FOXC1 expression in Meningiomas

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Background

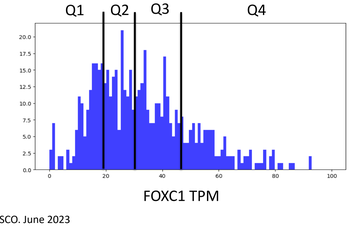
- Meningiomas account for nearly 1/3 of brain tumors and are characterized by a low mutational burden and dysregulation of DNA methylation.
- The promoter of FOXC1 is hypomethylated relative to dura in meningiomas of all grades and knockdown of FOXC1 in murine models causes craniofacial hypoplasia and absent frontal dura, suggesting a role as a meningeal identity gene.
- Here we perform a multi-omic analysis of FOXC1 expression in a large cohort of meningiomas

Methods

- Next-generation DNA sequencing (592 gene NextSeq panel; n = 150 or Agilent WES whole exome sequencing, n = 405) and whole mRNA (WTS, NovaSeq, 555) at Caris Life Sciences (Phoenix, AZ) were performed on 555 meningiomas (148 grade I, 255 grade II and 87 grade III) .
- Top quartile transcripts per million (TPM) for FOXC1 expression were considered high (FOXC1-H) and bottom quartile low (FOXC1-L).
- Immune cell infiltration was estimated using RNA deconvolution by QuantiSeq to calculate median cell fractions (MCF) or positive percentages (PP).
- Data were analyzed using X2/Fisher's-exact/Mann-Whitney U tests. A p-value < 0.05 after BH correction was considered significant.

Results

1: FOXC1 is widely expressed in meningiomas. (Q1: bottom quartile; Q4: top quartile)



	FOXC1 TPM
mean	33.1853
std	18.1827
min	0.296339
25%	19.473
50%	**30.2779**
75%	43.10865
max	118.216

ASCO. June 2023

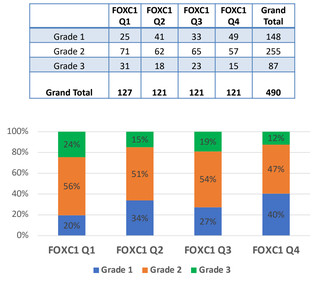
Results

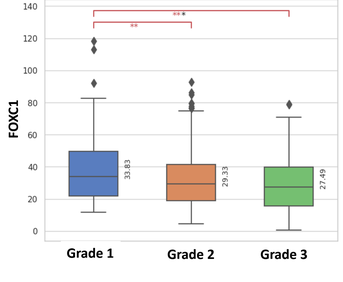
2: There were no significant differences in patient characteristics between FOXC1 expression quartiles.

	FOXC1 Q1	FOXC1 Q2	FOXC1 Q3	FOXC1 Q4	p-value
Count (N)	140	138	138	139	
Median Age [range] (N)	60 [8 - 87]	61.5 [5 - >89]	56 [15 - >89]	55 [2 - >89]	0.082
Female	56.4% (79/140)	60.9% (84/138)	59.4% (82/138)	61.9% (86/139)	0.807
Male	43.6% (61/140)	39.1% (54/138)	40.6% (56/138)	38.1% (53/139)	0.807

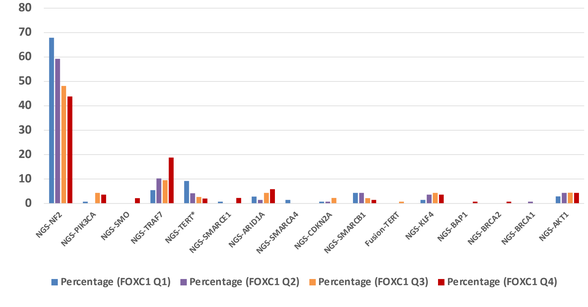
3: FOXC1 expression inversely correlated with WHO histologic grade.

