ABSTRACT
Purpose: To examine the global gene expression of cancer-related genes in esophageal squamous cell carcinoma (ESCC) through the use of Atlas Human Cancer Array membranes printed with 588 well-characterized human genes involved in cancer and tumor biology.

Experimental Design: Two human ESCC cell lines (HKESC-1 and HKESC-2) and one morphologically normal esophageal epithelium tissue specimen from the patient of which the HKESC-2 was derived were screened in parallel using cDNA expression arrays. The array results were additionally validated using semiquantitative PCR. The over-expression of oncogene MET was studied more extensively for its protein expression by immunohistochemistry in the two ESCC cell lines and their corresponding primary tissues and 61 primary ESCC resected specimens. Sixteen of these 61 ESCC cases also had available the corresponding morphologically normal esophageal epithelium tissues and were also analyzed for MET expression. The clinicopathological features associated with overexpression of the MET gene were also correlated.

Results: The results of cDNA arrays showed that 13 cancer-related genes were up-regulated ≥2-fold (CDC25B, cyclin D1, PCNA, MET, Jagged 2, Integrin α3, Integrin α6, Integrin β4, Caveolin-2, Caveolin-1, MMP13, MMP14, and BIGH3) and 5 genes were down-regulated ≤-2-fold (CK4, Bad, IGFBP2, CSPCP, and IL-1RA) in both ESCC cell lines at the mRNA level. Semiquantitative RT-PCR analysis of 9 of these differentially expressed genes, including the MET gene, gave results consistent with cDNA array findings. The immunostaining results of the expression of MET gene showed that MET was overexpressed in both ESCC cell lines and their corresponding primary tumors at the protein level, validating the cDNA arrays findings. The results of the clinical specimens showed that the MET gene was overexpressed in ESCC compared with normal esophageal epithelium in 56 of 61 cases (92%). Moreover, the overexpression of MET protein was more often seen in well/moderately differentiated than in poorly differentiated ESCC.

Conclusions: Multiple cancer-related genes are differentially expressed in ESCC, the oncogene MET is overexpressed in ESCC compared with normal esophageal epithelium, and its protein overexpression correlates with tumor differentiation in ESCC.

INTRODUCTION
Despite advances in multimodality therapy, the prognosis for patients with ESCC still remains poor, with an average 5-year survival rate <10% (1–5). The development of new treatment modalities, diagnostic technologies, and preventive approaches will require a better understanding of the molecular mechanisms underlying esophageal carcinogenesis. We have demonstrated earlier that cDNA arrays technology is a very useful tool for identifying differentially expressed genes in ESCC and reported the detection of 61 differentially expressed genes of 588 genes studied using Atlas Human cDNA Expression Arrays (6). In the present study, we specifically examined the global gene expression of cancer-related genes involved in the pathogenesis of ESCC by using the Human Cancer Array membranes printed with 588 well-characterized human genes involved in cancer and tumor biology. Among them, 235 genes were the same as those on Atlas Human cDNA Expression Arrays (6). The cancer-related genes analyzed in the present study are divided into six groups: (a) cell cycle regulators, growth regulators, and intermediate filament markers; (b) apoptosis, oncogenes, and tumor suppressors; (c) DNA damage response/repair and recombination; cell fate and development; and receptors; (d) cell adhesion and motility; and angiogenesis; (e) invasion regulators and cell-cell interactions; and (f) growth factors and cytokines. Using the Atlas Human cDNA Expression Arrays, 18 of 588 cancer-related genes examined were

identified to be differentially expressed in ESCC. Importantly, the mRNA of oncogene MET was found to be overexpressed in both the newly established ESCC cell lines HKESC-1 and HKESC-2. This prompted us to additionally examine its protein expression in the cell lines, their respective primary tissues, a large series of primary ESCC tumors, and corresponding morphologically normal esophageal epithelium tissues. Furthermore, we also analyzed the relationships between MET expression and the clinicopathological parameters of ESCC.

MATERIALS AND METHODS

ESCC Cell Lines and Control Specimen. Two human ESCC cell lines (HKESC-1 and HKESC-2) and one morphologically normal esophageal epithelium tissue specimen from the patient of which the HKESC-2 was derived were used for the Human Cancer cDNA Expression Arrays experiment (6). Both cell lines were established from Hong Kong Chinese patients with moderately differentiated ESCC: HKESC-1 from a 47-year-old man and HKESC-2 from a 46-year-old woman (7, 8). Both cell lines grew as adherent monolayers and cultured in Minimum Essential Medium with non-essential amino acids (MN) (Sigma, Saint Louis, MO) medium containing 10% fetal bovine serum (7, 8). Cells were harvested from passage 31 of HKESC-1 and passage 4 of HKESC-2 at 80–90% confluency, respectively. Unfortunately, the collected normal esophageal epithelium tissue from the patient of which the HKESC-1 was derived could not be used as a control, because the specimen was too small, and only a small amount of RNA could be extracted from it.

