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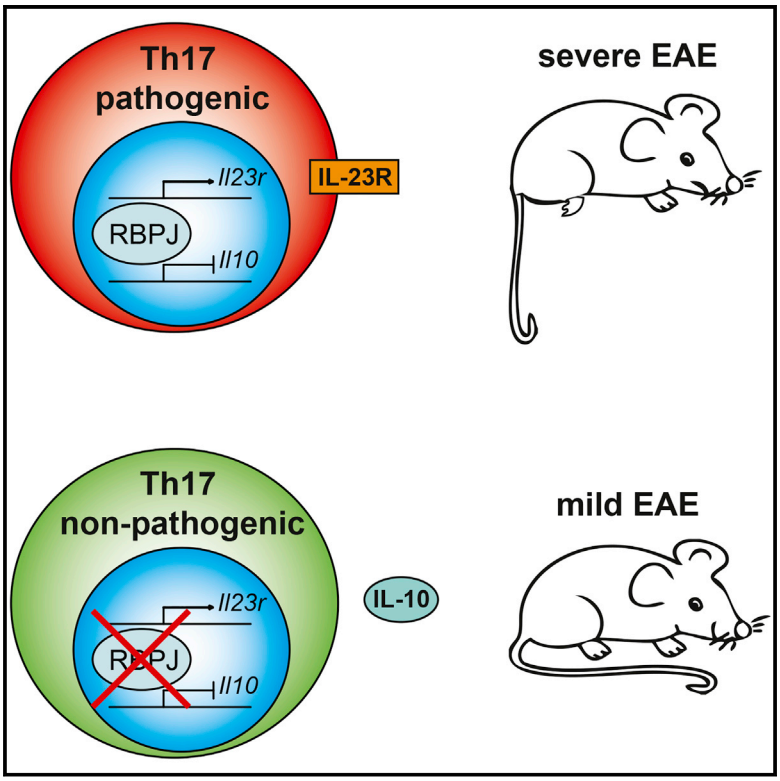
RBPJ Controls Development of Pathogenic Th17 Cells by Regulating IL-23 Receptor Expression

Graphical Abstract



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In Brief

Meyer zu Horste et al. find that RBPJ promotes the pathogenicity of Th17 cells by directly enhancing expression of the interleukin-23 receptor and repressing interleukin-10 production.

Highlights

- RBPJ promotes experimental CNS autoimmunity via the IL-23R
- RBPJ-deficient Th17 cells fail to express IL-23R and related transcripts
- RBPJ binds and *trans*-activates the *Il23r* promoter together with RORγt
- RBPJ represses expression of IL-10 in Th17 cells

Meyer zu Horste et al., 2016, Cell Reports *16*, 392–404
July 12, 2016
http://dx.doi.org/10.1016/j.celrep.2016.05.088

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Cell Reports
Article

RBPJ Controls Development of Pathogenic Th17 Cells by Regulating IL-23 Receptor Expression

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http://dx.doi.org/10.1016/j.celrep.2016.05.088

SUMMARY

Interleukin-17 (IL-17)-producing helper T cells (Th17 cells) play an important role in autoimmune diseases. However, not all Th17 cells induce tissue inflammation or autoimmunity. Th17 cells require IL-23 receptor (IL-23R) signaling to become pathogenic. The transcriptional mechanisms controlling the pathogenicity of Th17 cells and IL-23R expression are unknown. Here, we demonstrate that the canonical Notch signaling mediator RBPJ is a key driver of IL-23R expression. In the absence of RBPJ, Th17 cells fail to upregulate IL-23R, lack stability, and do not induce autoimmune tissue inflammation in vivo, whereas overexpression of IL-23R rescues this defect and promotes pathogenicity of RBPJ-deficient Th17 cells. RBPJ binds and *trans*-activates the *Il23r* promoter and induces IL-23R expression and represses anti-inflammatory IL-10 production in Th17 cells. We thus find that Notch signaling influences the development of pathogenic and non-pathogenic Th17 cells by reciprocally regulating IL-23R and IL-10 expression.

INTRODUCTION

Interleukin-17 (IL-17)-producing helper T cells (Th17 cells) have been identified as a distinct subset of effector $CD4^+$ T cells and are considered critical drivers of autoimmune tissue inflammation (Bettelli and Kuchroo, 2005; Korn et al., 2009). Differentiation of naive $CD4^+$ T cells into Th17 cells is achieved with the cytokines transforming growth factor (TGF)-β1 and IL-6 (Bettelli et al., 2006). This cytokine combination, however, generates Th17 cells, which co-produce IL-10 together with IL-17 and do not induce autoimmunity (Lee et al., 2012; McGeachy et al., 2007) and have therefore been called non-pathogenic Th17 cells. To acquire the ability to induce autoimmunity in vivo, IL-17-producing T cells need to either be re-stimulated with IL-23 (McGeachy et al., 2009) or be generated with alternative cytokine combinations triggering IL-23 receptor (IL-23R) expression and signaling, such as IL-1β, IL-6, and IL-23 (Ghoreschi et al., 2010) or TGF-β3 and IL-6 (Lee et al., 2012). IL-23R controls the production of a proinflammatory transcriptional module in Th17 cells (Lee et al., 2012), including many essential effector cytokines (Codarri et al., 2011; El-Behi et al., 2011). IL-23R is thus a key determinant of the pathogenicity of Th17 cells and of autoimmunity in general (Cua et al., 2003). Understanding the mechanism by which IL-23R regulates the functional phenotype of pathogenic and non-pathogenic Th17 cells and how this balance is transcriptionally regulated is therefore critical for the selective inhibition of pathogenic Th17 cells in human autoimmune diseases.

Differentiation of Th17 cells is transcriptionally controlled by the lineage-defining transcription factor RORγt (Ivanov et al., 2006; Xiao et al., 2014), and the transcriptional networks controlling Th17 cell differentiation have recently been identified in large-scale transcriptomic analyses (Ciofani et al., 2012; Yosef et al., 2013). Our study predicted that Notch signaling and RBPJ, a downstream regulator of Notch signaling, were two of the 22 major nodes that positively regulated the development of Th17 cells (Yosef et al., 2013). This is consistent with previous studies that demonstrated that pharmacological and antibody-mediated inhibition of Notch ameliorated Th17-dependent autoimmune disease models (Bassil et al., 2011; Jurynczyk et al., 2008; Keerthivasan et al., 2011; Reynolds et al., 2011). Despite these detailed transcriptomic data, the molecular mechanism by which Notch regulates Th17 development has not been identified. In addition, which subtype of Th17 cells (pathogenic or non-pathogenic) is regulated by Notch signaling has not been addressed.

Here we demonstrate that the canonical Notch signaling molecule RBPJ in Th17 cells regulates the development of pathogenic and non-pathogenic Th17 cells. We show that RBPJ directly promotes the expression of IL-23R by binding and *trans*-activating the *Il23r* promoter and repressing anti-inflammatory IL-10 production in Th17 cells. Consistent with this observation is that RBPJ-deficient Th17 cells show a non-pathogenic Th17 transcriptional profile, that RBPJ deficiency in Th17 cells protects mice from the development of experimental autoimmune encephalomyelitis (EAE), and that IL-23R overexpression rescues this defect. We have therefore identified a transcription factor that controls the generation of pathogenic and non-pathogenic Th17 cells by directly driving IL-23R expression and repressing production of the anti-inflammatory cytokine IL-10.