

Vehicular exhaust particles promote allergic airway inflammation through an aryl hydrocarbon receptor–notch signaling cascade

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Background: Traffic-related particulate matter (PM) has been linked to a heightened incidence of asthma and allergic diseases. However, the molecular mechanisms by which PM exposure promotes allergic diseases remain elusive.

Objective: We sought to determine the expression, function, and regulation of pathways involved in promotion of allergic airway inflammation by PM.

Methods: We used gene expression transcriptional profiling, *in vitro* culture assays, and *in vivo* murine models of allergic airway inflammation.

Results: We identified components of the Notch pathway, most notably Jagged 1 (Jag1), as targets of PM induction in human monocytes and murine dendritic cells. PM, especially ultrafine particles, upregulated T_H cytokine levels, IgE production, and allergic airway inflammation in mice in a Jag1- and Notch-dependent manner, especially in the context of the proasthmatic IL-4 receptor allele *Il4raR576*. PM-induced Jag1 expression was mediated by the aryl hydrocarbon receptor (AhR), which bound to and activated AhR response elements in the *Jag1* promoter. Pharmacologic antagonism of AhR or its lineage-specific deletion in CD11c⁺ cells abrogated the augmentation of airway inflammation by PM.

Conclusion: PM activates an AhR-Jag1-Notch cascade to promote allergic airway inflammation in concert with proasthmatic alleles. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: Traffic-related particulate matter, diesel exhaust particles, ultrafine particles, asthma, allergic airway inflammation, Jagged 1, Notch, aryl hydrocarbon receptor, airway hyper-responsiveness

Asthma is a major health problem worldwide, the prevalence of which has reached unprecedented levels in recent years.¹ Its increase to the status of a modern epidemic has been driven by the interaction of susceptibility genes in affected subjects with emerging environmental factors unleashed by the industrial revolution and lifestyle changes.² The latter include changes in microbial exposure integrated under the rubric of the hygiene hypothesis, changes in diet and activity, and, significantly, exposure to airborne particles and pollutants in carbon footprint-heavy economies.³ A large body of research has linked asthma development with urbanization and exposure to pro-oxidative, traffic-related air pollutants, most notably particulate matter (PM) and ozone, by virtue of their initiation of airway and systemic inflammation and their proallergic adjuvant function.⁴⁻⁷

The acute increase in the incidence of atopy and asthma in urban areas has been related in part to fine particles (FP; ≤ 2.5 μ m in diameter) and ultrafine particles (UFP; ≤ 0.18 μ m in diameter) of PM emitted by vehicular traffic, particularly that associated with diesel engines.⁸⁻¹¹ These particles have been reported to promote T_H2 and T_H17 cell responses and upregulate IgE production in the exposed host.^{6,12,13} They differentially affect the lung function of asthmatic patients, suggesting that genetic and epigenetic predispositions to atopy cooperatively promote the airway inflammatory responses seen after diesel exhaust particles (DEP) exposure.¹⁴

Ambient PM exposure acts as an adjuvant that primes the immune response to common environmental allergens.¹⁵ Intranasal instillation of ambient UFP derived from vehicular emissions enables a *de novo* immune response in the absence of added adjuvants.¹⁶ Recently, it was demonstrated that simple inhalation of ambient UFP could effectively boost the secondary immune response to an experimental allergen, indicating that vehicular traffic exposure might exacerbate allergic inflammation in already sensitized subjects.¹² Neither the precise molecular mechanisms by which PM exposure promotes allergic sensitization nor the identity of the PM subcomponents involved are clear. However, PM-induced oxidative stress can induce T_H skewing of the immune response through affecting the antigen-presenting function of dendritic cells (DCs).¹⁷⁻²¹ This could involve antigen uptake, antigen presentation, DC costimulatory activity, and cytokine production.

A range of genetic, immunologic, and whole-animal approaches were used to elucidate molecular mechanisms by

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Abbreviations used

AhR:	Aryl hydrocarbon receptor
BMDC:	Bone marrow–derived dendritic cell
CB:	Carbon black particles
DC:	Dendritic cell
DEP:	Diesel exhaust particles
DLL:	Delta-like ligand
DMSO:	Dimethyl sulfoxide
FICZ:	6-Formylindolo (3,2-b) carbazole
FP:	Fine particles
GSI:	Gamma-secretase inhibitor
Jag1:	Jagged 1
Notch1c:	Notch1 intracellular domain
OVA:	Ovalbumin
PAH:	Polycyclic aryl hydrocarbon
PAS:	Periodic acid–Schiff
PM:	Particulate matter
TLR4:	Toll-like receptor
UFP:	Ultrafine particles
WT:	Wild-type

which PM exposure can program antigen-presenting cells to promote allergic diseases. Here we provide evidence for a critical role for an aryl hydrocarbon receptor (AhR)–Jagged 1 (Jag1)–Notch pathway in mediating the proinflammatory effects of PM in patients with allergic airway inflammation in interaction with proatopic *Il4ra* alleles.

METHODS**Mice**

Il4ra^{R576} mice were previously described.²² The following mice were obtained from the Jax Labs (Bar Harbor, Me): BALB/c (wild-type [WT]), *Tlr4*^{−/−} (B6.B10ScN-Tlr4^{lps-del}), *Ahr*^{fl/fl} (*Ahr*^{tm3.1Bra}), *CD11c-cre* (B6.Cg-Tg[Itgax-cre]1-Reiz/J), and *Nlrp3*^{−/−} (B6.129S6-Nlrp3^{tm1Bhk/J}). *DO11.10Rag2*^{−/−} mice were obtained from Taconic Farms (Hudson, NY). They were crossed with *Il4ra*^{R576} mice to generate *DO11.10Rag2*^{−/−}/*Il4ra*^{R576} mice. *Nrf2*^{−/−} mice were a kind gift of Andre Nel.²³

Particles

DEP were a kind gift of Dr Andre Nel and have been described previously.²⁴ Carbon black particles (CB; <500 nm) were purchased from Sigma-Aldrich (St Louis, Mo). Ambient FP (≤2.5 μm) and UFP (≤0.18 μm) were collected in an urban area of downtown Los Angeles by using a high-volume ultrafine particle sampler²⁵ operating at 400 L/min and loaded with a Zeflur filter (supported polytetrafluoroethylene, 3.0-μm pore, 8 × 10 inches; Pall Life Sciences, Port Washington, NY). For investigating the volatile and nonvolatile UFP fractions, we collected 2 UFP samples: N-UFP, which were collected during nighttime plus morning traffic hours (ie, rich in semivolatile organics partitioned to the PM phase), and Af-UFP, which were collected during the afternoon, when partitioning is minimal. The respective particles were suspended in an aqueous solution, with the hydrophilic components becoming part of the solution, whereas the solid nonsoluble UFP cores are left in suspension. The particle-loaded filters were soaked in ultrapure water, followed by 5 minutes of vortexing and 30 minutes of sonication, to transfer the particles into solution. The entire mixture was administered intranasally, as indicated below. Endotoxin levels were less than 0.1 ng/mL (data not shown).

Derivation of DCs

Bone marrow–derived dendritic cells (BMDCs) were obtained by culturing bone marrow aspirates for 7 days with GM-CSF at 20 ng/mL. The cells were

either sham treated with PBS or treated with particles at 10 μg/mL in PBS for 18 hours before measurement of Notch pathway components by means of flow cytometry, real-time PCR, or both.

T-cell/BMDCs cocultures

Splenic CD4⁺DO11.10⁺RAG2^{−/−} T cells were purified by means of magnetic cell sorting negative selection (Miltenyi Biotec, Bergisch Gladbach, Germany). BMDCs were placed in aliquots at 2 × 10⁵ cells in 48-well plates and then either sham treated or treated with the respective PM species at 10 μg/mL per culture well overnight. For AhR inhibition experiments, BMDCs were treated with 30 nmol/L of the AhR antagonist CH223191 and washed after 16 hours. CD4⁺DO11.10⁺RAG2^{−/−} T cells were added at 4 × 10⁵ cells per well in a final volume of 0.5 mL of 10% FBS/RPMI. Cultures were treated with the ovalbumin (OVA)_{323–339} peptide at 1 μmol/L, as indicated. Notch pathway inhibitors included the gamma secretase inhibitor (GSI; Calbiochem, San Diego, Calif) added at 5 μmol/L and anti-murine Jag1 antibodies (BioLegend, San Diego, Calif) added at 2.5 μg/mL.

Allergic sensitization and challenge

Mice were sensitized to OVA by means of intraperitoneal injection of 100 μg of OVA in 100 μL of PBS and then boosted 2 weeks later with a second intraperitoneal injection of OVA in PBS. Control mice were sham sensitized and boosted with PBS alone. Starting on day 29, both OVA- and sham-sensitized mice were challenged with aerosolized OVA at 1% delivered through a Schuco 2000 nebulizer (Allied Health Care Products, St Louis, Mo) for 30 minutes daily for 3 days. Two hours before each OVA aerosol exposure, subgroups of mice were administered intranasally either PBS or PM (UFP, FP, or CB) at 10 μg/100 μL of PBS per instillation. Where indicated, GSI (0.3 mg/kg in dimethyl sulfoxide [DMSO] administered intranasally) or CH223191 (0.5 mg/kg in corn oil administered intraperitoneally) was introduced 4 hours before OVA challenge, with untreated mice receiving the DMSO vehicle, also intranasally. For anti-Jag1 antibody blocking, 150 μg of anti-Jag1 or isotype control antibodies in 100 μL of PBS buffer was administered daily for 3 consecutive days during OVA aerosol challenge. Mice were killed on day 32 after sensitization and analyzed. For dust mite–induced allergic airway inflammation, mice received 5 μg of lyophilized *Dermatophagoides pteronyssinus* extract in 100 μL of PBS intranasally for 3 days at the start of the protocol and then challenged with the same dose of *D. pteronyssinus* extract on days 15 to 17 with or without PM. Where indicated, mice were treated with isotype control or anti-Jag1 antibodies or with DMSO (sham) or the AhR antagonist CH223191, as indicated, on the same days (days 15–17) of *D. pteronyssinus* challenge. Mice were killed on day 18 and analyzed for measures of airway inflammation.

Lung histopathology staining

Paraffin-embedded lung sections were stained with hematoxylin and eosin, as previously described.²⁶ Lung inflammation was scored separately for cellular infiltration around the blood vessels and airways: 0, no infiltrates; 1, few inflammatory cells; 2, a ring of inflammatory cells 1 cell layer deep; 3, a ring of inflammatory cells 2 to 4 cells deep; and 4, a ring of inflammatory cells greater than 4 cells deep.²⁷ A composite score was determined by adding the inflammatory scores for both vessels and airways. The number and distribution of goblet cells was assessed by using periodic acid–Schiff (PAS) staining of mucin granules. Individual airways (bronchi/bronchioles) were scored for goblet cell hyperplasia according to the following scale: 0, no PAS-positive cells; 1, less than 5% PAS-positive cells; 2, 5% to 10% PAS-positive cells; 3, 10% to 25% PAS-positive cells; and 4, greater than 25% PAS-positive cells.²⁸

Statistical analysis

The Student 2-tailed *t* test, 1- and 2-way ANOVA, and repeated-measures 2-way ANOVA with Bonferroni posttest analysis of groups were used to compare test groups, as appropriate. A *P* value of less than .05 was considered statistically significant.

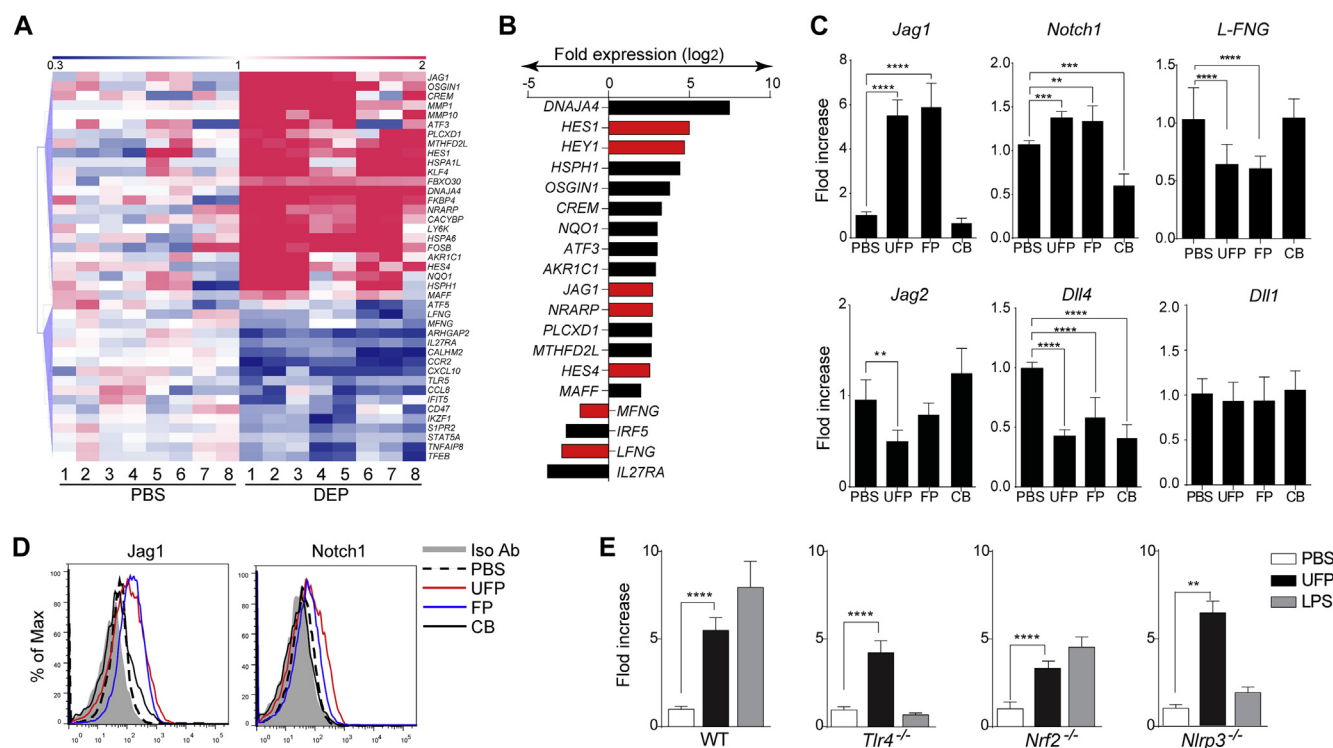


FIG 1. PM induces components of the Notch pathway in human peripheral blood monocytes and mouse BMDCs. **A**, Hierarchic clustering analysis of gene transcripts of human monocytes that were either sham treated with PBS or treated with DEP (10 μ g/mL for 4 hours). **B**, Gene expression fold change in human monocytes after treatment with DEP. Genes related to the Notch pathway are indicated in red. **C**, mRNA expression of the indicated Notch pathway component in BMDCs treated with PBS, UFP, FP, or CB (10 μ g/mL each). **D**, Flow cytometric analysis of Jag1 and Notch1 in murine BMDCs treated with PBS, UFP, or CB. **E**, Fold change of Jag1 transcripts in BMDCs derived from either WT, *Tlr4*^{-/-}, *Nr2*^{-/-}, or *Nlrp3*^{-/-} mice and treated with PBS, UFP (10 μ g/mL), or LPS (1 μ g/mL). For Fig 1, A and B, results are representative of 1 experiment (n = 8). For Fig 1, C-E, results are representative of 3 independent experiments (n = 10/15 mice per group). ***P* < .01, ****P* < .001, and *****P* < .0001, 1-way ANOVA with posttest analysis and the Student unpaired 2-tailed *t* test.

Study approval. All animal studies were reviewed and approved by the Boston Children's Hospital office of Animal Care Resources.

Other methods. Information on additional chemical reagents used, gene expression profiling, real-time PCR analysis, flow cytometry and intracellular staining reagents, antibodies and methods, IgE and cytokine ELISAs, measurement of airway hyperresponsiveness, chromatin immunoprecipitation assays, and luciferase assays is provided in the [Methods](http://www.jacionline.org) section in this article's Online Repository at www.jacionline.org.

