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Transcriptional Heterogeneity of Mast Cells and Basophils upon Activation

Krishan D. Chhiba, Chia-Lin Hsu, Sergejs Berdnikovs, and Paul J. Bryce

Mast cells and basophils are critical effector cells in type I immediate hypersensitivity reactions and associate with allergic disease pathology. The developmental pathways of mast cells and basophils are closely related but are also the subject of continuing controversy (1). In the bone marrow, mast cells and basophils are commonly considered to develop from common myeloid progenitor cells, which differentiate into granulocyte-monocyte progenitors, and become granulocyte progenitors. Functionally, granulocyte progenitors have been shown to differentiate into basophils or mast cell progenitors (MCPs) (2, 3). However, this model has been challenged by studies at the single-cell level that define MCP potential within a common myeloid population and not in the granulocyte/macrophage progenitor population (4). Common progenitors are also found in the spleen and can generate basophils and MCPs (5, 6). MCPs are released into the circulation and mature once they are in tissues; mature mast cells have a lifespan of weeks to months. Conversely, mature basophils circulate in the blood before being recruited to tissues and have a shorter lifespan (60–70 h). As a result of their developmental similarity, circulating basophils are often used as surrogates to study tissue-resident mast cell reactivity [e.g., the basophil activation test for diagnosing food allergy–associated reactivity (7)], but the similarity or heterogeneity between the two cell types is relatively unknown.

Generally, mast cells and basophils respond to many of the same stimuli, and their functional roles appear to overlap. The best-studied shared mechanism of activation between the cell types is cross-linking of the FceRI receptor, which promotes the release of histamine, as well as other granule mediators, eicosanoids, and inflammatory cytokines. In addition to activation through FceRI, mast cells and basophils express ST2, the receptor for IL-33. IL-33 is an “epithelial-derived” cytokine that promotes type 2–associated immune responses and has been strongly linked to allergy (8). Upon IL-33–mediated activation, mast cells have been shown to exhibit enhanced adhesion, survival, maturation, and production of several proinflammatory cytokines (9, 10). In basophils, IL-33–mediated activation has been described as promoting migration toward eotaxin and enhancing degranulation upon concurrent IgE-mediated activation (11). For cytokine production, basophils were also shown to respond poorly to IL-33 compared with IgE-mediated activation, but a relatively small number of mediators were studied (12, 13). Therefore, defining the transcriptional activation signatures of mast cells and basophils using a systems biology–based approach is likely to help understand the possible contributions of each cell type and the mode of activation to the progression of allergic diseases.

Recent evidence has shown that resting mast cells and basophils actually have relatively low transcriptional homology in mice and humans (14, 15), implying that they might be much more distinct than once thought. However, the similarities and/or differences in their transcriptional signatures upon activation are unknown. It is
well appreciated that mast cells have functions in health and disease. In line with their role as sentinel cells, mast cells encode pathways for the synthesis of a diverse array of mediators. They are critical players in the symptoms of anaphylaxis, mediate resistance to infection, and promote tumor rejection. Relatively less is known about basophil functions. Basophils rapidly secrete IL-4 and IL-13 upon IgE-mediated activation, play a role in the host defense against parasites, and promote Th2 responses through altering Ag presentation (13, 16). Although mast cells and basophils are believed to have nonredundant roles in immune regulation, the evidence supporting this idea has been scarce until now, and the distinct contributions of each cell type at rest and upon activation are beginning to be appreciated.

To better understand the functional differences and similarities between mast cells and basophils, we performed a large-scale comparison of the transcriptomes of murine mast cells and basophils at rest and upon activation by an adaptive-type (IgE cross-linking) or innate-type (IL-33) stimulation. Using homogeneous populations of mature mast cells and basophils derived from bone marrow, we also asked whether IgE- and IL-33–mediated activation induced similar or distinct gene signatures in both cell types. Through this nonbiased, large-scale approach, we provide evidence for heterogeneity between mast cell and basophil activation responses, as well as in the activation of each individual cell type by an innate- or adaptive-type stimuli. The cell- and activation-specific signatures identified in this study define novel gene networks and pathways that may contribute to understanding how the immune system responds to allergens and innate cytokines.