Human Cancer cDNA Arrays, Probes, Hybridization, and Data Analysis. Atlas Human Cancer cDNA Expression Arrays membranes used in this study were purchased from Clontech (Palo Alto, CA). The membrane contained 10 ng of each gene-specific cDNA from 588 known cancer-related genes and 9 housekeeping genes (Fig. 1). Several plasmid and bacteriophage DNAs and blank spots are also included as negative and blank controls to confirm hybridization specificity. A complete list of the 588 cancer-related genes with array positions and GenBank accession number of the Atlas Human Cancer Expression Arrays used here can be accessed at the website.4 Total RNA was extracted using the TRIzol reagent protocol (Life Technologies, Inc., Gaithersburg, MD) from the two ESCC cell lines (HKESC-1 and HKESC-2) and one corresponding morphologically normal esophageal epithelium from the patient of which the HKESC-2 was derived. mRNA was then isolated from the total RNA using the Straight A’s mRNA Isolation System (Novagen, Madison, WI). The 32P-labeled cDNA probes were generated by reverse transcription of 1 μg of mRNA of each sample in the presence of [α-32P]dATP. Equal amounts of cDNA probes (3 × 106 cpm/μl) from the ESCC cell lines and normal esophageal epithelium were then hybridized to separate Atlas Human Cancer cDNA array membranes for 24 h at 42°C and washed according to the supplier’s instructions. The array membranes were then exposed to X-ray film at −70°C for 2–5 days. Autoradiographic intensity was analyzed using AtlasImage analysis software.

GeneAmp RNA PCR Core kit (Perkin-Elmer, Branchburg, NJ).

° C for 10 min using the C for 1 h followed by 95 °C for 20–30 s, 1 min KCl) 1.9 or 2.4 mM of MgCl2, 0.5 μM of primers, 0.18 mM of deoxynucleotide triphosphate, and 1 unit AmpliTaq Gold DNA Polymerase. The hot-start PCR reaction was as follows: 95°C for 10 min followed by 25–40 cycles of 1 min denaturation at 94°C, 1 min annealing at 60°C (for primers of MET, Jagged, MMP13, MMP14, BIGH3, CK1, CK4, IL-1RA, and GAPDH) or 50°C (for primers of CSPC3), and 1 min extension at 72°C. The final step of extension was for 10 min at 72°C. The PCR reagents were purchased from Perkin-Elmer.

The sequences of gene specific primers for RT-PCR were the same as those of Cancer cDNA arrays (data not shown because of the copyright agreement by Clontech, Palo Alto, CA) except for the primers specific for MET, which were the same as described previously (9). All of the primers were synthesized by Integrated DNA Technologies Inc., Coralville, IA. The cycle number was optimized for each gene-specific primer pair to ensure that amplification was in the linear range, and the results were semiquantitative. PCR product (12 μl) was visualized by electrophoresis on a 1% agarose gel stained with ethidium bromide and quantitated by densitometry using a dual-intensity transilluminator equipped with Gelworks 1D Intermediate software (version 2.51).

**Collection of Tissues and Clinicopathological Data.** The tissues were obtained from 61 (50 men and 11 women) patients with ESCC resected between 1996 and 1998 in Queen Mary Hospital, The University of Hong Kong. The patient ages ranged from 41 to 83 years, with a mean age of 65 years. The specimens were dissected and examined in the fresh state. Representative tissue specimens from tumors and matching normal esophageal epithelium tissues were snap-frozen in liquid nitrogen and stored at −80°C. Other representative blocks were taken and processed in paraffin for histological examination. The carcinomas were found in the upper (n = 10, 16%), middle (n = 35, 57%), and lower (n = 16, 26%) third of the esophagus. The median length of the tumors was 5.5 cm (range, 1–11). The histology of the carcinomas was reviewed according to the criteria described previously (4). The ESCC tumors were well differentiated in 20 (33%) cases, moderately differentiated in 29 (48%), and poorly differentiated in 12 (20%). The carcinomas were staged according to the Tumor-Node-Metastasis classification (10). Many tumors were stage III (n = 35, 57%) or II (n = 23, 38%); of the remainder, 1 was stage I, and 2 were stage IV.

