Title: Type I interferon regulates IgE-mediated enhancement of rhinovirus-induced Th2 priming by primary human monocytes

Running title: Type I IFN regulates IgE-induced RV-driven Th2 priming

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Abbreviations:

APC- antigen presenting cell

αIgE- Rabbit anti-human IgE antibody

FcεRI- high-affinity IgE receptor

IFN- interferon

IgG- Rabbit whole IgG antibody

IL- interleukin

PBMCs- peripheral blood mononuclear cells

pDC – plasmacytoid dendritic cells

rh- recombinant human

RV- Rhinovirus

Th- CD4 helper T cell

TLR- toll-like receptor

TNF- tumor-necrosis factor

Abstract:

Rhinovirus infections are linked to the development and exacerbation of allergic diseases including allergic asthma. IgE, another contributor to atopic disease pathogenesis, has been shown to regulate dendritic cell antiviral functions and influence T cell priming by monocytes. We previously demonstrated that IgE-mediated stimulation of monocytes alters multiple cellular functions including cytokine secretion, phagocytosis, and influenza-induced Th1 priming. In this study, we investigate the effects of IgE-mediated allergic stimulation on monocyte-driven, RV-induced T cell priming utilizing primary human monocyte-T cell co-cultures. We demonstrate that IgE crosslinking of RV-exposed monocytes enhances monocyte-driven Th2 priming while inhibiting Th1 differentiation. This increase in RV-induced Th2 differentiation was regulated by IgE-mediated induction of IL-10 and inhibition of type I interferon. These findings suggest an additional mechanism by which two clinically significant risk factors for allergic disease exacerbations – IgE-mediated stimulation and rhinovirus infection, may synergistically promote Th2 differentiation and allergic inflammation.

Introduction:

The link between viruses and allergic diseases has long been appreciated, and is best represented by the coinciding increase in allergic asthma exacerbations with peaks in fall respiratory virus epidemics (1). Rhinoviruses (RV) are closely associated with allergic disease, representing the most frequently detected viruses in children with asthma exacerbations (1, 2). Early RV infection in allergic children also increases the risk of asthma development by 8-fold (3). The degree of atopy is similarly linked to disease severity; for example, serum allergen-specific IgE levels in allergic asthmatics directly correlate with virus-induced exacerbation severity (4). Clinically, decreasing serum IgE with omalizumab therapy reduces atopic disease exacerbations (5-7). In a recent study, children with allergic asthma treated with omalizumab had decreased RV-induced upper respiratory symptoms, shortened duration of virus shedding, and decreased peak virus titers (8), suggesting that IgE-mediated processes modulate RV infection *in vivo*.

Monocytes, antigen presenting cells (APCs) recruited to tissues during virus-induced allergic exacerbations (9), are modulated by the allergic environment (10-13). Several studies indicate roles for monocytes and monocyte-derived cells in RV-induced allergic disease pathogenesis. In asthmatic subjects, experimental RV-infection induced recruitment of monocytes and macrophages to the airways, which correlated with virus load, symptom scores and airway reactivity (9). Our group has shown that IgE crosslinking induces monocyte secretion of regulatory and pro-inflammatory cytokines, including IL-10, IL-6, and TNFα (11). IL-10 has been specifically linked to allergic disease pathogenesis and virus-induced wheezing (14-16), although its role in IgE-mediated monocyte antiviral responses remains unexplored. We recently demonstrated that critical monocyte antiviral functions, including influenza-induced upregulation

of antigen-presenting molecules and CD4 Th1 T cell priming are inhibited by IgE crosslinking (10). IgE-mediated regulation of monocyte functions during RV infection may thus play a role in promoting allergic inflammation.

Th2-mediated responses, a hallmark of allergic disease, are implicated in RV-induced inflammation. Enhanced Th2 inflammatory responses correlate with increased disease severity in allergic asthmatics experimentally infected with RV(17). While multiple cell types and mediators are likely involved, many studies support a role for both APCs and IgE in promoting Th2 responses. In cat allergic subjects, omalizumab treatment decreased *ex vivo* allergen-induced pDC-driven Th2 stimulation (18); similarly, monocyte-derived DCs from allergen-exposed atopic subjects induced CD4 T cell Th2 cytokine responses (19). These studies suggest that IgE-mediated APC stimulation may regulate Th2 priming during RV-induced allergic inflammation, although the mechanisms underlying this phenomenon remain undefined.

Type I interferons (IFN) are critical mediators of virus infection and also negatively regulate human Th2 development and effector functions *in vitro* (20, 21). IgE-mediated inhibition of APC antiviral IFN responses is one proposed mechanism involved in RV-induced allergic exacerbations (5, 22). IgE crosslinking inhibits influenza- and RV-induced IFN secretion from plasmacytoid dendritic cells (pDCs) and PBMCs (22-24), and omalizumab treatment in children with allergic asthma has recently been shown to restore these *ex vivo* antiviral IFN responses (22). Furthermore, the group with the greatest post-omalizumab increases in IFN had fewer asthma exacerbations (5), suggesting that virus-induced type I IFN plays an important role in regulating allergic inflammation *in vivo*.

While IgE-mediated effects likely contribute to virus-induced allergic disease, how IgE regulates antiviral responses to RV and promotes Th2-mediated allergic inflammation is unknown. Given the critical role of monocytes and monocyte-derived cells in antigen presentation and T cell differentiation, we investigated the impact of IgE-mediated stimulation on RV-induced monocyte-driven T cell differentiation. We show that IgE-driven effects on monocyte functions, including IL-10 production and inhibition of virus-induced IFN, enhance RV-induced Th2 development. These data provide evidence that IgE-mediated alteration of monocyte antiviral functions during RV infection may promote Th2-mediated inflammation to enhance allergic inflammation.

