Is Xenotransplantability of Human Colon Cancers in SCID Mice Affected by Angiogenic Factors?

Human malignant tumors transplanted in SCID (severe combined immunodeficiency) mice retain their original characteristics, such as histology (1), cytokine production (2,3), karyotype, and sensitivity to anticancer agents. This in vivo system has provided an opportunity to study viable human malignant cells without limitations on material supply. Since Rygaard and Povlsen (4) reported the successful transplantation of human malignant tumors into nude mice, various types of human tumors have been maintained in these animals. Although this system has enabled us to establish certain human malignant tumors as xenografts, only transferable tumors are serially maintained as xenograft tumors. It is not clearly understood what key properties and molecules of donor tumor lead to successful establishment of xenografts.

Vascular endothelial growth factor (VEGF) has been studied as a strong inducer of angiogenesis (5). VEGF plays an important role in neovascularization of various kinds of neoplasms. Four different isoforms of VEGF transcripts encoding polypeptides of 206, 189, 165, and 121 amino acids have been reported, and these isoforms possess different biologic activities. In our previous study, the cell-associated isoform VEGF189 was shown to be strongly associated with distant metastasis in human colon cancer (6). The factors that modulate angiogenesis are also probably associated with xenotransplantability. It has not been well defined how various angiogenic factors affect the xenotransplantability of human malignant tumors. We analyzed levels of expression of such factors as VEGF, thrombospondin 1 (TSP1), and TSP2 in human primary colon cancers in relation to their xenotransplantability in SCID mice. We also studied gene expression of VEGF receptor flt-1, KDR, TSP1 receptor (TSP1R)/CD36, and transforming growth factor-β (TGFβ). Activated K-ras oncogene and p53 accumulation were co-evaluated.

From October 1989 through October 1991, 35 primary colon cancers had been obtained by surgery and inoculated subcutaneously into SCID mice. Successful xenografts were obtained from 19 (54.3%) of these 35 cancers, and all established xenografts yielded serial transplants. The specimens showing cell-associated isoform VEGF189 were established as xenografts at a significantly higher incidence (13 of 19, 68.4%) than those (four of 16, 25.0%) lacking VEGF189 (P = .011; chi-squared test; Table 1). The transplantability was not significantly correlated

Table 1. Univariate analysis of the associations between xenotransplantability and angiogenesis-related factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Established</th>
<th>Failed</th>
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<tr>
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<td>8</td>
<td>10</td>
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<tr>
<td>No</td>
<td>6</td>
<td>3</td>
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*All P values (except for p53 accumulation) are two-sided and were derived using the chi-squared test; p53 accumulation was analyzed by Fisher’s test.
†Abeartan vascular endothelial growth factor (VEGF) expression was significantly correlated with xenotransplantability of colon cancer.
with expression of flt-1, KDR, TSP1, TSP2, TSP1 receptor (TSP1R)/CD36, or TGFβ1. There were no correlations between xenotransplantability and levels of expression of total VEGF, TSP1, activated K-ras oncogene or p53 accumulation. Pathologic features, including histologic differentiation, histologic type, degree of venous, or lymphatic invasion of tumor, did not show clear associations with xenotransplantability. Taken together, these results indicated that VEGF189 plays an important role in xenotransplantation in colon cancer. The factors present in human cancer stroma (flt-1, KDR, TSP1, TSP2, or TSP1R) do not affect xenotransplantability, whereas cancer cell-associated factors, such as VEGF preserved in xenografts, determine transplantability. The xenograft/SCID system can be used to evaluate donor cancer cells that should retain their original characteristics, including production of VEGF189 but not stromal cells. In conclusion, the xenotransplantability of human colon cancer in SCID mice is affected by cell-associated angiogenic factors.

