

Involvement of mast cells in eosinophilic esophagitis

J. Pablo Abonia, MD,^a Carine Blanchard, PhD,^a Bridget Buckmeier Butz, MHSA,^a Heather F. Rainey, BS,^a Margaret H. Collins, MD,^c Keith Stringer, MD,^c Philip E. Putnam, MD,^b and Marc E. Rothenberg, MD, PhD^a Cincinnati, Ohio

Background: Eosinophilic esophagitis (EE) is an emerging disorder with poorly understood pathogenesis.

Objective: Whereas prior studies have primarily focused on the role of eosinophils in disease diagnosis and pathogenesis, this study investigates the involvement of mast cells.

Methods: Total and degranulated mast cell counts were correlated to microarray and RT-PCR data to generate transcriptome expression profiles related to mast cell number and degranulation in patients with EE and healthy control subjects.

Results: Esophageal mastocytosis and mast cell degranulation were readily apparent in patients with EE compared with control subjects ($P < .01$), as assessed by staining for total mast cells and the presence of extracellular mast cell tryptase ($P < .01$). Microarray analysis revealed that mast cell levels correlated with the dysregulation of 0.8% (301 genes) of the genome, which was partially distinct from the genes that correlated with tissue eosinophilia. The expression of transcripts for the mast cell proteases carboxypeptidase A3 and tryptase, but not chymase, correlated with mast cell levels and distinguished patients with EE from control subjects. Suprabasilar mast cell counts ($P < .01$) and degranulation ($P < .01$) were proportional with *KIT* ligand mRNA expression. Treatment of patients with EE with swallowed fluticasone propionate normalized levels of mast cells and the mast cell-related transcriptome in responder patients.

Conclusion: Herein we have identified local mastocytosis and mast cell degranulation in the esophagi of patients with EE;

identified an esophageal mast cell-associated transcriptome that is significantly divergent from the eosinophil-associated transcriptome, with carboxypeptidase A3 mRNA levels serving as the best mast cell surrogate marker; and provided evidence for the involvement of *KIT* ligand in the pathogenesis of EE.

(*J Allergy Clin Immunol* 2010;■■■:■■■-■■■.)

Key words: Mast cells/basophils, eosinophils, human

Eosinophilic esophagitis (EE) is an emerging worldwide disease, as documented by case series from all continents except Africa, which appears to be a growing health problem with an annual incidence of at least 1:10,000 children.¹⁻³ The primary symptoms of EE (chest and abdominal pain, dysphagia, heartburn, vomiting, and food impaction) are also observed in patients with chronic esophagitis (CE), including those patients with gastroesophageal reflux disease (GERD).⁴⁻⁶ However, in contrast to GERD, EE occurs more frequently in male subjects (80%), appears to have a common familial form, has a high rate of associated atopic disease (70%), and is typically associated with a normal pH probe recording of the esophagus.^{1,7-10} Patients with EE respond inadequately to anti-GERD therapy alone but might respond to anti-inflammatory therapy, allergen elimination, or both, as determined by allergen testing or empiric dietary elimination.¹¹⁻¹³

Dissection of experimental EE models in mice has revealed that EE is triggered by both food and aeroallergens, whereas pollen exposure has been associated with cases of EE in human subjects and is clearly associated with atopic disorders, such as allergic rhinitis, asthma, and eczema, in pediatric and adult patients.^{12,14-17} However, nearly 25% of patients with EE are nonatopic and have no discernable evidence of allergic sensitization.^{1,8,18,19} It is important to understand the relationship between the allergic and non-allergic variants of EE and whether allergic and nonallergic esophagitis involve similar effector pathways, such as localized mastocytosis and mast cell activation, which might have significant implications for therapeutic strategies.

Previously, whole genome-wide expression analysis of esophageal tissue has uncovered a striking EE transcript signature that correlated with eosinophil levels and was similar across sexes and patient ages but completely distinct from CE. Notably, the top induced transcript in patients with EE was eotaxin-3, and levels of eotaxin-3 strongly correlated with disease severity; furthermore, a single nucleotide polymorphism in the eotaxin-3 gene was associated with disease susceptibility.^{20,21} Additional analyses of the EE transcriptome with respect to IL-13 demonstrated a dose-dependent increase in eotaxin-3 mRNA and protein from primary esophageal epithelial cell cultures after stimulation with IL-13,²² which is consistent with prior reports demonstrating increased levels of antigen-specific IL-5⁺ T_H2 cells in the blood

From the Divisions of ^aAllergy and Immunology, ^bPediatric Gastroenterology and Nutrition, and ^cPathology and Laboratory Medicine, Department of Pediatrics, Cincinnati Children's Hospital Medical Center.

Supported by National Institutes of Health grants 12HD028827 and AI057991 to J.P.A. and grants AI070235, AI045898, P30 DK078392, and DK076893; the Food Allergy Project; the Campaign Urging Research for Eosinophilic Disorders (CURED); and the Buckeye Foundations to M.E.R.

Disclosure of potential conflict of interest: J. P. Abonia has received research support from the National Institutes of Health, Ception Therapeutics, and the Children's Digestive Health and Nutrition Foundation. M. H. Collins has consulted for GlaxoSmithKline, Ception Therapeutics, and Meritage Pharma. M. E. Rothenberg has consulted for and is a speaker for Merck; has consulted for Centocor, Ception Therapeutics, Nycomed, Array Biopharma, Biocrystal Pharmaceuticals, Endo Pharmaceuticals, and Pierce A; has received research support from the National Institutes of Health, the Food Allergy and Anaphylaxis Network, and the Dana Foundation; is on the medical advisory board of the American Partnership for Eosinophilic Disorders; and is on the executive council of the International Eosinophil Society. The rest of the authors have declared they have no conflict of interest.

Received for publication February 12, 2010; revised March 26, 2010; accepted for publication April 1, 2010.

Reprint requests: Marc E. Rothenberg, MD, PhD, Cincinnati Children's Hospital Medical Center, Division of Allergy and Immunology, 3333 Burnet Ave, ML7028, Cincinnati, OH 45229. E-mail: rothenberg@cchmc.org.

0091-6749/\$36.00

© 2010 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2010.04.009

Abbreviations used

CCL26:	CC motif ligand 26
CE:	Chronic esophagitis
CPA3:	Carboxypeptidase A3 gene
CXCL1:	CXC motif ligand 1
CXCL6:	CXC motif ligand 6
EE:	Eosinophilic esophagitis
FP:	Fluticasone propionate
GERD:	Gastroesophageal reflux disease
H&E:	Hematoxylin and eosin
HPF:	High-powered field
HPRT:	Hypoxanthine guanine phosphoribosyltransferase
IHC:	Immunohistochemistry
KITLG:	KIT ligand gene
NL:	Normal
PPP2R2C:	Protein phosphatase 2 gene

of patients with EE.²³ Recently, a variant in thymic stromal lymphopoietin was also found to be associated with EE and might play a role in the male predominance found in this disorder because its receptor is encoded within a pseudoautosomal region for the X and Y chromosomes.²⁴

The high level of eosinophils in the esophagi of patients with EE, the identification of eotaxin-3 as a primary process in EE pathogenesis, and the correlation of eosinophils with the degree of epithelial cell hyperplasia all implicate the eosinophil as a primary effector cell in patients with EE.^{20,21} Indeed, murine models have established that eosinophils are required for induction of allergen-induced epithelial hyperplasia and remodeling in models of EE.¹⁴ However, mast cells might be particularly important in disease pathogenesis because they produce an abundance of cytokines that activate eosinophils and molecules that directly promote tissue remodeling, including fibrosis, a process that has been recently identified in patients with EE, even in pediatric patients.^{25,26} Recently, increased levels of mast cells in the esophagi of patients with EE have been identified; however, their phenotype, regulation, and role in disease have not been explored in detail.^{19,26-28} We now provide substantial evidence for the involvement of KIT ligand, esophageal mastocytosis, and mast cell activation in the pathogenesis of EE. In addition, we demonstrate that the esophageal genes associated with mast cell levels are distinct from those associated with eosinophil levels, at least in part, and that carboxypeptidase A3 (*CPA3*) mRNA serves as the best surrogate tissue marker for mast cells. Furthermore, we present molecular evidence that these processes of tissue mastocytosis and dysregulation of the mast cell transcriptomes are reversible with fluticasone propionate (FP) therapy and distinguish patients with EE from healthy control subjects and patients with CE.

METHODS**Esophageal samples**

Patients were selected without regard to age, race, atopic status, or sex, and their characteristics are described in Table I. A total of 29 patients were selected for microarray analysis based on their diverse clinical features. Except when indicated, none of the patients were undergoing therapy with glucocorticoids or dietary modification. An additional 13 patients with active EE were evaluated for mast cell counts, degranulation, and the effect on mast cell transcriptomes after treatment with FP. These patients were treated with 880 μ g/d

swallowed FP for 3 months and are described in detail by Konikoff et al.²⁷ Two biopsy specimens from each patient were collected from the distal esophagus less than 5 cm from the lower esophageal sphincter, with one sample immediately fixed in formalin before hematoxylin and eosin (H&E) staining and the second stored separately for microarray and RT-PCR analysis. A pathologic diagnosis from the H&E-stained sample was determined based on the maximum eosinophil count per high-powered field (HPF; $\times 400$ magnification; area of microscopic field, 0.22 mm²) and basal layer expansion according to established criteria and correlated with clinical findings.^{4,8,20,29} Normal biopsy specimens were obtained from patients who presented with symptoms consistent with GERD and EE but whose endoscopic and histologic appearances were ultimately normal. Patients with CE were defined as having 12 or fewer eosinophils per HPF, mild expansion of the basal layer (less than one third of the epithelium), or both and not requiring treatment with either steroid or dietary therapies. Patients with EE were defined as having 24 or more eosinophils per HPF, extensive basal layer hyperplasia (expansion to one third or more of the epithelium), and clinical evidence of disease. The maximum eosinophil counts and thickness of the basal layer were assessed after H&E staining. Mast cell counts were determined by using immunohistochemistry (IHC) for tryptase. Biopsy specimens were also assessed by staining for chymase using IHC and chloroacetate esterase activity.³⁰⁻³² This study was approved by the Institutional Review Board of the Cincinnati Children's Hospital Medical Center.

DNA microarray analysis

For each patient, a distal esophageal mucosal biopsy specimen was subjected to DNA microarray, as previously reported.³³ The genome-wide Human Genome U133 Plus 2.0 Array gene chip that encompasses 38,572 genes with 54,120 probe sets (<http://www.affymetrix.com>, technical note, part no. 701483 rev. 2) was used, and gene transcript levels were determined by using algorithms in the Microarray Analysis Suite and GeneSpring software (Agilent Technologies, Santa Clara, Calif). A base set of probe sets in transcriptome analyses was generated by requiring a minimum raw expression on the microarray of 250 (average difference) in at least 3 patient samples identifying 16,425 probe sets for use in all subsequent analyses.

Ontology assessment

We subjected the list of differentially expressed transcripts to gene ontology analysis by using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) and the Expression Analysis Systematic Explorer (EASE), a Web-based (<http://david.abcc.ncifcrf.gov>) application that provides access to a relational database of functional annotations.^{34,35}

RT-PCR analysis

The RNA samples (500 ng) were subjected to reverse transcription analysis by using Bioscript reverse transcriptase (Bio-Rad Laboratories, Hercules, Calif), according to the manufacturer's instructions. Human tryptase, chymase, *CPA3*, *CXCL6*, and *HPRT* were quantified by means of real-time PCR with the Roche LightCycler 480 instrument and Roche LightCycler 480 SYBR Green I master mix (Roche, Mannheim, Germany) as a ready-to-use reaction mix. Results were then normalized to *HPRT* amplified from the same cDNA mix and expressed as fold induction compared with the controls. cDNA were amplified by using the following primers: hTryptase (70 bp), gcgatgtggacaatgatgag and tccattatggggacattcac; hChymase (64 bp), acggaaactttgtgctgacg and ggctccaagggtgactgtta; h*CPA3* (94 bp), cccagatgctattgtttcccta and agaacatcagtgccaatctttg; h*CXCL6* (131 bp), agcccttttctaagaaagtca and tccagggatctccagaaac; and h*HPRT* (120 bp), cagactgaagagctattgtaatg and ccagtgtcaattatattccac.

IHC

Esophageal sections were individually immunostained with anti-tryptase (Cell Marque, CMA890), as previously reported.³⁶ Immunoreactive cells were counted ($\times 400$ magnification) and are expressed as maximum mast cell number per HPF.

TABLE I. Characterization of patients used to generate mast cell transcriptomes, therapy, and distal esophageal biopsy specimens

	Control subjects (n = 10)	Patients with CE (n = 6)	Patients with EE (n = 13)	P value*
Age at collection (y)	6.7 ± 1.2	10.8 ± 1.9	14.6 ± 3.4	NS
Age range (y)	1.5-12.9	4.6-17.8	1.8-45.2	—
Race	White: 7 Native Hawaiian/Pacific Islander: 1 Other: 2	White: 5 Other: 1	White: 12 Other: 1	NS
Sex	Female: 2 Male: 8	Female: 3 Male: 3	Female: 3 Male: 10	NS
History of atopy	5/10 (50%)	1/6 (17%)	10/13 (77%)	NS
Treatments 1 month before esophageal biopsy				
Systemic steroids	0	0	0	NS
Swallowed steroids	0	0	0	NS
Inhaled steroids	4	0	4	NS
Leukotriene inhibitors	0	1	3	NS
Acid-suppressive therapy	4	0	6	NS
Elimination diet	0	0	3	NS
Elemental diet	0	0	0	NS
Average eosinophil count per HPF	0	5.0 ± 2.0	84.7 ± 19.8	<.01
Range of eosinophil counts per HPF	0	0-12	25-248	—
Average total mast cell count per HPF (tryptase)	0.5 ± 0.3	1.8 ± 0.7	6.9 ± 1.4	<.01
Range of total mast cell counts per HPF (tryptase)	0-3	0-4	0-17	—
Average degranulated mast cell count per HPF (tryptase)	0.2 ± 0.2	0.8 ± 0.5	3.9 ± 0.9	<.01
Range of degranulated mast cell counts per HPF (tryptase)	0-2	0-3	0-13	—

Age, race, sex, atopic status, and therapy are derived from self-reported questionnaires and medical histories. Patients with any history of asthma, allergic rhinitis, or eczema were considered atopic. Average counts per HPF ($\times 400$ magnification) are based on the maximum count noted for eosinophils and mast cells per patient esophageal sample. *P* values were determined with the Student *t* test.

