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Filtering of the gene signature as the predictors of cisplatin-resistance in ovarian cancer

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Abstract

Background: Gene expression profiling and prediction of drug responses based on the molecular signature indicate new molecular biomarkers which help to find the most effective drugs according to the tumor characteristics. Objectives: In this study two independent datasets, GSE28646 and GSE15372 were subjected to meta-analysis based on Affymetrix microarrays. Material and Methods: In-silico methods were used to determine differentially expressed genes (DEGs) in the previously reported sensitive and resistant A2780 cell lines to Cisplatin. Gene Fuzzy Scoring (GFS) and Principle Component Analysis (PCA) were then used to eliminate batch effects and reduce data dimension, respectively. Moreover, SVM method was performed to classify sensitive and resistant data samples. Furthermore, Wilcoxon Rank sum test was performed to determine DEGs. Following the selection of drug resistance markers, several networks including transcription factor-target regulatory network and miRNA-target network were constructed and Differential correlation analysis was performed on these networks. Results: The trained SVM successfully classified sensitive and resistant data samples. Moreover, Performing DiffCorr analysis on the sensitive and resistant samples resulted in detection of 27 and 25 significant (with correlation ≥|0.9|) pairs of genes that respectively correspond to newly constructed correlations and loss of correlations in the resistant samples. Conclusions: Our results indicated the functional genes and networks in Cisplatin resistance of ovarian cancer cells and support the importance of differential expression studies in ovarian cancer chemotherapeutic agent responsiveness.

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Keywords

Cisplatin-resistance, Gene expression analysis, Ovarian neoplasm, Regulatory network

References

[1] Dressman HK, Berchuck A, Chan G, Zhai J, Bild A, Sayer R, et al. An integrated genomic-based approach to individualized treatment of patients with advanced-stage ovarian cancer. Am J Clin Oncol. 2007;25(5):517-525. doi: 10.1200/JCO.2006.06.3743

[2] Shen D-W, Pouliot LM, Hall MD, Gottesman MM. Cisplatin resistance: a cellular self-defense mechanism resulting from multiple epigenetic and genetic changes. Pharmacol Rev. 2012;64(3):706-721. doi: 10.1124/pr.111.005637

[3] Abad E, García-Mayea Y, Mir C, Sebastian D, Zorzano A, Potesil D, et al. Common metabolic pathways implicated in resistance to chemotherapy point to a key mitochondrial role in breast cancer. Mol Cell Proteom. 2019;18(2):231-244. doi: 10.1074/mcp.RA118.001102

[4] Sherman-Baust CA, Becker KG, Wood III WH, Zhang Y, Morin PJ. Gene expression and pathway analysis of ovarian cancer cells selected for resistance to cisplatin, paclitaxel, or doxorubicin. J Ovarian Res. 2011;4(1):21. doi: 10.1186/1757-2215-4-21

[5] Zeller C, Dai W, Steele NL, Siddiq A, Walley AJ, Wilhelm-Benartzi C, et al. Candidate DNA methylation drivers of acquired cisplatin resistance in ovarian cancer identified by methylome and expression profiling. Oncogene. 2012;31(42):4567. doi: 10.1038/onc.2011.611

[6] Li M, Balch C, Montgomery JS, Jeong M, Chung JH, Yan P, et al. Integrated analysis of DNA methylation and gene expression reveals specific signaling pathways associated with platinum resistance in ovarian cancer. BMC medical genomics. 2009;2(1):34. doi: 10.1186/1755-8794-2-34.

[7] Belorkar A, Wong L. GFS: fuzzy preprocessing for effective gene expression analysis. BMC bioinformatics. 2016;17(17):540. doi:10.1186/s12859-016-1327-8

[8] Kim H-Y. Statistical notes for clinical researchers: Nonparametric statistical methods: 1. Nonparametric methods for comparing two groups. Restor Dent Endod. 2014;39(3):235. doi: 10.5395/rde.2014.39.3.235

[9] Huang S, Cai N, Pacheco PP, Narrandes S, Wang Y, Xu W. Applications of support vector machine (SVM) learning in cancer genomics. Cancer Genom Proteom. 2018;15(1):41-51. doi: 10.21873/cgp.20063.

