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INTRODUCTION

The eosinophil and its role in physiology and disease: news and views

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Eosinophils infiltrate multiple organs under physiological conditions, pointing to a potential role in keeping homeostasis in these tissues. For instance, the lamina propria of the gastrointestinal tract, with the exception of the esophagus, is infiltrated by mature eosinophils. The eosinophils contribute to the maintenance of the intestinal homeostasis by preserving the epithelial barrier integrity, providing survival factors to IgA-producing B cells, and by limiting T cell responses [1]. Moreover, some eosinophils can also be found in the intraepithelial compartment. These eosinophils are characterized by a different expression of surface markers and seen as "inflammatory" eosinophils. Eosinophils have interactions not only with the microbiome but also with the enteric nervous system [2]. A clear pathological role of the eosinophil in the gastrointestinal tract is assumed in patients suffering from eosinophilic esophagitis (EoE) that is characterized by high eosinophil infiltration of the esophagus. Research in recent years, however, questioned the role of eosinophils in EoE development, and several clinical EoE variants seem to exist with atypical clinical presentations and/or other inflammatory cell infiltrations [3].

The possibility of the existence of multiple eosinophil subsets is currently a hot research topic. While early studies already distinguished between hypodense and normodense eosinophils, recently published work differentiates between tissue resident and inflammatory eosinophils. Progress in technology allows the analysis of single cells at both mRNA and protein levels. Although such techniques are particularly challenging when analyzing eosinophils, current data point to a

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This issue of *Seminars in Immunopathology* is dedicated to a pleotropic cell in the immune system, the eosinophil. The eosinophil is an evolutionary conserved cell, but the reason for this fact is largely unknown. Therefore, the specific role of the eosinophils in health and disease is a matter of intense investigation. Three main developments have pushed the field in the last 30 years or so: (1) the isolation of eosinophils from the blood and bone marrow with high purity, (2) the availability of experimental mouse models characterized by eosinopenia and hypereosinophilia, respectively, (3) new anti-eosinophil-targeted therapies used in eosinophilic diseases. Because of the increasing interest in the field of eosinophils and eosinophilic diseases, a theme issue as presented here appears to be timely. Although we are unable to cover all important developments, this issue publishes 12 review papers on new aspects of eosinophil biology, such as plasticity, autophagy, and cellular functions. In addition, we address important questions in eosinophilic diseases, such as classification, biomarkers, and results of specific anti-eosinophil therapies. In this *Editorial*, I would like to highlight some of the recent progress in the field.

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high heterogeneity among eosinophils which might reflect the great plasticity of eosinophils in response to signals from their environment. Such processes are already well investigated in differentiation processes within both eosinophil and neutrophil lineages [4]. However, the characterization of eosinophil subsets and their functional roles in physiology and inflammation are currently not understood.

Autophagy proceeds at a basal rate in virtually all cells because of its housekeeping function of organelle and protein turnover. It is therefore not unsurprising that defects in autophagy disturb cellular homeostasis and cause cellular dysfunction. The consequence of defective autophagy has been investigated in virtually all immune cells. A typical approach is to delete an essential autophagy gene and subsequently to investigate specific cellular function in such autophagy-deficient cells. In eosinophils, such an approach revealed that autophagy is required for their differentiation in the bone marrow, an observation which has also been made in other cell lineages. Surprisingly, however, autophagy-deficient eosinophils exhibited increased effector functions, such as the formation of functional eosinophil extracellular traps [5].

Several articles in this issue deal with the role of eosinophils in diseases. There are mouse and human data suggesting that eosinophils play important roles in both protective and pathogenic immune responses to helminth infections. This field has recently received additional attention since eosinophils may play, particularly in the context of helminth infections, immunomodulatory roles [6]. Besides a possible protective role in helminth infections, it has been suggested that eosinophils mediate antiviral activities. With the coronavirus disease 2019 (COVID-19) pandemic, the question needed to be answered is if eosinophils are involved in the immune response against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). There seems to be no evidence that patients with pre-existing eosinophilic disorders or patients with a targeted anti-eosinophil therapy have an increased risk for severe disease. Some studies suggest that a diagnosis of asthma may be associated with some degree of protection against severe disease [7]. This issue of *Seminars in Immunopathology* also covers the potential role of eosinophils in the pathogenesis of eosinophilic skin diseases [8] and pancreatic disorders [9].

