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Serine and arginine rich splicing factor 1 deficiency alters pathways involved in IL-17A expression and is implicated in human psoriasis

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Abstract

Serine and Arginine Rich Splicing Factor 1 (SRSF1) is a splicing factor that binds to exonic enhancers and stimulates splicing and is previously implicated with autoimmunity. Herein, we investigate the role of SRSF1 in regulating innate immune functions that are pertinent in the pathogenesis of auto-inflammatory diseases. Specifically, we show that conditional deletion of SRSF1 in mature lymphocytes resulted in higher expression of *il-17a* and *il-17 f* and an expansion of IL17A⁺ CD8 T cells. Mechanistically, the aberrant expression of IL-17A in SRSF1 cKO mice could not be attributed to alternative splicing of *il-17a* or *il-17 f* genes but possibly to defective CD11B⁺LY6C⁺ myeloid derived suppressor function in the spleen. Finally, meta-analysis of RNA-Seq collected from psoriasis patients demonstrate a clear correlation between SRSF1 and psoriasis that suggests a putative role of SRSF1 in IL-17A-induced psoriasis.

Keywords

SRSF1; IL-17; Psoriasis; Autoimmunity; Alternative splicing

1. Introduction

Psoriasis is a chronically inflammatory skin disease the manifestation of which includes epidermal hyperplasia, leukocyte infiltration, and memory T cell accumulation [1]. It

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has been increasingly appreciated that psoriasis is an immune mediated disease that is fueled by the dynamic interplay between T cells, dermal dendritic cells and keratinocytes. Therapeutics against the IL-23/IL-17A axis has shown excellent efficacy in psoriasis however the pathogenic mechanisms remain elusive [2,3].

IL-17A is elevated in multiple autoimmune diseases, including psoriasis [2]. Many factors regulate the expression and signaling of IL-17, including ROR γ t, RUNX1, STAT3, NF- κ B, as well as certain microRNAs [4]. IL-17A expression is also regulated by alternative splicing, a regulatory process enabling the generation of protein isoforms from a single gene [5–8]. Alternative splicing is a naturally occurring process that increases protein diversity [9]. However, dysregulated splicing has been linked with many diseases [10]. Specifically, the Serine and Arginine Rich Splicing Factor 1 (SRSF1), a splicing factor that binds to exonic enhancers and stimulates splicing, has been shown to influence Th17 differentiation [7,11]. SRSF1 is a multi-functional serine arginine protein that not only controls pre-mRNA splicing, but also regulates many other splicing independent activities such as nonsense-mediated mRNA decay, nuclear export of mRNA, and mTOR activation [12–15]. Recent studies have suggested that SRSF1 also plays an important role in autoimmunity [7,8,16]. Particularly, increased mRNA expression levels of *Il-17a* and *Il-17f* have been observed in regulatory T cells of a mouse model with T cell specific conditional knockout of *Srsf1* [8]. On the other hand, IL-17 has been shown to enhance the stability of CXCL1 mRNA by inhibiting the interaction between SRSF1 and CXCL1 in the TRAF cascade, which mediates IL-17 signaling [17,18]. These studies collectively suggest that SRSF1 is involved in multiple steps in the IL-17 signaling pathway.

Myeloid-derived suppressor cells (MDSCs) are a specific population of cells that can expand and suppress T cell responses during inflammation and infection. In mice, there are two types of MDSCs characterized by the co-expression of CD11B as well as either Ly6G (Ly6G⁺Ly6C⁻ granulocytes) or LY6C (Ly6G⁻Ly6C⁺ monocytes) [19]. Monocytic MDSCs are more suppressive than granulocytic MDSCs and in murine viral infection models, monocytic MDSCs have been found to suppress CD8⁺ T cells in the spleen [20]. MDSCs suppress T-cell function by down-regulating the expression of CD3 ζ chain in T cells [21]. Interestingly, SRSF1 also regulates mRNA expression of CD3 ζ chain in T cells [22]. In this study, we propose that SRSF1 might be involved in IL-17 signaling through MDSCs, which might support a putative role of SRSF1 in innate immune responses and autoinflammatory diseases such as psoriasis.

2. Methods

2.1. Animals

Srsf1^{fl/fl} (JAX: 018020) and *dLck*^{cre} (JAX: 012837) mice were purchased from Jackson Laboratory. *Srsf1*^{fl/fl} and *dLck*^{cre} mice were crossbred to generate *Srsf1*^{fl/fl}.*dLck*^{cre} conditional knockout mice, referred to as *Srsf1*^{fl/fl}.*dLck*^{cre}. Eight to twelve-week-old male and female mice were used in this study. All mice were bred and housed under specific pathogen-free conditions and exposed to a constant 12-h light-dark cycle in the animal facilities at Beth Israel Deaconess Medical Center (BIDMC). All experiments were

conducted in accordance with the guidelines and with the approval of the Institutional Animal Care and Use Committee of BIDMC.

2.2. Antibodies and reagents

CD3 (145-2C11, BioLegend), CD4 (GK1.5, Invitrogen), CD8a (53–6.7, BioLegend), CD25 (PC61, BioLegend), CD127 (A7R34, BioLegend), IL-17A (TC11-18H10.1, BioLegend), IL-17F (9D3.1C8, BioLegend), FOXP3 (MF-14, BioLegend), ROR γ t (B2D, BioLegend), Ly6C (HK1.4, BioLegend), Ly6G (1A8, BioLegend), CD11B (M1/70, BioLegend).

2.3. Acute lymphocytic choriomeningitis virus (LCMV) infection

Eight to twelve-week-old WT and Srsf1^{fl/f}.dLck^{cre} mice were infected with 2×10^5 PFU of Armstrong strain LCMV by *i.p.* injection. Age- and sex-matched mice injected with PBS served as controls. Bone marrow and splenocytes were harvested at 24 h post infection.

