Evidence for an Increased Somatomedin-C/Insulin-like Growth Factor I Content in Primary Human Lung Tumors

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ABSTRACT

Immunoreactive somatomedin-C/insulin-like growth factor I (SM-C/IGF I) content was measured in human neoplastic lung tissue obtained from surgery on 10 patients (seven epidermoid carcinoma, three adenocarcinoma), and in normal lung tissue obtained from the same excised portion. SM-C/IGF I content in lung tumors was 615 ± 123 (SE) milliunits/g of tissue (range, 214–1531), significantly higher (P < 0.01) than normal tissue (234 ± 51 milliunits/g of tissue; range, 37–537); in particular, every subject showed a clear-cut difference of SM-C/IGF I content between neoplastic and normal tissue (ratio, 3.41 ± 0.69; range, 1.4–7.2). The results were essentially unchanged when data were expressed relative to hemoglobin or DNA tissue content. By contrast, in peripheral plasma SM-C/IGF I concentration was 0.51 ± 0.17 units/ml, significantly lower (P < 0.01) than in 59- to 70-yr-old control subjects (1.10 ±0.13 units/ml). In conclusion, the lung tumors studied, irrespective of their histological structure, contain more SM-C/IGF I than does normal tissue. Whether this is due to a primary in situ production of SM-C/IGF I or is secondary to overproduction of other inducers such as platelet derived growth factor-like peptides is yet to be clarified. The reduced circulating SM-C/IGF I concentration seems to be related more to the nutritional status of the patients.

INTRODUCTION

Somatomedin/insulin-like growth factors are a family of growth hormone-dependent peptide hormones homologous with insulin which stimulate in vivo and in vitro cell replication. Among them SM-C/IGF31 has been fully characterized in its chemical structure (1) and has been shown to be not only strictly related to skeletal growth but has also been observed to be a critical progression factor on cultured fibroblasts, which have been previously rendered competent by other growth factors such as PDGF or fibroblast growth factor (2–4).

Although traditionally SM-C/IGF I was considered to originate in the liver (5–7), it has been recently observed that explant cultures from a variety of fetal mouse organs release SM-C/IGF I in the culture medium (8) and that adult rat tissues obtained from different organs (particularly lung) contain significant amounts of SM-C/IGF I (9). Furthermore it has been shown that SM-C/IGF I is synthesized by cultured human and rat fibroblasts (10–13). These findings suggest that SM-C/IGF I is ubiquitously synthesized and besides its action on skeletal growth may act through paracrine or autocrine mechanisms, with its biological action at or near its site of origin.

It has also been observed that malignant cells require less of exogenous growth factors than do their normal counterparts for optimal growth, suggesting that transformed cells might self-produce the amount of growth factors that they require (14, 15). Moreover, specific membrane receptors for epidermal growth factor have been found in five of six non-small cell lines of human lung cancer (16) and in biopsy specimens of human squamous cell carcinomas of the lung (17). In light of these findings, by measuring its content in normal and neoplastic tissue, we studied the possibility that primary lung tumors may produce increased amounts of SM-C/IGF I.

MATERIALS AND METHODS

Neoplastic lung tissue was obtained from surgery on ten patients affected with primary lung tumors who were submitted to pneumonectomy or lobectomy. Clinical data of the patients are reported in Table 1. At the same time a fragment of normal tissue was obtained from the excised portion as most distant as possible from the tumor mass. The samples were immediately weighed and stored in liquid nitrogen, then pulverized by a tissue pulverizer (Grindomat MM-Retsch). SM-C/IGF I was also measured in peripheral plasma of the same patients.
Table 1
Clinical data of subjects studied

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (Yr)</th>
<th>Stage of Disease</th>
<th>Histological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>60</td>
<td>IA: T2, N0, M0, G2</td>
<td>Epidermoid carcinoma</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>69</td>
<td>II: T2, N1, M0, G3</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>62</td>
<td>IV: T3, N0, M1, G2</td>
<td>Epidermoid carcinoma</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>73</td>
<td>IA: T2, N0, M0, G2</td>
<td>Epidermoid carcinoma</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>57</td>
<td>III: T2, N0, M0, G2</td>
<td>Epidermoid carcinoma</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>59</td>
<td>IA: T1, N0, M0, G2</td>
<td>Epidermoid carcinoma</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>71</td>
<td>IA: T1, N0, M0, G2</td>
<td>Epidermoid carcinoma</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>69</td>
<td>IB: T1, N1, M0, G2</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>74</td>
<td>IV: T3, N0, M1, G1</td>
<td>Epidermoid carcinoma</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>48</td>
<td>III: T3, N2, M0, G2</td>
<td>Adenocarcinoma</td>
</tr>
</tbody>
</table>

