Interleukin 16: a potential protective cytokine in idiopathic inflammatory myopathy

Sirs,

Idiopathic inflammatory myopathy (IIM) is a group of systemic autoimmune diseases characterised by muscle involvement. Previous research has shown that interleukin (IL)-16, an immunomodulatory cytokine secreted by leukocyte subpopulations (1) is implicated in the pathogenesis of autoimmune disorders (2, 3). This cross-sectional study aimed to investigate serum IL-16 levels in patients with IIM and assess its clinical significance.

Between June 2021 and March 2023, peripheral blood samples were collected from 35 healthy controls (HCs), 48 patients with IIM, and 6 patients with lipid storage myopathy (LSM) at West China Hospital, Sichuan University. Approval was obtained from the Ethics Committee of this hospital (no. 521, 2021) and all participants provided written informed consent before inclusion in the study.

The inclusion and exclusion criteria, as well as the scoring tools for IIM, are detailed in Supplementary Material S1. The serum IL-16 levels were measured using ELISA (RX106161H, Ruixinbio, China).

The clinical information of the participants is detailed in Supplementary Table S1. Our study showed that IL-16 levels were significantly elevated in both patients with IIM (64.98 *vs*. 90.03 pg/mL, $p<0.0001$) and LSM (64.98 *vs*. 88.92 pg/mL, $p=0.0001$) compared to HCs (Fig. 1A). Specifically, IL-16 levels in patients with dermatomyositis (DM) ($p<0.0001$), immune-mediated necrotising myopathy (IMNM) ($p<0.0001$), anti-synthetase syndrome (ASS) ($p<0.0001$), and unclassified IIM ($p=0.0048$) were all significantly higher than HCs (Fig. 1B). It was discovered that patients positive for specific autoantibodies of anti-EJ ($p=0.0157$), anti-Jo-1($p=0.0065$), anti-TIF1-γ ($p=0.0288$), anti-MDA5 ($p<0.0001$), anti-Mi-2 ($p=0.0015$), anti-SRP ($p=0.0002$), and patients negative for myositis-specific autoantibodies ($p=0.0017$) all exhibited higher levels of IL-16 (Fig. 1C). Notably, as shown in Fig.1D, serum IL-16 levels exhibited negative correlations with CRP (r= -0.4450, $p=0.0031$), ESR (r= -0.3381, $p=0.0285$), and CD8 count (r= -0.3678, $p=0.0273$), while showing a positive correlation with

