Harlan Sprague Dawley Inc. (Indianapolis, IN). The mice were taken care in facilities at the University of Tennessee (Knoxville, TN) approved by the American Association of Laboratory Animal Care where food, bedding and instruments were autoclaved. All investigations followed guidelines of the institutional animal care and use committee.

Virus

HSV-1 strain RE Tumpey was propagated in Vero cell monolayers (American Type Culture Collection CCL81; Manassas, VA, USA).

Infected Vero cells were harvested, titrated and stored in aliquots at -80°C until used.

HSV-1 infection and clinical scoring

C57BL/6 mice were given deep anesthesia and corneal infections were done by lightly scarifying corneas using a 27-gauge needle and a 3 μL drop that contained 10^4 plaque-forming units of HSV-1 RE was put on one eye. These mice were monitored for the development of SK lesions.

The SK lesion severity and angiogenesis in the eyes of mice were examined by slit-lamp biomicroscopy (Kowa Company, Nagoya, Japan). The scoring system was as follows: 0, normal cornea; +1, mild corneal haze; +2, moderate corneal opacity or scarring; +3, severe corneal opacity but iris visible; +4, opaque cornea and corneal ulcer; and +5, corneal rupture and necrotizing keratitis. The severity of angiogenesis was recorded as described previously [13]. According to this system, a grade of 4 for a given quadrant of the circle represents a centripetal growth of 1.5 mm toward the corneal center. The score of the four quadrants of the eye were then summed to derive the neovessel index (range, 0 to 16) for each eye at a given time point.

IL-28A administration

PEG-rIL-28m (IFNλ-2) (A Bristol-Myers Squibb Company, Seattle, WA) was formulated at a concentration of 12.93 mg/mL in PBS. It was administered intraperitoneally from day 1 to day 15 Post-infection and in another set of experiments from day 4 post-infection to day 15 post-infection. The control group received equal volume of PBS. The dose of IL-28A (200 μl I.P.) was chosen based on our preliminary studies and previous reports [8].

Viral titers

Eye swabs were taken from infected corneas which were treated with or without IL-28A using sterile swabs and were stored in -80°. After obtaining all viral titers of different day points, titrations were performed by a standard plaque assay. Titers were calculated as $\log_{10}$ pfu/ml as per standard protocol.

Quantification of mRNA expression levels by RT-PCR

Total mRNA from corneal cells was isolated using the mirVana miRNA Isolation kit (Ambion). cDNA was made with 500 ng of RNA (corneal samples). TaqMan gene expression assays for cytokines and chemokines were purchased from Applied Biosystems and quantified using the 7500 Fast real-time PCR system (Applied Biosystems). The expression levels of different molecules were normalized to that of β-actin using the ΔC_T method.

Flow cytometric analysis

On the day of termination, on day 15 p.i., corneas were excised, pooled group wise, and digested with Liberase (Roche Diagnostics Corporation, Indianapolis, IN) for 30 min at 37°C in a humidified atmosphere of 5% CO_2. Following incubation, the corneas were disrupted by grinding with a syringe plunger on a cell strainer and a single-cell suspension was made in complete RPMI 1640 medium. Cells were stimulated with phorbol 12-myristate 13-acetate (50 ng) plus ionomycin (500 ng) along with Golgi plug (brefeldin A) (10 μg/ml) and incubated for 4 h in a CO_2 incubator. Corneal single-cell suspensions after stimulation were stained for different surface staining molecules for fluorescence-activated cell sorting (FACS) analyses such as CD45 (53-6.7), LY6G (1A8), F4/80 (BM8), IFN-gamma (XMG1.2), FOXP3 (FJK-16S), CD4 (RM 4-5).

Draining lymph nodes (DLN) were obtained from mice terminated on day 15 post-infection and single-cell suspensions were made as described for corneal samples and were stimulated and stained for cell surface markers followed by intracellular staining. Cells were kept on ice throughout the procedure and staining was done in U-bottom 96-well plates. The stained samples were acquired with a FACS LSR (BD Biosciences) and the data were analyzed using FlowJo software.

STATISTICS

The statistical significance between the 2 groups treated with or without IL-28A was determined using unpaired, 1-tailed Student's *t* test. $P \leq 0.001$ (***), $P \leq 0.01$ (**), $P \leq 0.05$ (*) were considered significant, and results were expressed as means ± SEM and all experiments were repeated at least two times. For all statistical analysis, GraphPad Prism software (GraphPad Software, La Jolla, CA, USA) was used.

RESULTS

IL-28A has an inhibitory effect on HSV-1 induced immunopathology

To measure the effect of IL-28A on the pathogenesis of SK, mice were ocularly infected with HSV-1 and were treated daily with pegylated recombinant mouse IL-28A intraperitoneally (IP) starting one day before infection till d14pi. The SK lesions were then compared in severity with the control group in which mice were given PBS (IP). The

results showed that mice treated with IL-28A showed markedly reduced lesion severity (P<0.0001) on d14pi as compared to the control group. In addition, at d14pi, 45% eyes showed lesion scores of 3 or above in the control PBS group compared to none in the IL-28A recipient group **(Figure 1A)**. Corneal swabs were taken to measure viral titers on day 1, 2 and 4 and it was shown that IL-28A markedly reduced (2 log or more) viral titers as is seen on d1pi. to d4pi **(Figure 1B)**.

