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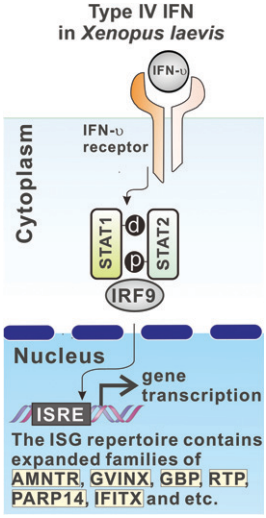
Transcription and Signaling of IFN in Amphibians

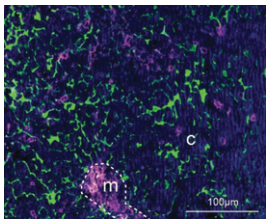


In this Top Read, Chen et al. (p. 1771) elucidate the transcription and signaling of type IV IFN, IFN-υ, in amphibians. The proximal promoter of IFN-υ has both IFN-sensitive responsive element and NF-κB sites, which bound to transcription factors IFN regulatory factor 1 (IRF1), IRF3, IRF7, and p65, resulting in the transcription of *ifn-υ*. IFN gene stimulating factor 3, composed of STAT1, STAT2, and IRF9, mediated signals downstream of IFN-υ binding its receptor. The IFN-stimulated genes consisted of many antiviral-related families. Five IFN-stimulated gene families were expanded based on phylogenetic and gene locus analysis: AMNTR, GVIN, GBP, RTP, and IFIT. Moreover, only AMNTR50 was shown to negatively regulate the expression of types I, III, and IV IFNs, by interacting with IRF3. Together, these data reveal how expression of IFN-υ is regulated and how its downstream signaling impacts amphibian immune responses.

Pathologic IL-6 Signaling in T Cells

Expression of a constitutively active IL-6R gp130 chain (Lgp130) in transgenic mice leads to dysfunctional hematopoietic cells, chronic inflammation, and formation of B cell malignancies. In this Top Read, Heinig et al. (p. 1717) showed that Lgp130 expression specifically in the T cell lineage sensitizes naive T cells toward T_H17 cell differentiation and leads to premature lung inflammation, but not to T cell lymphomas. Lgp130 expression only in $CD4^+$ T cells caused significant lung and liver inflammation, compromised lung function, accumulation of $ROR\gamma t^+$ T_H17 cells, and a reduction in $Foxp3^+$ T cells in all tissues, but no lymphomas. Postinfection with *Staphylococcus aureus*, Lgp130 expression increased T_H17 cell responses and led to loss of regulatory T cells in peripheral tissues. The data suggest that uncontrolled IL-6 signaling in T cells prevents development of peripheral tolerance and leads to excessive accumulation of T_H17 cells that causes premature lung damage, but unlike its effect in B cells, does not lead to T cell malignancies.

mTECs and DCs Orchestrate Treg Production



In this Top Read, Morimoto et al. (p. 1653) demonstrated that medullary thymic epithelial cells (mTECs) and dendritic cells (DCs) play a vital role in regulatory T cell (Treg) development in the thymus. Specific depletion of mTECs led to a greater decrease in Treg production compared with mice with depleted DCs. However, depletion of both mTECs and DCs further impaired Treg production, indicating nonredundant roles for these two cell types in Treg development. Phenotypic differences were seen in Tregs that developed in the absence of either mTECs or DCs, although no differences in their suppressive abilities were observed. Deletion of either mTECs or DCs resulted in distinct, organ-specific autoimmune lesions in each mouse model. Finally, mTECs, but not DCs, enhanced recruitment of non-Tregs producing IL-2 into the thymus to further enhance Treg production. Together, these data show that mTECs and DCs have cooperative, but distinct roles in the development of thymic Tregs.

Chromatin Regulator of T_{FH} Cell Differentiation

In this Top Read, Bélanger et al. (p. 1752) discovered that the chromatin regulator (CR) mixed lineage leukemia 1 (Mll1) controls the expression of at least three genes encoding transcription factors important for T follicular helper (T_{FH}) differentiation—*Bcl6*, *Lef1*, and *Tcf7*. First, a microRNA-adapted short hairpin RNA (shRNAmir) retroviral vector library targeting known mouse CRs was screened to monitor enrichment or depletion of genes in T_{FH} versus T_H1 cells after an acute viral infection. The shRNAmirs for the histone methyltransferase Mll1 were the most depleted from T_{FH} cells. Knockdown of *Mll1* reduced Bcl6 expression and differentiation of T_{FH} cells but had less impact on formation of germinal center-T_{FH} cells. Whereas loss of *Mll1* impeded Tfh differentiation after viral infection, it had no effect after protein immunization. A transcriptomics analysis showed that loss of *Mll1* enriched for a Th1 gene expression profile where Bcl6-regulated genes were unaffected, whereas expression of LEF-1 and TCF-1 was dysregulated in T_{FH} cells. Ectopic expression of Bcl6 rescued T_{FH} differentiation from *Mll1*-deficient $CD4^+$ T cells, whereas TCF-1 expression partially rescued, and LEF-1 expression had no effect. Altogether, these data indicate that the CR Mll1 regulates transcription factors important for T_{FH} differentiation and may be dependent on the context of Ag presentation.

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