Materials and Methods
Mice
C57BL/6J mice (4–6 wk old) were obtained from the Jackson Laboratory. ST2-knockout (ST2KO) mice were previously obtained from Dr. A. McKenzie and backcrossed to C57BL/6J mice for eight generations. All animal studies were performed under Institutional Animal Care and Use Committee guidelines and under protocols that have been approved by the Northwestern University Animal Care and Use Committee. The bone marrow from each individual mouse was used to generate independent cultures of mast cells and basophils, as outlined below.

Bone marrow–derived mast cells
Bone marrow–derived mast cells (BMMCs) were obtained by flushing bone marrow from femurs and tibias of mice. Cells were cultured in BMMC media (RPMI 1640 media containing 2 mM L-glutamine, 10% FBS [Atlanta Biologicals], 25 mM HEPES [Sigma], 1 mM sodium pyruvate [Sigma], 0.1 mM nonessential amino acids [Sigma], 100 U/ml penicillin, 100 μg/ml streptomycin [Corning], 0.05 mM 2-ME [Sigma]) and 30 ng/ml recombinant mouse (m)IL-3 (Miltenyi Biotec) for 4–6 wk. Purity was assessed by flow cytometry using PE–anti-mFcyRI (MAR-1; eBioscience) and allophycocyanin–anti-mCD117 (2B8; BioLegend) (Fig. 1A). IgE/Ag and IL-33 activation of BMBs was performed as described above for BMMCs (Fig. 1C).

RNA isolation and real-time PCR
RNA was isolated from unstimulated and stimulated cells with an RNeasy RNA Isolation Kit (QIAGEN). RNA quality assessment was performed using an Agilent 2100 Bioanalyzer. cDNA was synthesized with qScript cDNA Supermix (Quanta Biosciences). Gene expression was verified for select genes by real-time PCR using an ABI 7500 instrument and TaqMan probes (both from Applied Biosystems).

Microarray experiments and statistical analyses
RNA was hybridized to Illumina MouseWG-6 v2.0 arrays (catalog number BD-201-0202). Preprocessing steps, including quality control, background adjustment, and quantile normalization, were performed using the array analysis tools available at http://wwwARRAYANALYSIS.ORG using the lumi package and bgAdjust function (18). Variance stabilization was managed with a log2 transformation. Normalized data were filtered to remove unexpressed probes and beads with a detection p value < 0.01. Groups were compared using the limma adapted t test. Differentially expressed genes were identified using the Benjamini–Hochberg false discovery rate correction (p value ≤ 0.05). Heat maps were generated using GENE-E software (Broad Institute; http://broadinstitute.org/cancer/software/GENE-E).

Cell-specific signature validation
For each sample, the purity of each BMMC culture was determined to be >98% FceR1/CD117+ and each BMB culture was >98% FcεRI/CD117+/CD49b+ (Fig. 1B). To assess the specificity of the cellular transcriptome between our BMMC and BMB populations, we initially examined key genes that were described as reflecting a mast cell–specific signature in a recent study from the Immunological Genome Project Consortium (15), as well as genes for two basophil proteases that are not expressed in mast cells: Mcpt8 (Mcpt8) and Pcss34 (Mctp1) (19). As shown in Fig. 1D, all three mast cell cultures clustered together, whereas the basophil cultures also showed distinct clustering. Furthermore, the mast cell signature was highly reflective of the mast cell cultures, whereas basophils possessed a unique signature driven by Mcpt8 and Pcss34. Additionally, there was no significant expression of Mig, a transcription factor described as important for early commitment of basophil and mast cell lineages (20).

