Supplemental Table 1 Cytokines, growth factors and chemokines produced by activated mast cells

Class of product	Products
Cytokines	GM-CSF * \uparrow^{1-4} , IFN- α * \uparrow^{5} , IFN- β * ⁶ , IFN- γ * ^{4,7} , IL-1 α * $\uparrow^{4,8}$, IL-1 β * $\uparrow^{8,9}$, IL-1R antagonist \uparrow^{10} ,
&	IL-2 * ¹¹ , IL-3 *† ^{1,4,12-14} , IL-4 *† ^{9,12,15,16} , IL-5 *† ^{4,9,12,14} , IL-6 *† ^{4,12-14} , IL-8 (CXCL8) † ¹⁴ , IL-9 *† ^{13,14} ,
	IL-10 *† ^{17,18} , IL-11 † ¹⁹ , IL-12 *† ^{20,21} , IL-13 *† ^{9,14} , IL-14 † ¹⁹ , IL-15 † ²¹ , IL-16 *† ^{6,22} , IL-17E (IL-25
growth factors	*23
	IL-17F * ²³ , IL-18 <mark>†</mark> ¹⁹ , IL-22 (IL-TIF) * ²⁴ , LIF <mark>†</mark> ¹⁹ , LTβ <mark>†</mark> ¹⁹ , M-CSF *† ⁶ , MIF † ¹⁹ , SCF † ^{25,26} ,
	TGF-β1 *† ²⁷⁻²⁹ , TNF *† ^{13,14,27,30-32} , TSLP * ³³ , bFGF *† ^{28,34,35} , EGF † ²⁸ , IGF-1 * ³⁶ , NGF * ³⁷ ,
	PDGF-AA ^{†38} , PDGF-BB ^{†28} , VEGF * ^{†28,39,40}
Chemokines	CCL1 (TCA3/I309) *† ^{4,6,21} , CCL2 (MCP-1) *† ^{4,41,42} , CCL3 (MIP-1α) *† ^{4,43-45} , CCL3L1 (LD78β) † ¹⁹
	CCL4 (MIP-1β) *† ^{4,6,19} , CCL5 (RANTES) *† ^{21,44} , CCL7 (MCP-3) *† ^{6,45} , CCL8 (MCP-2) † ⁶ ,
	CCL11 (eotaxin) ⁺²¹ , CCL13 (MCP-4) ⁺¹⁹ , CCL16 (LEC/HCC-4) ⁺¹⁹ , CCL17 (TARC) * ^{+41,45} ,
	CCL20 (LARC) † ⁴⁵ , CCL22 (MDC) *† ^{41,45} , CXCL1 (Groα/KC) *† ⁶ , CXCL2 (Groβ/MIP-2) *† ^{6,44} ,
	CXCL3 (Groγ) ^{+²¹,CXCL10 (IP-10) *+^{21,46}, CXCL11 (I-TAC) +²¹, XCL1 (lymphotactin) *+^{19,47}}

Free radicals Nitric oxide $\ddagger \P^{20,48-50}$, superoxide $\ddagger \P^{51,52}$

Others Corticotropin-releasing factor $+^{53}$, urocortin $+^{53}$, substance P $*^{54}$

Note: Some of cytokines, growth factors and chemokines listed have been detected only at the mRNA level, only in studies of

in vitro-derived mast cells, and/or only from mast cells from a single species. For these products, black * and † : protein detected by ELISA or immunohistochemistry; red * and † : mRNA expression. *‡ : rodent, †¶ : human. Certain cytokines and growth factors, including TNF and VEGF, can be released from both preformed and newly synthesized pools; many others have been localized to mast cell cytoplasmic granules by immunohistochemistry.

References

Note: We have not attempted to cite every paper that has reported the mast cell expression of each of the products listed. References for many of the studies not listed below may be found in the references cited. Reviews of some of the earliest evidence that mast cells can produce cytokines, growth factors and chemokines may be found in: Gordon, J.R, Burd, P.R. and Galli, S.J. Mast cells as a source of multifunctional cytokines. *Immunology Today* **11**, 458-64. (1990) and Paul, W. E., Seder, R. A. & Plaut, M. Lymphokine and cytokine production by FccRI⁺ cells. *Adv Immunol.* **53**, 1-29 (1993).

