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Genetic and epigenetic alterations of human chromosome 3, investigated by NotI-microarrays in seven types of epithelial cancers

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Aim. To identify common and specific genetic/epigenetic changes of human chromosome 3, using the data of NotI-microarrays in seven types of epithelial cancers. **Methods.** We used descriptive statistics for the comparative analysis of NotI-microarray data from seven types of epithelial cancers. **Results.** The analysis of the NotI-microarrays showed significant changes (deletion or methylation) in 74 genes/loci in seven different epithelial cancers, namely colorectal, ovarian, renal, lung, breast, cervical and prostate. Five genes from the 3p14-3p24 region (*FOXP1, LRRC3B, NKiRAS1, RBSP3, ZIC4)* were altered in all cancer types. For fifteen genes deletion/methylation was found in a majority of tumors. For example, *ITGA9, GORASP1, IQSEC1, CGGBP1, NBEAL2* and *VHL* are localized in the 3p12-3p26 region; *PPP2R3A, FGF12, ALDH1L1, GATA2* and *PLCL2* are localized on the 3q13-3q28 region. Twenty-two genes out of 74 studied showed alterations specific for a single type of tumor. The largest number, 13 genes/loci was found in the prostate cancer. This suggests specific mechanisms of prostate cancer development. **Conclusions.** NotI-microarrays for human chromosome 3 allowed to identify several common genetic/epigenetic alterations and also tumor-specific changes in seven types of epithelial cancer.

Keywords: NotI-microarray, colorectal cancer, ovarian cancer, renal cancer, lung cancer, cervical cancer, breast cancer, prostate cancer, TSG, methylation, deletion, human chromosome 3.

Introduction

E. Zabarovsky and V. Kashuba groups investigated genetic/epigenetic alterations in human cancers by a large-scale method, named the NotI-microarray, for more than fifteen years. This method represents a comparative genome hybridization technology (Karolinska Institute International Patent WO02/086163 and PCT/SE02/00788 [1]), based on hybridization of the NotI-linking libraries, produced from tumor and normal genomic DNA [2]. It makes

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possible, to determine both, the genetic (deletions, amplifications) and epigenetic (methylation, demethylation) changes in the genomic DNA of the NotI-linked genes / loci, due to the sensitivity of the NotI restriction enzyme to a methylation status of CpG islands. Using this technology, 181 NotI-linking clones from different regions of human chromosome 3 were analyzed in more, than 250 malignant tumor samples, derived from different organs and tissues. [2, 3]. It is known that genetic and epigenetic disturbances of chromosome 3 have very important influence on carcinogenesis of different human cancers [4–6]. On chromosome 3 several well-known and putative tumor suppressor genes (TSG) as well as many cancer-associated genes are situated [3–7]. The 3p25-p26 region is harboring the well-known TSG, such as *VHL*; 3p12-p14.2 region contains the *FHIT* gene; 3p24 possesses the *RARB* gene and 3p21-p22 region includes the *RASSF1A* gene [8, 9]. However, a function and a role of many other genes of chromosome 3, which show alterations in different human cancer types, were largely unknown, before the NotI-microarray study.

The aim of the present work is to identify common and specific genetic/epigenetic changes of human chromosome 3, using the data of NotI-microarrays in seven types of epithelial cancer.

Materials and Methods

We have performed comparative analysis of the NotI-microarray data for 7 types of epithelial cancers [2, 10–18] using methods of descriptive statistics. Fisher's exact test and Chi-square criteria were used for analysis of methylation and/or deletion frequencies in groups of tumors with different patho-morphological characteristics [2, 10–18]. The cases with p-value below 0.05 were considered statistically significant. The Benjamini-Hochberg procedure with false discovery rate (FDR) 0.20 was used to correct p-value under multiple comparisons detection [19].

Results and Discussion

We have reviewed and summarized the data from different cohorts and with different data calculations for colorectal, ovarian, renal, lung, breast, cervical and prostate cancers [2, 10–18]. All the data represent epithelial tumors, investigated by NotI-microarrays. A fragment of NotI-microarray data is shown in Figure 1.

