Extracellular Signal-Mediated Activation of IRE1 Promotes TH17 Responses

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Abstract

Introduction

Heightened unfolded protein responses (UPRs) are associated with many TH17-driven inflammatory diseases. However, how UPRs participate in the deregulation of TH17 cells remains elusive.

Objective

We investigated the role of the UPR sensor IRE1 in TH17 cell function and the underlying mechanism.

Methods

Whether and how extracellular stimuli lead to IRE1 phosphorylation was explored by using flow cytometry, western blot, confocal microscopy, in vitro phosphorylation, and co-immunoprecipitation. T cell-specific *Ern1* (encoding IRE1)-deficient cells were used to examine the effects of IRE1 on TH17 responses.

Results

The UPR sensor IRE1 is highly expressed in TH17 cells relative to naïve $CD4^+$ T cells. Signals of cytokines (e.g. IL-23 and IL-6) and co-stimulation induce the IRE1-XBP1s axis. Among those, IL-23 activates IRE1 in a JAK2-dependent manner. This noncanonical activation of the IRE1-XBP1s pathway promotes UPRs and cytokine secretion by both human and mouse TH17 cells. *Ern1* (encoding IRE1)-deficiency decreases the expression of ER stress factors and impairs the differentiation and cytokine secretion of TH17 cells.

Conclusion

Our data indicate that IRE1, noncanonically activated by cytokine signals, promotes the secretory function of TH17 cells. The findings provide a novel insight into the fundamental understanding of UPRs in TH17-mediated diseases.

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