2.4. Flow cytometry

Flow cytometry was performed using a CytoFLEX LX Flow Cytometer (Beckman Coulter) and analyzed using FlowJo. Single cell suspension of mouse bone marrow cells or splenocytes were collected for flow cytometric analyses. ZombieNIR Viability Kit (BioLegend) staining was performed to eliminate dead cells. Surface staining was performed in PBS with Fc block at 4 °C for 30 min. For intracellular cytokine staining, cells were stimulated for 4 h in culture medium with PMA (1 mM, Sigma-Aldrich), Ionomycin (1 μ M, Sigma-Aldrich) and monensin (1 μ L/mL, BD Biosciences). Cytofix/Cytoperm and Perm/Wash buffer (BD Biosciences) were used for fixation and permeabilization. Appropriate antibodies were used for intracellular staining for cytokines or transcription factors according to manufacturer's instructions.

2.5. RNA-Seq analysis

RNA-Seq data of natural regulatory T cells (nTregs) of WT and Srsf1^{fl/f}.dLck^{cre} mice were acquired from the NCBI Gene Expression Omnibus (GEO) from the series under accession number: GSE173268. RNA-Seq data from human normal and psoriatic lesional skin samples were acquired from GEO from the series under accession numbers: GSE63980 and GSE121212. Four total datasets were used: three independent datasets (SRP165679, SRP026042, SRP057087) and one dataset comprised of two combined experimental datasets published by the same research group (SRP035988, SRP050971) [23–25]. The latter included 99 lesional psoriatic and 90 normal skin biopsies from subjects of European descent enrolled in the Southeast Michigan area. Psoriasis patients who volunteered for a skin biopsy underwent a wash-out period of all immunosuppressive medications prior to the procedure.

2.6. Bioinformatic analyses

Raw sequencing data were acquired in FASTQ format. Data quality was evaluated using FastQC [26] and data were pre-processed with Cutadapt [27] for adapter removal following best practices [28]. Alignment of sequencing reads to the reference genome (GRCh38 and GRCm38 for human and mouse, respectively) was performed using STAR [29], and the

quantification of reads was carried out with the SubRead package [30]. Gene expression level normalization and differential expression analysis was carried out using the DESeq2 Bioconductor R package (version 1.6.3) [31], while ClusterProfiler [32] was utilized for downstream functional investigations and pathway enrichment analyses. Differential expression p -values were corrected for multiple testing using the false discovery rate (FDR) and Storey's q -value [33]. Genes with adjusted $p < 0.05$ were considered as differentially expressed. Differential exon usage analysis was performed with DEXSeq. (v1.34.1) [34,35]. First, the exon annotation was created based on the GRCm38 Ensembl v98 gene annotation. Differential exon usage p -values were corrected for multiple testing using FDR method. Plots were generated in R using ggplot2 (v3.3.3) [36] ComplexHeatmap (v2.6.2) [37], and ggsashimi (v1.1.0) [38].

2.7. Statistical analyses

Comparisons between two groups were done by unpaired two-tailed Student's t -test. Non-parametric tests were applied to the datasets with non-Gaussian distribution. Statistical analyses were performed with GraphPad Prism 9.0 software (GraphPad Software). Data are shown as mean \pm standard error (SEM). P values < 0.05 were considered significant.

3. Results

3.1. Increased gene and protein expression of IL-17A in *Srsf1*^{fl/fl}.dLck^{cre} mice

In order to elucidate the role of SRSF1 in mature T cells, we crossed the *Srsf1*^{fl/fl} mice [39] with dLck^{Cre} mice [40], which express the Cre recombinase under the control of the *lck* distal promoter. Using this system, we deleted the floxed gene fragment selectively at the late stage in thymocyte development to conditionally inactivate SRSF1 in mature T cells (Fig. 1A). Analysis of the RNA-Seq data (GSE173268) showed that T cells from *Srsf1*^{fl/fl}.dLck^{cre} mice exhibited higher expression of *Il-17a* and *Il-17f* (Fig. 1B). In order to investigate whether the elevated *Il-17a* and *Il-17f* transcripts also reflect on the protein level in naïve state, we performed flow cytometric analysis on the splenocytes of *Srsf1*^{fl/fl}.dLck^{cre}. We confirmed the RNAseq observations by performing intracellular staining of IL-17A in various T cell subsets. We detected a significant elevation of IL-17A⁺CD8⁺ T cells in the *Srsf1*^{fl/fl}.dLck^{cre} mice (Fig. 1C) and a non-significant trend of elevated IL-17A and IL-17F protein in CD4⁺CD25^{high}CD127^{low} Tregs (data not shown).

3.2. Alternative splicing is not involved in the expression of *Il-17a* or *Il-17f* in *Srsf1*^{fl/fl}.dLck^{cre} mice

The observed difference in RNAseq and the protein levels of IL-17A in *Srsf1*^{fl/fl}.dLck^{cre} mice led us to speculate whether the elevated gene expression might be due to aberrant alternative splicing caused by SRSF1 deficiency. In order to directly capture the effect of SRSF1 deficiency in alternative splicing we compared differentially spliced genes between *Srsf1*^{fl/fl}.dLck^{cre} and control mice. Differential exon usage analysis identified 578 genes (667 exons) with potential differential usage of exons in *Srsf1*^{fl/fl}.dLck^{cre}, under a permissive FDR < 0.1 (Fig 2A). However, there were only 5 genes falling within the overlap between differentially expressed and differentially spliced genes identified. Further analysis detected that among the 578 genes with potential differential usage of exons,

43% had increased exon usage and 57% had decreased exon usage (Fig. 2B). Both *Il-17a* and *Il-17f*, although differentially expressed, were not differentially spliced (Fig. 2C, D). Following further manual evaluation, 2 out of 3 samples showed RNA processing patterns practically indistinguishable from the control group, while one sample showed some potential differential exon usage. Even under permissive statistical significance thresholds, investigations of differential exon usage did not reveal any statistically significant difference, pointing to differential expression events not directly affected by SRSF1 splicing activity. Subsequently, we analyzed transcription factors ROR γ t, STAT3, Stat5a, Stat5b, TBX21 and GATA3 that affect *Il-17a* and *Il-17f* expression, but did not detect any significant differential expression or alternatively splicing in these genes [41–43]. Next, we looked at differentially expressed genes (DEGs) that showed differential exon usage that could affect the secretion of IL-17A or IL-17F, such as Rab23, a molecule involved in vesicular trafficking, and Pikfyve, a molecule that affects a number of trafficking pathways. Further visual inspection suggested that the observed effect is limited to a small fraction of the exons (Fig. 2E, F). Taken together in these experiments we did not detect any significant changes that suggest SRSF1 mediated alternative splicing in the expression of *Il-17a* and *Il-17f*.