Notably, the greatest number of alterations is hetero- and homozygous deletions or methylation, in all reported data sets. Amplifications and demethylation were quite a rare event in epithelial tumors in comparison with leukemia [20]. Hence, deletions and methylation were in the focus of the present paper. Altogether, we found that 74 genes / loci of chromosome 3 exhibited significant changes in seven types of epithelial tumors. These results are presented in Table 1. It was found 40 genes/loci with changes from 3p arm and 34 genes/loci from 3q arm of chromosome 3. Five genes, namely *FOXP1, LRRC3B, NKIRAS1, RBSP3* and *ZIC4* altered in all seven studied tumor types. They are located in the 3p14-3p24 region.

Five genes/loci, namely *ITGA9, GORASP1, IQSEC1, CGGBP1* and *PPP2R3A*, showed genetic /epigenetic changes in six various types of tumor. Ten genes/loci — *WNT7A, NBEAL2, VHL, LOC285205, FGF12, ALDH1L1, GATA2, PLCL2, ABHD5/TOPAZ1, EPHB1* — had genetic /epigenetic alterations in five cancer types.

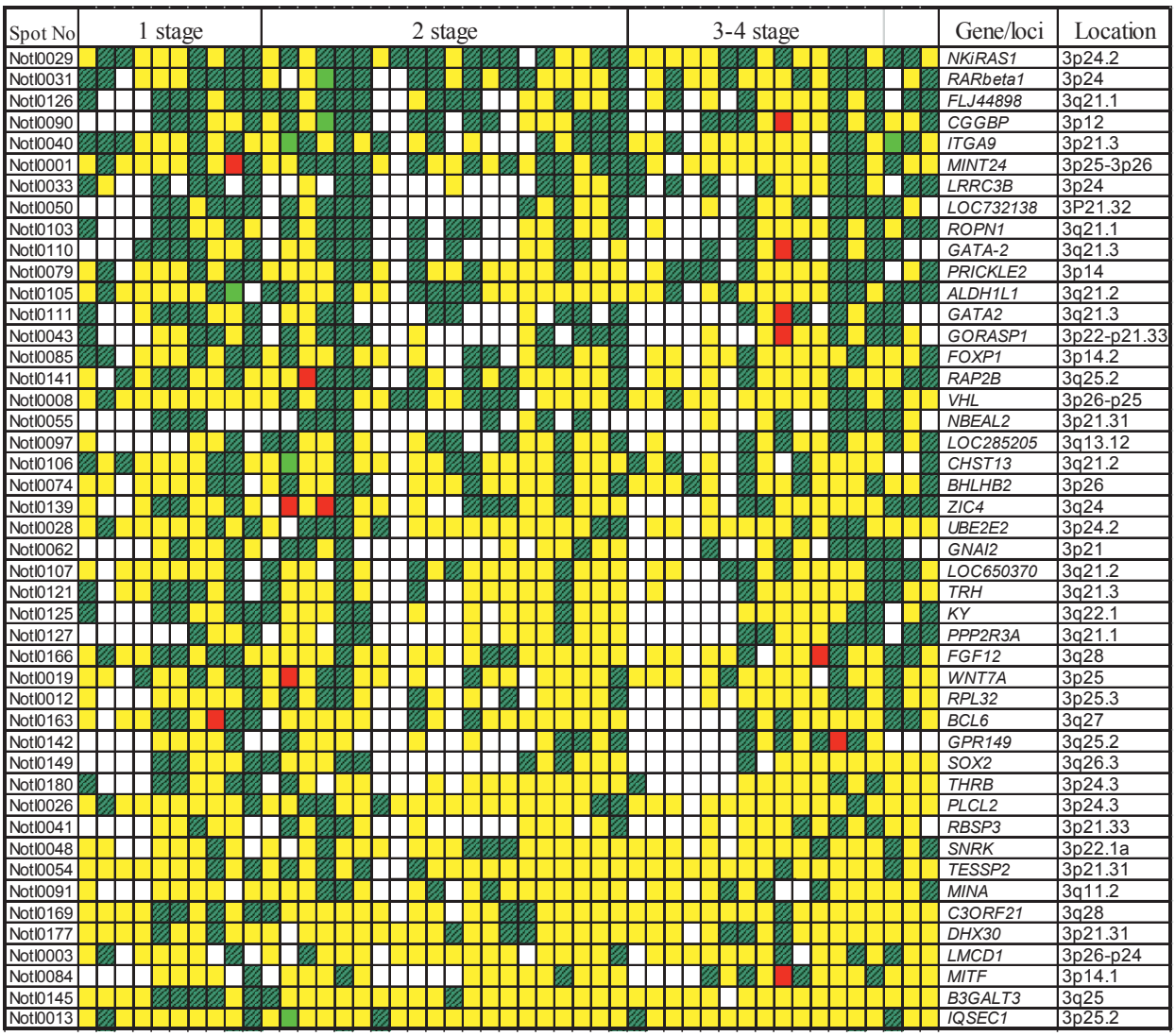

Fig. 1. A fragment of NotI-microarray data in breast tumors. Green and dark green with hatching squares: methylation/deletion (< 0.85), red: amplification/demethylation (> 1.5), yellow: unchanged (> 0.85, < 1.5), and white: no info. (grey and dark grey with hatching squares: methylation/deletion (< 0.85), black: amplification/demethylation (> 1.5), light grey: unchanged (> 0.85, < 1.5), and white: no info)

Genes *GORASP1, IQSEC1, CGGBP1, NBEAL2* and *VHL* are localized in the 3p12-3p26 region; genes *PPP2R3A, FGF12, ALDH1L1, GATA2* and *PLCL2* are situated in the 3q13-3q28 region. A large number of genes with the same changes in different epithelial tumors suggests the common mechanisms of cancer development and the function of these genes as putative tumor suppressor genes.

