International Immunopharmacology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Anti-tumor and immunomodulatory activity of iron hepta-tungsten phosphate oxygen clusters complex

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ARTICLE INFO

Article history:
Received 2 May 2015
Received in revised form 30 October 2015
Accepted 3 November 2015
Available online xxxx

Keywords:
Polyoxometalates (POMs)
Iron hepta-tungsten phosphate oxygen clusters complex (IHTPO)
Antitumor
Immunomodulatory
Th1 immune responses

ABSTRACT

Polyoxometalates (POMs) have attracted a considerable attention due to their unique structural characteristics, physicochemical properties and biological activities. In this study, iron hepta-tungsten phosphate oxygen clusters complex $Na_{12}H[Fe(HPW_7O_{28})_2]\cdot 44H_2O$ (IHTPO) was synthesized and evaluated for in vitro cytotoxic activities on human hepatoma HepG2, leukemia K562, lung carcinoma A549, and large cell lung cancer NCI-H460 cells, therapeutic efficacies on mice transplantable tumor, and immunomodulatory potentials on the immune response in tumor-bearing mice. IHTPO exhibited lower in vitro cytotoxic activities against four human tumor cell lines, with the IC_{50} values being higher than 62.5 μM (ca. 300 μg/ml). IHTPO, however, significantly inhibited the growth of S180 sarcoma transplanted in mice. It was further showed that IHTPO could not only significantly promote splenocytes proliferation, NK cell and CTL activity from splenocytes, but remarkably enhance serum antigen-specific IgG, IgG2a and IgG2b antibody levels in S180-bearing mice. IHTPO also significantly promoted Th1 cytokines IFN-γ and IL-2 production, and up-regulated the mRNA expression levels of IFN-γ, IL-2 and Th1 transcription factors T-bet and STAT-4 in splenocytes from the S180-bearing mice. These results suggested that IHTPO significantly inhibited the growth of mice transplantable tumor, and that its in vivo antitumor activity might be achieved by improving Th1 protective cell-mediated immunity. IHTPO could act as antitumor agent with immunomodulatory activity.

1. Introduction

Conventional chemotherapeutics and targeted antineoplastic agents have been developed based on the simplistic notion that cancer constitutes a cell-autonomous genetic or epigenetic disease. In spite of their high antitumor efficacy, numerous currently used chemotherapeutic drugs exhibit considerable adverse side effects and cumulative toxicities including immunosuppression, nervous and gastrointestinal injuries [1–3]. Furthermore, the development of resistance to chemotherapy is considered a major hindrance to treatment of various cancers, as a notable proportion of tumors relapses and develops resistance, eventually resulting in multidrug resistance following exposure to multiple anticancer drugs with prevalent structure and mechanisms of action [4]. The transformation of cells and the outgrowth of carcinomas take place in the face of the immune system. Nevertheless, the immune system is able to eradicate tumors, to stop them in their growth and/or to prevent its progression to metastasis [5]. The enhancement of host immune response has been recognized as a possible means of inhibiting tumor growth without harming the host [6]. Therefore, the discovery and identification of novel products capable of potentiating the immune function that can be used alone or in combination with other chemotherapeutic drugs has become an important goal of research in immunopharmacology and oncotherapy [7].

Polyoxometalates (POMs), as a unique class of versatile metal–oxygen cluster complexes, have become a large growing and appealing area in inorganic chemistry due to not only their esthetically topological properties but also their potential applications in catalysis, materials science, biology, magnetism, optics, and medicine [8,9]. POMs are widely used as inorganic building subunits to construct hybrid compounds with desired properties [10]. In 1970, Chermann et al. [11] firstly reported "silicotungstic acid supernatants" a potent inhibitor of murine leukemia and sarcoma viruses. Since then, many POMs were found to be potential antitumor, antiviral and antibacterial drugs [12–14]. The anticancer activities of POMs have recently become one of the frontier subjects in this field [15]. Vacant POMs may have different antitumor activity and cytotoxicity because of the change of charge density on oxygen atoms from polyanions [16,17]. Functional POMs could be generated via covalent grafting of organic functions, owing to their special properties of accepting or releasing specific number of elections [18]. In the past decades, researches were focused on mono-, di-, and tri-vacant POMs, however, penta-vacant POMs were rarely reported [19–23], which hinder the progress of POMs in medicine. Meanwhile, to date, there have been numerous reports on in vitro antitumor activities of the POMs, but their in vivo antitumor effects have seldom been well

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http://dx.doi.org/10.1016/j.intimp.2015.11.003
1567-5769/

studied [15]. In addition, they showed cytotoxic to tumor cell lines only at the higher concentration, with IC_{50} values being up to mg/ml [15].

In our previous works, a penta-vacant POMs, iron hepta-tungsten phosphate oxygen clusters complex ($Na_{12}H[Fe(PW_7O_{28})_2]\cdot 44H_2O$, IHTPO) (Fig. 1) has been synthesized and characterized. In this study, the in vitro cytotoxic activities of IHTPO on various human tumor cell lines were first examined. Moreover, the in vivo therapeutic efficacies of IHTPO on the growth of mouse transplantable S180 sarcoma were also studied. As the immune system plays an important role in anti-tumor defense, attempts have been made to analyze the underlying mechanism of the anti-tumor activity of IHTPO. On this basis, the effects of IHTPO on splenocyte proliferation, natural killer (NK) cell and cytotoxic T lymphocyte (CTL) activity, cytokine production from splenocytes, as well as tumor antigen-specific IgG, IgG2a, and IgG2b antibody levels in tumor-bearing mice have been investigated.

