Dr Marc Rothenberg discusses the research taking place at his lab, which seeks to regulate eosinophils – a type of leukocyte – for the development of treatments and cures for an emerging set of disorders, eosinophilic gastrointestinal diseases (EGIDs), that he has helped to describe...

What inspired the creation of the Rothenberg Laboratory? Could you offer insight into some of its major achievements to date?

The Rothenberg Laboratory is based on my continued interest, dedication, and enthusiasm for investigating the underlying causes of allergic and immunological processes and diseases. I aim to use my research findings to develop treatments and cures for related paediatric disorders (www.cincinnatichildrens.org/research/div/all-imm/labs/rothenberg). The lab’s research has resulted in many contributions including the recent identification of a gene locus (5q22) and gene variants (of thymic stromal lymphopoietin) that associate with eosinophilic esophagitis, as well as elucidating that the pathogenesis of this disease involves eosinophilia induced by IL-13-driven epithelial cell-derived eotaxin-3.

How prominent are eosinophilic diseases and eosinophilic gastrointestinal disorders?

The prevalence of ‘eosinophilic disorders’ is quite variable depending upon which disease one is referring to, as eosinophils are involved in diverse diseases including common inflammatory disorders such as asthma, less common diseases such as eosinophilic gastrointestinal disorders (EGIDs), and rare disorders such as hypereosinophilic syndrome. Thus, the prevalence can vary widely depending upon what criteria are used. Although EGIDs are not ‘new’, it is only within the past decade that they have been recognised as a distinct set of diseases and that diagnostic criteria have begun to be developed. For instance, the diagnostic criteria for eosinophilic esophagitis, the most common EGID, was only established in 2007 and is based solely on the number of eosinophils per area of patient esophageal tissue (> 15 eosinophils per high power field). For EGIDs alone, it is estimated that they occur in approximately 1 in 1,000 people.

New evidence has arisen in recent years that questions the long-held beliefs on the role of eosinophils. Could you offer further insight into this evidence?

Eosinophils have been considered end-stage cells involved in host protection against parasites. However, numerous lines of evidence show that eosinophils are pleiotropic, multi-functional leukocytes involved in initiation and propagation of diverse inflammatory responses, as well as modulators of innate and adaptive immunity.

New views on the role of eosinophils in homeostatic function are being examined, including developmental biology and innate and adaptive immunity (as well as interaction with mast cells and T cells). The molecular steps involved in eosinophil development and trafficking are being studied, as well as the role of eosinophils in disease processes, including infections, asthma, and gastrointestinal disorders. The consequences of eosinophil deficiency are being studied in genetically engineered mice.

Further to this, could you outline how this evidence could impact on the creation of new treatments?

Strategies for targeted therapeutic intervention in eosinophil-mediated mucosal diseases are being pursued, many of which are based on our increased understanding of the roles and functions of eosinophils gleaned from basic and translational studies. Research from the laboratory has defined a pathway for targeting eosinophils based on internalisation of the eosinophil-selective receptor CCR3. Additionally, anti-eosinophil therapy, such as anti-IL-5 and anti-IL-5Rα humanised antibodies, is being pursued and is now in clinical testing. Furthermore, as IL-13 has been demonstrated to be upstream of eosinophil accumulation, its blockade is now being pursued in eosinophilic esophagitis patients.

What progress has been made in examining the role of eosinophils in homeostatic function, as well as their interaction with mast cells and T cells?

Eosinophils have baseline roles in developmental processes, such as mammary gland development, and also interact with mast cells and T cells in a bi-directional...
Regulating gastrointestinal eosinophils

At the Rothenberg Laboratory, fundamental studies are underway that use molecular, genetic, and translational medicine techniques to develop therapeutic solutions for allergic reactions in the gastrointestinal tract, the causes of which are being unravelled at an unparalleled rate.

ONE TYPE OF white blood cell, known as eosinophils, constitutes a valuable component of the immune system. Its known functions include two crucial processes that contribute to our wellbeing. First, eosinophils destroy foreign substances that have been identified by other parts of the immune system as harmful, particularly substances related to parasitic infection. Second, eosinophils encourage inflammation, which can assist in isolating and controlling a disease site. However, if this inflammation is ongoing it can also cause harm to tissues, as in chronic disorders like allergies and asthma.

