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Title	T lymphocyte plasticity in chronic inflammatory diseases: The emerging role of the Ikaros family as a key Th17-Treg switch
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Publication date	2024-12-30
Original Citation	Ramón-Vázquez, A., Flood, P., Cashman, T. L., Patil, P. and Ghosh, S. (2024) 'T lymphocyte plasticity in chronic inflammatory diseases: The emerging role of the Ikaros family as a key Th17-Treg switch', Autoimmunity Reviews, 24(3), 103735 (13pp). https://doi.org/10.1016/j.autrev.2024.103735
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1016/j.autrev.2024.103735
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Download date	2026-11-15 03:24:55
Item downloaded from	https://hdl.handle.net/10468/16816



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Autoimmunity Reviews 24 (2025) 103735



Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev





T lymphocyte plasticity in chronic inflammatory diseases: The emerging role of the Ikaros family as a key Th17-Treg switch

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ARTICLE INFO

Keywords:
T cell plasticity
Ikaros family
Chronic inflammatory diseases
T cell differentiation
Transcriptional control

ABSTRACT

T helper (Th) 17 and regulatory T (Treg) cells are highly plastic CD4$^+$ Th cell subsets, being able not only to actively adapt to their microenvironment, but also to interconvert, acquiring mixed identity markers. These phenotypic changes are underpinned by transcriptional control mechanisms, chromatin reorganization events and epigenetic modifications, that can be hereditable and stable over time. The Ikaros family of transcription factors have a predominant role in T cell subset specification through mechanisms of transcriptional program regulation that enable phenotypical diversification. They are crucial factors in maintaining Th17/Treg balance and therefore, homeostatic conditions in the tissues. However, they are also implicated in pathogenic processes, where their transcriptional repression contributes to the control of autoimmune processes. In this review, we discuss how T cell fate, specifically in humans, is regulated by the Ikaros family and its interplay with additional factors like the Notch signaling pathway, gut microbiota and myeloid-T cell interactions. Further, we highlight how the transcriptional activity of the Ikaros family impacts the course of T cell mediated chronic inflammatory diseases like rheumatoid and psoriatic arthritis, inflammatory bowel disease, systemic lupus erythematosus and multiple sclerosis. We conclude by discussing recently developed therapeutics designed to target Ikaros family members.

1. Introduction

Chronic inflammatory diseases (CIDs), like rheumatoid and psoriatic arthritis (RA, PsA), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE) and multiple sclerosis (MS) are a heterogeneous type of autoimmune diseases that share exacerbated immune responses and sustained inflammation as a common feature. Generally, these are T cell-mediated diseases where different effector CD4$^+$ T helper (Th) cell subsets orchestrate cellular responses (typically subsets Th1, Th2, Th9, Th17 and Th22) causing chronic inflammation, cell recruitment and tissue destruction, in addition to other associated effects like fibrosis (involving Th2 and Th17). Typically, a breakdown in tolerance caused by an imbalance in the number and/or the functionality of specific T cell subsets is believed to mark the onset of these pathological processes [1–3].

T cells present precise surface markers, transcription factors: T-box transcription factor TBX21 (T-bet), GATA-binding factor 3 (GATA-3), RAR-related orphan receptor gamma (RORγt), Forkhead box P3 (FOXP3), Ikaros family of zinc-finger proteins, and release signature cytokines that determine and maintain their identity and function; therefore, T cell differentiation has traditionally been considered to result in discrete phenotypes [4]. Single cell profiling technologies like single-cell RNA sequencing, flow cytometry and mass cytometry [Cytometry by time of flight (CyTOF)] have identified heterogeneities in the effector T cell populations that have broadened the concept of cell differentiation to a continuum of cell fates [5–7]. In addition, T cells actively adapt to the microenvironment where they reside; consequently, their molecular and functional profiles differ among tissues and pathologies. In recent years, evidence has emerged around the presence of T cells exhibiting co-expression of lineage-determining markers and signature cytokines from different subsets in human CIDs [7–9]. This is indicative of human T cell subsets possessing 'plasticity', which is particularly frequent between Th17 and peripheral regulatory T (Treg) cells [2,10,11]. Importantly, the simultaneous presence of markers defining diverse subsets creates novel cell phenotypes that can favour autoimmune pathologies [12–14].

The Ikaros family of transcription factors have a predominant role in lymphopoiesis and other cellular processes like proliferation,

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https://doi.org/10.1016/j.autrev.2024.103735
Received 13 August 2024; Received in revised form 14 December 2024; Accepted 20 December 2024
Available online 22 December 2024
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differentiation, cell cycle arrest, apoptosis and tumorigenesis [15]. In addition, they mediate T cell subset specification, through mechanisms of transcriptional program regulation that enable phenotypical diversification. Interestingly, Ikaros members have emerged as novel susceptibility genes for different CIDs including IBD [16–18], psoriasis [19], SLE [20] and RA [21]. Genetic variants in Ikaros genes have also been reported to correlate with defects in T cell functioning, skewed differentiation and increased disease activity [22,23]. Importantly, Ikaros mediated mechanisms of disease have recently been identified that involve direct transcriptional control of genes promoting increased T cell activation and inflammatory cytokine production [24–27]. This evidence highlights the important role of the Ikaros family in T cell subset balance and control of immune responses.

In this review we focus on the role of Ikaros family members as key switches of human T cell 'plasticity' between Th17 and Tregs and their implication in human CIDs. We discuss specifically human studies that have investigated factors that direct T cell fate towards inflammatory (Th17) or tolerogenic (Treg) subsets with a focus on the Ikaros family of transcription factors. We also summarize recent advances on current therapeutic options targeting the Ikaros family members.

2. The Ikaros family and T helper (Th) cell plasticity

The Ikaros family comprises five members of C2H2 zinc finger-containing family of transcription factors: IKZF1 (IKAROS), IKZF2 (HELIOS), IKZF3 (AIOLOS), IKZF4 (EOS) and IKZF5 (PEGASUS). The Ikaros family can either activate or repress gene expression, depending on their interaction with other key transcriptional complexes [15]. They use different mechanisms to mediate these effects: (I) chromatin conformational changes: by directly binding through evolutionarily conserved alpha-helical motifs to chromatin remodelling complexes SWI/SNF or Nucleosome Remodelling and Deacetylase (NuRD) complexes, containing Mi-2 [28–30] (IKAROS and HELIOS) or Sin3 [31] (AIOLOS and EOS); (II) promoting RNA Pol II transcription initiation complex [32] and (III) interacting with co-repressors like C-terminal binding protein (CtBP) to mediate HDAC-independent transcriptional repression (EOS [28]), or by recruiting the polycomb repressive complex 2 (PRC2) to the gene promoter, which results in histone H3 lysine 27 trimethylation (H3K27me3) deposition, a mark of transcriptionally silent chromatin (IKAROS [33,34]).

The effects of the Ikaros family as master regulator of cell fate determination in hematopoietic and lymphoid cells comes as a result of their collaborative interaction with other protein complexes that orchestrate epigenetic mark deposition, chromatin remodelling at gene regulatory regions and transcriptional regulatory functions. Two relevant studies highlight the importance of the epigenome for the control and fine-tunning of gene expression in Th fate determination. First, a study on human fetal and adult T naïve cells revealed that upon TCR stimulation, fetal cells preferentially differentiate to a regulatory phenotype and these cells present two active Treg-specific super-enhancers in the *HELIOS* gene [35]. Addition of exogenous TGF-β enhanced the expression of Treg-specific genes and CRISPR-ablation of *HELIOS* induced the expression of proinflammatory genes like IFN-γ and transcription factors regulating Th1, Th2 and Th17 transcriptional signatures like PRDM1 (BLIMP1), GATA3, IKAROS and c-MAF. In another study, ectopic expression of IKAROS in a human skin epithelial cell line demonstrated that binding of IKAROS to regulatory sites reconfigured chromatin architecture into lymphoid-specific 3D chromatin loops that support lineage-specific gene expression and suppress activation of extra-lineage genes [36].

Studies on human innate lymphoid cell (ILC) plasticity, which express the same transcription factors as T cells for their development; for instance, T-bet and AIOLOS (ILC1), GATA-3 (ILC2), RORγt and HELIOS (ILC3), and where IKAROS is expressed in all the ILC subsets; constitute a convenient cell model for the identification of mechanisms that could be operating in other lymphoid lineages. It appears that there exists mutual gene expression regulation of IKAROS, AIOLOS and HELIOS proteins, as degradation of the two formers with lenalidomide leads to the upregulation of HELIOS and downregulation of ILC1 related genes [37]. These observations also suggest differential and specific roles for these transcription factors in the regulation of specific ILC subsets.

The process by which T cells acquire signature phenotypic traits from other T cell subsets, known as T cell 'plasticity', is more difficult to study in humans compared to mice. However, research on Th17 and Treg cells indicate that these cells are highly influenced by external cues and adapt their molecular and functional profiles, retaining mixed identity markers [38,39]. The cell's ability to respond to the environmental cues is conditioned firstly, to the expression of receptors and signaling molecules able to transmit the stimulus and; secondly, to the genetic machinery that enables a cellular response through transcriptional shifts, chromatin reorganization events and epigenetic changes [4,40–42]. Current technological tools for in-depth single-cell analysis prompts us to re-consider T cell subset classification due to the simultaneous presence of lineage-determining factors, epigenetic marks, markers expression ratios or a combination of the above. Potentially, expression of dynamic master regulators would confer cells with different capabilities for phenotypical adaptation and would explain why some interconversions between T cell subsets are more restrictive than others. Importantly, in the context of CIDs, disease-specific cues could be conditioning preferential phenotypical shifts that contribute to chronic inflammation (Fig. 1). We discuss below the relevance of the transcriptional activity of the Ikaros family and its interplay with additional factors that impact the course of T cell mediated CIDs.

3. Factors directing T cell subset specification

The nature and strength of external cues is crucial for shaping T cell fate, but this is also greatly conditioned by the cell's ability to respond and integrate them through its repertoire of receptors, transcription factors and signaling molecules, expressed at a certain timepoint. We discuss below the main signals influencing the differentiation of T cell subsets into Th17 or Treg (Table 1) following the spatiotemporal tiers of signaling described in Fig. 1. Other factors, acting through various or unknown receptors and signaling transduction pathways, like diet, are also discussed (Fig. 2).

3.1. *Surface receptors.*

3.1.1. *T cell receptor (TCR)*

TCR ligation and co-stimulatory molecules are the two required signals for Th cell development, in addition to cytokine stimulation. TCR signaling abnormalities or TCR-associated molecule defects can lead to autoimmune diseases [44,45]. The potency and duration of TCR signaling is crucial for fate decision towards Th17 or Treg. Studies in purified $CD4^+$ T cells have shown that low-strength CD3 stimulation in a pro-Th17 cytokine milieu strongly favours Th17 responses [46,47], but high-strength CD3 conditions induced high levels of FOXP3 and low release of IL-17 [47].

3.1.2. *Co-stimulatory molecules: CD28 and inducible costimulator (ICOS)*

CD28 is considered an important non-specific, TCR-independent second signal required for T cell activation. Despite the controversy regarding an absolute requirement of CD28 for human Th17 development, studies are coincident in that the impact of CD28 signaling depends on the signal strength emerging from the CD28-PI3K-AKT axis [48] and the metabolic switch to glycolysis during T cell activation, most likely achieved by upregulation of glucose transporter 1 (GLUT1) [49]. Other studies found that ICOS (a member of the CD28 family), but not CD28, is necessary for optimal expansion and enhanced function of human Th17 cells. In fact, CD28 ligation abrogated ICOS stimulation, dampened RORγt and IL-17 production and promoted aryl hydrocarbon receptor (*AHR*) expression [50]. A combination of increased TCR signal

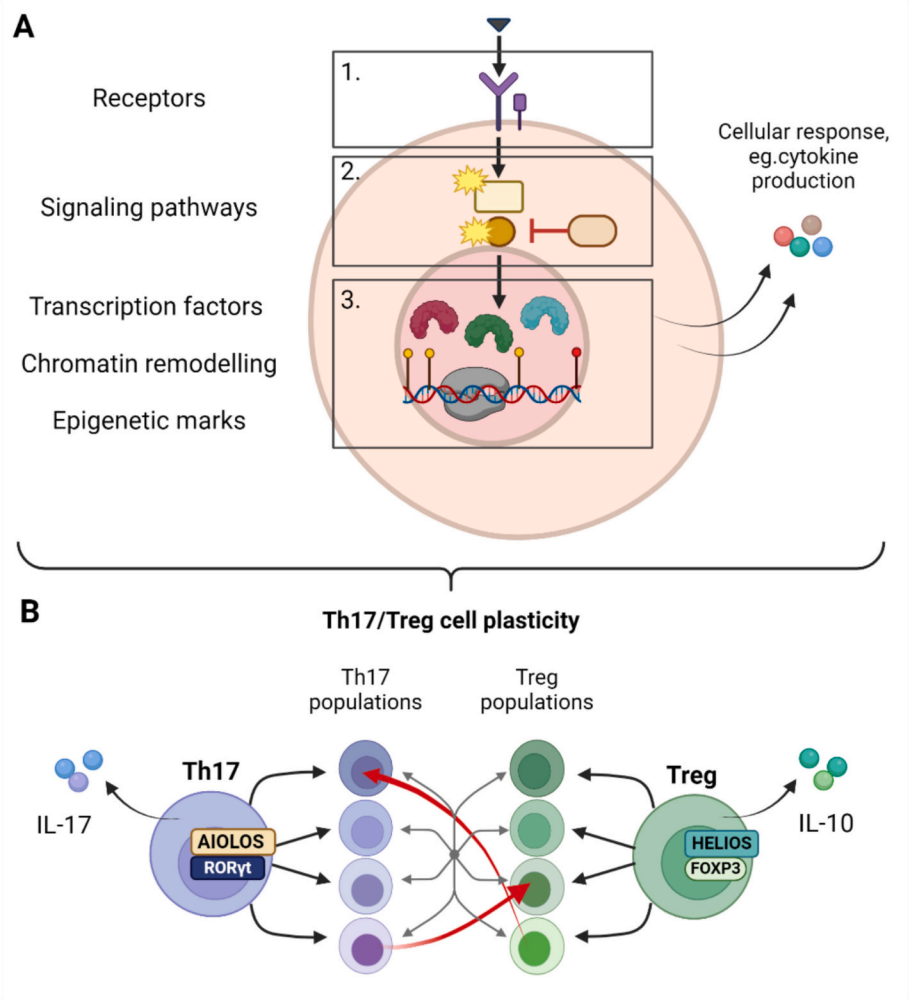


Fig. 1. T cell plasticity in Th17 and Treg compartments. A T cell plasticity is regulated through mechanisms at different levels: the presence of appropriate cellular receptors (1.) and activation of signaling pathways (2.) renders the cell responsive to extracellular cues, inducing gene expression changes (3.) that modulate cellular responses. The chromatin accessibility is controlled by the presence of permissive and repressive epigenetic marks and chromatin remodelling machinery, that impact the transcriptional activity of existent lineage-determining factors. B Current technologies for in-depth single-cell analysis have shown that effector T cell populations are, although heterogeneous, phenotypically largely similar [5,43]. Specifically, Th17 and Treg subsets are highly adaptive to tissue microenvironment, being able to modulate their intrinsic ability to produce cytokines and present different lineage-determining factors that would confer them a higher potential for plastic adaptation (split arrows). Pathological conditions could enhance preferential plasticity between specific subsets (red arrows). Created with BioRender.com.