RESULTS

SM-C/IGF I content in lung tumors was 615 ± 123 (SE) milliunits/g of tissue (range, 214–1531), significantly higher (P < 0.01) than in control tissue (234 ± 51 milliunits/g; range, 37–537); in particular all subjects evidenced a clear-cut difference of SM-C/IGF I content between neoplastic and normal tissue, this being that the ratio between the paired two values was always greater than 1 (3.41 ± 0.69; range, 1.4–7.2) (Fig. 1). Tissue concentration observed in stage I patients was lower than in patients in a more advanced stage in both neoplastic (422 ± 151 and 768 ± 202, respectively) and normal lung tissue (109 ± 25 and 292 ± 72). The linear regression analysis showed a significant correlation between the values recorded in the same subjects in control and in affected tissues (r = 0.69; P < 0.05) (Fig. 2). The difference was even more evident when the data were related to the hemoglobin concentration. Relative to DNA, SM-C/IGF I content was higher in neoplastic tissue with respect to paired control in seven of nine subjects, in spite of a higher DNA concentration in neoplastic tissue (Table 2). Immunoreactive SM-C/IGF I recovered from G-50 gel filtration showed parallel results, being always over 90% of the value observed after acid extraction. Iodinated SM-C/IGF I added in the pulverized sample was immunoprecipitated in the same amount in normal and neoplastic tissue (23.92 and 24.20%).

In peripheral plasma SM-C/IGF I concentration was 0.51 ± 0.17 units/ml, significantly (P < 0.01) lower than in 20 normal controls of age range 59–80 yr (1.10 ± 0.13 units/ml). The values observed were unrelated to both neoplastic and normal tissue peptide content (r = -0.08). The concentration in the lobar artery in the three subjects studied (0.52, 0.20, and 0.35 units/ml) was

Fig. 1. Immunoreactive somatomedin-C content in unaffected (control) and neoplastic lung tissue. mU, milliunits.

Fig. 2. Correlation between immunoreactive somatomedin-C content in unaffected (control) and neoplastic lung tissue. mU, milliunits.
SM-C/IGF I AND LUNG TUMORS

Table 2

SM-C/IGF I concentration in control and in neoplastic lung tissue extracts (expressed relative to tissue weight or to its hemoglobin or DNA content), and in peripheral plasma.

Only significant Ps are reported.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control tissue</th>
<th>Neoplastic tissue</th>
<th>Plasma (units/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>milliunits/g tissue</td>
<td>milliunits/mg hemoglobin</td>
<td>milliunits/mg DNA</td>
</tr>
<tr>
<td>Stage I</td>
<td>123</td>
<td>143</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>52</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>158</td>
<td>149</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>349</td>
<td>201</td>
<td>486</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>158 ± 52</td>
<td>154 ± 30</td>
<td>174 ± 108</td>
</tr>
<tr>
<td>P versus control</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

The data reported here show that in accord with the findings of D’Ercole et al. (9), normal lung tissue contains immunoreactive SM-C/IGF I. In neoplastic tissue the SM-C/IGF I content was clearly enhanced, irrespective of whether the values were related to weight, hemoglobin, or DNA content. It is impossible on the basis of the data available to clarify whether this increased SM-C/IGF I content is peculiar to the neoplastic cells or is due to the production of the interstitial cells. That these results were not due merely to a difference in SM-C/IGF I degrading activity in normal versus tumor tissue is demonstrated by the fact that iodinated SM-C/IGF I added prior to the extraction was immunoprecipitated in amounts similar to that of the two tissues. The SM-C/IGF I concentration relative to hemoglobin content excludes the possible interference of the different vascularization between normal and neoplastic tissue.

The finding of an increased peptide content could be explained on the basis of an enhanced in situ production of SM-C/IGF I or to increased uptake of circulating somatomedin. Most subjects, however, exhibited a SM-C/IGF I content per gram of tissue higher than that of the circulating concentration. Moreover while the circulating SM-C/IGF I concentration was in general lower in subjects in more advanced stages of the disease, the contrary was observed regarding tissue somatomedin concentration. These data and the fact that related to hemoglobin content the difference between normal and neoplastic tissue was even more evident seem to support the first hypothesis. The reduced circulating SM-C/IGF I concentration, particularly evident in subjects in more advanced stages, confirms the data reported by Marek and Schreibero (20), and could be explained on the basis of impaired nutritional status. It has been clearly shown by Isley et al. (21) that SM-C/IGF I concentration is reduced in undernutrition and that its concentration is restored on recovery.

It was surprising to note a significant correlation between SM-C/IGF I content in neoplastic and the corresponding normal tissue, in spite of the fact that during the collection of samples we were aware of possible cell dissemination around the tumoral tissue. For this reason normal samples were always collected as distant as possible from the tumor mass. An interpretation for this finding is that SM-C/IGF I or an unknown SM-C/IGF I inducer, overproduced in the tumoral mass and was spread around in a much larger area by interstitial or lymphatic diffusion. Although we could not test other organs, the fact that SM-C/IGF I was not increased in the systemic circulation and that in the three subjects tested the arteriovenous gradient was small suggests that this phenomenon has a local or intraorgan diffusion.

In conclusion, the lung tumors studied, irrespective of their histological structure seem to contain more SM-C/IGF I than does normal tissue. Whether this is due to a primary in situ production of SM-C/IGF I or is secondary to overproduction of other inducers such as PDGF-like peptides is yet to be clarified. Evidence has accumulated in recent years that PDGF or a closely related molecule is synthesized and released by certain human tumor cells in culture (22) and that growth and spread of cancer is stimulated by blood coagulation reactions (23, 24). In addition, it has been shown that PDGF is a potent stimulator of SM-C/IGF I synthesis (12). Therefore the finding of an increased SM-C/IGF I content in lung tumors could be due to primary in situ production or to overproduction of other inducers such as PDGF.

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