Results:

IgE-mediated allergic stimulation enhances RV-induced monocyte-driven CD4 Th2 cell development

We previously established a model of monocyte-driven T cell development to evaluate the effects of IgE-mediated allergic stimulation on monocyte-driven T cell priming (10). Using this system, we determined the impact of IgE-mediated stimulation on RV-induced naïve CD4 T cell priming by primary human monocytes (Figure 1 and Supplemental Figure 1). RV-exposure induced a small but significant increase in monocyte-driven Th2 differentiation (Fig. 1A). Notably, IgE crosslinking of monocytes significantly enhanced RV-driven Th2 priming (Fig. 1A) which positively correlated with baseline surface expression of the high affinity IgE receptor on monocytes (FcεRIα, Fig 1B). Similar to previous findings with influenza (10), the strong Th1 response induced by RV-exposed monocytes was inhibited by IgE crosslinking (Fig. 1C),

significantly altering the Th1/Th2 ratio (Fig. 1D). These data suggest that IgE-mediated allergic stimulation of human monocytes enhances RV-induced Th2 differentiation, shifts the Th1/Th2 balance towards allergic inflammation, and is related to monocyte FcεRIα expression.

IgE-induced IL-10 regulates RV-induced Th2 development

To investigate potential mechanisms underlying IgE-induced RV-driven Th2 development, we evaluated the role of monocyte-secreted cytokines. IgE-mediated stimulation of monocytes results in the production of IL-10 (11, 13), a cytokine known to regulate pro-inflammatory processes, including T cell development (25-27). Monocytes secreted IL-10 in response to IgE crosslinking, which was not altered by RV-exposure (Figure 2A). Blocking IL-10 reversed IgE-induced enhancement of RV-driven Th2 differentiation (Fig. 2B), without affecting Th1 differentiation (Fig. 2C). As expected, exogenous addition of IL-10 was not sufficient alone to enhance RV-induced monocyte-driven Th2 development (Fig. 2D), consistent with previous findings that IL-10 requires additional factors to influence Th2 development in naïve CD4 T cells (26, 27). These results indicate that additional IgE-mediated effects on monocytes combined with increased IL-10 secretion are required to enhance RV-induced Th2 development.

Type I interferon (IFN) negatively regulates RV-induced Th2 development

We next investigated the effects of IgE crosslinking on RV-induced IFN, a negative regulator of Th2 development. IgE crosslinking significantly impaired RV-induced monocyte secretion of IFNα 24h post virus exposure (Figure 3A). Exogenous IL-10 similarly inhibited RV-induced IFNα secretion (Fig. 3B). Blocking IL-10 in monocyte-T cell co-cultures partially

reversed IgE-mediated inhibition of IFNα (Fig. 3C), indicating that IL-10 contributes to the negative regulation of RV-induced IFN production in primary monocytes.

Because IFN can inhibit Th2 development in naïve human CD4 T cells *ex vivo* (21), IgE-mediated reduction of RV-IFN may enhance monocyte-driven Th2 priming. Exogenous IFNα reduced baseline monocyte-driven Th2 differentiation (Supplemental Figure 2A), and conversely enhanced Th1 priming (Supp Fig. 2B) of allogeneic naïve CD4 T cells. Addition of IFNα also decreased baseline RV-driven Th2 priming (Figure 4A), while blocking the type I IFN receptor (αIFNAR) significantly increased RV-induced monocyte-driven Th2 priming (Fig. 4B). Finally, addition of IFNα reversed IgE-mediated enhancement of RV-induced Th2 priming (Fig. 4C), indicating that IgE-mediated inhibition of RV-induced IFN is likely regulating monocyte-driven Th2 development.

Discussion:

Our study shows that IgE-mediated allergic stimulation of monocytes enhances RV-induced Th2 priming of naïve CD4 T cells, which is regulated by IgE-induced IL-10 production and inhibition of virus-induced IFN. In our proposed model (Figure 5), the combination of IgE-mediated allergic stimulation and RV infection leads to enhanced Th2 differentiation via IgE-induced effects on monocytes. IgE-induced IL-10 production inhibits monocyte type I IFN responses to RV infection. This reduction in IFN, combined with other IgE-induced factors such as altered expression of co-stimulatory molecules or cytokines, allows for increased Th2 differentiation due to the loss of negative regulation on Th2 cell development.

Although the impact of clinical allergic disease status was not evaluated in our study, we did measure monocyte FcεRIα expression which positively correlates with serum IgE levels and is an established surrogate marker for atopy (28). Our finding that monocyte FcεRIα expression correlates with IgE-enhanced RV-driven Th2 differentiation suggests that atopic status may influence IgE-induced Th2 priming *in vivo*, and highlights the relevance of this work to allergic disease. Monocytes recruited to the airway epithelium, the site of both RV infection and aeroallergen exposure, likely encounter allergen-induced IgE crosslinking and virus exposure simultaneously. IgE-mediated local monocyte IL-10 production and inhibition of type I IFN via feedback mechanisms on monocytes and paracrine effects on airway epithelial cells and other APCs could significantly impact local inflammatory responses, potentially enhancing virus replication, virus-induced tissue destruction, and virus-induced Th2 inflammation.

The role for IL-10 in allergic disease is complex; it has been shown to play a role in allergic diseases (15, 16) and virus-induced wheezing (14). IL-10 effector functions on innate immune cells and T regulatory (Treg) cells (29) are required for allergen tolerance and could suppress both viral and allergic inflammation *in vivo*. IL-10 can also suppress monocyte differentiation, expression of antigen presenting molecules, and monocyte-driven Th1 cell stimulation (13, 27, 30). While IL-10 can inhibit virus-induced type I IFN responses in human PBMCs (31), our results suggest a previously undescribed role for IL-10 in the inhibition of virus-induced IFN responses to promote Th2 inflammation. Consistent with this, atopic individuals have been shown to have elevated serum IL-10 (32) and increased IL-10 producing monocytes which promoted Th2 cytokine production in T cells *ex vivo* (15). In our system, IL-10 alone was not sufficient to enhance RV-driven Th2 development, consistent with previous reports that additional factors such as antigen presentation, co-stimulation, or other cytokines

such as IL-4, are required in combination with IL-10 to modulate APC-driven T cell differentiation (25, 26). Additional IgE-induced factors in our experiments could include IL-6 production, which stimulates IL-4 production in naïve CD4 T cells (33), or modulation of monocyte co-stimulatory molecules that enhance Th2 priming such as OX40 ligand (34) and CD80 (25). Monocyte expression of these molecules combined with IL-10-induced effects and loss of antiviral IFN could represent additional regulators of IgE-mediated Th2 development. Further studies are needed to fully elucidate the complex interaction between IgE-mediated signals and RV-induced monocyte-driven T cell development.