Principal component analysis and network diagrams
Functional gene set enrichment analysis was used to generate functional gene networks and identify hub genes by meta-grouping of individual gene term sets (referring Gene Ontology Biological Process and Kyoto Encyclopedia of Genes and Genomes Pathways) based on function similarity. The GeneTern Linker algorithm, implemented in the FGNet R package, was used for this analysis (parameters set for analysis: adjusted p value < 0.05; minimum support of three). Networks generated within this analysis were exported in graph modeling language format for further analysis and visualization using the iGraph R package. Cytoscape 3.2.1. was used to visualize individual metagroups and stimuli-specific versus shared network components. Principal component analysis (PCA) was performed using the Population PCA program (Scott Davis, Harvard Medical School) on the top 15% variable transcripts with a relative expression ≥ 120. Gene Set Enrichment Analysis (GSEA; Broad Institute) was used to determine enriched hallmark gene sets in activated mast cells and basophils (21). Circos visualization and enrichment heat maps were generated using http://metascape.org (22).

Results
IgE- and IL-33–activated mast cells are transcriptionally distinct
Mast cells and basophils are developmentally related, but they perform similar, as well as nonredundant, roles in allergic disease. One way to determine the degree of differences in their output responses to adaptive (IgE cross-linking) and innate (IL-33) stimuli is to use a nonbiased bioinformatics approach to interrogate the genetic changes that occur upon activation. Before performing a cell-specific comparison between mast cells and basophils, we asked whether the activation-specific transcriptome was distinct between IgE and IL-33 activation in each cell type. For mast cell activation, we set up an in vitro model using BMMCs, a well-validated technique for generating a homogeneous mast cell population, with an average purity > 98% (Fig. 1A) (23). BMMCs have properties of serosal- and mucosal-type mast cells and are extensively used to study FceR1 signaling (24). Using array-based technology, we analyzed the expression of >45,000 transcripts in unstimulated and IgE/Ag- or IL-33–stimulated BMMCs in tripli-

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cate, with each culture generated from individual mice. The microarray data presented in this article have been submitted to the National Center for Biotechnology Information’s Gene Expression Omnibus under accession number GSE96696 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE96696).

For IgE activation, cross-linking of anti-OVA–IgE with OVA for 4 h resulted in 785 differentially expressed genes (~4.0%) compared with unstimulated mast cells (adjusted p value ≤ 0.05). A heat map of upregulated and downregulated genes was generated by filtering (log2 fold change [log2FC] > 2, average expression
≥ 5, and \( p \leq 0.05 \)) and then ranking the top 50 transcripts according to their adjusted \( p \) value (Fig. 2A). From these top 50 genes, we observed three major patterns of gene expression: genes downregulated by IgE activation, genes upregulated by IgE activation, and genes upregulated by IgE and IL-33 activation. Of the differentially expressed genes, 309 genes were upregulated ≥2-fold, including \( IL33 \), as our laboratory had described previously (17). In contrast, 234 genes were downregulated ≥2-fold, illustrated by the balanced appearance of significant data points on the volcano plot (Fig. 2B). Among the genes with the highest fold change were \( Egr2 \) (72.26-fold), \( Ccl1 \) (67.24-fold), and \( Fxyd6 \) (62.30-fold) (Fig. 2C, 2D). Wild-type (WT) and ST2KO BMMCs that underwent IgE-mediated activation had virtually the same transcriptome. In fact, of the ~45,000 analyzed transcripts, pairwise comparison between the groups found that only \( Rpe \) was significantly upregulated (4.9-fold) in WT BMMCs.

We next performed a pairwise comparison of IL-33–stimulated versus unstimulated WT and ST2KO mast cells and identified 823 differentially expressed genes (~4.2%) that were statistically significant after 4 h. A heat map of the top 50 upregulated or downregulated genes illustrates two main subsets of transcripts: those induced by IL-33 but not IgE and those induced by both stimuli (Fig. 3A). Notably, the IL-33–induced genes remained unchanged in ST2KO BMMCs upon IL-33 stimulation. Pairwise comparison of unstimulated WT BMMCs and IL-33–stimulated ST2KO BMMCs again identified only \( Rpe \) as having a statistically

![Diagram](http://www.jimmunol.org/)

