Tumor profiles of brain metastases from NSCLC, breast cancer and melanoma

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Abstract #2060

Background: An estimated 70,000 diagnoses of brain metastases (BM) occur each year in the U.S., with an incidence of 5-7% in breast and melanoma and 20-45% in lung cancer. Despite its prominence, the biology of BM remains poorly understood. Several theories of BM development exist, including the linear progression model, which suggests that the metastatic capabilities of tumor cells develop at primary sites following the accumulation of alterations. The parallel progression model argues that tumor cells disseminate early and accumulate changes independently at the secondary site. We compare the tumor profiles of BM from common cancers to understand the biology and to identify differential treatment strategies.

Methods: Tumor samples were profiled using a multiparameter service (Caris Life Sciences, Phoenix, AZ), including sequencing (Sanger, NGS), protein expression (IHC) and amplification (ISH).

Results: 5391 NSCLC (931 BM, 5089 lung), 3956 breast cancer (98 BM, 3496 breast) and 761 melanoma (101 BM, 660 skin) unpaired samples were included. No significant differences were found in 48 genes between BM and the primary tumor sites, with the exception of PDK2 in breast cancer, which was mutated less in BM vs. the breast samples (10% vs. 26%, p = 0.02). In contrast, expression of TOP2A, TOPO1 and TS, and amplification of EGFR, were more prevalent in BM compared to the primary sites (table).

<table>
<thead>
<tr>
<th>Gene</th>
<th>BM</th>
<th>Primary</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOP2A</td>
<td>45</td>
<td>25</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TS</td>
<td>38</td>
<td>7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EGFR</td>
<td>82</td>
<td>33</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Conclusions: A similar genetic landscape with limited differences was seen in BM of NSCLC, melanoma and breast cancer compared to primary tumors. The limited differences are more consistent with a linear progression model in BM of NSCLC, melanoma and breast cancer compared to primary tumors.

Results

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Specimen site</th>
<th>Average age</th>
<th>Age range</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>65</td>
<td>31-91</td>
<td>Female 94%</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>61</td>
<td>23-97</td>
<td>Female 95%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>78</td>
<td>101</td>
<td>Female 36%</td>
</tr>
</tbody>
</table>

Figure 1: Percentages of brain metastases in the complete cohorts of NSCLC, breast cancer and melanoma tumors.

<table>
<thead>
<tr>
<th>BM Treatment</th>
<th>Breast cancer BM</th>
<th>NSCLC BM</th>
<th>Melanoma BM</th>
</tr>
</thead>
</table>
| 1. EGFR gene amplification frequency was higher in BM than tumors taken at the primary sites in all three cancer types. This difference is significant in breast cancer.

2. The significant overexpression of TOP2A protein in BM seen in all three cancer types suggests a potential therapeutic target.

3. An estimated 70,000 diagnoses of brain metastases (BM) occur each year in the U.S., with an incidence of 5-7% in breast and melanoma and 20-45% in lung cancer. Despite its prominence, the biology of BM remains poorly understood.

4. Several theories of BM development exist, including the linear progression model, which suggests that the metastatic capabilities of tumor cells develop at primary sites following the accumulation of alterations. The parallel progression model argues that tumor cells disseminate early and accumulate changes independently at the secondary site.

5. We compare the tumor profiles of BM from common cancers to understand the biology and to identify differential treatment strategies.

6. Tumor samples were profiled using a multiparameter service (Caris Life Sciences, Phoenix, AZ), including sequencing (Sanger, NGS), protein expression (IHC) and amplification (ISH).

7. 5391 NSCLC (931 BM, 5089 lung), 3956 breast cancer (98 BM, 3496 breast) and 761 melanoma (101 BM, 660 skin) unpaired samples were included. No significant differences were found in 48 genes between BM and the primary tumor sites, with the exception of PDK2 in breast cancer, which was mutated less in BM vs. the breast samples (10% vs. 26%, p = 0.02). In contrast, expression of TOP2A, TOPO1 and TS, and amplification of EGFR, were more prevalent in BM compared to the primary sites (table).

8. The solid star indicates that the comparison remains statistically significant after correction for multiple comparisons; empty stars indicate comparisons that are significant by Fisher-Exact test, but no longer significant after correction for multiple comparisons.

Results: Figure 2: Protein overexpression and gene amplification frequencies in brain metastases and tumors at the primary sites. Sample-size specific estimates of binomial proportions are compared with a z-test correction for multiple comparisons; empty stars indicate comparisons that are significant by Fisher-Exact test, but no longer significant after correction for multiple comparisons.

Results: Figure 3: Mutation frequencies in brain metastases and tumors taken from the primary sites for NSCLC, breast cancer and melanoma. The solid star indicates that the comparison remains statistically significant after correction for multiple comparisons; empty stars indicate comparisons that are significant by Fisher-Exact test, but no longer significant after correction for multiple comparisons.

Conclusions

1. The significant overexpression of TOP2A protein in BM seen in all three cancer types suggests a potential therapeutic target.

2. EGFR gene amplification frequency was higher in BM than tumors taken at the primary sites in all three cancer types. This difference is significant in breast cancer.

3. The significant overexpression of TOP2A protein in BM seen in all three cancer types suggests a potential therapeutic target..

References


3. In breast cancer, Her2 overexpression and gene amplification is higher in the BM while hormone receptor expression is lower in BM.

4. In breast cancer, 6 in NSCLC and 2 in melanoma.

5. 1 patient with Her2+ disease, no change in HR status was observed compared to the primary; In 1 patient with PR+ disease in the primary, the BM tumor was triple negative.

6. In 1 patient with ER+/PR+ disease, the BM tumor was ER negative; In 1 patient with Her2+ disease, no change in HR status was observed compared to the primary.