Disparity in PD-L1 expression between metastatic Uveal and Cutaneous Melanoma

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Background

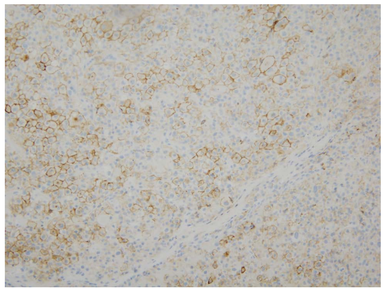
Programmed death-ligand 1 (PD-L1) is expressed by various cells such as dendritic cells and tumor cells [1]. In cancer, tumors evade the immune system by the interaction of PD-L1 with PD-1 receptor on activated T lymphocytes [2]. This interaction forms the basis for the use of PD-1/PD-L1 inhibitors in cancer immunotherapy.

Objective

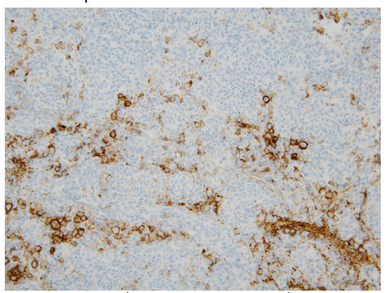
The purpose of this study is to investigate differences in expression of PD-L1 on tumor cells and PD-1 receptor on tumor infiltrating lymphocytes (TILs) between metastatic uveal melanoma (MUM) and metastatic cutaneous melanoma (MCM).

Methods

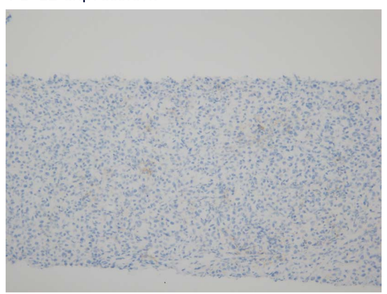
Biopsy specimens of MUM and MCM patients were analyzed for PD-L1 and PD-1 expression at a CLIA-certified lab (Caris Life Sciences). PD-L1 expression on melanoma cells was confirmed using validated, immunohistochemical staining with an anti-PD-L1 antibody (SP142, positivity ≥ 5% membranous staining of tumor cells). PD-1 expression on TILs was confirmed using the anti-PD-1 antibody (MRQ-22, positivity ≥ 1 TILs per high-power field). In total, 106 MCM and 18 MUM specimens were analyzed for PD-L1 expression, while 89 MCM and 17 MUM specimens were tested for PD-1 expression. All specimens that were tested for PD-1 expression were also tested for PD-L1 expression.



A. MCM to the skin, positive membranous PD-L1 expression.



B. MCM to spleen, positive membranous PD-L1 expression.



C. MUM to the liver, no PD-L1 expression.

Table 1. PD-L1 expression on metastatic melanoma

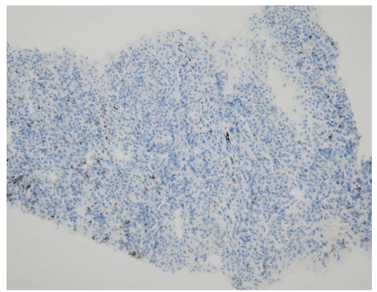
Cutaneous Melanoma			Uveal Melanoma		
Site of metastasis	Number of patients	PD-L1 expression	Site of metastasis	Number of patients	PD-L1 expression
Lymph nodes	33	6/33 (18.2%)	Liver	14	0%
Lungs	17	5/17 (29.4%)	Other**	4	0%
CNS	14	2/14 (14.3%)			
Liver	6	0%			
Skin/subcutaneous	16	5/16 (31.2%)			
Other*	20	4/20 (20%)			
	Total: 106	22 (20.8%)		Total: 18	

*Bone (n=2), spleen (n=2), soft tissue metastasis (n=16) **Bone , mediastinum , lymph node, omentum (n=4)

Table 2. PD-1 expression on TIL

Cutaneous Melanoma			Uveal Melanoma		
Site of metastasis	Number of patients	PD-1 expression	Site of metastasis	Number of patients	PD-1 expression
Lymph nodes	26	20/26 (76.9%)	Liver	13	7/13 (53.8%)
Lungs	15	11/15 (73.3%)	Other**	4	2/4 (50%)
CNS	13	10/13 (76.9%)			
Liver	3	2/3 (66.6%)			
Skin/subcutaneous	13	10/13 (76.9%)			
Other*	19	15/19 (78.9%)			
	Total: 89	68 (76.4%)		Total: 17	

*Bone (n=2), spleen (n=2), soft tissue metastasis (n=15) **Bone , mediastinum , lymph node, omentum (n=4)



D. MCM to the liver, no PD-L1 expression (dark brown=pigment).

Table 3. Correlation between PD-L1 expression and PD-1 expression

	PD-L1 (+) (n=18)	PD-L1 (-) (n=71)
PD-1 (+) (n=68)	18	50
PD-1 (-) (n=21)	0	21

MCM samples tested for both PD-L1 and PD-1 expression (n=89)

	PD-L1 (+) (n=0)	PD-L1 (-) (n=17)
PD-1 (+) (n=9)	0	9
PD-1 (-) (n=8)	0	8

MUM samples tested for both PD-L1 and PD-1 expression (n=17)

Results

The median age of the 106 MCM patients was 62 years (range: 29-88). 70% of these patients were male. The median age of the 18 MUM patients was 60.5 years (range: 32-81); 69% of these patients were male. Overall, 22/106 (20.8%) MCM specimens expressed PD-L1 (Table 1) (Image A,B). The highest rate of expression was seen in lung metastasis and skin metastasis of 29.4% and 31.2% respectively. In comparison, none of the MUM specimens showed PD-L1 expression (Image C), independent of metastasis sites (20.8% vs. 0%; p = 0.04). Interestingly, none of the metastatic **cutaneous** liver lesions (0/6) showed PD-L1 expression (Image D) either. PD-1 expression was seen in 68/89 (76.4%) and 9/17 (53%) of MCM and MUM specimens, respectively (Table 2). No significant difference was seen in PD-1 expression between the two groups (p = 0.09). For the 89 MCM specimens that were tested for both PD-L1 and PD-1 expression, all the specimens that tested positive for PD-L1 were also positive for PD-1 expression (Table 3)

Conclusion

While PD-1 expression was seen in both MUM and MCM, there was a stark difference in PD-L1 expression between them (20.8% vs. 0%; p = 0.04). A complete absence of PD-L1 expression by MUM tumor cells might explain the lack of therapeutic response to PD-1/PD-L1 inhibition and suggests an alternative mechanism via which it evades the immune system.

References

1. Dong, H. et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nature Med. 8, 793–800 (2002)

2. Freeman, G. J. et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J. Exp. Med. 192, 1027–1034 (2000)