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% 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 multiplatform service (Caris Life Sciences, Phoenix, AZ), including sequencing (Sanger, NGS), protein expression (IHC) and amplification (ISH).
Results: 5391 NSCLC (293 BM, 5098 lung), 3595 breast cancer (99 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 PIK3CA 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 as compared to the primary sites (table).

	Brain met %	Primary %	P
NSCLC			
TOPO2A	75	55	< 0.01
TOPO1	64	55	0.02
TS	35	22	< 0.01
EGFR FISH	36	28	ns
Breast			
TOPO2A	78	50	< 0.01
TOPO1	78	63	< 0.01
TS	39	28	0.04
EGFR FISH	31	14	< 0.01
Melanoma			
TOPO2A	76	46	< 0.01
TOPO1	61	57	ns
TS	56	45	ns
EGFR FISH	50	6	< 0.01

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 of cancer metastasis. Additionally ,this suggests that both primary tumor and BM would respond to similar chemotherapeutics with the consideration of effective blood-brain barrier-penetrant drugs. Small molecule inhibitors of EGFR could be considered due to increased EGFR amplification and the higher TOP2A, TOPO1 expression prompts consideration of topoisomerase inhibitors like etoposide or irinotecan.

Background

There is a renewed interest in using chemotherapy and biological agents that cross the blood-brain barrier following radiation therapy or radiosurgery in treating cancer patients with brain metastases. A comparison of biomarker profiles in brain metastases with tumors taken from the primary sites would help to understand the molecular events that drive cancer spread into the brain, as well as to identify therapeutic options that may be more effective in treating brain metastases.

Methods

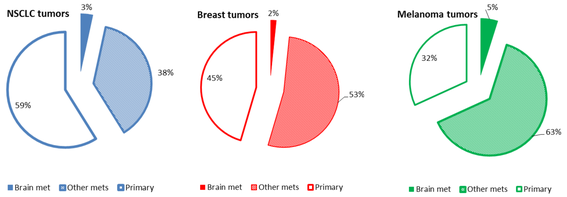
Tumors of NSCLC, breast cancer and melanoma were submitted to Caris Life Sciences (Phoenix, AZ) for tumor profiling analysis aimed to provide theranostic information. Retrospective biomarker analysis was performed on samples submitted from 2009- Jan 2015.
Specific testing included a combination of sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH/FISH).
Statistical analysis was performed using two-tailed Fisher-Exact test, and correction for multiple comparison was done by independent and positive regression dependent test statistics (Benjamini &Hochberg, 1995, J. R. Statis Soc. B)

Results

Table 1: Patient characteristics

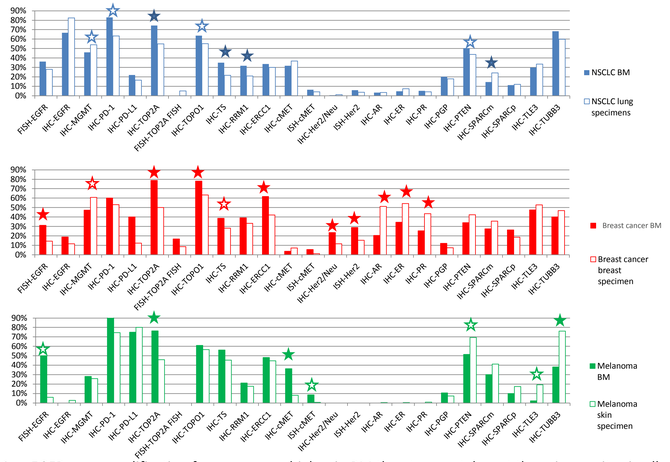
	Specimen site	N	Average age	Age range	Gender
NSCLC	Brain	293	61.0	31-91	Female: 54.9%
	Lung	5098	66.9	19-94	Female: 52.0%
Breast cancer	Brain	99	51.7	31-79	Female 100%
	Breast	3496	55.3	23-97	Female 99.3%
Melanoma	Brain	101	61.6	30-81	Female: 35.3%
	Skin	660	63.5	0-101	Female: 35.6%

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



Results

Figure 2: Protein overexpression and gene amplification frequencies in brain mets and tumors taken from the primary sites. Solid stars indicate comparisons that remain 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.