**IHC Staining of MET Gene.** Expression of the MET gene was investigated by streptavidin-biotin-peroxidase complex method. Briefly, 6-μm frozen sections were cut from two pellets harvested from cultured cell lines HKESC-1 and HKESC-2, the cell lines corresponding primary tissues and 61 primary ESCC tumors. Sixteen of these 61 ESCC cases also had available the corresponding morphologically normal esophageal epithelium tissues and were also analyzed for MET expression. After endogenous peroxidase activity was quenched and nonspecific binding was blocked, polyclonal rabbit anti-MET antibody (Santa Cruz Biotechnology, Santa Cruz, CA) was incubated at 4°C overnight at a dilution of 1:50. The secondary antibody was biotinylated swine antirabbit antibody (DAKO, Glostrup, Denmark) used at a dilution of 1:200 for 30 min at 37°C. After washing, sections were incubated with StreptABComplex/horseradish peroxidase (DAKO; 1:100 dilution) for 30

table 1: Summary of differentially expressed genes in both ESCC cell lines HKESC-1 and HKESC-2 when compared with one corresponding morphologically normal esophageal epithelium tissue specimen (N) from the patient of which the HKESC-2 was derived by Atlas Human Cancer cDNA Expression Arrays

<table>
<thead>
<tr>
<th>Arrays</th>
<th>Intensity ratio</th>
<th>Position</th>
<th>Name of gene</th>
<th>Chromosome location</th>
</tr>
</thead>
<tbody>
<tr>
<td>HKESC-1/N</td>
<td>HKESC-2/N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1k</td>
<td>CDC25B</td>
<td>20p13</td>
<td>2.0</td>
<td>2.1</td>
</tr>
<tr>
<td>A2l</td>
<td>Cyclin D1</td>
<td>11q13</td>
<td>2.2</td>
<td>2.0</td>
</tr>
<tr>
<td>A5e</td>
<td>PCNA</td>
<td>20pter-p12</td>
<td>2.2</td>
<td>2.6</td>
</tr>
<tr>
<td>B6h</td>
<td>MET</td>
<td>12p12.1</td>
<td>2.8</td>
<td>2.9</td>
</tr>
<tr>
<td>C3k</td>
<td>Jagged 2</td>
<td>14q32</td>
<td>3.7</td>
<td>3.4</td>
</tr>
<tr>
<td>D3k</td>
<td>Integrin α3</td>
<td>17</td>
<td>2.6</td>
<td>2.5</td>
</tr>
<tr>
<td>D3a</td>
<td>Integrin α6</td>
<td>2</td>
<td>3.3</td>
<td>3.2</td>
</tr>
<tr>
<td>D4g</td>
<td>Integrin β4</td>
<td>17q11-qter</td>
<td>2.4</td>
<td>2.7</td>
</tr>
<tr>
<td>D6k</td>
<td>Caveolin-2</td>
<td>7q31.1-q31.2</td>
<td>8.8</td>
<td>5.2</td>
</tr>
<tr>
<td>D6l</td>
<td>Caveolin-1</td>
<td>7q31.1</td>
<td>9.5</td>
<td>7.2</td>
</tr>
<tr>
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<td>11q22.3</td>
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<tr>
<td>E1k</td>
<td>MMP14</td>
<td>14q11-q12</td>
<td>4.5</td>
<td>4.9</td>
</tr>
<tr>
<td>F1f</td>
<td>BIGH3</td>
<td>5q31</td>
<td>2.2</td>
<td>2.3</td>
</tr>
<tr>
<td>A7g</td>
<td>CK4</td>
<td>12q13</td>
<td>1/50</td>
<td>1/69</td>
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<tr>
<td>B1i</td>
<td>Bad</td>
<td>11</td>
<td>1/2.1</td>
<td>1/4.3</td>
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<tr>
<td>C6c</td>
<td>IGFBP2</td>
<td>2q33-q34</td>
<td>1/8.9</td>
<td>1/2.5</td>
</tr>
<tr>
<td>D1a</td>
<td>CSPC3</td>
<td>15q26.1</td>
<td>1/3.0</td>
<td>1/2.2</td>
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<tr>
<td>F4d</td>
<td>IL-1RA</td>
<td>2q14.2</td>
<td>1/4.4</td>
<td>1/2.2</td>
</tr>
</tbody>
</table>

