Background: There is a great unmet clinical need to identify patients with thin primary cutaneous melanomas (T1, Breslow thickness ≤ 1 mm) who have a high risk for tumor recurrence and death from melanoma. Kin of IRRE-like protein 1 (KIRREL/NEPH1) is expressed in podocytes and involved in glomerular filtration, but its expression in human cancer has not yet been reported. Screening in the Human Protein Atlas portal revealed a particularly high expression of KIRREL in melanoma, both at the mRNA and protein levels. In this study, we followed up on these findings and examined the prognostic value of KIRREL in a population-based cohort of melanoma.

Methods: Immunohistochemical analysis of KIRREL was performed on tissue microarrays with a subset of primary tumors and paired lymph node metastases from an original cohort of 268 incident cases of melanoma in the Malmö Diet and Cancer study. Kaplan Meier analysis and Cox proportional hazards modelling were used to assess the relationship between KIRREL expression and time to recurrence (TTR) and melanoma-specific survival (MSS). The prognostic value of KIRREL mRNA expression was examined in 102 melanoma cases in The Cancer Genome Atlas (TCGA).

Results: Membranous/cytoplasmic expression of KIRREL was detected in 158/185 (85.4%) primary tumours and 18/19 (94.7%) metastases, in various fractions and intensities. High expression of KIRREL was significantly associated with several unfavourable clinicopathological factors. KIRREL expression was not prognostic in tumours >1 mm thickness, but in T1 tumours (n = 106, median thickness 0.58, range 0.08-1.00), high expression of KIRREL was significantly associated with a reduced TTR, independent of and outperforming absolute thickness in mm and ulceration (HR = 4.54, 95% CI 1.61-20.45), and borderline significantly associated with MSS. High mRNA levels of KIRREL were associated with a significantly reduced overall survival in the TCGA (p = 0.028).

Conclusions: KIRREL is not only a novel potential diagnostic marker for melanoma, but may also be a useful prognostic biomarker for improved stratification of patients with thin melanoma. These findings may be of high clinical relevance and therefore merit further validation.

Legal entity responsible for the study: Lund University.

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