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Review

The effect of the novel tellurium compound AS101 on autoimmune diseases

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ABSTRACT

Tellurium is a rare element, which has been regarded as a non-essential trace element despite its relative abundance in the human body. The chemistry of tellurium supports a plethora of activities, but its biochemistry is not clearly established to date. The small tellurium^{IV} compound, ammonium trichloro (dioxoethylene-*o,o′*) tellurate (AS101) developed and initially investigated by us, is currently being evaluated in Phase II clinical trials in psoriasis patients. AS101 is the first tellurium compound to be tested for clinical efficacy. This compound is a potent immunomodulator both in vitro and in vivo with a variety of potential therapeutic applications. The present review will focus on the immunomodulatory properties of AS101, and specifically, its effects in mitigating autoimmune diseases. AS101 has several activities that act on the immune system, including: 1) its ability to reduce IL-17 levels and to inhibit the function of Th17 cells; 2) its specific unique redox-modulating activities enabling the inhibition of specific leukocyte integrins such as α4β1 and α4β7, that are pivotal for diapedesis of macrophages and CD4$^+$ T inflammatory/auto-reactive cells into the autoimmune tissues; and 3) its ability to enhance the activity of regulatory T cells (Treg). These activities coupled with its excellent safety profile suggest that AS101 may be a promising candidate for the management of autoimmune diseases.

Contents

1. Introduction

1.1. Tellurium (Te)

The metalloid, tellurium, is a rare element, which has been regarded as a non-essential trace element. Nevertheless, a typical human body possesses >0.5 g of Te, exceeding the levels of all other trace elements in humans, except for iron, zinc and rubidium [1,2]. Moreover, it was

Abbreviations: MS, multiple sclerosis; IBD, inflammatory bowel diseases; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; MADCAM, mucosal addressin cell adhesion molecule; DSS, dextran sodium sulfate.

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suggested that tellurium, long thought to be toxic, would eventually be found to be an essential element, in a manner similar to selenium [3–5]. Toxicity of tellurium compounds depends on the chemical form and the quantity of the element consumed. The toxicology of tellurium has received less attention than that of selenium. This may be a result of the less frequent interaction of man and animals with this element and its compounds. Tellurium is less soluble than selenium at physiological pH and its oxidation to tellurite (TeO_3^{2-}), tellurate (TeO_4^{2-}) or TeO_2 occurs easily.

Tellurium can be incorporated into both inorganic and organic compounds. Many tellurium-based substances are redox-active, with the formal oxidation states of tellurium in these compounds ranging from −2 to +6 [6].

1.1.1. Biological activity of tellurium compounds

Michael Albeck's laboratory has synthesized a group of tellurium-based compounds with varied Te valences. The compounds exerting the most pronounced biological activities are Te^{IV} valences, including AS101 [ammonium trichloro (dioxoethylene-O,O_)tellurate] [7,8], and SAS [octa-O-bis-(R,R)-tartarate ditellurane] [8,9]. Our studies have pioneered a new area, demonstrating the potency of inorganic Te^{IV} compounds in biology. Our breakthrough in the field of translational medicine brought inorganic tellurium-based compounds such as AS101 into the clinic and introduced opportunities for the development of other tellurium-based compounds for applications in biology and medicine. This new and growing area includes an expanding list of compounds as can be seen in Table 1.

1.1.1.1. The tellurium compound, AS101. AS101 is a small, inorganic tellurium^{IV} compound (Fig. 1), currently being evaluated in Phase II clinical trials in psoriasis patients (unpublished data) and in the prevention of bone marrow toxicity induced by chemotherapy in cancer patients [17]. This compound is a potent immunomodulator both in vitro and in vivo with a variety of potential therapeutic applications [7,11,13,14,16,17,25,26]. Accumulated evidence suggests that much of the biological activity of AS101 and other Te^{IV} compounds such as SAS is directly related to its specific chemical interactions with cysteine thiol residues. The Te^{IV}–thiol chemical bond may lead to conformational changes or disulfide bond formation in a specific protein, possibly resulting in the loss of its biological activity, if the thiol residue is essential for the particular function [27,28]. Indeed, we demonstrated that AS101 and SAS specifically inactivate cysteine proteases, while exhibiting no effect on the other families of serine-, aspartic- and metalloproteases, in good agreement with predictions based on their unique Te^{IV}-thiol chemistry. Furthermore, the proteolytic activity of the inactivated cysteine proteases could be recovered by reducing agents such as $NaBH_4$, further supporting the suggestion that the inactivation process involves oxidation of the catalytic thiol to a disulfide [8,9].

