New biomarkers improve stratification of patients with melanoma

Linked Articles: Lira *et al.* Br J Dermatol 2020; **182**:138–146; Ellis *et al.* Br J Dermatol 2020; **182**:156–165.

Recent advances in targeted and immunotherapy have improved the outlook for many patients with metastatic melanoma.[1] Although identifying those who are most likely to respond to treatment remains a clinical challenge, the need to do so is ever greater because of diagnoses increasing by 42% in the past decade and continuing to rise.[2] Clinical characteristics and molecular markers (biomarkers) have become invaluable for the diagnosis, staging and selection of effective therapies; as well as for monitoring of disease progression in modern cancer care. Two useful new BJD studies identify novel biomarkers that can be easily incorporated into clinical practice and can discriminate patients with melanoma with improved survival.

The first study, by Lira *et al.*, explores how the melanocortin 1 receptor (MC1R) gene affects melanoma survival.[3] MC1R is a highly variable gene that regulates skin, hair colour and photosensitivity; and identifies a subset of the population at higher risk of melanoma. Germline variants in the gene most strongly associated with a fair complexion are termed 'R' variants, and variants conferring a weaker phenotype are defined as 'r' variants.[4] Previous studies have shown that the presence of MC1R variants, in addition to other epidemiological factors, are statistically independent predictors of melanoma survival.[4] Additionally, there is a sex bias in melanoma outcome, as women have a better prognosis overall and at any stage of disease.[2] The biology behind sex differences and prognosis is incompletely understood; however, ultraviolet exposure patterns, immune landscape alterations and differences in free radical reduction have all been proposed as potential contributors.[5]

In their study, Lira *et al.* hypothesize that MC1R status might influence survival of men and women differently.[3] To test this hypothesis, they analysed > 1000 patients from a cohort with melanoma from Barcelona, and correlated MC1R status to outcome. Their cohort is well balanced for age, skin phototype and Breslow, and differs only in the previously observed differences in anatomic site of the primary melanoma between sexes (men more trunk and women more lower limb disease) and ulceration. Importantly, there is an equal distribution of MC1R variants in both sexes. The authors determined that carrying any MC1R variant appeared protective in women in a multivariate analysis [hazard ratio

(HR) 0·57, 95% confidence interval (CI) 0·38–0·85, P = 0·006]. Previous studies have identified a significant protective effect conferred by MC1R variants[4] but have not looked to see if this was sex specific. The link between MC1R variants and better outcome in women opens novel research questions as to how sex influences MC1R expression and function.

It postulate that MC1R 'R' melanocytes have a decreased DNA repair capacity and a dampened response to oxidative damage, leading to a greater accumulation of DNA mutations.[6] Such accelerated damage within melanoma cells could inhibit melanoma progression in MC1R variant carriers. Also relevant is that a greater mutation burden is associated with enhanced neoantigen formation.[7] Therefore MC1R 'R' carriers may potentially respond better to immune therapies; a question that remains to be studied. Although MC1R status assessment is not part of the routine care of patients with melanoma, clinicians should be aware that germline variants may be a useful tool to stratify patients at greater risk of death.

The second study, published in the BJD by Ellis *et al.*, provides a new tool to improve stratification of patients with stage I melanoma.[8] Most cases of melanoma are diagnosed at an early stage [American Joint Committee on Cancer (AJCC) stage I–II],[2] which makes this study particularly useful. Detection of early-stage melanoma followed by early surgical excision results in very high cure rates. However, there remains a significant minority of patients with stage I disease who progress and die from melanoma, despite initially being told their cancer was likely curable.[9] Up to 12% of patients with stage I disease may have nodal disease on sentinel lymph node biopsy (SLNB), which means disease can reoccur in the early-stage population.[9] There is therefore a clinical need to better identify patients with stage I disease at high-risk of progression.

In their study, Ellis *et al.* examined 455 AJCC stage I tumours from three cohorts in the north east of England.[7] Using immunohistochemistry, they examined autophagy and beclin 1 regulator 1 (AMBRA1) and loricrin expression in the epidermis overlying the melanoma and compared this with the expression in neighbouring normal epidermis. Ellis and colleagues had previously identified AMBRA1 expression as lost in high-risk stage I primary melanoma,[10] but AMBRA1 expression alone was not found to be of prognostic value in clinical practice. In this new study, however, the addition of a second biomarker of epidermal differentiation, loricrin, can be used clinically with high sensitivity and specificity to stratify stage I patients at high and low risk of progression. In multivariate analysis of combined validation cohorts, high-risk AMBA1/loricrin (AMLo) expression carried a HR of 3·89 (95% CI

1·8–8·41, P < 0·001) of melanoma recurrence. Further prospective studies could address if patients at low risk of progression, as established using AMLo expression, can be discharged from follow-up earlier.

Significant advantages of performing this simple, combined immunohistochemistry test, is that in contrast to SLNB, which is offered to patients with Breslow > 1 mm, there is no added morbidity and far lower cost. To address specifically how AMLo performs compared with SLNB, Ellis *et al.* assessed another cohort of melanomas with AMLo staining and determined that 'AMLo low' patients have only a 1·4% chance of positive SLNB (95% CI 0–5%), demonstrating that this test can identify patients that would receive no further information from SLNB. Future studies should establish whether AMLo staining can be used at all stages of primary disease.

This study highlights how an alteration in the epidermal tumour microenvironment is associated with melanoma outcomes; and how this may be particularly relevant in early-stage disease. *In vitro* studies showing that differentiated keratinocytes play an important role in melanoma switching between radial and vertical growth-phase phenotypes[11] suggest the epidermis may not be a simple bystander in early melanoma progression.

Both of these studies identify biomarkers of outcome that have clear translational benefits to clinical practice. Furthermore, how these biomarkers may be involved in melanoma behaviour pose interesting biological questions, as often biomarkers are not bystanders but play critical roles in tumour biology.

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Conflicts of interest: none to declare.