3.3. *Srsf1*^{fl/fl}.dLck^{cre} Tregs possess distinct gene signatures associated with innate immunity

In order to explore the potential pathways that the altered gene expression of *Il-17a* and *Il-17f* in Tregs of *Srsf1*^{fl/fl}.dLck^{cre} mice might play a role in, we performed pathway enrichment and over-representation analysis. Our data showed that the differentially expressed genes are highly enriched in innate immune response pathways, as well as neutrophil and monocyte chemotaxis (Fig. 3A). Specifically, heatmap of the RNA-seq data showed that, among the differentially expressed genes involved in innate immunity, (Fig. 3B), the T cells of *Srsf1*^{fl/fl}.dLck^{cre} mice showed elevated chemokine expression related to monocytes and neutrophils, such as *Ccl3*, *Ccl1*, *Ccl17*, *Ccl20*, and *Ccl22* (Fig. 3C). These data suggested that *Srsf1* deficiency might regulate innate immunity.

3.4. *Srsf1*^{fl/fl}.dLck^{cre} mice have reduced innate immune responses upon acute viral infection

In order to demonstrate that *Srsf1* deficiency in T cells affects innate immunity, we performed flow cytometry analysis of bone marrow and spleen myeloid cells in WT and *Srsf1*^{fl/fl}.dLck^{cre} mice in their naive state or 24 h after LCMV infection. We found that *Srsf1*^{fl/fl}.dLck^{cre} mice exhibited lower frequency of total CD11B⁺ myeloid cells in bone marrow (Fig. 4A). In the spleen, however, *Srsf1*^{fl/fl}.dLck^{cre} mice exhibited significantly higher CD11B⁺ frequencies at naive state compared to their WT counterparts (Fig. 4B). The difference of CD11B⁺ cells in the bone marrow between *Srsf1*^{fl/fl}.dLck^{cre} and WT was not altered 24 h after acute LCMV infection (Fig. 4A). The difference of splenic CD11B⁺ myeloid cells between *Srsf1*^{fl/fl}.dLck^{cre} and WT was diminished 24 h after acute LCMV infection, as the frequency of CD11B⁺ myeloid cells doubled in WT mice but remained the same in *Srsf1*^{fl/fl}.dLck^{cre} mice (Fig. 4B).

We then investigated the effect of SRSF1 deficient T cells in MDSCs by measuring the frequencies of CD11B⁺Ly6G⁺Ly6C^{lo} polymorphonuclear MDSCs (PMN-MDSC) and

CD11B⁺Ly6G⁻Ly6C^{lo} monocytic MDSCs (M-MDSC) in the bone marrow and spleen, using flow cytometric markers as previously described [44]. We observed that *Srsf1*^{fl/fl}dLck^{cre} mice had higher frequencies of M-MDSC in the bone marrow and higher frequencies of PMN-MDSC in the spleen at naive state (Fig. 4C,D). However, 24 h after acute LCMV infection, unlike the WT mice, the splenic PMN-MDSC frequency of the *Srsf1*^{fl/fl}dLck^{cre} mice failed to expand (Fig. 4E). Both WT and *Srsf1*^{fl/fl}dLck^{cre} mice exhibited decreased PMN-MDSC frequency in the bone marrow 24 h after acute LCMV infection (Fig. 4F). Collectively our data suggest that ablation of SRSF1 in mature T cells affects innate immune responses.

3.5. SRSF1 is associated with human psoriasis and IL-17A

In order to understand the clinical implications of SRSF1 in the context of psoriasis, SRSF1 gene expression was evaluated in psoriasis lesional and healthy control skin. Two independently acquired datasets were used for this analysis and results are presented as dot-plots of log₂ transformed read counts [23–25]. In each case, SRSF1 was markedly elevated in psoriasis skin compared to healthy controls (Fig. 5A). Moreover, SRSF1 gene expression was significantly and positively correlated with *IL17A* expression (Fig. 5B-D).

4. Discussion

SRSF1 is regulating adaptive and innate immune functions pertinent to the pathogenesis of autoimmune and autoinflammatory diseases. Since SRSF1 is a splicing factor it would be expected to contribute to autoimmunity by gene expression regulation through alternatively splicing of mRNAs [12,45–49]. However, in our case, although we observed elevated gene expression levels of *Il-17a* and *Il-17f* in our transcriptomic analysis, we did not detect any difference in the splicing patterns between WT and the *Srsf1*^{fl/fl}dLck^{cre} mice in IL-17A or IL-17F, or any of the transcription factors that regulate their expression. A recent study that looked at alternatively splicing events in the *Srsf1*^{fl/fl}dLck^{cre} mice detected changes in IRF7 and IL-27RA but no indication on IL-17A or IL-17F [50]. These data suggest that the elevated *Il-17a* and *Il-17f* mRNA levels might be regulated by other mechanisms independent of alternative splicing.

An increase of *Il-17a* and *Il-17f* mRNA levels could also be achieved indirectly by inhibition of immune tolerance. Immune tolerance is achieved by multiple cell types including regulatory T cells (Tregs) and myeloid suppressor cells. Tregs play an important role in restraining skin inflammation [51], and psoriatic arthritis patients have low circulating Treg numbers [52]. Moreover, Treg-deficient mice exhibit autoimmune phenotypes that resemble symptoms of systemic autoimmunity with hyperkeratotic skin lesions [50,53]. Indeed, deficiency of SRSF1 in Tregs is associated with autoimmunity [8]. An effect on Tregs is highly plausible as the distal Lck promoter-driven Cre, also affects other cell types including innate-like T cells, including invariant NK T cells, mucosal-associated invariant T (MAIT) cells, and $\gamma\delta$ T cells [54]. In this study, however, we observed no difference in Treg frequency or IL-17A⁺Tregs in *Srsf1*^{fl/fl}dLck^{cre} mice. The discrepancy of IL-17A and IL-17F expression on the protein and mRNA level observed in this study supports previous findings that SRSF1 associates with translating ribosomes and

stimulates translation [55,56]. Without SRSF1, the elevation in the expression of *Il-17a* and *Il-17f* mRNA levels is diminished on the protein level. Since the changes in transcripts and proteins are not synchronized in the absence of SRSF1, proteomic studies are needed to comprehensively investigate the effect of SRSF1.

