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Steroid receptor coactivators in Treg and Th17 cell biology and function

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Steroid receptor coactivators (SRCs) are master regulators of transcription that play key roles in human physiology and pathology. SRCs are particularly important for the regulation of the immune system with major roles in lymphocyte fate determination and function, macrophage activity, regulation of nuclear factor κ B (NF- κ B) transcriptional activity and other immune system biology. The three members of the p160 SRC family comprise a network of immune-regulatory proteins that can function independently or act in synergy with each other, and compensate for - or moderate - the activity of other SRCs. Recent evidence indicates that the SRCs are key participants in governing numerous aspects of CD4⁺ T cell biology. Here we review findings that establish the SRCs as essential regulators of regulatory T cells (Tregs) and T helper 17 (Th17) cells, with a focus on their crucial roles in Treg immunity in cancer and Treg-Th17 cell phenotypic plasticity.

KEYWORDS

steroid receptor coactivators (SRCs), nuclear coactivators (NCoAs), Th17 cells, Treg cells, cell therapy

1 Introduction

CD4⁺ T cells are a major subset of T lymphocytes that are further divided into distinct subpopulations which play various pivotal roles in immunity. CD4⁺ T cells coordinate both innate and adaptive immune responses through their interaction with and modulation of other immune cells or by their direct action via cytokine signaling (1). However, CD4⁺ T cells function not only as helpers for other immune cells and communicators of immune response; different subtypes of CD4⁺ T cells have direct cytotoxic activity while others act as suppressors of inflammation (1, 2). The wide range of functionality seen in the diverse subclassifications of CD4⁺ T cells is controlled by dynamic transcriptional regulation at different stages during their development, as well as through adaptation of specific transcriptional programs as these cells react to cues in their microenvironment (3).

Nuclear receptor coregulators (coactivators and corepressors) are a large family of proteins that regulate transcription not by a direct interaction with the DNA, but rather by binding to nuclear receptors (NRs) and other transcription factors to promote the assembly of chromatin remodeling factors and transcriptional machinery (4, 5). Since the discovery and identification of the first nuclear coregulator, SRC-1, in 1995 (6) ~ 300 coregulators have been identified and characterized as critically important regulators of gene expression (7). SRCs represent a group of three homologous nuclear coregulators that share a high degree of structural similarity, and all have a molecular weight of approximately 160 kDa. All three SRCs play important roles in major physiological and pathological processes such as fertility, metabolism, wound healing, development, immunology and oncogenesis (8–10). The importance of the SRCs in immunology is understudied but is evidenced by studies that show their participation in fate determination and function of lymphocytes and macrophages, regulation of lymphoproliferation and the ability to interact with and coordinate the transcriptional activity of DNA-binding transcription factors (TFs) such as NF- κ B (11).

Tregs and Th17 cells represent two functionally antagonistic subpopulations of CD4⁺ T cells. Tregs play crucial roles in both moderation of local inflammatory processes and prevention of systemic autoimmunity (12, 13). In solid tumor malignancies the immunosuppressive activity of Tregs can contribute to immune evasion of tumor cells. Indeed, infiltration of Tregs into the tumor is highly correlated with poor prognosis and reduced survival rates (14, 15). On the other hand, even though that the immunological activity of IL-17A and the IL-17A-producing Th17 cells has been associated with immune regulation (16–18), the main immunological activity of Th17 cells is pro-inflammatory and their major physiological role is associated with clearance of extracellular pathogens (19–21). Th17 cells are also associated with various autoimmune diseases, such as psoriasis, rheumatoid arthritis (RA), Crohn's disease and multiple sclerosis (MS) (22). The pro-inflammatory phenotype of Th17 cells positions them as antagonistic counterparts to tolerogenic Tregs. Intriguingly, the differentiation of CD4⁺ cells into a Th17 subpopulation is very dynamic and includes a shared developmental axis with Tregs (23–25). In this review we highlight the literature that establishes the SRCs as essential regulators of Treg and Th17 cell differentiation, biology, and function. In the context of recent developments in gene editing and small molecule inhibitors (such as SI drugs) and stimulators for SRCs (such as MCB-613), we discuss the potential therapeutic benefit that can arise from targeting the SRCs in Tregs and Th17 cells.