*Compared between control subjects and patients with EE.

Mast cell number and extent of degranulation were assessed in the suprabasilar epithelium from control subjects, patients with CE, and patients with EE in a blinded fashion. While blinded, each esophageal sample was assessed for overall quality, and those deemed to be of inadequate quality were excluded from our final analyses with 3 or fewer HPFs that could be evaluated. The remaining samples had between 7 and 10 HPFs counted per subject, were used in generating the mast cell transcriptomes, and were quantified for the total number of mast cells and the number of degranulated mast cells per $\times 400$ HPF in the epithelium exclusive of the basal cell layer. Categorizing mast cells as intact or degranulated was dependent on the following definitions. Mast cells were counted as intact if they had discrete, focal, and well-circumscribed immunostaining for tryptase. Degranulated mast cells had discrete and relatively focal staining for tryptase but did not have well-circumscribed immunostaining (Fig 1). Up to a maximum of 10 HPFs were evaluated for each patient's sample, and the maximum counts for mast cell number and degranulation were used in the subsequent analyses. For samples evaluated after therapy with FP, the maximum mast cell count for superficial epithelium was also counted and used for further analyses.

Statistical analysis

Gene lists on microarrays were generated by studying differences in gene expression levels between 2 groups by using the Welch *t* test with a Benjamini and Hochberg false discovery rate correction.²¹ The mast cell-related transcriptome was generated by means of positive and negative correlations of gene expression with epithelial mast cell counts, as determined by using tryptase IHC in control subjects, patients with CE, and patients with EE. A *P* value of less than .05 for Spearman correlations between gene expression and epithelial mast cell counts was used as a cutoff, and this gene list was then filtered based on the Spearman *r* coefficient, with fold changes in expression noted in Tables E1 to E3 (available in this article's Online Repository at www.jacionline.org).

RESULTS

Patient and sample characterization for generation of mast cell transcriptomes

No significant differences were noted for patient age, race, and sex between control subjects, patients with CE, and patients with EE; however, atopy was common in patients with EE (Table I), which is consistent with previous studies.^{12,37,38} At the baseline visit, none of the patients were undergoing treatment with either systemic or swallowed steroids; however, several patients were undergoing therapy with leukotriene inhibitors, intranasal or inhaled steroids, and proton pump inhibitors at the time of biopsy. Elimination diets were ongoing in 3 of the patients with EE and none of the healthy control subjects or patients with CE. None of the patients in either control group or patients with EE were undergoing therapy with an elemental diet at the time of this evaluation. The average peak eosinophil count in patients with EE was 84.7 ± 19.8 and ranged between 25 and 248 eosinophils per HPF.

Mast cell distribution, number, and degranulation in patients with EE

In all patients mast cells could readily be found in peripapillary regions. In patients with EE relative to control subjects, mast cells were also often found within the epithelium outside of the basal layer, both in the interpapillary locations and in the superficial epithelium outside of the papillae. The average peak mast cell count per HPF $\pm$ SEM based on tryptase immunohistochemical staining was increased approximately 13-fold higher in patients

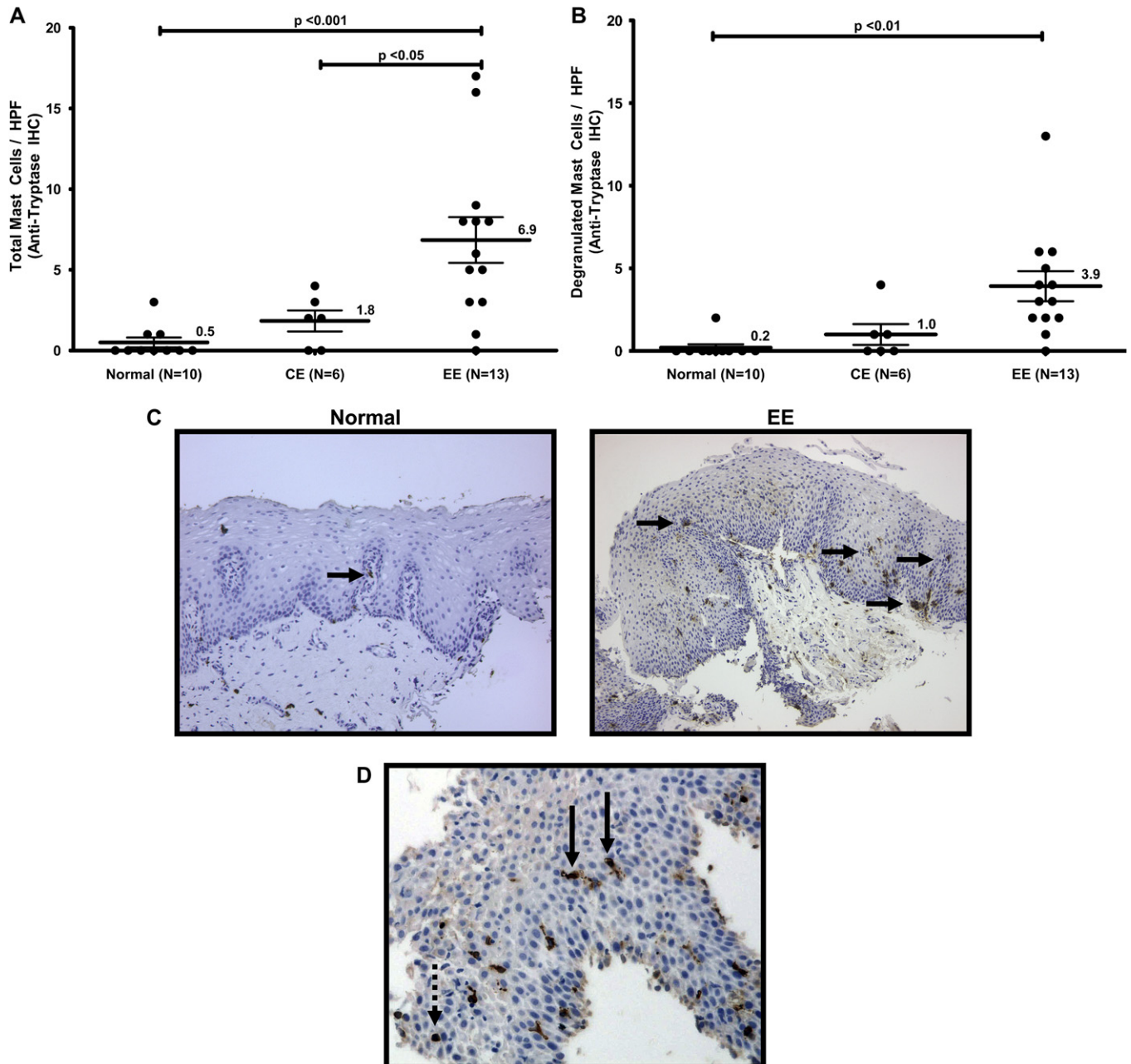


FIG 1. Mast cell counts in samples from patients with EE versus samples from control subjects or patients with CE. **A,** The maximum number of tryptase-positive mast cells per HPF in samples from patients with EE is increased (mean $\pm$ SEM) relative to that seen in samples from control subjects (*Normal*) and patients with CE. **B,** The maximum number of degranulated mast cells per HPF is increased in patients with EE relative to that seen in control subjects. **C,** Immunohistochemistry with anti-tryptase antibody in control subjects and patients with EE ($\times 40$ magnification). **D,** HPF ($\times 400$ magnification) from a patient with EE demonstrating an intact mast cell with a *dashed arrow* and degranulated mast cells with *solid arrows*.

with EE (6.9 ± 1.3 mast cells per HPF, $n = 13$) relative to healthy control subjects (0.5 ± 0.3 mast cells per HPF, $n = 10$; Fig 1, A; $P < .01$). However, although peak mast cell counts in the suprabasilar epithelium were increased in patients with EE, there was overlap between healthy control subjects and patients with EE based on tryptase staining alone, with a range of 0 to 3 mast cells per HPF in healthy control subjects and 0 to 17 mast cells per HPF in patients with EE. Patients with CE had an intermediate level relative to both control subjects and patients with EE, with a range

of 0 to 4 mast cells per HPF and an average of 1.8 ± 0.7 mast cells per HPF ($n = 6$; Fig 1, A). The patients with CE could be differentiated from the patients with EE, averaging approximately 3-fold fewer mast cells compared with the patients with EE ($P < .05$), whereas control subjects could not be differentiated from patients with CE on the basis of mast cell counts alone.

Mast cell degranulation was also assessed based on tryptase staining, with nearly all samples from patients with EE (92% [12/13]) demonstrating evidence of degranulation. The average

number of degranulated mast cells $\pm$ SEM per HPF was 0.2 ± 0.2 in control subjects, 1.0 ± 0.6 in patients with CE, and 3.9 ± 0.9 in patients with EE. These findings represent an approximately 20-fold increase in mast cell degranulation in patients with EE versus that seen in control subjects (Fig 1, B; $P < .01$), whereas no differences could be detected in comparisons of patients with CE with either control subjects or patients with EE. IHC was also performed for chymase, which could not be detected (data not shown). Furthermore, when using chloroacetate esterase staining for mast cells, which is dependent on chymase activity, we were unable to demonstrate histochemical staining for mast cells in either patients with EE or control subjects using standard methodologies (data not shown).

Mast cell-associated and EE-associated transcriptomes

Prior studies have demonstrated several dysregulated mast cell-related genes within the EE transcriptome.²⁰ In the current study a mast cell-related transcriptome was generated based on correlations of transcript levels from control subjects, patients with CE, and patients with EE with total mast cell counts, as determined by means of tryptase IHC. A minimum P value of less than .05 for the Spearman correlation coefficient identified a total of 1,632 genes that correlated with mast cell counts. These genes were then selected for a minimum 2-fold difference in patients with EE relative to control subjects (301 genes) and represent approximately 0.8% of the entire tested genome. We define these 301 genes as the mast cell-related transcriptome (see Table E1), of which approximately 50% (148/301 genes) overlapped with the original EE transcriptome that was based on eosinophil counts. Several genes historically related to mast cells were readily identified within this mast cell-related transcriptome, including KIT ligand (*KITLG*), tryptase (*TPSB2*), cathepsin C (*CTSC/DPPI*), *CPA3*, IL-8 receptor (*IL8RB/CXCR2*), phospholipase A₂ (*PLA2G4A*), and protein phosphatase 2 (*PPP2R2C*).³⁹⁻⁴⁶ Consistent with the absent findings for chymase IHC and chloroacetate esterase staining, the expression of chymase (*CMA1*),^{47,48} as detected by means of microarray analysis, was not different for patients with EE, patients with CE, and control subjects and was not found within the mast cell-related transcriptome. Additionally, expression of the mast cell-restricted protease tryptase $\gamma 1$ (*TPSG1*),⁴⁹ was below the limits of detection in all studied groups.

We aimed to determine which genes correlated with mast cell degranulation. Accordingly, we generated a mast cell degranulation-related transcriptome with a minimum cutoff P value of less than .05 for the Spearman correlation coefficient. A total of 1,298 genes were identified that correlated with mast cell degranulation, with 116 of those genes with a minimum 2-fold difference between patients with EE and control subjects (see Table E2). Two mast cell-related genes demonstrated altered steady-state transcript expression on microarray (*KITLG* and *PPP2R2C*) that were highly correlated with mast cell degranulation, with Spearman coefficient (r) values of greater than ± 0.85 ($+0.86$ for *KITLG* and -0.91 for *PPP2R2C*). The products of these genes have previously been directly associated with mast cell degranulation *in vivo* and *in vitro*.^{45,50-55} A comparison of the mast cell transcriptome (see Table E1) and the mast cell degranulation transcriptome (see Table E2) revealed significant overlap, with 112 genes in common between both transcriptomes, 184 genes unique

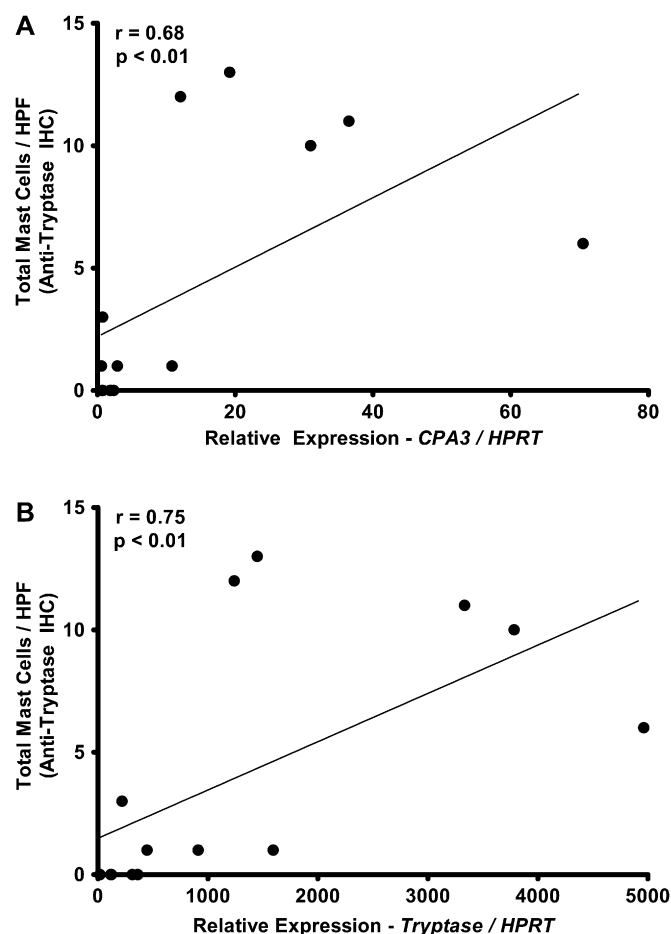


FIG 2. Relationship between mast cell counts and relative expression of *CPA3* and tryptase. Mast cell counts were determined by means of anti-tryptase IHC and correlated against the relative expression of *CPA3* ($r = 0.68$, $P < .01$; **A**) and tryptase ($r = 0.75$, $P < .01$; **B**), as determined by means of real-time PCR.

to the mast cell transcriptome, and 5 genes unique to the degranulation transcriptome.