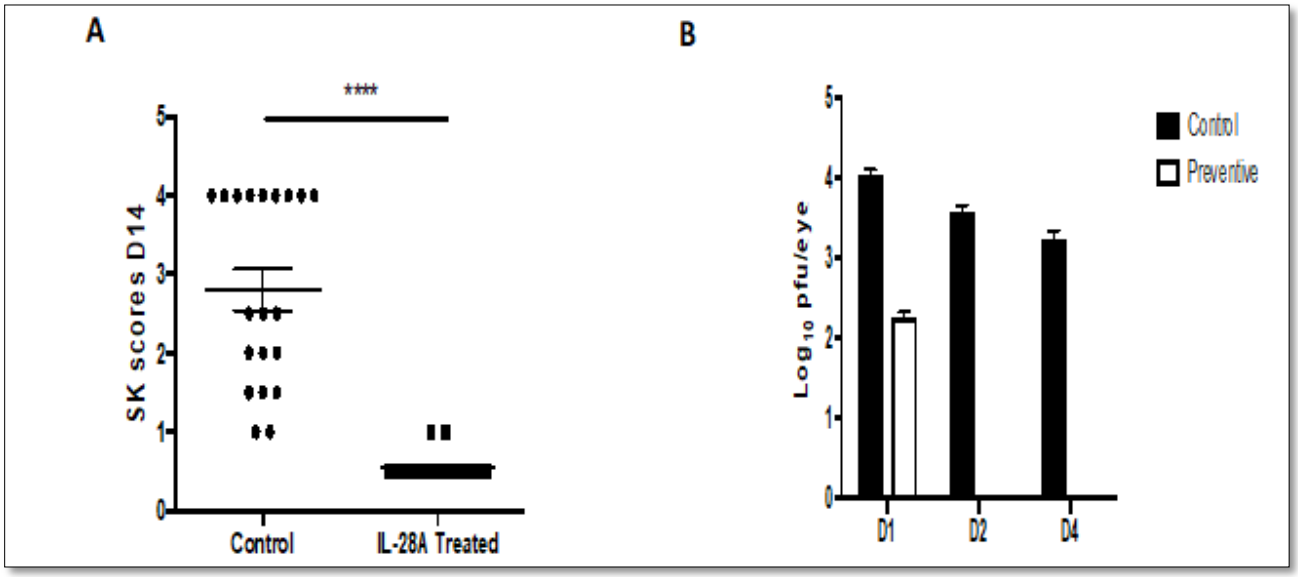

Figure 1. Prophylactic administration of IL-28A diminishes SK severity. C57BL/6 mice infected with HSV-1 (1×10^4 PFU) were I.P. treated everyday with IL-28A or PBS one day before infection to d14 pi. The disease progression was analyzed throughout time in a blinded manner. **A)** The progression of SK lesion severity was significantly reduced in a group of mice treated with IL-28A as compared with control mice given PBS. (n=10mice/group); **B)** To measure viral titers, eye swabs were taken from infected corneas from treated and control animals using sterile swabs on d1, d2 and d4 pi and titration was performed by standard plaque assay. The level of significance is determined by Student's t-test (unpaired).
**P 0.05, **P 0.01. Data represent mean ± SEM. These experiments are repeated two times. SSC: Side Scatter*

Effect of IL-28A on cellular infiltration in the cornea after HSV-1 infection

To evaluate the effects of IL-28A therapy on the extent of the inflammatory response, corneas were collected on d15pi from IL-28A treated and control animals (d-1). After collagen digestion, the corneas were processed to quantify the cellular infiltration by FACS. The results indicate that treatment with IL-28A significantly reduced the influx of neutrophils (by approx. 50 fold), CD4+T cells (by approx. 5 fold), CD45+ cells (by approx. 3 fold) and macrophages (by approx. 11 fold) as compared to control PBS group. The ratio of Treg to Th1 in corneas was also significantly increased (by approx. 1.6 fold) (**Figures 2A-2E**).

An additional evaluation was done using the DLN from the same mice. Cells isolated from individual DLN were stimulated for 4 h with PMA and ionomycin and CD4+T that were either IFN-γ producers or expressed the transcription factor Foxp3 were enumerated by FACS analysis. Our results show a reduced number of interferon gamma producing Th1 cells (3.8 fold) in the DLN of IL-28A treated animals as compared to control on d15pi. Additionally, the ratio of Treg to Th1 cells was increased after the IL-28A treatment (by 2.8 fold). In addition, reduced total numbers of CD4 T cells in DLN which were present in the DLN of the IL-28A treated group as compared controls (1.9 fold) **(Figures 3A-3C)**.

In additional studies, treatment with IL-28A caused the cessation of early neutrophil infiltration, which normally peaks at d2pi, in the cornea [2]. To measure such effects, corneas were pooled on d2 after treating the mice with IL-28A or control PBS starting d1 before infection. After collagen digestion, the corneas were processed to quantify neutrophils and macrophages by FACS. The results indicate that the treatment with IL-28A reduced the influx of neutrophils (by 5 fold) in the cornea at d2pi and macrophages by 10 fold **(Figure 3D and 3E)**.

To demonstrate the effect of IL-28A after HSV-1 infection

The effects of IL-28A were also evaluated when treatment was begun at 3 days after infection. Treatment was started at d3pi. At this time some virus is still present in the cornea and is actively replicating [14]. In such experiments treatment with IL-28A significantly (P=0.001) reduced the subsequent SK lesions when measured on d15 as compared to the control group **(Figures 4A and 4B)**.

