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Research paper

RelB regulates Th17 differentiation in a cell-intrinsic manner

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ABSTRACT

The role of the alternative NF-κB pathway is mainly attributed to the lymphoid organ formation and blood cancer. However, its involvement in lymphocyte differentiation is not clearly defined. Recently, we have shown that uncontrolled activation of alternative NF-κB in mice lacking the NF-κB inhibitory protein p100 ($p100^{-/-}$ mice) hinders plasmablast proliferation and diminishes T cell independent responses. Here we show that hyperactivation of this pathway leads to a cell-intrinsic T cell defects. p100-deficient T helper cells displayed both an activation and a proliferation defect *in vitro*. In addition, memory T cell formation was impaired *in vivo*. Moreover, $p100^{-/-}$ T cells failed to polarize into T helper 17 cells. This phenotype was dependent on increased RelB activation and suboptimal RORγt expression. Thus, our results demonstrate that RelB acts as a negative regulator of T cell activation and Th17 development. Targeting this pathway therefore could be beneficial in Th17-mediated pathologies.

1. Introduction

Inflammation is a crucial prerequisite of an efficient immune response. However, uncontrollable inflammation is frequently associated with autoimmune diseases, premature ageing and cancer (Zhong et al., 2016). In order to successfully intervene with immune pathologies, molecular and cellular mechanisms governing inflammation have to be fully understood. T lymphocytes, an essential part of the immune system, provide diverse and specific immune response, depending on the nature of the pathogen. While T helper (Th) 1, 2 and 17 cells orchestrate inflammation by secreting their signature cytokines IFNγ, IL-4 and IL-17 respectively, regulatory T cells (Tregs) suppress inflammation through multiple mechanisms (Josefowicz et al., 2012; Hirahara and Nakayama, 2016). Each Th subset is characterized by a specific set of transcription factors. Thus, Th1 cells rely on the expression of T-bet, Th2 cells depend on the presence of GATA3, Th17 cells require RORγt expression and Tregs use Foxp3. These factors may either act as master regulator factors like Foxp3 for Tregs or rather lineage-specifying as RORγt for Th17 cells (Josefowicz et al., 2012; Chang et al., 2014; Ciofani et al., 2012).

The nuclear factor-kappa B (NF-κB) family of transcription factors plays a crucial role in regulating the innate and adaptive immune system (Gerondakis and Siebenlist, 2010). The NF-κB family consists of 5 members that are c-Rel, p65 (RelA), RelB, p50 (NF-κB1) and p52 (NF-κB2) (Gilmore, 2006). NF-κB signaling is separated into two complementary and interacting pathways. The canonical (classical) pathway acts primarily through p65 and c-Rel heterodimers, whereas p52-RelB complexes represent a noncanonical (alternative) pathway. The alternative pathway is activated upon signaling through TNF-receptor super family members. Signals from the receptor lead to the degradation of the TRAF3 complex, stabilization of NF-κB-inducing kinase (NIK) and activation of inhibitor of NF-kappa-B kinase subunit alpha (IKKα), which further on phosphorylates p100, leading to its processing to p52 and the migration of p52-RelB heterodimers into the nucleus (Sun, 2011; Hacker et al., 2011).

While the role of the classical NF-κB signaling in T cells is well established, the role of its alternative counterpart is less studied and remains controversial (Gerondakis et al., 2014). Whereas mice with enhanced alternative NF-κB activity caused by TRAF3 deletion display defective T-cell responses (Xu et al., 1996; Xie et al., 2011), mice with overexpressed NIK in T cells succumb to lethal autoimmunity due to deficient suppressive activity of Tregs (Murray et al., 2011). Likewise,

Abbreviations: NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IFNγ, interferon gamma; IL-17, interleukin 17; BMC, bone marrow chimeras; RORγt, RAR-related orphan receptor gamma

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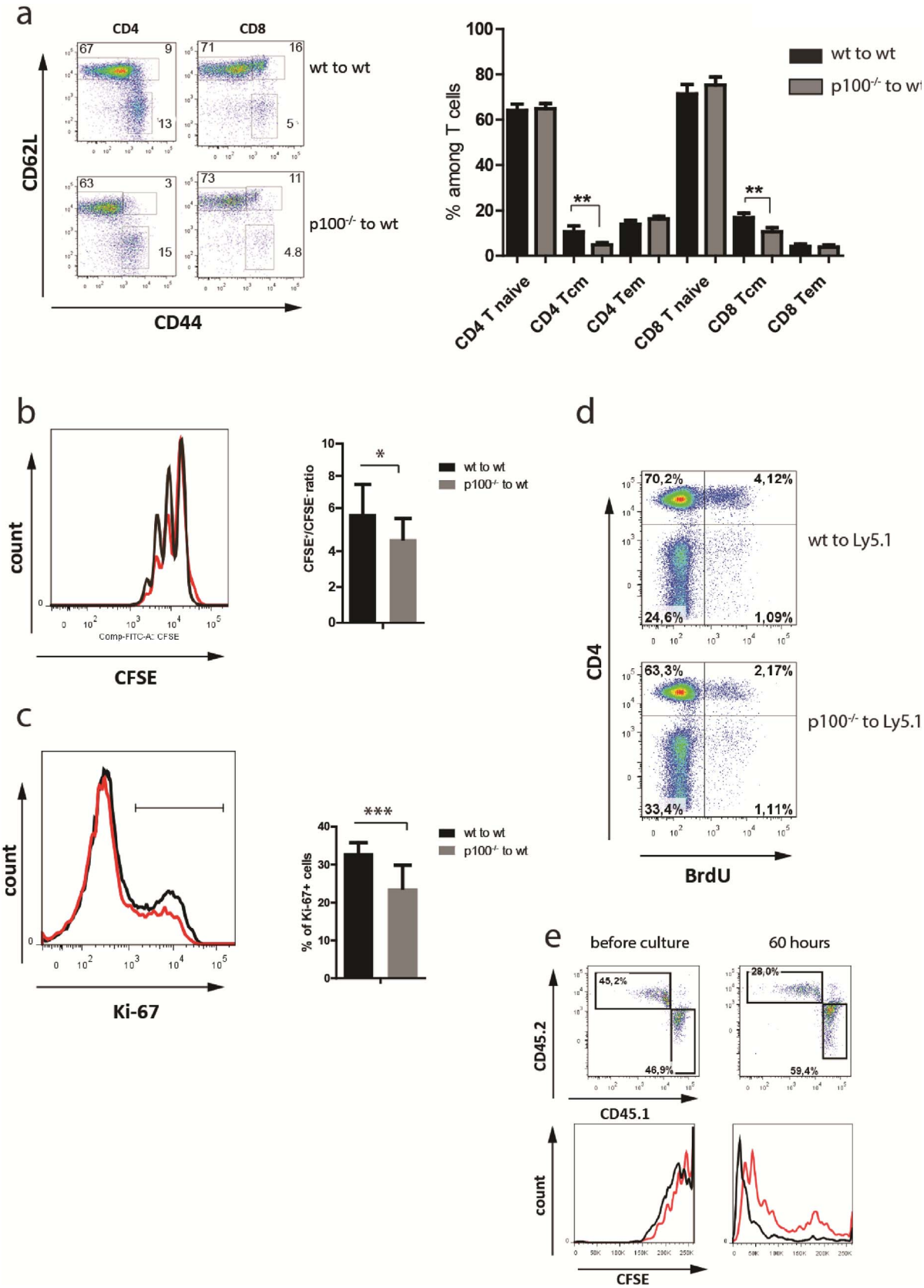

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