Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
South East European Journal of Immunology. 2025 Mar 31; 8(CITIM):044
https://doi.org/10.3889/seejim.2025.6106
eISSN: 1857-9388
Category: *CITIM - Cancer Immunotherapy & Immunomonitoring (CITIM2025)*
Section: *Invited Lectures*

Insights in genetic and epigenetic traits in cutaneous melanoma - new therapy targets

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Citation: Neagu M, Elena-Georgiana D, Constantin C, Surcel M, Munteanu A, Zurac S. Insights in genetic and epigenetic traits in cutaneous melanoma - new therapy targets.SEE J Immunol. 2025 Mar 27;8(CITIM):044. https://doi.org/10.3889/seejim.2025.6106.
Keywords: melanoma; mutation; droplet digital PCR
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Received: 01-Mar-2025
Accepted: 25-Mar-2025
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Funding: The study was financed by grants PN-III-P4-PCE-2021-0549 [PCE9/2022] and NASR, [PN 23.16.01.03]. Authors acknowledge the cooperation through COST Action CA21108 - European Network for Skin Engineering and Modelling, NETSKINMODELS.
Competing Interests: The authors have declared that no competing interests exis

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Abstract

The purpose of our study was to evaluate the genetic alterations that could affect the EGFR-RAS-RAF pathway in search of new druggable genetic targets.
Materials and methods. Paraffin embedded samples from patients diagnosed with skin melanoma (n=22) were evaluated using droplet digital PCR (ddPCR) in comparison to benign nevi (n=15) and normal skin samples (n=15). Samples were diagnosed using histology and immunohistochemistry (IHC) evaluation. The study was operated in accordance with the principles of the Declaration of Helsinki (according to Annex 4, National Law 104/2004 and application HG451/2004, amended in 2013), and with the approval of the Local Ethics Committee of Colentina Clinical Hospital, Bucharest, Romania (approval no. 25/2017). Patients and control subjects were informed of the study protocol and provided written informed consent prior to enrollment. The mutational status of healthy skin, nevi and melanoma specimens was assessed by ddPCR using *BRAF V600, NRAS G12/G13, NRAS Q61, KRAS Q61* and *EGFR* exon 19 deletions Screening Assays according to manufacturer's instructions.
Results. The samples subjected to ddPCR were analyzed also on RT-PCR and we found a perfect correlation between the data obtained on both technologies (Spearman correlation coefficient = 0.9913).We have found over 86% of the benign nevi harboring BRAF V600 mutations, while only 56% of skin melanomas harbored the same mutation. In melanomas BRAF mutations significantly associated with Breslow index and tumor infiltrating lymphocytes, whereas *NRAS* mutations (*NRAS* Q61 and *NRAS* G12/G13) correlated with Breslow index and the mitotic index. Particularly, malignant transformation to a BRAF wild-type melanocytic tumor occurred in one of our cases involving a benign nevus with BRAF V600 positivity. ddPCR technique is sensitive so that we detected have in a normal skin sample NRAS G12/Q61 mutation, while the benign nevus excised from the skin harbored BRAF mutation. The high mutation profile of benign nevi was associated with a high expression of cell cycle regulatory proteins that could explain the melanocyte's arrested cell cycle within a benign nevus.
Conclusion. The molecular profiling of tumorigenesis is important to follow the dynamics of melanocyte transformation towards melanoma and moreover can orient the patient therapy.