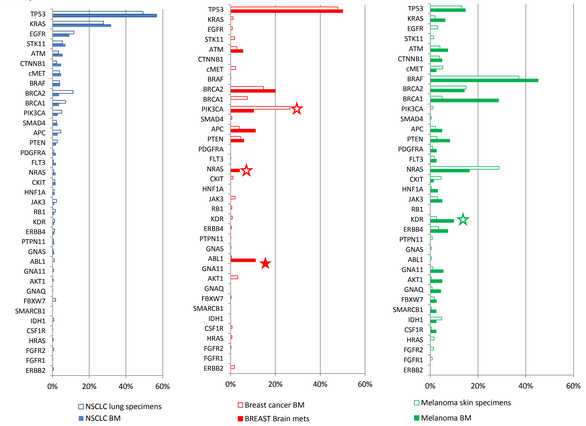
1. EGFR gene amplification frequency was higher in BM than tumors taken at the primary sites in all three cancer types. This difference is significant in breast cancer.
2. Proteins that indicate higher activity of DNA synthesis and cell proliferation (TOP2A, TOPO1 and TS) are overexpressed more frequently in BM than primary tumors. The difference seen in TOP2A is significant in all cancer types.
3. In breast cancer, Her2 overexpression and gene amplification is higher in the BM while hormone receptor expression is lower in BMs.
4. Even though not significant, higher PD-1 expression on TIL is observed in BM in all cancer types; PD-L1 is higher in the BM of NSCLC and breast cancer, but not in melanoma.
5. cMET expression prevalence suggest cMET as an important target in BM in melanoma.

Results: Analysis on paired samples

Paired samples comprising primary tumors and BM collected on a later date were identified: 5 pairs in breast cancer, 6 in NSCLC and 2 in melanoma.
1. Breast cancer: In the three triple-negative pairs, patient 1 had ER stained positive in the BM; patient 2 had TS expression lower in the BM; while patient 3 had increased TOPO1 expression in the BM compared to the primary; In 1 patient with PR+ disease in the primary, the BM tumor was triple negative; In 1 patient with Her2+ disease, no change in HR status was observed
2. NSCLC: TS was low in all 5 primary tumors, but was overexpressed in 3 out of 5 BM. cMET amplification was seen in 1 BM tumor while not in the matched primary tumor. Her2 amplification was lost in one BM while the matched primary tumor was positive.
3. Melanoma: 1 of the 2 pairs showed negative TOP2A staining in the primary sample and positive in the matched BM.

Results

Figure 3: Mutation frequencies in brain mets 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.



Genetic profiles of brain metastases remain largely similar to the primary tumors.
In NSCLC, no difference between BM and primary lung tumors reached statistical significance. In breast cancer, ABL1 mutation is significantly higher in BM. Lower PIK3CA and higher NRAS mutation rates were seen, however no longer significant after correction for multiple comparisons. In melanoma, higher KDR (VEGFR2) mutation was seen in BM, however no longer significant after correction for multiple comparisons.

Conclusions

1. The significant overexpression of TOP2A protein in BM seen in all three cancer types may underlie the success seen in treating patients with BM in these cancer types; similarly, the overexpression of TOPO1 protein in BM may explain the favorable outcome of topoisomerase 1 inhibitor treatments in BM.
2. The significant increase in EGFR amplification in BM prompts the consideration of EGFR-targeted therapies in clinical trials for patients.
3. Increased Her2 aberration by IHC and ISH supports the recent guideline updates in BM treatment in breast cancer.
4. cMET-targeted therapies and angiogenesis inhibitors warrant further investigation in melanoma BM treatments.

References

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