Enhancement of antiviral IFN responses has a potential therapeutic role in allergic disease, representing an area of intense clinical interest. In a clinical trial of inhaled IFNβ to prevent virus-induced asthma exacerbations, IFNβ treatment enhanced antiviral gene transcription in sputum cells and in sub-analysis of subjects with severe disease, decreased asthma symptom scores and promoted faster recovery of morning peak expiratory flow(35). In a murine model of RV-induced allergic airway disease, IFNα treatment blocked allergic inflammation induced by exposure to house-dust mite and RV infection in a TLR-7 deficient mouse (36). In our system, complementation of the IgE-induced IFN deficit by exogenous IFNα treatment fully reversed IgE-enhanced RV-driven Th2 priming by monocytes, supporting its critical role in regulating allergic inflammation and potential value as a therapeutic target in atopic diseases.

To our knowledge, this is the first report that IgE-mediated activation promotes RV-induced Th2 priming by human monocytes and that impaired IFN responses, reported in multiple *in vivo* and *ex vivo* studies of allergic disease pathogenesis, may contribute to Th2-mediated inflammation. Finally, we demonstrate that IFNα can reverse IgE-mediated induction of antiviral

Th2 differentiation in human cells. Given the close link between viruses and atopy in promoting allergic disease, and the critical role of monocytes in airway immune responses, this study provides another potential mechanism by which IgE-mediated allergic sensitization synergizes with RV infection to drive allergic inflammation. Further elucidation of molecular mechanisms underlying this process could uncover potential therapeutic targets for improved treatment and prevention of viral exacerbations of allergic diseases.

Methods:

Human Subjects

Samples were acquired from 2 sources: leukocyte-enriched blood samples from unknown donors through a local blood bank and blood samples from healthy volunteers. Unknown donors were deemed healthy enough for routine blood donation by the local blood bank. Studies were approved by the UT Southwestern institutional review board (Study # STU 122010-139). For known volunteers, written informed consent and assent were obtained.

Reagents and Media

Phosphate Buffered Saline (PBS) with fetal bovine serum (FBS) and EDTA (complete PBS, cPBS) and complete Roswell Park Memorial Institute Medium 1640 (cRPMI) were prepared as previously described (11). Rabbit anti-human IgE (αIgE) was purchased from Bethyl Laboratories (Montgomery, TX) and rabbit whole IgG control antibody (IgG) from Jackson ImmunoResearch (Westgrove, PA). Unless specified, recombinant human (rh) cytokines, anti-human cytokine and receptor antibodies were purchased from R&D Systems (Minneapolis, MN).

Purification of Immune Cells from Blood

Monocytes and naïve $CD4^+$ T cells were purified as previously described (10, 11). Purity was assessed by flow cytometry; monocytes were identified as CD14+ and naïve $CD4^+$ T cells as CD3+CD4+CD45RA+. Samples with <85% purity were excluded.

Monocyte Culture Conditions

Monocytes were cultured in cRPMI with recombinant human (rh) M-CSF (1 ng/ml) at a concentration of 1×10^6 cells/ml. αIgE (10 μg/ml), rabbit IgG isotype control (10 μg/ml), or IL-

10 (10 ng/ml), anti-IL-10 and anti-IL-10 receptor (IL10Ra) (5μg/mL each), or mouse IgG isotype controls were added to monocyte cultures at the start of culture. Purified Rhinovirus A serotype 16 (RV) (kindly provided by Jim Gern and Yury Bochkov, U Wisconsin) was added at a multiplicity of infection (MOI) 10. Cultures were incubated at 37°C for indicated times. Cells and supernatants were harvested for analysis or for T cell co-culture experiments.

Monocyte-T Cell Co-Culture

Monocytes were cultured as above in the presence or absence of αIgE, control IgG, or RV at 37°C for 18-24 hours and then mixed 1:1 with allogeneic naïve $CD4^+$ T cells. Cells were cultured in media containing 50 Units/mL recombinant human IL-2. For select experiments, mouse anti-human antibodies against IL-10, IL-10Rα, or IFNAR and IgG1 or IgG2b isotype controls were added at 5-10μg/mL each for a total mouse IgG concentration of 10 μg/ml prior to co-culture with T cells. As indicated, recombinant human (rh) IFNα (1000-10,000 IU/mL) was added at the initiation of co-culture. After 3 days of co-culture, T cells were cultured for an additional 3-4 days, rested and restimulated for flow cytometry analysis as previously described (10).

Flow Cytometry Analysis of Surface Antigens

The following fluorochrome-conjugated anti-human antibodies or molecules were used: CD3-peridinin chlorophyll protein complex (PerCP), CD4-allophycocyanin (APC), CD14-V450, CD45RA-phycoethrin (PE), FcεRIα-fluorescein (FITC), HLA-DR-APC-Cy7, and HLA-DR-FITC (BD Pharmingen, San Diego, CA). Staining and flow cytometry were performed as previously described (11). Samples were acquired on a BD LSR II flow cytometer (BD Biosciences) and analyzed with the FlowJo 8 software (FLOWJO, LLC, Ashland, OR).

