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□ Editorial □

Role of Microarray in Cancer Diagnosis

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Current cancer diagnosis and classification relies on clinical and histopathological information. However, some cases bring diagnostic confusion due to incomplete clinical information and atypical histopathologic features, together with the fact that criteria for histopathologic information is subjective.

Molecular diagnosis using tumor biomarkers offers precise and objective tumor diagnosis. Chromosomal changes and genetic mutations can be used in the molecular diagnosis of tumors. Loss of the long arm of chromosome 14 and activating mutation of *c-kit* are objective genetic changes in gastrointestinal stromal tumors (1-3), and gene rearrangement of bcr/abl is a diagnostic marker for acute myelogenous leukemia (4). However, molecular diagnosis is not generally accepted because of the scant number of objective tumor markers. Moreover, most of the genetic changes are not specific enough to accurately diagnose the tumors and comprehensive mutation databases for the tumors have not been explored (5).

Recently, DNA micro-array-based tumor gene expression profiles have been developed and used in the tumor diagnosis and classification. Many studies have demonstrated that a subset of genes is characteristically expressed in ovarian cancers (6), oral cancers (7), melanomas (8), colorectal carcinomas (9,10) and prostate carcinomas (11,12). Molecular classifications using DNA micro-array is useful for the determination of primary sites in metastatic carcinomas (13) and the classification of soft tissue sarcomas (14). Gene expression profiles by DNA microarray analysis show remarkable intertumoral variations in the same histologic type of tumors. These intertumoral variations can be used for precise molecular classifications and can provide opportunities for the evaluation of genetic changes. Gene expression profiles can successfully differentiate the type of leukemia (15) and the oncogenetic pathway for the T-cell leukemia (16). Additionally, several studies have demonstrated a subset of genes representing different genetic and biological changes in solid tumors. Hereditary breast carcinomas differed in germline mutation status of BRCA1 or BRCA2 (17), and hence, prognosis-related molecular classifications were possible in prostate carcinomas (12), lymphomas (18), and gastric carcinomas (19).

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Although DNA micro-array analysis for tumor diagnosis and classification is a promising diagnostic modality for the future, currently, there are many limitations. First of all, accurate diagnoses of individual tumors by gene expression profile alone are not always possible. This may be because no reference databases for comprehensive gene expression for cancer has been explored, and no specific group of biomarkers for the diagnosis of specific tumors have yet been developed. Secondly, the gene expression data shows remarkable variations within the same tumor. This may result from different gene expression profiles in the tumors and the different peritumoral lymphoid or stromal reaction status. Thirdly, early tumor detection is not possible by the gene expression profile. Currently, cancer diagnosis with the DNA micro-array is possible only when large amounts and high fractions of tumor cells are prepared. Detection of the membrane protein fragments or specific mutations in circulating tumor cells from body fluids is more effective and a popular approach in the early detection of tumors. The analysis of cancer specific mRNAs from body fluids containing tumor cells is another promising way; however, this can be more effectively carried out by RT-PCR (20,21) han by DNA micro-array. In spite of these limitations, DNA microarray can be best used for molecular classification based on genetic and biological changes.

In this month's issue, Bae et al (22). reported gene expression profiling of uterine leiomyomas. The authors analyzed the gene expression profiles of leiomyomas by using the cDNA micro-array. They compared the gene expression profile of leiomyomas to that of normal myometrium and found 21 up-regulated and 50 down-regulated genes. Interestingly, most of the up-regulated genes were ones known to have nucleic acid binding activity. This study is a good model for the evaluation of genes involved in multi-step carcinogenesis. The uterine myometrium is mostly composed of homogeneous myometrial cells, and leiomyoma is also a homogeneous tumor originating from myometrial cells. Moreover, leiomyosarcoma is another homogeneous mesenchymal tumor originating from myometrial cells, thus eliminating the heterogeneous peritumoral reaction. This unusual homogeneity of research materials enables one to find many valuable target genes by expression proteomics analysis.

It has been reported that DNA micro-array analysis can be a new method for the classification of soft tissue tumors (14). This method can further improve the method based on histolo-

gical findings. Specific expression of target genes, such as KIT expression in gastrointestinal stromal tumors, was noted within gene sets that distinguished different soft tissue tumors. DNA micro-array analysis for the multi-step model of malignant transformation in soft tissue tumors, such as leiomyomas and leimyosarcomas, will give important information for genes involved in malignant transformation of soft tissue tumors.