	FOXC1 Q1	FOXC1 Q2	FOXC1 Q3	FOXC1 Q4	Grand Total
Grade 1	25	41	33	49	148
Grade 2	71	62	65	57	255
Grade 3	31	18	23	15	87
Grand Total	**127**	**121**	**121**	**121**	**490**



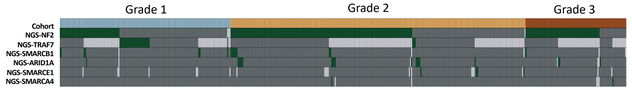


4: NF2 mutations were significantly more common in FOXC1^{low} than FOXC1^{hi} tumors (45% vs. 68%, q < 0.05).

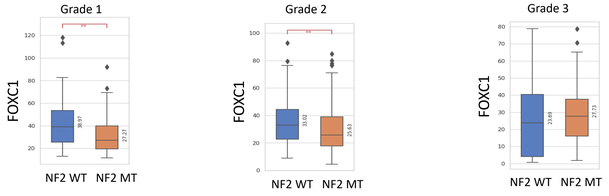


Results

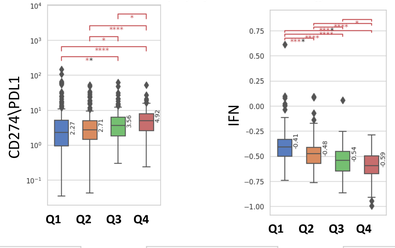
5. In WHO grade I &2 meningiomas, NF2^{wt} meningiomas exhibit higher levels of FOXC1 transcript expression than NF2^{mut} meningiomas.

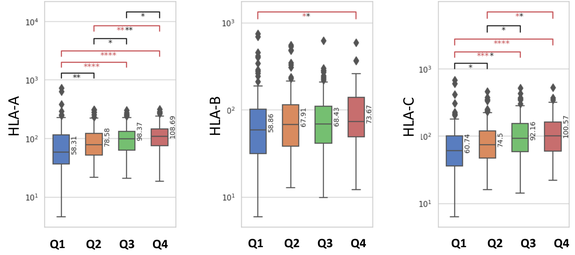


Green: mutation; grey: wildtype, white: no data available



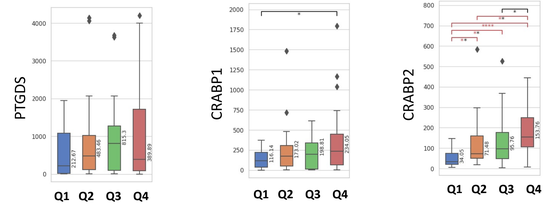
6: Low transcript levels of FOXC1 are correlated with low expression of both PDL1/CD274 and MHC-1 markers HLA-A/B/C) as well as a high interferon gamma signature (IFN).





Results

7: FOXC1 quartiles are correlated with expression levels of the meningeal markers PTGDS, CRAPBP1, and CRABP2.



Conclusions

- The craniofacial patterning transcription factor FOXC1 was found to be widely expressed in a large cohort of meningiomas.
- FOXC1 expression is inversely correlated with WHO tumor grade.
- FOXC1^{low} meningiomas are significantly more likely to harbor NF2 mutations than FOXC1^{hi} meningiomas.
- FOXC1 expression levels are correlated with high expression of other meningeal identify genes suggesting low levels of FOXC1 may represent de-differentiation to a more immature state.
- Multi-omic analysis reveals a significant relationship between FOXC1 transcript levels and key markers of the immune environment including PD-L1 transcript expression.
- Functional studies are warranted to determine whether FOXC1 is necessary for meningioma growth, whether FOXC1 plays a direct immunomodulatory role in meningiomas, and whether the lower FOXC1 expression levels in high grade tumors represent a more embryonic phenotype.

References

- Wedemeyer et al. 2022, Neurooncol Adv "Epigenetic dysregulation in meningiomas"
- Zarballs et al. 2008. PNAS "Cortical dysplasia and skull defects in mice with a Foxc1 allele reveal the role of meningeal differentiation in regulating cortical development."