Molecular and Clinical Correlates of HER3 expression in Melanoma

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Background

The overexpression of epidermal growth factor receptor family member HER3 has been implicated in several types of cancer, and recently, drugs targeting HER3 have shown promising clinical activity.[1] In melanoma, HER3 overexpression has been linked to both metastasis formation[2] and resistance to drug therapy in cell culture models.[3, 4]

Objectives

Here, we sought to characterise the expression of HER3 in 187 melanoma biopsies across 3 TMA cohorts: the TCGA cutaneous melanoma cohort[5] (n = 70), the mucosal melanoma cohort (n = 38), and a cohort of cutaneous melanoma specimens taken prior to treatment with immune checkpoint blockade (ICB) therapy (pre-ICB cohort) (n = 79).

Methods

We analysed the association between HER3 expression via immunohistochemistry, and molecular, clinical, and pathological variables across three melanoma tumour-micro-arrays (TMAs). Expression was scored using the Ruschoff/Hoffman method. Two expression thresholds were explored: ≥1+ versus 0, and <2+ versus ≥2+ .

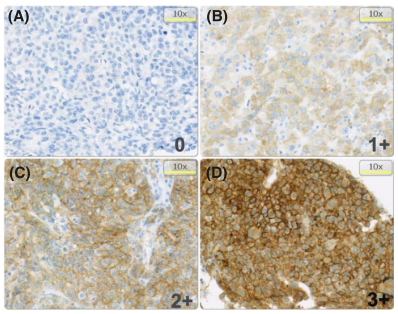

Figure 1. Representative images demonstrating the grading of HER3 expression based on membranous staining intensity. (A) HER3 IHC score = 0, (B) HER3 IHC score = 1+, (C) HER3 IHC score = 2+, (D) HER3 IHC score = 3+.

Results

HER3 expression (≥1+) was observed in 136 of 187 samples (~73%). HER3 expression was found to be markedly lower in the mucosal melanomas, with 17 of the 38 tumours (~45%) demonstrating no HER3 expression.

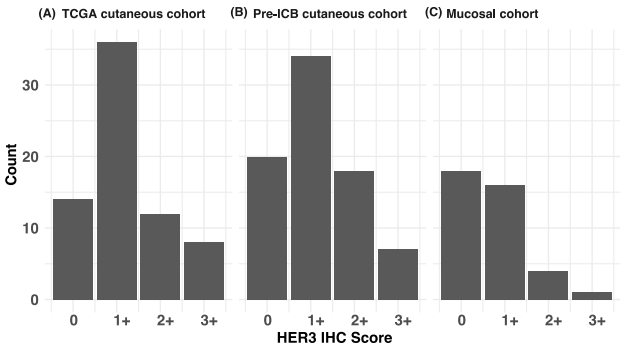

Figure 2. HER3 expression distribution in (A) TCGA, (B) Pre-ICB and (C) Mucosal TMA cohorts.

In cutaneous melanomas, there was a negative association between HER3 expression and mutational load in the TCGA cohort, overall survival after anti-PD-1-based immunotherapy in the pre-ICB cohort, and a trend towards negative association with PD-L1 IHC expression in the TCGA cohort.

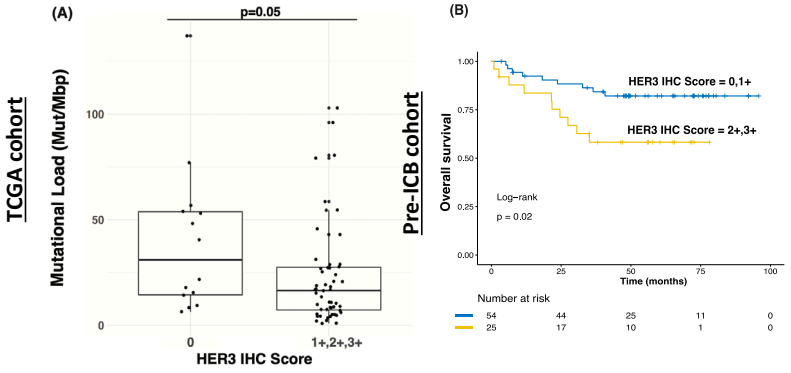

Figure 3. A) Association between HER3 status and total mutational load (Mut/Mbp) in the TCGA cohort. B) Association between HER3 status and overall survival outcome in the pre-ICB cohort.