[10] Noble WS. What is a support vector machine? Nat. Biotechnol. 2006;24(12):1565-1567. doi: 10.1038/nbt1206-1565.

[11] Han H, Cho J-W, Lee S, Yun A, Kim H, Bae D, et al. TRUST v2: an expanded reference database of human and mouse transcriptional regulatory interactions. Nucleic Acids Res. 2018;46(D1):D380-D386. doi: 10.1093/nar/gkx1013

[12] Xie B, Ding Q, Han H, Wu D. miRCancer: a microRNA– cancer association database constructed by text mining on literature. Bioinformatics. 2013;29(5):638-644. doi: 10.1093/bioinformatics/btt014

[13] Chen Y, Wang X. miRDB: an online database for prediction of functional microRNA targets. Nucleic Acids Res. 2020;48(D1):D127-D131. doi: 10.1261/rna.965408

[14] Li J-H, Liu S, Zhou H, Qu L-H, Yang J-H. starBase v2. 0: decoding miRNA-ceRNA, miRNA-ncRNA and protein–RNA interaction networks from large-scale CLIP-Seq data. Nucleic Acids Res. 2014;42(D1):D92-D97. doi: 10.1093/nar/gkt1248

[15] Vlachos IS, Zagganas K, Paraskevopoulou MD, Georgakilas G, Karagkouni D, Vergoulis T, et al. DIANA-miRPath v3. 0: deciphering microRNA function with experimental support. Nucleic Acids Res. 2015;43(W1):W460-W466. doi: 10.1093/nar/gkv403

[16] Chen J, Bardes EE, Aronow BJ, Jegga AG. ToppGene Suite for gene list enrichment analysis and candidate gene prioritization. Nucleic Acids Res. 2009;37(suppl_2):W305-W311. doi: 10.1093/nar/gkp427

[17] Fukushima A. DiffCorr: an R package to analyze and visualize differential correlations in biological networks. Gene. 2013;518(1):209-214. doi: 10.1016/j.gene.2012.11.028

[18] Duan Z, Feller AJ, Penson RT, Chabner BA, Seiden MV. Discovery of differentially expressed genes associated with paclitaxel resistance using cDNA array technology: analysis of interleukin (IL) 6, IL-8, and monocyte chemotactic protein 1 in the paclitaxel-resistant phenotype. Clin Cancer Res. 1999;5(11):3445-3453. doi: Published November 1999

[19] Tellez-Gabriel M, Ory B, Lamoureux F, Heymann M-F, Heymann D. Tumour heterogeneity: the key advantages of single-cell analysis. Int J Mol. 2016;17(12):2142. doi: 10.3390/ijms17122142

[20] Pils D, Horak P, Gleiss A, Sax C, Fabjani G, Moebus VJ, et al. Five genes from chromosomal band 8p22 are significantly down regulated in ovarian carcinoma. Cancer. 2005;104(11):2417-2429. doi: 10.1002/cncr.21538

[21] Kanamarlapudi V. Exchange factor EFA6R requires C-terminal targeting to the plasma membrane to promote cytoskeletal rearrangement through the activation of ADP-ribosylation factor 6 (ARF6). J Biol Chem. 2014;289(48):33378-33390. doi: 10.1074/jbc.M113.534156

[22] Westphalen CB, Quante M, Wang TC. Functional implication of Dclk1 and Dclk1-expressing cells in cancer. Small GTPases. 2017;8(3):164-671. doi: 10.1080/21541248.2016.1208792

[23] Chandrakesan P, Panneerselvam J, Qu D, Weygant N, May R, Bronze M, et al. Regulatory roles of Dclk1 in epithelial mesenchymal transition and cancer stem cells. J Carcinog Mutagen. 2016;7(2). doi: 10.4172/2157-2518.1000257

[24] Sureban SM, May R, Weygant N, Qu D, Chandrakesan P, Bannerman-Menson E, et al. XMD8-92 inhibits pancreatic tumor xenograft growth via a DCLK1-dependent mechanism. Cancer letters. 2014;351(1):151-161. doi: 10.1016/j. canlet.2014.05.011

[25] Sureban SM, May R, Mondalek FG, Qu D, Ponnurangam S, Pantazis P, et al. Nanoparticle-based delivery of siDCAMKL-1 increases microRNA-144 and inhibits colorectal cancer tumor growth via a Notch-1 dependent mechanism. J Nanobiotechnology. 2011;9(1):40. doi: 10.1186/1477-3155-9-40

[26] Korpal M, Lee ES, Hu G, Kang Y. The miR-200 family inhibits epithelial-mesenchymal transition and cancer cell migration by direct targeting of E-cadherin transcriptional repressors ZEB1 and ZEB2. J Biolog Chem. 2008;283(22):14910-14914.