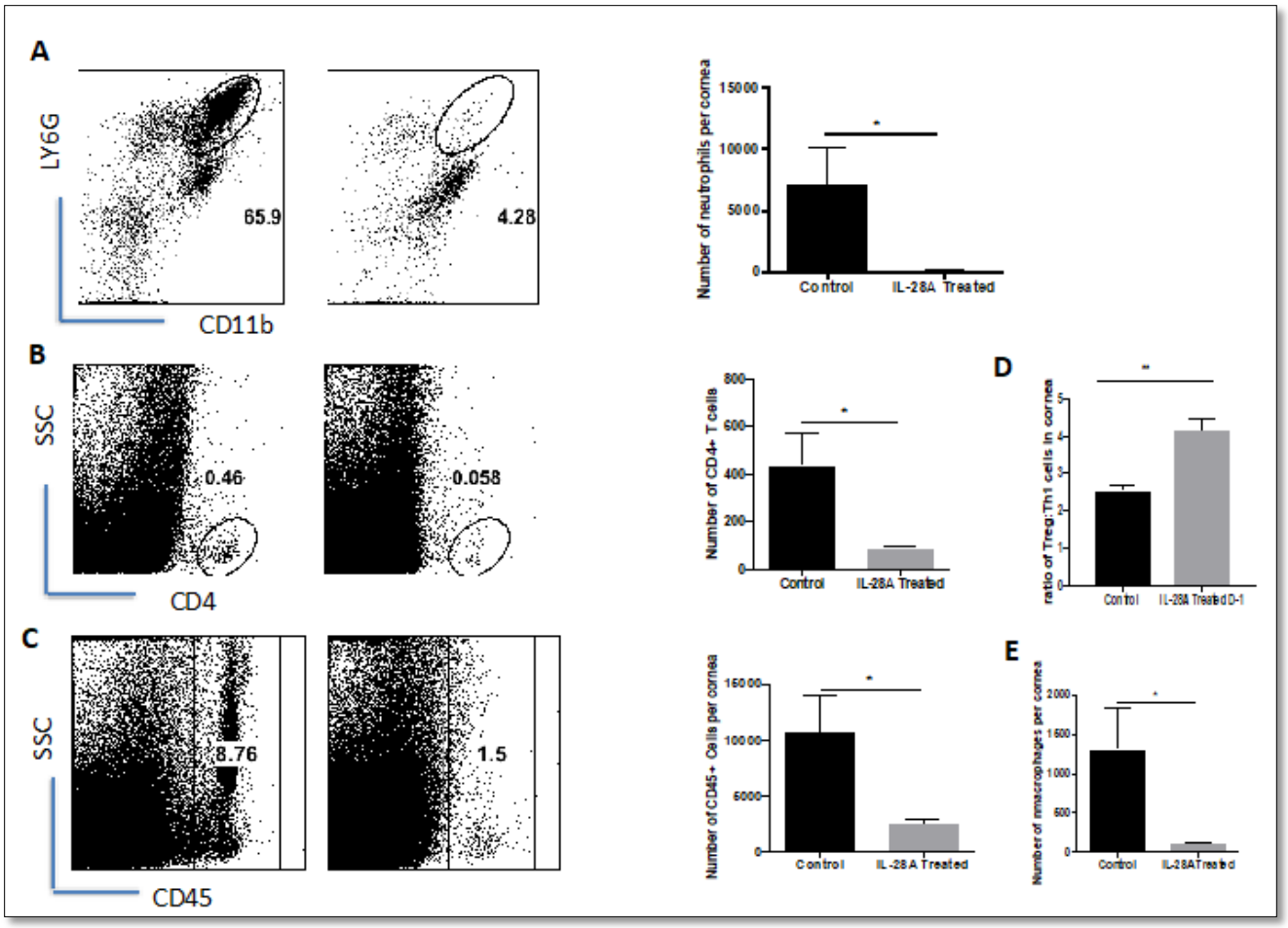

Figure 2. IL-28A treatment reduces cellular infiltration in corneas of HSV infected mice. C57BL/6 mice infected with HSV-1 (1×10^4 PFU) were I.P. treated everyday with IL-28A or PBS on day1 before infection to D14 P.I. **A**, Representative FACS plots and numbers of $CD11b^+$ $LY6G^+$ polymorphonuclear neutrophils gated on total $CD45^+$ cells infiltrated in the corneas of control and IL-28A treated mice. **B**, Representative FACS plots and numbers of $CD4^+$ T cells gated on total $CD45^+$ cells infiltrated in the corneas of control and IL-28A treated mice are shown. **C**, Total number of $CD45^+$ T cells and their representative FACS plots are shown. **D**, Histogram representing ratios of Treg to Th1 in the cornea at d15 pi. **E**, Histogram showing numbers of macrophages ($CD45^+$ $CD11b^+$ $F4/80^+$) infiltrating the cornea at d15 pi.
*Data represent mean ± SEM. All experiments are repeated three times. *P ≤ 0.05, **P ≤ 0.01*

In the control group, 50% of the eyes developed a lesion score of 3 or above as compared with the IL-28A treated group of animals in which only 16% of the eyes developed a disease score of 3 or more. SK lesion kinetics was done on d8, d12 and d14 pi and significant reduced lesion severity was measured on d14pi (P=0.001). This post infection regimen also resulted in diminished angiogenesis (P=0.001) scores when measured on d14pi **(Figures 4C and 4D)**. Ocular viral loads in the cornea on D2, D4 and D6 pi, were also observed and the results showed less virus at d4 (although not significant) with virus eradicated in the treatment group (but not controls) by d6pi **(Figure 4E)**.