When assessing the genes found in either the mast cell-related or degranulation-related transcriptomes, the mast cell-specific proteases *CPA3* and tryptase underwent the largest fold change in the expression of their respective transcripts in control subjects versus patients with EE. Validation studies demonstrated a 25-fold induction in the expression of *CPA3* mRNA in patients with EE relative to that seen in control subjects, as determined by means of real-time PCR analysis. *CPA3* expression directly correlated with mast cell counts, as determined by tryptase-positive cells ($r = 0.68$, $P < .01$; Fig 2, A). Tryptase mRNA (*TPSB2*) expression had a 10-fold increase in patients with EE relative to that seen in control subjects and correlated with tryptase IHC ($r = 0.75$, $P < .01$; Fig 2, B). No increase in chymase mRNA expression was noted by using real-time PCR in patients with EE versus control subjects, and there was no correlation between tryptase-derived mast cell counts and chymase expression (data not shown). Along with the increase in the primary mast cell proteases, *CPA3* and tryptase, on microarray analysis, demonstrated a 5-fold increase in the dipeptidyl peptidase I (*DPPI*, cathepsin C [*CTSC*]), an enzyme that activates mast cell chymase.^{41,56}

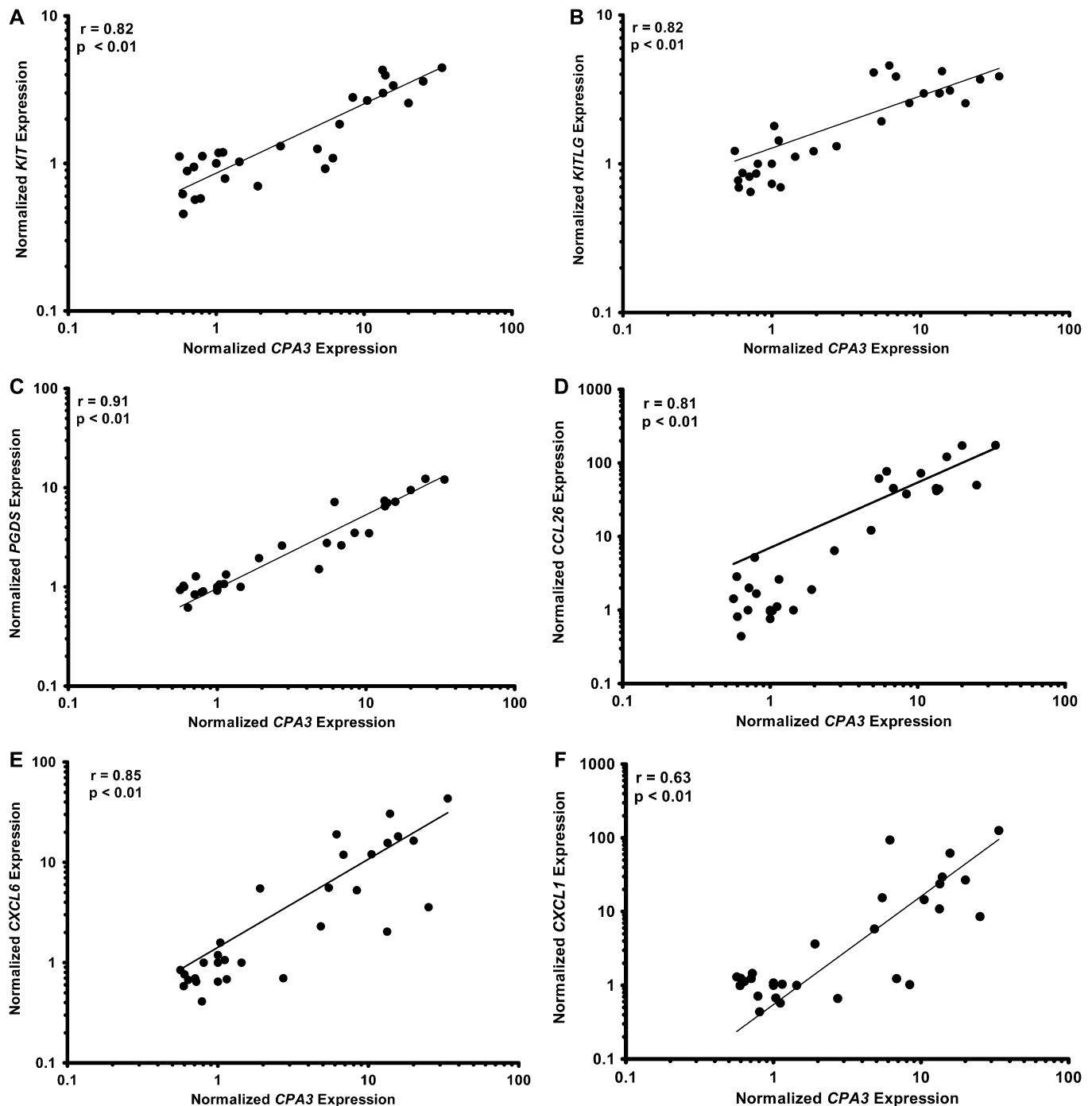


FIG 3. Correlation of *CPA3* expression with mast cell gene expression. Correlations between microarray expression of *CPA3* and mast cell-related genes, including *KIT* ($r = 0.82$, $P < .01$; **A**), *KITLG* ($r = 0.82$, $P < .01$; **B**), *PGDS* ($r = 0.91$, $P < .01$; **C**), *CCL26* ($r = 0.81$, $P < .01$; **D**), *CXCL6* ($r = 0.85$, $P < .01$; **E**), and *CXCL1* ($r = 0.63$, $P < .01$; **F**) are shown.

Mast cell-related genes

Identifying *CPA3* as a grossly dysregulated surrogate genetic marker for esophageal mast cells in patients with EE provided a valuable opportunity to dissect molecular processes associated with human mastocytosis. We therefore correlated global gene expression with the expression of *CPA3* mRNA. The ontology of genes that most correlated with *CPA3* are broadly based and associated with combined innate and adaptive immune responses,

including complement activation, natural killer cell cytotoxicity, mast cell activation, and programmed cell death (see Table E3). Strong correlations between *CPA3* and *c-Kit*, *KITLG*, and prostaglandin D₂ synthase (*PGDS*) expression were apparent with r values of 0.82, 0.82, and 0.91, respectively (Fig 3, A-C). When *CPA3* was compared with the chemokines overexpressed in patients with EE (*CCL26*, *CXCL6*, and *CXCL1*), strong correlations were readily apparent for *CCL26* ($r = 0.81$) and *CXCL6*

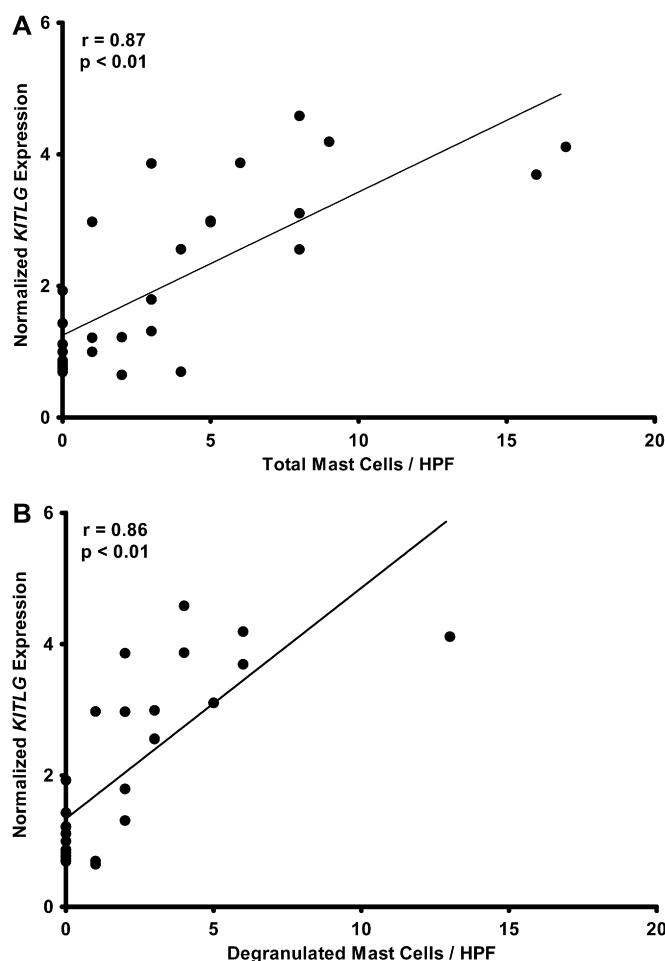


FIG 4. Correlation of *KITLG* expression with intact and degranulated mast cells. The normalized expression of *KITLG* is plotted against the maximum number of intact mast cells ($r = 0.87$, $P < .01$; **A**) or degranulated mast cells ($r = 0.86$, $P < .01$; **B**).

($r = 0.85$), whereas a weaker correlation was noted for *CXCL1* ($r = 0.63$; Fig 3, D-F). A clear correlation was noted between *KITLG* and total ($r = 0.87$) or degranulated ($r = 0.86$) mast cell counts (Fig 4). No statistically significant correlation was noted between peak eosinophil counts and the expression of *KITLG* (data not shown), which is consistent with the prominent role of *KITLG* in mast cell rather than eosinophil development.

Mast cell counts, gene expression, and treatment with FP

In those patients with evidence of response to FP treatment based on the normalization of esophageal eosinophil counts, mast cell counts, as determined by using tryptase IHC (1.5 ± 0.6 mast cells per HPF $\pm$ SEM) were equivalent to those seen in control subjects (0.5 ± 0.3 mast cells per HPF $\pm$ SEM) and were reduced compared with those seen in patients with EE with active disease (14.2 ± 2.7 mast cells per HPF $\pm$ SEM, $P < 0.05$). For those patients who did not respond to swallowed FP therapy, the mast cell counts were increased to the same extent as seen in patients with EE with active disease in comparison with control subjects (Fig 5, A). The expression of *CPA3* in patients who responded to FP

(*CPA3*, mean $\pm$ SEM, 1.5 ± 0.6) was equivalent to that seen in control subjects (*CPA3*, mean $\pm$ SEM, 1.1 ± 0.1) and was reduced compared with that seen in patients with active disease (*CPA3*, mean $\pm$ SEM, 14.2 ± 2.7 ; $P < .05$; Fig 5, B). Indeed, the expression of the entire mast cell transcriptome in patients with EE who have responded to FP treatment cannot be readily differentiated from that seen in control subjects, whereas dysregulation of the mast cell transcriptome is readily apparent in the patients with EE not responding to FP therapy (Fig 5, C). Similarly, in patients with CE, mast cell counts, *CPA3* expression, and the mast cell transcriptome are essentially equivalent in comparison with that seen in untreated control subjects.

DISCUSSION

Evidence is emerging that the immunopathogenesis of EE involves the complex interplay of a number of different cell types, including epithelial cells, lymphocytes, and mast cells. Recent research indicates that mast cells accumulate in the esophagus and their activation might be regulated by locally generated IgE, as well as other innate triggers, including mast cell secretagogues released from eosinophils.^{36,57,58} Notably, a detailed description of mast cell phenotype, activation, and mechanisms of recruitment and activation have not been delineated. We now confirm that substantial mastocytosis occurs in esophageal biopsy specimens obtained from patients with EE compared with those from control subjects and patients with chronic (noneosinophilic) esophagitis. In particular, mast cell accumulation in the epithelial layer distinguishes patients with EE from the 2 control groups. Mastocytosis occurred independent of the patient's age, sex, atopic status, and proton pump inhibitor therapy, indicating that it is a general phenomenon despite the distinct patient phenotypes. Furthermore, we report that mast cells undergo substantial degranulation in patients with EE compared with that seen in both control groups. Using a combination of approaches (gene chip analysis, real-time PCR, and IHC), we report that a unique mast cell phenotype is predominantly associated with tryptase and *CPA3* rather than chymase or tryptase $\gamma 1$. This emphasizes the unique mast cell phenotype or phenotypes in patients with EE because *CPA3* has typically been associated with connective tissue mast cells expressing both tryptase and chymase rather than the T cell-dependent mucosal mast cell phenotype that is associated with the expression of tryptase alone.⁵⁹ T cell-derived products, such as IL-5, have been shown to be involved in EE pathogenesis relative to that seen in patients with IgE-mediated food allergy; presumably this localized alteration in T_H2 subpopulations could be influencing mast cell protease expression and the general phenotype.²³ Of the known mast cell-specific genes, the transcript for *CPA3* was strongly associated with mast cells and represents the most severely dysregulated mast cell gene within the mast cell-related transcriptome. This finding has implications for other diseases with associated mastocytosis (eg, asthma) because this gene provides a molecular "fingerprint" for mast cells. Using both tryptase IHC and *CPA3* gene expression to quantitate mast cells, we identified a mast cell-associated transcriptome in patients with EE. Notably, only 148 (approximately 50%) of 301 genes composing the mast cell-related transcriptome overlapped with the eosinophil-associated EE transcriptome (490 genes), indicating that there are both shared and unique pathways involved in regulating these 2 cell types and their downstream pathways. In addition, the inflammatory consequences initiated by each of

