The histone deacetylase inhibitor belinostat ameliorates experimental autoimmune encephalomyelitis in mice by inhibiting TLR2/MyD88 and HDAC3/ NF-κB p65-mediated neuroinflammation

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1. 簡述論文的概要以及重大發現：

   多發性硬化症是一種發生在中樞神經系統 (CNS)的自體免疫性疾病。他是因為人體的自體免疫系統攻擊和破壞神經髓鞘而導致的致病。小膠質細胞(microglia)在 MS 裏扮演重要的角色，M1 小膠質細胞會釋放促發炎細胞因子導致發炎和 CNS 的損傷，M2 小膠質細胞能釋放抗炎細胞因子促進炎症消退。本研究發現組蛋白去乙酰化酶抑製劑 (HDACi) belinostat 能夠抑制 M1 小膠質細胞的激活和促炎細胞因子的表達，並通過抑制 TLR2/MyD88 和 HDAC3/ NF-κ B p65 信號通路，抑制神經炎症。

2. 對論文內容的提問：

   Belinostat 能夠透過抑制 TLR2/MyD88 和 HDAC3/ NF-κ B p65 信號通路改善 EAE，但還不確定抑制那一條信號通路對抑制炎症的作用較大。

3. 論文的缺點與評論：

   HDAC 在過去的認知中通常是參與在調控轉錄後修飾。透過去除 DNA 乙酰基，使染色質變得緊密，從而抑制 transcription 的過程。而在本篇研究中的 HDAC3 去乙酰化的對像是 p65，透過去乙酰化 p65，激活小膠質細胞 cGAMP-STING-IRF3 pathway，釋放 IFN-γ 和其他的發炎因子，促進神經炎的發生。

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ABSTRACT

Multiple sclerosis (MS) is a Th cell-mediated inflammatory demyelinating autoimmune disease. MS cannot be cured, and long-term drug treatment is still needed for MS patients. In this study, we examined the effect of belinostat, a pan-histone deacetylase inhibitor (HDACi), on experimental autoimmune encephalomyelitis (EAE) and elucidated its mechanism of action. We found that belinostat alleviates the clinical symptoms, histopathological central nervous system (CNS) inflammation and demyelination outcomes in EAE mice. Compared to the MS oral drug dimethyl fumarate (DMF) (100 mg/kg), belinostat (30 mg/kg) treatment exhibited better efficacy in improving the clinical symptoms of EAE mice. Belinostat treatment significantly suppressed the activation of M1 microglia and the proinflammatory cytokine expression; but it had no effects on the M2 microglial polarization. Belinostat also decreased both NO and iNOS levels in LPS-stimulated BV2 microglia. Accordingly, belinostat treatment of EAE mice significantly inhibited activation of the TLR2/MyD88 signaling pathway and downregulated the expression of HDAC3 while upregulating the acetylated NF-κB p65 levels. Taken together, these data demonstrate for the first time that belinostat ameliorates EAE in mice through inhibiting neuroinflammation via suppressing M1 microglial polarization, and implicating belinostat as a potential candidate for the treatment of multiple sclerosis.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) with pathological hallmarks including inflammation, demyelination, axonal loss and gliosis [1]. As a major cause of irreversible disability in young adults (those between ages 20 and 40 years), MS affects over 2.3 million people globally [2]. There is currently no cure for MS, and long-term drug treatment is still needed for MS patients. Based on current knowledge of MS pathophysiology, therapeutic strategies of MS include immunomodulatory therapy, anti-inflammatory therapy and anti-neurodegeneration therapy [3]. Over the last 20 years, several drugs corresponding to the above

Abbreviations: MS, multiple sclerosis; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; HDACs, histone deacetylases; HDACi, histone deacetylase inhibitor; DCs, dendritic cells; TSA, trichostatin A; LPS, lipopolysaccharide; MOG, myelin oligodendrocyte glycoprotein; CFA, complete Freund's adjuvant; DMF, dimethyl fumarate; CMC-Na, carboxymethylcellulose sodium; H&E, hematoxylin–eosin; LFB, luxol fast blue; MBP, myelin basic protein; GFAP, glial fibrillary acidic protein; DMEM, Dulbecco's modified Eagle's medium; FBS, fetal bovine serum; MCP-1, monocyte chemotactic protein-1; ELISA, enzyme-linked immunosorbent assay; RIPA, radioimmunoprecipitation assay; PVDF, polyvinylidene difluoride; iNOS, inducible nitric oxide synthase; MyD88, myeloid differentiation factor 88; IRAK-4, IL-1 receptor-associated kinase-4; TRAF-6, tumor necrosis factor receptor associated factor 6; IRF5, interferon regulatory factor 5; SEM, standard error of mean; H3K9, histone H3 lysine 9; H3K9Ac, acetylated H3K9; Arg-1, Arginase 1; TGF-β, transforming growth factor beta; TLRs, toll-like receptors; PRR, pathogen recognition receptors; DAMPs, danger associated molecular patterns; PAMP, pathogen associated molecular patterns; PBMC, peripheral blood mononuclear cell.

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