Flow Cytometry Analysis of Intracellular Cytokines

The following antibodies were used: IFNγ-PE-Cy7 and IL-4-PE (BD Biosciences, San Jose, CA). Cells were fixed in 2% paraformaldehyde and permeablized with 0.1% saponin in PBS to detect intracellular antigens. Samples were acquired and analyzed as above described. Gating of cytokine-expressing cells was guided by staining negative control (unstimulated cells) and positive control T cells differentiated under Th1- or Th2-inducing conditions (21). Percentages of total cytokine-positive populations were then determined. Th2 cells were identified as IL-4 single positive; Th1 cells were identified as the total IFNγ population (Supplemental Figure 1).

Cytokine Secretion Analysis

Supernatants were stored at -80°C until use. The following ELISA kits were used according to manufacturer recommendations: ELISA Max human ELISA for IL-10 (Biolegend, San Diego, CA), anti-pan human IFN alpha (Interferon Source, Cincinnati, OH). Absorbance was measured on a Biorad iMark microplate reader (Biorad, Hercules, CA) per manufacturer's instructions.

Data Analysis and Statistics

Data are presented as means ± standard error of the mean (SEM) or standard deviation (SD). In experiments containing 3 or more conditions, one-way or two-way (for experiments with multiple donors) repeated measures ANOVA and pairwise Tukey's post hoc comparisons were performed. For experiments comparing 2 conditions, paired t tests were performed with Holm-Sidak correction where appropriate. $p<0.05$ was considered significant, pertinent p values are noted in figures; significant as <0.05, <0.01, and <0.001, or >0.05 for non-significant (ns) values. All statistical analyses were performed using GraphPad Prism version 8.

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Figure Legends:

Figure 1. IgE crosslinking enhances RV-induced monocyte driven Th2 differentiation. Primary human monocytes were exposed to RV in the presence or absence of IgE crosslinking (αIgE) or isotype control (IgG) antibodies. Monocytes were co-cultured with allogeneic naïve CD4 T cells to evaluate monocyte-induced Th2 (A & B) or Th1 (C) differentiation. (A & C) Box and whisker plots of 95% confidence interval, mean, and min and max distribution. (B) Linear regression analysis demonstrating a positive correlation between monocyte surface FcεR1α expression and IgE crosslinking and RV-driven induced Th2 differentiation. Pearson correlation coefficient and two-tailed p value were determined, n=9 experiments. (D) Th1/Th2 ratio was calculated. Mean with standard error is shown. p values obtained by two-way ANOVA with post-hoc comparison (A, C, & D) for n=16 experiments.

Supplemental Figure 1. IgE crosslinking enhances RV-induced monocyte driven Th2 differentiation. Flow cytometry plots of a representative experiment from Figure 1 are shown. Primary human monocytes were exposed to RV in the presence or absence of IgE crosslinking (αIgE) or isotype control (IgG) antibody. Monocytes were co-cultured with allogeneic naïve CD4 T cells to evaluate monocyte-induced T cell development. Cells were gated based on cytokine expression as a % of total cells in the live, single cell gate. Th2 cells were identified as IL-4 single positive while Th1 cells were identified as the total IFNγ positive population.

Figure 2. IgE-induced IL-10 is required for IgE-mediated enhancement of RV-driven Th2 priming. (A) Primary human monocytes were exposed to mock or RV conditions in the presence or absence of IgE crosslinking antibody, and supernatants harvested for IL-10 ELISA analysis at

24 hours. (B & C) RV-exposed monocytes +/- IgE crosslinking were co-cultured with naïve CD4 T cells in the presence of IL-10 and IL-10 receptor blocking or isotype control antibodies and T cells evaluated for (B) Th2 or (C) Th1 differentiation; mean of 4 experiments with standard error shown, p values by two-way ANOVA with post-hoc analysis, $p>0.05$ was considered non-significant (ns). (D) Mock or RV-exposed monocytes were treated with IL-10 (10ng/mL), co-cultured with allogeneic CD4 T cells and evaluated for Th2 differentiation. Representative of n=3 experiments is shown.

Figure 3. IgE-mediated allergic stimulation and IL-10 negatively regulate RV-induced type I interferon. (A) Primary human monocytes were either mock or RV exposed in the presence or absence of (A) IgE crosslinking antibody or (B) 10ng/mL human IL-10, and supernatants evaluated for IFNα at 24 hours. (C) IFNα in monocyte-T cell co-culture supernatants at day 3 after culture in the presence or absence of IL-10 blocking antibodies. Representative of n=3 experiments shown, p values by one-way ANOVA and post-hoc analysis, $p>0.05$ was considered non-significant (ns).

Supplemental Figure 2. Type I interferon regulates monocyte-driven T cell development in monocyte-T cell co-cultures. Primary human monocytes were co-cultured with allogeneic naïve CD4 T cells +/- 1000IU/mL IFNα. T cells were then evaluated for expression of either (A) Th2 or (B) Th1 differentiation. Mean with standard error are shown, p values by two-way ANOVA with post-hoc analysis, n=3 experiments.

Figure 4. Type I interferon reverses IgE-mediated enhancement of RV-induced Th2

priming by primary monocytes. Primary human monocytes were exposed to RV in the presence or absence of IgE crosslinking (αIgE) or isotype control (IgG) antibody, co-cultured with allogeneic naïve CD4 T cells, and Th2 priming was measured on day 7. At the time of co-culture either (A & C) IFNα (10,000 IU/mL) or (B) anti-human IFNAR or isotype control antibodies (10μg/mL) were added. Mean with standard error are shown, p values by two-way ANOVA with post-hoc analysis, n=3 experiments.

Figure 5. Model of IgE-mediated enhancement of RV-induced monocyte-driven Th2 development. IgE-mediated allergic stimulation combined with RV exposure promotes Th2 priming by monocytes. IgE-induced effects including IL-10 production inhibit RV-driven type I IFN production by monocytes. The reduction of type I IFN-mediated negative regulation of Th2 development combined with other unknown Th2-promoting factors, such as co-stimulatory receptors or cytokines, drive increased Th2 development. This altered antiviral response may contribute to enhanced allergic inflammation.

