PD-1/PD-L1 and genomic expression profiling of meningiomas

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Abstract

BACKGROUND: Surgery and radiation are the standard treatment options for meningiomas; however, this is not always feasible. Expression profiling was performed to determine the presence of actionable biomarkers and to provide rationale for treatment directed at them.

METHODS: Meningioma patients were profiled by Caris Life Sciences using immunohistochemistry (IHC) to detect PD-1 on tumor-infiltrating lymphocytes and PD-L1 on tumor cells with the SP142 antibody. Next-generation sequencing, pyrosequencing, IHC, fragment analysis, and fluorescence in situ hybridization were used to determine mutational and expression status.

RESULTS: A total of 115 meningioma tumors were analyzed across grades (I: n=22; II: n=36; III: n=30, indeterminate: n=27) among which NextGen sequencing was performed on 76 tumors (63 with TruSeq panel on 45 genes and 16 with Agilent SureSelect panel). The median age of the cohort was 60, with a range spanning 6-90 years; 52% were female. The most frequent mutation (frameshift or truncating) across all grades occurred in the NF2 gene, at 63% (7/11). PD-L1 was expressed in 25% of grade III cases (2/8) but not in grade I or II tumors. PD-1+ T cells were present in 46% (24/52) of meningiomas. TOP2A and thymidylate synthase expression increased with grade (I=5%, II=22%, III=68% and I=5%, II=27%, III=46%, respectively); whereas progesterone receptor expression and the TP53 mutation frequency decreased with grade (I=78%, II=39%, III=30% and I=7%, II=4% and III=0, respectively). Occasionally (1-14%), other mutations were identified in the APC (L1129S), AKT1 (E13K), PIK3CA (H1047R, N345K), FBXW7 (L583X), TP53 (V197E, G112fs), PTCH1 (F88FS), and FOXO3 (L382fs) genes. IDH1/2 mutations were not present.
The most frequently overexpressed genes, regardless of grade, were EGFR (93%; n=44), followed by PTEN (77%; n=110), MRP1 (65%, n=23), PGP (62%; n=84), and then MGMT (55%; n=97).

CONCLUSIONS: If predicated on tumor expression, our data suggest that therapeutics directed toward NF2, EGFR, PTEN, MRP1, PGP, TS and PD-1 could be considered for most meningioma patients.

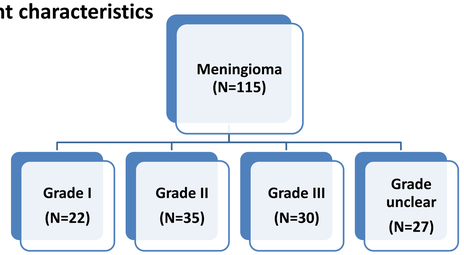
Background

Meningioma is the most common primary tumor of the central nervous system in adulthood. While WHO grade 1 tumors are histopathologically benign, a significant portion may experience recurrence. Furthermore, atypical (grade II) or anaplastic (grade III) meningioma present a more aggressive clinical course with the recurrent tumors often becoming refractory to surgery or radiation.

Genetic alterations including NF2, AKT1 and SMO have been shown to be important in the molecular pathogenesis of meningioma and may serve as therapeutic targets. We aim to use a combination of multiple technologies to interrogate the molecular alterations including protein expression and gene mutations in a large cohort of meningioma that could potentially direct therapy and provide insights to treatment options including chemo-therapeutic, targeted or immune-modulatory agents.

Results

Figure 1: Patient characteristics



Average Age:	**62.8**	**58.3**	**56.9**	**58.0**
Gender F/M%:	**59/41**	**56/44**	**43/57**	**52/48**

- The average age and female prevalence decrease as tumor grade increases; however the differences are not significant.

Results, continued

Figure 2: A) Protein expression frequencies in the 115 meningioma tumors studied; B) Selected protein expression frequencies in grade 1, 2 and 3 meningiomas. A line indicates statistically significant difference found between different grades of tumors (p<0.05).

