Editorial

Targeting Mast Cells and Basophils in Allergy and Beyond: Emerging Concepts

Abstract: Since the times of P. Ehrlich, F. D. von Recklinghausen, and O.Westphal, the research on mast cells and basophils made significant progression towards the recognition of their involvement in antimicrobial functions and of their role in mobilizing inflammation in wound healing, allergy, and autoimmunity. However, the role of mast cells in normal physiology is still poorly understood. Only in recent years, these cells are increasingly recognized as important effectors in number of pathways related mostly to tissue remodeling. The mast cells are capable to orchestrate inflammatory reactions and angiogenesis, they are frequently present near pre-neoplastic epithelial cells, etc. Absolute mast cell deficiency, as in the cross of Min mice to the C57BL/6-Kit$^{Wsh/Wsh}$ mice, can have overreaching immunological consequences.

Keywords: Immune cells, Mastocytosis, Connective tissue cells, Leukocytes, White blood cells, Granulocytes, Degranulation, Myeloid cells.

This issue of Current Pharmaceutical Design focuses on advances in the understanding of mast cell physiology, signaling, and on their pharmacological targeting. Several contributions in this issue are reviewing current understanding of the role of mast cells in the newly emerging fields of their action. A. C. Reid *et al.* is focusing at the role of mast cells in the treatment of myocardial ischemia, congestive hearth failure and hypertension. Preventing mast cell degranulation in the heart and inhibiting the mast-cell-mediated activation of local renin-angiotensin system is suggested to block its detrimental effects on cardiac rhytmicity. In the next paper, P. Heneberg is focusing on the role of mast cells and basophils in cancer onset and progression. Only recently, the mast cells appeared to be attractive targets of cancer therapies. Since this fact has not been reflected in most of the cancer stem cell-based studies, the vast majority of lineage antibody cocktails retain basophils, dendritic cells, and mast cells. The third paper, by R. Kennelly *et al*., sheds light on the emerging role of mast cells in tissue healing. Most of the knowledge in this field is dealing with healing regulated by skin mast cells, but the Kennelly's review is trying to summarize and provide conclusive evidence regarding the role of mucosal mast cells in healing and mucosal repair, particularly at surgically induced injury or bowel anastomoses.

Second part of this journal issue is focusing on emerging surface markers of mast cells and basophils, emphasizing their physiological role [1] and usefulness in detection of the respective cells and of their activity. In this issue, we focus on two novel mast cell interleukins, IL-19 (Y.-T. Azuma *et al.*) and IL-25 (D. Saadoun *et al.*; Fig. **1A**). Besides that, A. Wolanczyk-Medrala *et al.* are lifting the fog of current advances in development of basophil activation tests. These tests, introduced for the first time in 1994 [2], are now considered as superior to more conventional determination of IgE in serum due to their limited false positivities when compared with IgE assays. The basophil activation tests are still under development (Fig. **1B**) and number of surface markers was tested under various conditions. Most of the initial studies had employed CD203c, however the current spectrum used at least at the experimental level, includes also CD11b, CD11c, CD13, CD45, CD63, CD107a, and CD164. Use of the latter one is discussed *in extenso* in this journal issue.