An additional mechanism that SRSF1 may break tolerance is via the inhibition of myeloid-derived suppressor cells (MDSCs), which are major negative regulators of immune responses. MDSCs are categorized into two groups of cells, termed polymorphonuclear (PMN-MDSCs) and monocytic (M-MDSCs), which are phenotypically and morphologically similar to neutrophils and monocytes, respectively [57]. MDSCs suppress the immune responses of CD8⁺ T cells [20]. Our gene ontology pathway analysis showed many differentially expressed genes in the *Srsf1*^{fl/fl}dLck^{cre} mice that are involved in innate immunity pathways including cytokine receptors, neutrophil, and monocyte chemotaxis pathways that are pertinent to the function of MDSCs [58]. Moreover, our experiments with 24-h acute LCMV infection highlighted the impaired immune response to viral challenge and clearly demonstrated that the SRSF1 splicing factor regulates autoimmune processes through indirect effects on other cell types to prolong CD8 responses leading to autoimmunity. These data suggest an additional mechanism by which SRSF1 contributes to chronic inflammation leading to autoimmunity.

In psoriatic patient skin lesions, SRSF1 gene expression is consistently elevated across different bulk RNA-seq datasets. This observation is positively correlated to the elevated expression of IL-17A in psoriatic lesions [59]. However, psoriatic lesional skins encompass a variety of resident cells, including keratinocytes, mesenchymal cells, myeloid, in addition to resident T cells. In psoriatic skin, inflammatory T cells are found in the dermis and CD8⁺ T cells and neutrophils are found in the epidermis [59]. The skin samples collected from healthy donors and psoriatic patients for the analyses of this study were extracted by a punch biopsy method, which collected epidermis, dermis and superficial fat. Due to this heterogeneity it is unclear the high expression of SRSF1 in which cell type(s) has a dominant effect in the pathogenesis of psoriasis. It is also unclear, whether the elevation of SRSF1 expression is the cause or the consequence of the disease. Nor is it clear whether SRSF1 plays a pathogenic or a protective role in the pathophysiology of the disease. Other paradoxical observations have also been reported in psoriasis studies. For example, the mRNA level of CXCL17 is significantly higher in psoriatic skin than in normal skin, but it has been found that CXCL17 can attenuate Imiquimod-induced psoriasis-like skin inflammation by recruiting MDSCs and Tregs [60]. Therefore, our study provided new evidence to the potential SRSF regulation of autoimmunity by immunosuppressive cells. Although the exact function of SRSF1 in these cells remains elusive, the pleiotropic functions of SRSF1 in motility, cell division, and activation of mTOR pathway have been implicated with psoriasis [61–63]. A more global effect on inflammatory signaling may be perturbed by the aberrant signaling of SRSF1.

In addition to being a splicing factor, SRSF1 also functions as a shuttling protein that exports mRNA from the nucleus to the cytoplasm [65]. Eukaryotic cells produce mRNA in the nucleus through a series of events including 5' capping, 3'-end processing and splicing, which are coupled with transcription and exported from the nucleus to the cytoplasm where

it can be translated to generate proteins. SRSF1 is found to reduce the nuclear export of inflammatory mRNAs [65]. It is therefore possible that the elevated *Il-17a* and *Il-17 f* expression we observed in the RNA-seq data was the result of increased nuclear export in the absence of Srsf1 rather than altered AS events [66].

Collectively, understanding the role of SRSF1 in IL-17A signaling will pave the way to a detailed understanding of the pathophysiology of psoriasis that can be explored to develop novel therapeutic approaches for our patients.

5. Conclusion

In this study, we observed elevated *Il-17a* and *Il-17 f* mRNA expression level and reduced innate immune response in T cell specific Srsf1 knockout mice. We did not detect significant AS events in these mice, suggesting SRSF1 might regulate inflammation via its role as a shuttling protein over splicing factor. Although there is a clear correlation between SRSF1 gene expression and psoriasis, the mechanisms by which SRSF1 contributes to the pathogenesis of psoriasis requires further investigation.