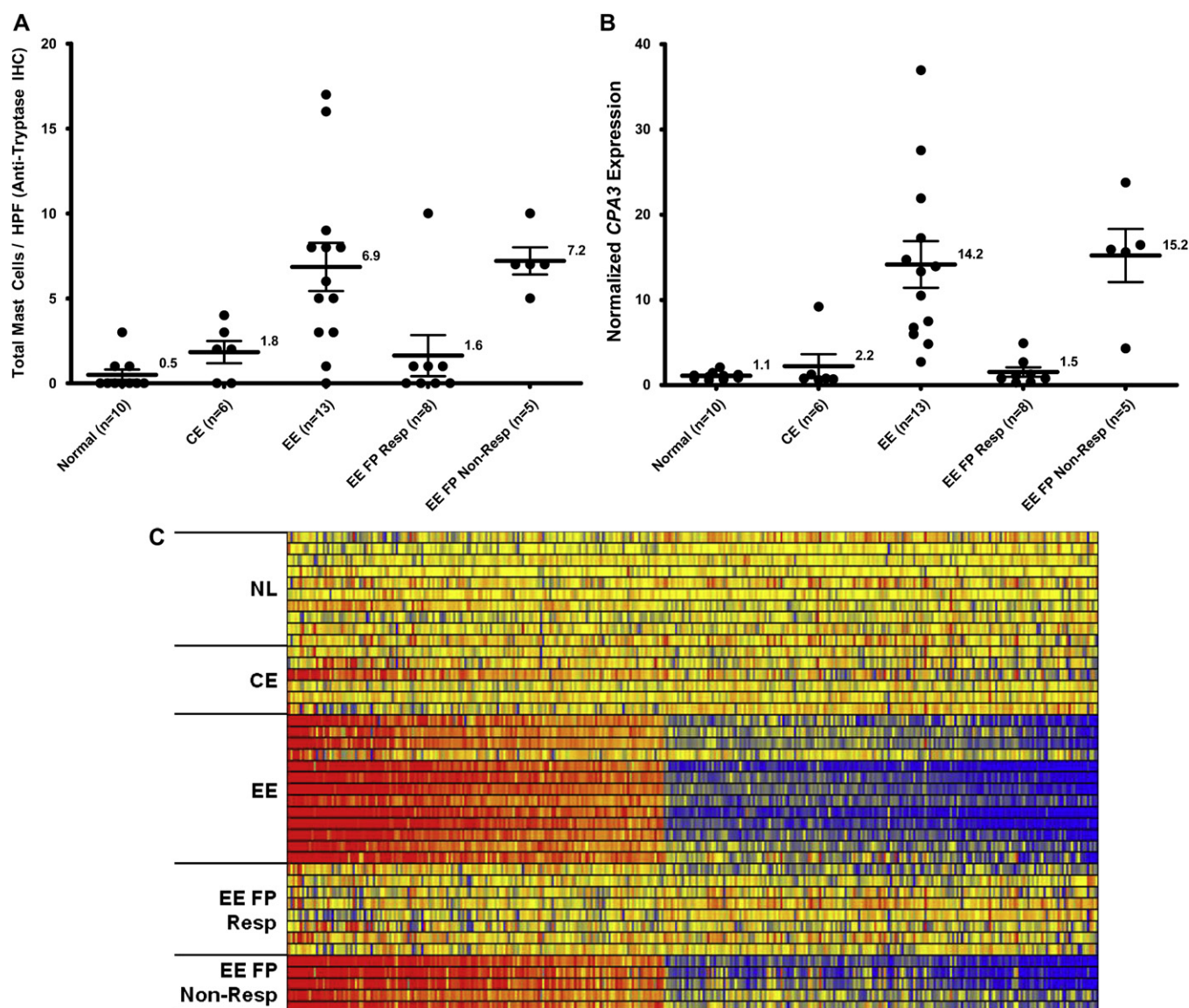


FIG 5. Mast cell counts, gene expression, and mast cell transcriptome in patients treated with swallowed FP. **A**, Maximum mast cell counts from control subjects (*Normal*), patients with CE, and patients with EE compared with those from patients with EE who responded to FP (*EE FP Resp*) or did not respond to FP (*EE FP Non-Resp*). Response to treatment with swallowed FP was defined as 1 or fewer eosinophils per HPF. **B**, CPA3 expression on microarray. **C**, The mast cell-related transcriptome under varying conditions listed above.

these 2 cells types are likely to be unique considering their distinct transcriptomes.

The mast cell-associated EE transcriptome provided a valuable opportunity to dissect mechanisms of mast cell accumulation and activation; indeed, we report that *KITLG* expression strongly correlated with both mast cell accumulation and activation. Several studies have found that the injection of KIT ligand into the skin results in mast cell degranulation, histamine release, localized swelling, and fibrin deposition.⁵²⁻⁵⁵ We report that the mast cell-associated transcriptome is completely reversible after successful therapy with swallowed FP, suggesting that the mast cell changes are likely secondary rather than constitutive to the elements of the esophagus that are assessed by the biopsy-associated transcriptome. It is notable that mast cell

responses in patients with asthma are not dramatically inhibited by glucocorticoids,^{60,61} highlighting that this response is relatively unique and encouraging in terms of therapy and prognosis. In contrast, treatment with mepolizumab does not clearly appear to dramatically affect mast cell numbers in at least 2 separate studies.^{62,63} It is unknown to date whether dietary therapies would alter these disease parameters as well.

In summary, we report that esophageal mastocytosis and degranulation occur in patients with EE and have identified a mast cell-associated esophageal transcriptome that distinguishes patients with EE from control subjects. This transcriptome only partially overlaps with the eosinophil-associated transcriptome and identifies unique upstream (*KITLG*) and downstream (*PGD2*) pathways involved in regulating mast cells and the inflammatory

response characteristic of patients with EE. Herein we have identified that tissue levels of *CPA3* serve as a strong surrogate marker for human mast cells. This finding is likely to have applications for other mast cell-associated diseases in which better mast cell assessments are needed (eg, asthma). As such, we have identified mast cell-associated responses that might have diagnostic value and further significance in terms of pathogenesis and therapeutic strategies.

We thank Cassie Kirby for her diligent work in support of this effort and Shawna Hottinger for her final edits of this manuscript.

Key messages

- Mast cells are increased and degranulated in patients with EE and are correlated with an atypical and modified phenotype associated with active disease.
- Esophageal transcriptomes differentiate mast cell-associated and eosinophil-associated processes, with *CPA3* as the most dysregulated mast cell gene in patients with EE.
- Evidence is provided for the selective regulation of mast cells by *KITLG*.

REFERENCES

- Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004;351:940-1.
- Gill R, Durst P, Rewalt M, Elitsur Y. Eosinophilic esophagitis disease in children from West Virginia: a review of the last decade (1995-2004). *Am J Gastroenterol* 2007;102:2281-5.
- Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* 2005;115:418-9.
- Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995;109:1503-12.
- Walsh SV, Antonioli DA, Goldman H, Fox VL, Bousvaros A, Leichtner AM, et al. Allergic esophagitis in children: a clinicopathological entity. *Am J Surg Pathol* 1999;23:390-6.
- Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol* 2004;113:11-28.
- Collins MH, Blanchard C, Abonia JP, Kirby C, Akers R, Wang N, et al. Clinical, pathologic, and molecular characterization of familial eosinophilic esophagitis compared with sporadic cases. *Clin Gastroenterol Hepatol* 2008;6:621-9.
- Sant'Anna AM, Rolland S, Fournet JC, Yazbeck S, Drouin E. Eosinophilic esophagitis in children: symptoms, histology and pH probe results. *J Pediatr Gastroenterol Nutr* 2004;39:373-7.
- Lim JR, Gupta SK, Croffie JM, Pfeifferkorn MD, Molleston JP, Corkins MR, et al. White specks in the esophageal mucosa: an endoscopic manifestation of non-reflux eosinophilic esophagitis in children. *Gastrointest Endosc* 2004;59:835-8.
- Jyonouchi S, Brown-Whitehorn TA, Spergel JM. Association of eosinophilic gastrointestinal disorders with other atopic disorders. *Immunol Allergy Clin North Am* 2009;29:85-97.
- Spergel JM, Brown-Whitehorn T, Beausoleil JL, Shuker M, Liacouras CA. Predictive values for skin prick test and atopy patch test for eosinophilic esophagitis. *J Allergy Clin Immunol* 2007;119:509-11.
- Assa'ad AH, Putnam PE, Collins MH, Akers RM, Jameson SC, Kirby CL, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol* 2007;119:731-8.
- Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;4:1097-102.
- Mishra A, Hogan SP, Brandt EB, Rothenberg ME. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001;107:83-90.
- Mishra A, Hogan SP, Brandt EB, Rothenberg ME. IL-5 promotes eosinophil trafficking to the esophagus. *J Immunol* 2002;168:2464-9.
- Fogg MI, Ruchelli E, Spergel JM. Pollen and eosinophilic esophagitis. *J Allergy Clin Immunol* 2003;112:796-7.
- Simon D, Marti H, Heer P, Simon HU, Braathen LR, Straumann A. Eosinophilic esophagitis is frequently associated with IgE-mediated allergic airway diseases. *J Allergy Clin Immunol* 2005;115:1090-2.
- Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology* 2003;125:1660-9.
- Straumann A, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001;108:954-61.
- Blanchard C, Wang N, Stringer KF, Mishra A, Fulkerson PC, Abonia JP, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006;116:536-47.
- Blanchard C, Wang N, Rothenberg ME. Eosinophilic esophagitis: pathogenesis, genetics, and therapy. *J Allergy Clin Immunol* 2006;118:1054-9.
- Blanchard C, Mingler MK, Vicario M, Abonia JP, Wu YY, Lu TX, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol* 2007;120:1292-300.
- Prussin C, Lee J, Foster B. Eosinophilic gastrointestinal disease and peanut allergy are alternatively associated with IL-5+ and IL-5(-) T(H)2 responses. *J Allergy Clin Immunol* 2009;124:1326-32.
- Rothenberg ME, Spergel JM, Sherrill JD, Annaiah K, Martin LJ, Cianferoni A, et al. Common variants at 5q22 associate with pediatric eosinophilic esophagitis. *Nat Genet* 2010;42:289-91.
- Aceves SS, Newbury RO, Dohil R, Bastian JF, Broide DH. Esophageal remodeling in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2007;119:206-12.
- Chehade M, Sampson HA, Morotti RA, Magid MS. Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2007;45:319-28.
- Konikoff MR, Noel RJ, Blanchard C, Kirby C, Jameson SC, Buckmeier BK, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 2006;131:1381-91.
- Kirsch R, Bokhary R, Marcon MA, Cutz E. Activated mucosal mast cells differentiate eosinophilic (allergic) esophagitis from gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 2007;44:20-6.
- Ruchelli E, Wenner W, Voytek T, Brown K, Liacouras C. Severity of esophageal eosinophilia predicts response to conventional gastroesophageal reflux therapy. *Pediatr Dev Pathol* 1999;2:15-8.
- Leder LD. The chloroacetate esterase reaction. A useful means of histological diagnosis of hematological disorders from paraffin sections of skin. *Am J Dermatopathol* 1979;1:39-42.
- Beckstead JH, Halverson PS, Ries CA, Bainton DF. Enzyme histochemistry and immunohistochemistry on biopsy specimens of pathologic human bone marrow. *Blood* 1981;57:1088-98.
- Friend DS, Gurish MF, Austen KF, Hunt J, Stevens RL. Senescent jejunal mast cells and eosinophils in the mouse preferentially translocate to the spleen and draining lymph node, respectively, during the recovery phase of helminth infection. *J Immunol* 2000;165:344-52.
- Zimmermann N, King NE, Laporte J, Yang M, Mishra A, Pope SM, et al. Dissection of experimental asthma with DNA microarray analysis identifies arginase in asthma pathogenesis. *J Clin Invest* 2003;111:1863-74.
- Dennis G Jr, Sherman BT, Hosack DA, Yang J, Gao W, Lane HC, et al. DAVID: Database for Annotation, Visualization, and Integrated Discovery. *Genome Biol* 2003;4:3.
- Hosack DA, Dennis G Jr, Sherman BT, Lane HC, Lempicki RA. Identifying biological themes within lists of genes with EASE. *Genome Biol* 2003;4:R70.
- Vicario M, Blanchard C, Stringer KF, Collins MH, Mingler MK, Ahrens A, et al. Local B cells and IgE production in the oesophageal mucosa in eosinophilic oesophagitis. *Gut* 2010;59:12-20.
- Aceves SS, Newbury RO, Dohil R, Schwimmer J, Bastian JF. Distinguishing eosinophilic esophagitis in pediatric patients: clinical, endoscopic, and histologic features of an emerging disorder. *J Clin Gastroenterol* 2007;41:252-6.
- Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol* 2005;95:336-43.
- Geissler EN, Liao M, Brook JD, Martin FH, Zsebo KM, Housman DE, et al. Stem cell factor (SCF), a novel hematopoietic growth factor and ligand for c-kit tyrosine kinase receptor, maps on human chromosome 12 between 12q14.3 and 12qter. *Somat Cell Mol Genet* 1991;17:207-14.
- Miller JS, Moxley G, Schwartz LB. Cloning and characterization of a second complementary DNA for human tryptase. *J Clin Invest* 1990;86:864-70.
- Sheth PD, Pedersen J, Walls AF, McEuen AR. Inhibition of dipeptidyl peptidase I in the human mast cell line HMC-1: blocked activation of tryptase,