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Figure 1

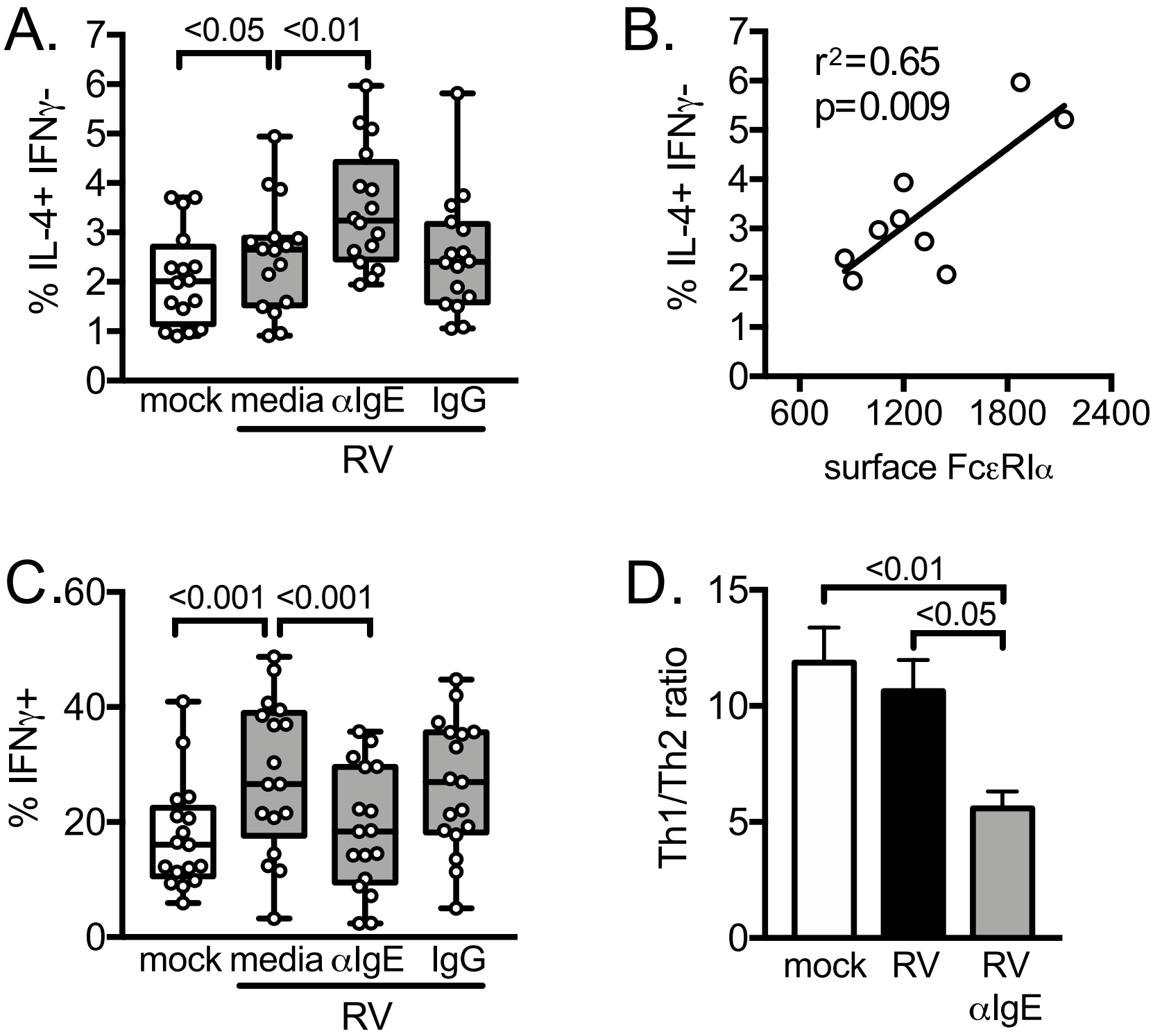
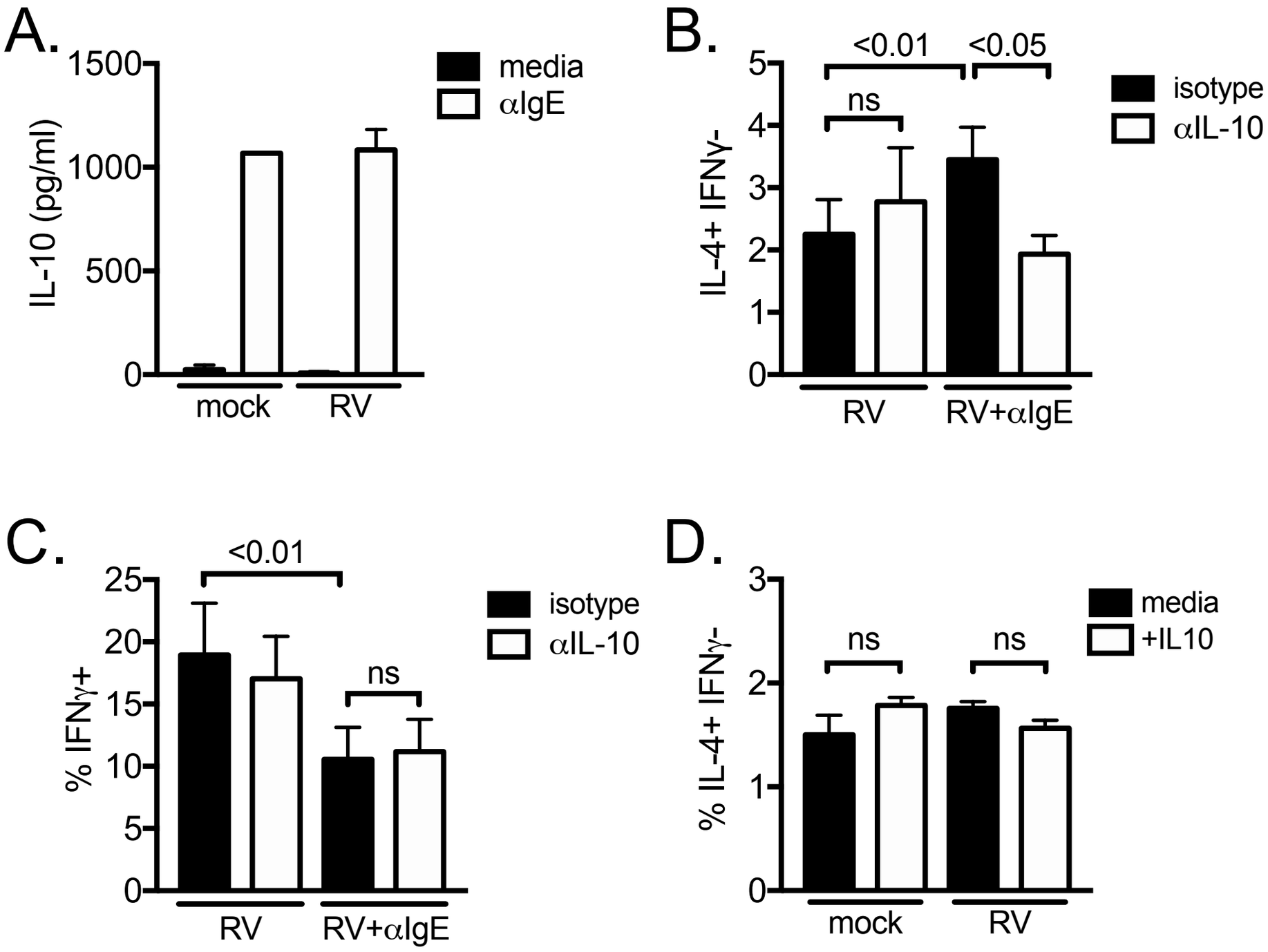