RESULTS

PM activates Jag1-Notch transcriptional circuitry

PM has been noted to reprogram antigen-presenting cells in favor of T_H2 responses. To understand the mechanisms by which PM mediates this function, we analyzed the gene expression profiles of human monocytes isolated from healthy volunteers in response to short-term *in vitro* exposure to DEP (4 hours at 10 μ g/mL) by using Affymetrix human genome U133 plus 2.0 arrays (Affymetrix, Santa Clara, Calif). Expression levels of 757 probes were found to be significantly changed between exposed and unexposed cultures at a 2-fold cutoff (see [Table E1](http://www.jacionline.org) in this article's Online Repository at www.jacionline.org). Affected genes included those involved in oxidative stress (*GCLM* and *AKR1C2*), heat shock response (*DNAJB4* and

HSP1AB), transcription factors (*CREM* and *FOSB*), and other cellular pathways (Fig 1, A and B).^{29,30} Importantly, DEP exposure affected the expression of several genetic components of the Notch pathway, which plays a key role in instructing T_H cell differentiation.³¹ It upregulated the expression of the Notch ligand gene *JAG1* and the Notch downstream genetic targets *HES1*, *HES4*, *HEY1*, and *NRARP*. DEP also suppressed the expression of lunatic fringe (*LFNG*) and manic fringe (*MFNG*), encoding 2 enzymes that modify Notch receptor species in favor of interaction with JAG1 and JAG2 (pro-T_H2) but not delta-type ligand (pro-T_H1) skewing.^{32,33}

DEP are composed primarily of FP and UFP, which have effective aerodynamic diameters of less than 2.5 μ m and less than 0.18 μ m, respectively.^{34,35} We examined the induction of components of the Notch pathway in murine BMDCs using size-fractionated FP and UFP, as well as chemically inert CB (effective aerodynamic diameter, 0.5 μ m). Expression of mRNA encoding Jag1 and, to a lesser extent, Notch1 was upregulated in BMDCs treated with FP and UFP, but not CB, as detected by using real-time PCR analysis (Fig 1, C). In contrast, other Notch-type receptors and ligands were either unaffected, such as Notch2, Notch4, and delta-like ligand (DLL) 1 and DLL3, or downregulated, such as DLL4 and Jag2 (Fig 1, C, and unpublished data). Flow cytometric analysis confirmed the

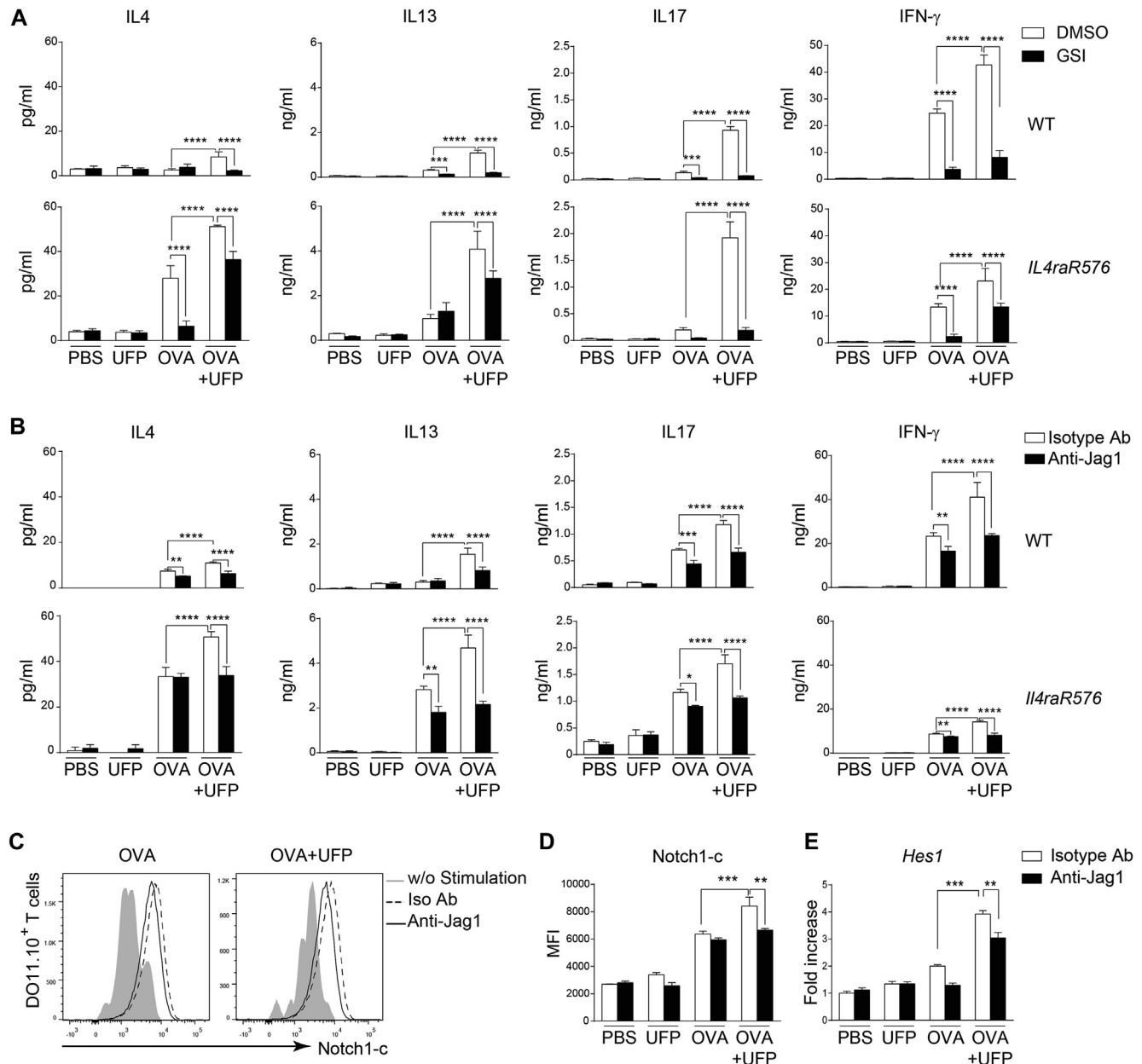


FIG 2. UFP promote T_H cytokine production in a Jag1-dependent manner. **A** and **B**, T_H cytokine production by naive WT and *Il4raR576* $CD4^+DO11.10^+Rag2^{-/-}$ T cells cocultured with OVA-pulsed BMDCs in the presence of UFP (10 μ g/mL), sham, GSI (5 μ mol/L), anti-Jag1 mAb, or an isotype control (2.5 μ g/mL). **C** and **D**, Flow cytometric analysis (Fig 2, **C**) and mean fluorescent intensity (Fig 2, **D**) of intracellular Notch1 (*Notch1-c*) expression in *Il4raR576* $CD4^+DO11.10^+Rag2^{-/-}$ T cells cocultured with OVA₃₂₃₋₃₃₉-pulsed BMDCs in the presence of UFP and anti-Jag1 mAb. **E**, *Hes1* mRNA expression by T cells cocultured as described in Fig 2, **B**. Results are representative of 3 independent experiments. * $P < .05$, ** $P < .01$, *** $P < .001$, and **** $P < .0001$, 2-way ANOVA with Bonferroni posttest analysis.

upregulation of Jag1 and Notch1 expression in BMDCs treated with UFP and FP but not CB (Fig 1, **D**).

To determine the mechanisms involved in Jag1 induction by PM, we examined the role of the Toll-like receptor (TLR) 4 pathway, which has been implicated in Jag1 regulation.³⁶ Unlike LPS, which induced *Jag1* expression in WT but not TLR4-deficient BMDCs, UFP induced Jag1 expression in both cell types (Fig 1, **E**). Similarly, DEP induction of Notch pathway components proceeded unaffected in BMDCs lacking in the

adaptor myeloid differentiation primary response gene-88, which is common to most TLRs (data not shown). We further examined the role of Nrf2-dependent oxidative stress pathway and the inflammasome pathway in the induction by PM of Jag1 expression in BMDCs. Both the Nrf2 and Nlrp3 pathways are known to be activated by DEP exposure, and Nrf2 activates Notch1 expression.³⁷⁻³⁹ Our results revealed that induction by UFP of *Jag1* transcription proceeded unaffected in Nrf2- and NLRP3-deficient BMDCs. In contrast, LPS-induced Jag1

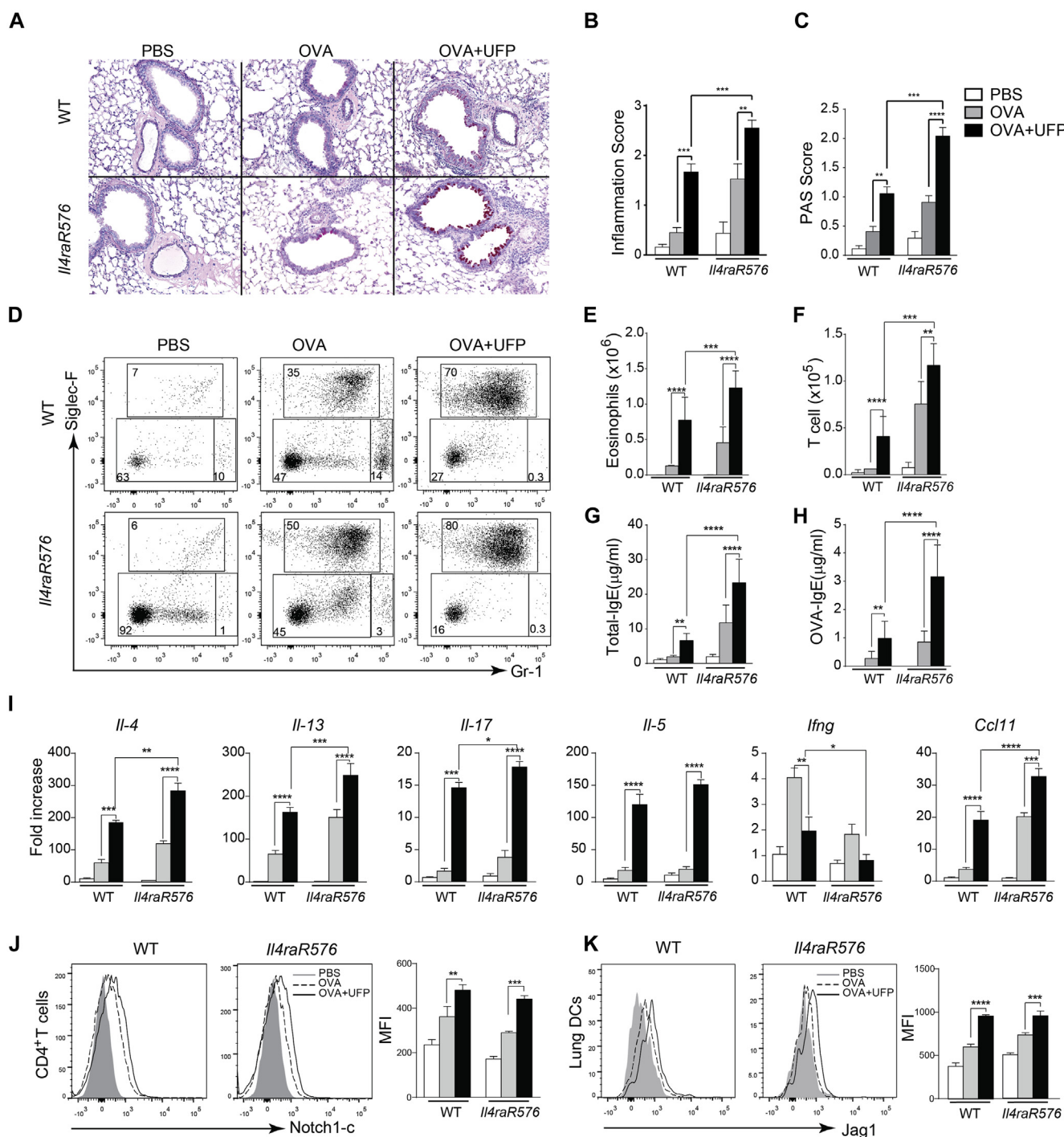


FIG 3. UFP synergize with *Il4raR576* to promote OVA-induced allergic airway inflammation. **A**, Representative PAS staining of lung sections isolated from WT and *Il4raR576* mice immunized/challenged with PBS/OVA (PBS), OVA/OVA (OVA), or OVA/OVA+UFP (OVA+UFP; $\times 200$ magnification). **B** and **C**, Inflammation (Fig 3, B) and PAS (Fig 3, C) scores from the mouse groups shown in Fig 3, A. **D**, Flow cytometric analysis of eosinophils (Siglec-F⁺Gr-1^{intermediate}) and neutrophils (Siglec-F⁺Gr-1^{high}) in bronchoalveolar lavage fluid of the mouse groups described in Fig 3, A. Numbers indicate average frequencies of the respective population in each rectangle. **E** and **F**, Eosinophil (Fig 3, E) and T-cell (Fig 3, F) absolute numbers in bronchoalveolar lavage fluid of the mouse groups described in Fig 3, A. **G** and **H**, Total (Fig 3, G) and OVA-specific (Fig 3, H) IgE levels in serum of the mouse groups described in Fig 3, A. **I**, *Il-4*, *Il-13*, *Il-17*, *Il-5*, *Ifng*, and *Ccl11* mRNA expression in WT and *Il4raR576* mice lung tissues after PBS, OVA, or OVA+UFP treatment. **J** and **K**, Flow cytometric analysis of Notch1c (Fig 3, J) and Jag1 (Fig 3, K) expression by the CD4⁺ T cells isolated from lungs of the mouse groups described in Fig 3, A. Results are representative of 3 independent experiments ($n = 5$ mice per group). * $P < .05$, ** $P < .01$, *** $P < .001$, and **** $P < .0001$, 2-way ANOVA with Bonferroni posttest analysis.

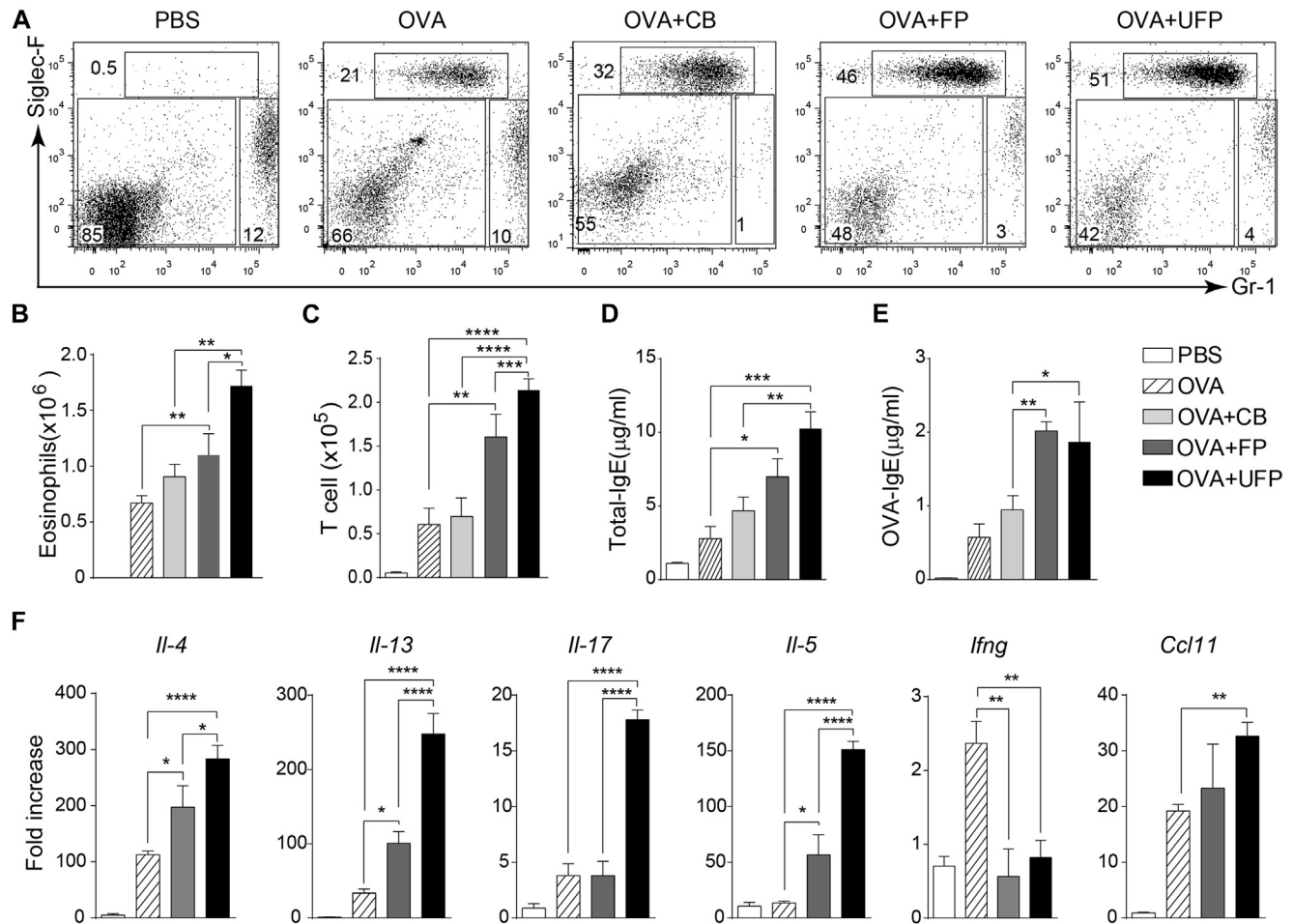


FIG 4. UFP and FP, but not CB, upregulated allergic airway inflammation in OVA-sensitized *Il4raR576* mice. **A**, Flow cytometric analysis of eosinophils and neutrophils in bronchoalveolar lavage fluid of *Il4raR576* mice in the PBS, OVA, OVA+CB, OVA+FP, or OVA+UFP groups. **B** and **C**, Absolute numbers of eosinophils (Fig 4, B) and T cells (Fig 4, C) in BAL fluid of the mouse groups from Fig 4, A. **D** and **E**, Total (Fig 4, D) and OVA-specific (Fig 4, E) IgE levels in serum from the mouse groups from Fig 4, A. **F**, *Il-4*, *Il-13*, *Il-17*, *Il-5*, *Ifng*, and *Ccl11* mRNA expression in lung tissues of the mouse groups from Fig 4, A. Results are representative of 2 independent experiments (n = 4-5 per group). **P* < .05, ***P* < .01, ****P* < .001, and *****P* < .0001, 2-way ANOVA with Bonferroni posttest analysis.

expression was abrogated in the setting of NLRP3 deficiency (Fig 1, E). Together, these data indicated that UFP-mediated induction of *Jag1* transcription proceeds independent of the TLR4/myeloid differentiation primary response gene-88, Nrf2, or NLRP3 pathways.

PM upregulates T_H cytokine expression through a Jag1-dependent mechanism

To examine whether Notch pathway activation by PM contributes to T_H cell skewing, we used an *in vitro* T_H cell differentiation system involving naive DO11.10⁺CD4⁺ T cells derived from DO11.10⁺Rag2^{-/-} mice. Naive DO11.10⁺CD4⁺ T cells were incubated with BMDCs that had either been sham pulsed with PBS or pulsed with the OVA peptide OVA₃₂₃₋₃₃₉. Culture supernatants were analyzed by means of ELISA for levels of the T_H2 cytokines IL-4 and IL-13, the T_H1 cytokine IFN-γ, and the T_H17 cytokine IL-17. Treatment of cell cocultures with OVA₃₂₃₋₃₃₉ peptide induced increased production of

all 4 T_H cytokines, which was further upregulated by addition of UFP (10 μg/mL). Treatment with GSI, an inhibitor of Notch signaling, suppressed the increase in T_H cytokine levels in response to UFP (Fig 2, A). In a parallel set of studies, treatment of cell cocultures with an anti-Jag1 but not an isotype control antibody blocked the superinduction by UFP of OVA peptide-induced cytokine production. In contrast, anti-Jag1 antibody treatment had a modest effect on cytokine production induced by the OVA peptide in the absence of UFP (Fig 2, B).