- but not of the predominant chymotryptic activity. *Biochem Pharmacol* 2003;66:2251-62.
42. Reynolds DS, Gurley DS, Stevens RL, Sugarbaker DJ, Austen KF, Serafin WE. Cloning of cDNAs that encode human mast cell carboxypeptidase A, and comparison of the protein with mouse mast cell carboxypeptidase A and rat pancreatic carboxypeptidases. *Proc Natl Acad Sci U S A* 1989;86:9480-4.
 43. Abonia JP, Austen KF, Rollins BJ, Joshi SK, Flavell RA, Kuziel WA, et al. Constitutive homing of mast cell progenitors to the intestine depends on autologous expression of the chemokine receptor CXCR2. *Blood* 2005;105:4308-13.
 44. Murakami M, Kudo I, Inoue K. Characteristics and possible functions of mast cell phospholipases A2. *Adv Exp Med Biol* 1992;318:27-34.
 45. Ludowyke RI, Holst J, Mudge LM, Sim AT. Transient translocation and activation of protein phosphatase 2A during mast cell secretion. *J Biol Chem* 2000;275:6144-52.
 46. Caughey GH, Raymond WW, Blount JL, Hau LW, Pallaoro M, Wolters PJ, et al. Characterization of human gamma-tryptases, novel members of the chromosome 16p mast cell tryptase and proctasin gene families. *J Immunol* 2000;164:6566-75.
 47. Urata H, Kinoshita A, Perez DM, Misono KS, Bumpus FM, Graham RM, et al. Cloning of the gene and cDNA for human heart chymase. *J Biol Chem* 1991;266:17173-9.
 48. Caughey GH, Zerweck EH, Vanderslice P. Structure, chromosomal assignment, and deduced amino acid sequence of a human gene for mast cell chymase. *J Biol Chem* 1991;266:12956-63.
 49. Wong GW, Tang Y, Feyfant E, Sali A, Li L, Li Y, et al. Identification of a new member of the tryptase family of mouse and human mast cell proteases which possesses a novel COOH-terminal hydrophobic extension. *J Biol Chem* 1999;274:30784-93.
 50. Costa JJ, Demetri GD, Harrist TJ, Dvorak AM, Hayes DF, Merica EA, et al. Recombinant human stem cell factor (kit ligand) promotes human mast cell and melanocyte hyperplasia and functional activation in vivo. *J Exp Med* 1996;183:2681-6.
 51. Bischoff SC, Dahinden CA. c-kit ligand: a unique potentiator of mediator release by human lung mast cells. *J Exp Med* 1992;175:237-44.
 52. Columbo M, Horowitz EM, Botana LM, MacGlashan DW Jr, Bochner BS, Gillis S, et al. The human recombinant c-kit receptor ligand, rhSCF, induces mediator release from human cutaneous mast cells and enhances IgE-dependent mediator release from both skin mast cells and peripheral blood basophils. *J Immunol* 1992;149:599-608.
 53. Wershil BK, Tsai M, Geissler EN, Zsebo KM, Galli SJ. The rat c-kit ligand, stem cell factor, induces c-kit receptor-dependent mouse mast cell activation in vivo. Evidence that signaling through the c-kit receptor can induce expression of cellular function. *J Exp Med* 1992;175:245-55.
 54. Hammerberg B, Olivry T, Orton SM. Skin mast cell histamine release following stem cell factor and high-affinity immunoglobulin E receptor cross-linking in dogs with atopic dermatitis. *Vet Dermatol* 2001;12:339-46.
 55. Feldweg AM, Friend DS, Zhou JS, Kanaoka Y, Daheshia M, Li L, et al. gp49B1 suppresses stem cell factor-induced mast cell activation-secretion and attendant inflammation in vivo. *Eur J Immunol* 2003;33:2262-8.
 56. Sakai K, Ren S, Schwartz LB. A novel heparin-dependent processing pathway for human tryptase. Autocatalysis followed by activation with dipeptidyl peptidase I. *J Clin Invest* 1996;97:988-95.
 57. Lucendo AJ, Navarro M, Comas C, Pascual JM, Burgos E, Santamaria L, et al. Immunophenotypic characterization and quantification of the epithelial inflammatory infiltrate in eosinophilic esophagitis through stereology: an analysis of the cellular mechanisms of the disease and the immunologic capacity of the esophagus. *Am J Surg Pathol* 2007;31:598-606.
 58. Lucendo AJ, Bellon T, Lucendo B. The role of mast cells in eosinophilic esophagitis. *Pediatr Allergy Immunol* 2009;20:512-8.
 59. Pejler G, Knight SD, Henningsson F, Wernersson S. Novel insights into the biological function of mast cell carboxypeptidase A. *Trends Immunol* 2009;30:401-8.
 60. Wallin A, Sandstrom T, Soderberg M, Howarth P, Lundback B, la-Cioppa G, et al. The effects of regular inhaled formoterol, budesonide, and placebo on mucosal inflammation and clinical indices in mild asthma. *Am J Respir Crit Care Med* 1999;159:79-86.
 61. Wallin A, Sue-Chu M, Bjerner L, Ward J, Sandstrom T, Lindberg A, et al. Effect of inhaled fluticasone with and without salmeterol on airway inflammation in asthma. *J Allergy Clin Immunol* 2003;112:72-8.
 62. Stein ML, Collins MH, Villanueva JM, Kushner JP, Putnam PE, Buckmeier BK, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol* 2006;118:1312-9.
 63. Straumann A, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut* 2010;59:21-30.

Online Repository

Involvement of mast cells in eosinophilic esophagitis¹

J. Pablo Abonia, MD,* Carine Blanchard, PhD,* Bridget Buckmeier Butz, MHSA,* Heather F. Rainey, BS,* Margaret H. Collins, MD,[¶] Keith Stringer, MD,[¶] Philip E. Putnam, MD,[†] and Marc E. Rothenberg, MD, PhD*

*Division of Allergy and Immunology, [†]Division of Pediatric Gastroenterology and Nutrition, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, 45229; [¶]Division of Pathology and Laboratory Medicine, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, 45229

¹ This work was supported by NIH grants 12HD028827, AI057991 to J.P.A, AI070235, AI45898, P30 DK0789392 and DK076893, the Food Allergy Project, the Campaign Urging Research for Eosinophilic Disorders (CURED), and the Buckeye Foundations to M.E.R.

² Address correspondence and reprint requests to Dr. Marc E. Rothenberg, Cincinnati Children's Hospital Medical Center, Division of Allergy and Immunology, 3333 Burnet Avenue, ML7028, Cincinnati, OH, 45229, USA; Phone (513) 636-7210; Fax: (513) 636-3310; E-mail address: rothenberg@cchmc.org

Supplementary Tables

Supplementary Table 1: Mast cell transcriptome derived from tryptase IHC counts. 354 Probesets encompassing 301 known genes of the mast cell transcriptome are listed. They are sorted according to their Spearman correlation with maximum epithelial mast cell counts.

Accession#	Spearman Correlation	Fold Change	Name	Description
219508_at	0.918	3.975	GCNT3	glucosaminyl (N-acetyl) transferase 3, mucin type
201739_at	0.909	3.242	SGK1	serum/glucocorticoid regulated kinase
217977_at	0.9	2.421	SEPX1	selenoprotein X, 1
226534_at	0.873	3.055	KITLG	KIT ligand
220048_at	0.864	2.576	EDAR	ectodysplasin A receptor
202037_s_at	0.864	3.974	SFRP1	secreted frizzled-related protein 1
226525_at	0.864	2.333	STK17B	Serine/threonine kinase 17b (apoptosis-inducing)
232306_at	0.855	18.24	CDH26	cadherin-like 26
228892_at	0.845	3.076	SH3RF2	SH3 domain containing ring finger 2
225615_at	0.845	2.566	IFFO2	hypothetical protein LOC126917
213078_x_at	0.836	2.447	LPCAT4	PLSC domain containing protein
202307_s_at	0.827	2.004	TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)
206765_at	0.827	5.247	KCNJ2	potassium inwardly-rectifying channel, subfamily J, member 2
227816_at	0.827	2.322	NTN1	Hypothetical LOC400572
211906_s_at	0.818	5.22	SERPINB4	serpin peptidase inhibitor, clade B (ovalbumin), member 4 ; serpin peptidase inhibitor, clade B (ovalbumin), member 4
203854_at	0.818	4.75	CFI	I factor (complement)
213457_at	0.809	2.24	MFHAS1	malignant fibrous histiocytoma amplified sequence 1
232165_at	0.809	6.244	EPPK1	epiplakin 1
219734_at	0.809	4.411	SIDT1	SID1 transmembrane family, member 1
214677_x_at	0.8	8.084	IGL@	immunoglobulin lambda locus ; immunoglobulin lambda constant 1 (Mcg marker) ; immunoglobulin lambda constant 2 (Kern-Oz- marker) ; immunoglobulin lambda variable 3-25 ; immunoglobulin lambda variable 2-14 ; immunoglobulin lambda joining 3
236979_at	0.8	8.051	BCL2L15	chromosome 1 open reading frame 178
207134_x_at	0.8	5.578	TPSB2	tryptase beta 2
40472_at	0.8	2.381	LPCAT4	PLSC domain containing protein
232164_s_at	0.791	6.262	EPPK1	epiplakin 1
1553589_a_at	0.791	2.84	PDZK1IP1	PDZK1 interacting protein 1
236045_x_at	0.791	3.627	---	LOC441801

231832_at	0.791	3.337	GALNT4	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 4 (GalNAc-T4)
-----------	-------	-------	--------	--

Supplementary Table 1: Mast cell transcriptome derived from tryptase IHC counts, *cont.*

Accession#	Spearman Correlation	Fold Change	Name	Description
201487_at	0.791	4.837	CTSC	cathepsin C
209500_x_at	0.791	2.623	TNFSF12- TNFSF13 ///	tumor necrosis factor (ligand) superfamily, member 13 ; tumor necrosis factor (ligand) superfamily, member 12-member 13
201061_s_at	0.782	2.382	STOM	stomatin
1557321_a_at	0.782	2.061	CAPN14	calpain 14
233663_s_at	0.782	21.57	CDH26	cadherin-like 26
217022_s_at	0.782	5.236	IGH@ /// IGHA1 /// IGHA2 /// LOC100126583	immunoglobulin heavy constant alpha 1 ; immunoglobulin heavy constant alpha 2 (A2m marker) ; hypothetical protein MGC27165
232231_at	0.773	5.547	RUNX2	runt-related transcription factor 2
203574_at	0.773	2.064	NFIL3	nuclear factor, interleukin 3 regulated
221218_s_at	0.773	3.233	TPK1	thiamin pyrophosphokinase 1
221671_x_at	0.773	5.96	IGK@ /// IGKC	immunoglobulin kappa constant ; immunoglobulin kappa variable 1-5
215121_x_at	0.773	5.702	IGL@	immunoglobulin lambda locus ; immunoglobulin lambda constant 1 (Mcg marker) ; immunoglobulin lambda constant 2 (Kern-Oz- marker) ; immunoglobulin lambda variable 3-25 ; immunoglobulin lambda variable 2-14
224795_x_at	0.773	6.801	IGK@ /// IGKC	immunoglobulin kappa constant ; immunoglobulin kappa variable 1-5
201106_at	0.773	2.281	GPX4	glutathione peroxidase 4 (phospholipid hydroperoxidase)
224916_at	0.773	3.705	TMEM173	hypothetical protein LOC340061
225647_s_at	0.773	6.523	CTSC	cathepsin C
206942_s_at	0.773	10.55	PMCH	pro-melanin-concentrating hormone
235768_at	0.773	2.626	SH3RF2	SH3 domain containing ring finger 2
1554352_s_at	0.764	2.106	DENND4A	c-myc promoter binding protein
210069_at	0.764	2.272	CHKB /// CPT1B	choline kinase beta ; carnitine palmitoyltransferase 1B (muscle)
231331_at	0.764	3.387	---	Transcribed locus
243582_at	0.764	2.622	SH3RF2	SH3 domain containing ring finger 2
220780_at	0.764	2.036	PLA2G3	phospholipase A2, group III
224929_at	0.764	2.584	TMEM173	hypothetical protein LOC340061
210095_s_at	0.755	2.386	IGFBP3	insulin-like growth factor binding protein 3
227480_at	0.755	6.686	SUSD2	sushi domain containing 2
211644_x_at	0.755	2.689	IGK@ /// IGKC /// IGKV3-20 /// IGKV3D-11 /// IGKV3D-15 /// LOC440871	immunoglobulin kappa constant ; immunoglobulin kappa constant

Supplementary Table 1: Mast cell transcriptome derived from tryptase IHC counts, cont.

Accession#	Spearman Correlation	Fold Change	Name	Description
202234_s_at	0.755	3.666	SLC16A1	solute carrier family 16 (monocarboxylic acid transporters), member 1
219630_at	0.755	2.882	PDZK1IP1	PDZK1 interacting protein 1
204702_s_at	0.755	2.714	NFE2L3	nuclear factor (erythroid-derived 2)-like 3
223710_at	0.755	43.87	CCL26	chemokine (C-C motif) ligand 26
238429_at	0.745	11.43	TMEM71	transmembrane protein 71
209546_s_at	0.745	4.132	APOL1	apolipoprotein L, 1
238725_at	0.745	2.336	IRF1	Transcribed locus, weakly similar to XP_496299.1 PREDICTED: hypothetical protein LOC148206 [Homo sapiens]
225968_at	0.745	2.021	PRICKLE2	prickle-like 2 (Drosophila)
209835_x_at	0.745	2.165	CD44	CD44 antigen (homing function and Indian blood group system)
205624_at	0.745	11.03	CPA3	carboxypeptidase A3 (mast cell)
221651_x_at	0.745	5.842	IGK@ /// IGKC	immunoglobulin kappa constant ; immunoglobulin kappa variable 1-5
209138_x_at	0.745	7.119	IGL@	Immunoglobulin lambda joining 3
224374_s_at	0.745	2.764	EMILIN2	elastin microfibril interfacer 2 ; elastin microfibril interfacer 2
218684_at	0.736	2.649	LRRC8D	leucine rich repeat containing 8 family, member D
226604_at	0.736	2.305	TMTCC3	SMILE protein
219197_s_at	0.736	6.754	SCUBE2	signal peptide, CUB domain, EGF-like 2
221766_s_at	0.736	2.043	FAM46A	family with sequence similarity 46, member A
225458_at	0.736	7.63	LOC25845	DKFZP564I1171 protein
225646_at	0.736	6.605	CTSC	cathepsin C
205890_s_at	0.736	6.699	GABBR1 /// UBD	ubiquitin D
216474_x_at	0.736	5.881	TPSAB1 /// TPSB2	tryptase alpha/beta 1 ; tryptase beta 2
235146_at	0.736	2.492	TMCC3	Transmembrane and coiled-coil domain family 3
223377_x_at	0.736	2.973	CISH	cytokine inducible SH2-containing protein
205159_at	0.736	2.965	CSF2RB	colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage) ; colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)
206513_at	0.736	2.7	AIM2	absent in melanoma 2
200706_s_at	0.727	3.005	LITAF	lipopolysaccharide-induced TNF factor
242961_x_at	0.727	2.357	DDX58	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58
212658_at	0.727	3.32	LHFPL2	lipoma HMGIC fusion partner-like 2
241382_at	0.727	2.67	PCP4L1	CDNA clone IMAGE:4792407
209976_s_at	0.727	2.386	CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1

Supplementary Table 1: Mast cell transcriptome derived from tryptase IHC counts, cont.