Table 1
Signals influencing Th17/Treg cell fates. Classification of the main intrinsic and extrinsic signals directing Th17/Treg differentiation by spatiotemporal tier of signaling. Referenced literature for each pathway is provided. See main text for details.

Tier of signaling	Molecules / Pathways	Impact on Th17/Treg fate decision	References
Surface receptors	TCR	Th17 (↓strength), Treg (↑strength)	[44–47,51]
	Co-stimulatory molecules (CD28, ICOS)	Th17↓ (CD28), Th17↑ (ICOS)	[48–51]
	Notch	Th17↑ (NOTCH-1, DLL4), Treg↑ (NOTCH-4, DLL1)	[52–57,145]
	Cytokine receptors	Th17↑ (inflammatory), Treg↑ (IL1RII, CD25), Th17 and Treg↑ (TGFBR II)	[58–77]
Intracellular signaling pathways	PI3K/AKT axis	Th17 (↓)	[48,78–81]
	mTOR	Th17↑ (mTORC1)	[82–85]
	STATs	Th17↑ (STAT3), Treg↑ (STAT5)	[26,66,86,87,115,117]
	SMADs	Th17 and Treg↑ (SMAD2, 3, 4), Treg↓ (SMAD7), Treg↑ (SMAD1)	[88,100]
	Ikaros family	Th1↓ IKAROS, Treg↑ HELIOS, Treg&Th17↑ AIOLOS, Treg↑ EOS	[22,89–111]
Gene transcription regulation	RUNX	Th17↓ (RUNX1), Th17↑ (RUNX3)	[65,104,112–114]
	miRNAs	Th17↑ (miR-301a, −590, −873, −17), Treg↓ (miR-4772-3p), Treg↑ (miR-125a-5p)	[115–121]
Other (mixed/unknown)	Dietary and metabolic cues (AhR, Vitamins A and D, Salts)	Th17 and Treg↑ (AhR), Treg↑ (vitD), Th17↓ (vit A), Th17↑ (NaCl), Th17↓ (KCl)	[50,87,125–136]
	Gut microbiota - T cell interactions	Th17↓ (*Gordonibacter sp., Eggerthella sp., Raoultibacter sp., Clostridium sp.*)	[137–142]
	Myeloid - T cell interactions	Th17↑ ($CD14^{+}HLA\text{-}DR^{+}$), Treg↑ ($CD14^{+}$ $HLA\text{-}DR^{-/low}$)	[143–145]

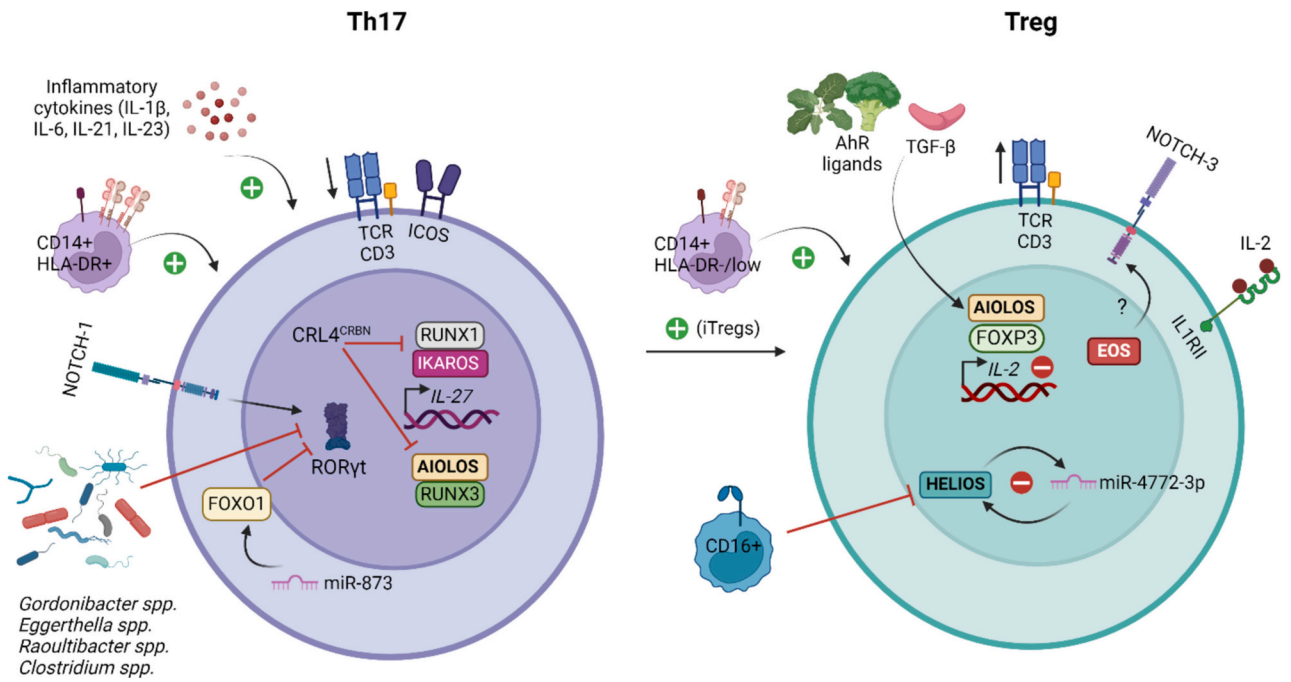


Fig. 2. Factors influencing the Ikaros-mediated Th17/Treg developmental balance. The main extrinsic (cytokines, gut microbiota, myeloid cell subsets, dietary components) and intrinsic (miRNAs, transcription factors) cues that impact Ikaros transcriptional regulation of T cell fates are depicted. See main text for details. Created with BioRender.com.

strength and ICOS *co*-stimulation maintained Th17 cells in a stem-like memory and polyfunctional state, as they produced more IL-17A, IFNγ, IL-2, and IL-22 than those co-stimulated with CD28 [51].

3.1.3. Notch

The role of Notch pathway activation in fuelling chronic inflammation is less clear than its role in cancer settings, which broadens the scope for research in human CIDs. Aside from its implication in T cell commitment, the role of the Notch pathway in T cell effector functions has been investigated for over two decades. Upon stimulation, the transcription of NOTCH-4 and Delta-like Ligand 1 (DLL1) dramatically and specifically increase in $CD4^+$ $CD25^+$ T cells, suggesting a role in the regulatory effects of T cells involving cell–to–cell communication [52]. Additionally, NOTCH-1 appears to have a role in human Th17 polarization by binding directly to and activating *IL-17* and *RORc* promoter activity *in vitro* [53].

Regarding interactions between the Notch and Ikaros families, the most insightful lessons come from studies in human cancer development and progression. In acute lymphoblastic leukaemia (ALL), approximately 50 % of adult patients possess *IKAROS* genetic mutations and this correlates to overall poor prognosis. Deficiency or reduction in IKAROS protein levels is deemed as a risk factor in the disease development and progression [54,55]. NOTCH-3 knockdown results in alternative splicing of signaling deficient *IKAROS* isoforms. This was dependent on RNA-binding protein Hu-antigen D (HuD), however, this was not the case for NOTCH-1 [56]. In non–small cell lung cancer, EOS was found significantly downregulated and correlated with poor clinical outcome. However, EOS forced expression supressed cancer growth and migration by strongly inhibiting NOTCH-3 signaling pathway [57]. However, the major brake of the Notch pathway is the tumor suppressor Phosphatase and Tensin Homolog (PTEN). PTEN inactivates the PI3K/Akt pathway, one of the main hyperactivated signaling pathways in cancer, that also negatively regulates Treg function when active (see section 3.2.1).

3.1.4. Cytokine receptors

Fine-tuning of IL-1 signaling is achieved through 2 receptors: type I receptor, IL-1RI, and the decoy type II receptor, IL-1RII. The induction of IL-1RII is dependent on TCR activation and controlled transcriptionally by nuclear factor of activated T cells 5 (NFAT)/FOXP3 protein complex [58,59]. Additionally, exposure of $IL\text{-}1RII^+$ memory $CD4^+$ T cells to IL-1β further increased the levels of FOXP3 [59]. IL-1RI has emerged as a reliable marker to define memory Treg cell populations, as its expression is restricted to HELIOS- Tregs, along with AIOLOS and CCR7, while EOS was found in $HELIOS^+$ Tregs [60]. Interestingly, IL-1β has a pivotal role in inflammatory signal amplification in RA and an aberrant baseline expression and induction of its receptors in synovial $CD4^+$ T cells has been reported [59]. However, another group found that IL-1RI was found in both $HELIOS^+$ and $HELIOS^-$ $FOXP3^+$ $CD4^+$ T cells in the rheumatic joint [61]. This evidence suggests that a balanced response to IL-1β is most likely achieved through differential expression of IL-1 receptors in the T cell compartment.

TGF-β1 is required for the development of both Th17 and Treg cells, therefore, the availability of this and other cytokines determines the reciprocal regulation of the Th17/Treg balance. In the absence of inflammatory cues, TGF-β1-induced FOXP3 protein inhibits Th17 cell differentiation by antagonizing RORγt function by means of direct protein interaction [62]. TGF-β1 also operates through FOXO1 (Forkhead Box Protein O1) to drive the pathogenic/non-pathogenic dichotomy of Th17 developmental cell fate [63–65].

Inflammatory stimuli from external cytokines are decisive for directing T cell differentiation towards a Th17 phenotype through various mechanisms. IL-1β antagonizes Treg differentiation by downregulating the production of IL-10 and synergizes with IL-23 to promote the secretion of IL-17. Cytokines IL-17 and IL-21 mediate a pro-inflammatory signal amplification loop [66]; IL-6 inhibits the expression of *FOXP3*; IL-15 is released by monocytes and triggers the production of IL-17 [67–69] and upregulates expression of IL-1RI on naïve T cells [70]. IL-23 induces Th17 phenotype stabilization, perpetuation of cell activation and cytokine production [71–73], while IL-27 has both pro- and anti-inflammatory effects [74–76]. Interestingly, a genetic variant (rs153109) identified as a risk allele in ulcerative colitis (UC) located in the *IL-27* promoter region, spans over a putative binding site for IKAROS [77]. Many of these inflammatory cytokines rely on STAT3 signal transduction, which constitutes a crucial signaling hub for the

induction of RORγt, the Th17 hallmark transcription factor [66].

IL-2 is a cytokine with pleiotropic effects that support the proliferation and differentiation of effector T cells. Tregs express IL-2 receptor (CD25) highly and constitutively, being able to respond vigorously with suppressor effects. However, IL-2-dependent effects occur at markedly lower concentrations in Tregs than in other effector T cells. IL-2 suppresses differentiation towards Th17, since one of the signaling pathways activated downstream of IL-2 involves activation of the PI3K/AKT axis, which is detrimental for Th17 differentiation.

3.2. Intracellular signaling pathways

3.2.1. PI3K/AKT axis

PI3K/AKT is an important axis controlling cell growth, migration, proliferation, and metabolism, acting on membrane PI(3,4,5)P3, that is opposed by the activity of PTEN and the PHLPP family of phosphatases, acting on AKT. PI3K/AKT pathway controls different aspects of Treg-Th1/Th17 'plasticity', Treg stability and function, in a context-dependent manner [78,79]. The importance of this pathway is shown in cancer patients using PI3K inhibition therapy, who develop colitis as a side effect due to the loss of suppressive function by Tregs [80,81].

3.2.2. Mechanistic target of rapamycin (mTOR)

mTOR is a protein kinase complex of 2 components: mTORC1 and mTORC2, which play distinct and pivotal roles in metabolism, cell growth, proliferation, survival and differentiation. Clinical trials for the use of sirolimus (rapamycin), a mTOR inhibitor, to treat diverse CIDs like RA [82], SLE [83], MS [84] or T1D [85] have shown a promising efficacy to alter the balance in the Treg-Th17 populations, by increasing the $CD4^{+}CD25^{+}FOXP3^{+}$ Treg populations and inhibiting IL-17 production.

