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EVALUATION OF THE POTENTIAL THERAPEUTIC EFFECTS OF THE BIOLOGICAL RESPONSE MODIFIER - INORGANIC PHOSPHATE COMPOUND 1 (MRB-CFI-1) IN CHEMICALLY INDUCED MICE TO COLORECTAL CANCER.

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Abstract

This study aimed to characterize and compare the histopathological and immunohistochemical effects of OncoTherad therapy associated or not with chemotherapy with 5-Fluouracil in the chemically induced Colorectal Cancer (CRC) and establish the possible mechanisms of action of these therapeutic associations involving the signaling pathway of the Toll-like Receptor 4. CRC was induced by dimethylhydrazine (DMH) in C57BL/6J mice. Animals from treated groups received, once a week, 15 mg/Kg of 5-FU or 25 mg/Kg of OncoTherad, over 10 weeks. Tissues were collected for histopathology evaluation and Immunohistochemical analyses. DMH was efficient to induce malignant lesions. Isolated administration with 5-FU was not effective in decreasing the occurrence of malignant lesions, but the treatment with OncoTherad resulted in a decrease of 20%. Ultimately, the association between immunotherapy and chemotherapy was the most effective, decreasing 60% lesions. In addition, the Onco Therad was able to activate the innate immune system by increasing the signaling pathway to interferon. Thus, immunotherapy with OncoTherad may be one new approach therapeutic for CRC and may act as adjunctive therapy to 5-Fluorouracil chemotherapy.

Key words:
Colorectal Cancer, Immunomodulator, OncoTherad

Introduction

The colorectal cancer (CRC), chronically affects the gastrointestinal tract (GIT), over-stimulating the immune system, consequently increasing the cellular recruitment, proliferative rate and genetic alterations. The first choice therapies for CRC are colectomy, radiotherapy and chemotherapy with 5-fluorouracil (5-FU). The chemotherapy is toxic for the bone marrow and TGI, resulting in adverse effects. Considering the importance of the development of drugs that could act as modulators of the immune system and reduce the side effects of the chemotherapy, our research group developed a synthetic nanostructured compound with antitumor and immunological properties, called OncoTherad. Thus, the general objectives of this project were to characterize and compare the histopathological and immunohistochemical effects of OncoTherad therapy in mice with chemically induced colorectal cancer submitted to 5-Fluouracil (5-FU) chemotherapy. Also, it was aimed to establish the possible mechanisms of action of these therapeutic associations involving the signaling pathway of the receptor of the innate immune system Toll-like (TLR) 4.

Results and Discussion

The animals were randomly divided into five experimental groups: Control; Tumor; Tumor+5-FU; Tumor+OncoTherad; Tumor+5-FU+OncoTherad. After histopathological evaluation, the presence of malignant lesions was observed in 100% of the animals, being 60% Carcinoma in situ and 40% Adenocarcinoma.

Table 1. Percentage of histopathological changes of animals with colorectal tumor induced and treated with 5-Fluorouracil (5-FU), Oncoterad and adjuvant therapy with 5-FU and OncoTherad.

	Grupos				
Histopatologia	Controle (n=5)	DMH (n=5)	DMH+5-FU (n=5)	DMH+ OncoTherad (n=5)	DMH+ 5-FU+ OncoTherad(n=5)
Normal	5(100%)*	-	-	-	1(20%)
Adenoma	-	-	-	1(20%)	2(40%)*
Carcinoma *in situ*	-	2(40%)	3(60%)*	3(60%)*	2(40%)
Adenocarcinoma	-	3(60%)*	2(40%)	1(20%)	-

Data were expressed as median ± 95% confidence interval (CI), with two-way ANOVA rating followed by Fisher LSD test.
** Statistical significance.*

Isolated administration with 5-FU was not effective in decreasing the occurrence of malignant lesions. 100% of the animals presented malignant lesions, 60% of which were Carcinoma in situ and 40% Adenocarcinoma. However, the treatment led to a 20% decrease in invasive lesions (adenocarcinoma) in relation to the untreated group. The treatment with OncoTherad only, resulted in a 20% decrease in malignant lesions. Ultimately, the association between immunotherapy and chemotherapy was the most effective, decreasing 60% lesions. Furthermore, OncoTherad immunotherapy promotes innate immune system activation mediated by TLR4, resulting in increased signaling pathway (MyD88, TRIF, IRF3) for interferon. Activation of the interferon signaling pathway correlated with decreased occurrence and progression of malignant lesions in colorectal cancer.

Conclusions

Thus, immunotherapy with OncoTtherad may be one new approach therapeutic for CRC and may act as adjunctive therapy to 5-Fluorouracil chemotherapy.

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