CHARACTERIZATION OF SB 11285 AS A NOVEL STING AGONIST FOR IMMUNOLOGY

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BACKGROUND AND INTRODUCTION

Immunotherapy has emerged as a transformative approach for the treatment of cancer. It is believed that the induction of IFNs and ISGs within the tumor microenvironment (TME) is essential for efficient immune-mediated anti-tumor response. Indeed, the cGAS-STING-TBK1/IκKβ-IRF3/NF-κB pathway provides a potential target within TME for immune-modulators to enhance the production of IFNs and ISGs [1,2].

We recently disclosed that SB 11285 is a highly potent STING agonist that induces the production of IFNs and ISGs in human monocytic cells [3,4]. Reported here are studies elucidating the mechanism of action (MOA) of SB 11285 and its potential for activating innate immune cells in the TME to elicit potent anti-tumour activity. SB 11285 was discovered by screening and SAR-based optimization of a proprietary focused library of dinucleotides for their ability to activate type I IFN signaling in conjunction with proprietary SZ14 cells that stably express ISG54 ISRE-luciferase reporter gene. We further characterized the immune-modulatory properties of SB 11285. The results are presented here.

MATERIALS AND METHODS

To investigate the MOA of SB 11285, we utilized various cell lines expressing type I IFN-inducible reporter genes, including SZ14 cells, and cells deficient in STING, as well as, TLR adaptor MyD88 (InvivoGen). Primary human innate immune cells were obtained from ZenBio and STING-deficient (goldenticket <Tmem173>) mouse cells from the Jackson Laboratory. Palmitoylation inhibitor, 2-BP, was obtained from Wako, and TBK1/IκKβ inhibitor, BX795, from InvivoGen. Analysis of type I IFN-inducible reporter activities, as well as, the production of type I IFN and other cytokines and chemokines were done using luciferase assays, ELISA and multiplexed ELISA (Quansys). IRF3 nuclear translocation and in vitro tumor cell growth inhibition were assessed using the ImageXpress Micro (Molecular Devices).

RESULTS

SB 11285 induces dose-dependent type I IFN response in SZ14 and THP1 cells

PBMCs isolated from healthy donors were treated with SB 11285 alone or controls (data not shown) for 20 hrs. The production of IFN-α and other cytokines in supernatants were measured using regular ELISA and the results are shown as pg/ml (average ± standard deviation of duplicate wells per concentration).

SB 11285 induces type I/II/III IFN and other cytokines and chemokines in mouse splenocytes and macrophages

REFERENCES


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