Acta Pharmacologica Sinica

www.nature.com/aps

ARTICLE

Bispecific antibody targeting both B7-H3 and PD-L1 exhibits superior antitumor activities

Hua-ying Li[1,2,3], Yi-li Chen[1]✉, Xiang-nan Deng[4], Huan-huan Li[1], Jie Tan[1], Guo-jian Liu[5], Yu-juan Zheng[3,6], Min Pei[1,7], Kai-ting Peng[3,6], Li-li Yue[3,8], Xiao-jia Chen[7], Yu Liu[8], Yong-shan Zhao[2] and Chun-he Wang[3,4,5,6,7,8]✉

Clinical application of PD-1 and PD-L1 monoclonal antibodies (mAbs) is hindered by their relatively low response rates and the occurrence of drug resistance. Co-expression of B7-H3 with PD-L1 has been found in various solid tumors, and combination therapies that target both PD-1/PD-L1 and B7-H3 pathways may provide additional therapeutic benefits. Up to today, however, no bispecific antibodies targeting both PD-1 and B7-H3 have reached the clinical development stage. In this study, we generated a stable B7-H3×PD-L1 bispecific antibody (BsAb) in IgG1-VHH format by coupling a humanized IgG1 mAb against PD-L1 with a humanized camelus variable domain of the heavy-chain of heavy-chain antibody (VHH) against human B7-H3. The BsAb exhibited favorable thermostability, efficient T cell activation, IFN-γ production, and antibody-dependent cell-mediated cytotoxicity (ADCC). In a PBMC humanized A375 xenogeneic tumor model, treatment with BsAb (10 mg/kg, i.p., twice a week for 6 weeks) showed enhanced antitumor activities compared to monotherapies and, to some degree, combination therapies. Our results suggest that targeting both PD-1 and B7-H3 with BsAbs increases their specificities to B7-H3 and PD-L1 double-positive tumors and induces a synergetic effect. We conclude that B7-H3×PD-L1 BsAb is favored over mAbs and possibly combination therapies in treating B7-H3 and PD-L1 double-positive tumors.

Keywords: cancer immunotherapy; B7-H3; PD-L1; bispecific antibodies; VHH; antibody-dependent cell-mediated cytotoxicity (ADCC)

Acta Pharmacologica Sinica (2023) 0:1–9; https://doi.org/10.1038/s41401-023-01118-2

INTRODUCTION

Programmed death ligand 1 (PD-L1), also named B7-H1, belongs to the B7 superfamily and is highly expressed in various tumors [1, 2]. When PD-L1 on tumor cells binds to programmed death 1 (PD-1) on effector T cells, it promotes the immune escape of tumors [3, 4]. PD-1 or PD-L1 antibodies block the interaction of PD-L1 with PD-1 and reduce the occurrences of immune escape, thereby enhancing the adaptive immunity against tumors [5]. However, a large number of patients do not respond to PD-1 or PD-L1 monotherapies [2, 3, 6]. Therefore, these antibodies are often used in combination with other antitumor agents [7].

Both the innate and adaptive immune systems are critical to immunological responses against cancers, and acting on both systems may greatly enhance the antitumor efficacy of immunotherapies for cancers [8, 9]. B7-H3 (CD276), also belonging to the B7 superfamily, may have impacts on both the innate and adaptive immune systems. There are two subtypes of B7-H3, 2Ig (2IgV+IgC) and 4Ig (4IgV+IgC), and 4Ig is the main subtype in human. A broad range of immune and non-immune cells express B7-H3, including dendritic cells (DCs), activated T cells, natural killer (NK) cells, fibroblasts, epithelial cells, osteoblasts, synoviocytes, and macrophages [10–15]. The counter receptors of B7-H3 have not been confirmed yet, but soluble B7-H3 has been shown to bind to T, NK T, and NK cells [16] and its degree of binding increases when T cells are activated [10]. Upon binding to NK cells, B7-H3 prevents them from the killing tumor cells, thus suppressing NK cells-mediated innate immunity [15]. It also suppresses T cell activation and proliferation, hence promoting the immune escape of cancer cells from adaptive immunity [17–19]. Thus, B7-H3 is potentially a unique immuno-oncology target that can mobilize both the innate and adaptive immune systems.

On the other hand, B7-H3 is a tumor-associated antigen (TSA) that is highly expressed in almost all solid tumors [20–22], as well as tumor-associated vasculature and stroma [23–25]. The level of B7-H3 expression often correlates with both poor prognosis and clinical outcomes in patients [26]. Therefore, solid tumors can be directly targeted by B7-H3-specific mechanisms, for example, antibody-dependent cell-mediated cytotoxicity (ADCC) [20], antibody-drug/radionuclide conjugates [21–23], and chimeric antigen receptor T cells. B7-H3 antibodies may also disrupt the tumor microenvironment and inhibit neovascularization. In

[1]Shanghai Mabstone Biotechnologies, Ltd., Shanghai 201203, China; [2]School of Life Science and Bio-Pharmaceutics, Shenyang Pharmaceutical University, Shenyang 110016, China; [3]Biotherapeutics Discovery Research Center, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China; [4]School of Chinese Materia Medica, Nanjing University of Chinese Medicine, Nanjing 210023, China; [5]Dartsbio Pharmaceuticals, Ltd., Zhongshan 528400, China; [6]University of Chinese Academy of Sciences, Beijing 100049, China; [7]Institute of Biomedicine & Department of Cell Biology, Jinan University, National Engineering Research Center of Genetic Medicine, Guangzhou 510632, China and [8]School of Life Science and Technology, China Pharmaceutical University, Nanjing 211198, China
Correspondence: Yi-li Chen (cheny@dartsbio.com) or Chun-he Wang (wangc@simm.ac.cn)
These authors contributed equally: Hua-ying Li, Yi-li Chen, Xiang-nan Deng

Received: 6 March 2023 Accepted: 28 May 2023
Published online: 16 June 2023