IMMUNOHISTOCHEMICAL EXPRESSION OF DUSP3 IN NEVUS-ASSOCIATED MELANOMAS

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ABSTRACT

Dual Specificity Phosphatase 3 (DUSP3) seems to participate in various cancers, with both tumor suppressing and promoting properties reported in melanoma. This study's objective is to investigate DUSP3's immunohistochemical expression among nevus-associated melanomas (NAMs) and thus its potential involvement in melanocytic oncogenesis from the standpoint of its post-translational levels. 42 biopsied NAMs from 42 individuals were collected for immunohistochemical staining. The nevus and melanoma compounds were evaluated separately per tumor. Positivity was based on the numerical and categorical Immunoreactive Score after evaluation of staining's intensity and proportion. A general decrease of DUSP3's positivity was observed in M-NAMs compared to N-NAMs [mean(SD) numerical IRS scores: N-NAMs: 4.0(2.9); M-NAMs: 1.9(1.1), p<0.001]. Remarkably, no strongly positive M-NAMs were observed while 21.4% of them developed from a negative nevus. Furthermore, paired analysis of the 84 matched NAM cases underscored a downgrade in DUSP3 positivity of M-NAM vs N-NAM per tumor (Wilcoxon signed-rank test: p<0.001). Univariate analysis revealed significant association when comparing N-NAMs with M-NAMs. Specifically, probability of N-NAM diagnosis against M-NAM was increased approximately 3 times (OR N-NAM vs M-NAM: 3.225, 95% CI: 1.745-5.961. p<0.001) per 1 unit increase of the categorical IRS score. Our findings highlight that poor DUSP3's positivity and even more DUSP3's negativity -therefore loss of DUSP3's expression- are more likely associated with melanocytic malignancy. This is the first study rigorously examining DUSP3's immunohistochemical expression in NAMs, contributing to the improved understanding of their oncogenesis and diagnostics.

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INTRODUCTION

Dual Specificity Phosphatase 3 (DUSP3), a member of the protein tyrosine phosphatase family, has been a subject of interest in cancer research due to its intricate role in tumorigenesis. Recent studies have shed light on the diverse functions of DUSP3 in cancer progression[1]. Particularly in melanoma both tumor suppressing and promoting properties have been reported. While some research suggests that DUSP3 acts as a tumor suppressor by inhibiting cell proliferation and promoting apoptosis in melanoma cells, other studies indicate its potential as a tumor promoter by enhancing cell survival and metastasis[2]. These conflicting findings underscore the complexity of DUSP3's involvement in cancer and emphasize the need for further investigation into its molecular mechanisms and therapeutic implications.

This study's objective is to investigate DUSP3's immunohistochemical expression among nevus-associated melanomas (NAMs) and thus its potential involvement in melanocytic oncogenesis from the standpoint of its post-translational levels.

METHODS AND MATERIALS

42 biopsied NAMs from 42 individuals were collected for immunohistochemical staining for DUSP3. Staining was performed per standard procedure. The nevus and melanoma compounds (N-NAMs and M-NAMs, respectively) were evaluated separately per tumor. Positivity was based on the numerical and categorical Immunoreactive Score (IRS) after evaluation of staining's intensity and proportion in conventional microscopy by two separate expert reviewers[3]. Appropriate statistical analysis was performed as per standard practice.

RESULTS

A general decrease of DUSP3's positivity was observed in M-NAMs compared to N-NAMs [mean (SD) numerical IRS scores: N-NAMs: 4.0 (2.9); M-NAMs: 1.9 (1.1), p<0.001]. Remarkably, no strongly positive M-NAMs were observed while 21.4% of them developed from a negative nevus. Furthermore, paired analysis of the 84 matched NAM cases underscored a downgrade in DUSP3 positivity of M-NAM vs N-NAM per tumor (Wilcoxon signed-rank test: p<0.001). Univariate analysis revealed significant association when comparing N-NAMs with M-NAMs. Specifically, probability of N-NAM diagnosis against M-NAM was increased approximately 3 times (OR N-NAM vs M-NAM: 3.225, 95% CI: 1.745-5.961. p<0.001) per 1 unit increase of the categorical IRS score.