Table 1
Biological activities of tellurium-based compounds.

Compounds	Biological activity	Reference
AS101	Anti-inflammatory activity	[10–13]
	Anti-viral activity	[14,15]
	Chemosensitization of cancer cells	[16]
	Prevention of chemotherapy induced toxicity	[17]
SAS	Anti-angiogenic activity	[18]
Organotelluroxetane RF-07	Anti-epileptic activity	[19]
3-Ethyl-3′-methyl-thiatelluracarbocyanine iodide	Anti-tumor activity	[20]
Unsymmetrical diorganyl-tellurium dichlorides	Bacteriocidal effect against Gram-negative bacteria	[21]
Chloro-telluroxetane Bis-vinylic organotellurane	Anti-viral activity	[22]
Diaryl tellurides NDBT	Anti-oxidant activity	[23]
Sulfonic acid-derived organotelluriums	Anti-parasitic activity	[24]

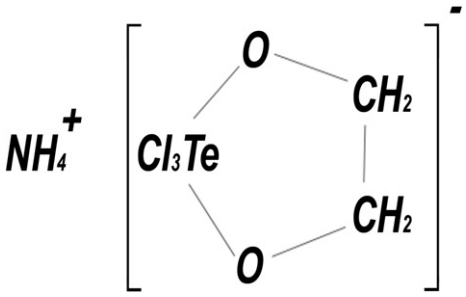

Fig. 1. The chemical structure of AS101.

In light of its chemical properties, AS101 has been shown to exert anti-inflammatory activity in various in vivo models [10–13,28], through the downregulation of IL-1β, IL-17 and IL-6 cytokine levels.

1.2. Integrins in autoimmunity

Integrins are transmembrane cell adhesion receptors composed of non-covalently associated α and β subunits that bind to cell-surface ligands, soluble ligands and extracellular matrix proteins [29]. These adhesive interactions are essential for leukocyte recirculation, migration into inflammatory sites, recognition of foreign antigens, and survival and proliferation [30–32]. The field of leukocyte cell adhesion holds considerable promise as a source of novel and potent targets for treatment of inflammation and autoimmune diseases [33]. For example, increased recruitment of leukocytes into inflamed tissue in chronic autoimmune disorders could be prevented by interfering with the mechanisms of leukocyte diapedesis [33]. There have been significant positive advances in both basic research and clinical development in this area. Basic research has yielded a detailed insight into the structural basis for the function of cell adhesion molecules, especially the interaction of integrins with their ligands [34,35].

Therapeutic interventions based on the use of monoclonal antibodies against cell adhesion molecules have been extensively studied. In preclinical studies using various animal models, promising results have been obtained demonstrating that blocking of adhesion receptors of the integrin and selectin families mitigated the inflammation process in models of ulcerative colitis [33,36,37], autoimmune encephalomyelitis [38], rheumatoid arthritis [39,40] and other pathologies.

2. Proposed mechanisms of the anti-autoimmune properties of AS101

Th17 cells are potent inflammatory mediators that contribute to a list of disorders such as lupus, IBD, RA, psoriasis, asthma, allergy and MS. Therapeutic strategies aimed at attenuating but not abrogating the IL-17/IL-17R response or other associated factors such as IL-6/IL-6R signaling may be promising means to ameliorate inflammatory and autoimmune diseases [41].

In mice, TGFβ and IL-6 initiate the differentiation of Th17 cells and activate RORγt. IL-6 upregulates IL-23R on the differentiated Th17 cells and, together with IL-23 or IL-21, promotes Th17 differentiation via activation of STAT3. Differentiation of Th17 cells is greatly impaired in STAT3 deficient T cells, marked by impaired RORγt expression. In human, differentiation is initiated by TGFβ and IL-21 which induce the transcription factor RORc, while IL-1β plus IL-6 are important for enhancing the amplification of Th17 cells [42].

Recently, it was shown that AS101 inhibits the differentiation of Th17 and reduces the production of IL-17 from these cells, partially by the induction of IL-2. Furthermore, AS101 blocked the activation of