Promoting *TERT* promoter mutations for prognostication in cutaneous oncology

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Dermatologists need to prognosticate skin cancers for optimal care. There are multiple scenarios in which that may prove difficult—especially in cases involving borderline or recurrent lesions. As molecular techniques in diagnostic dermatopathology proliferate, determining which studies may be of greatest value is essential. In this issue of the *Journal of the American Academy of Dermatology*, 2 studies focusing on telomerase reverse transcriptase gene (*TERT*) promoter mutations (TPMs) are presented.

Telomeres have been hypothesized to have key roles in aging and oncogenesis. Telomeres are present at the ends of eukaryotic chromosomes. TERT is a catalytic subunit of the telomerase enzyme responsible for catalyzing the addition of nucleotides to the end of a chromosome's telomeres. In normal cells, the shortening of telomeres has the ability to activate the senescence pathway (or the loss of a cell's power of division and growth). In malignancies, stabilization of telomere length by telomerase allows unlimited proliferation. Reactivation or re-expression of telomerase is believed to be a widespread feature of human cancers, although the genetic basis for this is yet to be determined.[1]

TPMs have been demonstrated in multiple cancers, including melanoma, glioma, hepatocellular carcinoma, urothelial carcinoma, and others, and are associated with adverse outcomes.[2] TPMs represent the most common noncoding mutations in human cancer; this has renewed the long-standing debate regarding whether cancer originates from telomerase-positive stem cells or whether telomerase reactivation is a final step in cellular transformation.[3]

Campos et al performed genetic profiling of TPMs in a retrospective series of cutaneous squamous carcinomas (cSCCs).[4] The predictive value of TPMs and clinicopathologic parameters was assessed by using logistic regression models; 152 cSCCs from 122 patients were analyzed for TPMs. The mutation rate was 31.6% (48 of 152) and was higher in invasive cSCCs (42 of 121 [34.7%]) than in in situ cSCCs (6 of 31 [19.4%]). Patient age older than 75 years was an independent predictor of local recurrence. TPMs were independent predictors of local recurrence and were associated with a higher risk of lymph node metastasis. The authors concluded that TPMs may prove to be a molecular biomarker with prognostic significance in invasive cSCC, but larger studies are needed to confirm these findings.

Dermatologists routinely face the concern of pigmentation in previously excised nevi (especially those removed with use of a shave technique). Walton et al examined the role of TPMs in recurrent nevi to determine whether the presence of hotspot TPMs distinguishes recurrent nevi from locally recurrent melanoma.[5] They analyzed 11 locally recurrent melanomas and 17 recurrent nevi, using melanoma and nevus controls to determine TPM status. Of the 11 recurrent melanomas, 9 were sequenced for TPMs; of these, 4 had hotspot TPMs. None of the 17 cases of recurrent nevus demonstrated a hotspot TPM. The authors concluded that "hotspot TPMs are significantly more frequent in recurrent melanomas and may serve as a diagnostic clue in histologically ambiguous cases."

It is human nature to desire a single test to provide "the answer" as to whether a lesion is benign or malignant. Practically, any such determination is based on clinicopathologic correlation of routine microscopy with multiple adjunctive immunohistochemical and/or molecular tests. Preliminary data suggest that TPMs may be promoted to front-runner

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status in cutaneous oncology prognostication, should further studies confirm these findings.

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JAAD Game Changers: Multivariate analysis of potential risk factors for lymph node metastasis in patients with cutaneous squamous cell carcinoma of the head and neck

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Capsule Summary

- Risk factors for metastasis from cutaneous squamous cell carcinoma are incorporated in tumor staging by the seventh edition of the American Joint Committee on Cancer - Cancer Staging Manual.
- We confirmed most risk factors and also identified moderate differentiation as a predictor for lymph node metastasis.
- Moderate differentiation can be considered in tumor staging.

How did this article change the practice of dermatology?

The independent risk factors for the development of lymph node metastasis in head and neck cutaneous squamous cell carcinoma include location on the ear, tumor diameter >50 mm, moderate and poor differentiation, and tumor thickness >2 mm. This article added moderate differentiation as a predictor for lymph node metastasis.[1]

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