Third part of this journal issue is focusing on the modulation of mast cell and basophil signaling in health and disease, with emphasis of pharmacotherapeutical outcomes. I. Shefler *et al*. describe the state-of-art knowledge on the communication between the mast cells and other immune cells mediated by membrane vesicles, exosomes and microparticles. This emerging field of research (Fig. **1C**) suggests that mast-cell-derived exosomes are key regulators of T cell response either through direct interaction with T cells, or through interaction with B cells or dendritic cells. This is probably two-way communication, as mast cells may also serve as recepients of microparticles released by activated T cells. Communication of mast cells and T cells through microvesicles is thought to be employed in a number of diseases regulated by T cells, but modulated also by mast cells, such as sarcoidosis, Crohn's disease, rheumatoid arthritis, and fibrosis. Mast cell communication through microparticles bears tremendous potential for specific and selective delivery of drugs to the mast cells or their targets. In the next review, Y. Suzuki *et al*. focus on the effects of three heavy metals, mercury, gold, and silver, at the mast cell function, including degranulation and secretion of cytokines and arachidonic acid metabolites. They discuss recent advances in the field, and suggest the mechanisms for the involvement of these toxic metals in the autoimmune disorders. A growing body of evidence suggests that the toxic metals exert their effects by at least partly overlapping mechanisms, which includes generation of intracellular reactive oxygen and nitrogen species, Ca^{2+} flux, and mitochondrial deregulation. In this regard, it is interesting to note, that e.g. sodium metavanadate was clinically used for the first time already in year 1899 [3]. Within the last decade, both vanadate and reactive oxygen species have been used in number of studies focusing on mast cells [4-6]. In the next paper, B. J. Shenker *et al.* focus on the modulation of phosphatidylinositol-3,4,5-trisphosphate (PIP3; Fig. **1D**) as a targeted therapy of mast-cell-mediated diseases. Instead of the inhibition of all cell activation processes, or instead of the blocking of action of proinflammatory mediators, the PIP3 modulation promises more specific regulation of mast cells function, especially when limited only at the target cell type. The authors describe the current knowledge about the mechanisms of action of phosphatidylinositol-3-kinase (PI3K) in mast cells, review the approaches that have been taken to regulate the PI3K in these cells, and suggest a novel approach to target the PIP3 and to deplete the intracellular levels of this phospholipid by employing the chimeric IgE-CdtB toxin, which acts as a lipid phosphatase [7, 8]. In the next contribution, Z. Ma and Z. Jiao review the current knowledge regarding the effects of macrolactam ascomycin derivative called pimecrolimus (SDZ ASM 981, Elidel Cream) on mast cells. This drug binds to macrophilin-12 and inhibits calcineurin. Its application results in strong anti-inflammatory effects within the skin. Besides T cells, it has been recognized to act on mast cells, where it blocks the release of both preformed and *de novo* synthetized mast cell mediators, and induces mast cell apoptosis. Pimecrolimus, similarly to another calcineurin inhibitors (Fig. **1E**), was shown to be used in the treatment of mastocytosis, especially of its cutaneous form [9-11]. In the last review, M. Triggiani *et al*. summarize current knowledge on the mast-cell-related effects of benzene and its metabolites, hydroquinone and benzoquinone (Fig. **1F**). Benzene is a common environmental pollutant, the typical sources of which are car emissions, cigarette smoke, and which also results from various industrial processes. The benzene metabolites are known to inhibit the release of preformed mast cell and/or basophil mediators, and *de novo* synthesis of leukotrienes and cytokines. The chronic exposure to benzene leads to enhanced susceptibility to infections, myelotoxicity, and to the cancer onset and progression. As the benzene metabolites stimulate the Th2 type immune response and inhibits the production of immunosuppressive cytokines, allergic sensitization is common phenotype associated with chronic benzene exposure.

The appropriate control of mast cell and basophil function is now considered to be highly important for treatment of number of human diseases. Involvement of mast cells and basophils in the body homeostasis is still incompletely understood, but the recent advances in the