1.1 SRC-3 is enriched in Tregs and important for their immune-suppressive function

SRC-3 plays an important role in the regulation of lymphoid cell proliferation, development and function (26–28). It has been demonstrated that SRC-3 deficiency in mice is associated with

inflammation (29–31), and that stimulation of SRC-3 with a small molecule stimulator, promotes anti-inflammatory processes such as the establishment of a pro-reparative environment after myocardial infarction (32). These observations suggest a specific role for SRC-3 as a moderator of inflammation. Indeed, interrogation of publicly available databases has revealed that in mice Tregs, SRC-3 expression is significantly higher relative to other lymphocyte subsets, and gene set enrichment analysis (GSEA) has shown that SRC-3 is the second most coexpressed coregulator in cells that express the hallmark transcription factor of Tregs - forkhead box P3 (FOXP3) (33). Similar indications also have been found in human samples showing enriched SRC-3 protein levels in lymphocytes compared to monocytes as well as coexpression of SRC-3 with FOXP3. Moreover, SRC-3 transcript levels were substantially higher in Tregs compared to the bulk population of CD4⁺ T cells, which further bolsters previously mentioned bioinformatic findings. The enriched expression of SRC-3 in Tregs implies its biological significance in this cell type. Indeed, SRC-3 knock down (KD) by RNA interference as well as its pharmacological inhibition in Tregs of human origin brought about a decrease of Treg marker genes, including *FOXP3* and *IL2RA*, at both transcript and protein levels (Figure 1A) (33). Further investigation into SRC-3 perturbation has revealed that treatment with an SRC-3 small molecule inhibitor – SI-2 (34) - affects the ability of resting CD4⁺ T cells to adopt a regulatory-like phenotype; generation of induced Tregs (iTregs) in an SRC-3 inhibitor-free environment, resulted in a population of cells with inhibitory activity, as manifested by their ability to suppress the proliferation of conventional CD4⁺ T cells. Conversely, generation of iTregs under pharmacological inhibition of SRC-3 resulted in impaired suppressive activity of these generated iTregs (Figure 1A). Furthermore, short-term pharmacological inhibition of SRC-3 in freshly isolated natural Tregs (nTregs) also resulted in a reduction in their suppressive activity (33). Importantly, SI-2 didn't possess any detectable toxic effects toward CD4⁺ T cells (33), which suggests that the change in their phenotype is attributed to SRC inhibition rather than general cell viability-related effects.

1.2 SRC-3 maintains pro-tumorigenic immunosuppression of Tregs

The immunosuppressive activity of Tregs is critical for the maintenance of immune homeostasis, and loss of their canonical suppressive functionality can lead to severe autoimmune disorders (35, 36). In cancer, Tregs can suppress the immune system, which contributes to immune evasion and promotion of tumor development and progression (37). SRC-3 is a pan-cancer oncogene that functions in a cell-autonomous manner within cancer cells, that is strongly associated with multiple malignancies (38–45) and has been particularly well studied in estrogen receptor positive breast cancer (BC) (38, 46–52). Therefore, it is not surprising that small molecules that perturb the activity of SRC-3 were able to significantly suppress the growth of BC cells in numerous *in vitro* and *in vivo* models (29, 53–55). However,