**FIGURE 2.** Transcriptional signature of IgE-activated mast cells. (A) Heat map of the top 50 significantly changed genes in BMMCs after IgE-mediated activation. (B) Volcano plot showing \( \log_{10}(p \text{ value}) \) versus \( \log_{2}(\text{FC}) \). Colored points represent \( p < 0.05 \) (red), \( \log_{2}(\text{FC}) > 2.5 \) (orange), and \( p < 0.05 \) and \( \log_{2}(\text{FC}) > 2.5 \) (green). Top 10 upregulated (C) and downregulated (D) genes after IgE-mediated activation, ranked by fold change.
Mast cell transcriptional signature after IL-33 activation. A heat map of the top 50 significantly changed genes in BMMCs after IL-33 stimulation. B) Volcano plot showing log10(p value) versus log2FC. Colored points represent p < 0.05 (red), log2FC > 2.5 (orange), and p < 0.05 and log2FC > 2.5 (green). Top 10 upregulated (C) and downregulated (D) genes after IL-33 stimulation, ranked by fold change.
linking and IL-33. IgE-mediated activation resulted in 3986 differentially expressed genes (20.5%) that achieved statistical significance with an adjusted $p$ value $\leq 0.05$. The heat map of the top 50 upregulated and downregulated genes included many transcripts encoding secreted cytokines and chemokines (Fig. 5A). Like in BMMCs, we observed $Il33$ induction upon IgE cross-linking but not after IL-33 stimulation. A volcano plot of the data from IgE stimulation demonstrates a wide spread of data points away from the origin that results from many transcripts having a large log$_2$FC and a low $p$ value (Fig. 5B). Of these displayed transcripts, 875 distinct genes increased by $\geq 2$-fold, and 730 genes decreased by $\leq 2$-fold. The genes with the highest fold change were upregulated $Ccl1$ (369.39-fold), $Il3$ (222.99-fold), and $Il2$ (107.41-fold) (Fig. 5C, 5D).

In response to IL-33 stimulation, WT, but not ST2KO, basophils displayed altered expression of 238 genes (1.2%) with statistical significance (142 were upregulated and 5 were downregulated $\leq 2$-fold). The heat map displays the top 39 genes expressed by IL-33–stimulated basophils (Fig. 6A). Unlike the previous groups, the pairwise comparison of IL-33–stimulated basophils and unstimulated basophils resulted in $<50$ transcripts that met the cut-offs: log$_2$FC $> 2$, average expression $\geq 5$, and $p \leq 0.05$. The rightward bias of the volcano plot illustrates that IL-33 increases the expression of most genes and decreases relatively few (Fig. 6B). The top three differentially regulated genes in IL-33–stimulated basophils were $Plat$ (73.18-fold), $Cxc2$ (22.24-fold), and $Tphg$ (19.54-fold) (Fig. 6C, 6D).

A network diagram constructed from the upregulated transcripts illustrates the groups of genes and pathways that appear to be IgE specific, IL-33 specific, and common responses to stimuli (Fig. 7). By GSEA, we identified the three most enriched hallmark gene sets in IgE-activated basophils: MYC-regulated genes (subgroup v1), genes upregulated during the unfolded protein response, and genes upregulated by STAT5 in response to IL-2 stimulation (Supplemental Fig. 1E). In contrast, IL-33–stimulated transcripts aligned with the following hallmark genes sets: genes upregulated by KRAS activation, genes defining the inflammatory response, and genes regulated by NF-$\kappa$B in response to TNF (Supplemental Fig. 1F).

**Mast cells and basophils are transcriptionally distinct from each other at rest and after stimulation**

As a final step in our analyses, we quantified the differences between mast cells and basophils at rest and after activation by comparing the lists of differentially expressed transcripts in all four groups from the pairwise comparisons illustrated above. Using a Circos plot, we illustrate matching genes among treatments and cell types by drawing purple lines to link identical genes in two given groups (Fig. 8A). The dark orange areas on the inner arc represent the subset of genes found in at least one other group, whereas the light orange areas signify the proportion of genes that are unique to the given group. A Venn diagram illustrating the specific numbers of overlapping versus unique genes between each group is shown in Fig. 8B, and a list of these genes is provided in Supplemental Table I. Surprisingly, only two genes ($Tnf$ and $Traf1$) were common to both cell types and both stimuli, and the numbers of unique genes within each specific cell-stimulus category dominated over those that were shared across categories. PCA using the top 15% of transcripts with the most variability (6473 probes) illustrates cell type–attributable variation captured by PC1 and PC2, as well as stimulation-specific variation along PC3 (Fig. 8C). A subset of genes representing the cell and stimulus-specific signatures was validated in independent cultures using real-time RT-PCR methods (Supplemental Fig. 2).
Taken together, our data suggest that the core transcriptional response to innate- and adaptive-type stimuli can be defined. We analyzed transcriptional responses in mast cells and basophils and define the cell-specific signature for these two stimuli. From the cell- and activation-specific profiles, we derive novel gene networks and pathways that may participate in how the immune system responds to allergens and innate cytokines.

