



Fig. 4 Cytokines and chemokines affect human basophils. Representative cytokines and chemokines that either enhance or directly trigger various functions of these cells are described. TEM: transendothelial migration. TBMM: trans-basement membrane migration.

or mast cells, but also on effector cells such as basophils and eosinophils.⁶¹⁻⁶⁴ Further studies assessing the precise roles of IL-33 in various allergic diseases will be important.

CONCLUSION

Basophils constitute the smallest subpopulation of leukocytes, but they seem to be powerful cells capable of secreting various bioactive mediators in tissues and in the blood, where they encounter allergens and/or their affecting cytokines/chemokines. In human peripheral blood, basophil density is strictly regulated: the percentage of basophils among total peripheral leukocytes usually does not exceed 2%. After undergoing maturation steps in the bone marrow, basophils enter the blood stream. After a rather short (hours to days) stay in the circulating blood, basophils are thought to be trapped in tissues with elevated levels of attracting molecules (Fig. 4). Although several features, such as metachromatic stain, histamine content and surface expression of FcεRI, indicated great similarities between basophils and mast cells, these two cell types are not very close in origin. Mast cells reside in the bone marrow only during the initial steps of their differentiation; mast cell progenitors enter the blood and then move into tissues where they proliferate and mature.¹⁰ Now we believe that eosinophils show a closer association with basophils; the mechanisms regulating differentiation/maturation of these cells are quite similar.¹¹ We thus think that the detailed analyses of the biological functions of mature basophils and eosinophils focusing on

cytokines and chemokines, as presented in this manuscript, are important. Interestingly, these substances discussed in this manuscript are also known to be important regulators of mature eosinophil functions,^{11,65} and the repertoires of cytokines/chemokines acting on basophil and eosinophil functions are mostly overlapping. For example, a CCR3 ligand, eotaxin, is a very potent chemoattractant for both basophils and eosinophils freshly isolated from peripheral blood.

However, in our studies, we have also found that the actions of cytokines and chemokines on basophils are not identical to those on eosinophils. Of course, substances that either modify or directly induce basophil degranulation cannot be theoretically extrapolated to eosinophils, since eosinophils do not manifest rapid degranulation. It has long been known that, among the three hemopoietic growth factors, IL-3, IL-5 and GM-CSF, IL-3 most potently activates various types of basophil functions, whereas IL-5 efficiently activates eosinophils. Their differences have so far been explained on the basis of the levels of their receptor expression in these cells. IL-3 receptor α chain (IL-3R α) mRNA is abundantly expressed in basophils, but in eosinophils IL-5R α mRNA is dominant among the α chains of the three cytokines (Fig. 1).²⁰ Thus, the receptor expression levels may be an important factor that determines the sensitivity and magnitude of the cells' responses to each cytokine/chemokine. The expression levels of cytokine/chemokine receptors are not always stable; transient or inducible expression of receptors will significantly

modify the actions of basophils at inflammatory sites. For example, basophil CXCR4 expression is strongly induced during culture for a few hours or one day, and basophils acquire responsiveness to the ligand, SDF-1, during culture.³⁵ Interestingly, basophil CXCR4 expression is almost completely suppressed by IL-3, and cells exposed continuously to IL-3 presumably retain relatively low sensitivity to SDF-1. In addition, IL-33 enhances basophil expression of the IL-33 receptor, ST2, and these cells, having been once exposed to IL-33, may maintain their response to this cytokine.⁶¹

Recent progress, especially regarding the *in vivo* roles of basophils, has greatly increased the attention paid to this small leukocyte subpopulation. Moreover, in this context, clarification of basophil-unique mechanisms will provide us with important insights into disease pathogenesis. Such information will, in turn, contribute to our understanding of the pathogenesis of various allergic diseases, including asthma and anaphylaxis, in which basophils (and eosinophils) play significant roles. Future studies analyzing these issues can also be expected to provide us with important clues that will be useful for establishing novel therapeutic strategies.

ACKNOWLEDGEMENTS

The authors thank Drs. Koichi Hirai, Akiko Komiya, Chitose Uchiyama and Hirokazu Yamada for helpful discussions, Ms. Chise Tamura for her precious technical assistance, and Ms. Yasuko Asada for her excellent secretarial work. This work was supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and grants-in-aid from the Ministry of Health, Labour and Welfare of Japan.

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アレルギー疾患の自己管理と個別化医療を目指した早期診断基準と
早期治療法の確立及びその有効性と有害事象の評価に関する研究

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