

# What we know (and don't know) about the biology and functions of mast cells and basophils

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## 1 | MAST CELLS AND BASOPHILS—UNIQUE, FASCINATING, IMPORTANT, AND MYSTERIOUS

It is easy to see why this volume of *Immunological Reviews* is dedicated to mast cells and basophils. Both cells are unique and fascinating in many ways. The mast cell has been claimed to express more receptors than any other cell type of the human body, and no cell is thought to make more mediators than it does. Both, mast cells and basophils, are uniquely located and designed for trigger-dependent responses: fast or slow, small or big, good or bad. Mast cells are held by many to be the deadliest cells of our body with mast cell-dependent anaphylaxis killing us within seconds. Yet, mast cells also appear to be important for health and survival, as there are no humans without them.

For this volume, we have invited renowned mast cell and basophil experts to provide clarification on some of the unanswered questions as well as the mysteries, myths and misconceptions surrounding mast cells and basophils, and to review and discuss some of the recent reports and findings that help us to better understand the biology and functions of these cells. The topics we selected are expertly addressed by 14 contributions, for which we thank all of the authors involved.

## 2 | WHAT WE KNOW AND WHAT WE DO NOT KNOW ABOUT THE BIOLOGY AND FUNCTIONS OF MAST CELLS AND BASOPHILS

### 2.1 | What are mast cells and basophils?

The first 2 contributions of this volume deal with the differences and similarities of mast cells and basophils<sup>1</sup> and with the heterogeneity of mast cells.<sup>2</sup> Mast cells and basophils are thought by many to be very

similar cells, with the main difference being their location in the body: basophils in the blood vs mast cells in tissues. Mast cells are traditionally viewed to fall into just 2 categories such as mucosal vs connective tissue-type cells, or they are classified according to their enzyme expression. Varrichi, Frossi, and coworkers describe why these are over-simplifications, how mast cells and basophils differ in many aspects, and that mast cells display a striking heterogeneity that reflects a complex interplay between tissue-specific and microenvironmental signals in their development and differentiation.

### 2.2 | Experimental models and imaging

Most of what we know today about mast cells and basophils comes from the use of experimental models and the development of novel ways to visualize these cells. Falcone and coworkers have summarized what almost 40 years of working with the rat basophilic leukemia cell line RBL has taught us about the response of mast cells and basophils to FcεRI-mediated activation, about the biology of their membrane receptors, their intracellular signaling pathways, their exocytosis pathways, and more.<sup>3</sup> The use of fluorescent reporter strains and intravital imaging has provided fascinating insights on the distribution and the real-time behavior of mast cells in situ. The paper by Tikoo and coworkers describes the spectrum of commonly used imaging approaches to study mast cells, and what we can and have learned from their use.<sup>4</sup>

### 2.3 | What is new on mast cell activation?

Mast cells and basophils show fine-tuned responses to activation. Halova and coworkers have summarized what we have recently learned about the role and mechanisms of priming and modulating mast cells and their responses to different activators.<sup>5</sup> Non-IgE-mediated mast cell activation is the topic of the contribution by Redegeld et al.<sup>6</sup> They focus on the role and relevance of pattern recognition receptors,

This article introduces a series of reviews covering Mast cells and Basophils and their functions appearing in Volume 282 of *Immunological Reviews*.

nuclear receptors, and receptors for alarmins in IgE-independent activation and subsequent immunological and inflammatory responses. The third in this group of papers deals with biomarkers of mast cell activation.<sup>7</sup> This is a hot topic as more and more patients are suspected to have mast cell activation disorders, which are ill characterized and require the development, characterization and use of readily available and reliable biomarkers of mast cell activation.

## 2.4 | How do mast cells and basophils interact with other cells, and what are the consequences?

Mast cells are a rich source of cytokines, chemokines, and growth factors. Mukai and co-workers review the broad spectrum of these types of mediators secreted by mast cells, and they discuss their autocrine, paracrine, local, and systemic effects.<sup>8</sup> Mast cells and eosinophils are of related origin and often accumulate together under both homeostatic and inflammatory conditions. In their contribution, Robida et al<sup>9</sup> compare mast cells and eosinophils and describe their overlapping and distinct features. They then review how these 2 cell types interact with each other and with their tissue environment in a variety of physiological and pathological settings. The colocalization of mast cells and nerves as well as their crosstalk has long been recognized to be important in neurogenic inflammation, itch, and pain. Gupta and co-workers review the latest insights in the underlying mechanisms, such as the production and release of algogenic and pruritogenic mediators by mast cells and the secretion of inflammatory and vasoactive neuropeptides by nerve fibers. Importantly, the authors also touch on the critical and increasingly better understood contribution of mast cells in the exacerbation, by psychological stress, of many chronic inflammatory conditions.<sup>10</sup>

## 2.5 | The role of mast cells in health and disease

The last five contributions of this volume deal with the role and relevance of mast cells in physiological and pathogenic pathways and the contribution of mast cells to the pathogenesis of selected diseases. Mast cells, today, are seen as sentinel cells that sense pathogens and initiate protective immune responses. Piliponsky et al<sup>11</sup> discuss the results of recent studies that show that mast cells can both promote host resistance to infections caused by bacteria and fungi or increase host morbidity and mortality by dysregulating protective immune responses. The controversial role of mast cells in fibrosis is reviewed by Peijler and Bradding.<sup>12</sup> Many fibrotic conditions are characterized by the accumulation of mast cells, suggesting that they play a role in promoting fibrosis or limiting it. There is evidence that they do both and this contribution describes the supporting evidence and implications.

