

Effects of the Immunomodulator P-MAPA in the Treatment of Non-Muscle Invasive Bladder Cancer: Interfaces between Energy Metabolism and Angiogenesis

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Abstract

In the neoplastic disease, adjustments in cellular energy metabolism are needed to stimulate cell division and therapies that work in these settings are a new therapeutic modality, as the immunomodulator P-MAPA. Thus, the objectives of this study were to characterize the histopathologic and molecular effects of immunotherapies with BCG and P-MAPA in the treatment of bladder cancer in rats and to establish possible mechanisms of action of these therapies involving cellular energy metabolism.

Key words:

Bladder Cancer, Metabolism, P-MAPA

Introduction

Uncontrolled cell proliferation is one of the main features of the neoplastic disease (1). To this end, adjustments in cellular energy metabolism and the formation of new blood vessels are needed to stimulate growth and cell division (2) and therapies that work in these settings are a new therapeutic modality. In this scenario highlights the immunomodulator P-MAPA, which for its great versatility and minimal cytotoxicity, opens a new perspective to fight some types of cancers, including non-muscle invasive bladder cancer (NMIBC) (3; 4; 5). Thus, the objectives of this study were to characterize the histopathologic and molecular effects of immunotherapies with BCG and P-MAPA in the treatment of NMIBC chemically induced in rats and to establish possible mechanisms of action of these therapies involving cellular energy metabolism.

Results and Discussion

For inducing NMIBC, 15 animals were chemically induced cancer at a dose of 1.5 mg / kg of N-methyl-N-Nitrosourea (MNU) dissolved in 0.3 ml of sodium citrate every 15 days a total of 4 doses. And other five animals were considered as control group. After that, the animals were divided into 4 groups: control group (Group 1): received an intravesical dose of 0.3 mL of 0.9% saline for 6 consecutive weeks; NMIBC group (Group 2): received the same treatment as Group 1; NMIBC + BCG group (Group 3): received one intravesical dose of BCG (10^6 UFC – 40 mg) diluted in 0.3 mL of 0.9% saline for 6 consecutive weeks; NMIBC + P-MAPA group (group 4): received one intravesical dose of the P-MAPA (5 mg/kg) dissolved in 0.3 ml of 0.9% saline for 6 consecutive weeks. After 16 weeks of treatment, animals were euthanized and the urinary bladders were collected and submitted to histopathological and immunohistochemical (GLUT1 - glucose uptake and citrate synthetase - CS) analysis. The specimens of urinary bladder of the group 1 do not represent structural alterations. The normal urothelium consists by 2-3 layers cells, as follows: a basal cells layer, an intermediary cell layer and a superficial layer formed by umbrella cells. In contrast, the specimens of urinary bladder of the group 2 showed several histopathological changes, such as: urinary bladder with urothelial carcinoma with invasion of the lamina propria (pT1), papillary carcinoma (pTa) and keratinizing squamous metaplasia. Nevertheless, in the animals treated with BCG (group 3), pTa was the

histopathologic alteration most frequently and the animals treated with P-MAPA showed histology similar to the control group. There was an intense cytoplasmic immunostaining for Glut1 in the groups 2, 3 and 4 and a moderate cytoplasmic immunostaining for the control group, showing that there was glucose uptake in all groups. Also there was an intense cytoplasmic immunostaining of CS in the control groups and group 4, however, there was a moderate immunostaining in groups 2 and 3, showing that treatment with P-MAPA resembles the patterns of the enzyme under normal cellular conditions.

Conclusions

Immunotherapy with P-MAPA showed better histological recovery when compared to treatment with BCG.

Acknowledgement

Support by Farmabrazil-Brazil, PIBIC/CNPq-Brazil (Process number 100714/2016-1) and FAPESP-Brazil (Process numbers 2014/11866-1) are also acknowledged.

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