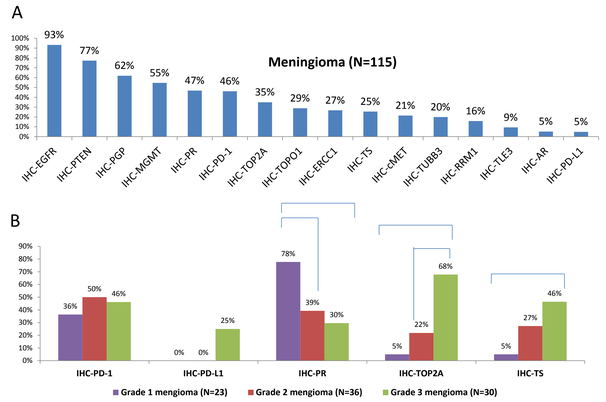
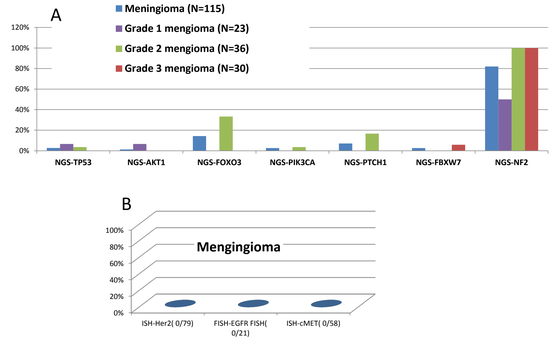


Figure 3: A) Mutation frequencies seen in the meningioma cohorts studied; B) No gene amplification tested by CISH or FISH were seen in the cohort studied.



Results, continued

Table 1: Specific protein changes found in each subgroup of meningiomas

	All Meningioma			Grade I Meningioma			Grade II Meningioma			Grade III Meningioma		
	Mutated (N)	Total N (MT+ WT)	%	Mutated (Protein changes)	Total N (MT+ WT	%	Mutated (Protein changes)	Total N (MT+WT)	%	Mutated (Protein changes)	Total N (MT+ WT)	%
NGS-TP53	2	74	3%	G112fs	15	7%	V197E	28	4%	0	16	0%
NGS-AKT1	1	76	1%	E17K	15	7%	0	28	0%	0	17	0%
NGS-FOXO3	2	14	14%	0	2	0%	2x L382fs	6	33%	0	4	0%
NGS-PIK3CA	2	76	3%	0	15	0%	N345K	28	4%	0	17	0%
NGS-PTCH1	1	14	7%	0	2	0%	F88fs	6	17%	0	4	0%
NGS-FBXW7	2	76	3%	0	15	0%	0	28	0%	L583X	17	6%
NGS-NF2	7	13	82%	F119del	2	50%	c.1120_1122+16del19; Q456X; c.448-1G>A; H304fs; V435fs; K159fs	6	100%	Frameshift; P91fs; F307fs	3	100%

Conclusions

1. There was a high prevalence of NF2 gene amplification in meningioma, especially in grade II and III subgroups supporting the investigation of FAK inhibitors in these tumors.
2. Aberrant activation of PIK3CA/Akt/mTor pathway as shown by PIK3CA/AKT1/FBXW7 mutations and SMO pathways as shown by PTCH1 mutation suggest the opportunities for targeted therapies in select subsets of patients.
3. Significantly elevated TOP2A and TS expression in grade III tumors is in line with the highly aggressive nature of the disease and suggest the potential utility of TOP2A inhibitors but also the lack of utility of fluorpyrimidnes including 5-FU and capecitabine in malignant meningioma.
4. Activation of PD-1/PD-L1 axis support the investigation of immune checkpoint inhibitors.

References

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- Brastianos, P.K., R. Berookhim, et. al. (2013) "Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations" Nat Genet. 2013 March ; 45(3): 285–289