Multi-Omics and Immune Cell Profiling of Metastatic Uveal Melanomas

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Background

Uveal melanoma (UM) is a rare tumor of the eye which is biologically distinct from cutaneous melanoma (CM). Treatment options for patients with metastatic uveal melanoma (mUM) are limited as mUM tends to be resistant to commonly used treatments for cutaneous melanoma. Therefore, a better understanding of the biology of this tumors is needed in order to develop new treatment options. Therefore, we aimed to examine a multi-omics profile of UM as compared to CM.

Methods

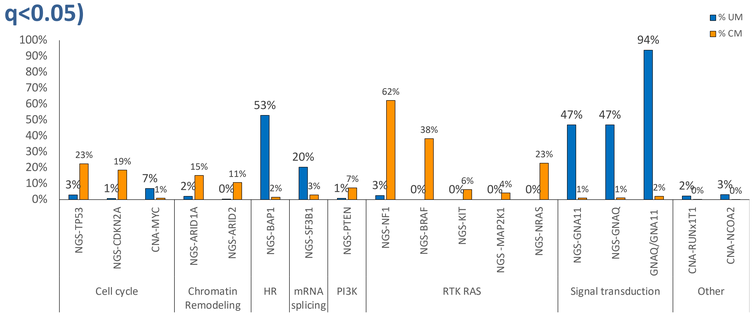
A total of 277 UM and 1,297 CM metastatic or primary samples were analyzed using next-generation sequencing (NextSeq, 592 genes and WES, NovaSeq, >700 genes) and whole transcriptome sequencing (WTS; NovaSeq) (Caris Life Sciences). Tumor mutational burden (TMB) was measured by totaling somatic mutations per tumor (TMB-high cutoff >10 mutations per MB). Immune cell fractions within the tumor microenvironment was estimated using QuantiSeq. T- cell inflamed score was calculated using gene expression data. Pathway gene enrichment analysis using WTS data was performed using GSEA. Biostatistical significance was determined using chi-square/Fisher-Exact or Wilcoxon rank sum test and adjusted for multiple comparisons.

Results

Table 1: Patient demographics for Uveal (UM) and cutaneous melanoma (CM).

Cancer Type	Overall Median age	Female (N)	Median Age Female	Male (N)	Median age Male	Total
Melanoma	67	493	65	804	67	1297
Uveal Melanoma	65	145	64	132	65	277

Figure 1: Significantly different alterations between UM and CM (all q<0.05)



Results

Figure 2: Oncoprint of N=277 UM tumors

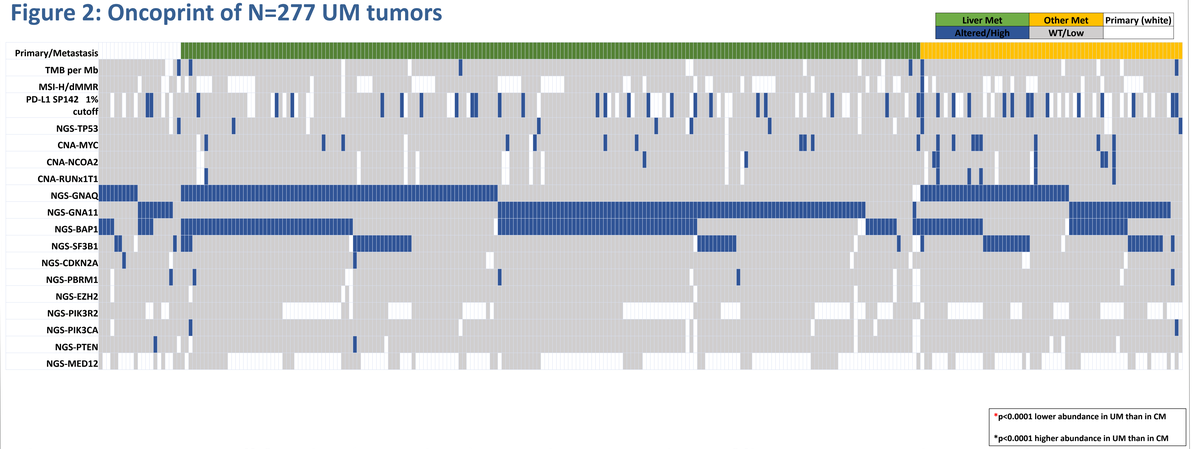


Figure 3a: Immune cell fraction (Quantiseq) assessing comparison of liver metastases in UM and CM.