A.
<0.05
<0.01
% IL-4+ IFNγ-
0
1
2
3
4
5
6
7
mock
media
αIgE
IgG
RV
B.
r2=0.65
p=0.009
% IL-4+ IFNγ-
0
1
2
3
4
5
6
7
600
1200
1800
2400
surface FcεRIα
C.
<0.001
<0.001
% IFNγ+
0
20
40
60
mock
media
αIgE
IgG
RV
D.
<0.01
<0.05
Th1/Th2 ratio
0
5
10
15
mock
RV
RV
αIgE

Figure 2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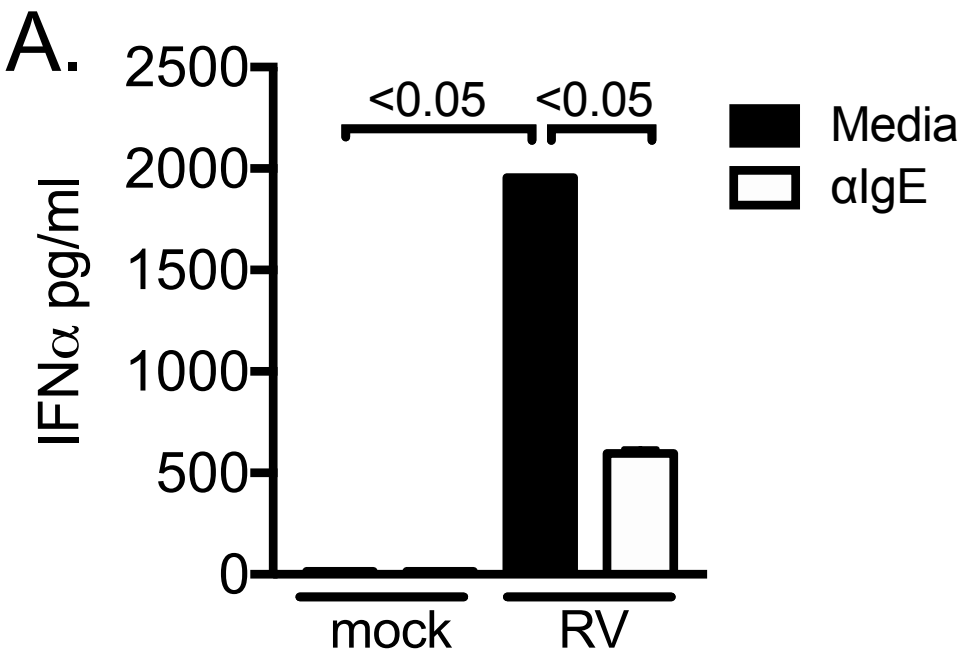
1000
500
0
mock
RV
media
αIgE
B.
IL-4+ IFNγ-
5
4
3
2
1
0
<0.01
<0.05
ns
RV
RV+αIgE
isotype
αIL-10
C.
% IFNγ+
25
20
15
10
5
0
<0.01
ns
RV
RV+αIgE
isotype
αIL-10
D.
% IL-4+ IFNγ-
3
2
1
0
ns
ns
mock
RV
media
+IL10