TETSUJI TOKUNAGA
MASATO NAKAMURA
YOSHIO OSHIKA
YASUYUKI OHNISHI
YOSHIITO UEYAMA

References


Notes

Affiliations of authors: T. Tokunaga, M. Nakamura, Y. Oshika, Department of Pathology, Tokai University School of Medicine, Isehara, Kanagawa, Japan; Y. Ueyama, Tokai University School of Medicine, Isehara, Kanagawa, and Central Institute for Experimental Animals, Kawasaki, Kanagawa; Y. Ohnishi, Central Institute for Experimental Animals, Kawasaki, Kanagawa.

Correspondence to: Masato Nakamura, M.D., Department of Pathology, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa, 259–1193, Japan.

Erratum: “Indoor Radon Exposure and Risk of Lung Cancer: a Nested Case–Control Study in Finland,” by Auvinen et al. [J Natl Cancer Inst 1996;88:966–72 (Issue 14)]. The authors report the following:

We made an error (misspecified conditional logistic regression model) that affectet all the matched results in the analysis of our previously published article (1). We have therefore reanalyzed the data. The revised results from the matched analysis are shown in the revised Tables 3–5. Unmatched results were not affected.

In general, all the odds ratios tend to be larger and confidence intervals wider compared with the incorrect results. However, the differences are not substantial (e.g., the significance levels remain unchanged); hence the conclusions are not fundamentally changed.

When the radon concentration was stratified, only the category with the highest radon concentration (≥10.8 pCi/L or ≥400 Bq/m³) suggested some elevation of risk (odds ratio = 2.7; 95% confidence interval = 0.8–9.2), even though the confidence intervals were wide and included unity (i.e., no risk elevation). This group also strongly influenced the linear risk estimate.

The revised risk estimates are consis-

### Revised Table 3. Unadjusted odds ratios (95% confidence intervals) by risk factor from matched analysis

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No. of case subjects</th>
<th>No. of control subjects</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking status</td>
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<tr>
<td>Never smokers</td>
<td>44</td>
<td>229</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>207</td>
<td>208</td>
<td>7.50 (4.18–13.5)</td>
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<tr>
<td>Current smokers</td>
<td>266</td>
<td>80</td>
<td>32.2 (17.2–60.3)</td>
</tr>
<tr>
<td>Intensity of cigarette smoking, cigarettes per day*</td>
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<tr>
<td>1–10</td>
<td>57</td>
<td>33</td>
<td>20.0 (9.72–41.2)</td>
</tr>
<tr>
<td>11–20</td>
<td>148</td>
<td>39</td>
<td>33.9 (17.1–67.0)</td>
</tr>
<tr>
<td>≥21</td>
<td>61</td>
<td>8</td>
<td>66.5 (25.8–172)</td>
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<td>Duration of cigarette smoking, y*</td>
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<tr>
<td>1–20</td>
<td>26</td>
<td>18</td>
<td>20.1 (6.69–66.0)</td>
</tr>
<tr>
<td>21–40</td>
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<td>5</td>
<td>33.2 (14.3–77.4)</td>
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<td>≥41</td>
<td>230</td>
<td>57</td>
<td>30.4 (15.8–58.4)</td>
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<td>Age at start of cigarette smoking, y*</td>
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<td>&lt;16</td>
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<td>47.6 (21.2–107)</td>
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<td>≥16</td>
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<td>74</td>
<td>14.3 (7.62–23.5)</td>
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<tr>
<td>Cigar smoking</td>
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<tr>
<td>Never smokers</td>
<td>43</td>
<td>228</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>Cigars only</td>
<td>460</td>
<td>284</td>
<td>15.2 (8.65–26.7)</td>
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<td>Cigar and cigarettes</td>
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<td>4</td>
<td>28.8 (7.80–106)</td>
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<td>Passive smoking</td>
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<td>Never smokers with passive smoking</td>
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<td>0.69 (0.28–1.74)</td>
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<td>81</td>
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<td>Occupational asbestos exposure</td>
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<td>1.00 (referent)</td>
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<tr>
<td>Ever</td>
<td>102</td>
<td>70</td>
<td>1.55 (1.12–2.16)</td>
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</table>

*Among current smokers, with never smokers as reference.