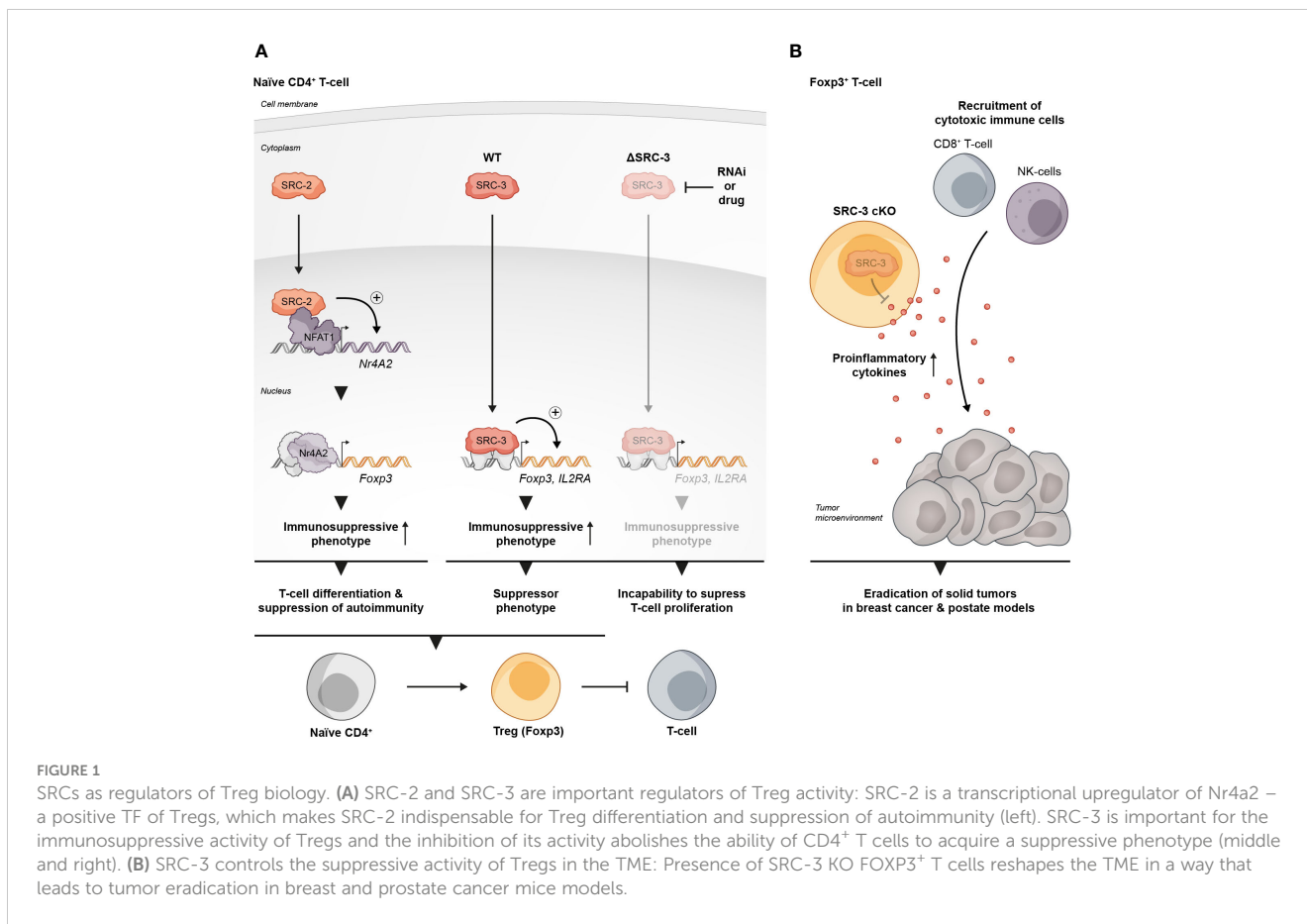


FIGURE 1

SRCs as regulators of Treg biology. (A) SRC-2 and SRC-3 are important regulators of Treg activity: SRC-2 is a transcriptional upregulator of Nr4a2 – a positive TF of Tregs, which makes SRC-2 indispensable for Treg differentiation and suppression of autoimmunity (left). SRC-3 is important for the immunosuppressive activity of Tregs and the inhibition of its activity abolishes the ability of CD4⁺ T cells to acquire a suppressive phenotype (middle and right). (B) SRC-3 controls the suppressive activity of Tregs in the TME: Presence of SRC-3 KO FOXP3⁺ T cells reshapes the TME in a way that leads to tumor eradication in breast and prostate cancer mice models.

intriguingly, it has been demonstrated that the small molecule inhibitor SI-2, can effectively suppresses BC tumor growth in an immune intact mouse at a much lower dose, by a process that is not limited to a direct inhibition of SRC-3 in cancer cells, but instead involves systemic modulation of the immune system and shaping of the composition of infiltrating immune cells in the tumor microenvironment (TME) (56). Specifically, the authors demonstrated that treatment of tumor bearing mice with SI-2 is associated with changes in the levels of circulating cytokines in a dose dependent manner; while high-dose treatment with SI-2 was associated with sharp increase of circulating cytokines that leads to systemic toxicity, low-dose treatment led to a moderate increase of cytokines and was associated with an increased infiltration of cytotoxic immune cells and reduced infiltration of Tregs into the TME. Moreover, the authors drew a direct relationship between low-dose SI-2 treatment and elevated levels of cytokines capable of exerting anti-cancer effects, such as IFN γ and CXCL9 – a chemokine that recruits cytotoxic immune cells into the TME. Importantly, low dose treatment with SI-2 of tumor bearing immunodeficient mice failed to suppress tumor growth, which underscores the importance of an intact host immune system toward the totality of the anti-tumor activity that is associated with SRC-3 inhibition. Of note, similar trends were observed in two BC models, when SRC-3 was directly inhibited in tumor cells

(shRNA) prior to inoculation; tumor growth was successfully suppressed by SI-2 treatment in a wild type (WT), but not immunodeficient mice. This observation implies that in addition to its role as an inhibitor of the SRC-3 oncogene in cancer cells, SI-2-mediated inhibition of SRC-3 in immune cells plays an essential role in tumor growth inhibition. Overall, this study highlights the centrality of immunomodulatory elements that are associated with SI-2-mediated anti-cancer activity.