REFERENCES

1. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279: 577-580.
2. Kim NG, Kim JJ, Ahn JY, Seong CM, Noh SH, Kim CB, Min JS, Kim H. Putative chromosomal deletions on 9P, 9Q and 22Q occur preferentially in malignant gastrointestinal stromal tumors. Int J Cancer 2000;85:633-638.
3. Choi YR, Kim H, Kang HJ, Kim NG, Kim JJ, Park KS, Paik YK, Kim HO, Kim H. Overexpression of high mobility group box 1 in gastrointestinal stromal tumors with KIT mutation. Cancer Res 2003;63:2188-2193.
4. Harder L, Gesk S, Martin-Subero JI, Merz H, Hochhaus A, Maass E, Feller A, Grote W, Siebert R, Fetscher S. Cytogenetic and molecular characterization of simultaneous chronic and acute myelocytic leukemia. Cancer Genet Cytogenet 2003; 142:80-82.
5. Ramaswamy S, Tamayo P, Rifkin R, Mukherjee S, Yeang CH, Angelo M, Ladd C, Reich M, Latulippe E, Mesirov JP, Poggio T, Gerald W, Loda M, Lander ES, Golub TR. Multi-class cancer diagnosis using tumor gene expression signatures. Proc Natl Acad Sci USA 2001;98:15149-15154.
6. Shridhar V, Lee J, Pandita A, Iturria S, Avula R, Staub J, Morrissey M, Calhoun E, Sen A, Kalli K, Keeney G, Roche P, Cliby W, Lu K, Schmandt R, Mills GB, Bast RC Jr, James CD, Couch FJ, Hartmann LC, Lillie J, Smith DI. Genetic analysis of early-versus late-stage ovarian tumors. Cancer Res 2001;61:5895-5904.
7. Alevizos I, Mahadevappa M, Zhang X, Ohyama H, Kohno Y, Posner M, Gallagher GT, Varvares M, Cohen D, Kim D, Kent R, Donoff RB, Todd R, Yung CM, Warrington JA, Wong DT. Oral cancer in vivo gene expression profiling assisted by laser capture micro-dissection and micro-array analysis. Oncogene 2001;20:6196-6204.
8. de Wit NJ, Burtscher HJ, Weidle UH, Ruiter DJ, van Muijen GN. Differentially expressed genes identified in human melanoma cell lines with different metastatic behaviour using high density oligonucleotide arrays. Melanoma Res 2002; 12:57-69.
9. Kitahara O, Furukawa Y, Tanaka T, Kihara C, Ono K, Yanagawa R, Nita ME, Takagi T, Nakamura Y, Tsunoda T. Alterations of gene expression during colorectal carcinogenesis revealed by cDNA micro-arrays after laser-capture micro-dissection of tumor tissues and normal epithelia. Cancer Res 2001;61:3544-3549.
10. Birkenkamp-Demtroder K, Christensen LL, Olesen SH, Frederiksen CM, Laiho P, Aaltonen LA, Laurberg S, Sorensen FB, Hagemann R, Orntoft TF. Gene expression in colorectal cancer. Cancer Res 2002;62:4352-4363.
11. Welsh JB, Sapinoso LM, Su AI, Kern SG, Wang-Rodriguez J, Moskaluk CA, Frierson HF Jr, Hampton GM. Analysis of gene expression identifies candidate markers and pharmacological targets in prostate cancer. Cancer Res 2001;61:5974-5978.
12. Giordano TJ, Shedden KA, Schwartz DR, Kuick R, Taylor JM, Lee N, Misek DE, Greenson JK, Kardia SL, Beer DG, Rennert G, Cho KR, Gruber SB, Fearon ER, Hanash S. Organ-specific molecular classification of primary lung, colon, and ovarian adenocarcinomas using gene expression profiles. Am J Pathol 2001;159:1231-1238.
13. Nielsen TO, West RB, Linn SC, Alter O, Knowling MA, O'Connell JX, Zhu S, Fero M, Sherlock G, Pollack JR, Brown PO, Botstein D, van de Rijn M. Molecular characterization of soft tissue tumors: a gene expression study. Lancet 2002;359: 1301-1307.
14. Golub TR, Slonim DK, Tamayo P, Huard C, Gaasenbeek M, Mesirov JP, Coller H, Loh ML, Downing JR, Caligiuri MA, Bloomfield CD, Lander ES. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science 1999;286:531-537.
15. Armstrong SA, Staunton JE, Silverman LB, Pieters R, den Boer ML, Minden MD, Sallan SE, Lander ES, Golub TR, Korsmeyer SJ. MLL translocations specify a distinct gene expression profile that distinguishes a unique leukemia. Nat Genet 2002;30:41-47.
16. Hedenfalk I, Duggan D, Chen Y, Radmacher M, Bittner M, Simon R, Meltzer P, Gusterson B, Esteller M, Kallioniemi OP, Wilfond B, Borg A, Trent J. Gene-expression profiles in hereditary breast cancer. N Engl J Med 2001;344:539-548.
17. Singh D, Febbo PG, Ross K, Jackson DG, Manola J, Ladd C, Tamayo P, Renshaw AA, D'Amico AV, Richie JP, Lander ES, Loda M, Kantoff PW, Golub TR, Sellers WR. Gene expression correlates of clinical prostate cancer behavior. Cancer Cell 2002;1:203-209.
18. Shipp MA, Ross KN, Tamayo P, Weng AP, Kutok JL, Aguiar RC, Gaasenbeek M, Angelo M, Reich M, Pinkus GS, Ray TS, Koval MA, Last KW, Norton A, Lister TA, Mesirov J, Neuberg DS, Lander ES, Aster JC, Golub TR. Diffuse large B-cell lymphoma outcome prediction by gene-expression profiling and supervised machine learning. Nat Med 2002; 8:68-74.
19. Chen X, Leung SY, Yuen ST, Chu KM, Ji J, Li R, Chan AS, Law S, Troyanskaya OG, Wong J, So S, Botstein D, Brown PO. Variation in gene expression patterns in human gastric cancers. Mol Biol Cell 2003;14:3208-3215.
20. Schuster R, Max N, Mann B, Heufelder K, Thilo F, Grone J, Rokos F, Buhr HJ, Thiel E, Keilholz U. Quantitative real-time RT-PCR for detection of disseminated tumor cells in peripheral blood of patients with colorectal cancer using different mRNA markers. Int J Cancer 2004;108: 219-227.

21. Bosma AJ, Weigelt B, Lambrechts AC, Verhagen OJ, Pruntel R, Hart AA, Rodenhuis S, van't Veer LJ. Detection of circulating breast tumor cells by differential expression of marker genes. Clin Cancer Res 2002;8:1871-1877.

22. Bae SM, Kim YW, Lee JM, Namkoong SE, Kim CK, Ahn WS. Expression profiling of cellular process in uterine leiomyoma: omic approaches and IGF-2 association with leiomyosarcoma. Cancer Res Treat 2004;36:31-42.