3.2.3. Signal transducer and activator of transcription (STATs)

As mentioned before, STAT3 is a key molecule for human Th17 cell differentiation. Upon STAT3 binding, IL-6 and IL-27 activate STAT1, this shapes the functional identity and effector characteristics of memory $CD4^{+}$ T cells, by regulating the transcriptional output of STAT3 [86]. This mechanism explains how immune cells can produce context-dependent cytokine responses and adapt their response to microenvironmental cues. Interestingly, another study shows that STAT3 also physically interacts with AIOLOS and recruits it to *Bcl-6* promoter during the Tfh differentiation process [87]. It remains an open question if this mechanism is also operative in the differentiation of other helper subsets and how the hierarchy of events takes place over time.

3.2.4. Mothers against decapentaplegic (SMADs)

TGF-β1 induces SMADs 2 and 3, that form a complex with SMAD4 and activate transcription of several genes including FOXP3 and RORγt. It also upregulates SMAD7, that acts as an inhibitor of the TGF-β1-induced signaling pathway. Interestingly, SMAD7 expression is increased in lesional tissue isolated from patients with IBD and its inhibition enables cells to respond to TGF-β1 and downregulate proinflammatory cytokines [88].

3.3. Gene transcription regulation

3.3.1. Ikaros family

In humans, interventional studies that interrogate each Ikaros protein for their contribution to Th cell differentiation are not always feasible. However, some relevant *in vitro* and patient studies on naturally occurring mutations have given important insights into the individual functions of Ikaros members in T cell differentiation, although genetic defects in the Ikaros genes usually result in generalized immune dysregulation and pleiotropic effects [22,89,90]. In mouse, the availability of genetic models has facilitated research on the biology of Ikaros proteins, leading to relevant findings [91–93] (reviewed in [94]), that may not necessarily align with human biology.

Germline heterozygous *IKAROS* gain-of-function (GOF) mutations have been reported in patients presenting with Th2 cell-driven topic and allergic diseases, dramatically reduced IL-2 production and low Th1 and Treg cell counts [22,89,95]. In addition, *in vitro* pulldown studies in human hematopoietic cell lines have demonstrated a direct interaction of IKAROS with all GATA transcription factors [96], among which GATA-3 has a predominant role in Th2 subset specification. Therefore, IKAROS protein appears to have a preferential role in inducing a Th2 transcriptional program. AIOLOS on the other hand, supresses IL-2/STAT5 signaling axis and represents the crucial transcription factor contributing to Th17 and T follicular helper (Tfh) phenotypes [97]. Treg are influenced by virtually all Ikaros family members, however some specific functions have been ascribed to individual members, like phenotype stabilization (HELIOS [98,99]), control of suppressive function (AIOLOS [100]) and function enhancement (EOS [99,101]). In addition, presence of HELIOS identifies natural thymic-derived Tregs (nTregs) over peripherally induced Tregs (iTregs) [102]. A study conducted in human NK cells shows that IKAROS and AIOLOS proteins directly regulate expression of *FOS/JUN* AP-1 family members, that are essential for cell development [103]. Although this transcriptional dependency has not been verified in other lymphocyte populations like T or B cells, it seems possible that this mechanism is conserved among the lymphoid lineage. Importantly, FOS proteins are known to co-repress Th17 fate specification through interaction with JUN and RUNX1 proteins [104]. In contrast, another AP-1 member, BATF, shares with FOS protein interacting partners and occupancy over regulatory regions of genes involved in Th17 lineage commitment, promoting Th17 differentiation [104]. Finally, PEGASUS is an "atypical" Ikaros family member, it dimerizes with other family members but recognizes distinct DNA-binding sites, as it contains a divergent N-terminal zinc finger domain [105]. The activity of PEGASUS has been associated to platelet development, function and ultrastructure [106] and has little or unknown contribution to T cell specification.

Homo and heterodimerization of Ikaros proteins is another important factor determining their functionality. Ikaros proteins can form homodimers and heterodimers with other members of the family. Studies on human mutations causing immune dysregulation have shown that Ikaros dimerization defective mutants, even if acting in haploinsufficiency manner, can disrupt interaction with chromatin remodelling protein complexes like histone deacetylase 1 (HDAC1) or NuRD complex and alter gene regulation [107,108]. Additionally, mutations in the C-terminal dimerization domain can affect protein stability and disrupt post-translational modifications like SUMOylation and phosphorylation leading to enhanced [95] or decreased [108,109] DNA-binding ability. Defective dimerization can impair the ability of Ikaros proteins to be recruited to pericentromeric heterochromatin in the nucleus, which has been observed for IKAROS [95,107,108,110] and HELIOS mutants [109] by fluorescence microscopy. A plausible explanation from the authors is that Ikaros dimers, in association with chromatin remodelling complexes, bind DNA elements in genes that are destined for inactivation and help recruit them to centromeric foci.

Another hereditary heterozygous missense mutation was recently found in the *AIOLOS* gene in patients with an impaired adaptive immunity disorder. Mutant AIOLOS homodimers and AIOLOS–IKAROS heterodimers did not bind the canonical AIOLOS–IKAROS DNA sequence, a phenomenon driven by the mutant AIOLOS variant that hijacks IKAROS function [111]. The gained ability of the mutant AIOLOS to specifically bind new DNA sequences would explain the pathological outcomes, but the mechanisms underlying the regulation of heterodimer and homodimer formation of Ikaros proteins and how functionality of AIOLOS–IKAROS heterodimers differ from IKAROS–IKAROS or AIOLOS–AIOLOS homodimers still needs to be investigated.

3.3.2. Runt-related transcription factors (RUNX)

The family of RUNX proteins regulate transcription by binding to other transcription factors and depending on the context, form co-repressor or activator complexes. A study conducted in the Jurkat human T cell line shows that RUNX1 influences Th17 differentiation by inducing *RORC* expression and by binding to it during IL-17 transcription. Additionally, RUNX1 also interacts with the transcription factor FOXP3, and this interaction is necessary for the negative effect of FOXP3 on Th17 differentiation [112]. On the other hand, *RUNX3* has been found as a susceptibility locus for psoriasis. Inhibition of this protein reduced the levels of IL-6, IL-20 and IL-22, and decreased the frequency of circulating Th17 and Th22 cells in patients with psoriasis [113]. Importantly, from a therapeutic point of view, RUNX1 and RUNX3 are relevant targets, as they selectively interact with IKAROS and AIOLOS and inhibit their CRBN-dependent degradation upon treatment with the immunomodulatory imide drug (IMiD) lenalidomide [114].

3.3.3. MicroRNAs (miRNAs)

MicroRNAs are short, single-stranded, non-coding RNAs that have an important role in gene regulation during homeostasis and pathogenic processes. A number of miRNAs have been found to be differentially expressed in diseased tissues of CIDs and importantly, circulating peripheral blood mononuclear cells (PBMCs) also reflect these changes. miR-125a-5p has low levels in Tregs under steady state conditions, but it is suspected to have a crucial function in the stabilization of Treg function by mediating *IL-6R* and *STAT3* transcript degradation upon cell activation in inflammatory conditions [115]. Crucially, specific pathological mechanisms and signaling pathways where miRNAs are involved have also been elucidated. Increased expression of miR-301a, miR-590, miR-873 and miR-17 promotes the differentiation of Th17 cells and IL-17A secretion, that perpetuates inflammation in IBD, SLE and RA. Mechanistically, miR-301a targets SNIP1, which primarily inhibits the TGF-β1 pathway [116]; miR-590 targets anti-proliferative protein Tob1, a known suppressor of Th17 commitment [117]; miR-873 downregulates FOXO1, an inhibitor of RORγt-Th17 program [63] and miR-17 suppresses Treg induction by inhibiting the expression of TGFBR II [118].

On the other hand, miRNAs expression is also affected by members of the Ikaros family. In the context of ALL, IKAROS protein regulates a microRNA network of up to 31 different miRNAs with implications in oncogenic cell growth and tumor suppression [119]. miR-128 expression levels is associated with microdeletions in the *IKAROS* gene and was deemed a relevant molecular marker to assess risk of leukaemia relapse [120]. Interestingly, a mutual negative regulation between miR-4772-3p and *HELIOS* was found in Treg cells, inhibiting each other's expression *in vitro* and therefore, miR-4772-3p downregulation promoted an enhanced Treg regulatory function [121].

3.4. Other

3.4.1. Dietary and metabolic cues

Dietary signals can have a deep impact on the course of inflammatory processes, as they represent the main direct source of antioxidants and nutrients for the maintenance of a healthy and well-functioning immune system. Increasing evidence suggests that specifically, the mediterranean diet has a positive impact on symptom management and risk of developing diverse CIDs [122–124]. In addition, dietary composition is inevitably intertwined with microbiota diversity, which is a factor that has gained recent attention regarding immune fitness maintenance.

3.4.1.1. AhR (aryl hydrocarbon receptor). AhR was first described as a receptor for xenobiotics, but it was later characterized as an important regulator of the development and function of immune cells in innate and adaptive responses. It binds a variety of exogenous ligands: dioxins, 6-formylindolo[3,2-*b*]carbazole (FICZ) [125], indolo-[3,2-b]-carbazole (ICZ) which is enriched in cruciferous vegetables [126]; and endogenous sources, like metabolites derived from diet or microbiota [127].

AhR expression is highly upregulated in $CD4^+$ T cells under Th17 differentiating conditions and is directly implicated in *IL-17A, IL-17F* and *IL-22* gene transcription as well as *CYP1A1* [128]. Stimulation with proinflammatory cytokines like IL-1β is required for *AhR* induction but IL-6 is essential, as it activates STAT3 which consequently binds to the *AhR* gene promoter, inducing its expression. The combination of AhR activation with TGFβ leads to a high expression of *SMAD1* and *AIOLOS* [100], SMAD1 binds to an upstream *FOXP3* gene enhancer to promote its expression and AIOLOS binds FOXP3 protein to form a complex that silences the *IL-2* gene and supresses inflammatory gene programs, while promoting the differentiation of functional Treg cells [100].

3.4.1.2. Vitamins A and D. The active form of vitamin D (1α,25-dihydroxyvitamin D3, 1,25(OH)2D3) is an important dietary factor positively influencing the abundance of FOXP3/IL-10-expressing $CD4^+$ T cells, by directly binding to Vitamin D response element (VDRE) sequences in the human *FOXP3* gene [129]. In addition, it enhances the expression of Treg-associated molecules like PD-1, CTLA-4, CD25, CD38, CD62L and GITR [130] and reduces the release of proinflammatory cytokines including IFNγ, IL-17, and IL-21 [131,132]. A metabolite of vitamin A, all-trans retinoic acid (ATRA) synergises with vitamin D in suppressing Th17 development from naïve and memory $CD4^+$ T cells [133].

3.4.1.3. Salts (sodium chloride and potassium chloride). Groundbreaking studies have demonstrated how high salt concentrations have a direct effect on stimulating human Th17 differentiation, promoting inflammation and inducing key pathogenic signature genes (*IL-17A, IL-23R, CSF2*)[134]. As expected, a more direct impact of diet and metabolism takes place in the intestinal environment compared to other tissues. A pilot study with healthy volunteers showed that after increased salt (NaCl) consumption the $CD4^+$ $IL\text{-}17A^+$ TNF^+ Th17 cell count was higher in blood [135]. In addition, this high-salt challenge had profound effects on microbiota and on beneficial *Lactobacillus* species, that were notably depleted after the treatment, suggesting an alteration of the natural intestinal microenvironment hampers their ability to thrive. These changes may be able to have, in the long term, a more generalized impact on health, promoting the development of CIDs. On the contrary, potassium chloride (KCl) has a suppressive effect on inflammation by reducing *IL-17* and *IFNγ* expression in $CD4^+$ T cells under *in vitro* Th17-polarizing conditions and promoting a tolerogenic phenotype by inducing the expression of *FOXP3* [136].

3.4.2. Gut microbiota – T cell interactions

Growing evidence indicates that disruption of gut microbiota composition (dysbiosis) favours the progression of inflammatory diseases through mechanisms like metabolic dysfunction, intestinal barrier damage and aberrant immune activation. The crosstalk between microbiota and host through diet, microbial antigens and metabolites can impact profoundly the host wellbeing and immune status. Although gut microbiota in non-IBD diseases is understudied, it represents a reliable readout for treatment response and pre-clinical manifestations of other CIDs [137]. Commensal bacterial species show different strategies to directly and indirectly impact the differentiation of intestinal Treg and Th17 cells. They provide microbial antigens that stimulate epithelial cell TGF-β1 production [138] and release byproducts from bile acid metabolism and fermentation of insoluble fibres [139]. For instance, the secondary bile acids 3-oxo-lithocholic acid (3-oxo-LCA) and isoLCA, produced by *Gordonibacter, Eggerthella, Raoultibacter* and *Clostridium* species, inhibit Th17 development by directly binding to and blocking RORγt activity [140]. However, more research is needed to understand the effects of individual microbial interactions with host susceptibility factors for CIDs, as some species also bear epitopes that

show molecular mimicry, exerting a potentially relevant role in breakdown of self-tolerance [137,141,142].