[27] Roybal JD, Zang Y, Ahn Y-H, Yang Y, Gibbons DL, Baird BN, et al. miR-200 Inhibits lung adenocarcinoma cell invasion and metastasis by targeting Flt1/VEGFR1. Mol Cancer Res. 2011 Jan 1;9(1):25-35. doi: 10.1158/1541-7786.MCR-10-0497

[28] Puiffe M-L, Le Page C, Filali-Mouhim A, Zietarska M, Ouellet V, Tonin PN, et al. Characterization of Ovarian Cancer Ascites on Cell Invasion, Proliferation, Spheroid Formation, Gene Expression in an In Vitro Model of Epithelial Ovarian Cancer. Neoplasia. 2007;9(10):820-IN828. doi: 10.1593/neo.07472

[29] Hsu F-H, Serpedin E, Hsiao T-H, Bishop AJ, Dougherty ER, Chen Y, editors. Identifying genes associated with chemotherapy response in ovarian carcinomas based on DNA copy number and expression profiles. GENSIPS, 2011 IEEE International Workshop on; 2011: IEEE. doi: 10.1109/GENSiPS.2011.6169438

[30] Wang C, Xiao Y, Hu Z, Chen Y, Liu N, Hu G. PEG10 directly regulated by E2Fs might have a role in the development of hepatocellular carcinoma. FEBS letters. 2008;582(18):2793-2798. doi: 10.1016/j.febslet.2008.07.009

[31] ZITAN Q, XUz Z. CHML suppresses cell growth and induces apoptosis in multiple human tumor lines. Anticancer Res. 1999;19:2893-2900.

[32] Barøy T, Chilamakuri CS, Lorenz S, Sun J, Bruland ØS, Myklebost O, et al. Genome Analysis of Osteosarcoma Progression Samples Identifies FGFR1 Overexpression as a Potential Treatment Target and CHM as a Candidate Tumor Suppressor Gene. PloS One. 2016;11(9):e0163859. doi: 10.1371/journal.pone.0163859

[33] Neilsen PM, Noll JE, Mattiske S, Bracken CP, Gregory PA, Schulz RB, et al. Mutant p53 drives invasion in breast tumors through up-regulation of miR-155. Oncogene. 2013;32(24):2992. doi: 10.1038/onc.2012.305

[34] Dankert JF, Pagan JK, Starostina NG, Kipreos ET, Pagano M. FEM1 proteins are ancient regulators of SLBP degradation. Cell Cycle. 2017;16(6):556-564. doi: 10.1080/15384101.2017.1284715

[35] Coyle-Thompson CA, Banerjee U. The strawberry notch gene functions with Notch in common developmental pathways. Development. 1993;119(2):377-395. doi: 10.1242/dev.119.2.377

[36] Suzuki C, Takahashi K, Hayama S, Ishikawa N, Kato T, Ito T, et al. Identification of Myc-associated protein with JmjC domain as a novel therapeutic target oncogene for lung cancer. Mol Cancer Ther. 2007;6(2):542-551. doi: 10.1158/1535-7163.MCT-06-0659

[37] Kavela S, Shinde SR, Ratheesh R, Viswakalyan K, Bashyam MD, Gowrishankar S, et al. PNUTS functions as a proto-oncogene by sequestering PTEN. CancerRes. 2013 Jan 1;73(1):205-214.. doi: 10.1158/0008-5472.CA--12-1394

[38] Mastropasqua F, Marzano F, Valletti A, Aiello I, Di Tullio G, Morgano A, et al. TRIM8 restores p53 tumour suppressor function by blunting N-MYC activity in chemo-resistant tumours. Mol Cancer. 2017;16(1):67. doi: 10.1186/s12943-017-0634-7

[39] Arango D, Corner GA, Wadler S, Catalano PJ, Augenlicht LH. c-myc/p53 interaction determines sensitivity of human colon carcinoma cells to 5-fluorouracil in vitro and in vivo. Cancer Res. 2001;61(12):4910-4915.