We also investigated the capacity of UFP treatment to promote T_H2 responses in the context of a T_H2-skewed genetic background. To that end, we used naive DO11.10⁺CD4⁺ T cells homozygous for *Il4raR576*, an allergy and asthma-associated human IL-4 receptor α chain polymorphism that is especially common in populations of African ancestry, including African Americans, and that promotes T_H2 responses and allergic airway inflammation.^{22,40} Naive DO11.10⁺CD4⁺ T cells, which were derived from DO11.10Rag2^{-/-} *Il4raR576* mice, expressed

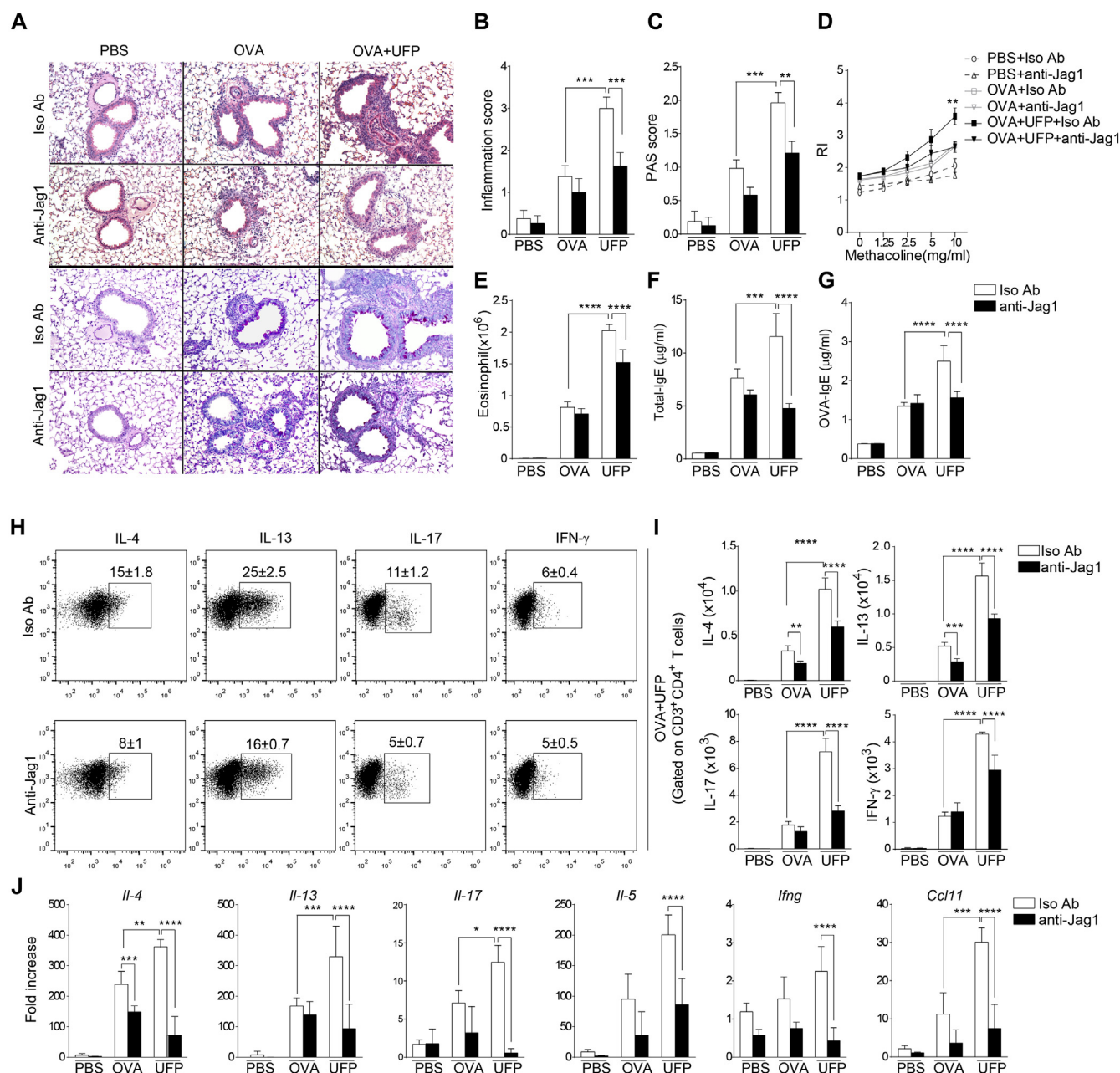


FIG 5. UFP enhance OVA-induced airway inflammation in a Jag1-dependent manner. **A**, Representative hematoxylin and eosin (upper panels) and PAS (lower panels) staining of lung tissues isolated from *Il4raR576* mice sensitized and challenged with OVA alone or together with UFP in the presence of anti-Jag1 or an isotype control mAb ($\times 200$ magnification). **B** and **C**, Inflammation (Fig 5, B) and PAS (Fig 5, C) scores in lung tissues of the mouse groups described in Fig 5, A. **D-G**, Airway hyperresponsiveness in response to methacholine (Fig 5, D), absolute numbers of eosinophils in bronchoalveolar lavage fluid (Fig 5, E), and total (Fig 5, F) and OVA-specific (Fig 5, G) levels in serum of the mouse groups described in Fig 5, A. **H**, Flow cytometric analysis of cytokine expression by $CD4^+$ T cells present in bronchoalveolar lavage fluid of *Il4raR576* mice sensitized with OVA together with UFP. **I**, Absolute numbers of lung $CD4^+$ T cells producing IL-4, IL-13, IL-17, and IFN- γ in bronchoalveolar lavage fluid of the mouse groups described in Fig 5, A. **J**, *Il4*, *Il13*, *Il17*, *Il5*, *Ifng*, and *Ccl11* mRNA expression in lung tissues of *Il4raR576* in the PBS, OVA, or OVA-UFP groups treated with either isotype control or anti-Jag1 mAbs. Results are representative of 2 independent experiments ($n = 5$ mice per group). * $P < .05$, ** $P < .01$, *** $P < .001$, and **** $P < .0001$, 2-way ANOVA with Bonferroni posttest analysis.

substantially more T_H2 cytokines and less IFN- γ when incubated with OVA₃₂₃₋₃₃₉-pulsed BMDCs than their counterparts of *DO11.10Rag2*^{-/-} mice (Fig 2, A and B). UFP upregulated the

production of T_H2 cytokines, as well as IL-17 and IFN- γ , and antigen-stimulated *DO11.10*⁺ $CD4^+$ *Il4raR576* T cells in a manner that was completely blocked by GSI and Jag1 antibody

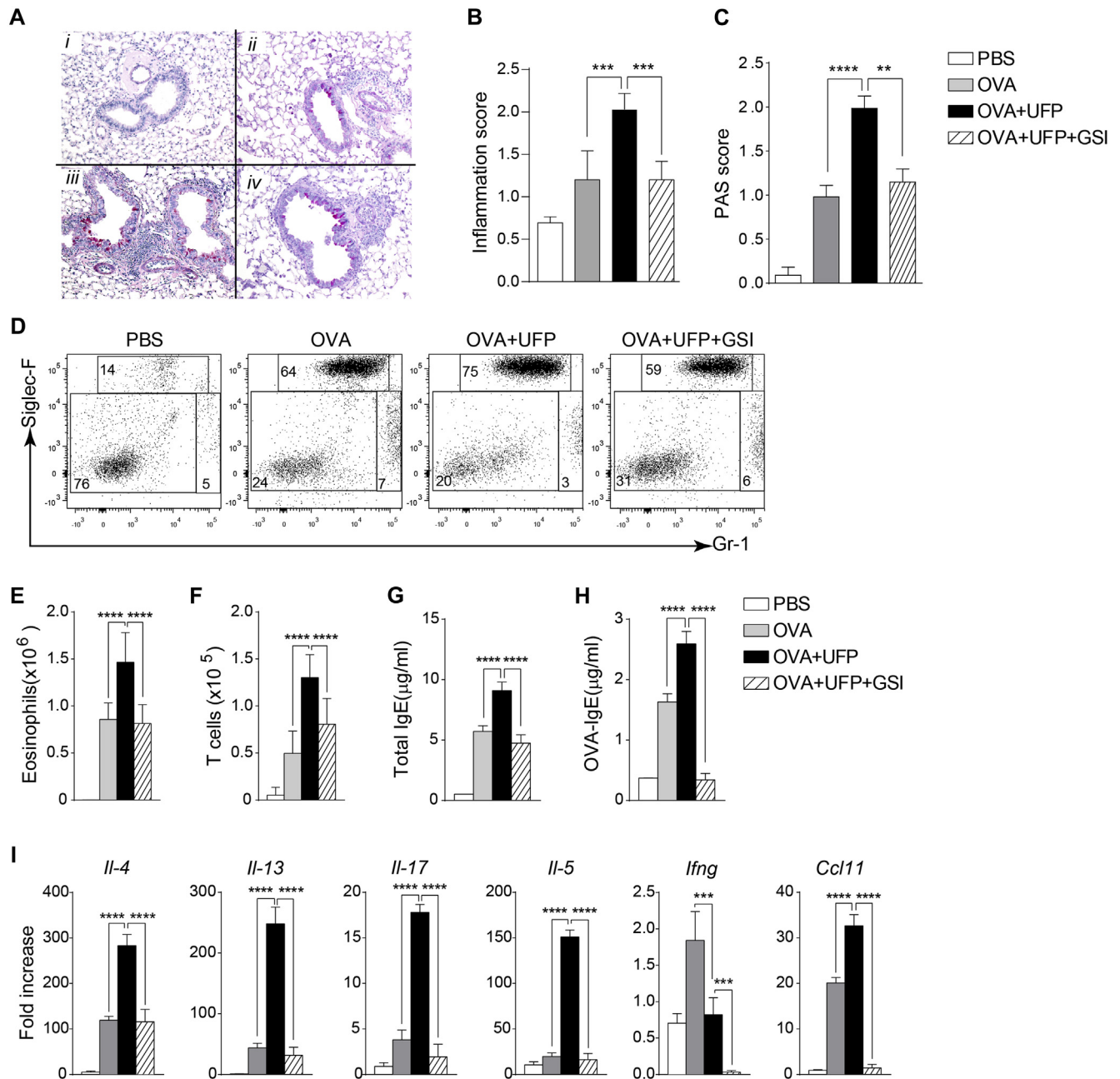


FIG 6. UFP promote OVA-induced airway inflammation in a Notch-dependent mechanism. **A**, Representative PAS staining of lung tissues of *Il4raR576* mice in the PBS (*i*), OVA (*ii*), OVA+UFP (*iii*), and OVA+UFP+GSI (*iv*) groups ($\times 200$ magnification). **B** and **C**, Inflammation and PAS scores of the mouse groups shown in Fig 6, **A**. **D**, Flow cytometric analysis of eosinophils and neutrophils in bronchoalveolar lavage fluid isolated from the mouse groups described in Fig 6, **A**. **E** and **F**, Absolute numbers of eosinophils (Fig 6, **E**) and T cells (Fig 6, **F**) in bronchoalveolar lavage fluid of the respective mouse groups. **G** and **H**, Total (Fig 6, **G**) and OVA-specific (Fig 6, **H**) levels in serum of the mouse groups described in Fig 6, **A**. **I**, *Il4*, *Il13*, *Il17*, *Il5*, *Ifng*, and *Ccl11* mRNA expression in lung tissues of *Il4raR576* mice in PBS, OVA, OVA+UFP, or OVA+UFP+GSI groups. Results are representative of 2 independent experiments ($n = 5$ per group). $**P < .01$, $***P < .001$, and $****P < .0001$, 1- and 2-way ANOVA with Bonferroni posttest analysis.

treatment relative to isotype control (Fig 2, *A* and *B*). Analysis of the expression of the active Notch1 intracellular domain (Notch1c), which mediates intracellular Notch1 signaling, revealed increased levels in OVA plus UFP-treated cells along with increased transcripts of the Notch target gene *Hes1* (Fig 2, *C-E*). Increased Notch1c expression and *Hes1*

transcripts induced by UFP were inhibited by treatment with the anti-Jag1 antibody (Fig 2, *C-E*). Overall, these results indicate that the Jag1/Notch pathway amplifies the production of T_H cytokines by naive T cells, with a skewing toward T_{H2} cytokines in the context of a pro-T_{H2} human polymorphism.

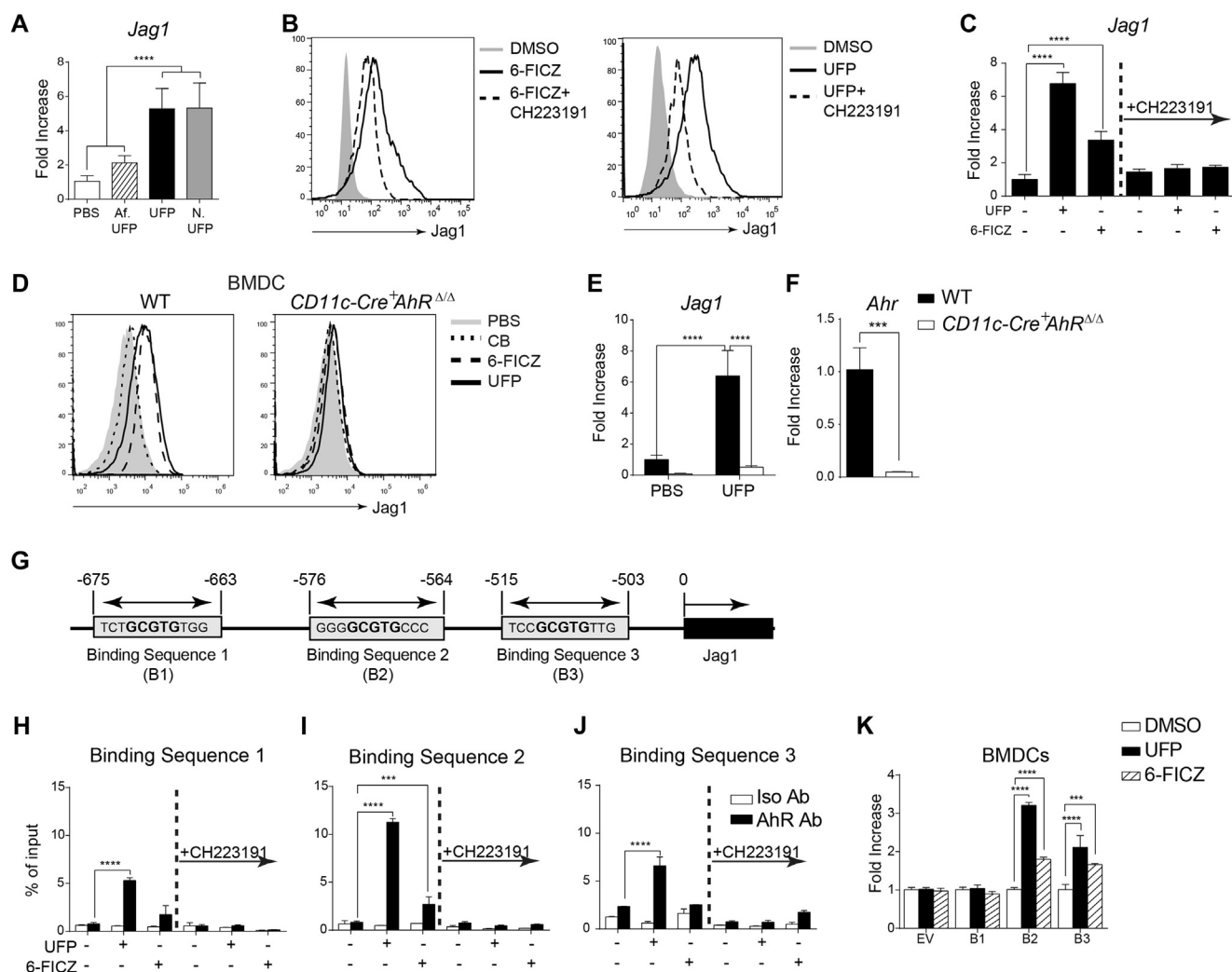


FIG 7. UFP activate AhR to induce *Jag1* expression. **A**, Fold change of *Jag1* transcripts in BMDCs treated with PBS, UFP collected during the afternoon (Af-UFP), total UFP, and UFP collected during nighttime plus morning traffic hours (N-UFP; 10 μ g/mL). **B** and **C**, Flow cytometric analysis of *Jag1* expression (Fig 7, B) and *Jag1* mRNA levels (Fig 7, C) in BMDCs treated with DMSO (sham), UFP, or the AhR agonist 6-FICZ in the presence or absence of the AhR antagonist CH223191. **D-F**, Flow cytometric analysis of *Jag1* expression (Fig 7, D) and *Jag1* (Fig 7, E) and *Ahr* (Fig 7, F) mRNA levels in WT or *CD11c-Cre⁺AhR^{Δ/Δ}* BMDCs. **G**, Schematic representation of candidate AhR binding sites in the proximal *Jag1* promoter. **H-J**, Chromatin immunoprecipitation analysis of AhR binding to candidate response elements in the *Jag1* promoter in BMDCs treated with the indicated reagents. **K**, Luciferase activity in BMDCs transfected with luciferase reporters driven by individual candidate *Jag1* AhR response elements and then treated with vehicle (DMSO), UFP, or 6-FICZ. Results are representative of 3 independent experiments (n = 3-7 per group). ****P* < .001 and *****P* < .0001, 1- and 2-way ANOVA with Bonferroni posttest analysis.