Since, neutrophils and other immune cells enter the cornea after viral clearance resulting in a tissue damaging lesion, it was relevant to examine the effect of IL-28A on the later stages of the disease development. We observed that after treating the mice with IL-28A starting d3pi, the progression of SK was decreased with reduced numbers of neutrophils (approx. 50 fold) and macrophages by 2.9 fold entering in the cornea when measured on d15pi (**Figures 5A and 5B**). In addition, in the DLN the number of interferon gamma producing Th1 cells was reduced (by 2 fold) with the ratio of Treg to Th1 cells increased (by approx. 1.5 fold) **(Figures 6A and 6B)**.

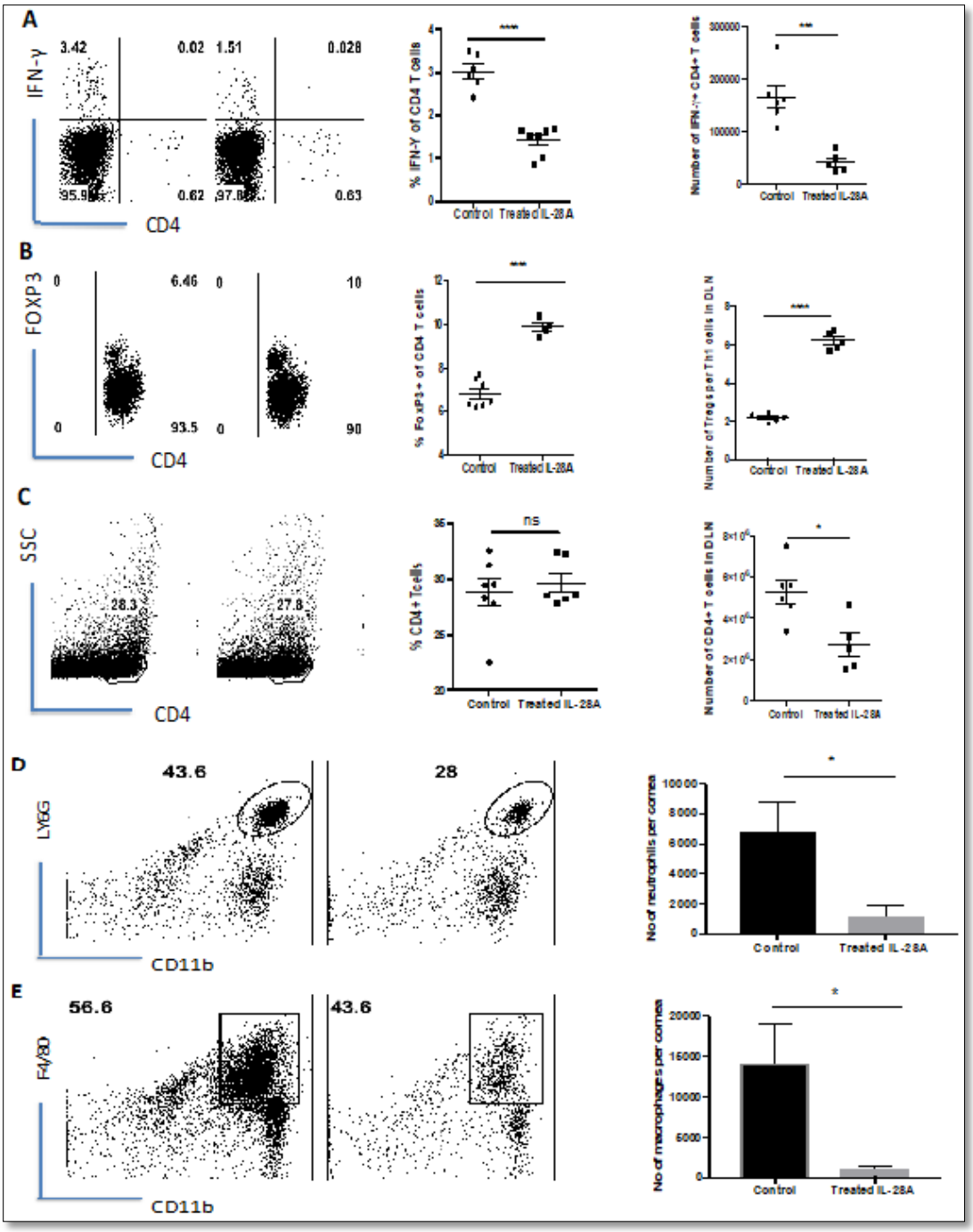

Figure 3. Effect of IL-28A treatment on Treg and effector T cells in DLN of IL-28A treated animals. C57BL/6 mice infected with HSV-1 (1×10^4 PFU) were I.P. treated everyday with IL-28A or PBS on day1 before infection to D14 P.I. **A**, It shows representative FACS plots and numbers of IFN-γ gated on total CD4 T cells. **B**, frequency and Cell numbers of $FOXP3^+$ $CD4^+$T Cells and the cell ratios for total number of Tregs per Th1 cell. **C,** Representative FACS plots and numbers of $CD4^+$ T cells in DLN in Il-28A treated animals. **D,** Representative FACS plots and numbers of $CD11b^+$ $LY6G^+$ polymorphonuclear neutrophils gated on total $CD45^+$ cells infiltrated in the corneas of control and IL-28A treated mice on D2 P.I. **E**, Representative FACS plots and numbers of $CD11b^+$ F4/80 macrophages gated on total $CD45^+$ cells infiltrated in the corneas of control and IL-28A treated mice on D2 P.I.