A more direct piece of evidence that SRC-3 perturbation in a specific type of immune cells contributes to tumor eradication was revealed in another study where it has been shown that a conditional KO (cKO) of SRC-3 in Tregs results in complete tumor clearance in an *in vivo* BC model (57). Using a syngeneic BC mouse cancer cell line in conjunction with the SRC-3 Treg cKO mice, the authors demonstrated that tumor eradication can be achieved when SRC-3 KO takes place in Tregs following tamoxifen induction of Cre-recombinase. SRC-3 KO in Tregs results in increased infiltration of cytotoxic immune cells into the tumor and elevated levels of IFN γ and CXCL9 in the TME. These observations strikingly recapitulate the effects of pharmacological inhibition of SRC-3 (56) and provide mechanistic insight into the anti-tumor phenotype of the SRC-3 KO Tregs. In the light of these data, the authors suggest a model where tumor-specific accumulation of the edited Tregs that secrete IFN γ , results in elevated levels of IFN γ in the TME. In the tumor,

IFN γ stimulates the production of CXCL9 by tumor and stromal cells, resulting in increased infiltration of CXCR3⁺ (CXCL9 receptor) cytotoxic immune cells (such as CD8⁺ T cells and Natural Killer cells) into the tumor that promotes its eradication (Figure 1B). Importantly, blockade of IFN γ through anti-IFN γ antibody (Ab) treatment, abolished the anti-tumor therapeutic effect of SRC-3 KO Tregs, which further solidifies the centrality of the IFN γ /CXCL9 axis to SRC-3 KO Treg-mediated tumor clearance. Of note, re-inoculation of cancer cells into the breast cancer-cured mice did not result in a newly developed tumor, demonstrating a long-term immunization-like effect of the SRC-3 KO Tregs. The authors also showed that SRC-3 KO Tregs can be harvested from tamoxifen-treated genetically engineered SRC-3^{fl/fl}:FOXP3^{Cre-ERT2/+} mice and then injected into tumor bearing mice, resulting in tumor eradication, thus demonstrating the translational therapeutic potential of this technology. Notably, the Treg cell-specific SRC-3 KO that leads to permanent eradication of solid tumors was not associated with any observed pathological phenotype, including autoimmunity or reproductive defects (56, 57). Complete tumor eradication that takes place in the absence of any autoimmune side effect is a striking outcome of this therapy. It can be partially explained by the concentration of SRC3 KO-Tregs in the TME, where they secrete IFN γ and activate the IFN γ /CXCL9 axis. Local activation of the IFN γ /CXCL9 axis, with no detectable increase in IFN γ within the lymphatic system, results in an immunologically hot (inflamed) tumor, but with minimal impact outside of the TME (58). Also, the fact that the three SRC-family members can compensate for one another, sets the foundation for reasonable speculation that SRC-1/2 compensate for SRC-3 activity in SRC3 KO-Tregs outside of the TME to support their immune-regulatory function and maintain homeostasis. However, there is yet more light to be shed on the exact mechanism by which SRC-3 KO shapes the phenotype of the SRC-3 KO-Tregs, that drives their trafficking into the tumor, and the possible role that the compensatory mechanisms between each SRC plays in the maintenance of Treg-mediated immune homeostasis.

1.3 SRC-2 is critical for CD4⁺ T cells activation and differentiation into FOXP3⁺ expressing Tregs

The role of SRC-2 as a coregulator of metabolic processes is very well established (59–62). In CD4⁺ T cells SRC-2 controls the upregulation of Slc7a5 (63) - an amino acid transporter that is crucial for amino acid supply from the extracellular environment into stimulated CD4⁺ T cells to fulfill the requirement of these cells for cytokine production and proliferation. CD4⁺ T cell-specific deficiency of SRC-2 results in resistance to autoimmune disorders and an impaired immune response, as has been demonstrated using experimental autoimmune encephalomyelitis (EAE) and colitis mice models (63). Importantly, forced expression of Slc7a5 in SRC-2 deficient CD4⁺ T cells restored the ability to induce EAE and rescued the proliferation defect of these cells, indicating that SRC-2