3.4.3. Myeloid – T cell interactions

Different subsets of myeloid cells determine fate decisions in the development of inflammatory or tolerogenic T cells. Presence of surface markers CD14 and HLA-DR in monocytes promote IL-17–secreting RORγt^{+} Th17 cells, while CD14^{+} HLA-DR$^{-/low}$ myeloid-derived suppressor cells (MDSCs) not only promote *de novo* FOXP3^{+} regulatory T cell development, but also enable the conversion of monocyte-induced Th17 cells to induced regulatory Tregs (iTreg) *in vitro* [143]. Another study found that CD16^{+} monocytes specifically supress HELIOS^{+} Treg cell proliferation through IL-12, while CD16- monocytes supress HELIOS- cells through tumor necrosis factor-alpha (TNF-α) [144]. Although CD16 expression was not examined in the first study, both conclude that inflammatory cytokines ultimately have control of T cell developmental outcome. The implication of the Notch ligand DLL4 in driving a pathogenic phenotype in human T cells was discovered by co-culture with DLL4 expressing CD1c^{+} dendritic cells. *In vitro* activation of CD1c^{+} dendritic cells with TLR7/8 agonist induced STAT3-dependent DLL4 expression, subsequent co-culture of the activated cells with CD4^{+} T cells promoted Th1/Th17 differentiation mediated by DLL4 [145]. These results open the possibility to research the capacity of the various Notch signaling components to induce pathogenic T cell states. In conclusion, dysregulated inflammatory circuits in myeloid cells may affect the balance of phenotypes in the lymphoid compartment.

In summary, Th17 and Treg developmental pathways are mutually interconnected and tight regulation of these pathways, mainly through transcriptional control, maintain a homeostatic balance of both T cell populations. These studies also highlight the relevance of further examining the cellular diversity of the myeloid compartment to predict CID prognosis, as they represent a source of signals directing T cell development. The contribution of gut microbiota and diet to the prevalence of inflammatory symptoms cannot be overlooked, although more holistic research is needed, rather than species-specific and individual food component contributions.

4. Transcriptional regulation of ikaros in T cell-mediated diseases

Genetic variants in the Ikaros genes highlight their association with different human chronic inflammatory and autoimmune diseases. Single nucleotide polymorphisms, although not evidently affecting the normal protein function, often results in a positive correlation with disease diagnosis (*AIOLOS* in RA [21], psoriasis [146], MS [147] and SLE [148]*; EOS* in type 1 diabetes [23], *IKAROS* [149] in primary Sjögren's syndrome, pSS). Downregulation or loss-of-function mutations on Ikaros genes is a common feature in PBMCs from SLE (*HELIOS* [109], *IKAROS* [150,151]) and IBD (*IKAROS* [18]) patients. While in other cases, Ikaros gene overexpression is observed in UC (IKAROS [152]), SLE (*AIOLOS* [153]) and RA (*IKAROS* and *AIOLOS* [153,154]). However, in RA, Ikaros aberrant expression varies depending on specific T cell subsets examined [155]. Strikingly, studies in different CIDs found that *HELIOS* expression was higher in RA [156] and the absolute numbers of circulating FOXP3^{+} HELIOS^{+} cells were normal in patients with moderately-to-highly active SLE [157] and pSS [158], although, as expected, no associated superior suppressive function was observed. These findings do not correlate, though, with observations of engineered Treg cells *in vitro*, where co-expression of *HELIOS* and *FOXP3* enhanced and stabilized their regulatory functions [159].

Mechanistic details of the link between Ikaros proteins and pathogenic processes are gradually beginning to be unravelled. Relevant studies on IKAROS, AIOLOS and HELIOS in human T cells found that a defective repressive function over their target genes leads to increased cell responsiveness and sensitivity to external cues. This is suggestive that ultimately, their transcriptional repression would be contributing to the control of autoimmune processes. In one of these studies, IKAROS was identified as a transcriptional repressor of the pore-forming calcium channel component ORAI calcium release-activated calcium modulator 3 (*ORAI3*) [25]. This protein had increased expression in naïve CD4^{+} T cells derived from patients with RA and PsA. Consequently, stimulation with arachidonic acid, a known precursor of the biosynthesis of pro-inflammatory mediators, induced a calcium influx and phosphorylation of components of the T cell receptor signaling pathway, leading to an enhanced cellular responsiveness. This process would also have a significant relevance in diseases where a consistent downregulation of Ikaros members is a signature feature. Interestingly, a study focused on Treg cells from RA patients revealed a generalized reduction in expression of all members of the Ikaros family [155], potentially rendering them more prone to activation. However, these mechanisms could be disease-specific, as although a down-regulated expression of *IKAROS* mRNA was observed in PBMCs from SLE patients, this was not correlated to an overexpression of *ORAI3* [150] (Fig. 3A). In another study, by using lenalidomide *in vitro* the authors revealed a transcriptional control of IKAROS over *CSF2*, which encodes the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) [24]. GM-CSF is a pleiotropic cytokine, and its presence correlates with disease severity in inflammatory and autoimmune diseases like IBD [160], RA [161] and MS [162]. In a study with a similar approach, pomalidomide-treated human Treg cells showed overproduction of IFN-γ, indicating that IKAROS and AIOLOS are required for the suppression of *IFNG* gene [27]. Importantly, an IFN-γ signature is present in inflamed tissues from CIDs [163](Fig. 3B).

Immune ageing is an important factor impairing adaptive immune responses that leads to cell immune malfunctioning and associated low-grade inflammation. A positive correlation between ageing and down-regulation of HELIOS protein was found in CD4^{+} T cells [26]. Naïve T cells from aged individuals display a predisposition to turn into effector, rather than regulatory, cells upon TCR activation and they show increased STAT5 activity as a consequence of IL-2 autocrine signaling. This study shows that HELIOS also exerts a repressive function on *CD25*, with loss of HELIOS in older age resulting in an overall amplified proliferative signal and excess TCR-induced differentiation exemplified by higher *IRF4, BATF* and *BLIMP1* expression [26] (Fig. 3C). Environmental factors like smoking, pollution and intake of processed foods have been linked to exacerbation of RA symptoms [164–166], in part due to the ability of these factors to cause cell damage, inflammation and oxidative stress [167,168]. In line with the oxidative stress theory of ageing [169], it would be interesting to investigate if exposure to these factors could cause accelerated cell ageing through these mechanisms and subsequent degradation of HELIOS in CD4^{+} T cells. In summary, alterations in gene expression control by Ikaros predispose T cells to present an enhanced responsive phenotype and possibly, a resistance to transdifferentiate into a more regulatory T cell type.

5. Ikaros family therapeutic targeting

Targeted treatment options for CIDs are scarce, relying mainly on the use of DMARDs (Disease-Modifying Antirheumatic Drugs), biologics like anti-tumor necrosis factor-alpha (TNF-α) monoclonal antibodies, small molecule drugs like JAK-STAT inhibitors and anti-inflammatory drugs (corticosteroids). A deeper investigation of disease signaling pathways and better refinement of druggable targets will prospectively improve the unsatisfactory response to current treatments and, ideally, stably redirect the pathological cellular phenotype to a more homeostatic phenotype. Anti- TNF-α biologics are currently the main treatment option for chronic inflammatory conditions. Surprisingly, a molecularly and functionally distinct IL-17^{+} CD4^{+} Th17 cell population characterized by high expression of AIOLOS was found to contribute towards the therapeutic effects of anti-TNF-α treatment by inducing and maintaining high levels of IL-10 [170,171].

The IMiDs lenalidomide and pomalidomide are analogues of

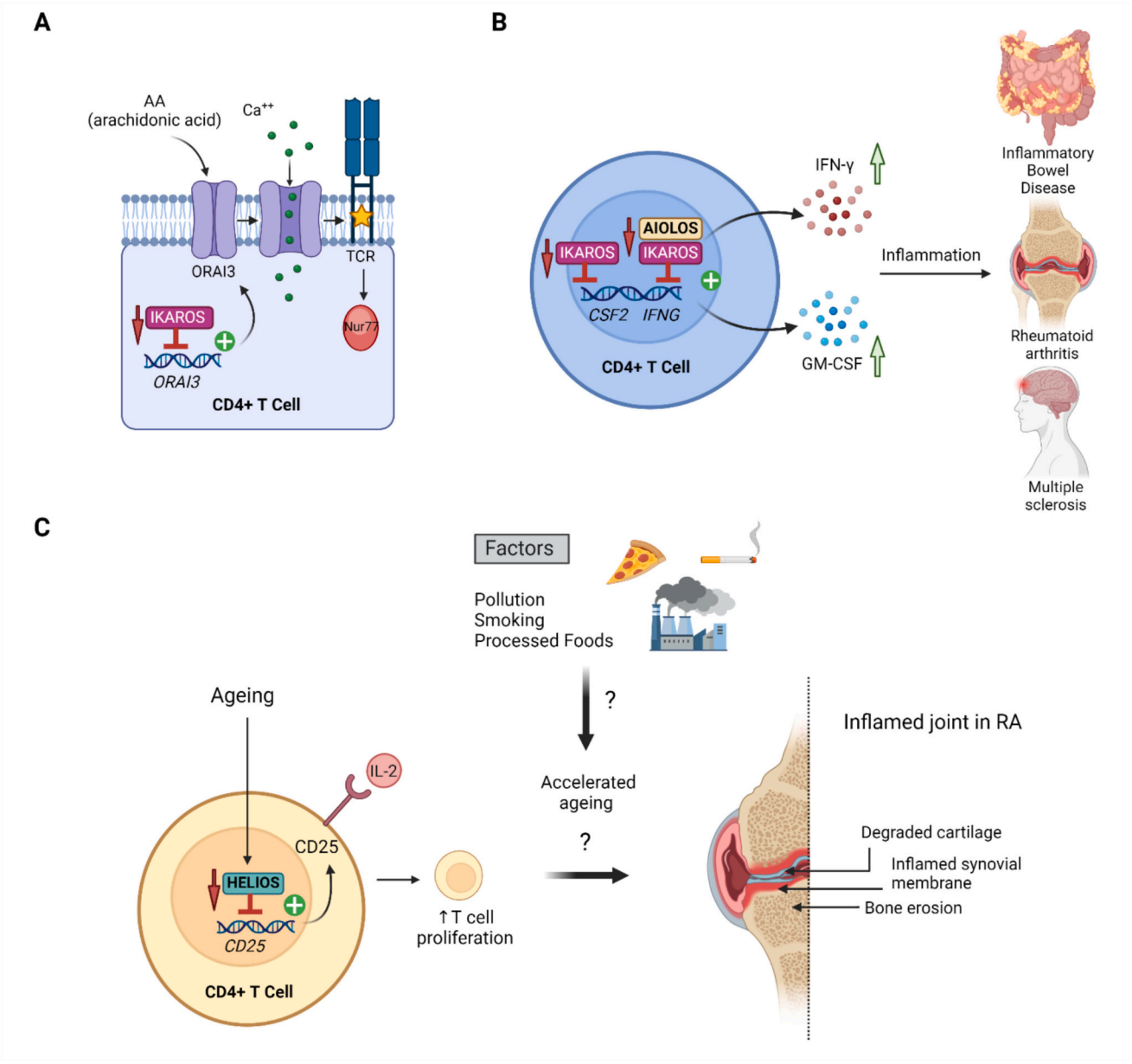


Fig. 3. Transcriptional control of Ikaros over key genes in the pathogenesis of autoimmune diseases. A Downregulated IKAROS abrogates the transcriptional repression over *ORAI3*, an arachidonic acid-regulated calcium selective channel, making T cells more sensitive to stimulation and highly responsive to autoantigenic stimulation. B A reduction in the expression of IKAROS in human T cells leads to increased IFN-γ and GM-CSF production, key cytokines in the pathogenesis of IBD, RA and MS. C Cellular ageing is responsible for HELIOS degradation in $CD4^+$ T cells, leading to *CD25* expression upregulation and rendering the cell more responsive to mitotic stimuli. External factors leading potentially to cell ageing and inflammation are depicted. Created with BioRender.com.

thalidomide, they serve as potent protein degraders and emerged as one of the milestones for the treatment of multiple myeloma. Their molecular mechanism of action is based on prompting specific IKAROS and AIOLOS degradation through Cereblon (CRBN) binding, that forms the CRL4 E3 ubiquitin ligase complex ($CRL4^{CRBN}$), and recognizes substrates for ubiquitination and subsequent proteasomal degradation. Therefore, these drugs are commonly known as "molecular glues". Novel thalidomide analogues have emerged for use in the clinic, named Cereblon E3 ligse Modulating Drugs (CELMoDs) that bind CRBN with higher affinity than lenalidomide or pomalidomide [172]. Some examples include avadomide (CC-122), iberdomide (CC-220), CC-885 and CC-92480. At present, they are currently being tested in clinical trials for the treatment of solid tumors, both as monotherapy and in combination with other drugs (NCT01421524; NCT02773030; NCT03374085). Another recent potent heterobifunctional molecule, NX-2127, that enables degradation of all known drug-resistant mutant forms of Bruton's tyrosine kinase, IKAROS and AIOLOS proteins, is currently on a first-in-human clinical trial (NCT04830137) [173]. The mechanism of action of another selective degrader, NVP-DKY709, that targets HELIOS and spares IKAROS and AIOLOS, was recently characterized [174]. Degradation of HELIOS with this compound made Tregs less inhibitory but also, exhausted effector T cells were more active *in vitro*, indicating that this would be a promising therapeutic option for settings other than chronic inflammatory conditions, where enhancing T cell activity is sought. Another class of compounds that target HELIOS and are also the only reported EOS degraders, substituted 3-(1-oxoisoindolin-2-yl)piperidine-2,6-dione compounds, have been reported in the International Patent Applications (WO 2019/038717 A1) [175]. The activity of this class of compounds was recently validated in human Treg cells *in vitro* [27]. These studies have laid the foundation for future drug design with the objective of

developing drugs with increased specificity that protect specific Ikaros proteins from degradation.