**Discussion**

Mast cells and basophils are developmentally related cells that play key effector roles in allergic and nonallergic diseases, and the extent of their functional similarities and differences in response is not yet fully understood. In this article, we broaden our understanding of these two cell types by asking whether heterogeneity exists between the transcriptome of mast cells and basophils at rest and upon activation with an innate type (IL-33) or adaptive type (IgE cross-linking) of stimuli. We use IL-33 as the innate stimuli, because it is well known to activate mast cells through ST2, it promotes type 2 immune responses (9, 10), and basophils also express ST2 and have been shown to respond to IL-33 (13, 25). To address the question above, we used a nonbiased, bioinformatics approach that provided a global analysis of the transcriptional changes that occurred in mast cells and basophils upon activation. Through PCA, we confirmed that mast cells and basophils have distinct transcriptional programs at rest and further defined that they also have distinct transcriptional programs upon activation with an adaptive- or innate-type stimulation (Fig. 8C). Also, through analyzing IgE-cross-linked and IL-33-stimulated mast cells and basophils independently, we surprisingly observed that transcriptional
differences were enhanced after activation (even with the same stimuli), suggesting even further functional differences.

Focusing on mast cells, IgE-activated mast cells shared a small transcriptional signature (327 genes) with IL-33–stimulated mast cells. Using this shared signature, we identified the hallmark gene sets enriched after both modes of activation: processes associated with allograft rejection, apoptosis, and cholesterol homeostasis (Supplemental Fig. 1D). Interestingly, activation of mast cells through FcεRI or ST2 dramatically increased expression of Ccl1 and Egr2. CCL1 is a chemokine that is important for regulating immune cell migration, specifically CD4+ T cell trafficking (26, 27). Other groups have reported the Egr2-dependent induction of CCL1 in mast cells after IgE-mediated activation (26–28), connecting these molecules to a shared regulatory pathway; however, production of CCL1 in mast cells after IL-33 stimulation has not been described previously. Furthermore, based on fold-change values, IgE–cross-linked basophils expressed more Ccl1 than did IgE-activated mast cells in our arrays; this finding may suggest a role for basophil-derived chemokines in CD4+ T cell regulation.

A surprising aspect of our findings is that basophils respond strongly to IgE-mediated activation and less potently to IL-33, unlike the balanced activation signatures seen with mast cells. Only 20 differentially expressed genes were shared between the two activation groups in basophils. Basophils activated via IgE cross-linking exhibited the most robust response among all of the tested groups, with 20.5% of the transcriptome altered upon activation, including genes regulated by MYC (subgroup v1 and v2), as well as genes participating in oxidative phosphorylation and the unfolded protein response. In contrast, the IL-33–altered genes in basophils reflected quite unexpected pathways, including heme metabolism, mitotic spindle assembly, and adipogenesis. The PCA plots further highlight the divergence of response phenotype in basophils, with IgE-activated basophils of both genotypes (WT and ST2KO) clustering tightly with one another but distantly from all other groups, including