TCGA cohort

Variable		Low HER3 (0/1+)	High HER3 (2+/3+)	P-value	Non-Expression HER3 (0)	Expression HER3 (1+/2+/3+)	P-value
Age - median		61	63	0.61	62	61.5	0.62
Gender - % (n)	Male	71 (32)	29 (13)	0.86	20 (9)	80 (36)	0.50
	Female	65 (11)	35 (6)		30 (5)	70 (12)	
	Unknown	87 (7)	13 (1)		0 (0)	100 (8)	
BRAF status - % (n)	WT	68 (25)	32 (12)	0.62	19 (7)	81 (30)	1.00
	Mutant	76 (25)	24 (8)		21 (7)	79 (26)	
NRAS status - % (n)	WT	81 (35)	19 (8)	0.03	28 (12)	72 (31)	0.09
	Mutant	54 (14)	46 (12)		8 (2)	92 (24)	
	Unknown	100 (1)	0 (0)		0 (0)	100 (1)	
TMB -median		17.8	12.8	0.38	31	16.4	0.05
IFN-gamma - median		9.1	9.6	0.52	9.3	9.1	0.77
PD-L1 IHC -median		0	0.01	0.30	0.015	0	0.07

Pre-ICB cohort

Variable		Low HER3 (0/1+)	High HER3 (2+/3+)	P-value	Non-Expression HER3 (0)	Expression HER3 (1+/2+/3+)	P-value
Age - median		65.7	65.4	0.91	70	63	0.27
Gender - % (n)	Male	71 (39)	29 (16)	0.63	27 (15)	73 (40)	0.75
	Female	62.5 (15)	37.5 (9)		21 (5)	79 (19)	
ECOG performance status - % (n)	0	68 (38)	32 (18)	1	30 (17)	70 (39)	0.31
	1	68 (15)	32 (7)		14 (3)	86 (19)	
	2	100 (1)	0 (0)		0 (0)	100 (1)	
8th AJCC staging - % (n)	IIIC	67 (8)	33 (4)	0.51	33 (4)	67 (8)	0.04
	M1A	75 (3)	25 (1)		50 (2)	50 (2)	
	M1B	57 (8)	43 (6)		7 (1)	93 (13)	
	M1C	79 (26)	21 (7)		36 (12)	64 (21)	
	M1D	60 (9)	40 (6)		7 (1)	93 (14)	
	Unknown	0 (0)	100 (1)		0 (0)	100 (1)	
Liver metastasis status - % (n)	Absent	63 (38)	37 (22)	0.15	27 (16)	73 (44)	0.77
	Present	84 (16)	16 (3)		21 (4)	79 (15)	
Treatment modality - % (n)	PD1	65 (26)	35 (14)	0.68	20 (8)	80 (32)	0.40
	IPI+PD1	72 (28)	28 (11)		31 (12)	69 (27)	
BRAF status - % (n)	WT	67 (37)	33 (18)	1	27 (15)	73 (40)	0.82
	Mutant	70 (16)	30 (7)		22 (5)	78 (18)	
	Unknown	100 (1)	0 (0)		0 (0)	100 (1)	
NRAS status - % (n)	WT	77 (33)	23 (10)	0.19	26 (11)	74 (32)	0.98
	Mutant	58 (14)	42 (10)		29 (7)	71 (17)	
	Unknown	58 (7)	42 (5)		17 (2)	83 (10)	
LDH - % (n)	Normal	74 (42)	26 (15)	0.31	26 (15)	74 (42)	0.77
	Elevated	58 (11)	42 (8)		21 (4)	79 (15)	
	Unknown	33 (1)	67 (2)		33 (1)	67 (2)	

Table 1. Summary of molecular and clinical characteristics of patients in the TCGA and pre-ICB TMA cohorts.

Conclusion

Overall, our results indicate that HER3 may be a promising therapeutic avenue in cutaneous melanoma worthy of further clinical evaluation.

References

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