TGF- β1- V-ATPase Pumps Interactions in Melanoma Metastasis Process

Martins, B.X.[1] , Arantes, E.C.[1] , Arruda, R.F.[1] , Souza, S.B.[1], Leandro, H.J.[2] , Carvalho, E.Q.C.[2] , Façanha, A.R.[1]

[1] Laboratório de Biologia Celular e Tecidual, Centro de Biociências e Biotecnologia, Universidade Estadual do Norte Fluminense, Rio de Janeiro, Brasil.

[2] Laboratório de Morfologia e Patologia Animal, Centro de Ciências e Tecnologias Agropecuárias, Universidade Estadual do Norte Fluminense, Rio de Janeiro, Brasil.

Introduction: Vacuolar-ATPase is a proton pump that plays an important role in maintaining acidic extracellular pH and differential electrochemical gradients in tumor cell membranes. Expression of V-ATPases subunits are upregulated in several cancers. Melanoma is the most lethal of cutaneous neoplasm skin, with high metastatic capacity and multidrug resistance. They have characteristically many oncogene mutations including high amount of TGF- β isoforms and a differential functional expression of V-ATPase proton pumps. Objectives: This work aims to describe a novel TGF- β1 – V-ATPase interaction in melanoma cells contrasting in metastatic potential. Material and Methods: It was analyzed the V-ATPase proton extrusion followed *in vivo* by proton fluxes and its enzymatic activity. It was also evaluated the evolution of melanoma cancer and additional therapies by histology, CT scans and clinical exams. Results and Discussion: It was observed that TGF- β1 strongly stimulates *in vitro* the V-ATPase proton activity, mainly in cells with low metastatic potential (B16F0). The extracellular pHs of these cells were dramatically more acidified upon addition of TGF- β1. *In vivo* treatments demonstrated that animals inoculated with melanoma cells and TGF- β1 developed more aggressive and invasive tumors than animals without TGF- β1. Treatment of these animals with V-ATPase inhibitors induces positive responses in regard to metastasis contention and increases their rate survive when compared to untreated animals. Conclusions: These results suggest that TGF- β1 can be related to the stimulation of proton pump activity and this interaction could potentiate the metastatic progression.

Keys Word: TGF- β1, Proton Pumps, Melanoma Cells.
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