- 1. Wodnar-Filipowicz, A., Heusser, C.H. & Moroni, C. Production of the haemopoietic growth factors GM-CSF and interleukin-3 by mast cells in response to IgE receptor-mediated activation. *Nature* **339**, 150-2. (1989).
- 2. Gomi, K., Zhu, F.G. & Marshall, J.S. Prostaglandin E2 selectively enhances the IgE-mediated production of IL-6 and granulocyte-macrophage colony-stimulating factor by mast cells through an EP1/EP3-dependent mechanism. *J Immunol* **165**, 6545-52. (2000).
- 3. Bressler, R.B. et al. Production of IL-5 and granulocyte-macrophage colony-stimulating factor by naive human mast cells activated by high-affinity IgE receptor ligation. *J Allergy Clin Immunol* **99**, 508-14. (1997).
- 4. Burd, P.R. et al. Interleukin 3-dependent and -independent mast cells stimulated with IgE and antigen express multiple

cytokines. J Exp Med 170, 245-57. (1989).

- 5. Kulka, M., Alexopoulou, L., Flavell, R.A. & Metcalfe, D.D. Activation of mast cells by double-stranded RNA: evidence for activation through Toll-like receptor 3. *J Allergy Clin Immunol* **114**, 174-82. (2004).
- Nakajima, T. et al. Marked increase in CC chemokine gene expression in both human and mouse mast cell transcriptomes following Fce receptor I cross-linking: an interspecies comparison. *Blood* 100, 3861-8. Epub 2002 Aug 01. (2002).
- Gupta, A.A., Leal-Berumen, I., Croitoru, K. & Marshall, J.S. Rat peritoneal mast cells produce IFN-γ following IL-12 treatment but not in response to IgE-mediated activation. *J Immunol* **157**, 2123-8. (1996).
- 8. Lin, T.J., Garduno, R., Boudreau, R.T. & Issekutz, A.C. Pseudomonas aeruginosa activates human mast cells to induce neutrophil transendothelial migration via mast cell-derived IL-1 α and β . *J Immunol* **169**, 4522-30. (2002).
- 9. Supajatura, V. et al. Differential responses of mast cell Toll-like receptors 2 and 4 in allergy and innate immunity. *J Clin Invest* **109**, 1351-9. (2002).
- 10. Hagaman, D.D. et al. Secretion of interleukin-1 receptor antagonist from human mast cells after immunoglobulin E-mediated activation and after segmental antigen challenge. *Am J Respir Cell Mol Biol* **25**, 685-91. (2001).
- 11. Oh, C.K., Filler, S.G. & Cho, S.H. Eukaryotic translation initiation factor-6 enhances histamine and IL-2 production in mast cells. *J Immunol* **166**, 3606-11. (2001).
- 12. Plaut, M. et al. Mast cell lines produce lymphokines in response to cross-linkage of FcεRI or to calcium ionophores. *Nature* **339**, 64-7. (1989).
- 13. Hultner, L. et al. In activated mast cells, IL-1 up-regulates the production of several Th2-related cytokines including IL-9. *J Immunol* **164**, 5556-63. (2000).
- 14. Lorentz, A., Schwengberg, S., Sellge, G., Manns, M.P. & Bischoff, S.C. Human intestinal mast cells are capable of

producing different cytokine profiles: role of IgE receptor cross-linking and IL-4. J Immunol 164, 43-8. (2000).