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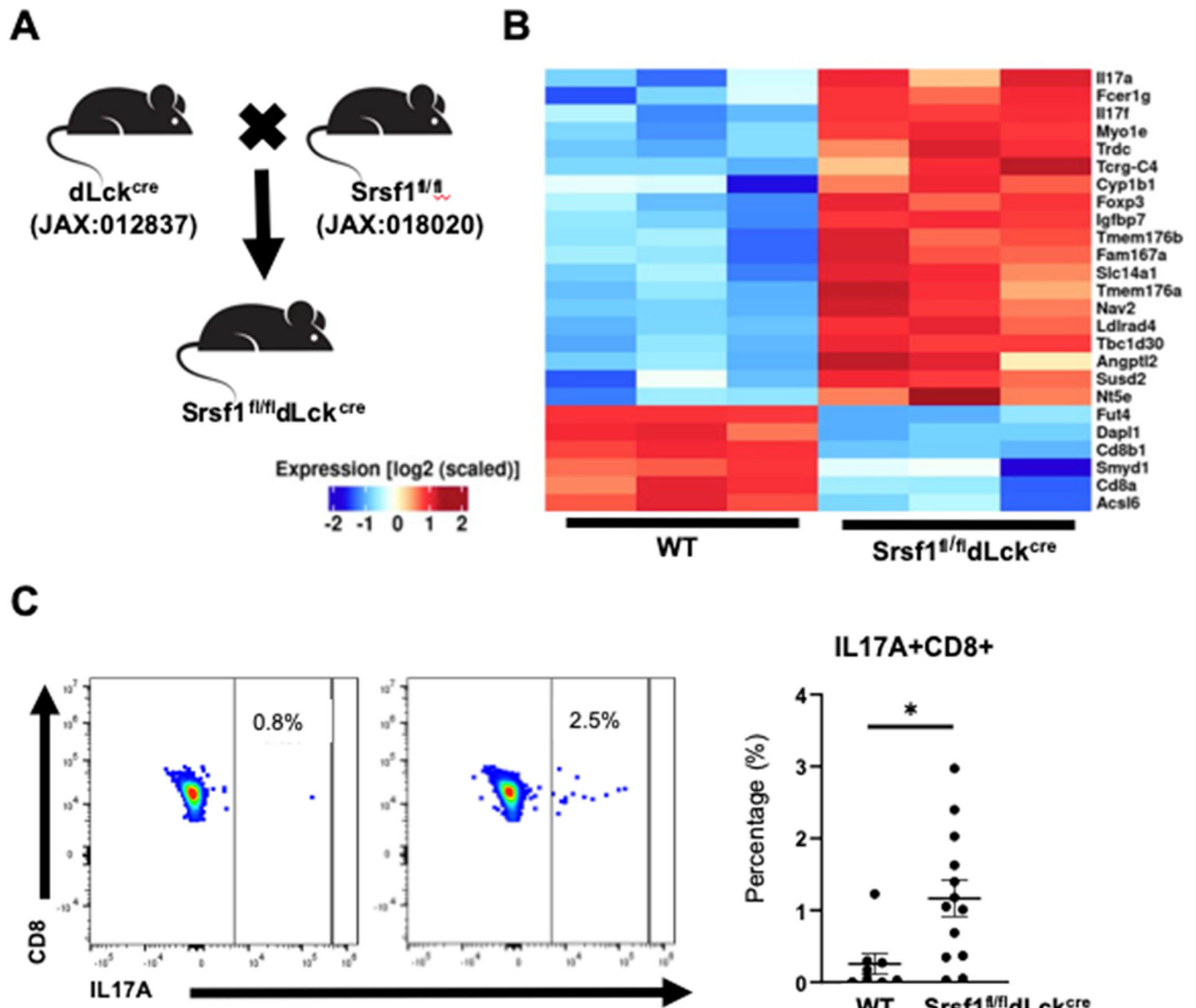
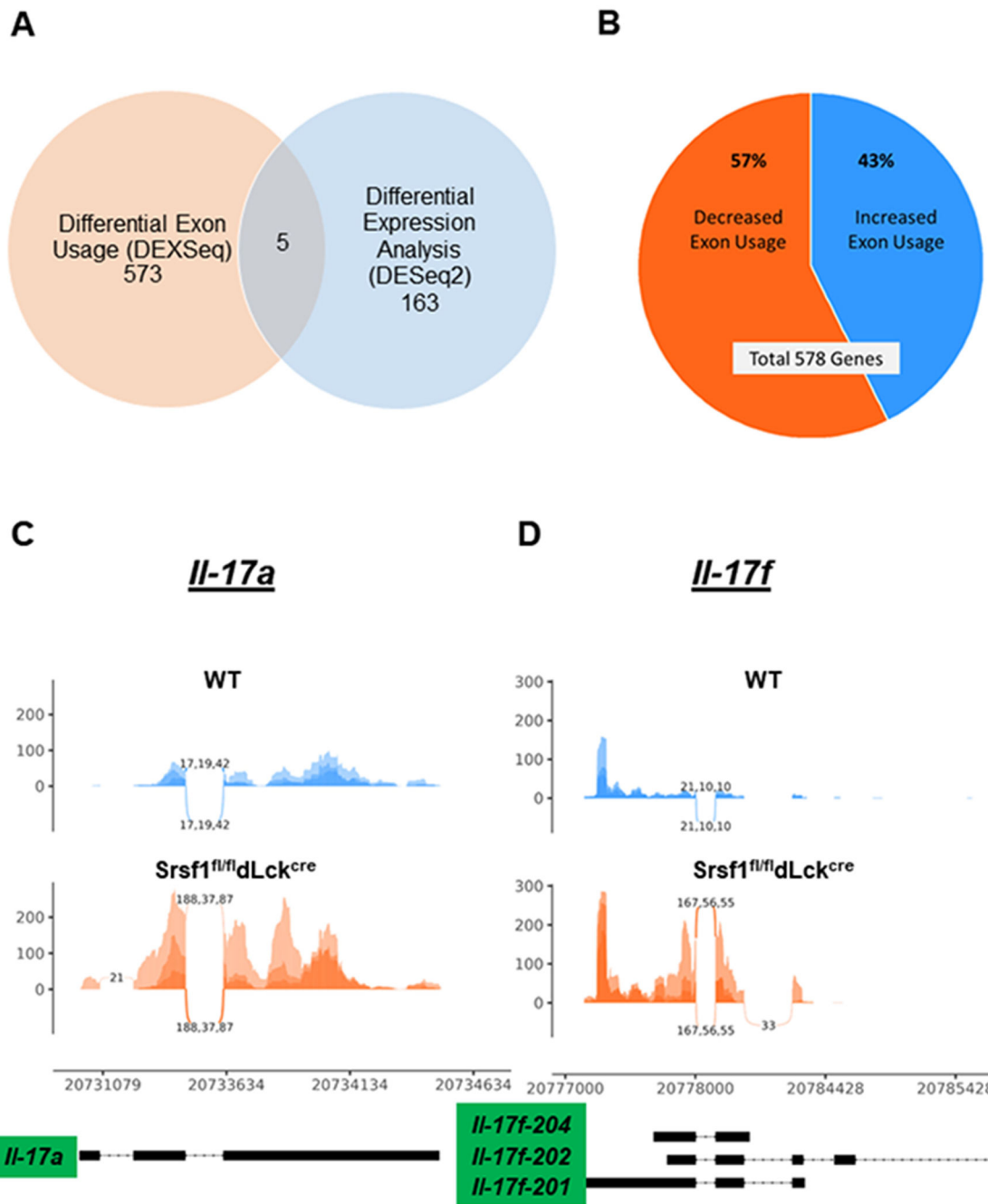


Fig. 1. Ablation of Srsf1 in T cells increases the mRNA expression and protein levels of IL-17A. (A) Schematic representation showing the strategy for generating the mouse model (Srsf1^{fl/fl}dLck^{cre}). (B) Heatmap of differential expressed genes showing top 25 significantly differentially expressed genes in CD4⁺CD25^{high}CD127^{low} nTregs from the splenocytes of WT and Srsf1^{fl/fl}dLck^{cre} mice ($n = 3$) by RNA-seq data (GSE 173268). (C) Representative pseudocolor plots showing IL-17A⁺ CD8⁺ T cells from the spleens. (WT: $n = 8$, Srsf1^{fl/fl}dLck^{cre}: $n = 13$). The percentage of respective population of each group is shown on the right. Student *t*-test, unpaired, nonparametric. * $p < 0.05$).



