Computational Biology and Chemistry 56 (2015) 71–83

Contents lists available at ScienceDirect

Computational Biology and Chemistry

journal homepage: www.elsevier.com/locate/compbiolchem

Gene expression patterns combined with network analysis identify hub genes associated with bladder cancer

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ARTICLE INFO

Article history:
Received 14 May 2014
Received in revised form 3 April 2015
Accepted 3 April 2015
Available online 15 April 2015

Keywords:
Bladder cancer
Hub genes
Co-expression network
Bioprocess

ABSTRACT

Objectives: To explore molecular mechanisms of bladder cancer (BC), network strategy was used to find biomarkers for early detection and diagnosis.
Methods: The differentially expressed genes (DEGs) between bladder carcinoma patients and normal subjects were screened using empirical Bayes method of the linear models for microarray data package. Co-expression networks were constructed by differentially co-expressed genes and links. Regulatory impact factors (RIF) metric was used to identify critical transcription factors (TFs). The protein–protein interaction (PPI) networks were constructed by the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) and clusters were obtained through molecular complex detection (MCODE) algorithm. Centralities analyses for complex networks were performed based on degree, stress and betweenness. Enrichment analyses were performed based on Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases.
Results: Co-expression networks and TFs (based on expression data of global DEGs and DEGs in different stages and grades) were identified. Hub genes of complex networks, such as *UBE2C*, *ACTA2*, *FABP4*, *CKS2*, *FN1* and *TOP2A*, were also obtained according to analysis of degree. In gene enrichment analyses of global DEGs, cell adhesion, proteinaceous extracellular matrix and extracellular matrix structural constituent were top three GO terms. ECM-receptor interaction, focal adhesion, and cell cycle were significant pathways.
Conclusions: Our results provide some potential underlying biomarkers of BC. However, further validation is required and deep studies are needed to elucidate the pathogenesis of BC.

1. Introduction

Radical radiotherapy of bladder cancer (BC) is associated with a relatively high rate of incomplete response or local recurrence with salvage cystectomy for treatment failures. While synchronous chemotherapy combined with radio-therapy improve locoregional control of BC (James et al., 2012), it may be time to further clinical trials and considered for certain specific patient groups (Stenzl et al., 2011). Although radical surgical removal of the bladder is considered as the standard treatment, many BC patients have a substantial number of coexisting illnesses that pose risks for radical surgical approaches (James et al., 2012).

Numbers of studies have been performed to explore molecular markers along progression of BC. For example, Sanchez-Carbayo et al. (2003) identified gene expression changes of early stage bladder tumors based on cDNA microarrays. *FGFR3* and *TP53*, which associated with change of tumor grade, tumor stage, and recurrences, were confirmed as molecular markers of urothelial neoplasms and recognized as key genetic pathways in the carcinogenesis (Cheng et al., 2011). PCNA is a 36 kDa nucleic–acidic protein essential for nuclear proliferation and appeared to increase gradually when the grade and stage of the tumor escalated (Yıldırım et al., 2014). When comparing BC vs. controls, as well as in non-muscle invasive vs. muscle invasive tumors and in low vs. high grade tumors, osteopontin (*OPN*, *SPP1*) are with at least 2-fold differential expression due to its multiple biological functions (Zaravinos et al., 2011). Besides Hung and Chiu (2015) have suggested potential pathways and potential gene fragments of pathways related to progress of BC based on protein networks with gene expression changes. These genes and pathways were promising cancer markers for early detection of BC, but mechanism

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http://dx.doi.org/10.1016/j.compbiolchem.2015.04.001
1476-9271/

Table 1
Global DEGs of BC.

No.	Genes
1	*COL4A2*
2	*IGFBP7*
3	*SPARC*
4	*ACTA2*
5	*COL4A1*
6	*BGN*
7	*HOXA11*
8	*COL3A1*
9	*PTPRN2*
10	*SRGAP3*
11	*KCND3*
12	*COL6A3*
13	*STK39*
14	*PHF15*
15	*PTRF*
16	*CCL15*
17	*SCARB1*
18	*ABO*
19	*PALLD*
20	*COL6A2*
21	*TJP3*
22	*INPP1*
23	*CCDC28A*
24	*PLCE1*
25	*FN1*
26	*BAG1*
27	*TAGLN*
28	*MXRA8*
29	*SLC16A5*
30	*LGALS4*
31	*TBC1D1*
32	*VWF*
33	*VIM*
34	*DNMBP*
35	*HSPG2*
36	*SRPX2*
37	*UPK3A*
38	*FABP4*
39	*TSPAN1*
40	*TPM1*
41	*AIM1*
42	*CLIC4*
43	*COL1A2*
44	*COL1A1*
45	*CCT5*
46	*ACLY*
47	*KCNQ1*
48	*SLC22A18*
49	*SPARCL1*
50	*ENG*
51	*PLTP*
52	*C9orf16*
53	*IGFBP2*
54	*CRYM*
55	*CCDC69*
56	*PRDX4*
57	*ANKMY2*
58	*TRIM31*
59	*COL6A1*
60	*ALDH1L1*
61	*MYH11*
62	*DAXX*
63	*MYL9*
64	*DDAH2*
65	*BOP1*
66	*DMTN*
67	*RNASE1*
68	*EPB41L3*
69	*PIGR*
70	*MGMT*
71	*TPM2*
72	*FLNA*
73	*DSG2*
74	*LGALS1*
75	*SLC4A2*
76	*ASS1*

Table 1 (*Continued*)

No.	Genes
77	*SLC20A2*
78	*MTUS1*
79	*HIST1H4C*
80	*PSMC2*
81	*CTGF*
82	*GNE*
83	*MMP7*
84	*NREP*
85	*SPP1*
86	*MALL*
87	*PLS1*
88	*LUM*
89	*GPR126*
90	*CBX1*
91	*CYP3A5*
92	*BLNK*
93	*QPRT*
94	*SMTN*
95	*PAPD7*
96	*SNRPB2*
97	*GARS*
98	*SCCPDH*
99	*MFGE8*
100	*RGS5*
101	*CDK4*
102	*EFNA1*
103	*PPM1H*
104	*PRPSAP1*
105	*UBE2C*
106	*VBP1*
107	*HS3ST1*
108	*ABLIM3*
109	*TJP2*
110	*CFD*
111	*ABR*
112	*CRYZ*
113	*DPYSL2*
114	*ACTG2*
115	*UBE2S*
116	*MSX2*
117	*C1S*
118	*ENO2*
119	*TCF12*
120	*SFXN3*
121	*PIK3IP1*
122	*SLC7A8*
123	*FLOT2*
124	*RNF19B*
125	*EIF4A1*
126	*TRIM14*
127	*ARHGAP12*
128	*ABLIM1*
129	*MECOM*
130	*HNF1B*
131	*MFAP2*
132	*TNFRSF14*
133	*ABCC3*
134	*LPXN*
135	*VGLL1*
136	*VAMP7*
137	*VCAN*
138	*CALU*
139	*TCF3*
140	*HEG1*
141	*CAV1*
142	*ACTL6A*
143	*CEACAM1*
144	*RAD21*
145	*COL5A2*
146	*ELF3*
147	*LPCAT4*
148	*FERMT2*
149	*CORO2A*
150	*ID1*
151	*COL7A1*
152	*KANK1*
153	*CKB*