Mast cells are widely held to be involved in the pathogenesis of many diseases, but only very few, such as mastocytosis and chronic urticaria, are viewed as genuinely mast cell-dependent disorders. Surprisingly, the role and relevance of mast cells in urticaria has not been reviewed and critically discussed during the last twenty years. Church et al<sup>13</sup> have taken on the task to put together the various independent lines of evidence that support the central role of mast cells

in urticaria, primarily chronic urticaria. In addition, they outline our current gaps in knowledge, unmet needs and unanswered questions. Steinhoff and co-workers discuss the role of mast cells and basophils in itch.<sup>14</sup> Their focus is on underlying mechanisms, mediators and receptors, especially on proteinase-activated receptors (PARs) and mas-related G protein-coupled receptors (Mrgprs). The final piece of this volume comes from Bonnekoh and coworkers and is on the role of mast cells in autoinflammation. Autoinflammatory diseases are caused by self-directed innate immunity with inflammasome-driven overproduction of interleukin-1. Recent studies have shown that mast cells can drive autoinflammatory responses and diseases and have started to identify some of the underlying mechanisms.<sup>15</sup>

## 3 | MAST CELL AND BASOPHIL RESEARCH—QUO VADIS?

More than 10 years have gone by since a mast cell volume has been published in *Immunological Reviews* (*Immunological Reviews* 2007, Volume 217, Issue 1), and a lot has happened in mast cell and basophil research since then. The current volume of *Immunological Reviews* can highlight only a few of the many advances in the understanding of mast cells and basophils that have been made over the past years. Mast cells were once only seen as “bad guys,” contributing only to allergy and autoimmunity. These days are long gone, and a large and increasing body of evidence, from numerous independent and recent studies, has changed this. Previously unrecognized roles for mast cells have been defined in the homeostatic control of tissue tolerance, in the regulation of immune response, and in the prevention and modulation of diseases. New and exciting data cast light on the development and terminal differentiation of mast cells and basophils. With every year, we understand better the role of the microenvironment in the acquisition of functional activity of mast cells and basophils both in normal and pathological conditions. Many ongoing projects are focused on better characterizing the unique ability of mast cells and basophils to integrate information from many different signaling pathways in order to initiate an appropriate immune response.

Mast cell and basophil research is thriving, and the community of mast cell and basophil fans and experts continues to grow. Much of the research is focused on providing a better understanding of the physiological and pathological functions of mast cells and basophils: What makes them good, what makes them bad? We are sure that the coming years will bring many more exciting and important new findings on the role of these cells in normal and pathological immune responses and beyond.

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and friends. Much of the research conducted by EMBRN members is focused on providing a better understanding of the physiological and pathological functions of mast cells and basophils: What makes them good, what makes them bad? Readers who are already exploring the unsolved mysteries of mast cells and basophils: Please visit the EMBRN website (<http://www.embrn.eu>), become an EMBRN member, and participate in our next EMBRN meeting in Uppsala, Sweden from the 17th to 19th of June of next year.

## CONFLICTS OF INTEREST

The authors have no financial disclosures or conflicts of interest in relation to this work.

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## REFERENCES

1. Varrichi G, Raap U, Rivellesse F, Marone G, Gibbs BF. Human mast cells and basophils – How are they similar how are they different? *Immunol Rev.* 2018;282:8-34.
2. Frossi B, Mion F, Sibilano R, Danelli L, Pucillo CEM. Is it time for a new classification of mast cells? What do we know about mast cell heterogeneity? *Immunol Rev.* 2018;282:35-46.
3. Falcone FH, Wan D, Barwary N, Sagi-Eisenberg R. RBL cells as models for in vitro studies of mast cells and basophils. *Immunol Rev.* 2018;282:47-57.
4. Tikoo S, Barki N, Jain R, et al. Imaging of mast cells. *Immunol Rev.* 2018;282:58-72.
5. Halova I, Rönnberg E, Draberova L, Vliagoftis H, Nilsson GP, Draber P. Changing the threshold – Signals and mechanisms of mast cell priming. *Immunol Rev.* 2018;282:73-86.
6. Redegeld FA, Yu Y, Kumari S, Charles N, Blank U. Non-IgE mediated mast cell activation. *Immunol Rev.* 2018;282:87-113.
7. Kabashima K, Nakashima C, Nonomura Y, et al. Biomarkers for evaluation of mast cell and basophil activation. *Immunol Rev.* 2018;282:114-120.
8. Mukai K, Tsai M, Saito H, Galli SJ. Mast cells as sources of cytokines, chemokines, and growth factors. *Immunol Rev.* 2018;282:121-150.
9. Robida PA, Puzzovio PG, Pahima H, Levi-Schaffer F, Bochner BS. Human eosinophils and mast cells: Birds of a feather flock together. *Immunol Rev.* 2018;282:151-167.
10. Gupta K, Harvima IT. Mast cell-neural interactions contribute to pain and itch. *Immunol Rev.* 2018;282:168-187.
11. Piliponsky AM, Romani L. The contribution of mast cells to bacterial and fungal infection immunity. *Immunol Rev.* 2018;282:188-197.
12. Bradding P, Pejler G. The controversial role of mast cells in fibrosis. *Immunol Rev.* 2018;282:198-231.
13. Church MK, Kolkhir P, Metz M, Maurer M. The role and relevance of mast cells in urticaria. *Immunol Rev.* 2018;282:232-247.
14. Steinhoff M, Buddenkotte J, Lerner EA. Role of mast cells and basophils in pruritus. *Immunol Rev.* 2018;282:248-264.
15. Bonnekoh H, Scheffel J, Kambe N, Krause K. The role of mast cells in autoinflammation. *Immunol Rev.* 2018;282:265-275.

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