*The level of significance is determined by Student's t-test (unpaired). *P 0.05, **P 0.01. Data represent mean ± SEM. These experiments are repeated three times. SSC: Side Scatter*

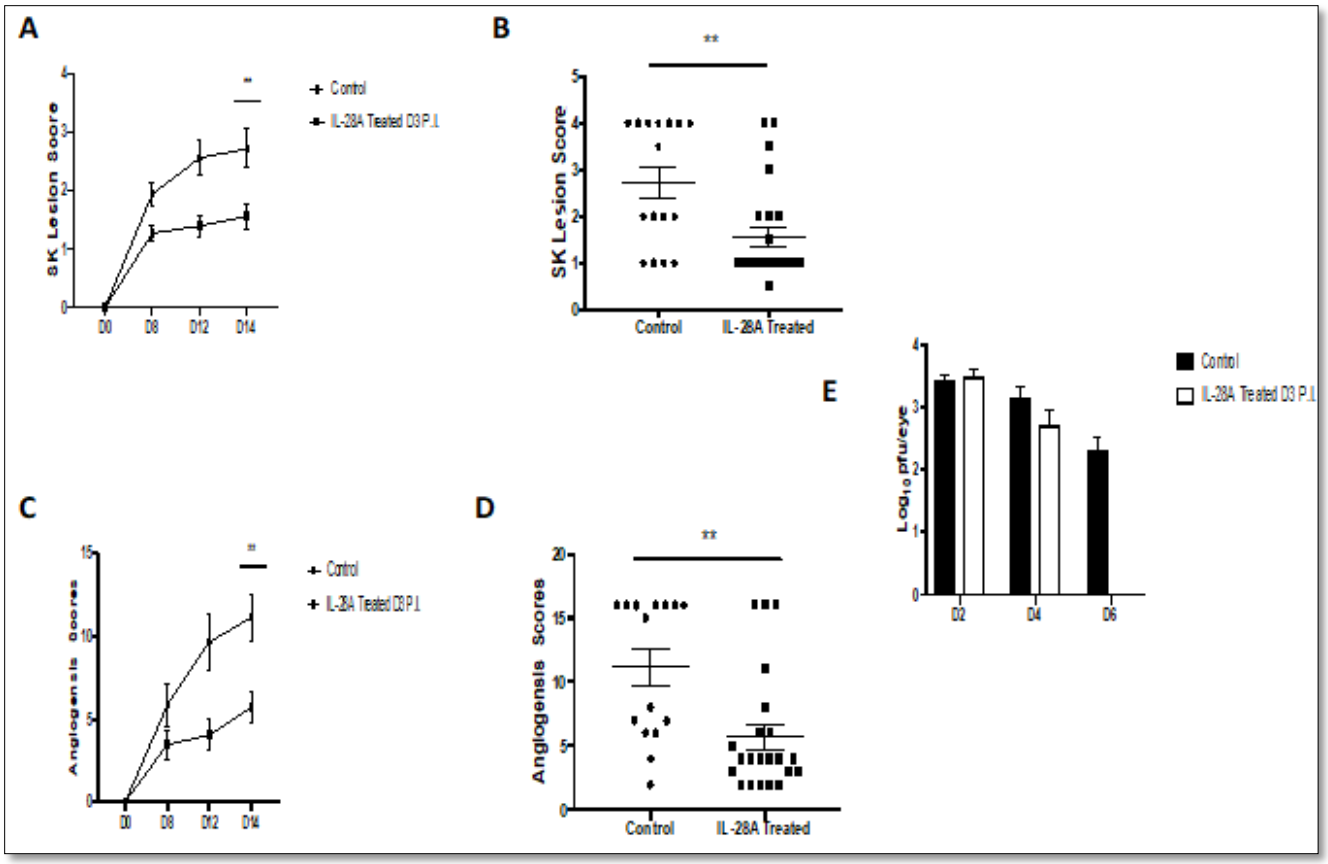

Figure 4. Therapeutic administration of IL-28A diminishes SK severity. C57BL/6 mice infected with HSV-1 (1×10^4 PFU) were I.P. treated everyday with IL-28A or PBS on day3 to D14 P.I. The disease progression was analyzed throughout time in a blinded manner (n=10 mice/group). **A**, Kinetics of SK severity is shown on D0, D8, D12 and D14 pi. **B**, The progression of SK lesion severity was significantly reduced in a group of mice treated with IL-28A as compared with control mice given PBS. **C**, Kinetics of angiogenesis was measured on D0, D8, D12 and D14 pi. **D**, The Progression of angiogenesis was significantly reduced in the group of mice treated with IL-28A as compared with control mice given PBS. **E**, To measure viral titers, eye swabs were taken from infected corneas from treated and control animals using sterile swabs on d2, d4 and d6 pi. and titration was performed by standard plaque assay.
*The level of significance is determined by Student's t-test (unpaired). *P 0.05, **P 0.01. Data represent mean ± SEM. These experiments are repeated two times. SSC: Side Scatter*

IL-28A functions through heterodimeric receptor chain

The signaling of interferon lambda occurs through its receptor, which consists of two subunits: IL28R1 (also called as IFN-λR1, IL28Rα) and IL-10R2 subunit [12]. To measure the expression of IL-28A receptor after HSV-1 infection, Q-RTPCR was used to determine mRNA levels at different times during the course of the disease progression. IL-28Rα was upregulated throughout the pathogenesis cycle. The IL-10R2 was also upregulated during the disease course and was maximally expressed at d2 and d15pi. Studies by others indicated that LTB4R recruits neutrophils [8,15]. Levels of LTB4R mRNA were quantified at several time points post infection. The results shows that LTB4R was detectable at d2 pi and was at its highest expression level at d15pi **(Figures 7A-7C)**.