impacts CD4⁺ T cells in a specific manner through the regulation of Slc7a5 expression. Interestingly, in Tregs, SRC-2 is not required for either proliferation or survival and deficiency of SRC-2 does not affect thymic development of natural Tregs (nTregs), as demonstrated by equal FOXP3 expression in CD4⁺ thymocytes regardless of whether the origin of these cells is FOXP3^{YFP-Cre} or SRC2^{fl/fl}:FOXP3^{YFP-Cre} mice (64). However, SRC-2 is essential for the ability of naïve CD4⁺ T cells to adopt a Treg phenotype *in vitro* in the presence of transforming growth factor beta (TGF β) (64). Moreover, when FOXP3⁻ CD4⁺ T cells were adoptively transferred into Rag^{-/-} recipient mice which lack the ability to produce mature T cells, they were able to establish stable FOXP3 expression, but when SRC-2 was cKO in a FOXP3-dependent manner, these cells fail to express FOXP3 (64). This indicates that SRC-2 is indispensable for the ability of CD4⁺ T cells to differentiate into Tregs *in vivo* with the implication that at a systemic level, mice with SRC-2 deficient Tregs have significantly higher concentrations of pro-inflammatory cytokines compared to their WT counterparts. Accordingly, these mice are at a much higher risk for autoimmune disorders as has been demonstrated by their inability to be protected from EAE. Supportive of these observations, aged SRC2^{fl/fl}:FOXP3^{YFP-Cre} mice spontaneously developed autoimmune-like phenotypes, manifested by splenomegaly, reduced FOXP3 expression and limited immunosuppressive activity in older animals (64). Eventually these phenotypic hallmarks of unrestrained immunity bring about increased numbers of pro-inflammatory T cells in the lungs, with subsequent tissue damage. Mechanistically, SRC-2 cKO in Tregs leads to the downregulation of four TFs - Myb, Irf4, Foxo1, and Nr4a2 - which all positively contribute to Treg differentiation. Additionally, ChIP-qPCR and immunoprecipitation assays revealed that SRC-2 is recruited by the TF NFAT1 to the Nr4a2 promoter (Figure 1A). Moreover, deletion of NFAT1/SRC-2 DNA binding sites significantly reduced Nr4a2 mRNA and protein expression. Furthermore, forced expression of Nr4a2 in SRC-2 deficient Tregs resulted in restored FOXP3 expression and the ability of SRC2^{fl/fl}:FOXP3^{YFP-Cre} cells to differentiate into Tregs. Collectively, these observations underscore the crucial role of SRC-2 in the transcriptional upregulation of Nr4a2, which solidifies its significance for proper differentiation and function of Tregs.