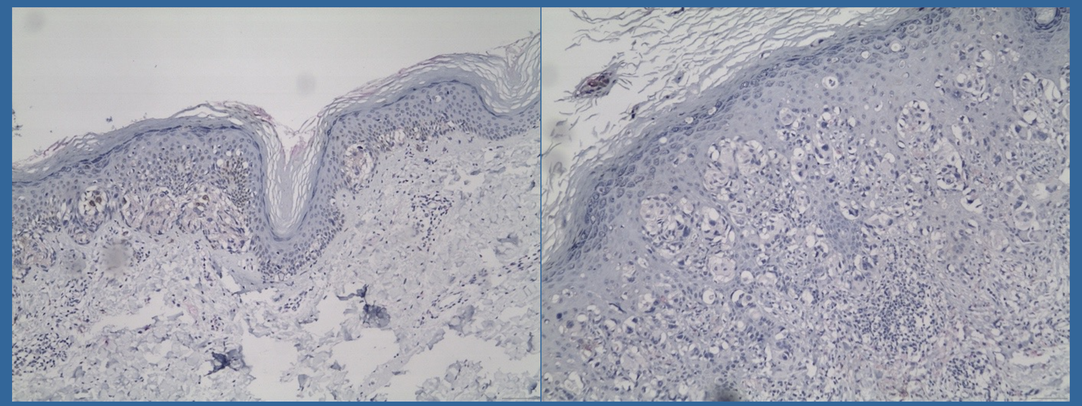

Figure 1. The moderately positive (IRS=8), compound N-NAM and the negative (IRS=1) M-NAM of the same NAM. 100x magnification.

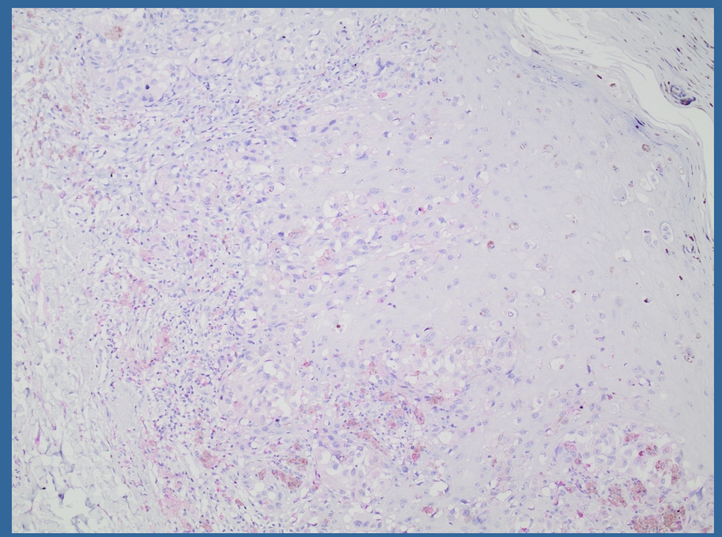

Figure 2. Image of a NAM, whose both nevic and melanomatous compounds are present, immunohistochemically stained for DUSP3. Positivity was classified according to the numerical and categorical IRS score. 100x magnification.

Malignant, melanocytic, cellular populations are found in the top left quarter of the image, negatively stained (IRS=1), whereas moderately positive (IRS=8) nevic nests are observed in the bottom half of the image.

DISCUSSION

The results of our study underscore the significance of Dual Specificity Phosphatase 3 (DUSP3) expression levels in melanocytic malignancy. Our findings indicate that low DUSP3 positivity and, particularly, the loss of DUSP3 expression are strongly correlated with the development of NAMs, whereas elevated levels of DUSP3 expression were consistently more prevalent in N-NAMs, showing significant differences from M-NAMs. The presence of DUSP3 appears to be more commonly linked to neoplasms that exhibit signs of senescence or reduced proliferation. This suggests a potential protective role of DUSP3 against malignancy, possibly functioning as a reactive and compensatory mechanism in response to oncogenic events. This ensures proper regulation of the cell cycle and helps maintain a state of oncogene-induced senescence within tumors[4]. Conversely, the loss of DUSP3's tumor-suppressing activity may lead to neoplastic cells transitioning into a hyperproliferative state, potentially representing an initial stage in the development of NAM[5, 6].

This novel insight, derived from the first comprehensive investigation of DUSP3's immunohistochemical expression in NAMs, enhances our knowledge of the oncogenic processes underlying these tumors and provides valuable insights for diagnostic purposes. By elucidating the role of DUSP3 in NAMs, our study contributes to the advancement of personalized medicine strategies and the development of targeted therapies for melanocytic malignancies.

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