IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2020; 10(23): 10498-10512. doi: 10.7150/thno.49480

Research Paper

Combination therapy with B7H3-redirected bispecific antibody and Sorafenib elicits enhanced synergistic antitumor efficacy

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Received: 2020.06.14; Accepted: 2020.08.05; Published: 2020.08.21

Abstract

Rationale: Current traditional treatment options are frequently ineffective to fight against ovarian cancer due to late diagnosis and high recurrence. Therefore, there is a vital need for the development of novel therapeutic agents. B7H3, an immune checkpoint protein, is highly expressed in various cancers, representing it a promising target for cancer immunotherapy. Although targeting B7H3 by bispecific T cell-engaging antibodies (BiTE) has achieved successes in hematological malignancies during recent years, attempts to use them for the treatment of solid cancers are less favorable, in part due to the heterogeneity of tumors. Sorafenib is an unselective inhibitor of multiple kinases currently being tested in clinical trials for several tumors, including ovarian cancer which showed limited activity and inevitable side effect for ovarian cancer treatment. However, it is able to enhance antitumor immune response, which indicates sorafenib may improve the efficiency of immunotherapy.

Methods: We evaluated the expression of B7H3 in ovarian cancer using online database and validated its expression of tumor tissues by immunohistochemistry staining. Then, B7H3 expression and the effects of sorafenib on ovarian cancer cell lines were determined by flow cytometry. In addition, 2D and 3D ovarian cancer models were established to test the combined therapeutic effect *in vitro*. Finally, the efficiency of B7H3×CD3 BiTE alone and its combination with sorafenib were evaluated both *in vitro* and *in vivo*.

Results: Our data showed that B7H3 was highly expressed in ovarian cancer compared with normal samples. Treatment with sorafenib inhibited ovarian cancer cell proliferation and induced a noticeable upregulation of B7H3 expression level. Further study suggested that B7H3×CD3 BiTE was effective in mediating T cell killing to cancer cells. Combined treatment of sorafenib and B7H3×CD3 BiTE had synergistic anti-tumor effects in ovarian cancer models.

Conclusions: Overall, our study indicates that combination therapy with sorafenib and B7H3×CD3 BiTE may be a new therapeutic option for the further study of preclinical treatment of OC.

Key words: Ovarian cancer; sorafenib; immunotherapy; B7H3; bispecific antibody