2. Material and methods

2.1. Reagents

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), concanavalin A (Con A), lipopolysaccharide (LPS), and rabbit anti-mouse IgG peroxidase conjugate were purchased from Sigma Chemical Co., Saint Louis, MO, USA; goat anti-mouse IgG2a and IgG2b peroxidase conjugate were from Southern Biotech. Assoc., Birmingham, AL, USA; RPMI-1640 medium and fetal calf serum (FCS) was from Gibco, Grand Island, NY, USA. Cytokine (IL-2 and IFN-γ) detecting ELISA kits were from Wuhan Boster Biological Technology Co. Ltd., Hubei, China. TRIzol was from Invitrogen, Carlsbad, CA, USA; revert Aid™ M-MuLV reverse transcriptase was from Fermentas, Boston, MA, USA; diethylpyrocarbonate (DEPC), ribonuclease inhibitor, oligo(dT)18 were from Sangon, Shanghai, China; goldview was from SBS Genetech Co., Ltd., Beijing, China; cyclophosphamide (CTX) was provided by Jiangsu Hengrui Company, Lianyungang, Chin; *cis*-diamminedichloride platinum (CDDP, positive drug) was purchased from Qilu Pharmaceutical Co., LTD., Jinan, Shandong, China.

2.2. Experimental animals and cell lines

ICR mice (Grade II, 5 weeks old) were purchased from Zhejiang Experimental Animal Center (Certificate No. SCXK 2008-0033, Hangzhou, China), and acclimatized for 1 week prior to use. Half of them were male and the others were female. Rodent laboratory chow and tap water were provided *ad libitum* and maintained under controlled conditions with a temperature of 24 ± 1 °C, humidity of 50 ± 10%, and a 12/12-h light/dark cycle. All the procedures were in strict accordance with the PR China legislation on the use and care of laboratory animals and approved by the Committee for Animal Experiments of Jinhua Polytechnic.

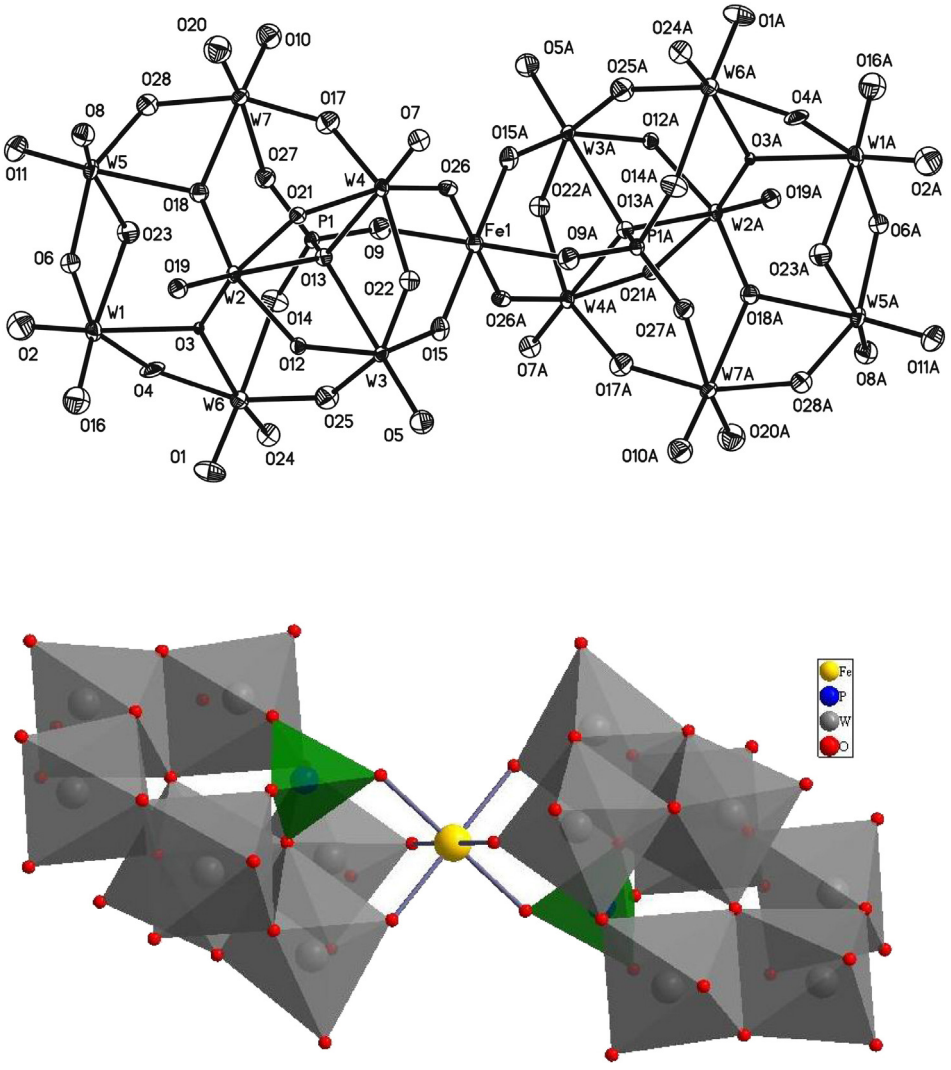

Fig. 1. Chemical structure of iron hepta-tungsten phosphate oxygen clusters complex $Na_{12}H[Fe(HPW_7O_{28})_2]\cdot 44H_2O$ (IHTPO). (a) Ball-and-stick representation of IHTPO; (b) polyhedral representation of IHTPO.

Please cite this article as: B. Zhang, et al., Anti-tumor and immunomodulatory activity of iron hepta-tungsten phosphate oxygen clusters complex, Int Immunopharmacol (2015), http://dx.doi.org/10.1016/j.intimp.2015.11.003