Twenty-two genes out of 74 have alterations only in the single type of tumor. The major part of them (13 genes / loci) is found in pros-

Table 1. **Genes and loci of chromosome 3 with changes (deletion/methylation) in seven types of epithelial cancers**

№	Number of localizations	Gene/locus	Location	OC	ColC	BC	CervC	LC	ccRCC	PC
1	**2**	**3**		**5**	**6**	**7**	**8**	**9**	**10**	**11**
1	7	***FOXP1***	3p13	*	*	*	*	*	*	*
2	7	***LRRC3B***	3p24.1	*	*	*	*	*	*	*
3	7	***NKIRAS1***	3p24.2	*	*	*	*	*	*	*
4	7	***RBSP3 (CTDSPL)***	3p22.2	*	*	*	*	*	*	*
5	7	***ZIC4***	3q24	*	*	*	*	*	*	*
6	6	***ITGA9***	3p22.2	*	*	*	*	*		*
7	6	***GORASP1***	3p22.2	*	*		*	*	*	*
8	6	***IQSEC1***	3p25.2-p25.1	*	*		*	*	*	*
9	6	***CGGBP1***	3p11.1	*	*	*	*	*		*
10	6	***PPP2R3A***	3q22.2-q22.3	*	*	*	*	*		*
11	5	***WNT7A***	3p25.1	*	*		*	*		*
12	5	***NBEAL2***	3p21.31	*	*			*	*	*
13	5	***VHL***	3p25.3		*	*	*	*	*	
14	5	***LOC285205***	3p13.12	*	*	*		*		*
15	5	***FGF12***	3q28-q29	*		*	*	*		*
16	5	***ALDH1L1***	3q21.3			*	*	*	*	*
17	5	***GATA2***	3q21.3	*	*	*		*		*
18	5	***PLCL2***	3p24.3		*		*	*	*	*
19	5	***ABHD5/TOPAZ1***	3p21.33/3p21.31	*			*	*	*	*
20	5	***EPHB1***	3q22.2	*			*	*	*	*
21	4	***NUDT16P***	3q22.1	*	*			*		*
22	4	***ROPN1***	3q21.1	*		*		*		*
23	4	***UBE2E2***	3p24.3		*	*	*	*		
24	4	***GNAI2***	3p21.31	*				*	*	*
25	4	***PRICKLE2***	3p14.1	*			*	*	*	
26	4	***RPL32***	3p25.2				*	*	*	*
27	4	***THRB***	3p24.2	*	*		*	*		
28	4	***BCL6***	3q27.3	*		*		*		*
29	4	***BHLHE40***	3p26.1			*	*	*		*
30	4	***FGD5***	3p25.1				*	*	*	*
31	4	***LRRN1***	3p26.2	*			*	*	*	
32	3	***FBLN2***	3p25.1	*				*		*