Human Cancer cDNA Expression Arrays. The arrays contain 588 human genes spotted in duplicate and divided into six functional categories (quadrants A–F). Three blank (G1, G8, and G15) and nine negative (G2–4, G9–11, and G16–18) controls are included to confirm hybridization specificity. Nine housekeeping genes (G5–7, G12–14, and G19–21) are also included in the arrays for normalizing mRNA abundance. Genomic DNA spots (dark dots) serve as orientation marks to facilitate in the determination of the coordinates of hybridization signals. A complete gene list with arrays coordinates and GenBank accession numbers is available at the website.4

cDNA (2 μl) was amplified in a 25-μl PCR reaction mixture containing 1× PCR buffer, (10 mM Tris-HCl, pH 8.3, 50 mM KCl) 1.9 or 2.4 mM of MgCl2, 0.5 μM of primers, 0.18 mM of deoxynucleotide triphosphate, and 1 unit AmpliTaq Gold DNA Polymerase. The hot-start PCR reaction was as follows: 95°C for 10 min followed by 25–40 cycles of 1 min denaturation at 94°C, 1 min annealing at 60°C (for primers of MET, Jagged, MMP13, MMP14, BIGH3, CK1, CK4, IL-1RA, and GAPDH) or 50°C (for primers of CSPC3), and 1 min extension at 72°C. The final step of extension was for 10 min at 72°C. The PCR reagents were purchased from Perkin-Elmer.

The sequences of gene specific primers for RT-PCR were the same as those of Cancer cDNA arrays (data not shown because of the copyright agreement by Clontech, Palo Alto, CA) except for the primers specific for MET, which were the same as described previously (9). All of the primers were synthesized by Integrated DNA Technologies Inc., Coralville, IA. The cycle number was optimized for each gene-specific primer pair to ensure that amplification was in the linear range, and the results were semiquantitative. PCR product (12 μl) was visualized by electrophoresis on a 1% agarose gel stained with ethidium bromide and quantitated by densitometry using a dual-intensity transilluminator equipped with Gelworks 1D Intermediate software (version 2.51).
min at 37°C. Negative controls were performed by replacing the primary antibody by normal serum. Each section was independently assessed by two histopathologists (Y. C. H. and K. Y. L.) without previous knowledge of the other data of the patients. All of the fields in the selected block were taken into consideration for assessment of immunostaining. The percentage of tumor cells stained of total tumor cells noted was reported. Representative areas of each section were selected, and cells were counted in at least four fields (at ×200). Scoring was based on the percentage of positive cells. The IHC staining was identified as (−): no expression; (+): <10% of cells were stained; (2+): 10–50% of cells stained; (3+): >50% of cells stained; (2+) – (3+) was defined as overexpression.

Statistical Analysis. Comparisons between groups were performed using the χ² test and t test when appropriate. P < 0.05 was used to determine statistical significance. All of the statistical tests were performed with the GraphPad Prism software version 3.0 (GraphPad Software, Inc., San Diego, CA).

RESULTS
Identification of Differentially Expressed Cancer-related Genes in ESCC by the Human Cancer cDNA Arrays. The general expression profiles of 588 cancer-related genes in HKESC-1 (Fig. 1A), HKESC-2 (Fig. 1B), and normal esophageal epithelium tissue (Fig. 1C) as determined by the Human Cancer cDNA Arrays are shown in Fig. 1. No signals were visible in the blank spots (G1, G8, and G15) and negative control spots (G2–4, G9–11, and G16–18; Fig. 1) indicating that the Cancer Arrays hybridization was highly specific. The comparison of the autoradiographic intensities between ESCC cell lines and normal esophageal epithelium showed that 13 genes were up-regulated and 5 genes down-regulated ≥2-fold in both cell lines (Table 1).

Confirmation of Differentially Expressed Cancer-related Genes by Semiquantitative RT-PCR. The semiquantitative RT-PCR results showed that MET, Jagged 2, MMP13, MMP14, and BIGH3 genes were up-regulated in cell lines HKESC-1 and HKESC-2, whereas CK4, CSPCP, and IL-1RA genes were down-regulated in HKESC-1 and HKESC-2 (Fig. 2). CK1 was down-regulated in HKESC-2 but not in HKESC-1. These results are similar to those detected by Human Cancer cDNA Arrays (Fig. 1).