Understanding of the biological effects underpinning the clinical efficacy of thalidomide-derived drugs for multiple myeloma have given further insights into the mechanistic details of Ikaros regulation of T cell effector functions [176,177]. Thalidomide and its derivative drugs, pomalidomide and lenalidomide, were originally developed as anti-inflammatory drugs and have long been known to reduce TNF-α mRNA [178,179]. However, for multiple myeloma treatment IMiDs are effective mostly due to their anti-angiogenic, pro-apoptotic and immunomodulatory properties, including cytotoxic T cell stimulation and increased IL-2 and IFN-γ production [180,181]. IMIDs also reduce regulator suppressor of cytokine signaling (SOCS)1 expression in immune cells, enhancing the immune response [182]. At the same time, strong anti-inflammatory effects have been demonstrated on myeloid cell populations by inhibiting monocyte and myeloid-derived dendritic cell production of proinflammatory cytokines like TNF-α, IL-12, IL-1β, IL-6 and augmenting IL-10 [183,184]. Despite this, clinical trials have demonstrated that thalidomide and lenalidomide are not effective at treating chronic inflammatory disease [185]. However, this apparent controversy can be explained based on the type of *in vitro* stimuli used in these studies to activate the cells (TLR ligands, mitogens) that don't necessarily mirror the stimulation received by cells in inflamed tissue during chronic disease.

6. Conclusions

The transcriptional activity of the Ikaros family is crucial for the T cell subset specification, but increasing evidence highlights its role in controlling pathogenic mechanisms in T cell mediated diseases. The Notch-Ikaros interplay is well explored in cancer settings, but new evidence has emerged around the role of specific Notch pathway components in T cell fate decisions. Understanding the interplay between Ikaros and other factors in conditioning human T cell ´plasticity´ has the potential to expand therapeutic targets for T cell fate redirection. Additionally, the study of the dynamics of 'plasticity' in the T cell compartment can instruct on the identification of optimal timepoints for therapeutic intervention or clinical outcome, potentially linked to T cell subset composition in diseased tissue.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by Science Foundation Ireland (SFI) Research Professorship Programme (20/RP/9007).

Data availability

No data was used for the research described in the article.

References

[1] Ehrenstein MR, Evans JG, Singh A, Moore S, Warnes G, Isenberg DA, et al. Compromised function of regulatory T cells in rheumatoid arthritis and reversal by anti-TNFα therapy. J Exp Med 2004;200:277–85. https://doi.org/10.1084/jem.20040165.
[2] Noack M, Miossec P. Th17 and regulatory T cell balance in autoimmune and inflammatory diseases. Autoimmun Rev 2014;13:668–77. https://doi.org/10.1016/j.autrev.2013.12.004.
[3] Weyand CM, Goronzy JJ. The immunology of rheumatoid arthritis. Nat Immunol 2021;22:10–8. https://doi.org/10.1038/s41590-020-00816-x.
[4] Bluestone JA, MacKay CR, O'Shea JJ, Stockinger B. The functional plasticity of T cell subsets. Nat Rev Immunol 2009;9:811–6. https://doi.org/10.1038/nri2654.
[5] Eizenberg-Magar I, Rimer J, Zaretsky I, Lara-Astiaso D, Reich-Zeliger S, Friedman N. Diverse continuum of CD4+ T-cell states is determined by hierarchical additive integration of cytokine signals. Proc Natl Acad Sci USA 2017;114:E6447–56. https://doi.org/10.1073/pnas.1615590114.
[6] Beriou G, Costantino CM, Ashley CW, Yang L, Kuchroo VK, Baecher-Allan C, et al. IL-17-producing human peripheral regulatory T cells retain suppressive function. Blood 2009;113:4240–9. https://doi.org/10.1182/blood-2008-10-183251.
[7] Shin Voo K, Wang Y-H, Santori FR, Boggiano C, Wang Y-H, Arima K, et al. Identification of IL-17-producing FOXP3 regulatory T cells in humans. Proc Natl Acad Sci USA 2009;106:4793–8. https://doi.org/10.1073/pnas.0900408106.
[8] Jung MK, Kwak JE, Shin EC. IL-17A-producing foxp3+ regulatory T cells and human diseases. Immune Netw 2017;17:276–86. https://doi.org/10.4110/in.2017.17.5.276.
[9] Cosmi L, Maggi L, Santarlasci V, Capone M, Cardilicchia E, Frosali F, et al. Identification of a novel subset of human circulating memory CD4+ T cells that produce both IL-17A and IL-4. J Allergy Clin Immunol 2010;125:222–30. https://doi.org/10.1016/j.jaci.2009.10.012.
[10] Ueno A, Jeffery L, Kobayashi T, Hibi T, Ghosh S, Jijon H. Th17 plasticity and its relevance to inflammatory bowel disease. J Autoimmun 2018;87:38–49. https://doi.org/10.1016/j.jaut.2017.12.004.
[11] Cerboni S, Gehrmann U, Preite S, Mitra S. Cytokine-regulated Th17 plasticity in human health and diseases. Immunology 2021;163:3–18. https://doi.org/10.1111/imm.13280.
[12] Mirlekar B. Co-expression of master transcription factors determines CD4+ T cell plasticity and functions in auto-inflammatory diseases. Immunol Lett 2020;222:58–66. https://doi.org/10.1016/j.imlet.2020.03.007.
[13] Ayyoub M, Deknuydt F, Raimbaud I, Dousset C, Leveque L, Bioley G, et al. Human memory FOXP3 Tregs secrete IL-17 ex vivo and constitutively express the T H 17 lineage-specific transcription factor RORt. Proc Natl Acad Sci 2009;106:8635–40.
[14] Kryczek I, Wu K, Zhao E, Wei S, Vatan L, Szeliga W, et al. IL-17+ regulatory T cells in the microenvironments of chronic inflammation and cancer. J Immunol 2011;186:4388–95. https://doi.org/10.4049/jimmunol.1003251.
[15] Xia R, Cheng Y, Han X, Wei Y, Wei X. Ikaros proteins in tumor: current perspectives and new developments. Front Mol Biosci 2021;8:788440. https://doi.org/10.3389/fmolb.2021.788440.
[16] McGovern DPB, Kugathasan S, Cho JH. Genetics of inflammatory bowel diseases. Gastroenterology 2015;149:1163–1176.e2. https://doi.org/10.1053/j.gastro.2015.08.001.
[17] Liu JZ, Van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet 2015;47:979–86. https://doi.org/10.1038/ng.3359.
[18] Eskandarian Z, Fliegauf M, Bulashevska A, Proietti M, Hague R, Smulski CR, et al. Assessing the functional relevance of variants in the Ikaros family zinc finger protein 1 (IKZF1) in a cohort of patients with primary immunodeficiency. Front Immunol 2019;10:568. https://doi.org/10.3389/fimmu.2019.00568.
[19] Zhang X, Sheng Y, Jin X, Xu J, Gao J, Du X, et al. Sequencing-based approach identified three new susceptibility loci for psoriasis. Nat Commun 2014;5:4331. https://doi.org/10.1038/ncomms5331.
[20] Han JW, Zheng HF, Cui Y, Sun LD, Ye DQ, Hu Z, et al. Genome-wide association study in a Chinese Han population identifies nine new susceptibility loci for systemic lupus erythematosus. Nat Genet 2009;41:1234–7. https://doi.org/10.1038/ng.472.
[21] Kurreeman FAS, Stahl EA, Okada Y, Liao K, Diogo D, Raychaudhuri S, et al. Use of a multiethnic approach to identify rheumatoid- arthritis- susceptibility loci, 1p36 and 17q12. Am J Hum Genet 2012;90:524–32. https://doi.org/10.1016/j.ajhg.2012.01.010.
[22] Hoshino A, Boutboul D, Zhang Y, Sun Kuehn H, Hadjadj J, Özdemir N, et al. Gain-of-function IKZF1 variants in humans cause immune dysregulation associated with abnormal T/B cell late differentiation. Sci Immunol 2022;7:7160.
[23] Lempainen J, Härkönen T, Laine A, Knip M, Ilonen J, Groop PH, et al. Associations of polymorphisms in non-HLA loci with autoantibodies at the diagnosis of type 1 diabetes: INS and IKZF4 associate with insulin autoantibodies. Pediatr Diabetes 2013;14:490–6. https://doi.org/10.1111/pedi.12046.
[24] Bernardi C, Maurer G, Ye T, Marchal P, Jost B, Wissler M, et al. CD4+ T cells require Ikaros to inhibit their differentiation toward a pathogenic cell fate. Proc Natl Acad Sci USA 2021;118:e2023172118. https://doi.org/10.1073/pnas.2023172118.
[25] Ye Z, Shen Y, Jin K, Qiu J, Hu B, Jadhav RR, et al. Arachidonic acid-regulated calcium signaling in T cells from patients with rheumatoid arthritis promotes synovial inflammation. Nat Commun 2021;12:907. https://doi.org/10.1038/s41467-021-21242-z.
[26] Zhang H, Jadhav RR, Cao W, Goronzy IN, Zhao TV, Jin J, et al. Aging-associated HELIOS deficiency in naive CD4+ T cells alters chromatin remodeling and promotes effector cell responses. Nat Immunol 2023;24:96–109. https://doi.org/10.1038/s41590-022-01369-x.
[27] Ichiyama K, Long J, Kobayashi Y, Horita Y, Kinoshita T, Nakamura Y, et al. Transcription factor Ikzf1 associates with Foxp3 to repress gene expression in Treg cells and limit autoimmunity and anti-tumor immunity. Immunity 2024;57:2043–60. https://doi.org/10.1016/j.immuni.2024.07.010.
[28] Koipally J, Georgopoulos K. A molecular dissection of the repression circuitry of Ikaros. J Biol Chem 2002;277:27697–705. https://doi.org/10.1074/jbc.M201694200.
[29] Dege C, Hagman J. Mi-2/NuRD chromatin remodeling complexes regulate B and T-lymphocyte development and function. Immunol Rev 2014;261:126–40. https://doi.org/10.1111/imr.12209.

[30] Sridharan R, Smale ST. Predominant interaction of both Ikaros and Helios with the NuRD complex in immature thymocytes. J Biol Chem 2007;282:30227–38. https://doi.org/10.1074/jbc.M702541200.

[31] Hu R, Sharma SM, Bronisz A, Srinivasan R, Sankar U, Ostrowski MC. Eos, MITF, and PU.1 recruit corepressors to osteoclast-specific genes in committed myeloid progenitors. Mol Cell Biol 2007;27:4018–27. https://doi.org/10.1128/mcb.01839-06.

[32] Bottardi S, Mavoungou L, Milot E. IKAROS: a multifunctional regulator of the polymerase II transcription cycle. Trends Genet 2015;31:500–8. https://doi.org/10.1016/j.tig.2015.05.003.

[33] Oravecz A, Apostolov A, Polak K, Jost B, Le Gras S, Chan S, et al. Ikaros mediates gene silencing in T cells through Polycomb repressive complex 2. Nat Commun 2015;6:8823. https://doi.org/10.1038/ncomms9823.

[34] Ne E, Crespo R, Izquierdo-Lara R, Rao S, Koçer S, Górska A, et al. Catchet-MS identifies IKZF1-targeting thalidomide analogues as novel HIV-1 latency reversal agents. Nucleic Acids Res 2022;50:5577–98. https://doi.org/10.1093/nar/gkac407.

[35] Ng MSF, Roth TL, Mendoza VF, Marson A, Burt TD. Helios enhances the preferential differentiation of human fetal CD4 + naïve T cells into regulatory T cells. Sci Immunol 2019;4:5947.

[36] Hu Y, Salgado Figueroa D, Zhang Z, Veselits M, Bhattacharyya S, Kashiwagi M, et al. Lineage-specific 3D genome organization is assembled at multiple scales by IKAROS. Cell 2023;186:5269–5289.e22. https://doi.org/10.1016/j.cell.2023.10.023.

[37] Mazzurana L, Forkel M, Rao A, Van Acker A, Kokkinou E, Ichiya T, et al. Suppression of Aiolos and Ikaros expression by lenalidomide reduces human ILC3−ILC1/NK cell transdifferentiation. Eur J Immunol 2019;49:1344–55. https://doi.org/10.1002/eji.201848075.

[38] Duhen T, Duhen R, Lanzavecchia A, Sallusto F, Campbell DJ. Functionally distinct subsets of human FOXP3+ Treg cells that phenotypically mirror effector Th cells. Blood 2012;119:4430–40. https://doi.org/10.1182/blood-2011-11-392324.

[39] Hovhannisyan Z, Treatman J, Littman DR, Mayer L. Characterization of interleukin-17-producing regulatory T cells in inflamed intestinal mucosa from patients with inflammatory bowel diseases. Gastroenterology 2011;140:957–65. https://doi.org/10.1053/j.gastro.2010.12.002.

[40] O'shea JJ, Paul WE. Mechanisms underlying lineage commitment and plasticity of helper CD4 + T cells. Science 1979;2010(327):1098–102. https://doi.org/10.1126/science.1178334.

[41] Koenen HJPM, Smeets RL, Vink PM, Van Rijssen E, Boots AMH, Joosten I. Human CD25highFoxp3pos regulatory T cells differentiate into IL-17 producing cells. Blood 2008;112:2340–52. https://doi.org/10.1182/blood-2008-01-133967.

[42] Dupage M, Bluestone JA. Harnessing the plasticity of CD4+ T cells to treat immune-mediated disease. Nat Rev Immunol 2016;16:149–63. https://doi.org/10.1038/nri.2015.18.