Continued Table 1

1	2	3	4	5	6	7	8	9	10	11
33	3	***KY***	3q22.2		*			*		*
34	3	***PPM1M***	3p21.2	*					*	*
35	3	***MINA***	3q11.2			*		*		*
36	3	***TRH***	3q22.1	*		*		*		
37	3	***LOC285375***	3p25.1	*			*			*
38	2	***MINT24***	3p.26		*	*				
39	2	***RARB***	3p24.2		*	*				
40	2	***LOC732138***	3p.21.32		*	*				
41	2	***GPR149***	3q25.2					*		*
42	2	***LMCD1***	3p25.3		*			*		
43	2	***RAP2B***	3q25.2			*				*
44	2	***SOX2***	3q26.33			*				*
45	2	***PAQR9***	3q23	*				*		
46	2	***LOC650370***	3q21.2		*	*				
47	2	***CHST13***	3q21.3	*		*				
48	2	***SOX14***	3q22.3				*			*
49	2	***ANKRD28***	3p25.1		*			*		
50	2	***FSTL1***	3q13.33			*				*
51	2	***PDZRN3***	3p13				*			*
52	1	***FLJ44898***	3q21.1			*				
53	1	***B3GALNT1***	3q26.1							*
54	1	***EPHB3***	3q27.1							*
55	1	***KBTBD8***	3p14.1							*
56	1	***LRRC58***	3q13.33							*
57	1	***PARP3***	3p21.2							*
58	1	***TMEM45A***	3q12.2							*
59	1	***ACPL2 (PXYLP1)***	3q23			*				
60	1	***CHCHD6/C3orf46***	3q21.3							*
61	1	***CKLFSF6***	3p22.3		*					
62	1	***CLASP2***	3p22.3							*
63	1	***CMTM8***	3p22.3							*
64	1	***DZIP1L***	3q22.3							*
65	1	***HMGB1L5(Pseudo)***	3p24.3							*
66	1	***MANF***	3p21.2							*
67	1	***MITF***	3p13					*		
68	1	***USP19***	3p21.31							*

Continued Table 1

1	2	3	4	5	6	7	8	9	10	11
69	1	***MOBP***	3p22.1	*						
70	1	***DCBLD2***	3q12.1; 3	*						
71	1	***FNDC3B***	3q26.31			*				
72	1	***C3ORF21 (XXYLT1)***	3q29			*				
73	1	***DHX30***	3p21.31			*				
74	1	***ABTB1/PODXL2***	3q21	*						

Notes: OC — ovarian cancer; ColC — colorectal cancer; BC — breast cancer; CervC — cervical cancer; LC — lung cancer; ccRCC — clear cell renal cell carcinoma; PC — prostate cancer; * — genes / loci with significant differences with FDR = 0.2.

tate cancer. This may indicate specific mechanisms of carcinogenesis of the prostate that are different from other localizations.

Noteworthy, earlier many investigations have been focused on studying the genes of the 3p arm of the chromosome 3 [2, 5, 6], whereas little attention has been paid to the genes of the 3q arm. The results of NotI-microarrays show the involvement of 3q arm genes / loci in the carcinogenesis of epithelial tumors of all seven localizations. For example, the *ZIC4* gene encodes the Zic family member 4 that is important in the development.