UFP upregulate allergic airway inflammation in interaction with a proallergic human *IL4RA* polymorphism

To determine the effect of PM treatment *in vivo*, we examined the influence of exposure to PM on the allergic response of WT BALB/c mice compared with that of mice harboring the *Il4raR576* polymorphism.²² Accordingly, WT and *Il4raR576* mice were sensitized by means of intraperitoneal injection of OVA and then challenged by means of inhalation of 1% aerosolized OVA once daily over 3 successive days. Control mice were sham sensitized with PBS and challenged with aerosolized OVA. Subgroups of mice were treated intranasally with UFP (10 μ g per instillation) or PBS 2 hours

before the OVA aerosol challenge.⁴¹ Sensitization and challenge of WT mice with OVA resulted in a modest eosinophilic airway inflammatory response that was amplified by the inclusion of PM exposure during the OVA challenge phase. In contrast, OVA sensitization and challenge of *Il4raR576* mice resulted in robust airway inflammation that was also amplified by PM exposure (Fig 3, A-I). Airway eosinophilia and T-cell infiltration, total and OVA-specific IgE responses, and T_H2 and T_H17 responses in OVA-sensitized and challenged mice were all augmented by UFP exposure. Furthermore, there was synergistic interaction between UFP and the *Il4raR576* allele in eliciting many of these responses (Fig 3, A-I). UFP treatment induced increased

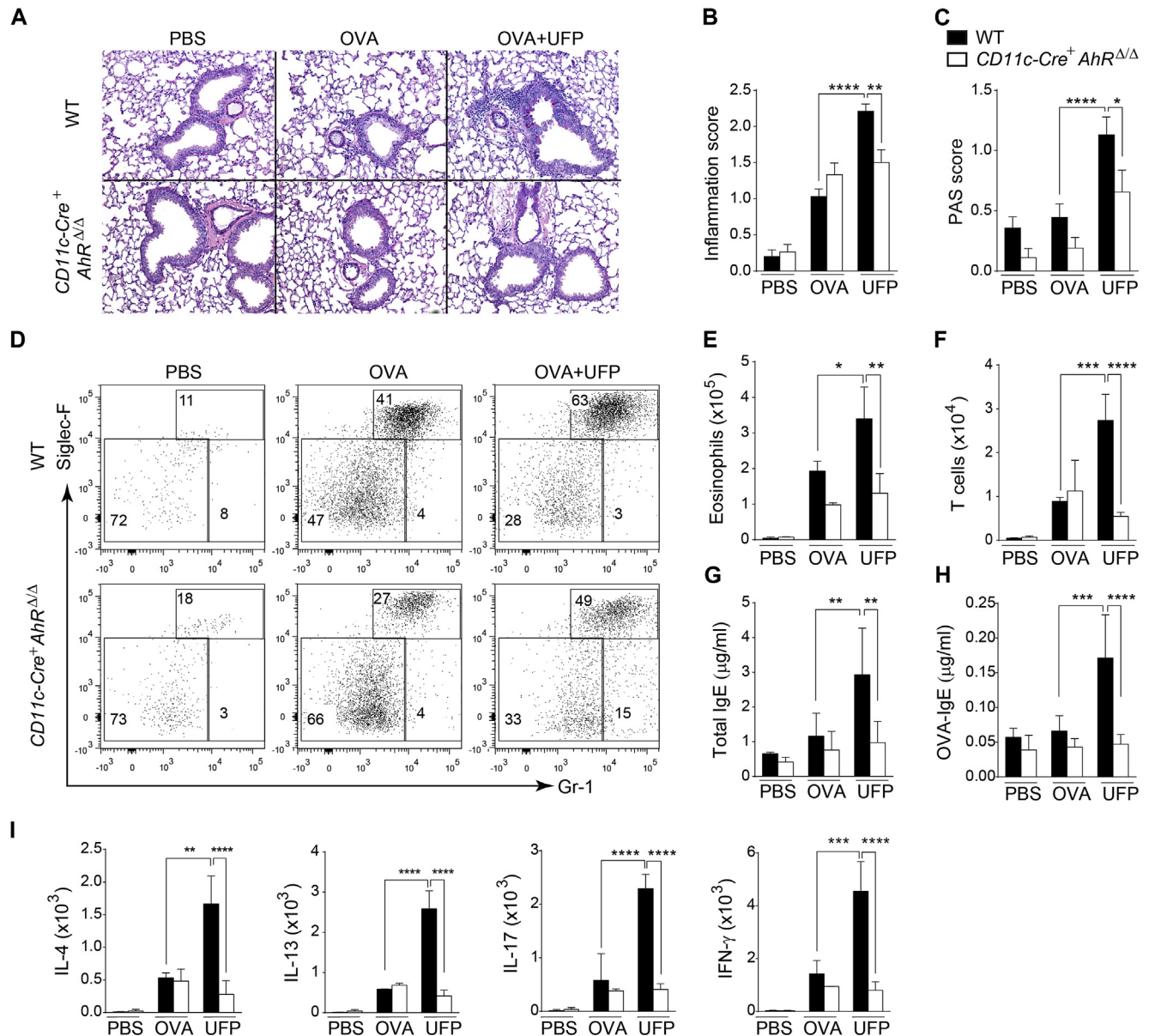


FIG 8. AhR lineage-specific deletion in CD11c⁺ cells confers protection against OVA- and OVA+UFP-induced airway inflammation. **A**, Representative PAS-stained sections of lung tissue isolated from WT and CD11c-Cre⁺ AhR^{Δ/Δ} mice in the PBS, OVA, or OVA+UFP groups (×200 magnification). **B** and **C**, Histologic inflammation (Fig 8, B) and PAS (Fig 8, C) scores in lung tissues isolated from the mouse groups described in Fig 8, A. **D**, Flow cytometric analysis of eosinophils and neutrophils in bronchoalveolar lavage fluid of WT and CD11c-Cre⁺ AhR^{Δ/Δ} mice in the PBS, OVA, or OVA+UFP groups. **E** and **F**, Eosinophil (Fig 8, E) and T-cell (Fig 8, F) absolute numbers in bronchoalveolar lavage fluid of WT and CD11c-Cre⁺ AhR^{Δ/Δ} mice in the PBS, OVA, or OVA+UFP groups. **G** and **H**, Total (Fig 8, G) and OVA-specific (Fig 8, H) IgE levels in serum of the mouse groups described in Fig 8, A. **I**, Absolute numbers of lung CD4⁺ T cells secreting IL-4, IL-13, IL-17, and IFN-γ in bronchoalveolar lavage fluid of the mouse groups described in Fig 8, A. Results are representative of 2 independent experiments (n = 5 mice per group). *P < .05, **P < .01, ***P < .001, and ****P < .0001, 2-way ANOVA with Bonferroni posttest analysis.

Notch1c expression of similar magnitude in lung T cells of OVA-sensitized and challenged WT and *Il4ra576* mice (Fig 3, J). UFP also upregulated to a similar degree the expression of Jag1 in DCs of treated mice of both genotypes (Fig 3, K). These results establish a gene-environment interaction between UFP and the *Il4ra576* allele in inducing allergic airway inflammation *in vivo*.

We also examined the capacity of UFP to complement the effects of a naturally occurring allergen, house dust mite (*D pteronyssinus*), in association with the *Il4ra4576* allele. Results were concordant with those observed with OVA sensitization and challenge. Whereas WT mice showed augmented inflammation with a combination of UFP and a low dose of *D pteronyssinus* (5 μg) in inducing airway inflammation,

this interaction was markedly amplified in the context of the *Il4ra4576* allele (see Fig E1 in this article's Online Repository at www.jacionline.org). These results confirm that UFP promote airway inflammation induced by a human allergen in the context of a proasthmatic human allele.

Il4raR576 mice were sensitized and challenged with OVA alone or together with FP, UFP, or CB to elucidate the effect of different PMs in allergic airway response. In line with their respective abilities to upregulate *Jag1* expression, UFP and FP, but not CB, upregulated allergic airway inflammation in OVA-sensitized *Il4raR576* mice (Fig 4). UFP were more effective on a mass basis than FP in enhancing OVA-induced airway inflammation, which is consistent with their increased surface area/weight ratio and higher penetrance into the airways.³⁵

UFP upregulate allergic airway inflammation in a Jag1-dependent manner

We next examined the effect of treatment with anti-Jag1 or an isotype control antibody on the airway inflammatory response in *Il4raR576* mice sensitized and challenged with OVA alone or together with UFP. Anti-Jag1 antibody treatment had little or no effect on the OVA challenge response in terms of tissue inflammation, goblet cell metaplasia airway hyperresponsiveness, airway eosinophilia, and IgE antibody response. In contrast, it inhibited the potentiation of the parameters induced by UFP (Fig 5, A-G). Similarly, anti-Jag1 antibody treatment inhibited the upregulation in cytokine production induced by UFP treatment of OVA-sensitized and challenged mice, including IL-4, IL-5, IL-13, IL-17, and IFN- γ , as well as the eosinophil chemotactic factor CCL11 (Fig 5, H-J). In a separate set of experiments, treatment of *Il4raR576* mice with GSI, a Notch pathway inhibitor, also reversed the upregulation by PM of these parameters of allergic airway inflammation, which is consistent with a role for this pathway in disease promotion by PM (Fig 6).

The role of Jag1 in mediating the upregulation by UFP of allergic airway inflammation was also verified by using house dust mites (*D pteronyssinus*) as an allergen. As in the OVA model, UFP augmented several parameters of airway inflammation induced by *D pteronyssinus*, including airway eosinophilia and T_H cytokine production in a Jag1-dependent manner. These results identified Jag1 induction as a common mechanism by which UFP upregulate airway inflammation by different allergens (see Fig E2 in this article's Online Repository at www.jacionline.org).

UFP upregulate Jag1 through an AhR-dependent mechanism

PM, particularly UFP, contains polycyclic aromatic hydrocarbons that act in part through the AhR receptor to induce cellular responses.^{42,43} UFP collected at night and in the early morning, which are enriched in polycyclic aryl hydrocarbons (PAHs) and other semivolatile hydrocarbons, were more effective in inducing Jag1 expression in mouse BMDCs than those collected in the afternoon, which are depleted of those compounds (Fig 7, A). An obligate role for the AhR in the induction by UFP of Jag1 expression was confirmed by several approaches. The AhR agonist 6-formylindolo (3,2-b) carbazole (6-FICZ) recapitulated the capacity of UFP to induce Jag1 protein

and transcript expression in BMDCs, as determined by means of flow cytometry and real-time PCR analysis, respectively. Reciprocally, the selective AhR receptor antagonist CH223191 inhibited the capacities of UFP and 6-FICZ to induce Jag1 expression (Fig 7, B and C). Importantly, deletion of a floxed *AhR* allele in BMDCs by coexpression of a CD11c-driven Cre recombinase transgene (*CD11c-Cre⁺AhR ^{Δ/Δ}*) abolished Jag1 induction by UFP and 6-FICZ (Fig 7, D). This was associated with profoundly decreased expression of mRNA encoding *Jag1* and *Ahr*, as determined by means of real-time PCR (Fig 7, E and F).

We analyzed the murine *Jag1* promoter for evidence of AhR response elements and identified candidate binding sites that incorporate the conserved central GCGTG core of the consensus AhR response element (T/GNNGCGTGA/CG/CA) in the proximal promoter region at positions -675, -575, and -515 (Fig 7, G).⁴⁴ Chromatin immunoprecipitation assays confirmed that stimulation with UFP and, to lesser extent, 6-FICZ resulted in immunoprecipitation of all 3 sites with an AhR antibody, with site 2 being the most active (Fig 7, H-J). We further analyzed the capacity of the respective sites to drive expression of a luciferase reporter gene under control of a minimal promoter in primary BMDCs. Stimulation of transfected cells with UFP or 6-FICZ resulted in increased luciferase expression driven by site 2 and, to a lesser extent, site 3, whereas site 1 was inactive (Fig 7, K). A luciferase reporter driven by a Jag1 promoter sequence spanning all 3 sites exhibited similar activity to one driven by site 2, indicating that the latter is the main target of AhR in the proximal *Jag1* promoter (data not shown). These results establish that UFP activate AhR to induce *Jag1* expression through a mechanism involving direct transcriptional activation of the Jag1 promoter.

We analyzed the role of AhR in upregulation by UFP of T_H cytokine expression in naive DO11.10⁺CD4⁺ *Il4raR576* T cells activated by OVA₃₂₃₋₃₃₉-pulsed BMDCs by using the AhR antagonist CH223191. Results revealed that treatment with CH223191 inhibited the upregulation by UFP of T_H cytokine expression in activated DO11.10⁺ T cells (see Fig E3, A, in this article's Online Repository at www.jacionline.org). Treatment with the AhR antagonist decreased the expression of Notch1c and the transcription of the Notch target gene *Hes1* in activated DO11.10⁺ T cells (see Fig E3, B-D). These results, together with those of Fig 5, are consistent with the upregulation by UFP of T_H cytokine expression in DO11.10⁺ T cell/OVA₃₂₃₋₃₃₉-pulsed DC cultures through an AhR-Jag1-mediated mechanism.

We determined the effect of lineage-specific deletion of AhR in CD11c⁺ cells on the airway inflammation seen in mice sensitized and challenged with OVA alone or with UFP. CD11c cell-specific deletion of AhR in *CD11c-Cre⁺AhR ^{Δ/Δ}* mice had a modest effect on the OVA challenge response in terms of airway eosinophilia, IgE antibody generation, and T_H cytokine production. In contrast, it inhibited the potentiation of these parameters induced by UFP (Fig 8). We further confirmed these results using the AhR antagonist CH223191, which was administered during the challenge phase to *Il4raR576* mice sensitized and challenged with OVA or *D pteronyssinus* alone or in the presence of UFP. CH223191 treatment had a modest effect on OVA or *D pteronyssinus* challenge responses in terms of airway eosinophilia, IgE antibody generation, and T_H cytokine production but inhibited the potentiation of these parameters

induced by UFP (see Figs E4 and E5 in this article's Online Repository at www.jacionline.org). Overall, these results supported a central role for AhR activation in mediating the trophic effects of UFP on allergic airway inflammation.

DISCUSSION

In this report we provide evidence that traffic-related PM, a major environmental pollutant implicated in increased incidence and severity of asthma, acts to promote allergic airway inflammation by modulating the expression of components of the Notch pathway. Studies on human monocytes and murine DCs confirmed the upregulation by PM of specific components of the Notch pathway, including Jag1, Notch1, and Fringe enzymes, as well as downstream targets of the Notch pathway. Furthermore, upregulation by PM of allergic airway inflammation was dependent on induction of Jag1 expression, which occurred through an AhR-dependent mechanism. These results outline a mechanistic cascade through which PM modulates the function of key developmental and regulatory pathways implicated in the differentiation of T_H subsets to promote disease.

The functional significance of the modulation of Notch pathway component expression by PM was revealed in both *in vitro* and *in vivo* studies. *In vitro* PM augmented the capacity of OVA₃₂₃₋₃₃₉ peptide-presenting BMDCs to induce T_H1, T_H2, and T_H17 cytokines in naive DO11.10⁺ T cells in a Jag1-dependent fashion. These results are consistent with the recently reported function of Notch as an unbiased amplifier of T_H cell differentiation.⁴⁵ In the context of a pro-T_H2 genetic element, the human *Il4ra*576 polymorphism, PM also upregulated production of the different T_H cytokines, although with a T_H2-skewed profile that reflected the inherent T_H2 bias of the responding *Il4ra*576 T cells. *In vivo* PM exposure also interacted with *Il4ra*576 to promote allergic airway inflammation in a Notch pathway-dependent manner. These findings implied that the inflammatory outcome of exposure to PM is orchestrated by Notch signaling under the influence of the prevailing T_H bias of the responding host. Thus PM might interact with host proallergic and proasthmatic genetic factors to promote allergic diseases and asthma. Similarly, PM components might interact with other genetic host factors to promote different outcomes, such as chronic obstructive lung disease and atherosclerosis.

The mechanism by which PM induced Notch pathway components involved activation of the AhR pathway. Treatment with a selective AhR inhibitor or deletion of AhR in CD11c⁺ DCs abrogated the induction by PM of Jag1 expression in BMDCs and suppressed their capacity to upregulate T_H cytokine expression by antigen-specific naive T cells. Pharmacologic AhR inhibition or lineage-specific deletion of AhR in CD11c⁺ cells also abrogated upregulation by PM of airway inflammation. Induction by AhR of Jag1 expression involved direct activation of the Jag1 promoter at specific AhR response elements. PM, especially UFP, is enriched in PAHs, agonistic ligands for the AhR that have been previously tied to the adjuvant-like effect of these particles.^{44,46,47} Our results provide a molecular basis for PM adjuvancy by linking AhR activation by PAHs of PM to the induction of Jag1 expression on antigen-presenting cells and, consequently, Notch signaling in T cells.

Unlike larger particles, UFP are not regulated by the US Environmental Protection Agency. Nevertheless, comparison of the different particles revealed that UFP were, per unit weight, the

most effective among the particles tested in inducing Jag1-dependent airway inflammation. The smaller effective aerodynamic diameter of UFP enables deeper penetration into the airways compared with larger particles. Also, the larger surface area per particle unit weight, greater PAH content, and higher oxidant potential all enable more potent biological responses.⁴⁷ Aside from the respiratory system, UFP exposure has been associated with cardiovascular and neurologic diseases, especially atherosclerosis.⁴⁸⁻⁵⁰ The role of the AhR-Jag1/Notch pathway in mediating the extrapulmonary effects of UFP and other particles remains to be established.

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Key messages

- Traffic-related PM activates AhR to induce the expression of the Notch ligand Jag1 on antigen-presenting cells.
- Jagged-Notch interaction promotes allergic airway inflammation.
- The AhR-Jag1-Notch cascade acts in concert with proasthmatic alleles to mediate heightened allergic airway inflammation.

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**Vehicular Exhaust Particles Promote Allergic Airway Inflammation via an Aryl
Hydrocarbon Receptor-Notch Signaling Cascade**

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SUPPLEMENTARY METHODS

Reagents The aryl hydrocarbon receptor (AhR) ligand 6-Formylindolo (3,2-b) carbazole (FICZ) and AhR antagonist CH223191 were purchased from Santa Cruz Biotechnology, Inc. The gamma secretase inhibitor (GSI) L-685,458 was from EMD Millipore (Billerica, MA) Lyophilized dust mites (*D. Pteronyssinus*) whole body extract was obtained from Greer (Lenoir, NC)

Gene expression profiling. Human peripheral blood monocytes were purified by magnetic bead sorting, and their purity was verified >90% by flow cytometry (Miltenyi Biotec). Monocytes were either sham treated with PBS or exposed for 4 hours to DEP at 10 µg/ml/culture well in PBS. Total RNA was derived and used to create probes for Affymetrix 133 2.0 chips. For the analysis of gene expression measures, all Affymetrix data were normalized using the justRMA algorithm from the Bioconductor group ¹. Pair-wise comparisons were made between the untreated/treated samples such that probe sets which showed at least a 2-fold change in expression, as specified for the respective group comparisons, were selected out for further analysis. Results represent mean fold change values that scored at $p < 0.05$ by Student's unpaired two-tailed T test adjusted for multiple comparisons with a false discovery rate (FDR) ≤ 0.15 ².

Real time PCR analysis. cDNA was reverse transcribed from 2 µg of RNA/sample and used in real-time PCR assays that employed Taqman (Applied Biosystems) and SYBR green-based reagents (Life Technologies). The comparative Ct (threshold cycle) method normalized to GAPDH was used to analyze relative changes in gene expression. The fold-change was calculated as $2^{-\Delta\Delta Ct}$ for negative $\Delta\Delta Ct$ values (indicating a fold change increase) and $-2^{\Delta\Delta Ct}$ for positive $\Delta\Delta Ct$ values (indicating a fold change decrease).

Flow cytometry and intracellular staining. Single-cell suspensions were stained with the indicated antibodies and analyzed on LSRIIFortessa cytometer (Becton Dickinson). Cytokine expression in CD4⁺ T cells was determined by stimulating cells with PMA (20 ng/ml) plus

ionomycin (1 µg/ml) for 4 hours in the presence of Golgi-plug (BD Biosciences) followed by intracellular staining for the respective cytokine using the eBioscience Fixation/Permeabilization buffer following the manufacturer's instructions. Fluorescence-conjugated mAbs used were obtained from BD Biosciences, Biolegend and eBioscience. Anti-CD3-FITC, PECy7, PerCPCy5.5 (145 2C11), anti-CD4-AF700 (GK1.5), anti-CD8-PerCPCy5.5 (53-6.7), anti-B220-APC (RA3-6B2), anti-F4/80-Pacific Blue (BM8), anti-CD11b-PerCPCy5.5 (M1/70), anti-MHC II I-Ad (39-10-8) and Anti-CD45-AF700 (30-F11) were purchased from Biolegend. Anti-CD4 eFluor 450 (GK1.5), anti-CD19-FITC (6D5), anti-Gr-1-PerCPCy5.5 (RB6-8C5), anti-IL4-PE-CF594 (11B11, BD), anti-IL13-PE(eBio13A), anti-IL17-PECy7 (eBio17B7), anti-IFN-γ-APC (XMG1.2), anti-Jagged-1-PE (HMJ1-29) anti-Notch1-APC (22E5) and anti-CD11c-PECy7(N418) were obtained from eBioscience. Anti-Siglec-F-PE (E50-2440) was purchased from BD Bioscience.