[43] Luo Y, Xu C, Wang B, Niu Q, Su X, Bai Y, et al. Single-cell transcriptomic analysis reveals disparate effector differentiation pathways in human Treg compartment. Nat Commun 2021;12:3913. https://doi.org/10.1038/s41467-021-24213-6.

[44] Li P, Wang X, Zhao MQ, Li LJ, Zhang C, Li BZ, et al. TCR-CD3ζ gene polymorphisms and expression profile in rheumatoid arthritis. Autoimmunity 2016;49:466–71. https://doi.org/10.1080/08916934.2016.1174855.

[45] Katsuyama T, Tsokos GC, Moulton VR. Aberrant T cell signaling and subsets in systemic lupus erythematosus. Front Immunol 2018;9:1088. https://doi.org/10.3389/fimmu.2018.01088.

[46] Kastirr I, Crosti M, Maglie S, Paroni M, Steckel B, Moro M, et al. Signal strength and metabolic requirements control cytokine-induced Th17 differentiation of uncommitted human T cells. J Immunol 2015;195:3617–27. https://doi.org/10.4049/jimmunol.1501016.

[47] Purvis HA, Stoop JN, Mann J, Woods S, Kozijn AE, Hambleton S, et al. Low-strength T-cell activation promotes Th17 responses. Blood 2010;116:4829–37. https://doi.org/10.1182/blood-2010-03-272153.

[48] Revu S, Wu J, Henkel M, Rittenhouse N, Menk A, Delgoffe GM, et al. IL-23 and IL-1β drive human Th17 cell differentiation and metabolic reprogramming in absence of CD28 Costimulation. Cell Rep 2018;22:2642–53. https://doi.org/10.1016/j.celrep.2018.02.044.

[49] Macintyre AN, Gerriets VA, Nichols AG, Michalek RD, Rudolph MC, Deoliveira D, et al. The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. Cell Metab 2014;20:61–72. https://doi.org/10.1016/j.cmet.2014.05.004.

[50] Paulos CM, Carpenito C, Plesa G, Suhoski MM, Varela-Rohena A, Golovina TN, et al. The inducible Costimulator (ICOS) is critical for the development of human TH17 cells. Sci Transl Med 2010;2:55ra78. https://doi.org/10.1126/scitranslmed.3000448.

[51] Wyatt MM, Huff LW, Nelson MH, Neal LR, Medvec AR, Rangel Rivera GO, et al. Augmenting TCR signal strength and ICOS costimulation results in metabolically fit and therapeutically potent human CAR Th17 cells. Mol Ther 2023;31:2120–31. https://doi.org/10.1016/j.ymthe.2023.04.010.

[52] Ng WF, Duggan PJ, Ponchel F, Matarese G, Lombardi G, David Edwards A, et al. Human CD4 CD25 cells: a naturally occurring population of regulatory T cells. Blood 2001;98:2736–44.

[53] Keerthivasan S, Suleiman R, Lawlor R, Roderick J, Bates T, Minter L, et al. Notch signaling regulates mouse and human Th17 differentiation. J Immunol 2011;187:692–701. https://doi.org/10.4049/jimmunol.1003658.

[54] Mullighan CG, Su X, Zhang J, Radtke I, Phillips LAA, Miller CB, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med 2009;360:470–80. https://doi.org/10.1056/nejmoa0808253.

[55] Tokunaga K, Yamaguchi S, Iwanaga E, Nanri T, Shimomura T, Suzushima H, et al. High frequency of IKZF1 genetic alterations in adult patients with B-cell acute lymphoblastic leukemia. Eur J Haematol 2013;91:201–8. https://doi.org/10.1111/ejh.12155.

[56] Bellavia D, Mecarozzi M, Campese AF, Grazioli P, Talora C, Frati L, et al. Notch3 and the Notch3-upregulated RNA-binding protein HuD regulate Ikaros alternative splicing. EMBO J 2007;26:1670–80. https://doi.org/10.1038/sj.emboj.7601626.

[57] Wang Y, Zhao H, He Y, Zhang P, Zeng C, Du T, et al. IKZF4 acts as a novel tumor suppressor in non–small cell lung cancer by suppressing Notch signaling pathway. Cell Signal 2023;107:110679. https://doi.org/10.1016/j.cellsig.2023.110679.

[58] Mercer F, Kozhaya L, Unutmaz D. Expression and function of TNF and IL-1 receptors on human regulatory T cells. PLoS One 2010;5:e8639. https://doi.org/10.1371/journal.pone.0008639.

[59] Kim DH, Kim HY, Cho S, Yoo SJ, Kim WJ, Yeon HR, et al. Induction of the IL-1RII decoy receptor by NFAT/FoxP3 blocks IL-1β-dependent response of TH17 cells. Elife 2021;10:1–72. https://doi.org/10.7554/eLife.61841.

[60] Raffin C, Pignon P, Celse C, Debien E, Valmori D, Ayyoub M. Human memory Helios− FOXP3+ regulatory T cells (Tregs) encompass induced Tregs that express Aiolos and respond to IL-1β by downregulating their suppressor functions. J Immunol 2013;191:4619–27. https://doi.org/10.4049/jimmunol.1301378.

[61] Müller M, Herrath J, Malmström V. IL-1R1 is expressed on both Helios+ and Helios-FoxP3+CD4+ T cells in the rheumatic joint. Clin Exp Immunol 2015;182:90–100. https://doi.org/10.1111/cei.12668.

[62] Zhou L, Lopes JE, Chong MMW, Ivanov II, Min R, Victora GD, et al. TGF-B-induced Foxp3 inhibits TH17 cell differentiation by antagonizing RORγt function. Nature 2008;453:236–40. https://doi.org/10.1038/nature06878.

[63] Liu L, Liu Y, Yuan M, Xu L, Sun H. Elevated expression of microRNA-873 facilitates Th17 differentiation by targeting forkhead box O1 (Foxo1) in the pathogenesis of systemic lupus erythematosus. Biochem Biophys Res Commun 2017;492:453–60. https://doi.org/10.1016/j.bbrc.2017.08.075.

[64] Zhang M, Guan Y, Han M, Kong F, Xu A, Jin X, et al. Foxo1 drives the TGFβ1-dependent dichotomy of Th17 cell fates. J Leukoc Biol 2024. https://doi.org/10.1093/jleuko/qiae004. qiae004.

[65] Tripathi SK, Välikangas T, Shetty A, Khan MM, Moulder R, Bhosale SD, et al. Quantitative proteomics reveals the dynamic protein landscape during initiation of human Th17 cell polarization. IScience 2019;11:334–55. https://doi.org/10.1016/j.isci.2018.12.020.

[66] Yang L, Anderson DE, Baecher-Allan C, Hastings WD, Bettelli E, Oukka M, et al. IL-21 and TGF-β are required for differentiation of human T H17 cells. Nature 2008;454:350–2. https://doi.org/10.1038/nature07021.

[67] Ziolkowska M, Koc A, Luszczykiewicz G, Ksiezopolska-Pietrzak K, Klimczak E, Chwalinska-Sadowska H, et al. High levels of IL-17 in rheumatoid arthritis patients: IL-15 triggers in vitro IL-17 production via Cyclosporin A-sensitive mechanism 1. J Immunol 2000;164:2832–8.

[68] Halvorsen EH, Strønen E, Hammer HB, Goll GL, Sollid LM, Molberg.. Interleukin-15 induces Interleukin-17 production by synovial T cell lines from patients with rheumatoid arthritis. Scand J Immunol 2011;73:243–9. https://doi.org/10.1111/j.1365-3083.2010.02498.x.

[69] Sisto M, Lorusso L, Lisi S. TLR2 signals via NF-κB to drive IL-15 production in salivary gland epithelial cells derived from patients with primary Sjögren's syndrome. Clin Exp Med 2017;17:341–50. https://doi.org/10.1007/s10238-016-0429-y.

[70] Lee W-W, Kang SW, Choi J, Lee S-H, Shah K, Eynon EE, et al. Regulating human Th17 cells via differential expression of IL-1 receptor. Blood 2010;115:530–40. https://doi.org/10.1182/blood-2009.

[71] Wilson NJ, Boniface K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD, et al. Development, cytokine profile and function of human interleukin 17-producing helper T cells. Nat Immunol 2007;8:950–7. https://doi.org/10.1038/ni1497.

[72] Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science 1979;2006(314):1461–3. https://doi.org/10.1126/science.1135245.

[73] Neurath MF. IL-23 in inflammatory bowel diseases and colon cancer. Cytokine Growth Factor Rev 2019;45:1–8. https://doi.org/10.1016/j.cytogfr.2018.12.002.

[74] Wang Q, Chen F, Peng Y, Yi X, He Y, Shi Y. Research Progress of Interleukin-27 in inflammatory bowel disease. Inflamm Bowel Dis 2024;30:303–10. https://doi.org/10.1093/ibd/izad153.

[75] Cui X, Jiao C, Wang D, Ye Z, Ma J, Tang N, et al. Elevated levels of IL-27 are associated with disease activity in patients with Crohn's disease. Mediat Inflamm 2021;2021:5527627. https://doi.org/10.1155/2021/5527627.

[76] Diveu C, McGeachy MJ, Boniface K, Stumhofer JS, Sathe M, Joyce-Shaikh B, et al. IL-27 blocks RORc expression to inhibit lineage commitment of Th17 cells. J Immunol 2009;182:5748–56. https://doi.org/10.4049/jimmunol.0801162.

[77] Yu W, Zhang K, Wang Z, Zhang J, Chen T, Jin L. Functional variant in the promoter region of IL-27 alters gene transcription and confers a risk for ulcerative colitis in northern Chinese Han. Hum Immunol 2017;78:287–93. https://doi.org/10.1016/j.humimm.2017.01.002.

[78] Soond DR, Slack ECM, Garden OA, Patton DT, Okkenhaug K. Does the PI3K pathway promote or antagonize regulatory T cell development and function? Front Immunol 2012;3:244. https://doi.org/10.3389/fimmu.2012.00244.

[79] Pompura SL, Dominguez-Villar M. The PI3K/AKT signaling pathway in regulatory T-cell development, stability, and function. J Leukoc Biol 2018;103:1065–76. https://doi.org/10.1002/JLB.2MIR0817-349R.

