TH17 cells promote CNS inflammation by sensing danger signals via Mincle

Quanri Zhang , Weiwei Liu , Han Wang , Hao Zhou1, Katarzyna Bulek, Xing Chen , Cun-Jin Zhang , Junjie Zhao , Renliang Zhang, Caini Liu , Zizhen Kang, Robert A. Berme, George Dubyak , Derek W. Abbott, Tsan Sam Xiao , Laura E. Nagy & Xiaoxia Li

NATURE COMMUNICATIONS

Room:236 **Speaker** : JIA-NI,DONG **Date** : 2023.03.03 **Advisor** : Dr. SHU-FEN WU

1. **簡述論文的概要以及重大發現：**

   多發性硬化症(MS)是一種發生在中樞神經系統 (CNS)的自體免疫性疾病。導致疾病的發生是由於人體自身的免疫系統攻擊及破壞神經髓鞘。TH_{17} 細胞與 MS 發病機制息息相關。C 型凝集素受體 (CLR)是一種模式識別受體(PRR)，藉由辨識並結合 pathogen and damage associated molecular patterns，進而去誘導下游訊號活化引起免疫反應。本篇以 MS 為研究對象。本研究發現 TH_{17} 細胞透過 C 型凝集素受體 Mincle 感知危險信號進而去促進 CNS 的發炎，且 TH_{17} 細胞中 Mincle 的缺失會影響其致病的能力。

2. **對論文內容的提問：**

   在本篇研究中發現β-glucosylceramide 是一種由垂死細胞所釋放的 Mincle 配體，以 Mincle 依賴性的方式促進 TH_{17} 細胞增殖。但是否還有其他的危險信號可以重新激活中樞神經系統中的 TH_{17} 細胞，並刺激 TH_{17} 細胞的增殖和轉化為炎性 TH17 細胞?

3. **論文的缺點與評論：**

   在誘導 EAE 時主要用 HK-Mtb 的 cord factor (TDM)作為佐劑，且已知 TDM 為 Mincle 的配體，雖然在作者的研究中表示 HK-Mtb 與 Mincle 結合啟動下游訊號表現，其影響 TH_{17} 分化的作用有限。導致這樣結果的產生有幾種可能的因素，在 HK-Mtb 中存在其他 T 細胞配體，例如 HK-Mtb 還含有 TLR2、TLR4 和 TLR9 配體，而 TLR2 和 TLR4 的訊號表現都可以促進 TH_{17} 細胞的作用和自體免疫疾病的發病機制；此外 Mincle 與其他受體相比，對於 HK-Mtb 中配體的敏感性有所差異。例如，與 TLR2 相比，Mincle 需要更高濃度的 HK-Mtb 來激活。因此 HK-Mtb 誘導 TH_{17} 細胞的反應實際有那些訊號參與還需要進一步去研究。本篇研究作者提出與以往不同的訊號路徑，並探討其對於 TH_{17} 細胞致病力以及自體免疫疾病的影響。

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-022-30174-1 OPEN

TH17 cells promote CNS inflammation by sensing danger signals via Mincle

Quanri Zhang[1], Weiwei Liu[1], Han Wang[1], Hao Zhou[1,11], Katarzyna Bulek[1,2], Xing Chen[1], Cun-Jin Zhang[3], Junjie Zhao[1], Renliang Zhang[4], Caini Liu[1], Zizhen Kang[5], Robert A. Bermel[6], George Dubyak[7], Derek W. Abbott[8], Tsan Sam Xiao[8], Laura E. Nagy[1,9,10,12✉] & Xiaoxia Li[1,12✉]

The C-type lectin receptor Mincle is known for its important role in innate immune cells in recognizing pathogen and damage associated molecular patterns. Here we report a T cell-intrinsic role for Mincle in the pathogenesis of experimental autoimmune encephalomyelitis (EAE). Genomic deletion of Mincle in T cells impairs TH17, but not TH1 cell-mediated EAE, in alignment with significantly higher expression of Mincle in TH17 cells than in TH1 cells. Mechanistically, dying cells release β-glucosylceramide during inflammation, which serves as natural ligand for Mincle. Ligand engagement induces activation of the ASC-NLRP3 inflammasome, which leads to Caspase8-dependent IL-1β production and consequentially TH17 cell proliferation via an autocrine regulatory loop. Chemical inhibition of β-glucosylceramide synthesis greatly reduces inflammatory CD4+ T cells in the central nervous system and inhibits EAE progression in mice. Taken together, this study indicates that sensing of danger signals by Mincle on TH17 cells plays a critical role in promoting CNS inflammation.

[1] Department of Inflammation and Immunity, Cleveland Clinic, Lerner Research Institute, Cleveland, OH, USA. [2] Department of Immunology, Faculty of Biochemistry, Biophysics, and Biotechnology, Jagiellonian University, Krakow, Poland. [3] Department of Neurology, Nanjing Drum Tower Hospital, Medical School and the State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing, Jiangsu, China. [4] Proteomics and Metabolomics Core, Department of Research Core Services, Lerner Research Institute, Cleveland, OH, USA. [5] Department of Pathology, University of Iowa, Iowa, IA, USA. [6] Mellen Center for Multiple Sclerosis, Cleveland Clinic, Cleveland, OH, USA. [7] Department of Physiology and Biophysics, University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA. [8] Department of Pathology, Case Western Reserve University, Cleveland, OH, USA. [9] Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, OH, United States. [10] Department of Molecular Medicine, Case Western Reserve University, Cleveland, OH, United States. [11] Present address: Division of Transplant Surgery, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA. [12] These authors jointly supervised this work: Laura E. Nagy, Xiaoxia Li. ✉email: nagyl3@ccf.org; lix@ccf.org