IgE and Th cytokine ELISAs. Total and OVA-specific IgE concentrations were measured by using sandwich ELISAs as previously described³. BAL fluid and co-culture supernatant were assayed by cytokine detection kits purchased from eBioscience.

Measurement of airway hyper-responsiveness. Airway resistance was measured 24 h after the last day of OVA or OVA/UFP challenge. The mice were anesthetized and instrumented for the measurement of pulmonary mechanics (BUXCO Electronics) as detailed ⁴. Baseline lung resistance (RL) and responses to aerosolized saline (0.9% NaCl) were measured first, followed by responses to increasing doses (0.32 to 10 mg/ml) of aerosolized acetyl-β-methylcholine chloride (methacholine; Sigma-Aldrich). The three highest values of RL obtained after each dose of methacholine were averaged to obtain the final values for each dose.

Chromatin Immunoprecipitation (ChIP) assays. Sham- or UFP-treated BMDCs (10⁷ cells per sample) were fixed by 0.75% formaldehyde for 30 minutes at RT. Glycine was added to a final concentration of 125 mM, and the cells were treated with 750 l lysis buffer and sonicated for

20 min. The supernatants were collected and 2 μ g anti-AhR antibodies (RPT-9, Thermo Scientific, IL) or isotype control antibody were added for each 25 μ g DNA. The mixes were incubated with 20 μ l of protein G beads overnight at 4°C. Protein/DNA complex was treated with 100 μ g proteinase K at 65°C for 6 hours to reverse cross-links. DNA products were further purified with DNA Clean & Concentrator (ZYMO Research, CA). The retrieved DNA was analyzed for presence of the candidate AhR binding sites by real time-PCR using SYBR Green dye and the following primers: *Jag1* AhR B1-F: 5'-CCTTCCAGGTTTCCTTTC TCC-3', *Jag1* AhR B1-R: 5'-GAGAAGGGGTTGGAAGTTGC-3'. *Jag1* AhR B2-F: 5'-CAACTTCCAACCCCTTCTCA-3', *Jag1* AhR B2-R: 5'-GCATGCGCGATTGTTAATATTCA-3', *Jag1* AhR B3-R: 5'-TTGTTCCGCGTGTGAGA AG-3', *Jag1* AHR B3-R: 5'-GGCTGCAGGTAACACAATGA-3'. AhR DNA binding capacity was calculated by taking the ratio of the amount of pull-down versus input DNA.

Luciferase assays. Candidate AhR response elements (AREs) located in the *Jag1* promoter region were subcloned into pTA-Luc luciferase vector. Constructs were transfected into 1×10^7 BMDCs by electroporation using the Amaxa system. Cells were further treated with indicated reagents for 18 hours. Luciferase activity of transfected cells was assayed by Luciferase Assay System (Pormega, WI) and measured by luminometer. Fold induction was calculated by taking the ratio of the readout of target vector and empty vector.

SUPPLEMENTAL FIGURE LEGENDS

Figure E1. UFP synergizes with the *Il4raR576* pro-allergic allele to promote dust mite (DM)-induced allergic airway inflammation. **(A)** Flow cytometric analysis of eosinophils and neutrophils in the BAL fluid of WT and *Il4raQ576R* mice treated with PBS, DM or DM+UFP. **(B and C)** Total number of eosinophils **(B)** and T cells **(C)** in the BAL fluids of the mouse groups described in panel **(A)**. **(D)** Flow cytometric analysis of the cytokine expression by CD4⁺ T cells isolated from the lung of WT and *Il4raQ576R* mice treated with DM and UFP. **(E)** Absolute numbers of lung CD4⁺ T cells producing IL-4, IL13, IL-17 and IFN- γ in the BAL fluids of DM- and UFP-treated WT and *Il4raQ576R* mice. Results are representative of two independent experiments. N=5/group. *p<0.05, **<0.01, ***<0.001, ****<0.0001 by two way ANOVA with Bonferroni post test analysis.

Figure E2. UFP enhance DM-induced airway inflammation in a Jag1-dependent manner. **(A)** Representative PAS staining of lung tissues isolated from *Il4raR576* mice sensitized with PBS, DM or DM+UFP and in association with anti-Jag1 or an isotype control mAb (200X magnification). **(B and C)** Inflammatory **(B)** and PAS **(C)** scores of the mouse groups described in panel **(A)**. **(D and E)** Absolute numbers of eosinophils **(D)** and T cells **(E)** in the BAL fluids the mouse groups described in panel **(A)**. **(F)** Flow cytometric analysis of cytokine expression by lung CD4⁺ T cells isolated from *Il4raR576* mice sensitized with DM+UFP and in association with anti-Jag1 or an isotype control mAb. **(G)** Absolute numbers of lung CD4⁺ T cells producing IL-4, IL13, IL-17 and IFN- γ in the BAL fluids of *Il4raR576* mice sensitized with PBS, DM or DM+UFP and in association with anti-Jag1 or an isotype control mAb. Results are representative of 2 independent experiments. N=5/group. *p<0.05, **<0.01, ***<0.001, ****<0.0001 by two way ANOVA with Bonferroni post test analysis.

Figure E3. UFP promote Th cytokine production in an AhR-dependent mechanism. **(A)** Th cytokine production by naïve *Il4ra*^{R576} CD4⁺DO11.10⁺Rag2^{-/-} T cells co-cultured with BMDCs treated with PBS (sham), UFP, OVA₃₂₃₋₃₃₉ or UFP+OVA₃₂₃₋₃₃₉ in presence or absence of CH223191. **(B and C)** Representative flow cytometric analysis **(B)** and MFI **(C)** of Notch1 intracellular expression by *Il4ra*^{R576}CD4⁺DO11.10⁺Rag2^{-/-} T cells co-cultured with BMDCs sham-treated (DMSO) or CH223191 treated. **(D)** *Hes1* mRNA levels in T cell co-cultured as described in panel **(A)**. Results are representative of 3 independent experiments. N=3/group. *p<0.05, **<0.01, ***<0.001, ****<0.0001 by two way ANOVA with Bonferroni post test analysis.

Figure E4. UFP promotes OVA-induced airway inflammation in an AhR-dependent mechanism. **(A)** Representative PAS staining sections of lung tissues isolated from *Il4ra*^{R576} mice treated with PBS, OVA or OVA+UFP in the presence of either CH223191 or the vehicle control (200X magnification). **(B and C)** Inflammation score **(B)** and PAS scores **(C)** of the mouse groups described in panel **(A)**. **(D)** Flow cytometric analysis of eosinophils and neutrophils in the BAL fluid of the mouse groups described in panel **(A)**. **(E and F)** Absolute numbers of eosinophils **(E)** and T cells **(F)** in the BAL fluids of the mouse groups described in panel **(A)**. **(G and H)** Total IgE **(G)** and OVA-specific IgE **(H)** serum levels in the mouse groups described in panel **(A)**. **(I and J)** Flow cytometric analysis **(I)** and absolute numbers **(J)** CD4⁺T cells producing IL-4, IL13, IL-17 and IFN- γ in the BAL fluid of *Il4ra*^{R576} mice treated with PBS, OVA or OVA+UFP in the presence of either CH223191 or the vehicle control. Results are representative of 3 independent experiments, N=4-5/group. *p<0.05, **<0.01, ***<0.001, ****<0.0001 by two way ANOVA with Bonferroni post test analysis

Figure E5. UFP promotes DM-induced airway inflammation in AhR-dependent mechanism. **(A)** representative PAS staining sections of lung tissues isolated from *Il4ra*^{R576} mice treated with

PBS, DM or DM+UFP in the presence of CH223191 or vehicle control (200X magnification). **(B)** and **(C)** Inflammation score **(B)** and PAS scores **(C)** of the mouse groups described in panel **(A)**. **(D)** Flow cytometric analysis of eosinophils and neutrophils in the BAL fluid of the mouse groups described in panel **(A)**. **(E)** and **(F)** Absolute numbers of eosinophils **(E)** and T cells **(F)** in the BAL fluids of the mouse groups described in panel **(A)**. **(G)** and **(H)** Flow cytometric analysis **(G)** and absolute numbers **(H)** CD4⁺T cells producing IL-4, IL13, IL-17 and IFN- γ in the BAL fluid of the mouse groups described in panel **(A)**. Results are representative of 3 independent experiments, N=4-5/group. *p<0.05, **<0.01, ***<0.001, ****<0.0001 by two way ANOVA with Bonferroni post test analysis

SUPPLEMENTAL TABLE

Table E1.

Differentially expressed genes induced by DEP treatment of human monocytes. Monocytes of individual donors were either sham treated (PBS) or treated with DEP (10 μ g/ml for 4 h). Genes were selected with a 2 fold change cutoff filter, with p value p<0.05 by paired two tailed test and an FDR $\leq$ 0.15. Changes in gene fold change expression are expressed on a log2 scale.

SUPPLEMENTAL REFERENCES

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SUPPLEMENTAL TABLE

Table E1.

Differentially expressed genes induced by DEP treatment of human monocytes. Monocytes of individual donors were either sham treated (PBS) or treated with DEP (10 µg/ml for 4 h), then analyzed for differentially expressed gene transcripts. Genes were selected with a 2 fold change cutoff filter, with p value $p < 0.05$ by paired two tailed test and an FDR ≤ 0.15 . Changes in gene fold change expression are expressed on a log2 scale.

Gene Symbol	Probe ID	logFC	t	P.Value	adj.P.Val
DNAJA4	1554333_at	7.492	15.981	0.000	0.005
DNAJA4	225061_at	7.139	14.377	0.000	0.008
DNAJA4	1554334_a_at	7.088	12.209	0.000	0.013
HSPA6	117_at	6.882	6.171	0.000	0.065
BRE	1568768_s_at	6.688	15.532	0.000	0.005
NA	235573_at	6.021	9.976	0.000	0.021
HSPA1B	202581_at	5.978	5.897	0.000	0.069
HSPA6	213418_at	5.725	4.682	0.002	0.117
DNAJB1	200664_s_at	5.502	4.698	0.002	0.116
HSPA1L	233694_at	5.274	4.235	0.003	0.146
NA	234986_at	5.231	6.697	0.000	0.056
GCLM	203925_at	5.205	7.196	0.000	0.049
FKBP4	200894_s_at	5.192	8.019	0.000	0.037
DNAJB4	203811_s_at	5.123	5.910	0.000	0.069
GCLM	236140_at	5.100	6.335	0.000	0.063
DNAJB4	203810_at	5.076	4.597	0.002	0.121
HES1	203394_s_at	5.002	10.123	0.000	0.021
HSPB1	201841_s_at	4.787	4.848	0.002	0.109
FOSB	202768_at	4.667	8.713	0.000	0.030
C16orf81	1553449_at	4.664	10.591	0.000	0.018
BAG3	217911_s_at	4.631	4.573	0.002	0.122
HSPA2	211538_s_at	4.494	7.466	0.000	0.043
HSPE1	205133_s_at	4.444	4.386	0.003	0.134
HSPH1	208744_x_at	4.424	4.468	0.002	0.128
SERPINH1	207714_s_at	4.379	5.980	0.000	0.068
NR4A2	204621_s_at	4.187	5.523	0.001	0.077
NR4A2	216248_s_at	4.169	7.550	0.000	0.042
HSPH1	206976_s_at	4.155	5.029	0.001	0.099
ERRFI1	224657_at	4.124	4.955	0.001	0.102
SPAG5	203145_at	4.117	6.107	0.000	0.066

ZEB1	208078_s_at	4.096	6.421	0.000	0.062
NA	227140_at	4.077	8.904	0.000	0.029
HIST1H2AM	214481_at	4.066	4.370	0.003	0.135
NA	242300_at	4.028	9.050	0.000	0.028
DHRS9	224009_x_at	3.999	6.953	0.000	0.052
NA	243791_at	3.913	5.953	0.000	0.069
NA	228655_at	3.810	6.013	0.000	0.068
HOMER1	213793_s_at	3.804	6.189	0.000	0.065
OSGIN1	219475_at	3.780	4.646	0.002	0.118
LY6K	223687_s_at	3.779	6.433	0.000	0.062
NA	244080_at	3.767	8.258	0.000	0.033
EID3	231292_at	3.710	7.890	0.000	0.039
NR4A2	204622_x_at	3.684	5.667	0.001	0.073
DHRS9	223952_x_at	3.679	6.729	0.000	0.055
NA	236898_at	3.646	8.825	0.000	0.030
ULBP2	238542_at	3.585	4.226	0.003	0.147
JMY	241985_at	3.557	5.013	0.001	0.099
ACAT2	222011_s_at	3.550	6.068	0.000	0.066
TM7SF4	221266_s_at	3.514	6.856	0.000	0.052
HIST1H2BG	210387_at	3.435	4.429	0.003	0.132
FBXO30	226541_at	3.427	6.831	0.000	0.053
AREG	205239_at	3.420	5.827	0.000	0.070
NA	1560869_a_at	3.412	6.446	0.000	0.061
KLF4	220266_s_at	3.361	5.545	0.001	0.077
NA	1555858_at	3.343	8.303	0.000	0.033
NA	1555860_x_at	3.330	6.859	0.000	0.052
FNIP2	1569352_at	3.326	4.413	0.003	0.133
TSPYL2	218012_at	3.290	6.695	0.000	0.056
CREM	230511_at	3.283	5.593	0.001	0.076
HSP90AB1	1557910_at	3.272	5.171	0.001	0.091
PMAIP1	204286_s_at	3.241	5.392	0.001	0.082
NA	243918_at	3.145	4.736	0.002	0.114
PMAIP1	204285_s_at	3.133	4.674	0.002	0.117
HSPA1L	210189_at	3.130	5.126	0.001	0.093
KLF4	221841_s_at	3.104	4.707	0.002	0.116
RASD1	223467_at	3.095	4.972	0.001	0.101
EIF2AK3	218696_at	3.066	6.882	0.000	0.052
THAP2	230380_at	3.051	5.489	0.001	0.078
INHBA	210511_s_at	3.030	5.810	0.001	0.071
NA	227044_at	3.021	5.073	0.001	0.096
GPR109B	205220_at	2.987	6.099	0.000	0.066
PTTG1	203554_x_at	2.980	5.430	0.001	0.081
SETDB2	1564970_at	2.976	5.669	0.001	0.073

MAF	206363_at	2.967	5.093	0.001	0.095
TUFT1	205807_s_at	2.949	7.250	0.000	0.048
DHRS9	219799_s_at	2.929	4.195	0.003	0.148
ERN1	235745_at	2.914	7.106	0.000	0.051
TncRNA	214657_s_at	2.903	4.491	0.002	0.128
CREM	209967_s_at	2.902	13.236	0.000	0.011
ANXA1	233011_at	2.873	4.777	0.002	0.112
NSMAF	232148_at	2.841	5.581	0.001	0.077
HSPD1	243372_at	2.791	5.841	0.000	0.070
ELL2	214446_at	2.787	5.028	0.001	0.099
GADD45B	207574_s_at	2.764	17.378	0.000	0.004
TM4SF19	228606_at	2.758	4.367	0.003	0.135
RASGEF1B	1553785_at	2.757	4.404	0.003	0.133
ARRDC3	224797_at	2.751	4.521	0.002	0.126
CTH	217127_at	2.750	4.965	0.001	0.102
JAG1	231183_s_at	2.727	4.234	0.003	0.146
NRARP	226499_at	2.721	7.825	0.000	0.040
KLHL21	203068_at	2.689	5.632	0.001	0.074
NA	239845_at	2.674	4.452	0.002	0.130
MTHFD2L	220346_at	2.653	4.488	0.002	0.128
AKR1C2	211653_x_at	2.650	4.294	0.003	0.141
ZC3HAV1	225634_at	2.644	10.625	0.000	0.018
GADD45B	209304_x_at	2.631	5.804	0.001	0.071
FOSL1	204420_at	2.625	6.338	0.000	0.063
NA	237204_at	2.603	4.559	0.002	0.123
CTNNAL1	202468_s_at	2.597	4.467	0.002	0.128
NA	242007_at	2.588	4.997	0.001	0.100
RRAD	204802_at	2.573	5.861	0.000	0.070
NRIP3	219557_s_at	2.564	6.981	0.000	0.052
FLJ20489	48106_at	2.561	4.764	0.002	0.112
HES4	227347_x_at	2.556	6.283	0.000	0.064
LY9	231124_x_at	2.504	5.708	0.001	0.073
NA	235652_at	2.503	4.657	0.002	0.118
PHLDA2	209803_s_at	2.489	4.259	0.003	0.144
HSPA8	208687_x_at	2.430	6.736	0.000	0.055
FLJ21865	220349_s_at	2.402	6.370	0.000	0.062
JMJD1C	228793_at	2.395	5.568	0.001	0.077
NA	1570623_at	2.392	10.658	0.000	0.018
HOMER1	226651_at	2.377	4.490	0.002	0.128
ADNP2	203322_at	2.339	8.789	0.000	0.030
ASPH	242037_at	2.298	5.508	0.001	0.078
DUSP5	209457_at	2.298	4.939	0.001	0.102
EFNB2	202668_at	2.297	4.610	0.002	0.120