Expression of MET Gene in ESCC Cell Lines and Their Respective Primary Tissues. The immunostaining results of MET expression in ESCC cell lines HKESC-1 and HKESC-2

HKESC-2 was derived. A, determination of optimal number of PCR cycles for different gene-specific primer pairs. mRNA from HKESC-1 was used to determine the optimal number of PCR cycles for genes MET, Jagged 2, MMP13, MMP14, and BIGH3. mRNA from the normal esophageal epithelium was used to determine optimal number of PCR cycles for genes CK1, CK4, CSPCP, and IL-1RA. B, expression of MET (31 cycles), Jagged 2 (31 cycles), MMP13 (31 cycles), MMP14 (31 cycles), BIGH3 (31 cycles), CK1 (35 cycles), CK4 (28 cycles), CSPCP (40 cycles), IL-1RA (28 cycles), and GAPDH (25 cycles) genes in two ESCC cell lines HKESC-1 and HKESC-2 and one corresponding morphologically normal esophageal epithelium (Normal) from the patient of which the HKESC-2 was derived. PCR products were electrophoresed on 2% agarose gel containing ethidium bromide.
and their corresponding primary tissues were summarized in Table 2. MET protein was found to be overexpressed in both the ESCC cell lines (HKESC-1 and HKESC-2) and the primary tumors from which these cell lines were established (Table 2).

**Expression of MET Gene in Primary ESCC Tumors and Morphologically Normal Esophageal Epithelium Tissues.** The IHC staining results of MET expression in 61 primary ESCC tumors and 16 corresponding morphologically normal esophageal epithelium tissues are summarized in Table 3 and shown in Fig. 3. As shown in Table 3, MET was overexpressed in ESCC in 56 of 61 cases (92%). MET protein had a significantly higher incidence of overexpression in ESCCs than morphologically normal esophageal epithelium tissues ($P < 0.0001$; Table 3). The expression of MET protein was localized in the cytoplasm and cell membrane of tumor cells (Fig. 3).

**The Clinicopathological Features Associated with Overexpression of the MET Gene.** The clinicopathological features of cases showing MET overexpression and negative cases of primary ESCC were compared in Table 4. MET overexpression had significant correlation with ESCC differentiation ($P < 0.0001$) but had no relationship with the patient gender, age, tumor size, site, or stage (Table 4). The well/moderately differentiated ESCC showed more intense expression of MET than poorly differentiated ones ($P < 0.0001$; Table 3).

**DISCUSSION**

We have demonstrated previously that the cDNA arrays is a very powerful tool for identifying differentially expressed genes in ESCC (6), because this approach permits the investigation of hundreds of genes simultaneously in one experiment. In the current study, we have used the Human Cancer cDNA Expression Arrays to specifically study the global differential expression of cancer-related genes in two human ESCC cell lines (HKESC-1 and HKESC-2). We have identified 18 cancer-related genes differentially expressed in both of these ESCC cell lines, 13 of which were up-regulated $\geq$2-fold (CDC25B, cyclin D1, PCNA, MET, Jagged 2, Integrin $\alpha$3, Integrin $\alpha$6, Integrin $\beta$4, Caveolin-2, Caveolin-1, MMP13, MMP14, and BIGH3) and 5 of which were down-regulated $\geq$2-fold (CK4, Bad, IGFBP2, CSPCP, and IL-1RA) in both ESCC cell lines at mRNA level. These results of the up-regulation of CDC25B and cyclin D1 genes in ESCC obtained in this study confirmed our earlier results on the overexpression of these genes in ESCC, which were obtained using Atlas Human cDNA expression arrays (6). Subsequent RT-PCR analysis of 9 of these differentially expressed genes including MET, Jagged 2, MMP-13, MMP-14, BIGH3, CK4, CSPCP, and IL-1RA confirmed the differential profiles uncovered by Human Cancer cDNA arrays hybridization.