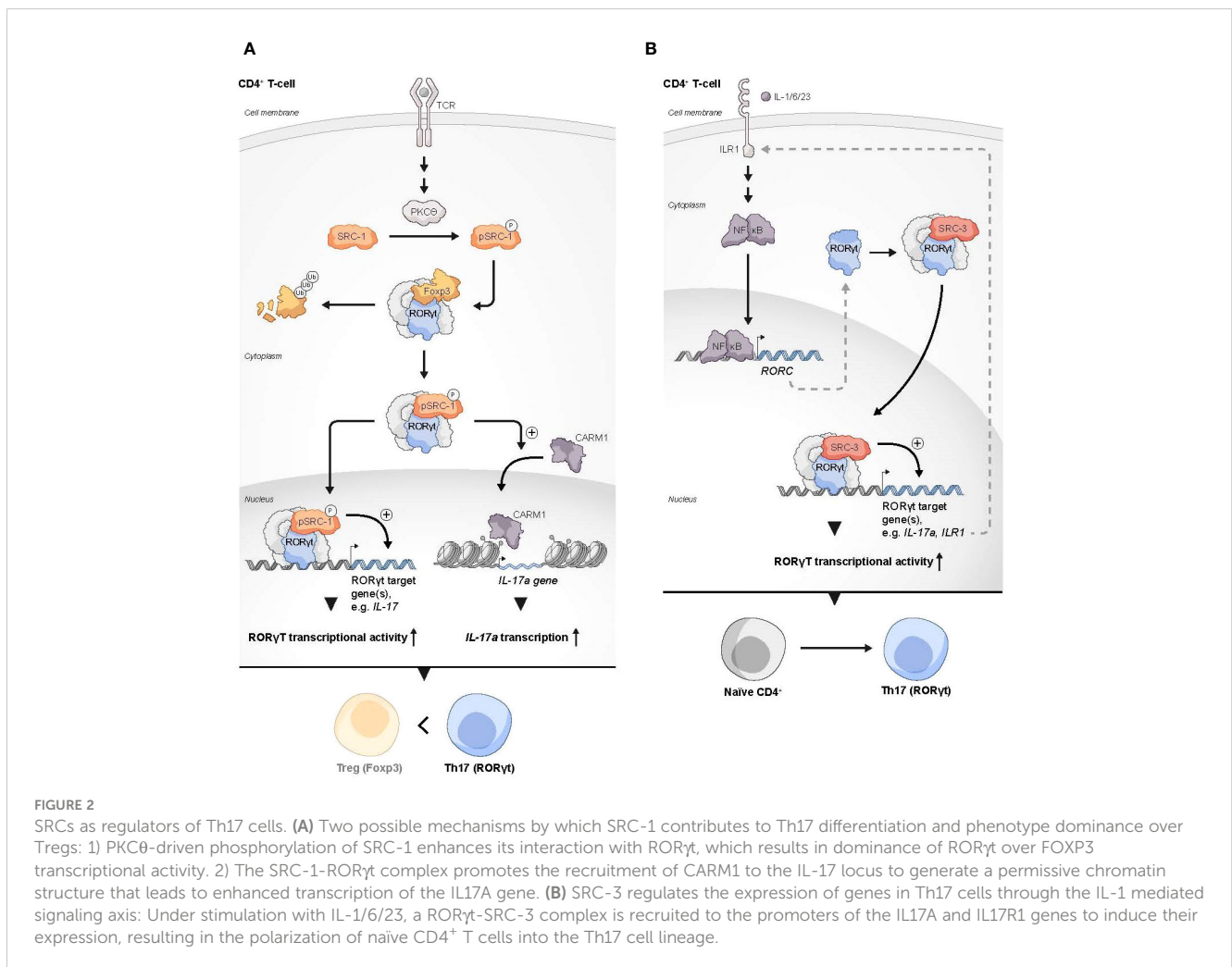
1.4 SRC-1 and SRC-3 are critical regulators of Th17 cell differentiation

Th17 cells represent a pro-inflammatory subtype of CD4⁺ T cells, that are critically important for the clearance of extracellular pathogens but also are often associated with autoimmune disorders (21). Retinoic acid-related orphan receptor (ROR) γ t is a hallmark TF expressed in Th17 cells, since it regulates the production of the signature cytokine produced by these cells - IL17A (65, 66). Though Th17 cells and Tregs both originate from naïve CD4⁺ T cells, once they commit to their specific phenotype, they become reciprocally inhibitory toward each other's function

and differentiation. Treg vs Th17 cell fate decision of CD4⁺ T cells at their early developmental stages might partially rely on TGFβ signaling, and fine regulation is required at these stages for the stable lineage commitment of both cell types (67–69). TGFβ-driven determination of Treg vs Th17 cell fate ultimately depends on the cytokine environment in which the TGFβ signaling takes place, since the cytokine milieu regulates the equilibrium of the competitive interplay between FOXP3 and ROR-family TFs in developing CD4⁺ T cells (70). Furthermore, in certain biological contexts, Tregs have the potential to undergo redifferentiation and transform into effector Th17-like cells. This transformation is marked by reduced expression of FOXP3 and the ability to produce IL17A (2, 25).

RORγt uses its activation function (AF)2 domain to recruit SRC-1 and SRC-2 through the interaction with their LXXLL motifs (71). In thymocytes, RORγt recruitment of SRCs is necessary for a robust RORγt-mediated transcriptional activity and thymocyte survival, while during later stages of T cell development, the interaction of SRC-1 with RORγt is critically important for the establishment of the Th17 phenotype (71). The mechanism that

underlies RORγt-SRC-1 transcriptional cooperation involves protein kinase C (PKC)-θ mediated phosphorylation of SRC-1 conserved serines 1271 and 1272 (72). Phosphorylated SRC-1 has an enhanced engagement with RORγt. As a result of the strong engagement of RORγt with the phosphorylated SRC-1, FOXP3 that binds directly to RORγt and antagonizes its transcriptional activity (70, 73) is displaced from its complex with RORγt and subjected to proteosomal degradation, while an SRC-1-bound RORγt acquires a higher DNA-binding capability and transcriptional activity (72). Moreover, the SRC-1-RORγt complex promotes the recruitment of the CARM1 methyltransferase to the *il17* locus to modify its chromatin methylation pattern and generate a permissive chromatin structure that leads to amplified IL-17a transcription (72). This unveils the two roles that SRC-1 has in promoting the differentiation of Th17 cells, either by direct up-regulation of RORγt activity and/or recruitment of CARM1 to key loci of genes that drive the Th17 cell phenotype. Collectively, SRC-1 activity skews the balance between FOXP3 and RORγt programs towards the latter, which leads to a phenotypic dominance of Th17 cells and a simultaneous decrease in the Treg phenotype (Figure 2A).