LOC338758	238893_at	2.280	4.728	0.002	0.114
LOC440944	232052_at	2.270	10.254	0.000	0.021
MUM1	223348_x_at	2.253	5.822	0.000	0.070
FXR2	222050_at	2.251	5.236	0.001	0.088
PLK2	201939_at	2.249	5.218	0.001	0.089
MUM1	221290_s_at	2.244	7.627	0.000	0.042
LOC647190	1566079_at	2.237	10.895	0.000	0.018
DUSP4	204015_s_at	2.216	4.856	0.002	0.108
CACYBP	201382_at	2.215	6.453	0.000	0.061
ASPH	209135_at	2.214	4.373	0.003	0.135
TTC32	226838_at	2.185	4.660	0.002	0.118
HSPA8	224187_x_at	2.165	6.277	0.000	0.064
NA	244397_at	2.162	4.589	0.002	0.121
NA	244341_at	2.147	7.981	0.000	0.037
EIF5	208707_at	2.146	5.523	0.001	0.077
MYO10	1554026_a_at	2.132	4.700	0.002	0.116
PPID	204186_s_at	2.131	5.038	0.001	0.098
SETDB2	1564972_x_at	2.115	4.399	0.003	0.133
ODC1	200790_at	2.112	9.743	0.000	0.023
HES1	203395_s_at	2.104	5.076	0.001	0.096
BCL10	1557257_at	2.102	6.160	0.000	0.065
NA	233303_at	2.094	4.807	0.002	0.110
NA	228346_at	2.079	5.916	0.000	0.069
GADD45G	204121_at	2.057	4.381	0.003	0.135
C6orf106	217924_at	2.048	4.205	0.003	0.148
KHDRBS3	209781_s_at	2.018	4.476	0.002	0.128
CSRP2	207030_s_at	2.018	4.657	0.002	0.118
RGS1	216834_at	2.009	6.940	0.000	0.052
IFRD1	202146_at	1.999	5.414	0.001	0.082
MAFF	36711_at	1.999	6.385	0.000	0.062
NA	230201_at	1.991	4.480	0.002	0.128
NAP1L5	228063_s_at	1.979	5.009	0.001	0.099
MUM1	229033_s_at	1.976	5.040	0.001	0.098
NA	239331_at	1.968	4.379	0.003	0.135
DKFZp451A211	1556114_a_at	1.960	4.218	0.003	0.147
FNIP1	1559060_a_at	1.959	5.352	0.001	0.083
HEY1	218839_at	1.944	4.790	0.002	0.111
ETNK1	224454_at	1.940	5.373	0.001	0.083
EMP1	1564796_at	1.936	4.491	0.002	0.128
FAM46A	221766_s_at	1.932	5.110	0.001	0.094
NA	241893_at	1.909	9.230	0.000	0.028
HTRA3	226944_at	1.903	5.730	0.001	0.073
TOB1	202704_at	1.896	6.146	0.000	0.065

BEX2	224367_at	1.873	5.601	0.001	0.076
GCLC	202922_at	1.859	4.408	0.003	0.133
LOC23117	81737_at	1.846	5.531	0.001	0.077
NA	231199_at	1.838	4.577	0.002	0.122
NA	242975_s_at	1.823	5.551	0.001	0.077
HSPA4	208815_x_at	1.823	5.549	0.001	0.077
IRS2	209184_s_at	1.822	12.260	0.000	0.013
C7orf53	239203_at	1.814	7.371	0.000	0.045
SNORA28	241843_at	1.789	4.210	0.003	0.148
N4BP2L1	229718_at	1.785	5.341	0.001	0.083
NR4A1	202340_x_at	1.763	8.463	0.000	0.031
LOC100133660	230082_at	1.754	4.210	0.003	0.148
SPTY2D1	235440_at	1.752	4.887	0.001	0.106
IRS2	209185_s_at	1.738	4.671	0.002	0.118
NA	222900_at	1.731	5.951	0.000	0.069
NA	221200_at	1.723	4.792	0.002	0.111
NA	230048_at	1.715	4.646	0.002	0.118
TP53INP2	224836_at	1.711	6.989	0.000	0.052
NA	243371_at	1.704	4.187	0.003	0.148
NUDC	210574_s_at	1.698	6.211	0.000	0.065
JMJD1C	224933_s_at	1.696	4.886	0.001	0.106
MBOAT7	211037_s_at	1.679	6.591	0.000	0.059
NA	242836_at	1.623	6.026	0.000	0.068
NBEAL1	1554106_at	1.589	4.192	0.003	0.148
FXR1	201637_s_at	1.548	5.800	0.001	0.071
NA	236699_at	1.547	6.265	0.000	0.064
LOC644656	229870_at	1.541	5.518	0.001	0.077
BANP	228928_x_at	1.539	6.223	0.000	0.065
KLF5	209211_at	1.530	4.278	0.003	0.142
NA	242431_at	1.515	5.209	0.001	0.089
SYK	207540_s_at	-1.500	-5.411	0.001	0.082
C17orf42	219146_at	-1.502	-8.373	0.000	0.032
NA	222275_at	-1.502	-4.247	0.003	0.145
LOC283267	226793_at	-1.504	-4.892	0.001	0.106
CSRP2BP	228544_s_at	-1.506	-5.983	0.000	0.068
DDX20	224315_at	-1.506	-5.407	0.001	0.082
HDHD2	223155_at	-1.507	-4.941	0.001	0.102
PURA	204020_at	-1.507	-4.759	0.002	0.112
NUP133	202184_s_at	-1.509	-5.352	0.001	0.083
SLC29A3	219344_at	-1.510	-5.205	0.001	0.089
TIMP2	231579_s_at	-1.511	-4.865	0.001	0.107
SLC7A6	203580_s_at	-1.511	-4.328	0.003	0.139
FRAT2	209864_at	-1.512	-5.455	0.001	0.079

EIF2B4	215482_s_at	-1.513	-4.647	0.002	0.118
OGFOD1	225110_at	-1.513	-4.469	0.002	0.128
RIOK1	224450_s_at	-1.516	-4.545	0.002	0.124
GLT1D1	229770_at	-1.517	-8.912	0.000	0.029
DDX28	40255_at	-1.518	-6.095	0.000	0.066
TRIM13	230192_at	-1.519	-4.830	0.002	0.109
LOC644096	44669_at	-1.520	-4.609	0.002	0.120
NA	226116_at	-1.521	-4.651	0.002	0.118
SF3B3	200687_s_at	-1.522	-7.749	0.000	0.041
STAT5A	203010_at	-1.522	-7.916	0.000	0.038
TXNL4A	202836_s_at	-1.528	-4.989	0.001	0.100
KPNA6	226976_at	-1.530	-4.527	0.002	0.126
VPS26B	225483_at	-1.532	-4.287	0.003	0.141
ADRBK2	204184_s_at	-1.535	-4.467	0.002	0.128
NA	240121_x_at	-1.536	-5.720	0.001	0.073
ANAPC5	208722_s_at	-1.537	-4.413	0.003	0.133
PALB2	219530_at	-1.540	-5.836	0.000	0.070
NA	241344_at	-1.540	-4.610	0.002	0.120
ANGEL2	221825_at	-1.545	-4.472	0.002	0.128
LDB1	203451_at	-1.548	-4.974	0.001	0.101
PRMT5	1564520_s_at	-1.550	-4.656	0.002	0.118
ZNHIT6	218932_at	-1.551	-5.647	0.001	0.074
TAF1B	216941_s_at	-1.552	-4.526	0.002	0.126
CRLS1	225324_at	-1.552	-4.443	0.003	0.131
TSFM	212656_at	-1.553	-6.917	0.000	0.052
IKZF1	227344_at	-1.556	-5.408	0.001	0.082
BICD2	212702_s_at	-1.556	-4.808	0.002	0.110
DAGLB	226640_at	-1.556	-5.365	0.001	0.083
ANAPC4	232524_x_at	-1.557	-5.528	0.001	0.077
PPAN	221649_s_at	-1.559	-5.417	0.001	0.082
NA	244650_at	-1.559	-5.144	0.001	0.092
GTPBP4	218239_s_at	-1.560	-8.027	0.000	0.037
OSCAR	1554503_a_at	-1.565	-4.429	0.003	0.132
DCTD	201572_x_at	-1.566	-4.260	0.003	0.144
RP9	227852_at	-1.566	-4.840	0.002	0.109
AGGF1	222661_at	-1.567	-12.177	0.000	0.013
VPS13C	235023_at	-1.569	-5.319	0.001	0.084
LTV1	225748_at	-1.572	-7.546	0.000	0.042
FAM62A	208858_s_at	-1.572	-6.800	0.000	0.054
ARMC10	1554480_a_at	-1.575	-4.686	0.002	0.117
ELOVL1	218028_at	-1.575	-4.407	0.003	0.133
NMT1	201158_at	-1.576	-4.739	0.002	0.114
AKAP1	201675_at	-1.576	-4.823	0.002	0.110

ARHGAP1	202117_at	-1.577	-5.206	0.001	0.089
NDUFS2	201966_at	-1.580	-7.265	0.000	0.048
SLC25A11	207088_s_at	-1.580	-4.237	0.003	0.146
ATR	209903_s_at	-1.580	-4.652	0.002	0.118
ABCC10	213485_s_at	-1.580	-5.324	0.001	0.084
CEP350	213956_at	-1.583	-4.326	0.003	0.139
MLXIP	202519_at	-1.584	-5.569	0.001	0.077
USP4	202681_at	-1.585	-5.113	0.001	0.094
MRPL12	203931_s_at	-1.586	-4.896	0.001	0.106
STUB1	233049_x_at	-1.586	-4.866	0.001	0.107
EIF3B	208688_x_at	-1.586	-7.924	0.000	0.038
NA	235459_at	-1.587	-5.981	0.000	0.068
C18orf55	223180_s_at	-1.588	-6.237	0.000	0.065
POLR3A	231763_at	-1.588	-4.932	0.001	0.102
SMCR7L	204593_s_at	-1.589	-5.653	0.001	0.073
AGPS	225108_at	-1.589	-4.340	0.003	0.138
EXOSC10	207541_s_at	-1.589	-4.781	0.002	0.112
AGL	203566_s_at	-1.591	-4.318	0.003	0.140
PPIL1	222500_at	-1.595	-4.196	0.003	0.148
SDCCAG8	227785_at	-1.596	-4.733	0.002	0.114
ABHD10	218633_x_at	-1.597	-4.868	0.001	0.107
TRADD	1729_at	-1.597	-6.466	0.000	0.061
NARG1	222837_s_at	-1.600	-4.470	0.002	0.128
DNAJA3	1554078_s_at	-1.601	-5.195	0.001	0.089
ST14	202005_at	-1.602	-4.343	0.003	0.138
NCF1B	214084_x_at	-1.603	-5.112	0.001	0.094
RHOT1	222148_s_at	-1.605	-4.487	0.002	0.128
NSUN2	223076_s_at	-1.607	-4.304	0.003	0.141
SPTLC2	203128_at	-1.607	-5.355	0.001	0.083
SUFU	222749_at	-1.608	-4.862	0.001	0.108
PIK3AP1	226459_at	-1.608	-5.241	0.001	0.088
TCF3	209153_s_at	-1.610	-4.289	0.003	0.141
PARP1	208644_at	-1.610	-6.504	0.000	0.060
SF3A3	203818_s_at	-1.611	-6.655	0.000	0.057
SMARCC1	201075_s_at	-1.611	-4.574	0.002	0.122
NXT1	218708_at	-1.613	-4.255	0.003	0.144
NFATC1	211105_s_at	-1.613	-4.407	0.003	0.133
DLAT	213149_at	-1.616	-4.379	0.003	0.135
RANBP6	213019_at	-1.616	-5.917	0.000	0.069
C6orf203	223576_at	-1.616	-4.481	0.002	0.128
ZNF260	1558700_s_at	-1.619	-6.903	0.000	0.052
GPR172A	222155_s_at	-1.620	-4.319	0.003	0.140
BMP2K	219546_at	-1.620	-4.622	0.002	0.120

ARID1A	218917_s_at	-1.622	-6.609	0.000	0.058
NA	229359_at	-1.624	-4.933	0.001	0.102
NA	228918_at	-1.627	-5.280	0.001	0.086
OAZ1	215947_s_at	-1.632	-4.947	0.001	0.102
NA	225509_at	-1.634	-5.708	0.001	0.073
GTF2I	201065_s_at	-1.635	-4.215	0.003	0.147
CDK5	204247_s_at	-1.636	-5.011	0.001	0.099
IGKC	221651_x_at	-1.637	-5.021	0.001	0.099
F11R	221664_s_at	-1.639	-6.111	0.000	0.066
NA	227367_at	-1.640	-5.900	0.000	0.069
RP11-345P4.4	217122_s_at	-1.641	-4.946	0.001	0.102
LRRC8D	218684_at	-1.643	-7.570	0.000	0.042
ELP3	227075_at	-1.644	-5.892	0.000	0.069
C1orf107	204700_x_at	-1.644	-4.796	0.002	0.111
SGPL1	212321_at	-1.645	-4.546	0.002	0.124
C18orf1	207996_s_at	-1.649	-4.648	0.002	0.118
PHF15	212660_at	-1.649	-5.077	0.001	0.096
ABCE1	201872_s_at	-1.650	-5.271	0.001	0.087
LOC728554	224623_at	-1.652	-4.960	0.001	0.102
ZNF689	227294_at	-1.656	-8.406	0.000	0.031
LRIG2	238653_at	-1.658	-6.163	0.000	0.065
B3GALT6	225733_at	-1.662	-5.715	0.001	0.073
TRNT1	222754_at	-1.664	-5.464	0.001	0.079
MLLT6	224784_at	-1.666	-4.341	0.003	0.138
FLJ11506	202852_s_at	-1.667	-4.368	0.003	0.135
TK2	204227_s_at	-1.668	-4.811	0.002	0.110
BAG5	202985_s_at	-1.671	-4.200	0.003	0.148
PRKX	204061_at	-1.672	-4.313	0.003	0.140
VASP	202205_at	-1.673	-4.938	0.001	0.102
SNX5	217792_at	-1.673	-6.645	0.000	0.057
BRD3	203825_at	-1.674	-5.531	0.001	0.077
LOC644617	221235_s_at	-1.680	-4.286	0.003	0.141
LIX1L	225793_at	-1.680	-4.777	0.002	0.112
RFX5	202963_at	-1.683	-4.287	0.003	0.141
ST14	216905_s_at	-1.685	-4.217	0.003	0.147
NA	213848_at	-1.686	-4.918	0.001	0.104
COX4NB	218057_x_at	-1.687	-4.186	0.003	0.148
TGDS	208249_s_at	-1.687	-5.212	0.001	0.089
WDR68	224748_at	-1.688	-5.768	0.001	0.071
ARHGAP9	224451_x_at	-1.688	-4.689	0.002	0.117
PEX11B	202658_at	-1.689	-6.097	0.000	0.066
NA	232095_at	-1.689	-5.208	0.001	0.089
TMEM51	218815_s_at	-1.692	-6.530	0.000	0.060

IKBKB	209342_s_at	-1.692	-4.292	0.003	0.141
STEAP3	218424_s_at	-1.693	-6.302	0.000	0.063
CSTF1	32723_at	-1.693	-8.636	0.000	0.031
RFC5	203209_at	-1.693	-5.721	0.001	0.073
LOC729082	225332_at	-1.695	-4.178	0.004	0.149
TIMM23	225535_s_at	-1.695	-6.169	0.000	0.065
PAPD1	233873_x_at	-1.696	-4.749	0.002	0.113
ZFP36L2	201368_at	-1.697	-4.472	0.002	0.128
KIAA1147	223162_s_at	-1.699	-7.528	0.000	0.042
WDR43	214662_at	-1.701	-7.396	0.000	0.045
KIAA1432	226221_at	-1.703	-4.318	0.003	0.140
STUB1	227625_s_at	-1.705	-5.400	0.001	0.082
RTN2	34408_at	-1.706	-4.274	0.003	0.142
TMCC1	213351_s_at	-1.708	-5.794	0.001	0.071
WDR81	226738_at	-1.708	-5.067	0.001	0.097
ZBTB47	226484_at	-1.713	-4.674	0.002	0.117
MGAT4A	231283_at	-1.713	-5.378	0.001	0.082
C7orf42	224688_at	-1.715	-5.235	0.001	0.088
RPE	225039_at	-1.715	-4.558	0.002	0.123
TRIM27	212118_at	-1.718	-6.333	0.000	0.063
POU2F2	229750_at	-1.720	-5.764	0.001	0.071
DDHD2	212690_at	-1.722	-6.051	0.000	0.067
COQ9	212228_s_at	-1.722	-4.304	0.003	0.141
POU2F2	228343_at	-1.726	-4.641	0.002	0.118
ORAI1	226531_at	-1.730	-5.574	0.001	0.077
FYCO1	218204_s_at	-1.732	-4.579	0.002	0.122
NA	214807_at	-1.735	-4.795	0.002	0.111
AK2	212174_at	-1.736	-4.400	0.003	0.133
EIF3B	203462_x_at	-1.736	-6.093	0.000	0.066
MBOAT1	227379_at	-1.740	-4.765	0.002	0.112
INPP5D	203332_s_at	-1.741	-4.588	0.002	0.121
COBRA1	202757_at	-1.742	-4.815	0.002	0.110
ANKRD46	212731_at	-1.744	-4.397	0.003	0.133
GORASP1	215749_s_at	-1.744	-6.691	0.000	0.056
MRPS34	218112_at	-1.745	-7.475	0.000	0.043
EXOC6	226259_at	-1.746	-4.666	0.002	0.118
C12orf59	236646_at	-1.747	-5.500	0.001	0.078
ZNF689	227445_at	-1.748	-4.883	0.001	0.106
MRP63	204386_s_at	-1.748	-5.532	0.001	0.077
KIAA2013	224708_at	-1.749	-6.615	0.000	0.058
KIAA1468	225506_at	-1.750	-5.145	0.001	0.092
IGL@	215121_x_at	-1.750	-7.028	0.000	0.052
FBXO21	212229_s_at	-1.753	-6.661	0.000	0.057

