Metastasizing and Non-Metastasizing Thick Melanomas: Clinicopathological Predictors and Molecular profiling

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Background

Cutaneous melanoma (CM) is the most aggressive form of skin cancer and its worldwide incidence rises faster than that of any other cancer (1). Early stages can successfully be treated by surgery, but once metastasis has occurred, the prognosis is infaust. Prognosis can be predicted on the basis of the stage of the patient and depends on a number of clinicopathological parameters, including thickness and ulceration of the primary melanoma (2). However, some 5-10% of thick (≥2mm) melanomas do not follow this scenario and run an unpredictable course. In our earlier study on thick primary melanomas (≥2mm) from UZ (n=141) and Leeds database (n=141), we did not find an association between outcome and clinicopathological parameters. We therefore compare the molecular composition of thick primary melanomas that did metastasize with a matched group of thick primary melanomas that did not metastasize, aiming to identify a gene signature associated with non-metastasizing melanomas.

Methods

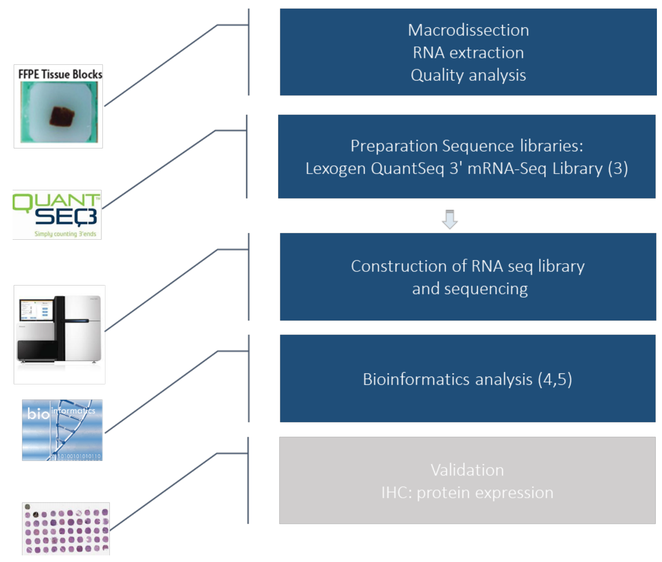
We investigated 24 thick primary cutaneous melanomas, i.e. 12 pairs of thick melanomas matched for all clinicopathological prognostic markers (gender, age (<40, 40-59 years, >=60 years), site, Breslow thickness, ulceration, and mitotic count) but differing in the outcome and with a follow-up period of at least 5 years (Table 1). To investigate the underlying biological processes, we performed differential gene expression analysis and pathway analysis comparing thick non-metastasizing (M-) and thick metastasizing melanomas (M+) (3,4,5) (figure 1). The results were validated using the Leeds dataset (n=179).

Table 1 Demographic variables of patients with thick melanoma

Characteristics	Contrast	Frequency (n)	Percent (%)
Metastasis	No	12	50
	Yes	12	50
Subtype	SSM	4	16,7
	ND	13	54,2
	AL	7	29,2
Gender	Gender		
	Female	6	25
	Male	18	75
Ulceration	No	8	33,3
	Yes	16	66,7
Mitosis	No	4	16,7
	Yes	20	83,3
Age	40-59	8	33,3
	>=60y	16	66,7
Location	Extremity	11	45,8
	Trunk	6	25
	Head and neck	7	29,2
Breslow interval	2 mm-4mm	11	47,8
	>4 mm	12	52,2

Abbreviations: SSM: Superficial spreading melanoma; NM: nodular melanoma; AL: AL, acrolentiginous melanoma. Age is expressed in years and Breslow thickness in mm.