Neutrophil influx and pro-inflammatory cytokines are restricted at the target site by IL-28A

Previous studies showed that IL-28A down regulates LTB4R and other neutrophil recruitment mediators and also limits the access of neutrophils to the target site [8]. To examine the effect of IL-28A, mice were infected with HSV-1 and treated with IL-28A I.P. every day. On d15 pi, corneas were pooled to measure the mRNA levels of LTB4R, MAC1, LFA1 and PSGL1. The results indicated that treatment with IL-28A reduced (by 2 fold) the levels of LTB4R and other neutrophil mediators in the treated group. In addition, the expression of other pro-inflammatory cytokines was also measured in the cornea in the treated group. The results show that mRNA levels of IL-6 and pro-IL-1β were significantly reduced in IL-28A treated group as compared to controls (by 2 to 3 fold) **(Figure 8)**.

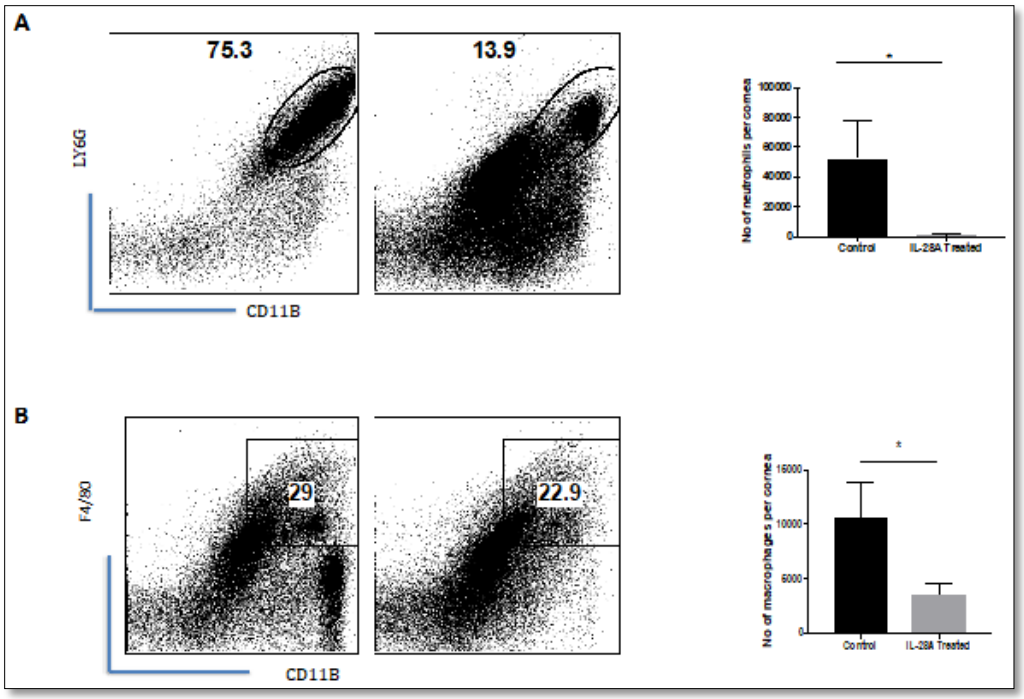

Figure 5. IL-28A treatment reduces cellular infiltration in corneas of HSV infected mice Starting D3 P.I. C57BL/6 mice infected with HSV-1 (1×10^4 PFU) were I.P. treated everyday with IL-28A or PBS on d3pi to d14pi. **A**, Representative FACS plots and reduced numbers of neutrophils in Il-28A treated animals. **B,** Representative FACS plots and reduced numbers of macrophages in IL-28A treated animals.
*The level of significance is determined by Student's t-test (unpaired). *P 0.05, **P 0.01. Data represent mean ± SEM. These experiments are repeated three times*