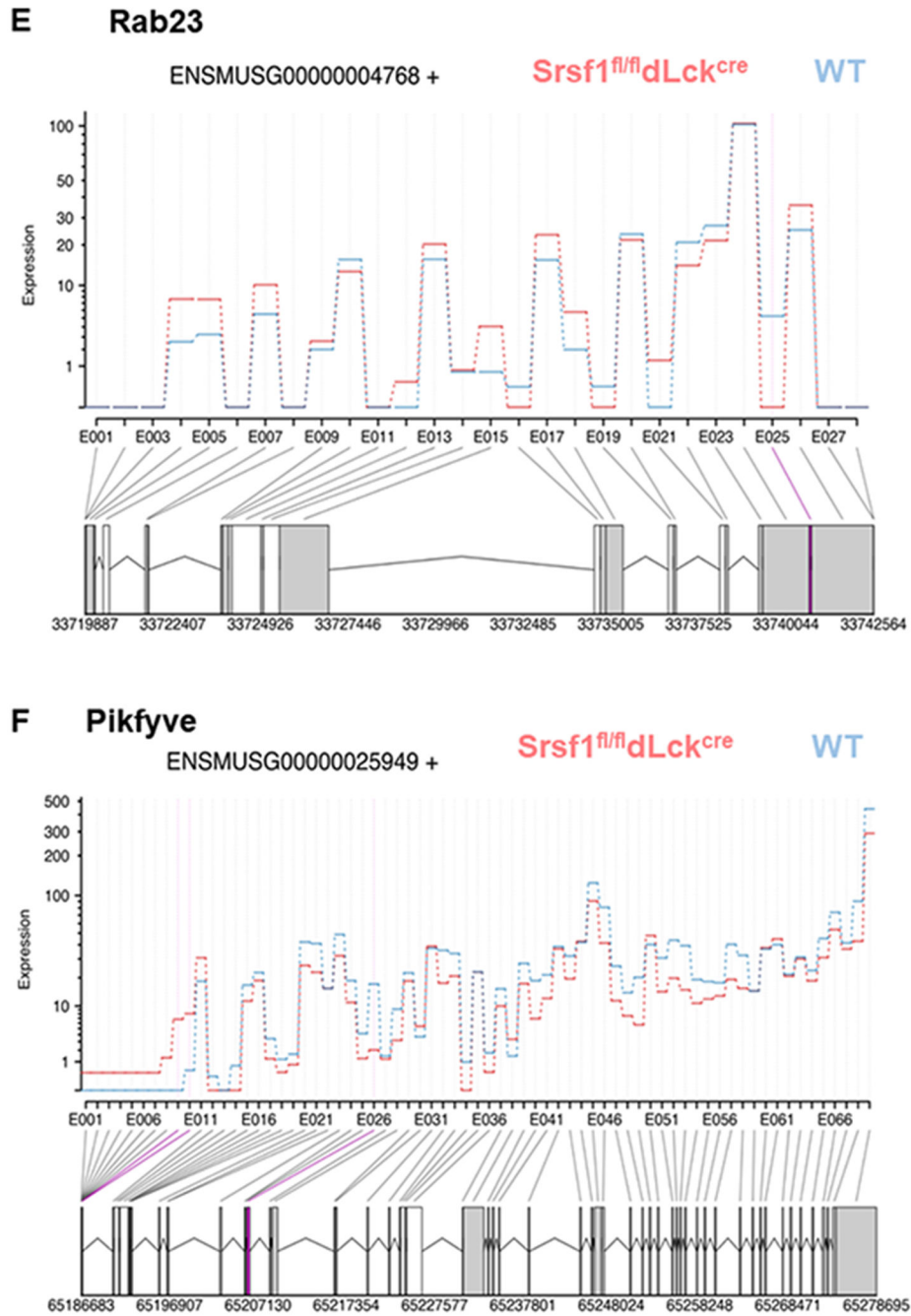


Fig. 2. Alternative splicing does not regulate the expression of IL-17a/IL-17 f in *Srsf1^{fl/fl}dLck^{cre}* mice. (A) Venn diagram shows the overlap between differentially expressed genes and genes with differential exon usage. (B) Pie chart shows the proportion of genes with increased or decreased exon usage out of a total of 578 genes with differential usage of exons in *Srsf1^{fl/fl}dLck^{cre}* (FDR < 0.1). (C—D) Sashimi plots show read coverage and exon-exon junctions (numbers on arches indicate junction reads) of IL-17a (C) and IL-17 f (D). (E-F)

Plots showing differential exon usage in *Rab23* (E) and *Pikfyve* (F) between WT and *Srsf1*^{fl/fl}*dLck*^{cre}.