Figure 3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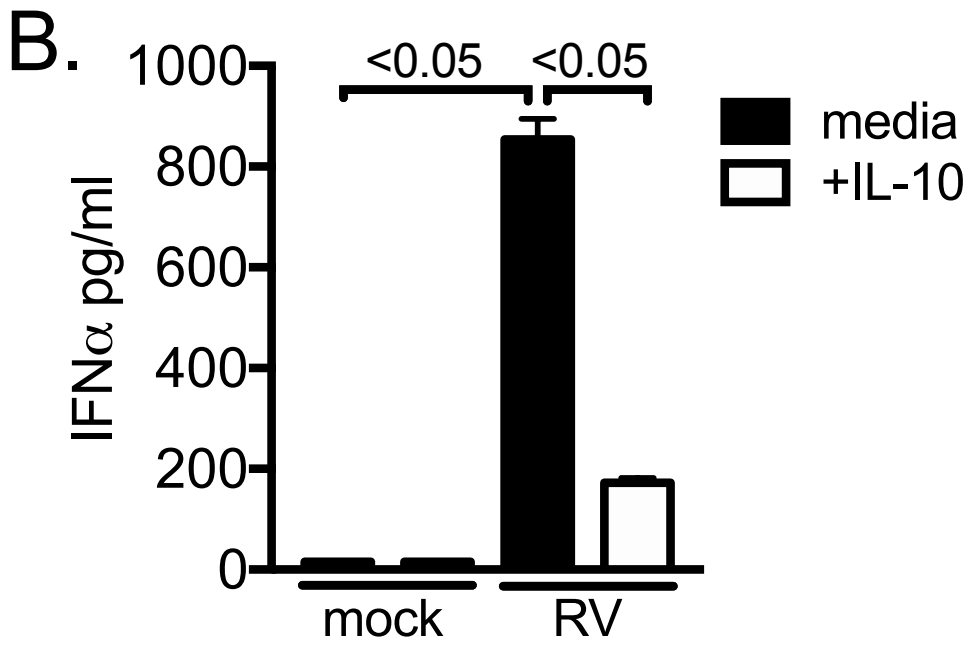
1500
1000
500
0
IFNα pg/ml
<0.05
<0.05
Media
αIgE
mock
RV