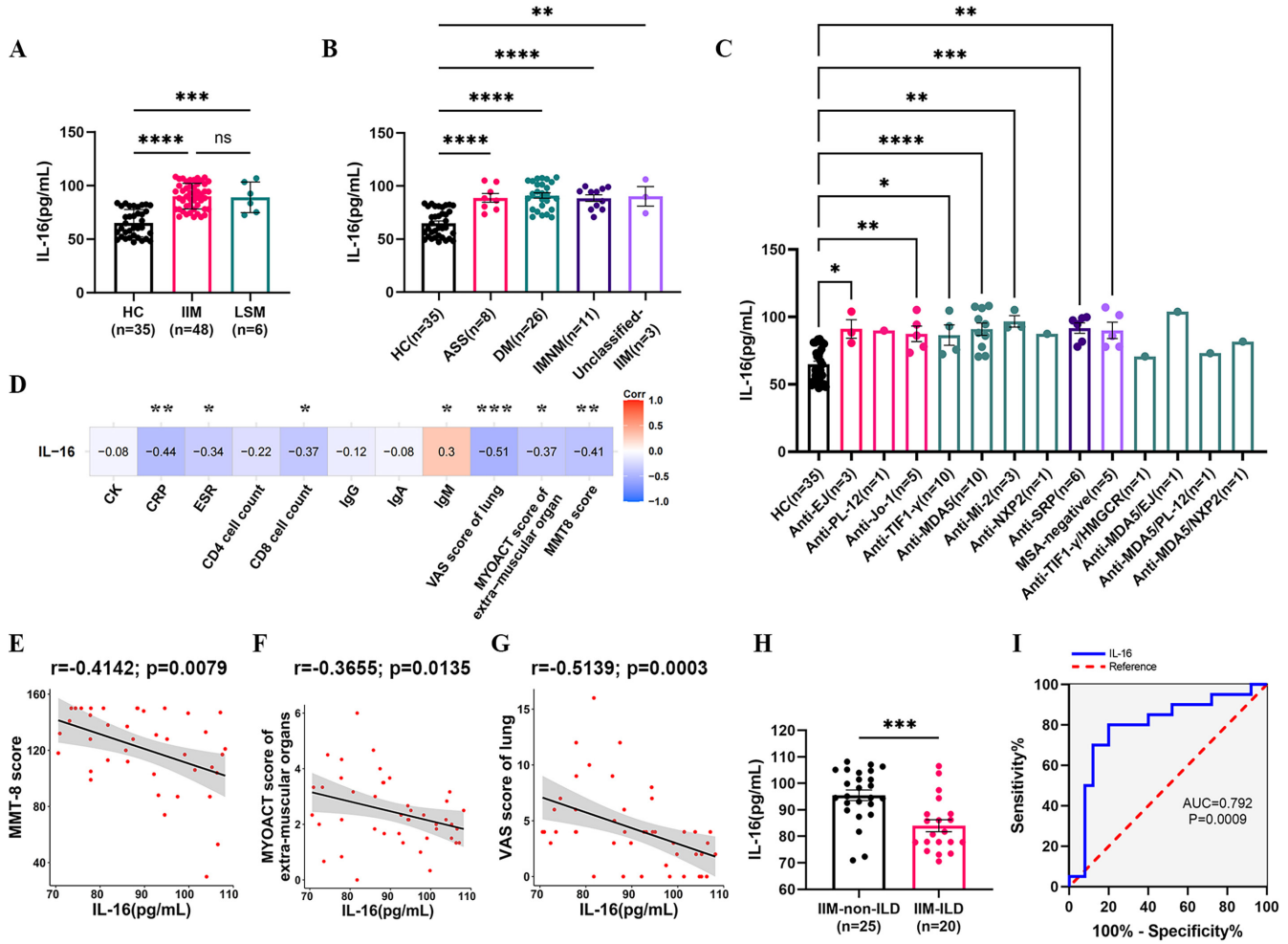

Fig. 1. Serum IL-16 levels are elevated and may have a protective role in patients with IIM.

A: Serum IL-16 levels in HC, patients with IIM and LSM. **B**: Serum IL-16 levels in HC and patients with ASS, DM, IMNM, and unclassified IIM. **C**: Serum IL-16 levels in HC and patients with IIM classified by MSAs. **D**: The heat map of correlation analysis between serum IL-16 level and selected clinical indicators and myositis scores. The numbers in the coloured squares are the values of the correlation coefficient r. Correlation analysis (Spearman) plot between serum IL-16 level and MMT8 scores (n=40) (**E**), or MYOCAT score for extra-muscular organs involvement (n=45) (**F**) or VAS of lung (n=45) (**G**). **H**: Serum IL-16 levels in patients with IIM-non-ILD and IIM-ILD. **I**: The receiver operating characteristic curve evaluation for the diagnostic value of IL-16 in patients with IIM-non-ILD or IIM-ILD.

HC: healthy control; IIM: idiopathic inflammatory myopathy; LSM: lipid storage myopathy; ASS: anti-synthetase syndrome; DM: dermatomyositis; IMNM: immune-mediated necrotising myopathy; EJ: glycyl-tRNA synthetase; PL-12: alanyl-tRNA synthetase; Jo-1: histidyl-tRNA synthetase; TIF1-γ: transcription intermediary factor 1-γ; MDA5: melanoma differentiation-associated gene 5; NXP2: nuclear matrix protein 2; SRP: signal recognition particle; MSA: myositis-specific autoantibody; HMGCR: hydroxymethylglutaryl-CoA reductase; CK: creatine kinase; MYOACT: myositis disease activity assessment visual analogue scale; VAS: visual analogue score; MMT8: manual muscle testing 8; ILD: interstitial lung disease; AUC: area under the curve.

Data are expressed as mean with SEM. *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$.

serum IgM (r=0.3042, p=0.0422). Additionally, serum IL-16 levels were negatively associated with MMT8 score (r= -0.4142, p=0.0079; Fig. 1E), MYOCAT score for extra-muscular organs involvement (r= -0.3655, p=0.0135; Fig. 1F), and VAS for lungs (r= -0.5139, p=0.0003; Fig. 1G) in patients with IIM. Moreover, IIM patients with interstitial lung disease (IIM-ILD) had lower IL-16 levels compared to those without ILD (IIM-non-ILD) (95.49 *vs*. 84.02 pg/mL, p=0.0004; Fig. 1H). Receiver operating characteristic curve analysis supported the potential of IL-16 levels as a serum marker to differentiate between IIM-ILD and IIM-non-ILD (cut-off value = 89.13 pg/mL, sensitivity = 80%, specificity = 80%, area under the curve = 0.7920, p=0.0009; Fig. 1I).

IL-16 has been implicated in exacerbating muscle-related conditions (4, 5) and lung inflammation (6). However, our research revealed increased serum IL-16 levels in patients with IIM and LSM. Additionally, we also observed a potential protective role of IL-16 in IIM, possibly attributed to its ability to promote the formation and migration of regulatory T cells, thereby exerting an immunosuppressive function (7). While advancements have been made in IIM, the diagnosis of IIM-ILD still heavily relies on imaging techniques (8). Our study found IL-16 can be used to differentiate between IIM-ILD and IIM-non-ILD. This study is limited by the relatively small sample size of IIM subtypes and its single-centre design, and future research will address these limitations and delve deeper into the role of IL-16 in IIM.

Together, the serum IL-16 levels may have a protective role in IIM and could potentially be used as a biomarker for predicting the presence of ILD in IIM.

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