**FIGURE 6.** Basophil transcriptional signature after IL-33 activation. (A) Heat map of the top 50 significantly changed genes in BMBs after IL-33 stimulation. (B) Volcano plot showing log₁₀(p value) versus log₂FC. Colored points represent p < 0.05 (red), log₂FC > 2.5 (orange), and p < 0.05 and log₂FC > 2.5 (green). Top 10 upregulated (C) and downregulated (D) genes after IL-33 stimulation, ranked by fold change.
IL-33–activated basophils. Interestingly, we do show that amphiregulin (AREG), a growth factor in the epidermal growth factor family that is known to be involved in allergic responses, is induced in basophils by both IgE cross-linking and IL-33 (Fig. 5A). Previously, it was reported that human basophils produced AREG in response to IL-3, and the investigators suggested that basophil-derived AREG contributed to tissue remodeling and repair (29, 30). Recently, AREG derived from type 2 innate lymphoid cells was shown to mediate their tissue-protective function in intestinal tissue (31). In this article, we provide the first evidence, to our knowledge, to suggest that activated basophils could participate in similar tissue-remodeling processes during type 2 immune responses in allergic diseases through their expression of AREG.

In this study, we include ST2-deficient cells and observe virtually no significant transcriptional differences compared with WT cells at rest and upon IgE-mediated activation. The lack of a response in ST2KO mast cells and basophils to IL-33 illustrates the necessity of the ST2 receptor and the specificity of the IL-33–activation signature. Because we previously demonstrated that IgE cross-linking promoted IL-33 expression in mast cells (17, 32) (and now also in basophils, as shown above), we postulated that preformed or induced IL-33 could feed back through the ST2 receptor to potentiate cellular activation. Because the IgE-activated transcriptome was identical in WT and ST2KO BMMCs and BMBs, this type of autocrine regulation of IL-33/ST2 signaling, as has been proposed to occur in dendritic cells (33), seems unlikely. However, a caveat to this concept is that we investigated only one time point (4 h); thus, although our findings seem to rule out any contribution of preformed IL-33, the potential remains for a later influence of induced IL-33 being secreted and functioning in an autocrine fashion.

Although a recent study by Dwyer et al. (15) derives mast cell– and basophil-specific transcriptional signatures at rest, our work extends these findings by characterizing the responses of these cell types after activation by innate- and adaptive-type stimuli. Indeed, this comparative analysis of mast cells and basophils after activation provides additional evidence that these cells may independently regulate immune responses during active disease. This finding challenges the general assumption that circulating basophils can be used as functional surrogates for tissue-resident mast cells and, at the very least, highlights the need for caution in doing so in research or clinical practice.

A potential caveat in our study is that the use of bone marrow–derived primary cells might not fully extrapolate in phenotype to tissue-derived cells, as was the approach used by Dwyer et al. (15) for the Immunological Genome Project Consortium. However, two key points can be raised when considering our findings within the context of that previous study. First, as we show in Fig. 1, the mast cells generated for our study demonstrate a clear preservation of their reported “mast cell signature,” indicating that BMMCs reflect a core mast cell transcriptomic profile and not that of a precursor or other lineage cell. Second, using bone marrow–derived primary cells actually provides us with the distinct advantage of profiling transcriptional responses in highly homogeneous populations of mast cells and basophils, because they have been generated under similar culture and activation conditions; moreover, these cells were generated without using techniques that could unintentionally activate the cells, such as

**FIGURE 7.** Network diagram of upregulated genes in IgE-activated or IL-33–stimulated basophils.
enzymatic disruption or mechanical separation. Indeed, Dwyer et al. [15] actually reported upregulation of several key genes upon digestion enzyme exposure that we demonstrate in this article as reflecting activation signatures, including Egr2 and Cell, implicating basal activation of endogenous mast cells during the methods currently used to extract them from tissues. For this reason, it is likely impossible to discriminate stimulus-specific signatures using tissue-isolated mast cells with the clarity that we have been able to achieve in this study using a homogeneous bone marrow–derived cell population.

In conclusion, we demonstrate that mast cells and basophils have cell- and activation-specific transcriptional signatures. The limited homology that we observe between these cell types after activation is likely impossible to extract them from tissues. For this reason, it is likely impossible to discriminate stimulus-specific signatures using tissue-isolated mast cells with the clarity that we have been able to achieve in this study using a homogeneous bone marrow–derived cell population.

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Disclosures

The authors have no financial conflicts of interest.

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