- 15. Brown, M.A. et al. B cell stimulatory factor-1/interleukin-4 mRNA is expressed by normal and transformed mast cells. *Cell* **50**, 809-18. (1987).
- 16. Bradding, P. et al. Immunolocalization of cytokines in the nasal mucosa of normal and perennial rhinitic subjects. The mast cell as a source of IL-4, IL-5, and IL-6 in human allergic mucosal inflammation. *J Immunol* **151**, 3853-65. (1993).
- 17. Marietta, E.V., Chen, Y. & Weis, J.H. Modulation of expression of the anti-inflammatory cytokines interleukin-13 and interleukin-10 by interleukin-3. *Eur J Immunol* **26**, 49-56. (1996).
- Varadaradjalou, S. et al. Toll-like receptor 2 (TLR2) and TLR4 differentially activate human mast cells. *Eur J Immunol* 33, 899-906. (2003).
- 19. Sayama, K. et al. Transcriptional response of human mast cells stimulated via the FcεRI and identification of mast cells as a source of IL-11. *BMC Immunol* **3**, 5. (2002).
- Coulombe, M., Battistini, B., Stankova, J., Pouliot, P. & Bissonnette, E.Y. Endothelins regulate mediator production of rat tissue-cultured mucosal mast cells. Up-regulation of Th1 and inhibition of Th2 cytokines. *J Leukoc Biol* **71**, 829-36. (2002).
- Okumura, S. et al. Identification of specific gene expression profiles in human mast cells mediated by Toll-like receptor
 4 and FcεRI. *Blood* 102, 2547-54. Epub 2003 Jul 10. (2003).
- 22. Rumsaeng, V. et al. Human mast cells produce the CD4⁺ T lymphocyte chemoattractant factor, IL-16. *J Immunol* **159**, 2904-10. (1997).
- 23. Ikeda, K. et al. Mast cells produce interleukin-25 upon FcεRI-mediated activation. *Blood* 101, 3594-6. Epub 2003 Jan 02. (2003).
- 24. Dumoutier, L., Louahed, J. & Renauld, J.C. Cloning and characterization of IL-10-related T cell-derived inducible

factor (IL-TIF), a novel cytokine structurally related to IL-10 and inducible by IL-9. J Immunol 164, 1814-9. (2000).

- 25. Zhang, S. et al. Human mast cells express stem cell factor. *J Pathol* **186**, 59-66. (1998).
- 26. Patella, V. et al. Stem cell factor in mast cells and increased mast cell density in idiopathic and ischemic cardiomyopathy. *Circulation* **97**, 971-8. (1998).
- Gordon, J.R. & Galli, S.J. Promotion of mouse fibroblast collagen gene expression by mast cells stimulated via the FcεRI. Role for mast cell-derived transforming growth factor β and tumor necrosis factor α. *J Exp Med* 180, 2027-37. (1994).
- 28. Toda, S. et al. Growth factor-expressing mast cells accumulate at the thyroid tissue-regenerative site of subacute thyroiditis. *Thyroid* **10**, 381-6. (2000).
- 29. Kendall, J.C., Li, X.H., Galli, S.J. & Gordon, J.R. Promotion of mouse fibroblast proliferation by IgE-dependent activation of mouse mast cells: role for mast cell tumor necrosis factor-*α* and transforming growth factor-*β*1. *J Allergy Clin Immunol* **99**, 113-23. (1997).
- 30. Young, J.D., Liu, C.C., Butler, G., Cohn, Z.A. & Galli, S.J. Identification, purification, and characterization of a mast cell-associated cytolytic factor related to tumor necrosis factor. *Proc Natl Acad Sci U S A* **84**, 9175-9. (1987).
- Gordon, J.R. & Galli, S.J. Mast cells as a source of both preformed and immunologically inducible TNF-α/cachectin.
 Nature 346, 274-6. (1990).
- 32. Klein, L.M., Lavker, R.M., Matis, W.L. & Murphy, G.F. Degranulation of human mast cells induces an endothelial antigen central to leukocyte adhesion. *Proc Natl Acad Sci U S A* **86**, 8972-6. (1989).
- 33. Soumelis, V. et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol* **3**, 673-80. (2002).
- 34. Reed, J.A., Albino, A.P. & McNutt, N.S. Human cutaneous mast cells express basic fibroblast growth factor. Lab Invest

72, 215-22. (1995).