Some of these differentially expressed genes identified here have been reported previously to be implicated in the pathogenesis of other malignancies or esophageal cancer. For example, it is well known that cyclin D1 is a key cell cycle regulator in the G1 to S phase progression; through a complex with CDK4, it phosphorylates and inactivates retinoblastoma
gene protein. The abnormalities of proto-oncogene cyclin D1 have been implicated in the tumorigenesis of numerous tumor types including ESCC (11). Previously, overexpression and/or amplification of cyclin D1 has been consistently found in ESCC (11–13). In this study, the mRNA of cyclin D1 showed overexpression in the two ESCC cell lines. These indicate that cyclin D1 overexpression is a very common molecular event in ESCC and may play an important role in the carcinogenesis of ESCC. In addition, our Cancer Array hybridization results demonstrated that several genes related to cell adhesion and invasion were overexpressed in HKESC-1 and HKESC-2. Although integrin α6 has been shown to be overexpressed in esophageal cancer (14), the expression of integrin α3, integrin β4, MMP13, or MMP14, to our knowledge, has not been reported before in ESCC. The integrins are major adhesion-receptor proteins that mediate cell migration and invasion. The MMP family has been shown to be involved in proteolytic degradation of the extracellular matrix to enhance tumor cell movement. The identification of these novel molecular alterations provided promising targets for assessment of invasion and metastatic potential of ESCC in the future.

MET oncogene was originally identified as a tumor-transforming gene (15, 16). It is located on chromosome 7q31 (15). This oncogene encodes a Mr 190,000 tyrosine kinase receptor for hepatocyte growth factor (17). A vast body of clinical and experimental data has demonstrated that the MET oncogene plays a crucial role in tumorigenesis of many tumors. MET gene has been found to be overexpressed in thyroid carcinomas (18, 19), gastric carcinomas and colorectal carcinomas (18, 19), ovarian carcinomas (20), endometrial carcinomas (21), pancreatic carcinomas (22, 23), renal cell carcinomas (24, 25), breast carcinomas (26–28), and prostatic carcinomas (29). These findings suggested that increased expression of the MET oncogene in human tumors might confer a selective growth advantage to tumor cells. However, information about MET expression in ESCC is very limited. An earlier study has indicated that MET mRNA was overexpressed in ESCC (30), but there has been no information about MET expression at the protein level in ESCC.

In this study, the Human Cancer cDNA arrays hybridization revealed that oncogene MET mRNA was expressed at a much higher level in ESCC than in normal tissue. Subsequent RT-PCR analysis additionally confirmed the findings from the Cancer cDNA arrays. With IHC, the majority of ESCC (56/61, 92%) was found to have significantly enhanced expression of MET compared with morphologically normal esophageal epithelium (P < 0.0001). Also, the findings provided additional evidence that MET mRNA was overexpressed during the development of ESCC.

In the current study, there was significant correlation between MET overexpression and ESCC differentiation (P < 0.0001). The well- or moderately differentiated ESCC had much more elevated MET expression than the poorly differentiated ones. This is in keeping with previous findings in other tumors (20, 31, 32). Di Renzo et al. (20) found MET to be most overexpressed in differentiated ovarian carcinomas. Huntsman et al. (31) observed that MET expression was enhanced in most benign ovarian tumors and appeared to be maximally overexpressed in borderline tumors and well-differentiated ovarian carcinomas. In renal cell carcinoma, a close relationship was observed between MET overexpression and the chromophophil subtype with a papillary growth pattern (32). However, in a number of tissues, MET becomes increasingly overexpressed as tumors become poorly differentiated (33). These combined findings suggest that the relationship of MET expression to tumor differentiation seems to vary among different tumor types.

In this study, MET protein was found to be overexpressed in both ESCC cell lines (HKESC-1 and HKESC-2) and the primary tumors from which these cell lines were established. This demonstrated that MET protein is overexpressed in vitro and in vivo in ESCC. More extensive examination in 61 cases of surgically resected ESCC samples provided additional evidence that the majority of ESCC tumors had MET overexpression in the natural history of ESCC development. The MET oncogene can be activated by overexpression (17), gene rearrangements (15), or mutations (34). Thus, the observed MET overexpression in ESCC in this study can be presumed to lead to MET activation and play a role in the pathogenesis of ESCC.

In conclusion, 18 cancer-related genes of 588, including MET, were identified to be differentially expressed in HKESC-1 and HKESC-2. Among these for the first time MET protein was...
noted to be overexpressed in ESCC as compared with morphologically normal esophageal epithelium tissues, and the overexpression of MET was found to correlate with tumor differentiation in ESCC. These findings suggest that the activation of MET oncogene via overexpression might be important in the pathogenesis of ESCC.

REFERENCES

Profiling of Differentially Expressed Cancer-related Genes in Esophageal Squamous Cell Carcinoma (ESCC) Using Human Cancer cDNA Arrays: Overexpression of Oncogene MET Correlates with Tumor Differentiation in ESCC

Ying Chuan Hu, King Yin Lam, Simon Law, et al.


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