In recent years, there has been an effort to adapt the definition and classification of hypereosinophilic syndromes according to the progress in our understanding of the pathogenesis of these diseases. These new insights resulted in diagnostic criteria and more specific therapies [10]. New biomarkers, such as thymus and activation-regulated chemokine (TARC), are currently tested, and their value for diagnosis and disease monitoring assessed [11]. Together with a better understanding of the pathogenesis of eosinophilic disorders, their role in disease has been evaluated with clinical studies using targeted anti-eosinophil therapies. These studies suggest that eosinophils play a central role in eosinophilic asthma, eosinophilic granulomatosis with polyangitis, eosinophilic rhinosinusitis with nasal polyps, and hypereosinophilic syndromes [12].

In spite of the progress in our understanding of the biology of eosinophils and the pathogenesis of eosinophilic diseases, several questions remain to be answered. For example, we don't know what is the risk of a long-term depletion of eosinophils. Do these therapies deplete resident eosinophils? What is the exact role of such physiologically infiltrating eosinophils in the different organs? Which subsets of eosinophils exist, and what are their functions under both normal and inflammatory conditions? Which of these subsets are depleted under anti-eosinophil therapies? Do regulatory eosinophils exist which limit inflammation? Finally, the role of eosinophils in tissue regeneration, metabolism, and cancer remains unclear. It is hoped that with the recent advances in technology and novel anti-eosinophil therapies we can address these and other questions and obtain at least some answers in the near future.

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Declarations

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References

1. Gurtner A, Gonzalez-Perez I, Arnold IC (2021) Intestinal eosinophils, homeostasis and response to bacterial intrusions. Semin Immunopathol. https://doi.org/10.1007/s00281-021-00856-x
2. Coakley G, Wang H, Harris NL (2021) Intestinal eosinophils: multifaceted roles in tissue homeostasis and disease. Semin Immunopathol. https://doi.org/10.1007/s00281-021-00851-2
3. Biedermann L, Straumann A, Greuter T, Schreiner P (2021) Eosinophilic esophagitis – established facts and new horizons. Semin Immunopathol. https://doi.org/10.1007/s00281-021-00855-y
4. Berdnikovs S (2021) The twilight zone: plasticity and mixed ontogeny of neutrophil and eosinophil granulocyte subsets. Semin Immunopathol. https://doi.org/10.1007/s00281-021-00862-z
5. Germic N, Hosseini A, Yousefi S, Karaulov A, Simon HU (2021) Regulation of eosinophil functions by autophagy. Semin Immunopathol. https://doi.org/10.1007/s00281-021-00860-1
6. Mitre E, Klion AD (2021) Eosinophils and helminth infection: protective or pathogenic? Semin Immunopathol. https://doi.org/10.1007/s00281-021-00870-z
7. Rosenberg HF, Foster PS (2021) Eosinophils and COVID-19: diagnosis, prognosis, and vaccination strategies. Semin Immunopathol. https://doi.org/10.1007/s00281-021-00850-3

8. Radonjic S, Brüggen MC, Feldmeyer L, Simon HU, Simon D (2021) Eosinophils in skin diseases. Semin Immunopathol. https://doi.org/10.1007/s00281-021-00868-7
9. Manohar M, Kandikattu HK, Upparahalli Venkateshaiah S, Vadavalli CS, Mishra A (2021) Eosinophils in the pathogenesis of pancreatic disorders. Semin Immunopathol. https://doi.org/10.1007/s00281-021-00853-0
10. Valent P, Degenfeld-Schonburg L, Sadovnik I, Horny HP, Arock M, Simon HU, Reiter A, Bochner BS (2021) Eosinophils and eosinophil-associated disorders: immunological, clinical, and molecular complexity. Semin Immunopathol. https://doi.org/10.1007/s00281-021-00863-y
11. Catherine J, Roufosse F (2021) What does elevated TARC/CCL17 expression tell us about eosinophilic disorders? Semin Immunopathol. https://doi.org/10.1007/s00281-021-00857-w
12. Kuang FL, Bochner BS (2021) Lessons learned from targeting eosinophils in human disease. Semin Immunopathol. https://doi.org/10.1007/s00281-021-00849-w