Like SRC-1, SRC-3 also plays an essential role in ROR γ t-driven Th17 cell differentiation. Through a physical interaction with ROR γ t and under specific proinflammatory stimulation with IL-1/6/23, SRC-3 is recruited to the *il17* and *il1r1* loci to polarize naïve CD4⁺ T cells into the Th17 cell lineage (74) (Figure 2B). SRC-3-mediated commitment of naïve CD4⁺ T cells to the Th17 cell lineage manifests in an upregulation of Th17 cell signature genes and an increased number of IL-17 producing cells among WT CD4⁺ T cells as compared to SRC-3-KO CD4⁺ T cells. Reduced binding of the acetyltransferase p300 to the *il17* and *il1r1* loci, that is associated with SRC-3 deficiency, suggests that an ROR γ t-mediated recruitment of SRC-3 brings about a recruitment of p300 to establish an open chromatin structure that facilitates the transcription of Th17 signature genes. Importantly, a K313R mutation of ROR γ t that specifically disrupts the ability of ROR γ t to interact with SRC-3 but not SRC-1, impairs healthy differentiation and development of Th17, but not thymocytes (75). Intriguingly, under TGF β /IL-6 stimulation, SRC-3 deficient naïve CD4⁺ T cells successfully adopt the Th17 cell phenotype (74). This implies two different pathways for Th17 cell differentiation, and that the SRC-3-driven one utilizes an IL-1/IL1R1 signaling axis. However, further investigation is required to shed more light on the details of the mechanistic differences between these pathways. As previously mentioned, exposure of naïve human CD4⁺ T cells to a pharmacological inhibitor of SRC-3 affects the ability of these cells to acquire a suppressive phenotype under Treg-inducing conditions *ex vivo* (33). Nonetheless, genetic deficiency of SRC-3 in a mouse model did not appear to impair 'naïve CD4⁺ T cells to Tregs' polarization (74). This apparent discrepancy might reflect differences in the manner that the Treg phenotype is acquired (e.g., *ex vivo* induction versus *in vivo* natural polarization) as well as variations between the model organisms. However, as opposed to the neutral effect of SRC-3 deficiency in mice toward Treg polarization, the increase in the Treg-like phenotype that is associated with SRC-1 deficiency (72), suggests a potentially different nature of interactions of these two coactivators with the ROR γ t-FOXP3 complex.

2 Summary and future perspectives

Since the discovery and cloning of the first SRC, SRC-1, almost 30 years ago (6), these coactivators have been established as critical regulators of gene expression with broad range of impact on human physiology and pathology. Specifically in immunology, the SRCs have diverse biological functionalities that include interactions with major immune system TFs such as NF- κ B and ROR γ t, involvement in immune cell fate determination and development as well as control of their proliferation (11). In this review, we have highlighted the roles of the SRCs in the biology of two, functionally antagonistic, subtypes of CD4⁺ T cells – Tregs and Th17 cells; SRC-3 is one of the most highly expressed coactivators in Tregs and is important for their suppressive function. Indeed, the

importance of SRC-3 to Treg biology is reflected in the anti-tumor phenotype of SRC-3 deficient Tregs, that when recruited to the TME exert a pro-inflammatory phenotype which drives the infiltration of immune effector cells into the tumor and eventually brings about tumor eradication. SRC-2 is indispensable for the development and proper function of Tregs, since it regulates the expression of a panel of TFs that are important for Treg differentiation, including Nr4a2, that directly targets FOXP3 and regulates Treg suppression activity (76).

All SRCs can physically interact with the major TF of Th17 cells, ROR γ t, through their conserved NR binding LXXLL motif, pointing to the significant role that the SRCs play in Th17 cell biology. Indeed, it has been shown that PKC- θ -mediated phosphorylation of SRC-1 enhances its physical interaction with ROR γ t and drives the establishment of Th17 cell phenotype, rather than the Treg phenotype in naïve CD4⁺ T cells. Under inflammatory conditions, SRC-3 interaction with ROR γ t promotes pathogenic inflammation through the IL-1/IL1R1 signaling axis. The positive contribution of the SRCs to the establishment of Th17 cell phenotype has physiological implications as reflected in the resistance to autoimmunity that is associated with SRC-1 and SRC-3 deficiency in the EAE mice model (72, 74).