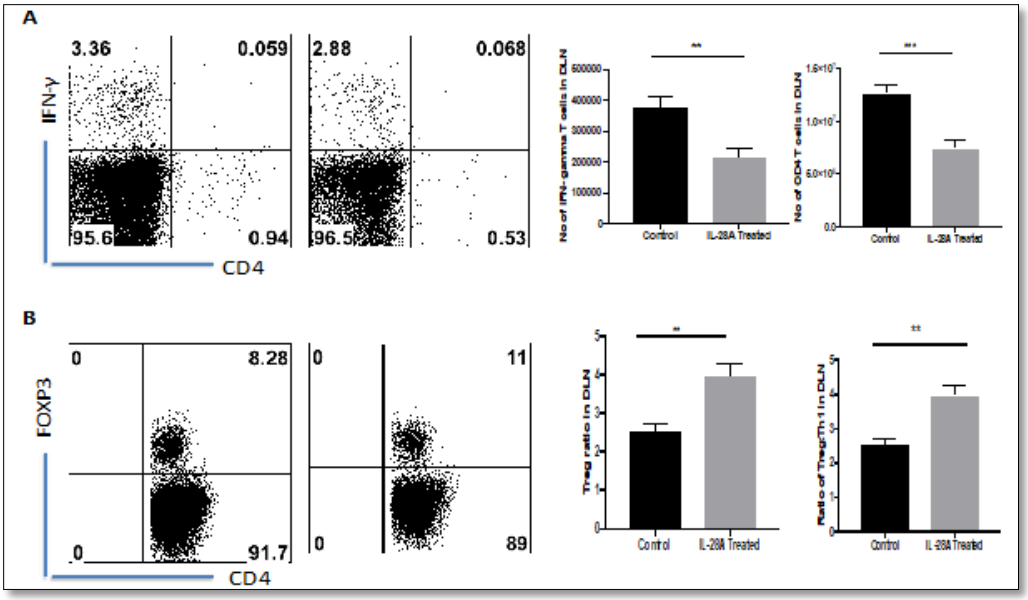

Figure 6. IL-28A treatment reduces effector T cells in DLN of IL-28A treated animals of HSV infected mice Starting D3 P.I. C57BL/6 mice infected with HSV-1 (1×10^4 PFU) were I.P. treated everyday with IL-28A or PBS on d3pi to d14pi. **A**, It shows representative FACS plots and numbers of IFN-γ gated on total $CD4^+$ T cells and total $CD4^+$ T cells. **B**, frequency and cell numbers of $FOXP3^+$ $CD4^+$T Cells and cell ratios for total number of Tregs per Th1 cell.
*The level of significance is determined by Student's t-test (unpaired). *P 0.05, **P 0.01. Data represent mean ± SEM. These experiments are repeated three times*

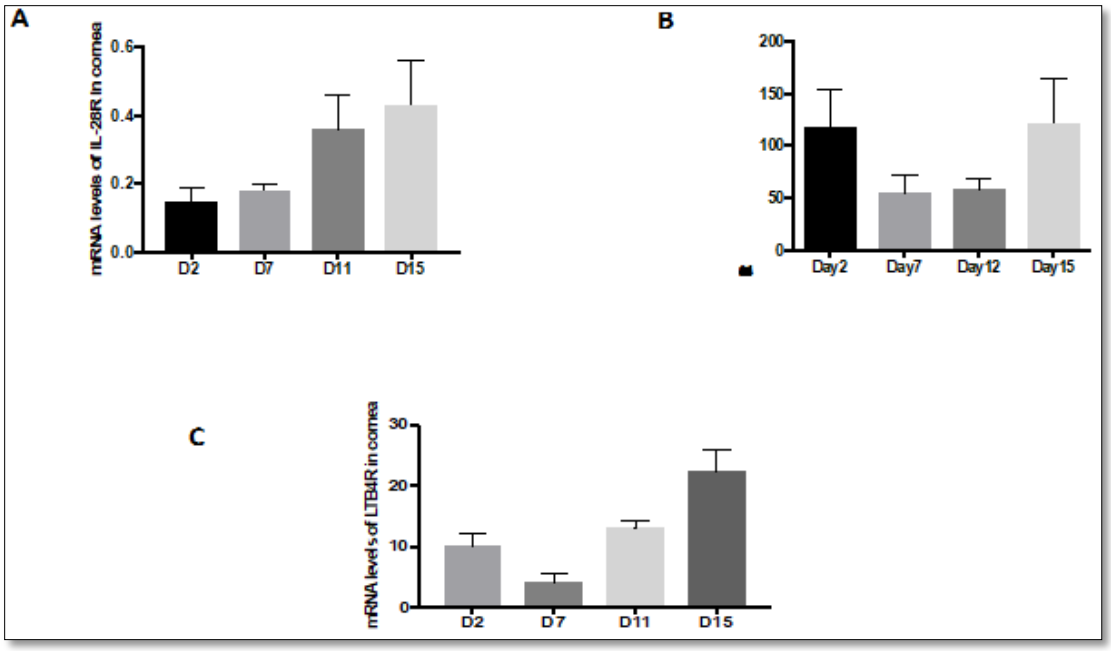

Figure 7. Interferon lambda constitutes two chains: C57BL/6 mice infected with HSV-1 (1×10^4 PFU). **A**, Corneas were collected on D2, 7,11 and 15 and were processed and total RNA was extracted using MiRNA isolation kit and then q-RT-PCR was performed on the isolated RNA to measure the levels of IL-28R expression. **B,** q-RT-PCR was performed on the isolated RNA to measure the levels of IL-10βR expression. **C,** mRNA levels of LTB4R in cornea is shown on D2, D7, D11 and D15 pi.

*The level of significance is determined by Student's t-test (unpaired). *P 0.05, **P 0.01. Data represent mean ± SEM. These experiments are repeated three times*