[40] VanKlompenberg MK, Leyden E, Arnason AH, Zhang J-T, Stefanski CD, Prosperi JR. APC loss in breast cancer leads to doxorubicin resistance via STAT3 activation. Oncotarget. 2017;8(61):102868. doi: 10.18632/oncotarget.22263

[41] Castellano G, Torrisi E, Ligresti G, Malaponte G, Militello L, Russo AE, et al. The involvement of the transcription factor Yin Yang 1 in cancer development and progression. Cell Cycle. 2009;8(9):1367-1372. doi: 10.4161/cc.8.9.8314

[42] Kashyap V, Bonavida B. Role of YY1 in the pathogenesis of prostate cancer and correlation with bioinformatic data sets of gene expression. Genes Cancer. 2014;5(3-4):71. doi: 10.18632/genesandcancer.12

[43] Godwin P, Baird A-M, Heavey S, Barr M, O'Byrne K, Gately KA. Targeting nuclear factor-kappa B to overcome resistance to chemotherapy. Frontiers in oncology. 2013;3:120. doi: 10.3389/fphar.2012.00202

[44] Lam E-F, Francis R, Petkovic M. FOXO transcription factors: key regulators of cell fate. Portland Press Limited; 2006. doi: 10.1042/BST0340722

[45] Gomes AR, Brosens JJ, Lam EW-F. Resist or die: FOXO transcription factors determine the cellular response to chemotherapy. Cell Cycle. 2008;7(20):3133-3136. doi: 10.4161/cc.7.20.6920

[46] Zheng H, Bae Y, Kasimir-Bauer S, Tang R, Chen J, Ren G, et al. Therapeutic antibody targeting tumor-and osteoblastic niche-derived jagged1 sensitizes bone metastasis to chemotherapy. Cancer Cell. 2017;32(6):731-747.e6. doi: 10.1016/j. ccell.2017.11.002

[47] Li C-M, Margolin AA, Salas M, Memeo L, Mansukhani M, Hibshoosh H, et al. PEG10 is a c-MYC target gene in cancer cells. Cancer Res. 2006;66(2):665-672. doi: 10.1158/0008-5472.CAN-05-1553

[48] Barry SP, Townsend PA, Knight RA, Scarabelli TM, Latchman DS, Stephanou A. STAT3 modulates the DNA damage response pathway. Int J Exp Pathol. 2010;91(6):506-514. doi: 10.1111/j.1365-2613.2010.00734.x

[49] Coster G, Goldberg M. The cellular response to DNA damage: a focus on MDC1 and its interacting proteins. Nucleus. 2010;1(2):166-178. doi: 10.4161/nucl.1.2.11176

[50] Ambros V. The functions of animal microRNAs. Nature. 2004;431(7006):350. doi: 10.1038/nature02871

[51] Hu YW, Kang CM, Zhao JJ, Nie Y, Zheng L, Li HX, et al. Lnc RNA PLAC 2 down regulates RPL 36 expression and blocks cell cycle progression in glioma through a mechanism involving STAT 1. J Cell Mol Med. 2018;22(1):497-510. doi: 10.1111/jcmm.13338

[52] Jiang Z, Dong X, Li Z-G, He F, Zhang Z. Differential coexpression analysis reveals extensive rewiring of Arabidopsis gene coexpression in response to Pseudomonas syringae infection. Sci Rep. 2016;6:35064. doi: 10.1038/srep35064

[53] Stavropoulou V, Xie J, Henriksson M, Tomkinson B, Imreh S, Masucci MG. Mitotic infidelity and centrosome duplication errors in cells overexpressing tripeptidyl-peptidase II. Cancer Res. 2005;65(4):1361-1368. doi: 10.1158/0008-5472.CAN-04-2085

[54] Duensing S, Darr S, Cuevas R, Melquiot N, Brickner AG, Duensing A, et al. Tripeptidyl Peptidase II Is Required for c-MYC–Induced Centriole Overduplication and a Novel Therapeutic Target in c-MYC–Associated Neoplasms. Genes Cancer. 2010;1(9):883-892. doi: 10.1177/1947601910389605