NA	235352_at	-1.754	-9.090	0.000	0.028
ASH2L	209517_s_at	-1.756	-5.332	0.001	0.083
RUFY3	213939_s_at	-1.759	-5.607	0.001	0.075
RBM17	224780_at	-1.760	-6.086	0.000	0.066
GPR65	214467_at	-1.761	-4.368	0.003	0.135
COX18	227442_at	-1.762	-4.448	0.002	0.130
MNT	204206_at	-1.762	-5.940	0.000	0.069
ARHGEF10L	1570511_at	-1.763	-4.340	0.003	0.138
PPP1R8	207830_s_at	-1.765	-4.193	0.003	0.148
MED8	213127_s_at	-1.765	-4.391	0.003	0.134
SNUPN	207438_s_at	-1.768	-4.808	0.002	0.110
ZNF264	230063_at	-1.768	-5.099	0.001	0.095
CTNND1	211240_x_at	-1.768	-6.915	0.000	0.052
APPL1	218158_s_at	-1.772	-4.283	0.003	0.142
TBL2	212685_s_at	-1.774	-4.299	0.003	0.141
MFNG	204153_s_at	-1.774	-5.884	0.000	0.070
SNTB2	226685_at	-1.775	-6.098	0.000	0.066
DDX23	40465_at	-1.782	-5.252	0.001	0.088
MTERFD1	219363_s_at	-1.784	-4.944	0.001	0.102
SRI	208921_s_at	-1.786	-4.767	0.002	0.112
NA	1553979_at	-1.793	-5.081	0.001	0.096
APOL3	221087_s_at	-1.798	-4.813	0.002	0.110
KIAA1826	227418_at	-1.798	-5.226	0.001	0.088
TBC1D14	224622_at	-1.805	-4.391	0.003	0.134
C6orf89	224977_at	-1.805	-6.077	0.000	0.066
C19orf12	223983_s_at	-1.806	-5.357	0.001	0.083
ZNF45	222028_at	-1.806	-4.201	0.003	0.148
WDR36	226180_at	-1.809	-4.669	0.002	0.118
ACOX1	227962_at	-1.816	-5.704	0.001	0.073
TLR5	210166_at	-1.818	-5.151	0.001	0.092
WDR8	236381_s_at	-1.819	-4.633	0.002	0.119
GIMAP5	64064_at	-1.820	-8.918	0.000	0.029
NA	227125_at	-1.820	-4.816	0.002	0.110
NOL10	222684_s_at	-1.820	-6.275	0.000	0.064
RAB42	1552846_s_at	-1.821	-4.199	0.003	0.148
SAMM50	201570_at	-1.822	-4.689	0.002	0.117
SUCLA2	202930_s_at	-1.826	-4.201	0.003	0.148
EIF2S1	201142_at	-1.826	-4.768	0.002	0.112
PECAM1	208983_s_at	-1.826	-4.954	0.001	0.102
MCM3	201555_at	-1.827	-4.583	0.002	0.122
EIF3B	211501_s_at	-1.827	-4.721	0.002	0.115
MTF1	205323_s_at	-1.829	-4.204	0.003	0.148
EIF2B5	212351_at	-1.832	-5.777	0.001	0.071

KIAA0513	204546_at	-1.833	-4.472	0.002	0.128
MRPL19	203465_at	-1.834	-4.237	0.003	0.146
BMP2K	226853_at	-1.834	-5.786	0.001	0.071
SRPRB	218140_x_at	-1.838	-4.814	0.002	0.110
NUDCD3	201270_x_at	-1.840	-6.091	0.000	0.066
ZNF264	205917_at	-1.841	-5.922	0.000	0.069
TOR1B	209593_s_at	-1.842	-5.636	0.001	0.074
DDX28	203785_s_at	-1.842	-6.173	0.000	0.065
HEATR6	65493_at	-1.842	-4.895	0.001	0.106
TSPAN14	223314_at	-1.847	-5.300	0.001	0.085
PRMT6	223275_at	-1.851	-6.351	0.000	0.063
C14orf139	219563_at	-1.857	-6.125	0.000	0.066
B3GALT6	1553959_a_at	-1.859	-4.661	0.002	0.118
ATMIN	201855_s_at	-1.859	-4.504	0.002	0.128
EBNA1BP2	201323_at	-1.861	-4.287	0.003	0.141
ZMYND8	209049_s_at	-1.862	-4.921	0.001	0.104
MRPS18B	208907_s_at	-1.862	-4.307	0.003	0.140
PPP1R9B	225124_at	-1.862	-6.360	0.000	0.062
GGA3	209411_s_at	-1.866	-4.836	0.002	0.109
FSCN1	201564_s_at	-1.868	-4.370	0.003	0.135
RPP38	205562_at	-1.871	-4.784	0.002	0.111
C22orf28	200042_at	-1.873	-6.102	0.000	0.066
NA	226885_at	-1.873	-5.398	0.001	0.082
PSMB9	1555852_at	-1.877	-4.482	0.002	0.128
ASCL2	229215_at	-1.878	-10.657	0.000	0.018
RIPK5	214663_at	-1.879	-5.648	0.001	0.074
BLCAP	201032_at	-1.882	-6.922	0.000	0.052
PTCD3	217895_at	-1.885	-4.861	0.001	0.108
LOC100128501	229296_at	-1.887	-4.543	0.002	0.124
FADD	202535_at	-1.889	-4.185	0.003	0.148
METT11D1	218366_x_at	-1.890	-11.850	0.000	0.014
FBXO21	212231_at	-1.892	-5.424	0.001	0.081
CD81	200675_at	-1.893	-5.611	0.001	0.075
TGOLN2	212040_at	-1.893	-4.893	0.001	0.106
EP400	212375_at	-1.895	-4.328	0.003	0.139
IKBKB	209341_s_at	-1.895	-4.875	0.001	0.107
C9orf69	224962_at	-1.898	-4.373	0.003	0.135
CSTF1	202190_at	-1.899	-6.756	0.000	0.055
C15orf39	204494_s_at	-1.902	-4.704	0.002	0.116
POGK	239392_s_at	-1.903	-4.943	0.001	0.102
ATF5	204999_s_at	-1.905	-4.820	0.002	0.110
C16orf53	218300_at	-1.907	-5.354	0.001	0.083
NA	227107_at	-1.908	-4.487	0.002	0.128

MAP4	212566_at	-1.915	-5.384	0.001	0.082
MRPL16	217980_s_at	-1.915	-4.477	0.002	0.128
MLXIP	225157_at	-1.917	-4.571	0.002	0.122
IPO8	225528_at	-1.918	-4.410	0.003	0.133
NA	225276_at	-1.920	-5.223	0.001	0.088
NA	244352_at	-1.921	-4.736	0.002	0.114
SLC25A11	209003_at	-1.923	-5.563	0.001	0.077
CSRP2BP	228543_at	-1.923	-6.790	0.000	0.054
NA	211976_at	-1.924	-8.514	0.000	0.031
FLJ90757	1566558_x_at	-1.925	-6.639	0.000	0.057
SNX17	200991_s_at	-1.929	-5.192	0.001	0.089
NA	241891_at	-1.931	-11.676	0.000	0.015
SERF1A	223538_at	-1.933	-5.830	0.000	0.070
HLA-C	224795_x_at	-1.934	-5.251	0.001	0.088
GNPTAB	212959_s_at	-1.935	-4.869	0.001	0.107
NA	235735_at	-1.935	-5.826	0.000	0.070
GEMIN4	205527_s_at	-1.937	-7.151	0.000	0.049
CASP2	226032_at	-1.937	-5.922	0.000	0.069
LRRC47	212904_at	-1.938	-5.731	0.001	0.073
MKL1	212748_at	-1.939	-6.317	0.000	0.063
C16orf57	1554016_a_at	-1.941	-4.370	0.003	0.135
DLAT	212568_s_at	-1.949	-4.348	0.003	0.138
HNRNPR	232004_at	-1.954	-7.199	0.000	0.049
ZNF652	205594_at	-1.960	-5.400	0.001	0.082
TOR1A	202349_at	-1.962	-5.021	0.001	0.099
RASA1	202677_at	-1.962	-4.192	0.003	0.148
GTF3C2	204366_s_at	-1.964	-5.572	0.001	0.077
PLAGL2	202925_s_at	-1.968	-6.895	0.000	0.052
VGLL4	212399_s_at	-1.975	-7.627	0.000	0.042
ICMT	201609_x_at	-1.977	-5.844	0.000	0.070
AKNA	225701_at	-1.980	-5.692	0.001	0.073
RERE	200940_s_at	-1.986	-4.645	0.002	0.118
NA	227749_at	-1.986	-6.322	0.000	0.063
BMF	226530_at	-1.986	-5.524	0.001	0.077
NA	225176_at	-1.995	-5.621	0.001	0.075
NA	204552_at	-1.996	-6.487	0.000	0.061
RASA4	212706_at	-1.996	-5.706	0.001	0.073
CIAPIN1	208968_s_at	-1.999	-4.510	0.002	0.127
NANP	228073_at	-2.000	-5.478	0.001	0.079
KIAA1274	231887_s_at	-2.006	-7.089	0.000	0.051
CTNND1	208862_s_at	-2.008	-5.602	0.001	0.076
TBC1D9B	212052_s_at	-2.010	-4.520	0.002	0.126
PPARD	37152_at	-2.010	-8.706	0.000	0.030

METT11D1	223528_s_at	-2.015	-6.000	0.000	0.068
COASY	201913_s_at	-2.015	-4.799	0.002	0.111
MAP3K5	203837_at	-2.017	-4.841	0.002	0.109
TH1L	225865_x_at	-2.021	-4.495	0.002	0.128
ANAPC4	226917_s_at	-2.021	-5.945	0.000	0.069
P2RX7	207091_at	-2.024	-4.655	0.002	0.118
RNF187	212155_at	-2.025	-5.667	0.001	0.073
NADK	208919_s_at	-2.026	-4.463	0.002	0.129
C10orf119	217905_at	-2.027	-6.572	0.000	0.059
C8orf38	235509_at	-2.028	-4.910	0.001	0.104
TADA3L	215273_s_at	-2.035	-4.309	0.003	0.140
METT11D1	223988_x_at	-2.036	-11.314	0.000	0.016
MAP3K5	203836_s_at	-2.037	-4.500	0.002	0.128
XPO5	223056_s_at	-2.038	-12.121	0.000	0.013
RUNX3	204197_s_at	-2.040	-7.952	0.000	0.038
FAM105A	219694_at	-2.043	-5.244	0.001	0.088
PRKACA	202801_at	-2.045	-4.297	0.003	0.141
SIPA1	204164_at	-2.046	-5.654	0.001	0.073
NOC3L	218889_at	-2.047	-7.090	0.000	0.051
TRIAP1	218403_at	-2.048	-5.685	0.001	0.073
MCOLN2	230110_at	-2.051	-4.481	0.002	0.128
FAM89B	212484_at	-2.052	-8.494	0.000	0.031
MRPS7	217932_at	-2.053	-5.143	0.001	0.092
APBB1IP	230925_at	-2.054	-6.271	0.000	0.064
NOL9	218754_at	-2.055	-7.591	0.000	0.042
HDGF	200896_x_at	-2.057	-7.652	0.000	0.042
CHST2	203921_at	-2.061	-4.231	0.003	0.146
LRPPRC	211615_s_at	-2.061	-4.616	0.002	0.120
IMP3	221688_s_at	-2.062	-7.878	0.000	0.039
FKBP5	224840_at	-2.062	-10.513	0.000	0.019
C1orf131	226242_at	-2.065	-4.796	0.002	0.111
PCNX	229287_at	-2.065	-4.842	0.002	0.109
PNPT1	225291_at	-2.066	-6.242	0.000	0.065
WDR68	224730_at	-2.070	-4.190	0.003	0.148
CD84	205988_at	-2.074	-5.659	0.001	0.073
NA	226348_at	-2.078	-5.001	0.001	0.100
C19orf66	53720_at	-2.079	-6.820	0.000	0.053
ABCE1	201873_s_at	-2.080	-5.358	0.001	0.083
TMF1	214948_s_at	-2.084	-8.129	0.000	0.035
NA	225139_at	-2.088	-5.530	0.001	0.077
ETV6	225764_at	-2.092	-7.070	0.000	0.051
NUP35	225470_at	-2.097	-5.666	0.001	0.073
TRIM13	229943_at	-2.097	-5.388	0.001	0.082

FTSJ2	222130_s_at	-2.099	-5.688	0.001	0.073
IGL@	209138_x_at	-2.101	-4.763	0.002	0.112
KPNA6	212103_at	-2.103	-4.497	0.002	0.128
NOL11	221970_s_at	-2.104	-6.424	0.000	0.062
DDX47	220890_s_at	-2.107	-6.536	0.000	0.060
C8orf33	218187_s_at	-2.109	-6.398	0.000	0.062
MAP4	243_g_at	-2.114	-4.206	0.003	0.148
KIAA0152	200617_at	-2.121	-5.152	0.001	0.092
IFIT5	203595_s_at	-2.124	-5.302	0.001	0.085
DNMT1	201697_s_at	-2.125	-4.950	0.001	0.102
NUP93	202188_at	-2.130	-4.528	0.002	0.126
MYO1G	244654_at	-2.141	-5.533	0.001	0.077
GIMAP4	219243_at	-2.146	-4.348	0.003	0.138
FLJ90757	1566557_at	-2.156	-4.321	0.003	0.140
SMCR7L	204594_s_at	-2.157	-11.446	0.000	0.016
MKI67IP	224714_at	-2.161	-5.246	0.001	0.088
GIMAP6	229367_s_at	-2.162	-8.508	0.000	0.031
GNB4	225710_at	-2.164	-5.586	0.001	0.076
NA	232687_at	-2.168	-6.688	0.000	0.056
DDX20	223331_s_at	-2.169	-5.297	0.001	0.085
METTL2A	225253_s_at	-2.172	-7.156	0.000	0.049
ANKRD49	219069_at	-2.179	-4.435	0.003	0.132
ATF5	204998_s_at	-2.179	-6.197	0.000	0.065
FHOD1	218530_at	-2.180	-8.446	0.000	0.031
BCR	202315_s_at	-2.182	-5.110	0.001	0.094
NA	228444_at	-2.184	-6.555	0.000	0.060
ORAI3	221864_at	-2.188	-5.046	0.001	0.098
SH2D3C	226673_at	-2.192	-9.158	0.000	0.028
RAB40C	227698_s_at	-2.195	-5.285	0.001	0.086
ZBTB46	227329_at	-2.203	-8.660	0.000	0.031
NA	212608_s_at	-2.207	-6.533	0.000	0.060
FUT4	209892_at	-2.210	-5.359	0.001	0.083
MRPS26	225196_s_at	-2.210	-6.936	0.000	0.052
NSL1	209484_s_at	-2.212	-7.205	0.000	0.049
PDHB	211023_at	-2.217	-4.338	0.003	0.138
CNP	208912_s_at	-2.217	-6.073	0.000	0.066
MRPS35	217942_at	-2.218	-6.330	0.000	0.063
FBXL10	226215_s_at	-2.222	-5.704	0.001	0.073
PTPRJ	227396_at	-2.222	-4.971	0.001	0.101
UNC84B	212144_at	-2.233	-5.248	0.001	0.088
EHD4	209536_s_at	-2.237	-4.766	0.002	0.112
ADORA2A	205013_s_at	-2.239	-5.062	0.001	0.097
ANP32A	201051_at	-2.240	-6.713	0.000	0.056

IFNAR1	225669_at	-2.246	-7.613	0.000	0.042
CMTM3	1555705_a_at	-2.246	-6.937	0.000	0.052
C5orf24	1553106_at	-2.248	-4.425	0.003	0.132
EIF2B1	201632_at	-2.252	-4.485	0.002	0.128
METT10D	226744_at	-2.256	-7.817	0.000	0.040
NA	212605_s_at	-2.257	-6.357	0.000	0.062
NA	227184_at	-2.260	-4.686	0.002	0.117
RNF220	219988_s_at	-2.271	-7.335	0.000	0.046
GPR157	227970_at	-2.272	-6.156	0.000	0.065
PECAM1	208981_at	-2.274	-4.605	0.002	0.121
DFFB	206752_s_at	-2.274	-6.041	0.000	0.067
ZNF362	226820_at	-2.275	-4.962	0.001	0.102
RNF19B	213038_at	-2.285	-6.061	0.000	0.066
C10orf54	225372_at	-2.286	-4.429	0.003	0.132
F8A1	203274_at	-2.287	-5.528	0.001	0.077
OAS1	205552_s_at	-2.292	-4.572	0.002	0.122
LAIR1	210644_s_at	-2.300	-4.674	0.002	0.117
ACP5	204638_at	-2.301	-5.501	0.001	0.078
C19orf2	222266_at	-2.305	-5.818	0.000	0.070
BCOR	219433_at	-2.307	-5.553	0.001	0.077
CCDC12	226011_at	-2.315	-5.398	0.001	0.082
GRB2	223049_at	-2.319	-4.777	0.002	0.112
CENTA2	219358_s_at	-2.324	-6.648	0.000	0.057
C2orf18	225695_at	-2.327	-4.461	0.002	0.129
MAK16	211686_s_at	-2.337	-5.566	0.001	0.077
TRIOBP	210276_s_at	-2.339	-4.299	0.003	0.141
NA	214949_at	-2.346	-4.351	0.003	0.138
CECR5	218592_s_at	-2.347	-6.062	0.000	0.066
COG2	203073_at	-2.349	-6.526	0.000	0.060
CIAPIN1	208424_s_at	-2.352	-6.787	0.000	0.054
LSM10	225593_at	-2.354	-4.703	0.002	0.116
MREG	219648_at	-2.355	-6.237	0.000	0.065
MKI67IP	224713_at	-2.360	-6.521	0.000	0.060
RNF166	227726_at	-2.373	-7.504	0.000	0.042
LSM6	205036_at	-2.374	-4.417	0.003	0.133
CD300LF	1553043_a_at	-2.380	-4.839	0.002	0.109
RAB3D	225001_at	-2.381	-8.960	0.000	0.029
CD47	226016_at	-2.381	-5.666	0.001	0.073
ATG7	222709_at	-2.386	-7.578	0.000	0.042
GIT2	225558_at	-2.387	-5.178	0.001	0.091
NUDT19	235384_at	-2.397	-4.691	0.002	0.117
PAPD1	218947_s_at	-2.404	-8.109	0.000	0.035
NA	230391_at	-2.412	-4.407	0.003	0.133

LYSMD2	226748_at	-2.420	-9.055	0.000	0.028
USP3	226652_at	-2.421	-5.635	0.001	0.074
C2orf68	238768_at	-2.422	-4.972	0.001	0.101
GIMAP1	1552318_at	-2.430	-5.712	0.001	0.073
SMCR7L	221516_s_at	-2.430	-5.385	0.001	0.082
CMTM3	224733_at	-2.432	-5.488	0.001	0.078
NA	240173_at	-2.452	-8.593	0.000	0.031
GIMAP5	218805_at	-2.454	-8.451	0.000	0.031
GFM1	225153_at	-2.459	-4.424	0.003	0.132
APOBEC3G	204205_at	-2.465	-4.999	0.001	0.100
PLXNA1	221538_s_at	-2.466	-5.023	0.001	0.099
NA	235661_at	-2.468	-6.903	0.000	0.052
FAM114A1	213455_at	-2.477	-4.290	0.003	0.141
FAM78A	227002_at	-2.481	-10.178	0.000	0.021
NA	225411_at	-2.488	-4.840	0.002	0.109
RCC2	224578_at	-2.496	-4.187	0.003	0.148
LNPEP	231866_at	-2.496	-5.992	0.000	0.068
MFSD8	228282_at	-2.501	-7.341	0.000	0.046
LOC146346	225918_at	-2.503	-6.444	0.000	0.061
MRPS23	223156_at	-2.503	-5.541	0.001	0.077
S1PR2	227684_at	-2.506	-7.504	0.000	0.042
PIK3CD	203879_at	-2.511	-5.558	0.001	0.077
INTS9	203941_at	-2.517	-6.780	0.000	0.054
IFIT5	203596_s_at	-2.531	-4.614	0.002	0.120
GIMAP1	1552316_a_at	-2.543	-4.208	0.003	0.148
ZNF652	225266_at	-2.551	-4.516	0.002	0.126
GPRIN3	1556698_a_at	-2.552	-5.016	0.001	0.099
BTBD14A	212993_at	-2.553	-5.002	0.001	0.100
ZNF641	226509_at	-2.554	-5.901	0.000	0.069
SLA	203760_s_at	-2.559	-4.293	0.003	0.141
TNFAIP8L2	223583_at	-2.561	-5.321	0.001	0.084
NA	235286_at	-2.561	-5.243	0.001	0.088
PRELID1	223032_x_at	-2.575	-4.778	0.002	0.112
EIF2AK2	213294_at	-2.576	-4.403	0.003	0.133
PECAM1	208982_at	-2.586	-4.892	0.001	0.106
UBAC1	202151_s_at	-2.598	-6.464	0.000	0.061
ADAR	201786_s_at	-2.611	-5.363	0.001	0.083
NA	230741_at	-2.612	-5.690	0.001	0.073
DDX58	222793_at	-2.621	-4.615	0.002	0.120
GAS2L1	31874_at	-2.621	-4.449	0.002	0.130
BTG2	201236_s_at	-2.625	-5.066	0.001	0.097
CKLF	221058_s_at	-2.630	-5.311	0.001	0.084
ARRB1	222756_s_at	-2.634	-4.982	0.001	0.101