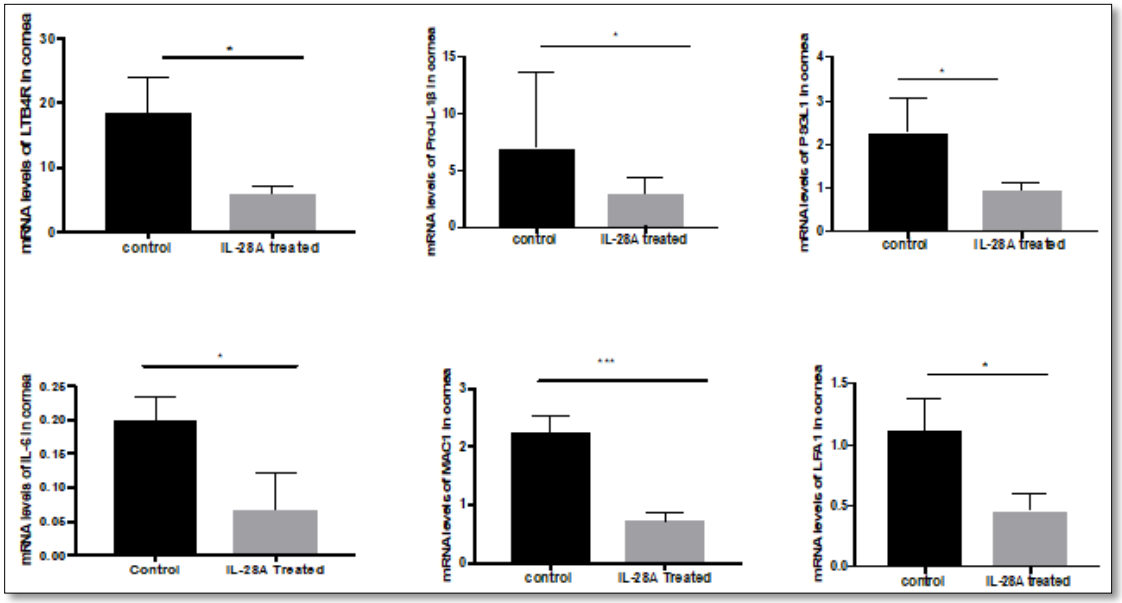

Figure 8. Interferon lambda downregulates neutrophil recruitment mediators and also pro-inflammatory cytokine levels: C57BL/6 mice infected with HSV-1 (1×10^4 PFU) and were treated with IL-28A. Corneas were collected on D2, 7 and 15 and were processed and total RNA was extracted using MiRNA isolation kit and then QRT-PCR was performed on the isolated RNA to measure the levels of LTB4R expression and other neutrophil recruitment mediators and pro-inflammatory cytokine levels were compared to the control group. The level of significance is determined by Student's t-test (unpaired).

**P 0.05, **P 0.01. Data represent mean ± SEM. These experiments are repeated three times*

DISCUSSION

Ocular infection with HSV-1 involves pathogenic events initiated by two main factors and these result in a chronic immunoinflammatory lesion in the cornea. The first event involves replication of virus in corneal epithelial cells, which is followed by inflammation in the corneal stroma that is composed of pathogenic T cells and non-lymphoid inflammatory cells [2,16]. The consequence is damage of the cornea which can result in human blindness [16]. This report evaluates the effect of type III interferon (IL-28A) treatment, an approach expected to target both viral replication and the inflammatory response. It was shown that when therapy was started before infection, virus replication was markedly inhibited and the resultant SK lesion expression strikingly diminished. In addition, delaying therapy until 3 days after infection, a time before lesions appeared also resulted in significantly reduced SK lesions. However, treatment begun when lesions were fully developed had no beneficial effects. The anti-inflammatory effects of IL-28A appeared to be directed at several cell types but neutrophil infiltration appeared to be the most affected. This outcome was likely explained by reduced expression of molecules such as LTB4R, MAC-1 and PSGL1 involved in neutrophil recruitment [8]. However, the post infection treatment also led to reduced T cells and macrophages as compared to untreated controls.

Stromal Keratitis is a problem lesion in humans and it often leads to blindness [2,16]. Its current management usually involves a combination of antivirals and corticosteroids but this is less than ideal since long term therapy with steroids can result in many side effects [17,18]. Alternative approaches are needed and our results would indicate that IL-28A might merit a trial if therapy could be begun in the early stages of the syndrome. Thus, at least in the mouse model system, therapy was both antiviral and anti-inflammatory. The latter effect was of particular relevance since damage to the cornea and its function of allowing light to pass through it to the retina unimpeded, is mainly the consequence of an inflammatory reaction orchestrated by T cells, but mainly caused by non-lymphoid inflammatory cells such as neutrophils and macrophages [2]. The anti-inflammatory activity of IL-28A, as reported in several studies, may act mainly on neutrophil function and to prevent cell infiltration to inflammatory sites [8]. Moreover, interferon lambda itself is less inflammatory as compared with type I interferons [19]. Some studies using IL-28A on autoimmune lesions showed that the anti-inflammatory effects were directed primarily at neutrophils and acts by reducing the generation of reactive oxygen species (ROS) by neutrophils [20]. We did not measure such effects in our system but could show that IL-28A therapy did inhibit the expression of molecules such as LTB4R, MAC-1 and PSGL1 involved in non-lymphoid inflammatory cell recruitment, particularly neutrophils.

Some reports that have evaluated the effects of interferon lambda on the outcome of a virus infection came to conclusions that differ from our own report. Thus, one study on the outcome of influenza infection in mice advocated that IL-29 (Interferon lambda type 1) was beneficial since it enhanced CD4 Th1 responses which acted to control infection [21,22]. We observed that administering type 2 interferon lambda (IL-28A) had an opposite effect in the case of a CD4 Th1 cell orchestrated inflammatory reaction to HSV-1. However, whereas we did observe inhibitory effects on Th1 cells there was less inhibition on CD4 regulatory T cells (Treg). This resulted in a change in the ratio of Treg: Th1 which might help to explain the beneficial effects of the IL-28A therapy. Thus, changing the balance of T cell functional types to favor Treg is a therapeutic aim for several autoimmune lesions as well as viral induced immunopathologies [23].

Whereas, we could show that IL-28A therapy was a useful approach to limit the severity of SK, there remains a major caveat. Thus, to achieve beneficial effects the treatment is required at a very early stage during the syndrome. In our mouse studies treatment at 6 days after infection or beyond had little or no effect on lesion severity (data not shown). Thus, once lesions are fully expressed, IL-28A would not be expected to be of any help. However, people who do suffer herpes recurrences often have pre-clinical signs before any lesion become clinically evident [24]. Conceivably, treatment with interferon type III (IL-28A) might be logical to use starting at the preclinical stage and to complement such therapy with additional approaches such as non-steroidal anti-inflammatory drugs or drugs derived from polyunsaturated fatty acids such as resolvins which we ourselves are pursuing [25].

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