Dysregulation of interleukin-18 receptor accessory protein in neutrophils of patients with systemic lupus erythematosus

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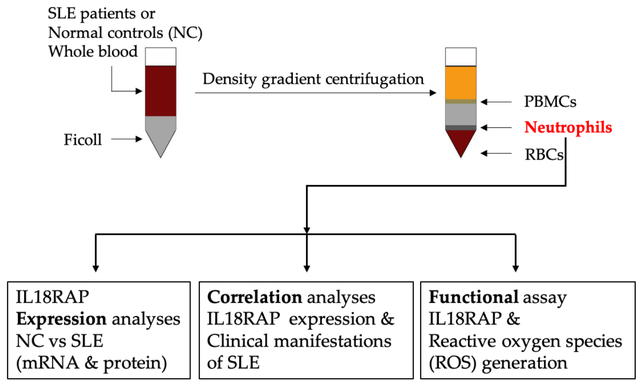
Abstract

Interleukin-18 receptor accessory protein (IL18RAP) is an indispensable subunit of the IL-18 receptor complex to mediate high affinity IL-18 binding and signalling transduction. IL-18 in systemic lupus erythematosus (SLE) has been mostly focused on its role as a type 1 T helper cell driving cytokine. The functional significance of IL18RAP in mediating IL-18 driven response in myeloid cells in SLE remains largely unexplored. This study aimed to investigate the expression and function significance of IL18RAP in neutrophils of SLE patients. Expression of IL18RAP in neutrophils was compared between healthy controls and SLE patients by qRT-PCR and Western Blotting. Modulation of IL18RAP expression in neutrophils was assayed by *in vitro* culture with patient sera and interferon-α (IFN-α). Neutrophils' ability to produce reactive oxygen species (ROS) upon stimulation was evaluated in combination with recombinant IL-18 and IL18RAP blocking antibodies. Increased expressions of IL18RAP mRNA and protein were observed in neutrophils from SLE patients, particularly those with history of nephritis. IL18RAP expression correlated negatively with complement 3 level and positively with disease activity, with higher expression in patients exhibiting renal and immunological manifestations. Its expression could be upregulated by SLE sera with high interferon level or by recombinant IFN-α. Neutrophils from SLE patients showed higher IL-18-mediated enhancement in ROS generation in an IL18RAP-dependent manner. These findings suggests that IL-18 could contribute to SLE pathogenesis through mediating neutrophil dysfunction via the upregulated IL18RAP expression.

Introduction

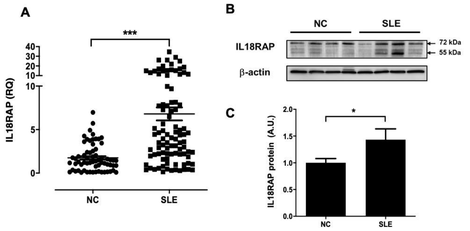
- Systemic lupus erythematosus (SLE) is a female biased autoimmune disorder that affects multiple organ systems. The proinflammatory cytokine, interleukin-18 (IL-18) plays a pathological role in the development of SLE[1,2].
- IL-18 receptor accessory protein (IL18RAP) is an indispensable subunit of IL-18R complex to mediate high affinity IL-18 binding and subsequent signalling transduction[3,4].
- In our screening assay, we observed an elevated expression of IL18RAP in peripheral leukocytes of lupus nephritis (LN) patients and its expression level was highly correlated with neutrophil-associated genes.

Methodology

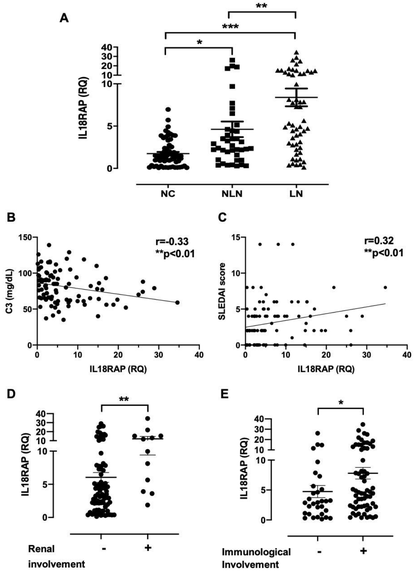


Results

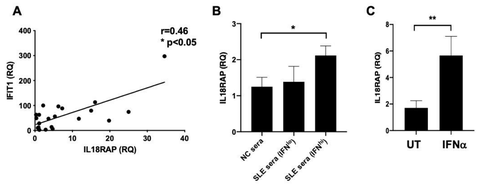
1. Increased expression of IL18RAP in neutrophils from SLE patients



2. Correlation analyses between IL18RAP expression and clinical manifestations of SLE patients

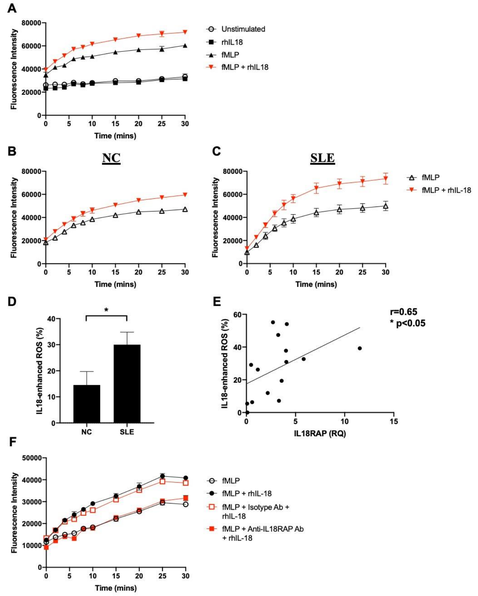


3. Regulatory effect of type I interferon (IFN) on IL18RAP expression in neutrophils



Results

4. IL-18 enhances fMLP-mediated ROS generation in neutrophils via IL18RAP



Conclusions

In summary, we have revealed an overexpression of IL18RAP in neutrophils which is associated with disease activity and renal involvement in SLE patients. Type I IFN in the inflammatory milieu could have caused the upregulation, and in turn confer IL-18-mediated enhancement in ROS generation. These findings provide new insights on the role of IL-18 in contributing to the dysregulated neutrophil functions, which is now known to play a crucial role in SLE and LN development.

References

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