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

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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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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

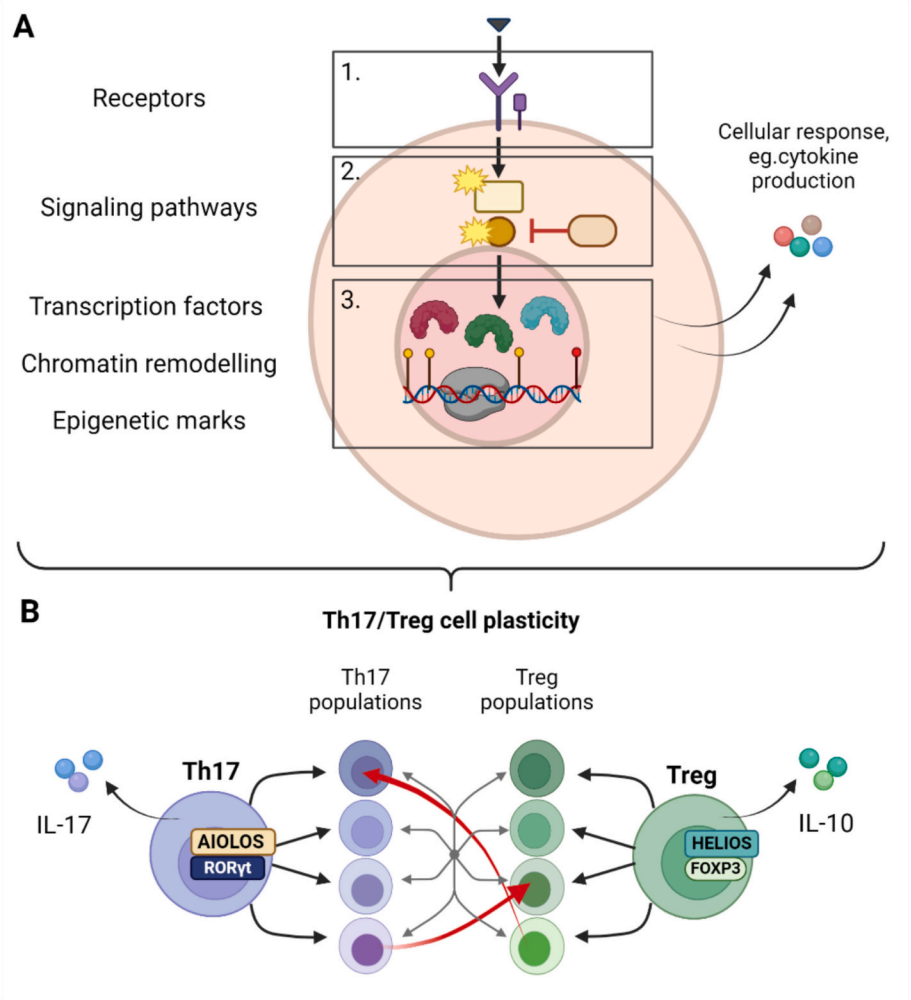

Fig. 1. T cell plasticity in Th17 and Treg compartments. A T cell plasticity is regulated through mechanisms at different levels: the presence of appropriate cellular receptors (1.) and activation of signaling pathways (2.) renders the cell responsive to extracellular cues, inducing gene expression changes (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]