B.
1000
800
600
400
200
0
IFNα pg/ml
<0.05
<0.05
media
+IL-10
mock
RV

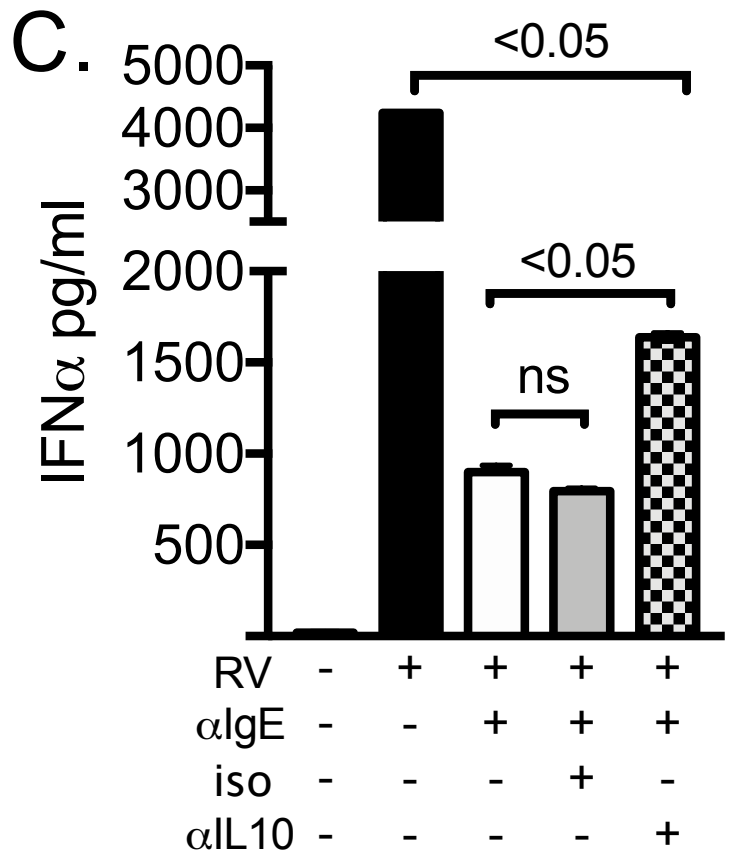

C.
5000
4000
3000
2000
1500
1000
500
IFNα pg/ml
<0.05
<0.05
ns
RV - + + + +
αIgE - - + + +
iso - - - + -
αIL10 - - - - +

Figure 4

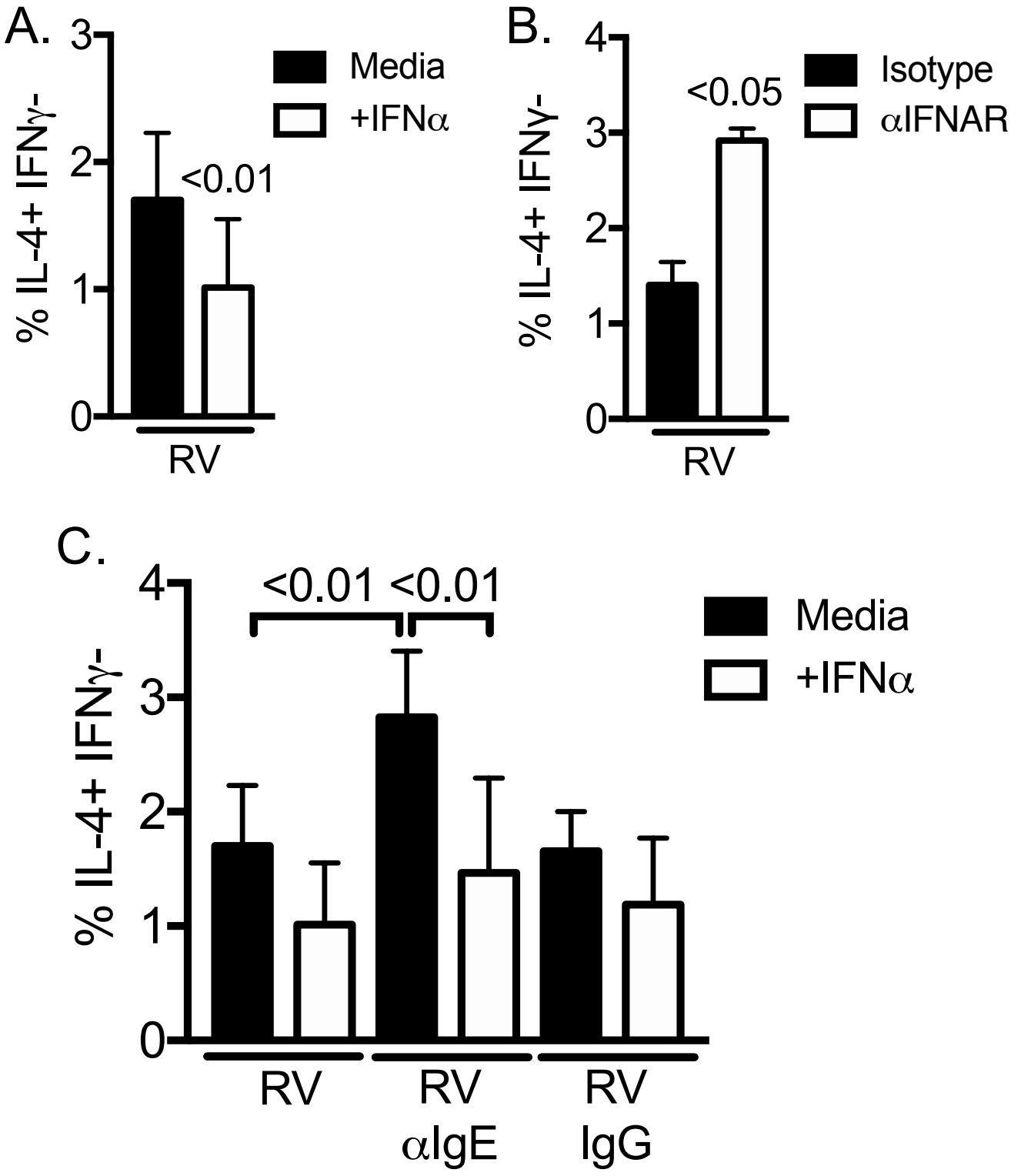
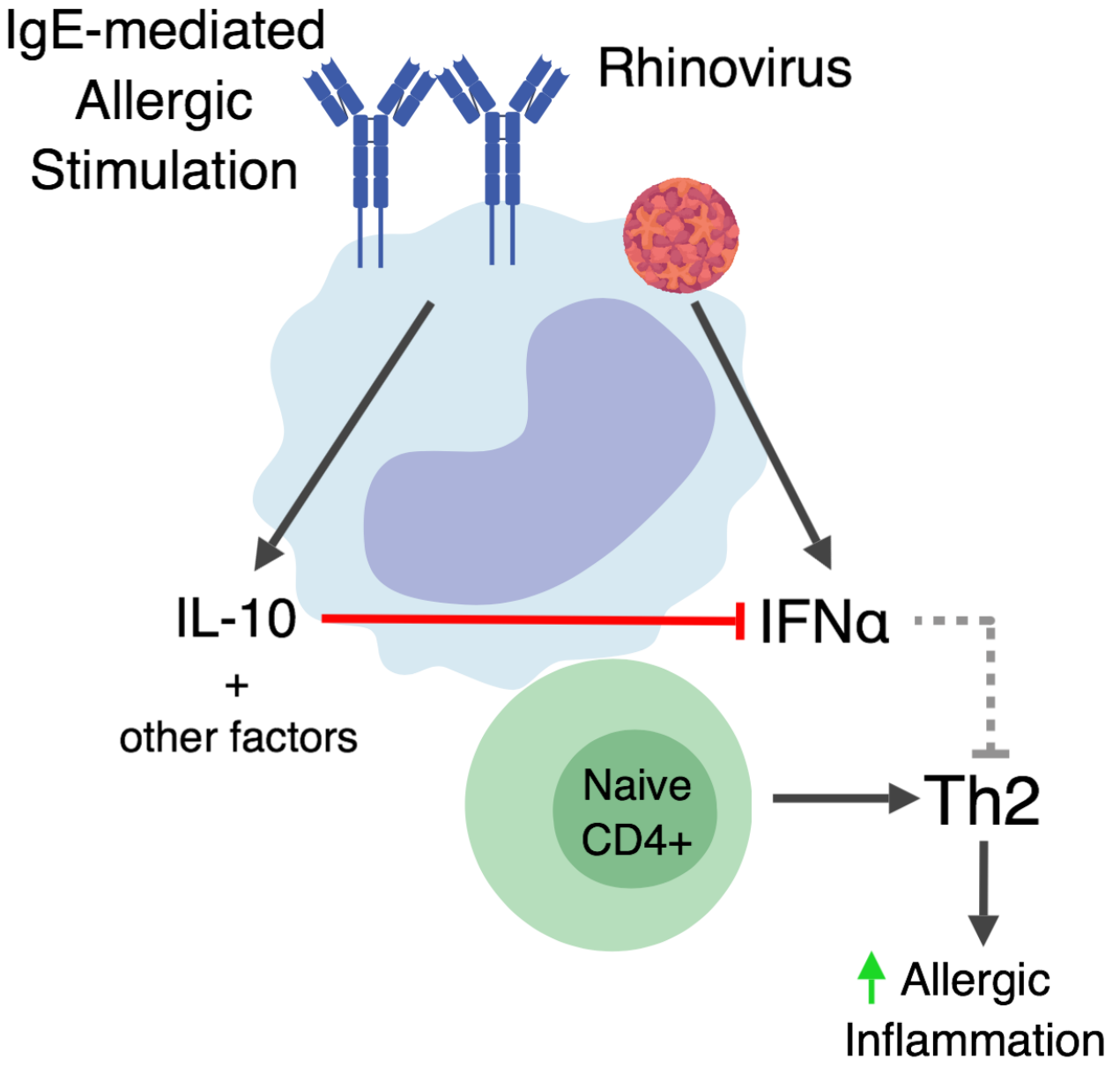

A.
% IL-4+ IFNγ-
3
2
1
0
<0.01
Media
+IFNα
RV
B.
% IL-4+ IFNγ-
4
3
2
1
0
<0.05
Isotype
αIFNAR
RV
C.
% IL-4+ IFNγ-
4
3
2
1
0
<0.01
<0.01
Media
+IFNα
RV
RV
αIgE
RV
IgG

Figure 5


IgE-mediated
Allergic
Stimulation
Rhinovirus
IL-10
+
other factors
IFNα
Naive
CD4+
Th2
Allergic
Inflammation