EBioMedicine 25 (2017) 20–21

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Dual Mechanisms for Balancing Th17 and Treg Cell Fate by CREB

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ARTICLE INFO

Article history:
Received 31 October 2017
Accepted 31 October 2017
Available online 10 November 2017

Keywords:
Th17 cells
Regulatory T cells
CREB

ABSTRACT

Th17 cells, which express the cytokine IL-17A, and master regulator RORγt, are important in the inflammatory response to fungal and bacterial pathogens, but also have a pathogenic role in many inflammatory disorders. In contrast, regulatory T cells (Treg), expressing the Foxp3 transcription factor, have a suppressive function and can dampen an immune response. The appropriate balance of these distinct effector functions is critical for an effective immune response and autoimmunity can arise if this process goes awry. In this issue, Wang et al. demonstrate a critical role for the transcription factor CREB (cyclic AMP-responsive element binding protein) in regulating the balance between inflammatory Th17 and suppressive Treg cells with implications for autoimmunity.

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Th17 cells, which express the cytokine IL-17A, and master regulator RORγt, are important in the inflammatory response to fungal and bacterial pathogens, but also have a pathogenic role in many inflammatory disorders. In contrast, regulatory T cells (Treg), expressing the Foxp3 transcription factor, have a suppressive function and can dampen an immune response. The appropriate balance of these distinct effector functions is critical for an effective immune response and autoimmunity can arise if this process goes awry. In this issue, Wang et al. demonstrate a critical role for the transcription factor CREB (cyclic AMP-responsive element binding protein) in regulating the balance between inflammatory Th17 and suppressive Treg cells with implications for autoimmunity.

Development of pathogenic Th17 and suppressive Treg cells is known to be reciprocally regulated, partly caused by a direct antagonistic interaction between the master transcription factors, RORγt and Foxp3 (Zhou et al., 2008). Although TGF-β can promote the development of both subsets, the addition of pro-inflammatory cytokines, such as IL-6 and IL-23, favors Th17 cell fate (Korn et al., 2009). Additional transcription factors (BATF, STAT3), metabolites (sterols, retinoic acid) and post-translational modifications that influence the Th17/Treg balance have also been described (Rutz et al., 2016). The demonstration here (Wang et al., 2017) that CREB also regulates the Th17/Treg cell balance identifies a new layer of potential regulation by additional external environmental cues.

CREB is a basic leucine zipper transcriptional activator known to play a role in many diverse physiological systems including memory, circadian rhythms, and gluconeogenesis (Shaywitz and Greenberg, 1999). Diverse stimuli activate CREB by phosphorylation of a key serine residue (Ser133) via kinases stimulated by cyclic AMP, Ca^{2+}, growth factors, and stress signals. Phosphorylation allows recruitment of CREB binding protein (CBP), a large coactivator that contacts proteins of the general transcription machinery, such as RNA polymerase II, to facilitate gene transcription. Previous work identified functional CREB binding sites (CREs) in *Il17a-IL17f* and *Foxp3* loci in vitro but here, Wang et al., used conditional knockout mice to provide clear genetic evidence for a T cell intrinsic role for CREB in balancing Th17 versus Treg cell fate in vivo, and consequently, in Th17-cell mediated disease. Mice that lacked CREB specifically in all CD4 T cells or Th17 cells expressing IL-17F were resistant to disease in a mouse model of multiple sclerosis, with fewer infiltrating Th17 cells and more Tregs present in the nervous system. In a second disease model, lack of CREB in T cells also prevented colitis, with more Tregs and fewer Th17 cells in the draining lymph nodes. Mechanistically, CREB directed Th17 cell differentiation through binding to CRE sites in the *il17a-f* gene locus and synergizing with RORγt to drive gene expression. CREB also played a second, important and specific role in regulating the function of inducible Treg cell. In contrast to prior in vitro work (Kim and Leonard, 2007), CREB deficiency did not affect Foxp3 expression in either natural Treg (nTreg) or induced Treg (iTreg) cells; nor did it affect their suppressive activity, or nTreg cell homeostasis in young mice. Rather CREB deficiency enhanced the survival of induced Tregs in the presence of TGF-β alone to levels normally seen in wild type cells in the presence of TGF-β and IL-2. Increased survival

DOI of original article: https://doi.org/10.1016/j.ebiom.2017.10.010.
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https://doi.org/10.1016/j.ebiom.2017.10.031
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occurred via reduced expression of p27, a potent cyclin-dependent kinase inhibitor of G1 cell cycle progression, containing CRE binding sites in its promoter. Thus, CREB exhibits two different modes of action regulating T cell differentiation, both promoting a Th17 gene expression program and reducing Treg proliferation and survival.

While this study highlights a dual role of CREB in balancing Th17 versus Treg fate, additional questions and new directions arise. Interestingly, in vitro Th17 cell differentiation was reduced when CREB was deleted by cells expressing IL-17F but not when deletion was directed by CD4, in contrast to the in vivo findings. This may suggest the existence of compensatory mechanisms if CREB is deleted during the early stage of T cell development, since IL-17F expression occurs after T cell activation and differentiation, but CD4 is expressed during thymus development of T cells. The authors suggest compensation by other CREB-related transcription factors, ATF1 and CREM, may account for this discrepancy and these proteins do form homodimers and heterodimers with overlapping DNA binding specificity. However, a diverse role of CREB at different T cell developmental stages cannot be excluded as well. Th17 cells are known to have a high degree of plasticity in their phenotype and function, with pathogenic and non-pathogenic Th17 subsets driven by specific environmental factors (Stockinger and Omenetti, 2017). Furthermore, multiple waves of transcription of different genes occur over time during Th17 differentiation (Yosef et al., 2013). Given the convergence of diverse, external stimuli on CREB activity in other biological systems, it is likely that differences in specific conditions in vitro and in vivo are also important and this raises the intriguing question of what additional factors might regulate Th17 cell development by this mechanism. The authors use small molecule inhibitors to provide evidence that TCR engagement leads to CREB phosphorylation at Ser133 via activation of PKC-θ. Encouragingly, this is consistent with a prior study showing reduced Th17 cell differentiation in PKC-θ deficient mice, although it will be important to confirm the PKC-θ-CREB-dependent interaction genetically, as PKC inhibitors are notoriously non-selective. In addition, CREB is regulated by other phosphorylation sites in the protein and additional tissue specific coactivators associations independently of Ser133 phosphorylation (Altarejos and Montminy, 2011). Prostaglandin E2 (PGE2) is one example of a lipid mediator that can activate CREB-dependent transcription through G-protein coupled receptor, cAMP/PKA signaling, and nuclear localization of CREB-related transcription coactivator (CRTC) proteins to enhance IL-17 expression (Boniface et al., 2009). It will be interesting to see if other hormones and metabolites can impact T cell function via CREB in a similar way. The identification of pathways that can negatively regulate CREB activity to rebalance Th17 and Treg function could provide new strategies for therapeutic intervention in human inflammatory disease.

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