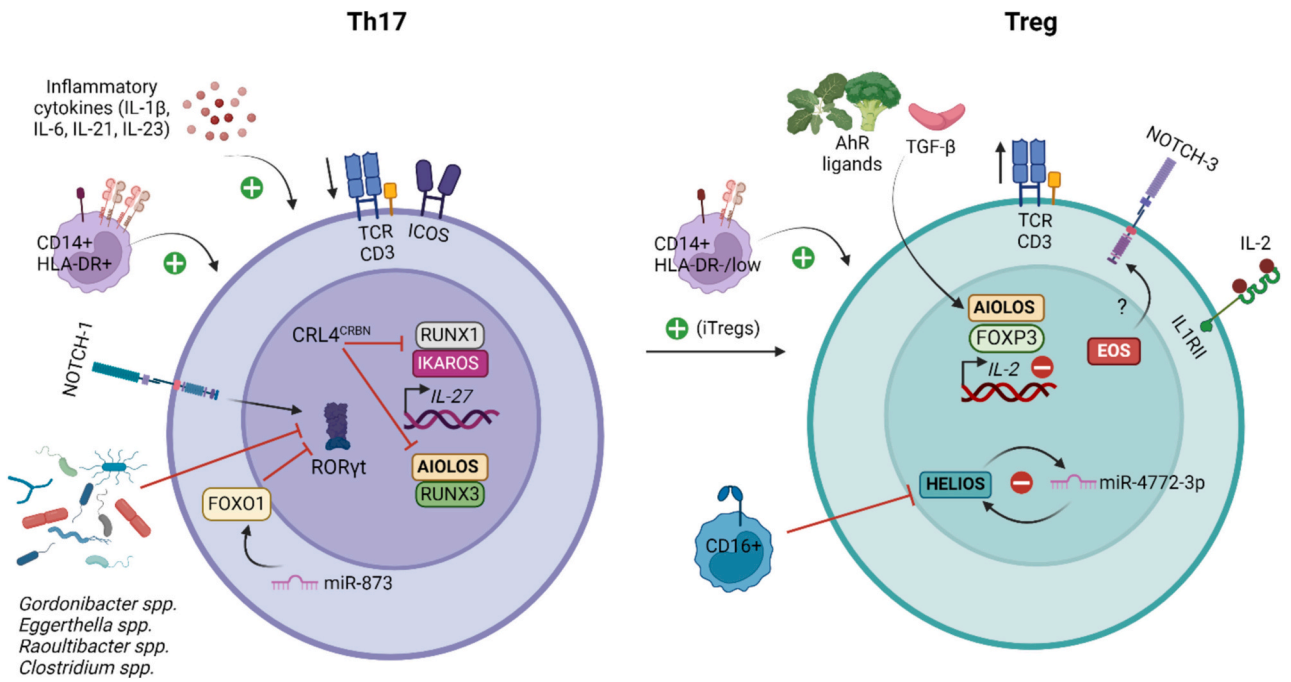

Fig. 2. Factors influencing the Ikaros-mediated Th17/Treg developmental balance. The main extrinsic (cytokines, gut microbiota, myeloid cell subsets, dietary components) and intrinsic (miRNAs, transcription factors) cues that impact Ikaros transcriptional regulation of T cell fates are depicted. See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

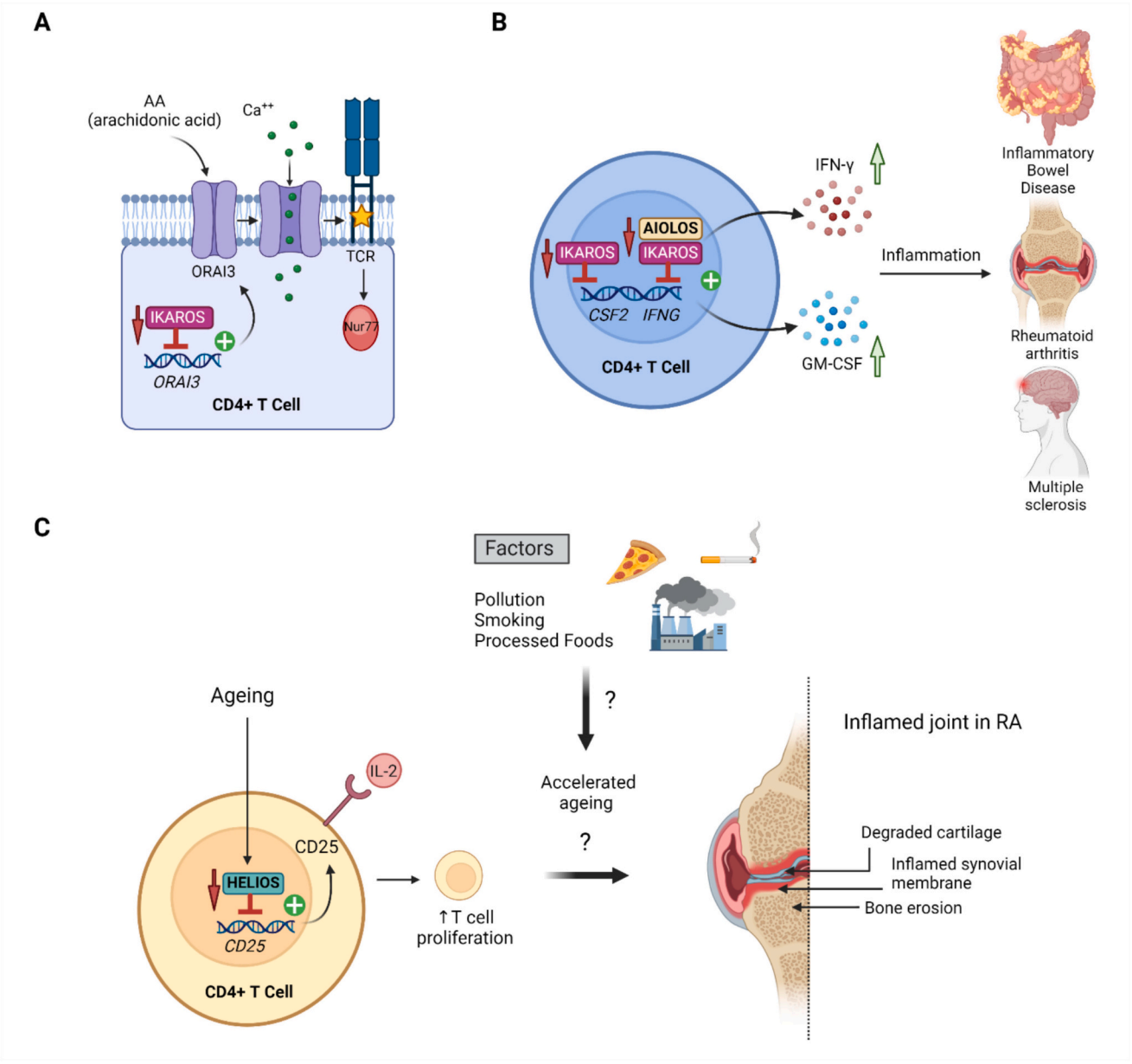

Fig. 3. Transcriptional control of Ikaros over key genes in the pathogenesis of autoimmune diseases. A Downregulated IKAROS abrogates the transcriptional repression over *ORAI3*, an arachidonic acid-regulated calcium selective channel, making T cells more sensitive to stimulation and highly responsive 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.

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Data availability

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

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