The SRCs have historically been considered 'undruggable' proteins, primarily due to their lack of high-affinity ligand binding pockets (7, 77). However, recent success in developing small molecule inhibitors and stimulators counter this view and show that it is possible to manipulate the activity of the SRCs (29, 34), presenting an opportunity for new therapeutic venues. Unsurprisingly, since the SRCs are very well established oncoproteins, their conception as pharmacological targets was first directed toward malignant diseases. However, recent accumulation of evidence that established the SRCs as important coregulators in the biology and function of Th17 cells and Tregs, implies their manipulation in these immune cells in autoimmune disorders and cancer as an exciting new immunotherapeutic area for development. Indeed, it has been shown that a systemic treatment with an SRC-3 inhibitor significantly suppressed BC progression in a syngeneic mouse model, not only in part due to a direct inhibition of SRC-3 in cancer cells, but primarily due to the immunological boost induced by the inhibitor (56). A recent study has shown that a cKO of SRC-3 in Tregs results in tumor eradication in BC and prostate cancer mouse models (57), inferring a direct impact of SRC-3 on cancer immunology. Moreover, the demonstration that *ex vivo* edited SRC-3 KO Tregs can be adaptively transferred to effect tumor eradication, provides the impetus for the development of an SRC-3 KO gene edited Treg-based cell therapy for solid tumors.

These recent studies unveil the immense therapeutic potential of manipulating the activity of SRCs in immune cells (Table 1), and future studies should shed more light on the translational potential of this approach by leveraging the discovery of small molecules that selectively target the SRCs as well as powerful CRISPR-Cas based

TABLE 1 Changes in Tregs and Th17 phenotypes associated with manipulations of SRC activities.

SRC protein	Manipulation	Observed phenotype	Reference
SRC-1	Overexpression	Enhanced differentiation of naïve CD4 ⁺ T cells into IL-17 producing cells <i>in vitro</i> .	(72)
	KD	Reduce production of IL-17 by CD4 ⁺ T cells <i>in vitro</i> .	
	KO	Decrease percentage of IL-17 producing cells and increased percentage of FOXP3-expressing cells among general lymphocyte population.	
	KO	Immunosuppressive phenotype dominance that is exemplified by resistance of SRC-1 ^{-/-} mice to the development of EAE.	
SRC-2	KO	cKO in FOXP3 ⁺ cells results in impaired ability of naïve CD4 ⁺ T cells to differentiate into iTregs <i>in vitro</i> under priming conditions with TGFβ.	(64)
	KO	cKO in FOXP3 ⁺ cells impairs the ability of these cells to acquire Treg phenotype <i>in vivo</i> .	
SRC-3	none	Enriched in Tregs.	(33)
	pharmacological inhibition	Failure of resting CD4 ⁺ T cells to adapt Treg phenotype under inducible Treg condition <i>in vitro</i> .	
	pharmacological inhibition	Inhibition of tumor growth in BC mouse models after systemic treatment with SI-2, which is associated with a decrease of FOXP3 ⁺ cells and increase of cytotoxic immune cells (CD8 ⁺ T cells, NK cells) and proinflammatory cytokines in the TME.	(56)
	KO		

(Continued)

TABLE 1 Continued

SRC protein	Manipulation	Observed phenotype	Reference
		cKO in FOXP3 ⁺ cells <i>in vivo</i> induces elevated levels of proinflammatory cytokines and increase of cytotoxic immune cells (CD8 ⁺ T cells, NK cells) in the TME and eradication of solid tumors in mice (BC and prostate cancer models).	

gene editing tools (78). The concept of inhibiting Th17 cell activity in an autoimmune disease through the use of small molecules that target the RORs has been recently introduced (79, 80). The key role of SRCs in Th17 cell biology potentiates pharmacological targeting of these proteins as an alternative approach to treat this class of disorders. However, further research is necessary to validate these approaches.

Author contributions

YG: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. OS: Writing – original draft, Writing – review & editing. SH: Writing – original draft, Writing – review & editing. DML: Writing – original draft, Writing – review & editing. BWO: Writing – original draft, Writing – review & editing.

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Conflict of interest

YG, SH, DML and BWO are paid consultants by and disclose an equity position in CoRegan, Inc.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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