APPL1	222538_s_at	-2.637	-4.340	0.003	0.138
FMNL3	227844_at	-2.642	-7.451	0.000	0.043
NA	237104_at	-2.648	-8.260	0.000	0.033
FGL2	227265_at	-2.648	-4.313	0.003	0.140
NUP62	202153_s_at	-2.651	-6.043	0.000	0.067
PARP12	218543_s_at	-2.653	-5.075	0.001	0.096
MRPS12	204331_s_at	-2.667	-6.196	0.000	0.065
CTNND1	208407_s_at	-2.670	-4.819	0.002	0.110
CNPY3	1556389_at	-2.674	-6.923	0.000	0.052
ANKFY1	224900_at	-2.707	-6.158	0.000	0.065
TLR7	220146_at	-2.714	-4.791	0.002	0.111
DDX58	218943_s_at	-2.719	-5.639	0.001	0.074
NA	43511_s_at	-2.730	-10.003	0.000	0.021
SLA	203761_at	-2.746	-5.321	0.001	0.084
FPR3	230422_at	-2.757	-4.413	0.003	0.133
NA	230640_at	-2.760	-7.727	0.000	0.042
HIVEP3	235122_at	-2.775	-4.338	0.003	0.138
GIMAP8	235306_at	-2.778	-6.170	0.000	0.065
PRELID1	224232_s_at	-2.782	-6.935	0.000	0.052
GTF3C2	212429_s_at	-2.794	-4.594	0.002	0.121
IL27RA	205926_at	-2.800	-8.789	0.000	0.030
TAP1	202307_s_at	-2.804	-5.451	0.001	0.079
SLC2A6	220091_at	-2.823	-6.204	0.000	0.065
NUP62	230966_at	-2.825	-5.341	0.001	0.083
NA	49111_at	-2.825	-16.080	0.000	0.005
TMEM203	225052_at	-2.830	-4.263	0.003	0.144
RGS19	204336_s_at	-2.839	-7.870	0.000	0.039
NA	229968_at	-2.870	-8.399	0.000	0.031
TAF5	210053_at	-2.876	-8.119	0.000	0.035
RPS6KA1	203379_at	-2.878	-6.972	0.000	0.052
TBC1D2B	212796_s_at	-2.887	-12.565	0.000	0.013
LFNG	228762_at	-2.890	-9.880	0.000	0.022
PPM1M	226074_at	-2.896	-5.177	0.001	0.091
NA	221861_at	-2.910	-9.656	0.000	0.023
CCL8	214038_at	-2.915	-5.364	0.001	0.083
NA	229383_at	-2.924	-4.400	0.003	0.133
LRRC25	1559502_s_at	-2.930	-5.431	0.001	0.081
IFNGR2	201642_at	-2.937	-5.543	0.001	0.077
FMNL3	238823_at	-2.954	-5.853	0.000	0.070
PTPMT1	223808_s_at	-2.955	-5.371	0.001	0.083
TNFAIP8L1	227420_at	-2.965	-5.796	0.001	0.071
NA	217529_at	-2.966	-5.684	0.001	0.073
RNF135	223592_s_at	-2.969	-4.681	0.002	0.117

TRIM14	203148_s_at	-3.033	-4.308	0.003	0.140
NAV1	224772_at	-3.037	-13.661	0.000	0.010
ARHGAP30	226219_at	-3.043	-4.414	0.003	0.133
TFEB	50221_at	-3.060	-6.917	0.000	0.052
VASH1	203940_s_at	-3.070	-6.222	0.000	0.065
FTSJ2	218356_at	-3.081	-5.014	0.001	0.099
ORAI2	231406_at	-3.120	-5.773	0.001	0.071
NA	1558397_at	-3.138	-7.681	0.000	0.042
GIMAP6	219777_at	-3.148	-11.101	0.000	0.018
CCR2	207794_at	-3.157	-5.776	0.001	0.071
TLR8	229560_at	-3.171	-4.238	0.003	0.146
AIM1	212543_at	-3.180	-4.952	0.001	0.102
NFE2L3	204702_s_at	-3.195	-9.084	0.000	0.028
ENG	201809_s_at	-3.200	-4.489	0.002	0.128
ARHGEF10L	221656_s_at	-3.208	-5.856	0.000	0.070
FAM89B	32209_at	-3.220	-5.962	0.000	0.068
ARRB1	222912_at	-3.230	-9.376	0.000	0.026
CKLF	223451_s_at	-3.298	-6.000	0.000	0.068
PTGFRN	224937_at	-3.302	-5.288	0.001	0.085
ST8SIA4	230836_at	-3.305	-5.399	0.001	0.082
TNIP1	207196_s_at	-3.320	-4.490	0.002	0.128
NA	229121_at	-3.322	-6.735	0.000	0.055
SERPINF1	202283_at	-3.392	-6.388	0.000	0.062
MKL2	218259_at	-3.406	-5.493	0.001	0.078
HTRA1	201185_at	-3.449	-4.234	0.003	0.146
SASH3	204923_at	-3.517	-7.496	0.000	0.042
ARHGAP22	206298_at	-3.526	-10.375	0.000	0.020
DBR1	234295_at	-3.529	-10.773	0.000	0.018
CALHM2	57715_at	-3.593	-9.481	0.000	0.025
IL27RA	222062_at	-3.782	-6.427	0.000	0.062
IFIT1	203153_at	-3.812	-5.788	0.001	0.071
CCL4	204103_at	-3.869	-4.664	0.002	0.118
NA	228869_at	-3.892	-6.845	0.000	0.053
IFIT2	226757_at	-3.937	-5.999	0.000	0.068
CXCL10	204533_at	-3.982	-7.512	0.000	0.042
CALHM2	221565_s_at	-4.300	-7.327	0.000	0.046
IFIT3	229450_at	-4.319	-5.599	0.001	0.076
CCR2	206978_at	-7.060	-17.556	0.000	0.004

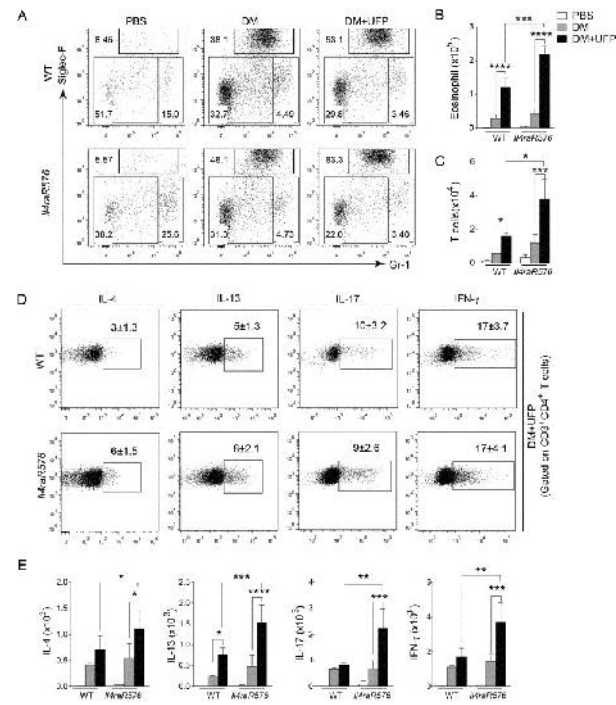


Fig E1

Mingcan Xia , Loida Viera-Hutchins , Maria Garcia-Lloret , Magali Noval Rivas , Petra Wise , Sean A. McGhee , Zena...

Vehicular exhaust particles promote allergic airway inflammation through an aryl hydrocarbon receptor–notch signaling cascade

Journal of Allergy and Clinical Immunology, 2015

<http://dx.doi.org/10.1016/j.jaci.2015.02.014>

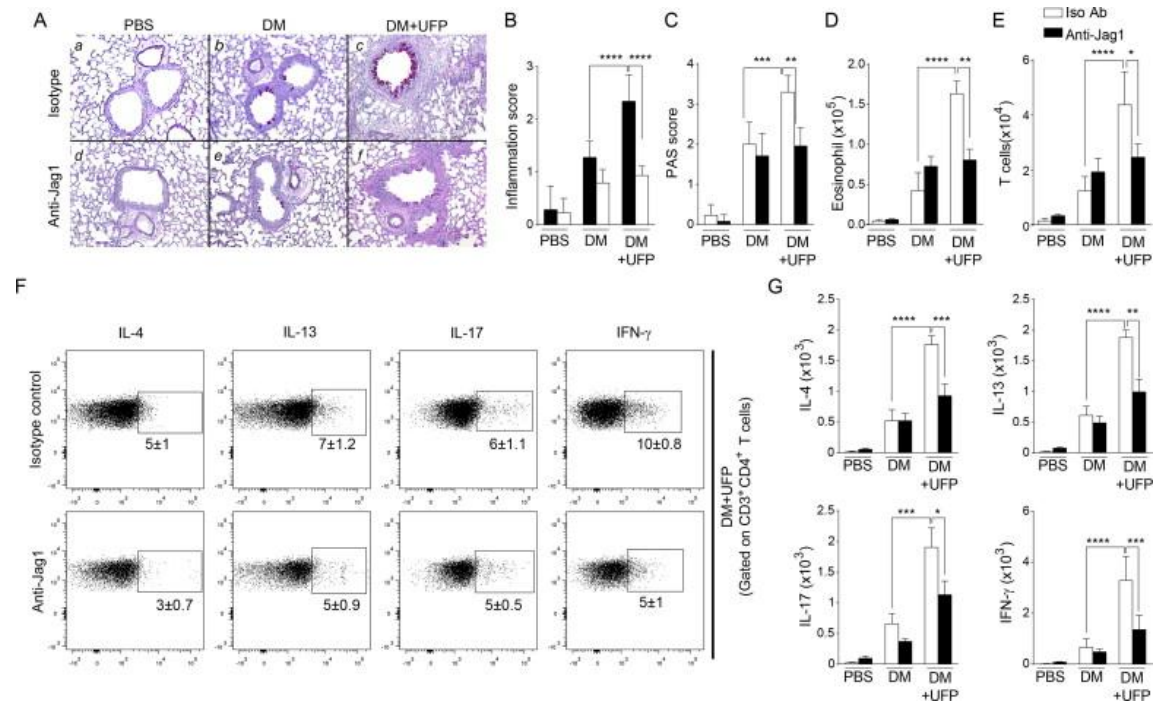


Fig E2

Mingcan Xia , Loida Viera-Hutchins , Maria Garcia-Lloret , Magali Noval Rivas , Petra Wise , Sean A. McGhee , Zena...

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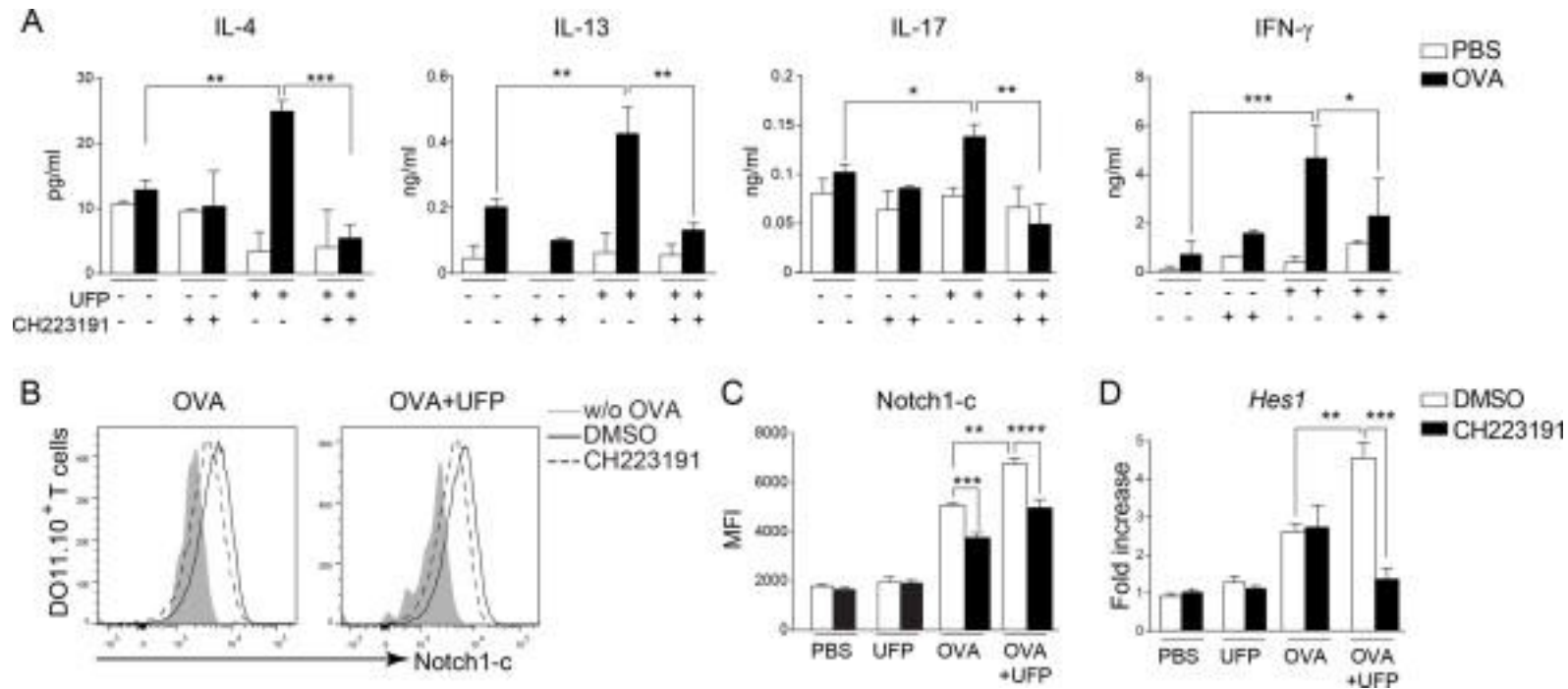


Fig E3

Mingcan Xia , Loida Viera-Hutchins , Maria Garcia-Lloret , Magali Noval Rivas , Petra Wise , Sean A. McGhee , Zena...

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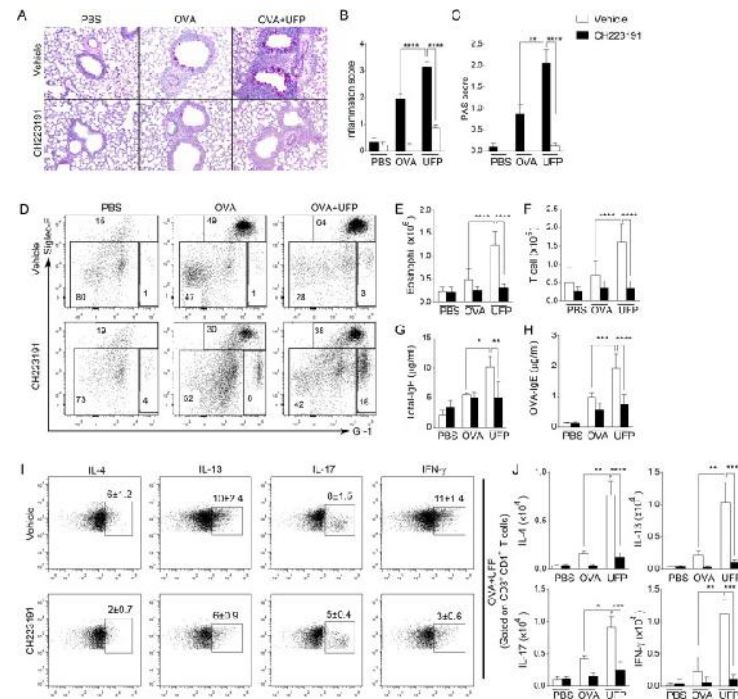


Fig E4

Mingcan Xia , Loida Viera-Hutchins , Maria Garcia-Lloret , Magali Noval Rivas , Petra Wise , Sean A. McGhee , Zena...

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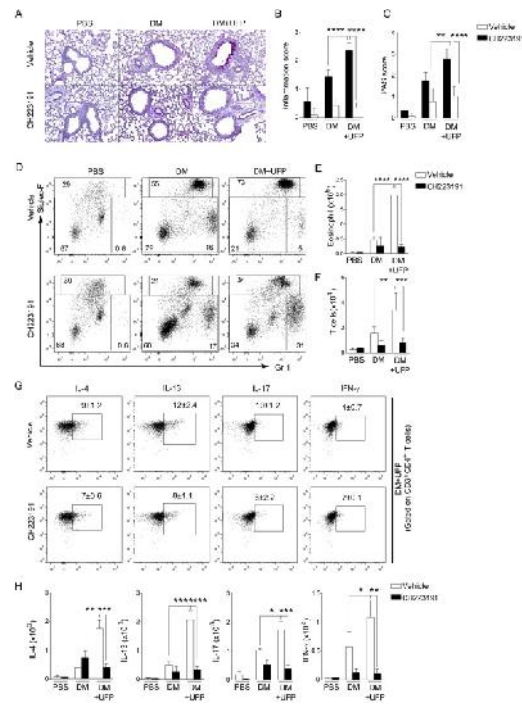


Fig E5

Mingcan Xia , Loida Viera-Hutchins , Maria Garcia-Lloret , Magali Noval Rivas , Petra Wise , Sean A. McGhee , Zena...

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