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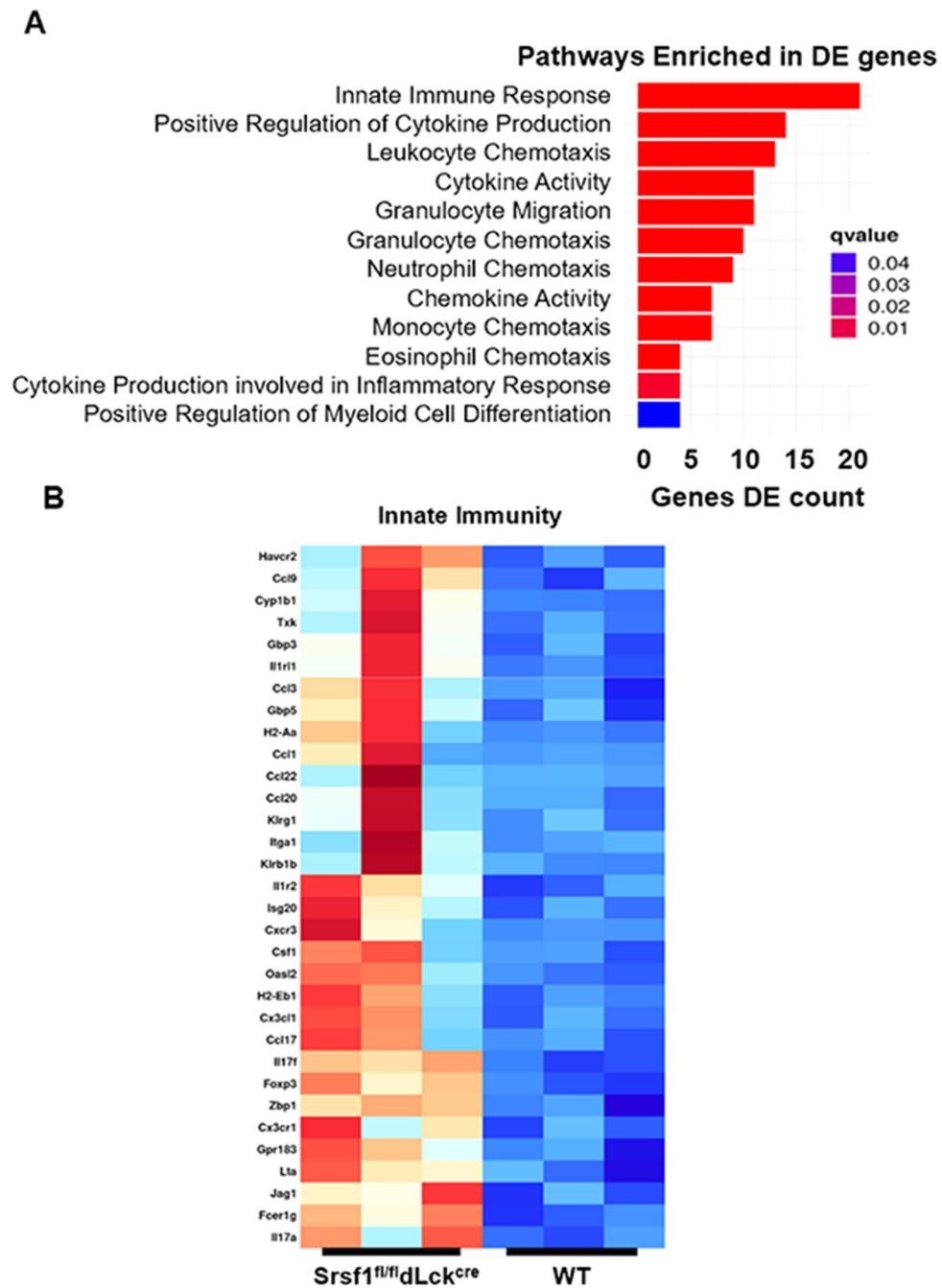


Fig. 3. *Srsf1*^{fl/fl}.dLck^{cre} Treg cells possess distinct gene signatures associated with myeloid cells. (A) Top enriched innate immune pathways of differentially expressed genes (DEGs) between WT and *Srsf1*^{fl/fl}.dLck^{cre}. (B) Heatmaps showing DEGs related to innate immunity.