Accession#	Spearman Correlation	Fold Change	Name	Description
225688_s_at	0.727	6.741	PHLDB2	pleckstrin homology-like domain, family B, member 2
221795_at	0.727	3.829	NTRK2	neurotrophic tyrosine kinase, receptor, type 2
205192_at	0.727	2.246	MAP3K14	mitogen-activated protein kinase kinase kinase 14
223541_at	0.727	2.824	HAS3	hyaluronan synthase 3
215388_s_at	0.727	2.586	CFH /// CFHR1	complement factor H ; complement factor H-related 1
207181_s_at	0.727	2.118	CASP7	caspase 7, apoptosis-related cysteine peptidase
209301_at	0.718	5.298	CA2	carbonic anhydrase II
208792_s_at	0.718	2.02	CLU	clusterin (complement lysis inhibitor, SP-40,40, sulfated glycoprotein 2, testosterone-repressed prostate message 2, apolipoprotein J)
204580_at	0.718	3.842	MMP12	matrix metalloproteinase 12 (macrophage elastase)
231513_at	0.718	4.942	---	Potassium inwardly-rectifying channel, subfamily J, member 2
208788_at	0.718	2.095	ELOVL5	ELOVL family member 5, elongation of long chain fatty acids (FEN1/Elo2, SUR4/Elo3-like, yeast)
210314_x_at	0.709	3.266	TNFSF13	tumor necrosis factor (ligand) superfamily, member 13 ; tumor necrosis factor (ligand) superfamily, member 12-member 13
1553454_at	0.709	8.739	RPTN	repetin
1552367_a_at	0.709	2.89	SCIN	scinderin
227702_at	0.709	2.057	CYP4X1	cytochrome P450, family 4, subfamily X, polypeptide 1
236489_at	0.709	4.749	---	Transcribed locus
209374_s_at	0.7	3.934	IGHM	immunoglobulin heavy constant mu
1555870_at	0.7	2.144	RNF207	chromosome 1 open reading frame 188
210102_at	0.7	2.597	VWA5A	loss of heterozygosity, 11, chromosomal region 2, gene A
225457_s_at	0.7	5.644	LOC25845	DKFZP564I1171 protein
205980_s_at	0.691	2.12	ARHGAP8 /// LOC553158 /// PRR5	Rho GTPase activating protein 8 ; PRR5-ARHGAP8 fusion
217109_at	0.691	4.066	MUC4	mucin 4, tracheobronchial
209101_at	0.691	2.067	CTGF	connective tissue growth factor
201859_at	0.691	3.033	SRGN	proteoglycan 1, secretory granule
204490_s_at	0.691	2.022	CD44	CD44 antigen (homing function and Indian blood group system)
228707_at	0.691	2.248	CLDN23	claudin 23
203256_at	0.691	2.612	CDH3	cadherin 3, type 1, P-cadherin (placental)
210809_s_at	0.682	16.25	POSTN	periostin, osteoblast specific factor

Supplementary Table 1: Mast cell transcriptome derived from tryptase IHC counts, *cont.*

Accession#	Spearman Correlation	Fold Change	Name	Description
213800_at	0.682	2.09	CFH	complement factor H
220622_at	0.682	10.71	LRRC31	leucine rich repeat containing 31
209031_at	0.682	2.267	CADM1	Immunoglobulin superfamily, member 4
222444_at	0.682	2.222	ARMCX3	armadillo repeat containing, X-linked 3
204396_s_at	0.673	3.606	GRK5	G protein-coupled receptor kinase 5
230788_at	0.673	2.611	GCNT2	glucosaminyl (N-acetyl) transferase 2, I-branching enzyme
213258_at	0.673	2.624	TFPI	Tissue factor pathway inhibitor (lipoprotein-associated coagulation inhibitor)
207826_s_at	0.673	2.307	ID3	inhibitor of DNA binding 3, dominant negative helix-loop-helix protein
228847_at	0.673	2.061	EXOC3	SEC6-like 1 (<i>S. cerevisiae</i>)
200972_at	0.673	2.525	TSPAN3	tetraspanin 3
204803_s_at	0.664	2.595	RRAD	Ras-related associated with diabetes
210664_s_at	0.664	2.21	TFPI	tissue factor pathway inhibitor (lipoprotein-associated coagulation inhibitor)
215176_x_at	0.664	4.514	LOC100130100	Immunoglobulin kappa light chain variable region (IGKV gene), clone 25
221223_x_at	0.664	2.496	CISH	cytokine inducible SH2-containing protein
202796_at	0.664	4.063	SYNPO	synaptopodin
227525_at	0.664	2.329	GLCC11	glucocorticoid induced transcript 1
209900_s_at	0.664	3.481	SLC16A1	solute carrier family 16 (monocarboxylic acid transporters), member 1
200973_s_at	0.664	2.342	TSPAN3	tetraspanin 3
218960_at	0.664	2.336	TMPRSS4	transmembrane protease, serine 4
205683_x_at	0.655	5.621	TPSAB1	tryptase alpha/beta 1
207328_at	0.655	26.7	ALOX15	arachidonate 15-lipoxygenase
225598_at	0.655	2.552	SLC45A4	solute carrier family 45, member 4
1553177_at	0.645	2.454	SH2D1B	SH2 domain containing 1B
210367_s_at	0.645	2.443	PTGES	prostaglandin E synthase
238827_at	0.645	2.599	---	SH3 domain containing ring finger 2
243585_at	0.645	18.8	ATP13A5	ATPase type 13A5
213502_x_at	0.645	2.166	LOC91316	similar to bK246H3.1 (immunoglobulin lambda-like polypeptide 1, pre-B-cell specific)
208829_at	0.645	2.213	TAPBP	TAP binding protein (tapasin)
207076_s_at	0.636	2.073	ASS1	argininosuccinate synthetase
224772_at	0.636	2.04	NAV1	neuron navigator 1
226621_at	0.636	2.015	---	Oncostatin M receptor
235988_at	0.636	2.752	GPR110	G protein-coupled receptor 110
218804_at	0.636	15.8	ANO1	transmembrane protein 16A
206932_at	0.636	4.029	CH25H	cholesterol 25-hydroxylase
205051_s_at	0.636	2.592	KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
1552365_at	0.636	2.732	SCIN	scinderin
223423_at	0.627	5.762	GPR160	G protein-coupled receptor 160

Supplementary Table 1: Mast cell transcriptome derived from tryptase IHC counts, cont.

Accession#	Spearman Correlation	Fold Change	Name	Description
223386_at	0.627	2.01	FAM118B	hypothetical protein FLJ21103
204591_at	0.627	4.325	CHL1	cell adhesion molecule with homology to L1CAM (close homolog of L1)
200704_at	0.627	3.178	LITAF	lipopolysaccharide-induced TNF factor
207386_at	0.627	2.909	CYP7B1	cytochrome P450, family 7, subfamily B, polypeptide 1
206632_s_at	0.627	2.576	APOBEC3B	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B
221796_at	0.618	3.886	NTRK2	neurotrophic tyrosine kinase, receptor, type 2
1553970_s_at	0.618	2.058	CEL	carboxyl ester lipase (bile salt-stimulated lipase)
225478_at	0.618	2.757	MFHAS1	Malignant fibrous histiocytoma amplified sequence 1
206726_at	0.618	5.094	PGDS	prostaglandin D2 synthase, hematopoietic
217023_x_at	0.618	3.421	TPSAB1 /// TPSB2	tryptase alpha/beta 1
219597_s_at	0.618	2.202	DUOX1	dual oxidase 1
205910_s_at	0.618	2.065	CEL	carboxyl ester lipase (bile salt-stimulated lipase)
222793_at	0.609	2.555	DDX58	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58
204158_s_at	0.609	2.141	TCIRG1	T-cell, immune regulator 1, ATPase, H ⁺ transporting, lysosomal V0 protein a isoform 3
1555638_a_at	0.609	2.893	SAMSN1	SAM domain, SH3 domain and nuclear localisation signals, 1
209030_s_at	0.609	2.293	CADM1	immunoglobulin superfamily, member 4
218484_at	-0.609	0.281	NDUFA4L2	NADH:ubiquinone oxidoreductase MLRQ subunit homolog
210117_at	-0.609	0.498	SPAG1	sperm associated antigen 1
225671_at	-0.609	0.496	SPNS2	MYB binding protein (P160) 1a
1561134_at	-0.609	0.499	---	Full length insert cDNA clone ZD63G05
239697_x_at	-0.609	0.465	C3orf67	FLJ42117 protein
206448_at	-0.609	0.192	ZNF365	zinc finger protein 365
227736_at	-0.609	0.431	C10orf99	chromosome 10 open reading frame 99
215997_s_at	-0.609	0.496	CUL4B	cullin 4B
244056_at	-0.609	0.0865	SFTA2	surfactant associated protein G
224329_s_at	-0.609	0.492	CNFN	cornifelin ; cornifelin
210462_at	-0.609	0.417	BLZF1	basic leucine zipper nuclear factor 1 (JEM-1)
220907_at	-0.618	0.473	GPR110	G protein-coupled receptor 110
228810_at	-0.618	0.216	CCNYL1	hypothetical protein FLJ40432
223625_at	-0.618	0.475	FAM126A	down-regulated by Ctnnb1, a
221830_at	-0.618	0.464	RAP2A	RAP2A, member of RAS oncogene family
202242_at	-0.618	0.436	TSPAN7	tetraspanin 7
234351_x_at	-0.618	0.46	TRPS1	trichorhinophalangeal syndrome I

Supplementary Table 1: Mast cell transcriptome derived from tryptase IHC counts, *cont.*

Accession#	Spearman Correlation	Fold Change	Name	Description
213624_at	-0.618	0.446	SMPDL3A	sphingomyelin phosphodiesterase, acid-like 3A
204326_x_at	-0.618	0.457	MT1X	metallothionein 1X
210609_s_at	-0.618	0.375	TP53I3	tumor protein p53 inducible protein 3
206059_at	-0.618	0.481	ZNF91	zinc finger protein 91 (HPF7, HTF10)
218319_at	-0.618	0.442	PELI1	pellino homolog 1 (Drosophila)
203167_at	-0.618	0.485	TIMP2	TIMP metalloproteinase inhibitor 2
1554999_at	-0.627	0.259	RASGEF1B	RasGEF domain family, member 1B
217508_s_at	-0.627	0.436	C18orf25	chromosome 18 open reading frame 25
235479_at	-0.627	0.479	CPEB2	cytoplasmic polyadenylation element binding protein 2
214455_at	-0.627	0.288	HIST1H2BC	histone 1, H2bc
209395_at	-0.627	0.425	CHI3L1	chitinase 3-like 1 (cartilage glycoprotein-39)
206710_s_at	-0.627	0.104	EPB41L3	erythrocyte membrane protein band 4.1-like 3
211737_x_at	-0.627	0.442	PTN	pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1) ; pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)
226649_at	-0.627	0.474	PANK1	pantothenate kinase 1
209424_s_at	-0.627	0.349	AMACR /// C1QTNF3	alpha-methylacyl-CoA racemase
204348_s_at	-0.636	0.408	AK3L1	adenylate kinase 3-like 1
225585_at	-0.636	0.413	RAP2A	RAP2A, member of RAS oncogene family
204750_s_at	-0.636	0.266	DSC2	desmocollin 2
220800_s_at	-0.636	0.477	TMOD3	tropomodulin 3 (ubiquitous)
211994_at	-0.636	0.465	WNK1	RAD52 homolog (S. cerevisiae) ; RAD52 homolog (S. cerevisiae)
225354_s_at	-0.636	0.481	SH3BGRL2	SH3 domain binding glutamic acid-rich protein like 2
206004_at	-0.636	0.215	TGM3	transglutaminase 3 (E polypeptide, protein-glutamine-gamma-glutamyltransferase)
1559942_at	-0.636	0.498	MDFIC	MyoD family inhibitor domain containing
210519_s_at	-0.636	0.343	NQO1	NAD(P)H dehydrogenase, quinone 1
215704_at	-0.636	0.191	FLG	filaggrin
243786_at	-0.636	0.397	ZDHHC20	zinc finger, DHHC-type containing 20

Supplementary Table 1: Mast cell transcriptome derived from tryptase IHC counts, cont.

Accession#	Spearman Correlation	Fold Change	Name	Description
1569607_s_at	-0.636	0.282	ANKRD20A1 /// ANKRD20A2 /// ANKRD20A3 /// ANKRD20A4 /// C21orf81 /// LOC100132733 /// LOC284232 /// LOC643187 /// LOC647595 /// LOC653436 /// LOC727770 /// LOC728783	ankyrin repeat domain 20 family, member A1 ; chromosome 21 open reading frame 81 ; similar to ankyrin repeat domain 20A ; OTTHUMP00000015360 ; ankyrin repeat domain 20 family, member A2
201667_at	-0.645	0.423	GJA1	gap junction protein, alpha 1, 43kDa (connexin 43)
236738_at	-0.645	0.255	LOC401097	Similar to LOC166075
203946_s_at	-0.645	0.436	ARG2	arginase, type II
238551_at	-0.645	0.498	FUT11	fucosyltransferase 11 (alpha (1,3) fucosyltransferase)
213680_at	-0.645	0.314	KRT6B	keratin 6B
204047_s_at	-0.645	0.417	PHACTR2	phosphatase and actin regulator 2
207038_at	-0.645	0.365	SLC16A6	solute carrier family 16 (monocarboxylic acid transporters), member 6
222513_s_at	-0.645	0.334	SORBS1	sorbin and SH3 domain containing 1
205328_at	-0.655	0.158	CLDN10	claudin 10
1552928_s_at	-0.655	0.451	MAP3K7IP3	TAK1-binding protein 3
1557126_a_at	-0.655	0.357	PLD1	phospholipase D1, phosphatidylcholine-specific
209616_s_at	-0.655	0.172	CES1	carboxylesterase 1 (monocyte/macrophage serine esterase 1)
229838_at	-0.655	0.452	NUCB2	nucleobindin 2
214657_s_at	-0.655	0.475	NCRNA00084	Trophoblast-derived noncoding RNA
230748_at	-0.655	0.328	SLC16A6	solute carrier family 16 (monocarboxylic acid transporters), member 6 ; similar to solute carrier family 16, member 6; monocarboxylate transporter 6
205489_at	-0.655	0.231	CRYM	crystallin, mu
209466_x_at	-0.655	0.416	PTN	pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)
202468_s_at	-0.655	0.226	CTNNAL1	catenin (cadherin-associated protein), alpha-like 1
224480_s_at	-0.655	0.225	AGPAT9	hypothetical protein MGC11324 ; hypothetical protein MGC11324
219976_at	-0.664	0.482	HOOK1	hook homolog 1 (Drosophila)
1554921_a_at	-0.664	0.419	SCEL	sciellin
207980_s_at	-0.664	0.377	CITED2	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2

Supplementary Table 1: Mast cell transcriptome derived from tryptase IHC counts, cont.

