Comprehensive molecular profiling of murine melanoma progression identifies independent prognostic factors for melanoma patients

Flávia Eichemberger Rius[1,2], Ana Carolina Monteiro[1,3], Alice Santana Morais[1], Ana Luisa Pedroso Ayub[1], Diogo Pessoa[4], Fernando Andrade[5], Hatylas Azevedo[6], André Fujita[5], Regine Schneider-Stock[3], Christopher Mason[2], Eduardo Moraes Reis[4], Miriam Galvonas Jasiulionis[1]

[1]Pharmacology Department, Universidade Federal de São Paulo, São Paulo, Brazil; [2]Department of Physiology and Biophysics, Weill Cornell Medicine, New York, United States; [3]Institute of Pathology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [4]Institute of Chemistry, Universidade de São Paulo, São Paulo, Brazil; [5]Institute of Mathematics and Statistics, Universidade de São Paulo, São Paulo, Brazil; [6]Aché Laboratórios Farmacêuticos.

Cutaneous melanomas are extremely aggressive tumors, and although significant advances have been obtained with targeted and immune therapies, acquired resistance is still a common problem. Several molecular alterations have been described in melanomas; however, there is no integrated view about the alterations involved in different stages of melanoma genesis. In this context, the identification of molecular pathways altered during melanoma progression might contribute not only to a better understanding of melanoma biology but also to the discovery of both novel potential targets to therapy and biomarkers for prognosis and response to therapies. Our group has previously established and explored a murine model of malignant transformation and tumor progression consisting of: a spontaneously immortalized melanocyte lineage called melan-a; pre-malignant melanocytes named 4C, obtained after subjecting melan-a cells to 4 cycles of adhesion impediment; a non-metastatic melanoma cell line, 4C11-, obtained after a limiting dilution of spheroids formed by 4C adhesion impediment; and a metastatic cell line, 4C11+, obtained after spontaneously loss of p53 by 4C11- cells. This *in vitro* sequential model was explored here to obtain a comprehensive view of molecular alterations related to both early and late stages of melanoma genesis. In this regard, transcriptome (NanoString, and RNA-Seq), methylome (ERRBS), and miRnome (Taqman miRNAs arrays and NanoString) profiles were analyzed in each cell line in order to reveal molecular pathways dynamically altered during melanoma progression. Genes and miRNAs selected based on our murine model were mapped to their human orthologues and data of human melanoma samples obtained from TCGA were separated in two groups according to the median gene expression or promoter methylation values among samples in the cohort. Then, uni- and multivariate COX regression analyses were performed to select possible prognostic markers for relapse-free survival. Among molecular alterations identified from our cellular model, the expression of *SNAI1*, *VAV1*, *CHD1*, *ANGPT2* and miR-142-3p, and the promoter methylation of *VEGFC* and *ANGPT2* in human melanoma samples were shown to correlate to melanoma patient survival, thus being promising prognostic factors for melanoma.

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