- 35. Qu, Z. et al. Synthesis of basic fibroblast growth factor by murine mast cells. Regulation by transforming growth factor beta, tumor necrosis factor alpha, and stem cell factor. *Int Arch Allergy Immunol* **115**, 47-54. (1998).
- 36. de Pablo, F., Banner, L.R. & Patterson, P.H. IGF-I expression is decreased in LIF-deficient mice after peripheral nerve injury. *Neuroreport* **11**, 1365-8. (2000).
- 37. Leon, A. et al. Mast cells synthesize, store, and release nerve growth factor. *Proc Natl Acad Sci U S A* 91, 3739-43.
 (1994).
- 38. Kanbe, N. et al. Production of fibrogenic cytokines by cord blood-derived cultured human mast cells. *J Allergy Clin Immunol* **106**, S85-90. (2000).
- Boesiger, J. et al. Mast cells can secrete vascular permeability factor/ vascular endothelial cell growth factor and exhibit enhanced release after immunoglobulin E-dependent upregulation of Fcε receptor I expression. *J Exp Med* 188, 1135-45. (1998).
- 40. Matsushima, H., Yamada, N., Matsue, H. & Shimada, S. The effects of endothelin-1 on degranulation, cytokine, and growth factor production by skin-derived mast cells. *Eur J Immunol* **34**, 1910-9. (2004).
- 41. Oliveira, S.H. & Lukacs, N.W. Stem cell factor and igE-stimulated murine mast cells produce chemokines (CCL2, CCL17, CCL22) and express chemokine receptors. *Inflamm Res* **50**, 168-74. (2001).
- 42. Lee, S.A. et al. Molecular regulation of interleukin-13 and monocyte chemoattractant protein-1 expression in human mast cells by interleukin-1β. *Am J Respir Cell Mol Biol* **31**, 283-91. Epub 2004 Jun 10. (2004).
- 43. Yano, K. et al. Production of macrophage inflammatory protein-1α by human mast cells: increased anti-IgE-dependent secretion after IgE-dependent enhancement of mast cell IgE-binding ability. *Lab Invest* **77**, 185-93. (1997).
- 44. Matsushima, H., Yamada, N., Matsue, H. & Shimada, S. TLR3-, TLR7-, and TLR9-mediated production of

proinflammatory cytokines and chemokines from murine connective tissue type skin-derived mast cells but not from bone marrow-derived mast cells. *J Immunol* **173**, 531-41. (2004).

- 45. Wakahara, S. et al. Gene expression profiles for FcεRI, cytokines and chemokines upon FcεRI activation in human cultured mast cells derived from peripheral blood. *Cytokine* **16**, 143-52. (2001).
- 46. Mori, Y. et al. Tyk2 is essential for IFN-α -induced gene expression in mast cells. *Int Arch Allergy Immunol* **134**, 25-9. (2004).
- 47. Rumsaeng, V., Vliagoftis, H., Oh, C.K. & Metcalfe, D.D. Lymphotactin gene expression in mast cells following Fcε receptor I aggregation: modulation by TGF-β, IL-4, dexamethasone, and cyclosporin A. *J Immunol* **158**, 1353-60. (1997).
- 48. Bissonnette, E.Y., Hogaboam, C.M., Wallace, J.L. & Befus, A.D. Potentiation of tumor necrosis factor- α -mediated cytotoxicity of mast cells by their production of nitric oxide. *J Immunol* **147**, 3060-5. (1991).
- 49. Bidri, M. et al. Mast cells as a source and target for nitric oxide. *Int Immunopharmacol* 1, 1543-58. (2001).
- 50. Gilchrist, M., McCauley, S.D. & Befus, A.D. Expression, localization, and regulation of NOS in human mast cell lines: effects on leukotriene production. *Blood* **104**, 462-9. Epub 2004 Mar 25. (2004).
- 51. Henderson, W.R. & Kaliner, M. Immunologic and nonimmunologic generation of superoxide from mast cells and basophils. *J Clin Invest* **61**, 187-96. (1978).
- 52. Yoshimaru, T. et al. Blockade of superoxide generation prevents high-affinity immunoglobulin E receptor-mediated release of allergic mediators by rat mast cell line and human basophils. *Clin Exp Allergy* **32**, 612-8. (2002).
- 53. Kempuraj, D. et al. Corticotropin-releasing hormone and its structurally related urocortin are synthesized and secreted by human mast cells. *Endocrinology* **145**, 43-8. Epub 2003 Oct 23. (2004).
- 54. Katsuno, M. et al. Neuropeptides concentrations in the skin of a murine (NC/Nga mice) model of atopic dermatitis. J

Dermatol Sci 33, 55-65. (2003).