[80] Eschweiler S, Ramírez-Suástegui C, Li Y, King E, Chudley L, Thomas J, et al. Intermittent PI3Kδ inhibition sustains anti-tumour immunity and curbs irAEs. Nature 2022;605:741–6. https://doi.org/10.1038/s41586-022-04685-2.
[81] Chellappa S, Kushekhar K, Munthe LA, Tjønnfjord GE, Aandahl EM, Okkenhaug K, et al. The PI3K p110δ isoform inhibitor Idelalisib preferentially inhibits human regulatory T cell function. J Immunol 2019;202:1397–405. https://doi.org/10.4049/jimmunol.1701703.
[82] Wen H-Y, Wang J, Zhang S-X, Luo J, Zhao X-C, Zhang C, et al. Clinical study low-dose Sirolimus Immunoregulation therapy in patients with active rheumatoid arthritis: a 24-week follow-up of the randomized, open-label. Parallel-Controlled Trial J Immunol Res 2019;7684352:1–10.
[83] Lai ZW, Kelly R, Winans T, Marchena I, Shadakshari A, Yu J, et al. Sirolimus in patients with clinically active systemic lupus erythematosus resistant to, or intolerant of, conventional medications: a single-arm, open-label, phase 1/2 trial. Lancet 2018;391:1186–96. https://doi.org/10.1016/S0140-6736(18)30485-9.
[84] Bagherpour B, Salehi M, Jafari R, Bagheri A, Kiani-Esfahani A, Edalati M, et al. Promising effect of rapamycin on multiple sclerosis. Mult Scler Relat Disord 2018; 26:40–5. https://doi.org/10.1016/j.msard.2018.08.009.
[85] Long SA, Rieck M, Sanda S, Bollyky JB, Samuels PL, Goland R, et al. Rapamycin/IL-2 combination therapy in patients with type 1 diabetes augments Tregs yet transiently impairs β-cell function. Diabetes 2012;61:2340–8. https://doi.org/10.2337/db12-0049.
[86] Twohig JP, Cardus Figueras A, Andrews R, Wiede F, Cossins BC, Derrac Soria A, et al. Activation of naïve CD4 + T cells re-tunes STAT1 signaling to deliver unique cytokine responses in memory CD4 + T cells. Nat Immunol 2019;20:458–70. https://doi.org/10.1038/s41590-019-0350-0.
[87] Read KA, Powell MD, Baker CE, Sreekumar BK, Ringel-Scaia VM, Bachus H, et al. Integrated STAT3 and Ikaros zinc finger transcription factor activities regulate Bcl-6 expression in CD4+ Th cells. J Immunol 2017;199:2377–87. https://doi.org/10.4049/jimmunol.1700106.
[88] Monteleone G, Kumberova A, Croft NM, McKenzie C, Steer HW, MacDonald TT. Blocking Smad7 restores TGF-β1 signaling in chronic inflammatory bowel disease. J Clin Invest 2001;108:601–9. https://doi.org/10.1172/JCI12821.
[89] Kuehn HS, Boast B, Rosenzweig SD. Inborn errors of human IKAROS: LOF and GOF variants associated with primary immunodeficiency. Clin Exp Immunol 2023;212:129–36. https://doi.org/10.1093/cei/uxac109.
[90] Shahin T, Kuehn HS, Shoeb MR, Gawriyski L, Giuliani S, Repiscak P, et al. Germline biallelic mutation affecting the transcription factor Helios causes pleiotropic defects of immunity. Sci Immunol 2021;6:3981.
[91] Kim HJ, Barnitz RA, Kreslavsky T, Brown FD, Moffett H, Lemieux ME, et al. Stable inhibitory activity of regulatory T cells requires the transcription factor Helios. Science 1979;2015(350):334–9. https://doi.org/10.1126/science.aad0616.
[92] Thomas RM, Pahl MC, Wang L, Fa Grant S, Hancock WW, Wells AD. Foxp3 depends on Ikaros for control of regulatory T cell gene expression and function. Elife 2023;12:91392. https://doi.org/10.7554/eLife.
[93] Ichiyama K, Long J, Kobayashi Y, Horita Y, Kinoshita T, Nakamura Y, et al. Transcription factor Ikzf1 associates with Foxp3 to repress gene expression in Treg cells and limit autoimmunity and anti-tumor immunity. Immunity 2024;57: 2043–60. https://doi.org/10.1016/j.immuni.2024.07.010.
[94] Powell MD, Read KA, Sreekumar BK, Oestreich KJ. Ikaros zinc finger transcription factors: regulators of cytokine signaling pathways and CD4+ T helper cell differentiation. Front Immunol 2019;10:1299. https://doi.org/10.3389/fimmu.2019.01299.
[95] Hoshino A, Picard BH, Polychronopoulou S, Kelaidi C, Azarnoush S, Kracker S, et al. Loss-of-phosphorylation of IKZF1 results in gain-of-function associated with immune dysregulation. J Allergy Clin Immunol 2024;154:229–236.e2. https://doi.org/10.1016/j.jaci.2024.01.029.
[96] Bottardi S, Mavoungou L, Bourgoin V, Mashtalir N, Affar EB, Milot E. Direct protein interactions are responsible for Ikaros-GATA and Ikaros-Cdk9 cooperativeness in hematopoietic cells. Mol Cell Biol 2013;33:3064–76. https://doi.org/10.1128/mcb.00296-13.
[97] Quintana FJ, Jin H, Burns EJ, Nadeau M, Yeste A, Kumar D, et al. Aiolos promotes T H17 differentiation by directly silencing Il2 expression. Nat Immunol 2012;13: 770–7. https://doi.org/10.1038/ni.2363.
[98] Getnet D, Grosso JF, Goldberg MV, Harris TJ, Yen HR, Bruno TC, et al. A role for the transcription factor Helios in human CD4+CD25+ regulatory T cells. Mol Immunol 2010;47:1595–600. https://doi.org/10.1016/j.molimm.2010.02.001.
[99] Wang ES, Verano AL, Nowak RP, Yuan JC, Donovan KA, Eleuteri NA, et al. Acute pharmacological degradation of Helios destabilizes regulatory T cells. Nat Chem Biol 2021;17:711–7. https://doi.org/10.1038/s41589-021-00802-w.
[100] Gandhi R, Kumar D, Burns EJ, Nadeau M, Dake B, Laroni A, et al. Activation of the aryl hydrocarbon receptor induces human type 1 regulatory T cell-like and Foxp3 + regulatory T cells. Nat Immunol 2010;11:846–53. https://doi.org/10.1038/ni.1915.
[101] Rieder SA, Metidji A, Glass DD, Thornton AM, Ikeda T, Morgan BA, et al. Eos is redundant for regulatory T cell function but plays an important role in IL-2 and Th17 production by CD4+ conventional T cells. J Immunol 2015;195:553–63. https://doi.org/10.4049/jimmunol.1500627.
[102] Thornton AM, Korty PE, Tran DQ, Wohlfert EA, Murray PE, Belkaid Y, et al. Expression of Helios, an Ikaros transcription factor family member, differentiates Thymic-derived from peripherally induced Foxp3+ T regulatory cells. J Immunol 2010;184:3433–41. https://doi.org/10.4049/jimmunol.0904028.
[103] Goh W, Sudholz H, Foroutan M, Scheer S, Pfefferle A, Delconte RB, et al. IKAROS and AIOLOS directly regulate AP-1 transcriptional complexes and are essential for NK cell development. Nat Immunol 2024;25:240–55. https://doi.org/10.1038/s41590-023-01718-4.
[104] Shetty A, Tripathi SK, Junttila S, Buchacher T, Biradar R, Bhosale SD, et al. A systematic comparison of FOSL1, FOSL2 and BATF-mediated transcriptional regulation during early human Th17 differentiation. Nucleic Acids Res 2022;50: 4938–58. https://doi.org/10.1093/nar/gkac256.
[105] Perdomo J, Holmes M, Chong B, Crossley M. Eos and Pegasus, two members of the Ikaros family of proteins with distinct DNA binding activities. J Biol Chem 2000; 275:38347–54. https://doi.org/10.1074/jbc.M005457200.
[106] Leinoe E, Kjaersgaard M, Zetterberg E, Ostrowski S, Greinacher A, Rossing M. Highly impaired platelet ultrastructure in two families with novel IKZF5 variants. Platelets 2021;32:492–7. https://doi.org/10.1080/09537104.2020.1764921.
[107] Koipally J, Heller EJ, Seavitt JR, Georgopoulos K. Unconventional potentiation of gene expression by Ikaros. J Biol Chem 2002;277:13007–15. https://doi.org/10.1074/jbc.M111371200.
[108] Kuehn HS, Niemela JE, Stoddard J, Mannurita SC, Shahin T, Goel S, et al. Germline IKAROS dimerization haploinsufficiency causes hematologic cytopenias and malignancies. Blood 2021;137:349–63.
[109] Shahin T, Mayr D, Shoeb MR, Kuehn HS, Hoeger B, Giuliani S, et al. Identification of germline monoallelic mutations in IKZF2 in patients with immune dysregulation. Blood Adv 2022;6:2444–51. https://doi.org/10.1182/bloodadvances.2021006367.
[110] Cobb BS, Morales-Alcelay S, Kleiger G, Brown KE, Fisher AG, Smale ST. Targeting of Ikaros to pericentromeric heterochromatin by direct DNA binding. Genes Dev 2000;14:2146–60. https://doi.org/10.1101/gad.816400.
[111] Yamashita M, Kuehn HS, Okuyama K, Okada S, Inoue Y, Mitsuiki N, et al. A variant in human AIOLOS impairs adaptive immunity by interfering with IKAROS. Nat Immunol 2021;22:893–903. https://doi.org/10.1038/s41590-021-00951-z.
[112] Zhang F, Meng G, Strober W. Interactions among the transcription factors Runx1, RORγt and Foxp3 regulate the differentiation of interleukin 17-producing T cells. Nat Immunol 2008;9:1297–306. https://doi.org/10.1038/ni.1663.
[113] Fu D, Song X, Hu H, Sun M, Li Z, Tian Z. Downregulation of RUNX3 moderates the frequency of Th17 and Th22 cells in patients with psoriasis. Mol Med Rep 2016; 13:4606–12. https://doi.org/10.3892/mmr.2016.5108.
[114] Zhou N, Gutierrez-Uzquiza A, Zheng XY, Chang R, Vogl DT, Garfall AL, et al. RUNX proteins desensitize multiple myeloma to lenalidomide via protecting IKZFs from degradation. Leukemia 2019;33:2006–21. https://doi.org/10.1038/s41375-019-0403-2.
[115] Li D, Kong C, Tsun A, Chen C, Song H, Shi G, et al. MiR-125a-5p decreases the sensitivity of Treg cells toward IL-6-mediated conversion by inhibiting IL-6R and STAT3 expression. Sci Rep 2015;5:14615. https://doi.org/10.1038/srep14615.
[116] He C, Shi Y, Wu R, Sun M, Fang L, Wu W, et al. MIR-301a promotes intestinal mucosal inflammation through induction of IL-17A and TNF-α in IBD. Gut 2016; 65:1938–50. https://doi.org/10.1136/gutjnl-2015-309389.
[117] Liu Q, Gao Q, Zhang Y, Li Z, Mei X. MicroRNA-590 promotes pathogenic Th17 cell differentiation through targeting Tob1 and is associated with multiple sclerosis. Biochem Biophys Res Commun 2017;493:901–8. https://doi.org/10.1016/j.bbrc.2017.09.123.
[118] Wang L, Wang C, Jia X, Yu J. Circulating exosomal miR-17 inhibits the induction of regulatory T cells via suppressing TGFBR II expression in rheumatoid arthritis. Cell Physiol Biochem 2018;50:1754–63. https://doi.org/10.1159/000494793.
[119] Kogut S, Paculova H, Rodriguez P, Boyd J, Richman A, Palaria A, et al. Ikaros regulates microRNA networks in acute lymphoblastic leukemia. Epigenomes 2022;6:37. https://doi.org/10.3390/epigenomes6040037.
[120] Krzanowski J, Madzio J, Pastorczak A, Tracz A, Braun M, Tabarkiewicz J, et al. Selected miRNA levels are associated with IKZF1 microdeletions in pediatric acute lymphoblastic leukemia. Oncol Lett 2017;14:3853–61. https://doi.org/10.3892/ol.2017.6599.
[121] Yu WQ, Ji NF, Gu CJ, Sun ZX, Wang ZX, Chen ZQ, et al. Downregulation of miR-4772-3p promotes enhanced regulatory T cell capacity in malignant pleural effusion by elevating Helios levels. Chin Med J 2019;132:2705–15. https://doi.org/10.1097/CM9.0000000000000517.
[122] Charneca S, Ferro M, Vasques J, Carolino E, Martins-Martinho J, Duarte-Monteiro AM, et al. The Mediterranean diet, and not dietary inflammatory index, is associated with rheumatoid arthritis disease activity, the impact of disease and functional disability. Eur J Nutr 2023;62:2827–39. https://doi.org/10.1007/s00394-023-03196-8.
[123] Hashash JG, Elkins J, Lewis JD, Binion DG. AGA clinical practice update on diet and nutritional therapies in patients with inflammatory bowel disease: expert review. Gastroenterology 2024;166:521–32. https://doi.org/10.1053/j.gastro.2023.11.303.
[124] Pocovi-Gerardino G, Correa-Rodríguez M, Callejas-Rubio JL, Ríos-Fernández R, Martín-Amada M, Cruz-Caparros MG, et al. Beneficial effect of Mediterranean diet on disease activity and cardiovascular risk in systemic lupus erythematosus patients: a cross-sectional study. Rheumatology (United Kingdom) 2021;60: 160–9. https://doi.org/10.1093/rheumatology/keaa210.
[125] Rannugs A, Rannugq U, Rosenkranzll HS, Winqvistq L, Westerholmii R, Agurellg E, et al. Certain photooxidized derivatives of tryptophan bind with very high affinity to the ah receptor and are likely to be endogenous signal substances. J Biol Chem 1987;262:15422–7. https://doi.org/10.1016/s0021-9258(18)47743-5.
[126] Zhou L. AHR function in lymphocytes: emerging concepts. Trends Immunol 2016; 37:17–31. https://doi.org/10.1016/j.it.2015.11.007.
[127] Zelante T, Iannitti RG, Cunha C, DeLuca A, Giovannini G, Pieraccini G, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity 2013;39:372–85. https://doi.org/10.1016/j.immuni.2013.08.003.