Accession#	Spearman Correlation	Fold Change	Name	Description
227410_at	-0.664	0.321	FAM43A	family with sequence similarity 43, member A
206199_at	-0.664	0.402	CEACAM7	carcinoembryonic antigen-related cell adhesion molecule 7
1553989_a_at	-0.664	0.49	ATP6V1C2	ATPase, H+ transporting, lysosomal 42kDa, V1 subunit C isoform 2
233534_at	-0.664	0.29	KRTAP3-2	keratin associated protein 3-2
1565162_s_at	-0.664	0.454	MGST1	microsomal glutathione S-transferase 1
214107_x_at	-0.673	0.439	LOC440434	hypothetical protein FLJ11822
226881_at	-0.673	0.403	GRPEL2	GrpE-like 2, mitochondrial (E. coli)
209744_x_at	-0.673	0.466	ITCH	itchy homolog E3 ubiquitin protein ligase (mouse)
206561_s_at	-0.673	0.382	AKR1B10	aldo-keto reductase family 1, member B10 (aldose reductase)
203131_at	-0.673	0.471	PDGFRA	platelet-derived growth factor receptor, alpha polypeptide
214451_at	-0.673	0.324	TFAP2B	transcription factor AP-2 beta (activating enhancer binding protein 2 beta)
223279_s_at	-0.673	0.449	UACA	uveal autoantigen with coiled-coil domains and ankyrin repeats
1553785_at	-0.673	0.405	RASGEF1B	RasGEF domain family, member 1B
227506_at	-0.673	0.481	SLC16A9	solute carrier family 16 (monocarboxylic acid transporters), member 9
202464_s_at	-0.673	0.467	PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3
215090_x_at	-0.673	0.458	LOC440434	hypothetical protein FLJ11822
1553286_at	-0.682	0.472	ZNF555	zinc finger protein 555
238164_at	-0.682	0.492	USP6NL	USP6 N-terminal like
214446_at	-0.682	0.421	ELL2	elongation factor, RNA polymerase II, 2
1558920_at	-0.682	0.04120	LOC10012859	CDNA FLJ27094 fis, clone SPL04370
201397_at	-0.682	0.496	PHGDH	phosphoglycerate dehydrogenase
224836_at	-0.682	0.47	TP53INP2	tumor protein p53 inducible nuclear protein 2
1553333_at	-0.682	0.184	C1orf161	chromosome 1 open reading frame 161
223720_at	-0.682	0.195	SPINK7	esophagus cancer-related gene-2
218507_at	-0.682	0.223	C7orf68	hypoxia-inducible protein 2
202129_s_at	-0.682	0.376	RIOK3	RIO kinase 3 (yeast) ; RIO kinase 3 (yeast)
1561685_a_at	-0.682	0.34	LOC441178	hypothetical LOC441178
231875_at	-0.682	0.335	KIF21A	kinesin family member 21A
1553077_at	-0.682	0.378	SDR9C7	orphan short-chain dehydrogenase / reductase
228010_at	-0.682	0.261	PPP2R2C	protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), gamma isoform
214621_at	-0.682	0.0772	GYS2	glycogen synthase 2 (liver)
227337_at	-0.691	0.466	ANKRD37	ankyrin repeat domain 37

Supplementary Table 1: Mast cell transcriptome derived from tryptase IHC counts, *cont.*

Accession#	Spearman Correlation	Fold Change	Name	Description
227309_at	-0.691	0.409	YOD1	YOD1 OTU deubiquinating enzyme 1 homolog (yeast)
204112_s_at	-0.691	0.413	HNMT	histamine N-methyltransferase
215536_at	-0.691	0.418	HLA-DQB2	major histocompatibility complex, class II, DQ beta 2
223074_s_at	-0.691	0.357	AIF1L	chromosome 9 open reading frame 58
204048_s_at	-0.691	0.266	PHACTR2	phosphatase and actin regulator 2
209425_at	-0.691	0.452	C1QTNF3	alpha-methylacyl-CoA racemase
235068_at	-0.691	0.461	ZDHHC21	zinc finger, DHHC-type containing 21
230585_at	-0.691	0.499	---	Transcribed locus
241455_at	-0.7	0.413	---	Similar to A1661453 protein
241233_x_at	-0.7	0.319	C21orf81	chromosome 21 open reading frame 81
204716_at	-0.7	0.385	CCDC6	coiled-coil domain containing 6
212479_s_at	-0.7	0.422	RMND5A	hypothetical protein FLJ13910
239430_at	-0.709	0.156	IGFL1	insulin growth factor-like family member 1
201848_s_at	-0.709	0.237	BNIP3	BCL2/adenovirus E1B 19kDa interacting protein 3
209426_s_at	-0.709	0.398	AMACR /// C1QTNF3	alpha-methylacyl-CoA racemase
220191_at	-0.709	0.367	GKN1	gastrokine 1
214600_at	-0.709	0.5	TEAD1	TEA domain family member 1 (SV40 transcriptional enhancer factor)
212681_at	-0.709	0.103	EPB41L3	erythrocyte membrane protein band 4.1-like 3
207802_at	-0.715	0.0431	CRISP3	cysteine-rich secretory protein 3
203675_at	-0.718	0.432	NUCB2	nucleobindin 2
214364_at	-0.718	0.473	MTERFD2	MTERF domain containing 2
235170_at	-0.718	0.374	ZNF92	zinc finger protein 92 (HTF12)
220309_at	-0.718	0.446	TTC22	tetratricopeptide repeat domain 22
209921_at	-0.718	0.452	SLC7A11	solute carrier family 7, (cationic amino acid transporter, y+ system) member 11
222725_s_at	-0.727	0.367	PALMD	palmdelphin
1557016_a_at	-0.727	0.17	C1orf177	chromosome 1 open reading frame 177
201849_at	-0.727	0.165	BNIP3	BCL2/adenovirus E1B 19kDa interacting protein 3
213652_at	-0.727	0.252	PCSK5	Proprotein convertase subtilisin/kexin type 5
220197_at	-0.727	0.4	ATP6V0A4	ATPase, H+ transporting, lysosomal V0 subunit a isoform 4
201468_s_at	-0.727	0.41	NQO1	NAD(P)H dehydrogenase, quinone 1
223075_s_at	-0.727	0.281	AIF1L	chromosome 9 open reading frame 58
218723_s_at	-0.736	0.407	C13orf15	response gene to complement 32
204797_s_at	-0.736	0.217	EML1	echinoderm microtubule associated protein like 1
226423_at	-0.736	0.301	PAQR8	progesterone and adipoQ receptor family member VIII
203699_s_at	-0.736	0.377	DIO2	deiodinase, iodothyronine, type II

Supplementary Table 1: Mast cell transcriptome derived from tryptase IHC counts, cont.

Accession#	Spearman Correlation	Fold Change	Name	Description
215103_at	-0.736	0.473	CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18
211538_s_at	-0.736	0.238	HSPA2	heat shock 70kDa protein 2
210145_at	-0.736	0.462	PLA2G4A	phospholipase A2, group IVA (cytosolic, calcium-dependent)
208126_s_at	-0.745	0.46	CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18 ; cytochrome P450, family 2, subfamily C, polypeptide 18
225914_s_at	-0.745	0.437	CAB39L	calcium binding protein 39-like
1559170_at	-0.745	0.275	---	Similar to ankyrin repeat domain 20A ; Hypothetical gene supported by NM_032250
203224_at	-0.745	0.473	RFK	riboflavin kinase
200906_s_at	-0.745	0.444	PALLD	palladin
204058_at	-0.745	0.269	ME1	Malic enzyme 1, NADP(+)-dependent, cytosolic
201534_s_at	-0.755	0.492	UBL3	ubiquitin-like 3
201195_s_at	-0.755	0.459	SLC7A5	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5
1570596_at	-0.755	0.326	---	CDNA clone IMAGE:5266087
207356_at	-0.755	0.341	DEFB4	defensin, beta 4
205559_s_at	-0.755	0.216	PCSK5	proprotein convertase subtilisin/kexin type 5
209283_at	-0.755	0.24	CRYAB	crystallin, alpha B
201341_at	-0.755	0.469	ENC1	ectodermal-neural cortex (with BTB-like domain)
210479_s_at	-0.755	0.39	RORA	RAR-related orphan receptor A
213725_x_at	-0.764	0.279	XYLT1	hypothetical protein LOC283824
228653_at	-0.764	0.216	SAMD5	SAM domain containing 1
213279_at	-0.764	0.425	DHRS1	dehydrogenase/reductase (SDR family) member 1
1552634_a_at	-0.764	0.32	ZNF101	zinc finger protein 101
223845_at	-0.764	0.499	FLJ20674	hypothetical protein BC001437
205560_at	-0.764	0.275	PCSK5	proprotein convertase subtilisin/kexin type 5
223574_x_at	-0.764	0.438	PPP2R2C	protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), gamma isoform
228538_at	-0.764	0.489	ZNF662	zinc finger protein 662
204141_at	-0.764	0.362	TUBB2A	tubulin, beta 2
206008_at	-0.764	0.473	TGM1	transglutaminase 1 (K polypeptide epidermal type I, protein-glutamine-gamma-glutamyltransferase)
206605_at	-0.764	0.169	P11	26 serine protease
205863_at	-0.764	0.321	S100A12	S100 calcium binding protein A12 (calgranulin C) ; S100 calcium binding protein A12 (calgranulin C)
1563894_at	-0.773	0.341	LOC441178	hypothetical LOC441178

Supplementary Table 1: Mast cell transcriptome derived from tryptase IHC counts, cont.

Accession#	Spearman Correlation	Fold Change	Name	Description
205363_at	-0.773	0.297	BBOX1	butyrobetaine (gamma), 2-oxoglutarate dioxygenase (gamma-butyrobetaine hydroxylase) 1
231033_at	-0.773	0.343	---	Full length insert cDNA clone YI40A07
218843_at	-0.773	0.308	FNDC4	fibronectin type III domain containing 4
218736_s_at	-0.782	0.447	PALMD	palmdelphin
227280_s_at	-0.782	0.318	CCNYL1	Hypothetical protein FLJ40432
241014_at	-0.782	0.346	LOC339400	hypothetical protein LOC339400
241946_at	-0.782	0.442	ZDHHC21	zinc finger, DHHC-type containing 21
204393_s_at	-0.782	0.282	ACPP	acid phosphatase, prostate
225990_at	-0.782	0.454	BOC	brother of CDO
222745_s_at	-0.791	0.474	C15orf29	chromosome 15 open reading frame 29
222223_s_at	-0.791	0.385	IL1F5	interleukin 1 family, member 5 (delta)
207008_at	-0.791	0.298	IL8RB	interleukin 8 receptor, beta
201467_s_at	-0.791	0.35	NQO1	NAD(P)H dehydrogenase, quinone 1
220724_at	-0.791	0.234	FLJ21511	hypothetical protein FLJ21511
242998_at	-0.791	0.435	RDH12	retinol dehydrogenase 12 (all-trans and 9-cis)
207206_s_at	-0.809	0.196	ALOX12	arachidonate 12-lipoxygenase
210426_x_at	-0.809	0.485	RORA	RAR-related orphan receptor A
220723_s_at	-0.818	0.281	FLJ21511	hypothetical protein FLJ21511
1564307_a_at	-0.827	0.437	A2ML1	alpha-2-macroglobulin-like 1
220664_at	-0.827	0.101	SPRR2C	small proline-rich protein 2C
238846_at	-0.827	0.494	TNFRSF11A	tumor necrosis factor receptor superfamily, member 11a, NFkB activator
1553960_at	-0.836	0.395	SNX21	chromosome 20 open reading frame 161
204992_s_at	-0.836	0.469	PFN2	profilin 2
229584_at	-0.845	0.427	LRRK2	leucine-rich repeat kinase 2
228376_at	-0.845	0.474	GGTA1	Glycoprotein, alpha-galactosyltransferase 1
203429_s_at	-0.855	0.49	C1orf9	chromosome 1 open reading frame 9
219669_at	-0.927	0.441	CD177	CD177 antigen

Supplementary Table 2: Mast cell degranulation related transcriptome derived from tryptase IHC counts. 130 Probesets encompassing 116 known genes of the mast cell degranulation related transcriptome are listed. They are sorted according to their Spearman correlation with maximum degranulated epithelial mast cell counts.

