中文題目：自體免疫腦脊髓炎模式中 TRAIL 藉由非誘導凋亡方式抑制 T 細胞受體訊息傳導並抑制 T 細胞活化與自體發炎

英文題目：An apoptosis-independent role of TRAIL mediates suppression of T cell activation and autoimmune inflammation in experimental autoimmune encephalomyelitis

作　　者：全以祖[1]，蔡慧芳[2]，許秉寧[3]

服務單位：[1]國泰綜合醫院風濕免疫科，[2]雙和醫院腎臟內科，[3]台大醫院風濕免疫科

Background: Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) promotes cell apoptosis by binding to death-inducing TRAIL receptor (TRAIL-R), preferentially in transformed cells. Although non-transformed cells are insensitive to TRAIL-induced apoptosis, accumulating evidence has shown that TRAIL can regulate immune responses and immune cell homeostasis in autoimmune diseases. However, the immunoregulatory mechanism of TRAIL in modulating autoimmune responses is still not clear. The purpose of this study is to address the immune-regulatory role and molecular mechanism of TRAIL in regulating T cell activation in autoimmune diseases.

Methods: TRAIL was administered to mice to induce experimental autoimmune encephalomyelitis (EAE), and to evaluate its impact on neuroinflammation and disease activity. The effects of TRAIL on neuroantigen [myelin oligodendrocyte glycoprotein $(MOG)_{35–55}$]-activated T cell proliferation and cytokine production were investigated. TRAIL-treated $MOG_{35–55}$-activated splenic Th17 cells were further adoptively transferred into Rag1 KO mice to induce passive EAE. Gene expression profiles of CD4 T cells from EAE mice treated with TRAIL were analyzed by RNA sequencing and transcriptome analysis.

Result: TRAIL suppressed autoimmune encephalomyelitis and inhibited T cell reactivity to neuro-antigen without triggering apoptosis in EAE, and the effects were dependent on TRAIL-R signaling. Moreover, TRAIL directly inhibited activation of $MOG_{35–55}$-activated CD4 T cells, resulting in suppression of neuroinflammation and reduced disease activity in adoptive transfer-induced EAE. Importantly, TRAIL/TRAIL-R signaling directly inhibited phosphorylation of proximal T cell receptor (TCR)-associated tyrosine kinases in activated CD4 T cells and downregulated signaling genes in RNA sequencing and transcriptome analysis.

Conclusion: In conclusion, TRAIL/TRAIL-R interaction regulates CD4 T cell activation in autoimmune inflammation and directly suppresses T cell activation via inhibiting TCR signaling, suggesting that TRAIL-R serves as a novel immune checkpoint in T cell responses to regulate autoimmune inflammation.