Frequency of telomerase reverse transcripter promoter mutations in desmoplastic melanoma subtypes: analyses of 76 cases

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Estimates of the frequency of telomerase reverse transcripter (*TERT*) mutations in desmoplastic melanoma (DM) are limited. DM is categorized into subtypes, pure and mixed, differing in prognosis, suggesting genetic heterogeneity. Given this, our aims were to determine the incidence of *TERT* promoter mutations in DM subtypes and to evaluate its relationship with established histopathologic prognosticators, *BRAF* and *RETp* status, and neurofibromin protein expression. Of the archival annotated samples retrieved, 76 cases of DM (48 pure and 28 mixed) fulfilled the criteria for inclusion. PCR amplification of the *TERT* promoter region was performed on DNA extracted from formalin-fixed paraffin-embedded tissue using primers 5′-GCCGATTCGACCTCTCTCC-3′ (forward) and 5′-CAGCGCTGCCTGAAACTC-3′ (reverse). For each case, appropriate C > T mutations were identified on the electropherograms. Univariate analysis using χ^2-test was carried out to identify potential confounders; a nested case–control study of demographic, clinical, histopathological, and genetic determinants was carried out using multiple logistic regression. Significant differences in *TERT* promoter mutation frequencies were noted in the subtypes (mixed vs. pure; 15/28, 54% vs. 11/48, 23%, respectively, $P = 0.0066$). After adjusting for potential confounding, multivariate analyses indicated a three-fold increase in the odds of the *TERT* mutation for those with the mixed subtype compared with the pure subtype ($P = 0.04$, adjusted odds ratio = 3.32). No other significant associations were noted (sex/junctional component/ Breslow depth/ulceration/mitoses/host response/*RETp*, *BRAF* status, and neurofibromin protein expression). Our findings, the largest to date investigating *TERT* promoter mutations in DM, support the hypothesis that the subtypes have distinct genetic drivers and underscore the relevance of telomere integrity in the etiopathogenesis of the mixed variant. *Melanoma Res* 26:361–366 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Mutations in telomerase reverse transcripter mutations (*TERT*) gene promoters, noted in certain human cancers, have been reported in melanoma relatively recently in two separate studies [1–3]. In the first, independent mutations within the *TERT* core promoter with a ultraviolet (UV) signature were noted in 71% of melanomas of an unspecified histopathologic subtype and in the second, 74% of human cell lines derived from metastatic melanoma. Subsequent studies confirmed the association of UV-induced *TERT* promoter mutations in melanoma and the association of these mutations with an aggressive biologic behavior, lending credence to observations that *TERT* promoter mutations may be useful as an independent adverse prognosticator [4–7].

Despite the above, estimates of the frequency of *TERT* mutations in desmoplastic melanoma (DM), a relatively rare variant of spindle cell melanoma that occurs more commonly on chronically sun-exposed sites, are extremely limited in terms of studies as well as samples analyzed [8]. DM is divided into two distinct subtypes: pure desmoplastic melanoma (PDM) if at least 90% of tumoral cells show classical spindled cytomorphology and mixed desmoplastic melanoma (MDM) if the spindled cytomorphology is less than 90% with the rest composed of tumoral cells with an epithelioid cytomorphology [9–11]. These two variants differ not only in morphology but also pathogenesis, immunohistochemical profile, and prognosis, suggesting differential progression at the molecular and genetic levels [12,13]. In one study of approximately equal

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