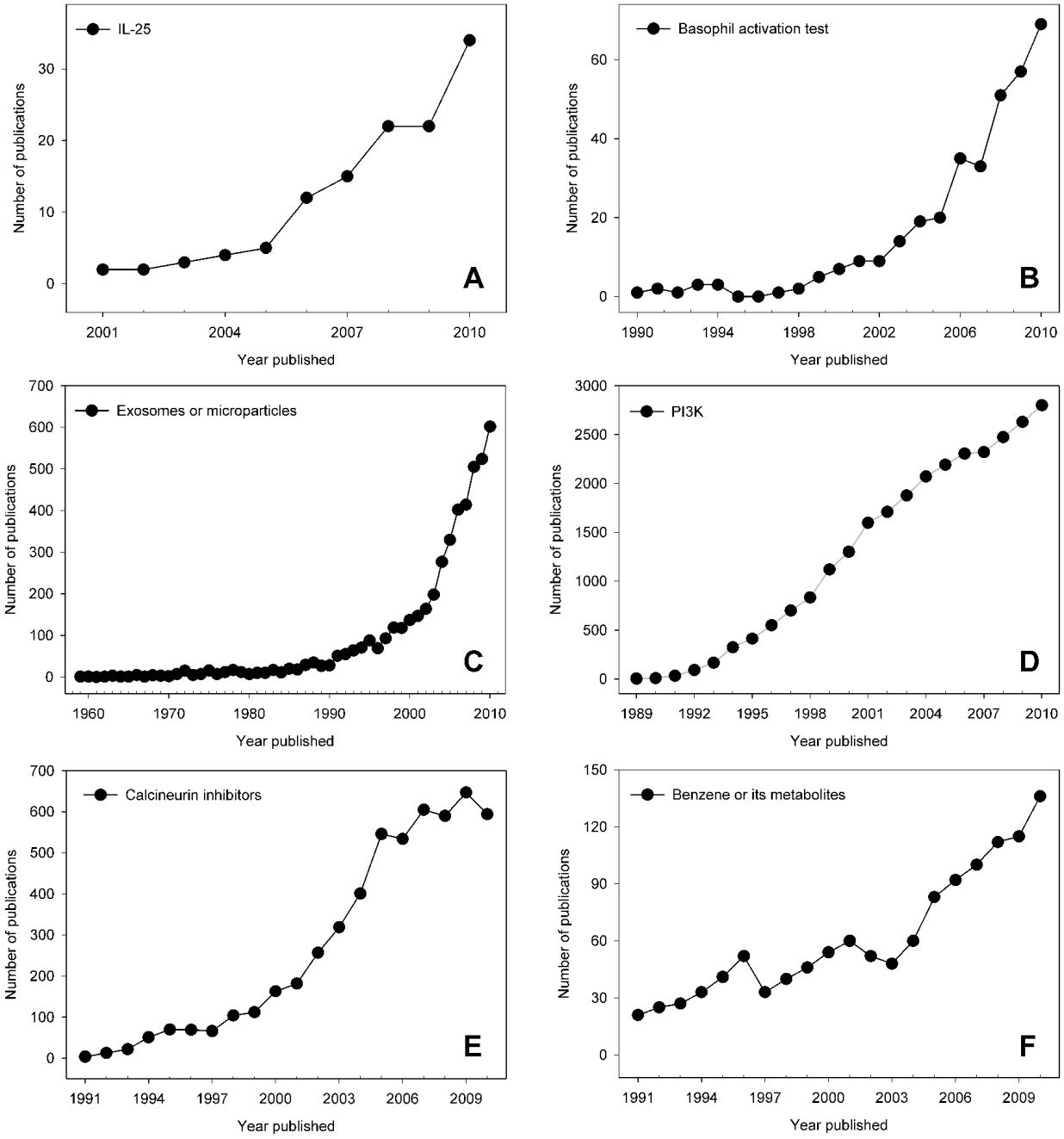

Fig. (1). Bibliometrical analysis confirmed rapidly growing interest in the topics discussed in this journal issue. The WOS analyses were performed as described [17]. Briefly, WOS database platform was searched for number of publications on **(A)** IL-25 (Topic=(IL-25); n=141), **(B)** basophil activation test (Topic=(basophil activation test); n=364), **(C)** microparticles (Title=(exosomes OR microparticles); n=5,084), **(D)** PI3K (Topic=(phosphatidylinositol-3-kinase OR pi3k); n=28,960), **(E)** calcineurin inhibitors (Topic=(calcineurin inhibitor*); n=5,668), **(F)** benzene and its metabolites in relation to the medical research (Topic=(benzene OR hydroquinone OR benzoquinone) AND Topic=(immune OR health); n=1,303). Results of any WOS "Topic" searches are shown only from year 1991 onwards, as the results of such search protocols are highly skewed when applying for the longer time period, WOS "Title" search is shown in full time-frame as it is not affected by the changes affecting the respective database platform [17]. Numbers on papers published in 2011 were incomplete and thus are excluded from the figure. All searches were performed on 8. Jul. 2011.

field, e.g. [12-16], allow to extend the range of diseases, where modulation of mast cell and/or basophil action is considered as clinically relevant therapeutic target. Use of novel approaches, described in part in this journal issue, should facilitate the further improvements in near future.

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