IJAE
Vol. 120, n. 1 (Supplement): 54, 2015
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Targeting of NAADP-dependent calcium signalling impairs growth and invasiveness of murine melanoma and tumor angiogenesis

Annarita Favia[1], Irene Pafumi[1], Marianna Desideri[2], Camilla Montesano[3], Daniela Passeri[4], Augusto Orlandi[4], Donatella Del Bufalo[2], Manuel Sergi[5], Elio Ziparo[1], Fioretta Palombi[1], Antonio Filippini[1]

[1] Department of Anatomy, Histology, Forensic Medicine and Orthopaedics, Unit of Histology and Medical Embryology, Sapienza University of Rome, Italy - [2] Experimental Chemotherapy Laboratory, Regina Elena National Cancer Institute, Rome, Italy - [3] Department of Chemistry, Sapienza University of Rome, Italy - [4] Department of Biomedicine and Prevention, Institute of Anatomic Pathology, Tor Vergata University Policlinic of Rome, Italy - [5] Faculty of Biosciences and Technologies for Food, Agriculture and Environment, University of Teramo, Teramo, Italy

We have recently identified a novel transduction pathway through which Vascular Endothelial Growth Factor (VEGF) controls experimentally induced neoangiogenesis, specifically involving endothelial VEGF receptor subtype 2 and the release of intracellular calcium from NAADP (Nicotinic Acid Adenosine Dinucleotide Phosphate) responsive acidic stores (1). We have now extended this research to an in vivo model of tumor angiogenesis and show that the pharmacologic NAADP inhibitor Ned-19 (2) impairs the vascularization, growth and metastatic spreading of the very aggressive VEGF producing murine tumor, B16 melanoma. In parallel in vitro experiments, we tested whether Ned-19 could directly affect the production of VEGF by the tumor cells, and found that treatment of B16 cells with Ned-19 unexpectedly results in increased VEGF release. These observations indicate that in our model 1) tumor angiogenesis is impaired by Ned-19 even in the presence of increased exposure to VEGF and 2) that NAADP system is active also in B16 melanoma cells. On the basis of this second observation further possible direct effects of Ned-19 on melanoma cell aggressiveness such as growth and invasivity are presently investigated and preliminary results suggest that NAADP system inhibition could potentially represent a two-fold therapeutic strategy, directly targeting both tumor angiogenesis and tumor cell growth.

References

[1] Favia A et al. (2014) VEGF-induced neoangiogenesis is mediated by NAADP and two-pore channel-2-dependent Ca^{2+} signaling, Proc Natl Acad Sci U S A 44, e4706-e4715; doi: 10.1073
[2] Galione A., (2014) A primer of NAADP-mediated Ca^{2+} signalling: From sea urchin eggs to mammalian cells, Cell Calcium, doi: 10.1016

Keywords:
Tumor vascularization; melanoma; calcium signalling; metastasis.