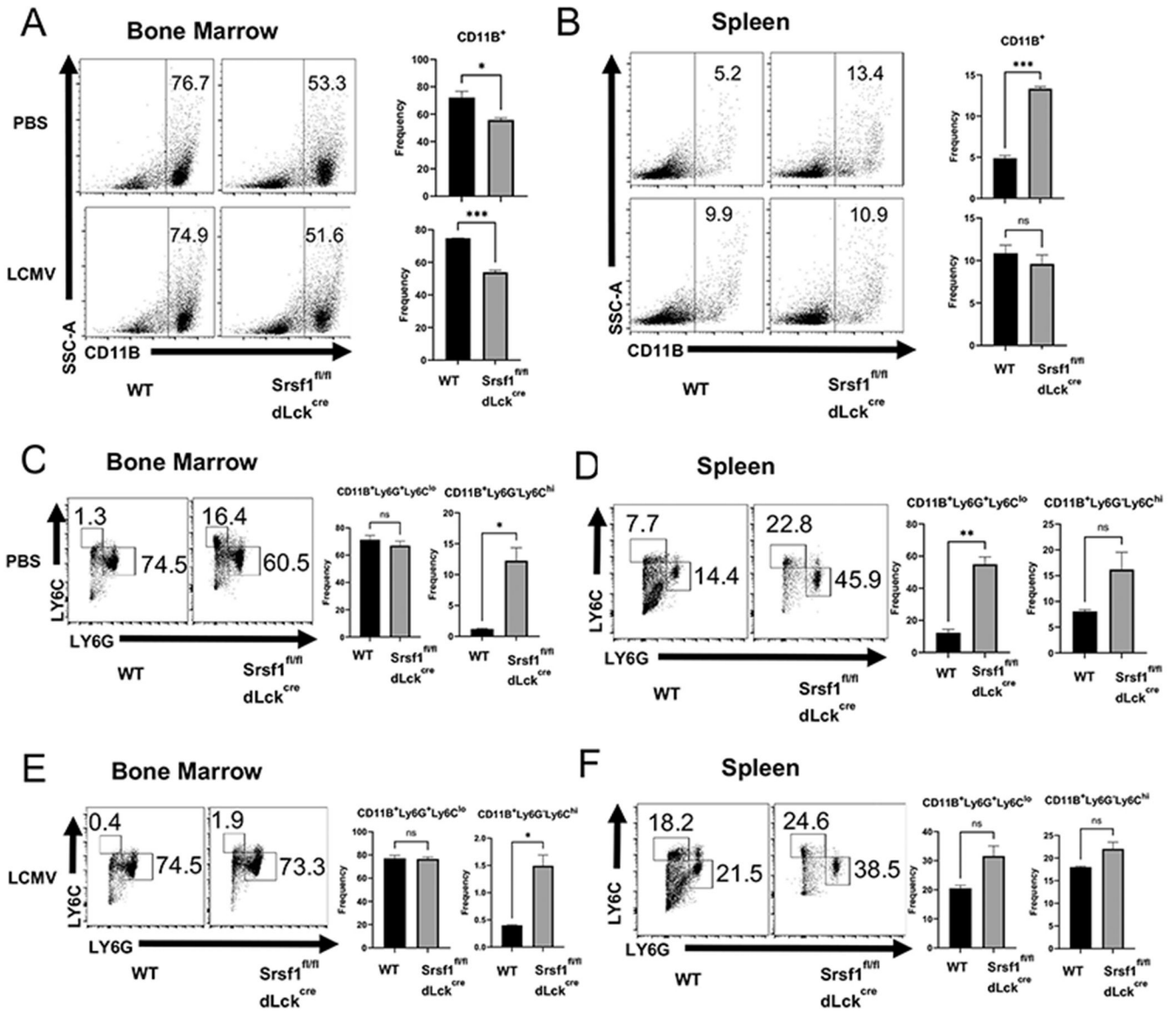


Fig. 4. Srsf1 deficiency in T cells affects innate immune cell distribution and migration. Dot plots and graphs showing the populations of CD11B⁺ myeloid cells in bone marrow and spleen of WT and Srsf1^{fl/fl}dLck^{cre} mice in naive state (A, B) and 24 h after acute LCMV infection (C, D). Dot plots and graphs showing the populations of PMN-MDSC (CD11b⁺Ly6G⁺Ly6C^{lo}) and M-MDSC (CD11b⁺Ly6G⁺Ly6C^{hi}) in the bone marrow and spleen of WT and Srsf1^{fl/fl}dLck^{cre} mice in naive state (E, F) and 24 h after acute LCMV infection (G, H). Experiments were performed twice with at least 3 mice per group. Student t-test, unpaired, *, $P < 0.05$, **, $P < 0.01$, ***, $P < 0.001$.

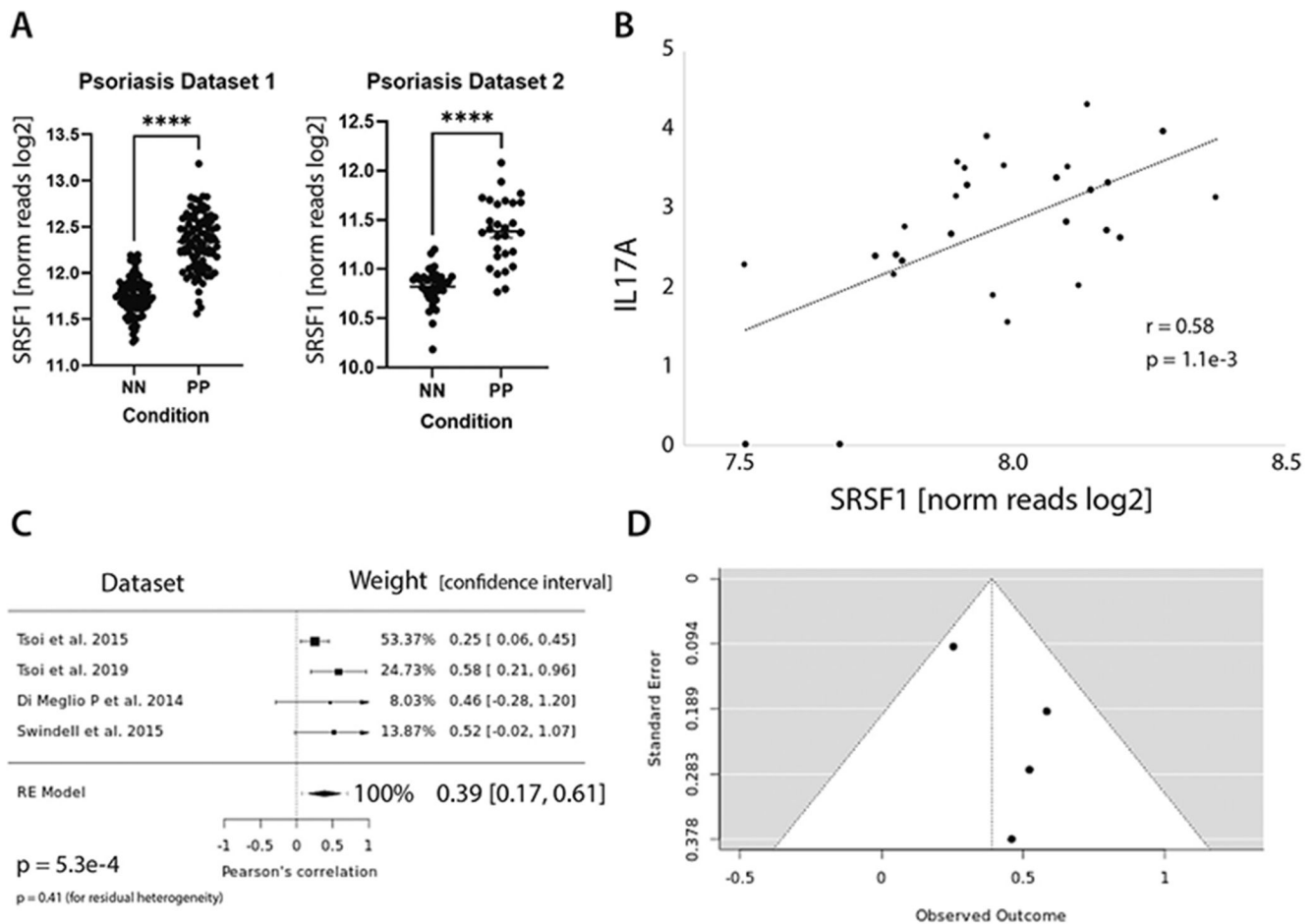


Fig. 5. SRSF1 gene expression is associated with human psoriasis and IL-17A. A) Graphs comparing SRSF1 gene expression (normalized log₂ reads) in the skin biopsies of Psoriatic Patients (PP) and Non-lesional Normal skin biopsies of healthy donors (NN) from two independent studies. (Student t-test, unpaired, ****, $P < 0.0001$.) B) representative scatter plot of SRSF1 association with *IL17A* C) Forest and D) Funnel plots of meta-analysis across all four RNAseq datasets.