Figure 1: Differential gene expression analysis and pathway analysis in thick melanoma

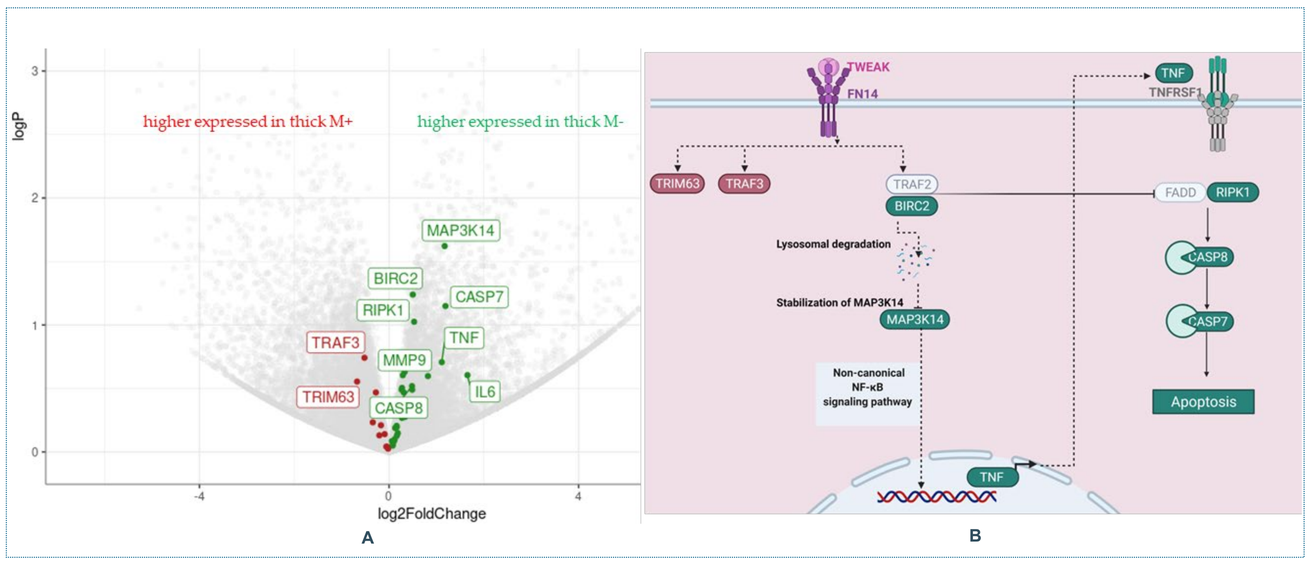


Patients with high Breslow thickness melanomas with available remaining FFPE tissue were identified from the files of the pathology departments at University Hospitals in Leuven, Belgium (study series; n = 4) and at the Melanoma Institute Australia in Sydney, Australia (n = 14) and Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw, Poland (n = 6).

Results

TNF-like weak inducer of apoptosis (TWEAK) pathway was upregulated in thick non-metastasizing melanomas. MAP3K14 (NIK1), BIRC2 (cIAP1), RIPK1, CASP7, CASP8, TNF play an important role in the inhibition of proliferation and invasion of tumor cells via the activation of the non-canonical NF-κB signaling pathway (figure 2). In particular, this pathway sensitizes melanoma cells to TNF-alpha and activates the apoptosis module of the TWEAK pathway in thick non-metastasizing melanomas. Also, in validation database (Leeds) we found an upregulation of TWEAK pathway in thick CM. (3)

Figure 2: TNF-like weak inducer of apoptosis (TWEAK) pathway upregulated in thick melanomas.



A Volcano Plot for differential gene expression: red dots are genes significantly over-expressed in thick M+ (left) , and green dots are genes significantly over-expressed in thick M- (right) (Pathway analysis by Asier Antoranz Martinez)
B Apoptosis module of the TWEAK pathway (Created with Biorender): Genes overexpressed in thick M- (green) and genes overexpressed in thick M+ (red)
Abbreviations: OG: oncogene; TSG: tumor suppressor gene

Conclusion

We identified a gene signature associated with non-metastasizing melanomas. In particular, the TWEAK-induced activation of the noncanonical NF-_B signaling pathway, which induces production of TNF-alpha and sensitizes tumor cells to death, may play a protective role in thick non-metastasizing melanomas. The exploitation of these genes and pathway may open future therapeutic avenues

Acknowledgements

References

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