Accession#	Spearman Correlation	Fold Change	Name	Description
217977_at	0.976	2.421	SEPX1	selenoprotein X, 1
206765_at	0.905	5.247	KCNJ2	potassium inwardly-rectifying channel, subfamily J, member 2
207134_x_at	0.905	5.578	TPSB2	tryptase beta 2
210069_at	0.905	2.272	CHKB /// CPT1B	choline kinase beta ; carnitine palmitoyltransferase 1B (muscle)
219734_at	0.905	4.411	SIDT1	SID1 transmembrane family, member 1
201739_at	0.905	3.242	SGK1	serum/glucocorticoid regulated kinase
228892_at	0.905	3.076	SH3RF2	SH3 domain containing ring finger 2
211906_s_at	0.881	5.22	SERPINB4	serpin peptidase inhibitor, clade B (ovalbumin), member 4 ; serpin peptidase inhibitor, clade B (ovalbumin), member 4
226525_at	0.881	2.333	STK17B	Serine/threonine kinase 17b (apoptosis-inducing)
201106_at	0.857	2.281	GPX4	glutathione peroxidase 4 (phospholipid hydroperoxidase)
226534_at	0.857	3.055	KITLG	KIT ligand
209374_s_at	0.857	3.934	IGHM	immunoglobulin heavy constant mu
213457_at	0.833	2.24	MFHAS1	malignant fibrous histiocytoma amplified sequence 1
220048_at	0.833	2.576	EDAR	ectodysplasin A receptor
242961_x_at	0.833	2.357	DDX58	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58
232306_at	0.833	18.24	CDH26	cadherin-like 26
231513_at	0.833	4.942	---	Potassium inwardly-rectifying channel, subfamily J, member 2
202307_s_at	0.833	2.004	TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)
219597_s_at	0.833	2.202	DUOX1	dual oxidase 1
1557321_a_at	0.833	2.061	CAPN14	calpain 14
204803_s_at	0.833	2.595	RRAD	Ras-related associated with diabetes
225615_at	0.833	2.566	IFFO2	hypothetical protein LOC126917
219508_at	0.833	3.975	GCNT3	glucosaminyl (N-acetyl) transferase 3, mucin type
203854_at	0.833	4.75	CFI	I factor (complement)
220780_at	0.833	2.036	PLA2G3	phospholipase A2, group III
206513_at	0.81	2.7	AIM2	absent in melanoma 2
231832_at	0.81	3.337	GALNT4	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 4 (GalNAc-T4)
202037_s_at	0.81	3.974	SFRP1	secreted frizzled-related protein 1
215446_s_at	0.81	3.792	LOX	lysyl oxidase
223541_at	0.81	2.824	HAS3	hyaluronan synthase 3
226604_at	0.81	2.305	TMTC3	SMILE protein

Supplementary Table 2: Mast cell degranulation related transcriptome derived from tryptase IHC counts, *cont.*

Accession#	Spearman Correlation	Fold Change	Name	Description
210314_x_at	0.786	3.266	TNFSF13	tumor necrosis factor (ligand) superfamily, member 13 ; tumor necrosis factor (ligand) superfamily, member 12-member 13
40472_at	0.786	2.381	LPCAT4	PLSC domain containing protein
224916_at	0.786	3.705	TMEM173	hypothetical protein LOC340061
225647_s_at	0.786	6.523	CTSC	cathepsin C
205192_at	0.786	2.246	MAP3K14	mitogen-activated protein kinase kinase kinase 14
209976_s_at	0.786	2.386	CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1
210095_s_at	0.786	2.386	IGFBP3	insulin-like growth factor binding protein 3
202234_s_at	0.786	3.666	SLC16A1	solute carrier family 16 (monocarboxylic acid transporters), member 1
227816_at	0.762	2.322	NTN1	Hypothetical LOC400572
212658_at	0.762	3.32	LHFPL2	lipoma HMGIC fusion partner-like 2
205624_at	0.762	11.03	CPA3	carboxypeptidase A3 (mast cell)
219630_at	0.762	2.882	PDZK1IP1	PDZK1 interacting protein 1
200706_s_at	0.762	3.005	LITAF	lipopolysaccharide-induced TNF factor
1553589_a_at	0.762	2.84	PDZK1IP1	PDZK1 interacting protein 1
235146_at	0.762	2.492	TMCC3	Transmembrane and coiled-coil domain family 3
209031_at	0.762	2.267	CADM1	Immunoglobulin superfamily, member 4
207826_s_at	0.762	2.307	ID3	inhibitor of DNA binding 3, dominant negative helix-loop-helix protein
201487_at	0.762	4.837	CTSC	cathepsin C
1552367_a_at	0.762	2.89	SCIN	scinderin
230788_at	0.738	2.611	GCNT2	glucosaminyl (N-acetyl) transferase 2, I-branching enzyme
236489_at	0.738	4.749	---	Transcribed locus
203256_at	0.738	2.612	CDH3	cadherin 3, type 1, P-cadherin (placental)
243582_at	0.738	2.622	SH3RF2	SH3 domain containing ring finger 2
225457_s_at	0.738	5.644	LOC25845	DKFZP564I1171 protein
213078_x_at	0.738	2.447	LPCAT4	PLSC domain containing protein
209138_x_at	0.738	7.119	IGL@	Immunoglobulin lambda joining 3
215121_x_at	0.738	5.702	IGL@	immunoglobulin lambda locus ; immunoglobulin lambda constant 1 (Mcg marker) ; immunoglobulin lambda constant 2 (Kern-Oz-marker) ; immunoglobulin lambda variable 3-25 ; immunoglobulin lambda variable 2-14
214677_x_at	0.738	8.084	IGL@	immunoglobulin lambda locus ; immunoglobulin lambda constant 1 (Mcg marker) ; immunoglobulin lambda constant 2 (Kern-Oz-marker) ; immunoglobulin lambda variable 3-25 ; immunoglobulin lambda variable 2-14 ; immunoglobulin lambda joining 3
205683_x_at	0.714	5.621	TPSAB1	tryptase alpha/beta 1

Supplementary Table 2: Mast cell degranulation related transcriptome derived from tryptase IHC counts, *cont.*

Accession#	Spearman Correlation	Fold Change	Name	Description
224795_x_at	0.714	6.801	IGK@ /// IGKC	immunoglobulin kappa constant ; immunoglobulin kappa variable 1-5
221671_x_at	0.714	5.96	IGK@ /// IGKC	immunoglobulin kappa constant ; immunoglobulin kappa variable 1-5
216474_x_at	0.714	5.881	TPSAB1 /// TPSB2	tryptase alpha/beta 1 ; tryptase beta 2
213800_at	0.714	2.09	CFH	complement factor H
227480_at	0.714	6.686	SUSD2	sushi domain containing 2
223720_at	-0.714	0.195	SPINK7	esophagus cancer-related gene-2
204058_at	-0.714	0.269	ME1	Malic enzyme 1, NADP(+)-dependent, cytosolic
214107_x_at	-0.714	0.439	LOC440434	hypothetical protein FLJ11822
241946_at	-0.714	0.442	ZDHHC21	zinc finger, DHHC-type containing 21
204797_s_at	-0.714	0.217	EML1	echinoderm microtubule associated protein like 1
219976_at	-0.714	0.482	HOOK1	hook homolog 1 (Drosophila)
223625_at	-0.714	0.475	FAM126A	down-regulated by Ctnnb1, a
241014_at	-0.714	0.346	LOC339400	hypothetical protein LOC339400
241455_at	-0.714	0.413	---	Similar to A1661453 protein
204716_at	-0.714	0.385	CCDC6	coiled-coil domain containing 6
200906_s_at	-0.714	0.444	PALLD	palladin
214446_at	-0.714	0.421	ELL2	elongation factor, RNA polymerase II, 2
224329_s_at	-0.714	0.492	CNFN	cornifelin ; cornifelin
233534_at	-0.738	0.29	KRTAP3-2	keratin associated protein 3-2
231875_at	-0.738	0.335	KIF21A	kinesin family member 21A
213279_at	-0.738	0.425	DHRS1	dehydrogenase/reductase (SDR family) member 1
220723_s_at	-0.738	0.281	FLJ21511	hypothetical protein FLJ21511
234351_x_at	-0.738	0.46	TRPS1	trichorhinophalangeal syndrome I
228653_at	-0.738	0.216	SAMD5	SAM domain containing 1
209744_x_at	-0.738	0.466	ITCH	itchy homolog E3 ubiquitin protein ligase (mouse)
1563894_at	-0.762	0.341	LOC441178	hypothetical LOC441178
214364_at	-0.762	0.473	MTERFD2	MTERF domain containing 2
227337_at	-0.762	0.466	ANKRD37	ankyrin repeat domain 37
206059_at	-0.762	0.481	ZNF91	zinc finger protein 91 (HPF7, HTF10)
1559942_at	-0.762	0.498	MDFIC	MyoD family inhibitor domain containing
214451_at	-0.762	0.324	TFAP2B	transcription factor AP-2 beta (activating enhancer binding protein 2 beta)
210461_s_at	-0.762	0.434	ABLIM1	actin binding LIM protein 1
211538_s_at	-0.762	0.238	HSPA2	heat shock 70kDa protein 2
228010_at	-0.762	0.261	PPP2R2C	protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), gamma isoform
204048_s_at	-0.762	0.266	PHACTR2	phosphatase and actin regulator 2
203225_s_at	-0.762	0.289	RFK	riboflavin kinase
227309_at	-0.762	0.409	YOD1	YOD1 OTU deubiquinating enzyme 1 homolog (yeast)
235170_at	-0.762	0.374	ZNF92	zinc finger protein 92 (HTF12)

Supplementary Table 2: Mast cell degranulation related transcriptome derived from tryptase IHC counts, *cont.*

Accession#	Spearman Correlation	Fold Change	Name	Description
227280_s_at	-0.786	0.318	CCNYL1	Hypothetical protein FLJ40432
223217_s_at	-0.786	0.462	NFKBIZ	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta
215090_x_at	-0.786	0.458	LOC440434	hypothetical protein FLJ11822
213624_at	-0.786	0.446	SMPDL3A	sphingomyelin phosphodiesterase, acid-like 3A
1565162_s_at	-0.786	0.454	MGST1	microsomal glutathione S-transferase 1
225990_at	-0.786	0.454	BOC	brother of CDO
206448_at	-0.786	0.192	ZNF365	zinc finger protein 365
201849_at	-0.786	0.165	BNIP3	BCL2/adenovirus E1B 19kDa interacting protein 3
239430_at	-0.786	0.156	IGFL1	insulin growth factor-like family member 1
222725_s_at	-0.786	0.367	PALMD	palmdelphin
220664_at	-0.81	0.101	SPRR2C	small proline-rich protein 2C
204992_s_at	-0.81	0.469	PFN2	profilin 2
1553286_at	-0.81	0.472	ZNF555	zinc finger protein 555
220907_at	-0.81	0.473	GPR110	G protein-coupled receptor 110
1552634_a_at	-0.81	0.32	ZNF101	zinc finger protein 101
222223_s_at	-0.833	0.385	IL1F5	interleukin 1 family, member 5 (delta)
210426_x_at	-0.833	0.485	RORA	RAR-related orphan receptor A
219669_at	-0.833	0.441	CD177	CD177 antigen
203946_s_at	-0.833	0.436	ARG2	arginase, type II
220191_at	-0.833	0.367	GKN1	gastrokein 1
208126_s_at	-0.833	0.46	CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18 ; cytochrome P450, family 2, subfamily C, polypeptide 18
204141_at	-0.857	0.362	TUBB2A	tubulin, beta 2
228376_at	-0.857	0.474	GGTA1	Glycoprotein, alpha-galactosyltransferase 1
203699_s_at	-0.857	0.377	DIO2	deiodinase, iodothyronine, type II
211734_s_at	-0.857	0.455	FCER1A	Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide ; Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide
210479_s_at	-0.881	0.39	RORA	RAR-related orphan receptor A
203224_at	-0.905	0.473	RFK	riboflavin kinase
223574_x_at	-0.905	0.438	PPP2R2C	protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), gamma isoform
215103_at	-0.929	0.473	CYP2C18	cytochrome P450, family 2, subfamily C, polypeptide 18
222745_s_at	-0.929	0.474	C15orf29	chromosome 15 open reading frame 29
228538_at	-0.952	0.489	ZNF662	zinc finger protein 662
203429_s_at	-0.976	0.49	C1orf9	chromosome 1 open reading frame 9

Supplementary Table 3 Ontology of genes related to the CPA3 transcriptome			
Term	Count	Percent	P-value
Immune response	54	16.51%	9.47E-15
Defense response	56	17.13%	3.42E-14
Response to biotic stimulus	57	17.43%	5.22E-14
Organismal physiological process	74	22.63%	2.52E-10
Response to stimulus	75	22.94%	4.49E-09
Response to pest, pathogen or parasite	28	8.56%	4.32E-08
Response to other organism	28	8.56%	1.5E-07
Humoral immune response	12	3.67%	0.0000259
Response to stress	33	10.09%	0.000107
Cell adhesion	23	7.03%	0.000315
Positive regulation of cellular process	19	5.81%	0.000795
Response to wounding	15	4.59%	0.001841
Positive regulation of biological process	20	6.12%	0.001919
Proteolysis	21	6.42%	0.003549
Inflammatory response	10	3.06%	0.003593
Regulation of signal transduction	10	3.06%	0.005324
Tissue development	9	2.75%	0.00609
Response to external stimulus	16	4.89%	0.008022
Cell-cell adhesion	9	2.75%	0.016276
Protein kinase cascade	10	3.06%	0.021093
Cell-cell signaling	15	4.59%	0.023919
Cell proliferation	15	4.59%	0.024315
Positive regulation of cellular physiological process	13	3.98%	0.031258
Apoptosis	15	4.59%	0.031597
Programmed cell death	15	4.59%	0.032445
Cell communication	63	19.27%	0.035654
Positive regulation of physiological process	13	3.98%	0.040907
Cell death	15	4.59%	0.041454
Death	15	4.59%	0.043454
Negative regulation of cellular process	17	5.20%	0.051646
Development	36	11.01%	0.052366
Cellular lipid metabolism	13	3.98%	0.052921
Carboxylic acid metabolism	13	3.98%	0.055635
Organic acid metabolism	13	3.98%	0.057226
Lipid metabolism	15	4.59%	0.067307
Regulation of apoptosis	10	3.06%	0.070611
Regulation of programmed cell death	10	3.06%	0.072646
Signal transduction	56	17.13%	0.085726
Negative regulation of biological process	17	5.20%	0.086457
Morphogenesis	14	4.28%	0.091977
Not listed	156		
Other, less than 2.5%	136		