It participates in the regulation of transcription by RNA-polymerase II, but it has very low expression levels. It has deletion/methylation changes in all seven tumor localization. Our data are confirmed by other researchers on another type of epithelial cancer (bladder cancer) [21]. Importantly, these epigenetic changes could be detected in biological fluids, such as urine, while it is impossible to detect the *ZIC4* expression levels.

Another gene from 3q arm with deletion/methylation changes in 6 tumor localizations is *PPP2R3A*. This gene encodes one of the regulatory subunits of the protein phosphatase 2, which is implicated in the negative control of cell growth and division [22]. However, the genetic/epigenetic changes of this gene in epithelial cancers were not known until our studies.

Four genes from 3q arm, which have deletion/methylation in 5 localizations of epithelial tumors are *FGF12, ALDH1L1, GATA2, EPHB1. FGF12* is a member of the FGF family which is involved in a variety of biological processes, including cell growth, morphogenesis, tissue repair, tumor growth, and invasion [23]. The methylation of *FGF12* in colorectal cancers was shown [24]. Our study has confirmed this type of the *FGF12* epigenetic changes in prostate cancer [18]. It is revealed as a putative biomarker in esophageal cancer [25]. The *ALDH1L1* gene encodes the aldehyde dehydrogenase 1 family member L1. Loss of function (epigenetic silencing) or expression of *ALDH1L1* is associated with increased cell motility, decreased apoptosis and cancer progression [26]. On the other hand, *ALDH1L1* is the indicative gene of cancer cell stemness and it is a biomarker in colon cancer, which is associated with worth prognosis [27].

GATA2 encodes a member of the GATA family of zinc-finger transcription factors. It conducts transcriptional signals in particular from the androgen receptor [28]. *GATA2* has a multifaceted function in prostate cancer aggressiveness and is a highly attractive target for treatments of lethal prostate cancer [29]. The *GATA2* expression is associated with poor prognosis in acute myeloid leukemia [30]. The *EPHB1* gene encodes a transmembrane protein which is a receptor for ephrin-B1. Loss of the ephrin receptor (EphB1) expression may be associated with aggressive cancer phenotypes in acute myelogenous leukemia [31]. The tumor suppressor function of *EPHB1* in breast, colon and lung cancers was shown [32].

Noteworthy, the alterations of many genes (*ITGA9, LRRC3B, FGF12, GORASP1, NKIRAS1, CTDSPL (RBSP3), GATA2, SEMA3B, IQSEC1, PPM1M1, PRICLE2, BHLHE40 et al.*), which were found by NotI-microarrays, have been confirmed by other methods, such as LOH, MSP, bisulfite sequencing, deletion analysis and expression studies [10–18]. The TSG function for several genes was confirmed in model systems (cell lines, experimental animals), using transient and constitutive expression of these genes [33–35].

Moreover, we have investigated genetic/epigenetic changes and expression of some genes, which have no NotI-site, from well-known TSG *RASSF1A* 3p21.31 region. We have shown deletion/methylation changes by NotI-microarray in some tumor localization of genes from this region (3p21.31) named *NBEAL2, GNAI2, TOPAZ1*. Our study has confirmed genetic/epigenetic changes and loss of expression for *GPX1* and *SEMA3B* in renal and lung cancers [35–37]. Data of other investigators have revealed the down regulation of *HYAL1, HYAL2, RASSF1A* (3p21.31 region) in non-small cell lung cancer [34]. These data indicate the multiple inactivation of TSG and potential TSG clusters in human chromosome 3.

Conclusions

The analysis of the data, obtained with NotI-microarrays for human chromosome 3, identified several common genetic/epigenetic alterations in seven types of epithelial cancer and tumor-specific changes as well. These data make a basis for the creation of special sets of markers for early diagnostics, prediction of a course of disease, and evaluation of efficacy and a choice of therapy.

