan CK, Aimagambetova G, Ukybassova T, Kongrtay K, Azizan A. Human Papillomavirus Infection and Cervical Cancer: Epidemiology, Screening, and Vaccination-Review of Current Perspectives. // J Oncol. 2019 Oct 10;2019:3257939. doi: 10.1155/2019/3257939.
3. Mendoza-Almanza G., Ortíz-Sánchez E., Rocha-Zavaleta L., Rivas-Santiago C., Esparza-Ibarra E., Olmos J. Cervical cancer stem cells and other leading factors associated with cervical cancer development // Oncol. Lett., 2019. - vol. 18, no. 4, pp. 3423–3432.
4. Wang L, Zuo X, Xie K, Wei D. The Role of CD44 and Cancer Stem Cells. Methods Mol Biol. 2018;1692:31-42. doi: 10.1007/978-1-4939-7401-6_3.

5. Organista-Nava J., Gómez-Gómez Y., Garibay-Cerdenares O. L., Leyva-Vázquez M. A., Illades-Aguiar B. Cervical cancer stem cell-associated genes: Prognostiimplications in cervical cancer // Oncol. Lett.- 2019. - vol. 18, no. 1, pp. 7–14,
6. Ortiz-Sánchez E. et al. Characterization of cervical cancer stem cell-like cells: phenotyping, stemness, and human papilloma virus co-receptor expression.// Oncotarget. 2016; 7(22): 31943–31954.
7. Wu L. et al. TGF-β1-induced CK17 enhances cancer stem cell-like properties rather than EMT in promoting cervical cancer metastasis via the ERK1/2-MZF1 signaling pathway // FEBS J.- 2017. - vol. 284, no. 18, pp. 3000–3017.

SUMMARY

STEM CELL INDEX IN THE PROGRESSION OF CERVICAL INTRAEPITHELIAL NEOPLASIA

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Stem cells represent the small subpopulation of healthy and cancerous tissues, which are characterised with increased proliferation and self-renewal properties. From the many different markers of stem cells, we have investigated the stem cell index during the progression of cervical intraepithelial neoplasia (CIN), based on the immunohistochemical expression of CD44 in total of 140 tissue samples from uterine cervix. In addition, we have performed the profound correlation analysis of CD44 with different epithelial-mesenchymal, proliferation, apoptosis and hormonal markers at both protein and mRNA level. The results of our study indicated that, stem cell index based on the CD44 detection is significantly increased with the progression of cervical intraepithelial neoplasia. In addition, CD44 expression significantly correlates with the epithelial-mesenchymal transition, proliferation-apoptotic features and ER status in both protein and mRNA level. Two, groups of cervical intraepithelial lesions as well as carcinoma can be identified based on the expression of CD44, Ki67, Cas3 and ER. To the best of our knowledge we are first to demonstrate such findings in CIN and cervical carcinoma and identified characteristics could be used for the early assessment of CIN patient prognosis and for the relevant clinical management.

Keywords: stem cell index, progression of cervical intraepithelial neoplasia, CIN, immunohistochemical expression of CD44.

РЕЗЮМЕ

ОСОБЕННОСТИ РАСПРЕДЕЛЕНИЯ СТВОЛОВЫХ КЛЕТОК ПРИ ПРОГРЕССИИ ИНТРАЭПИТЕЛИАЛЬНЫХ НЕОПЛАЗИЙ ШЕЙКИ МАТКИ

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Стволовые клетки являются малочисленной популяцией клеток как в нормальных, так и в опухолевых тканях, характеризуются высокой способностью к самообновлению и пролиферации. Среди многочисленных маркеров стволовых клеток, для изучения особенностей их распределения, авторами применена иммуногистохимическая экспрессия маркера CD44 на 140 тканевых образцах шейки матки. Проведен корреляционный анализ между CD44 и другими маркерами прогрессии интраэпителиальных неоплазий шейки матки, таких как эпителиально-мезенхимальные маркеры трансформации, пролиферативно-апоптозные маркеры и рецептор эстрогена.

Результаты исследования показали, что стволовоклеточный индекс значительно увеличивается в процессе прогрессии интраэпителиальных неоплазий шейки матки и достоверно коррелирует с маркерами эпителиально-мезенхимальной трансформации и пролиферативно-апоптозными, также как с ER статусом. В интраэпителиальных неоплазиях шейки матки возможно выделение двух различных фенотипных групп по экспрессии маркеров CD44, Ki67, Cas3 и ER, которые коррелируют с прогрессией интраэпителиальных неоплазий шейки матки. Данные проведенного исследования в дальнейшем возможно использовать для оценки риска прогрессии интраэпителиальных неоплазий шейки матки и разработки адекватного клинического менеджмента.

რეზიუმე

ღეროვანი უჯრედების განაწილების თავისებურებები საშვილოსნოს ყელის ინტრაეპითელური ნეოპლაზიის პროგრესიის დროს

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ღეროვანი უჯრედები წარმოადგენენ მცირე უჯრედულ პოპულაციას როგორც ნორმალურ,ისე სიმსივნურ ქსოვილებში, ხასიათდებიან თვითგანახლების და პროლიფერაციის მაღალი უნარით. ღეროვანი უჯრედების მრავალ მარკერებს შორის შესწავლილია ღეროვანი უჯრედების განაწილების თავისებურებები CD44-ის იმუნოჰისტოქიმიური ექსპრესიის მიხედვით 140 საშვილოსნოს ყელიდან აღებულ ქსოვილოვან მასალაში. ჩატარდა კორელაციური ანალიზი CD44-სა და საშვილოსნოს ყელის ინტრაეპითელური ნეოპლაზიის პროგრესიის სხვა მარკერებს შორის,როგორებიცაა ეპითელურ-მეზენქიმური ტრანსფორმაციის მარკერები, პროლიფერაციულ-აპოპტოზური მარკერები და ესტროგენის რეცეპტორი.

კვლევის შედეგებმა აჩვენა, რომ ღეროვანი უჯრედების ინდექსი მნიშვნელოვნად იზრდება საშვილოსნოს ყელის ინტრაეპითელური ნეოპლაზიების პროგრესიის პროცესში. ღეროვანი უჯრედების ინდექსი სარწმუნო კორელაციაშია ეპითელურ-მეზენქიმური ტრანსფორმაციის და პროლიფერაციულ-აპოპტოზურ მარკერებთან, ისევე, როგორც ER სტატუსთან. საშვილოსნოს ყელის ინტრაეპითელურ ნეოპლაზიებში შესაძლებელია ორი ფენოტიპურად განსხვავებული ჯგუფის გამოყოფა CD44, Ki67, Cas3 და ER ექსპრესიის მიხედვით, რომლებიც კორელაციაშია საშვილოსნოს ყელის ინტრაეპითელური ნეოპლაზიების პროგრესიასთან. კვლევის შედეგები შესაძლებელია მომავალში გამოყენებული იყოს საშვილოსნოს ყელის ინტრაეპითელური ნეოპლაზიების პროგრესიის რისკის განსაზღვრის და შესაბამისად ადექვატური კლინიკური მენეჯმენტის შემუშავების მიზნით.