[128] Veldhoen M, Hirota K, Westendorf AM, Buer J, Dumoutier L, Renauld JC, et al. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature 2008;453:106–9. https://doi.org/10.1038/nature06881.
[129] Kang SW, Kim SH, Lee N, Lee W-W, Hwang K-A, Shin MS, et al. 1,25-Dihyroxyvitamin D3 promotes FOXP3 expression via binding to vitamin D response elements in its conserved noncoding sequence region. J Immunol 2012;188:5276–82. https://doi.org/10.4049/jimmunol.1101211.
[130] Urry Z, Chambers ES, Xystrakis E, Dimeloe S, Richards DF, Gabryšová L, et al. The role of 1α,25-dihydroxyvitamin D3 and cytokines in the promotion of distinct Foxp3+and IL-10+ CD4+ T cells. Eur J Immunol 2012;42:2697–708. https://doi.org/10.1002/eji.201242370.
[131] Jeffery LE, Burke F, Mura M, Zheng Y, Qureshi OS, Hewison M, et al. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. J Immunol 2009;183:5458–67. https://doi.org/10.4049/jimmunol.0803217.
[132] Colin EM, Asmawidjaja PS, Van Hamburg JP, Mus AMC, Van Driel M, Hazes JMW, et al. 1,25-Dihydroxyvitamin D3 modulates Th17 polarization and interleukin-22 expression by memory T cells from patients with early rheumatoid arthritis. Arthritis Rheum 2010;62:132–42. https://doi.org/10.1002/art.25043.
[133] Ikeda U, Wakita D, Ohkuri T, Chamoto K, Kitamura H, Iwakura Y, et al. 1α,25-Dihydroxyvitamin D3 and all-trans retinoic acid synergistically inhibit the differentiation and expansion of Th17 cells. Immunol Lett 2010;134:7–16. https://doi.org/10.1016/j.imlet.2010.07.002.
[134] Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, Linker RA, et al. Sodium chloride drives autoimmune disease by the induction of pathogenic TH 17 cells. Nature 2013;496:518–22. https://doi.org/10.1038/nature11868.
[135] Wilck N, Matus MG, Kearney SM, Olesen SW, Forslund K, Bartolomaeus H, et al. Salt-responsive gut commensal modulates TH17 axis and disease. Nature 2017;551:585–9. https://doi.org/10.1038/nature24628.
[136] Goyal S, Rampal R, Kedia S, Mahajan S, Bopanna S, Yadav DP, et al. Urinary potassium is a potential biomarker of disease activity in ulcerative colitis and displays in vitro immunotolerant role. Sci Rep 2017;7:18068. https://doi.org/10.1038/s41598-017-18046-x.
[137] Lin L, Zhang K, Xiong Q, Zhang J, Cai B, Huang Z, et al. Gut microbiota in pre-clinical rheumatoid arthritis: from pathogenesis to preventing progression. J Autoimmun 2023;141:103001. https://doi.org/10.1016/j.jaut.2023.103001.
[138] Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, et al. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature 2013;500:232–6. https://doi.org/10.1038/nature12331.
[139] Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. Nat Rev Immunol 2016;16:341–52. https://doi.org/10.1038/nri.2016.42.
[140] Paik D, Yao L, Zhang Y, Bae S, D'Agostino GD, Zhang M, et al. Human gut bacteria produce TH17-modulating bile acid metabolites. Nature 2022;603:907–12. https://doi.org/10.1038/s41586-022-04480-z.
[141] Greiling TM, Dehner C, Chen X, Hughes K, Iñiguez AJ, Boccitto M, et al. Commensal orthologs of the human autoantigen Ro60 as triggers of autoimmunity in lupus. Sci Transl Med 2018;10:2306.
[142] Ruff WE, Dehner C, Kim WJ, Pagovich O, Aguiar CL, Yu AT, et al. Pathogenic autoreactive T and B cells cross-react with Mimotopes expressed by a common human gut commensal to trigger autoimmunity. Cell Host Microbe 2019;26:100–113.e8. https://doi.org/10.1016/j.chom.2019.05.003.
[143] Hoechst B, Gamrekelashvili J, Manns MP, Greten TF, Korangy F. Plasticity of human Th17 cells and iTregs is orchestrated by different subsets of myeloid cells. Blood 2011;117:6532–41. https://doi.org/10.1182/blood-2010-11-317321.
[144] Zhong H, Yazdanbakhsh K. Differential control of Helios+/−Treg development by monocyte subsets through disparate inflammatory cytokines. Blood 2013;121:2494–502. https://doi.org/10.1182/blood.
[145] Meng L, Bai Z, He S, Mochizuki K, Liu Y, Purushe J, et al. The Notch ligand DLL4 defines a capability of human dendritic cells in regulating Th1 and Th17 differentiation. J Immunol 2016;196:1070–80. https://doi.org/10.4049/jimmunol.1501310.
[146] Zhang X, Sheng Y, Jin X, Xu J, Gao J, Du X, et al. Sequencing-based approach identified three new susceptibility loci for psoriasis. Nat Commun 2014;5:4331. https://doi.org/10.1038/ncomms5331.
[147] Keshari PK, Harbo HF, Myhr KM, Aarseth JH, Bos SD, Berge T. Allelic imbalance of multiple sclerosis susceptibility genes IKZF3 and IQGAP1 in human peripheral blood. BMC Genet 2016;17:59. https://doi.org/10.1186/s12863-016-0367-4.
[148] Lessard CJ, Adrianto I, Ice JA, Wiley GB, Kelly JA, Glenn SB, et al. Identification of IRF8, TMEM39A, and IKZF3-ZPBP2 as susceptibility loci for systemic lupus erythematosus in a large-scale multiracial replication study. Am J Hum Genet 2012;90:648–60. https://doi.org/10.1016/j.ajhg.2012.02.023.
[149] Qu S, Du Y, Chang S, Guo L, Fang K, Li Y, et al. Common variants near IKZF1 are associated with primary Sjögren's syndrome in Han Chinese. PLoS One 2017;12:e0177320. https://doi.org/10.1371/journal.pone.0177320.
[150] Hu W, Sun L, Gao J, Li Y, Wang P, Cheng Y, et al. Down-regulated expression of IKZF1 mRNA in peripheral blood mononuclear cells from patients with systemic lupus erythematosus. Rheumatol Int 2011;31:819–22. https://doi.org/10.1007/s00296-010-1576-1.
[151] Van Nieuwenhove E, Garcia-Perez JE, Helsen C, Rodriguez PD, van Schouwenburg PA, Dooley J, et al. A kindred with mutant IKAROS and autoimmunity. J Allergy Clin Immunol 2018;142:699–702. https://doi.org/10.1016/j.jaci.2018.04.008.
[152] Zhang B, Sun T. Transcription factors that regulate the pathogenesis of ulcerative colitis. Biomed Res Int 2020;2020:7402657. https://doi.org/10.1155/2020/7402657.
[153] Cai X, Liu X, Du S, Xu X, Liu A, Ge X, et al. Overexpression of Aiolos in peripheral blood mononuclear cell subsets from patients with systemic lupus erythematosus and rheumatoid arthritis. Biochem Genet 2016;54:73–82. https://doi.org/10.1007/s10528-015-9702-0.
[154] Rivellese F, Congia M, Mauro D, Bombardieri M, Lewis M, Pitzalis C. THU0070 the transcription factors ikaros and aiolos are expressed in the synovial membrane of early rheumatoid arthritis patients in association with synovial lymphoid aggregates. Ann Rheum Dis 2018;77:259. https://doi.org/10.1136/annrheumdis-2018-eular.6442.
[155] Dittrich-Salamon M, Meyer A, Yan S, Steinbach-Knödgen E, Kotschenreuther K, Stahl D, et al. Regulatory T cells from patients with rheumatoid arthritis are characterized by reduced expression of Ikaros zinc finger transcription factors. Cells 2022;11:2171. https://doi.org/10.3390/cells11142171.
[156] Zafari P, Yari K, Mostafaei S, Iranshahi N, Assar S, Fekri A, et al. Analysis of Helios gene expression and Foxp3 TSDR methylation in the newly diagnosed rheumatoid arthritis patients. Immunol Investig 2018;47:632–42. https://doi.org/10.1080/08820139.2018.1480029.
[157] Golding A, Hasni S, Illei G, Shevach EM. The percentage of FoxP3+Helios+ treg cells correlates positively with disease activity in systemic lupus erythematosus. Arthritis Rheum 2013;65:2898–906. https://doi.org/10.1002/art.38119.
[158] Liu C, Guan Z, Zhao L, Song Y, Wang H. Elevated level of circulating CD4+Helios+FoxP3+ cells in primary Sjogren's syndrome patients. Mod Rheumatol 2017;27:630–7. https://doi.org/10.1080/14397595.2016.1226470.
[159] Seng A, Krausz KL, Pei D, Koestler DC, Fischer RT, Yankee TM, et al. Coexpression of FOXP3 and a Helios isoform enhances the effectiveness of human engineered regulatory T cells. Blood Adv 2020;4:1325–39. https://doi.org/10.1182/bloodadvances.2019000965.
[160] Castro-Dopico T, Fleming A, Dennison TW, Ferdinand JR, Harcourt K, Stewart BJ, et al. GM-CSF calibrates macrophage defense and wound healing programs during intestinal infection and inflammation. Cell Rep 2020;32:107857. https://doi.org/10.1016/j.celrep.2020.107857.
[161] Avci AB, Feist E, Burmester GR. Targeting GM-CSF in rheumatoid arthritis. Clin Exp Rheumatol 2016;34:39–44.
[162] Rasouli J, Ciric B, Imitola J, Gonnella P, Hwang D, Mahajan K, et al. Expression of GM-CSF in T cells is increased in multiple sclerosis and suppressed by IFN-β therapy. J Immunol 2015;194:5085–93. https://doi.org/10.4049/jimmunol.1403243.
[163] Zhang F, Mears JR, Shakib L, Beynor JI, Shanaj S, Korsunsky I, et al. IFN-γ and TNF-α drive a CXCL10+ CCL2+ macrophage phenotype expanded in severe COVID-19 lungs and inflammatory diseases with tissue inflammation. Genome Med 2021;13:64. https://doi.org/10.1186/s13073-021-00881-3.
[164] Di Giuseppe D, Discacciati A, Orsini N, Wolk A. Cigarette smoking and risk of rheumatoid arthritis: a dose-response meta-analysis. Arthritis Res Ther 2014;16:R61. https://doi.org/10.1186/ar4498.
[165] Adami G, Viapiana O, Rossini M, Orsolini G, Bertoldo E, Giollo A, et al. Association between environmental air pollution and rheumatoid arthritis flares. Rheumatology (United Kingdom) 2021;60:4591–7. https://doi.org/10.1093/rheumatology/keab049.
[166] Chang K, Yang SM, Kim SH, Han KH, Park SJ, Il Shin J. Smoking and rheumatoid arthritis. Int J Mol Sci 2014;15:22279–95. https://doi.org/10.3390/ijms151222279.
[167] Navarro-Compán V, Melguizo-Madrid E, Hernández-Cruz B, Santos-Rey K, Leyva-Prado C, González-Martín C, et al. Interaction between oxidative stress and smoking is associated with an increased risk of rheumatoid arthritis: a case-control study. Rheumatology (United Kingdom) 2013;52:487–93. https://doi.org/10.1093/rheumatology/kes286.
[168] Martínez Leo EE, Peñafiel AM, Hernández Escalante VM, Cabrera Araujo ZM. Ultra-processed diet, systemic oxidative stress, and breach of immunologic tolerance. Nutrition 2021:91–2. https://doi.org/10.1016/j.nut.2021.111419.
[169] Luo J, Mills K, le Cessie S, Noordam R, van Heemst D. Ageing, age-related diseases and oxidative stress: what to do next? Ageing Res Rev 2020;57:100982. https://doi.org/10.1016/j.arr.2019.100982.
[170] Evans HG, Roostalu U, Walter GJ, Gullick NJ, Frederiksen KS, Roberts CA, et al. TNF-α blockade induces IL-10 expression in human CD4+ T cells. Nat Commun 2014;5:3199. https://doi.org/10.1038/ncomms4199.
[171] Ridley ML, Fleskens V, Roberts CA, Lalnunhlimi S, Alnesf A, O'Byrne AM, et al. IKZF3/Aiolos is associated with but not sufficient for the expression of IL-10 by CD4+ T cells. J Immunol 2020;204:2940–8. https://doi.org/10.4049/jimmunol.1901283.
[172] Gao S, Wang S, Song Y. Novel immunomodulatory drugs and neo-substrates. Biomark Res 2020;8:1–8. https://doi.org/10.1186/s40364-020-0182-y.
[173] Montoya S, Bourcier J, Noviski M, Lu H, Thompson MC, Chirino A, et al. Kinase-impaired BTK mutations are susceptible to clinical-stage BTK and IKZF1/3 degrader NX-2127. Science 2024;383:eadi5798. https://doi.org/10.1126/science.adi5798.
[174] Bonazzi S, d'Hennezel E, Beckwith REJ, Xu L, Fazal A, Magracheva A, et al. Discovery and characterization of a selective IKZF2 glue degrader for cancer immunotherapy. Cell Chem Biol 2023;30:235–247.e12. https://doi.org/10.1016/j.chembiol.2023.02.005.
[175] Beckwith REJ, Bonazzi S, Cernijenko A, Fazal A, Tichkule RB, Visser MS. 3-(1-oxoisoindolin-2-yl)piperidine-2,6-dione derivatives and uses thereof. 2024.
[176] Cippitelli M, Stabile H, Kosta A, Petillo S, Gismondi A, Santoni A, et al. Role of aiolos and ikaros in the antitumor and immunomodulatory activity of imids in

multiple myeloma: better to lose than to find them. Int J Mol Sci 2021;22:1–13. https://doi.org/10.3390/ijms22031103.
[177] Lu G, Middleton RE, Sun H, Naniong MV, Ott CJ, Mitsiades CS, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of ikaros proteins. Science 1979;2014(343):305–9. https://doi.org/10.1126/science.1244917.
[178] Moreira AL, Sampaio EP, Zmuidzinas A, Frindt P, Smith KA, Kaplan G. Thalidomide exerts its inhibitory action on tumor necrosis factor α by enhancing mRNA degradation. J Exp Med 1993;177:1675–80.
[179] Muller GW, Chen R, Huang S-Y, Corral LG, Min Wong L, Patterson RT, et al. Amino-substituted thalidomide analogs: potent inhibitors of TNF-alpha production. Bioorg Med Chem Lett 1999;9:1625–30.
[180] D'amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci USA 1994;91:4082–5.
[181] Haslett PAJ, Corral LG, Albert M, Kaplan G. Thalidomide Costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8 subset. J Exp Med 1998;187:1885–92.
[182] Görgün G, Calabrese E, Soydan E, Hideshima T, Perrone G, Bandi M, et al. Immunomodulatory effects of lenalidomide and pomalidomide on interaction of tumor and bone marrow accessory cells in multiple myeloma. Blood 2010;116:3227–37. https://doi.org/10.1182/blood-2010-04-279893.
[183] Yamamoto K, Kitawaki T, Sugimoto N, Fujita H, Kawase Y, Takaori-Kondo A, et al. Anti-inflammatory modulation of human myeloid-derived dendritic cell subsets by lenalidomide. Immunol Lett 2019;211:41–8. https://doi.org/10.1016/j.imlet.2019.05.012.
[184] Gordon JN, Prothero JD, Thornton CA, Pickard KM, Di Sabatino A, Goggin PM, et al. CC-10004 but not thalidomide or lenalidomide inhibits lamina propria mononuclear cell TNF-α and MMP-3 production in patients with inflammatory bowel disease. J Crohns Colitis 2009;3:175–82. https://doi.org/10.1016/j.crohns.2009.03.001.
[185] Mansfield JC, Parkes M, Hawthorne AB, Forbes A, Probert CSJ, Perowne RC, et al. A randomized, double-blind, placebo-controlled trial of lenalidomide in the treatment of moderately severe active Crohn's disease. Aliment Pharmacol Ther 2007;26:421–30. https://doi.org/10.1111/j.1365-2036.2007.03385.x.