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Генетичні та епігенетичні порушення хромосоми 3 людини, визначені за допомогою NotI-мікропанелей в сімох локалізаціях епітеліальних злоякісних пухлин

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Мета: Знайти загальні та специфічні генетичні / епігенетичні зміни хромосоми людини 3, за допомогою NotI-мікропанелей у епітеліальних новоутвореннях семи різних локалізацій. **Методи:** Було використано методи дескриптивної статистики для порівняльного аналізу даних NotI-мікропанелей у семи локалізаціях злоякісних пухлин. **Результати.** Порівняльний аналіз даних NotI-мікропанелей показав значні зміни / метилування 74 генів / локусів у семи локалізаціях раку (товстої кишки, яєчників, нирок, легенів, молочних залоз, шийки матки, передміхурової залози). П'ять генів мають зміни у всіх 7 типах раку (*FOXP1, LRRC3B, NKiRAS1, RBSP3, ZIC4*). Вони були в основному з 3p14-3p24 регіону. П'ятнадцять генів мають делецію / метилювання в 6 та 5 локалізаціях раку. Серед них гени/локуси розташовані приблизно у 3p12-3p26 регіоні (*ITGA9, GORASP1, IQSEC1, CGGBP1, NBEAL2, VHL*), 3q13-3q28 регіоні (*PPP2R3A, FGF12, ALDH1L1, GATA2, PLCL2*). Двадцять два гени з 74 мають зміни тільки в одній локалізації раку. Переважна кількість їх (13 генів / локусів) зустрічається для раку передміхурової залози. Це може свідчити про специфічні механізми канцерогенезу передміхурової залози, які відрізняються від інших локалізацій.**Висновки:** Аналіз даних NotI-мікропанелей 3-ї хромосоми людини виявив ряд як загальних генетичних/епігенетичних порушень, так і пухлино-специфічні зміни.

Ключові слова: NotI-мікропанелі, рак товстої кишки, рак яєчників, рак нирки, рак легенів, рак шийки матки, рак молочної залози, рак передміхурової залози, гени-супресори росту пухлин, метилювання, делеція, хромосома 3 людини.

Генетические и эпигенетические изменения хромосомы 3 человека, определённые с помощью NotI-микропанелей в семи локализациях эпителиальных злокачественных опухолей

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Цель: Установить общие и специфичные для опухолей генетические / эпигенетические изменения хромосомы 3 человека с помощью NotI-микропанелей в эпителиальных новообразованиях при семи различных локализациях. **Методы:** Были использованы методы дескриптивной статистики для сравнительного анализа данных NotI-микропанелей в семи локализациях злокачественых опухолей. **Результаты.** Анализ NotI-микропанелей показал значительные изменения делеции / метилирования 74 генов / локусов в семи локализациях рака (толстой кишки, яичника, почек, легких, груди, шейки матки, предстательной железы). Пять генов имеют изменения во всех 7 типах рака (*FOXP1, LRRC3B, NKiRAS1, RBSP3, ZIC4*). Они были в основном из региона 3p14-3p24. Пятнадцать генов имеют делецию / метилирование в 6 и 5 локализациях рака. Среди них есть в регионе 3p12-3p26 (*ITGA9, GORASP1, IQSEC1, CGGBP1, NBEAL2, VHL*), в пределах 3q13-3q28 региона (*PPP2R3A, FGF12, ALDH1L1, GATA2, PLCL2*). Двадцать два гена из 74 имеют изменения только в одной локализации рака. Преобладающее число из них (13 генов / локусов) обнаружено для рака предстательной железы. Это может указывать на конкретные механизмы канцерогенеза предстательной железы, которые отличаются от других локализаций. **Выводы.** Анализ данных NotI-микропанелей 3-й хромосомы человека выявил ряд как общих генетических/эпигенетических нарушений в семи локализациях рака, так и опухоль-специфические изменения.

Ключевые слова: NotI-микропанели, рак толстой кишки, рак яичников, рак почки, рак легких, рак шейки матки, рак молочной железы, рак предстательной железы, гены-супрессоры роста опухолей, метилирование, делеция, хромосома 3 человека.

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