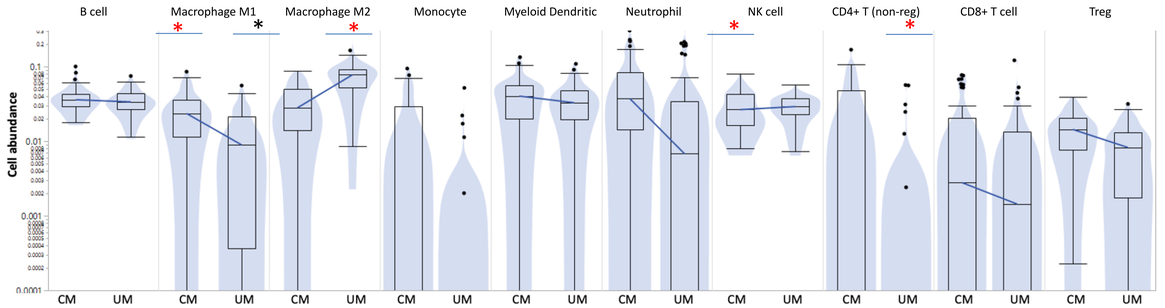
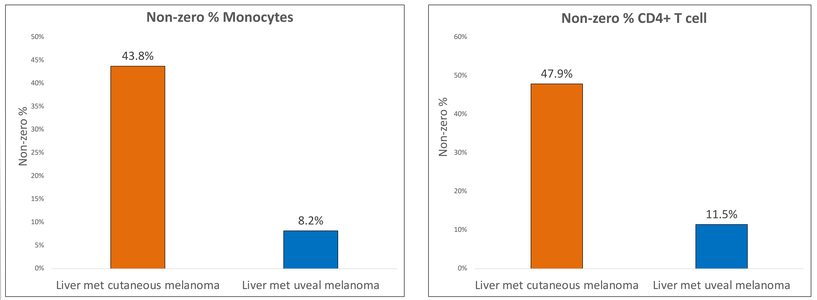
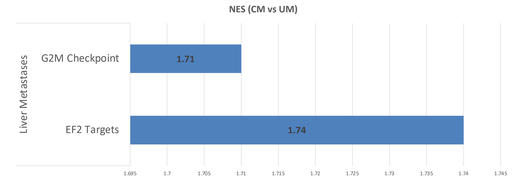


Figure 3b: Immune cell fraction (Quantiseq) assessing comparison of liver metastases in UM and CM showing non-zero % for Monocytes and CD4+ T cell infiltration.



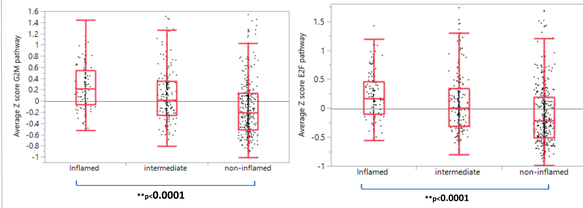
Immune Cell	KW p value Liver Met (UM vs CM)
B cell	0.2462
Macrophage M1	****p<0.0001**
Macrophage M2	****p<0.0001**
Monocyte	****p<0.0001**
Neutrophil	0.0041
NK	0.8739
T cell CD4+ (non-regulatory)	****p<0.0001**
T cell CD8+	0.1696
Tregs	**0.0003**
Myeloid dendritic	0.2511

Figure 4: GSEA comparison of UM and CM liver metastases



	Pathway	NES (CM vs UM)
Liver Met	EF2 Targets	p<0.0001
	G2M Checkpoint	p<0.0001

Figure 5: G2M/E2F Z scores were highest in inflamed and lowest in non-inflamed for CM/UM combined.



Conclusions

- UM compared to CM had a higher rate of GNAQ/11 (93.8% vs. 2.1%), SF3B1 (20.4% vs 3%), and BAP1 (52.9% vs. 1.5%) mutations. UM also had higher levels of MYC (7% vs 0.9%), NCOA2 (3.1% vs 0.1%), and RUNX1T1 genomic amplifications (2.3% vs 0.2%) (all q<0.05).
- Assessing liver metastases only, UM had higher abundance of M2 macrophages but lower abundance of M1 macrophages, monocytes, CD4+ T cells and T regs when compared to CM (all p<0.05).
- GSEA comparison in liver metastases of UM and CM samples showed G2M checkpoint (NES 1.74, p<0.0001) and E2F targets pathway (NES 1.71 p<0.0001) were both higher in CM. No other significant differences were noted.
- When comparing T-cell inflamed, intermediate, and non-inflamed tumors from any site, CM or UM, the average Z scores for both G2M and E2F were highest for inflamed and lowest for non-inflamed, P≤0.0001. A similar trend of higher Z score was seen for TMB high vs TMB low tumors, p≤0.0001. This suggests the G2M checkpoint and E2F targets may contribute/correlate with response to immunotherapy.