Typically, eosinophils account for less than 7 per cent of the circulating white blood cells – 100 to 500 eosinophils per microlitre of blood. Having a low number of eosinophils does not commonly cause health problems as other parts of the immune system are able to compensate. On the other hand, having an increased number of eosinophils, known as eosinophilia – as observed in eosinophilic disorders – can cause major issues. These disorders are categorised by the area affected, such as the gastrointestinal (GI) tract in EGIDs and the esophagus in eosinophilic esophagitis.

Developing a pharmaceutical target for the treatment of eosinophilic disorders is the driving force behind the work at the Rothenberg Laboratory at Cincinnati Children’s Hospital Medical Center in Ohio (www.cincinnatichildrens.org/research/div/all-imm/labs/rothenberg). The hospital was established in 1883 and aims for global leadership in research, education, and innovation designed to improve child health. The lab, led by Dr. Marc Rothenberg, specifically focuses on EGIDs, hypereosinophilic syndrome, asthma, and food allergies. In acknowledgment of the Rothenberg Laboratory’s stellar record of research accomplishment, the National Institute of Allergy and Infectious Diseases (NIAID) recently recognised Rothenberg with an NIH MERIT Award to extend funding of his long-standing investigation into regulation of GI eosinophils. “The backing of the research programme through this award will provide an extraordinary opportunity to enhance our long-term, in-depth pursuit of developing the best therapy, and eventual cure, for eosinophilic gastrointestinal diseases,” says Rothenberg. “With the MERIT Award extending these studies for another 10 years, I am hopeful that truly meaningful research will be accelerated.”

Research at the Rothenberg Laboratory synthesises knowledge from basic studies in various fields to improve the understanding of allergic responses within mucosal tissues, including the GI tract and lungs, and to investigate basic, translational, and clinical techniques and, in particular, new concepts in modern genetics. The lab’s research employs a broad spectrum of approaches and cutting-edge techniques in cell biology, signal transduction, molecular biology, genetics, genomics, and bioinformatics including mouse modelling, genetic engineering, genome-wide association studies, and hematopoietic stem cell manipulation. The vast multidisciplinary expertise and resources provided by colleagues and collaborations within and across divisions of Cincinnati Children’s Hospital Medical Center and within the Cincinnati Center for Eosinophilic Disorders (www.cchmc.org/cced) enables the Rothenberg Laboratory to stay at the forefront of available methodologies with which to test their hypotheses. Rothenberg is committed to increasing collaboration at a national level to facilitate the research and development of therapies and an eventual cure for these disorders, and he and his colleagues have recently launched the Registry for Eosinophilic Gastrointestinal Disorders – REGID (www.regid.org).

FIGURE 1. PATHOGENIC STEPS ECLUCIDATED BY THE ROTHENBERG LABORATORY
INTELLIGENCE

REGULATION OF GASTROINTESTINAL EOSINOPHILS

OBJECTIVES

Dr Rothenberg’s research projects are focused on elucidating the mechanisms of allergic responses, especially in mucosal tissues (eg, lung and gastrointestinal tract), in order to identify novel pharmaceutical targets for the treatment of patients with eosinophilic diseases. His studies employ novel in vivo and in vitro models in conjunction with patient data.

KEY COLLABORATORS

The main collaborators on this study are Dr Rothenberg’s local research team of postdoctoral fellows, graduate and undergraduate students, and technicians as well as faculty colleagues. Collaborations within and across divisions of Cincinnati Children’s Hospital Medical Center and within the Cincinnati Center for Eosinophilic Disorders have been very influential in this research.

FUNDING

NIH – NIAID • NIH – NIDDK • Department of Defense • CURED - Campaign Urging Research for Eosinophilic Disorders • FAAN - Food Allergy and Anaphylaxis Network • Buckeye Foundation • Food Allergy Project • Food Allergy Initiative

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aspects of eosinophilic disorders, with the end goal being to produce solutions to clinical problems. Novel in vivo and in vitro models of allergic responses are used and have already led to great advances in identifying and biologically characterising major pathways involved in regulating allergic responses. In vivo approaches, such as transgenic and gene-targeted mice, are also applied to test chemokines and cytokines, key signalling molecules in the immune system. Additionally, patient samples are studied to evaluate the mechanisms responsible for eosinophil development and activation in patients diagnosed with disorders such as eosinophilic esophagitis and hypereosinophilic syndrome as well as to identify possible genes that predispose patients to eosinophilic disorders. Rothenberg believes that coordinating the basic and clinical research is vital to the development of better diagnostic criteria and therapies for eosinophilic disorders.

Eosinophils have long been considered as solely end-stage immune cells involved in host protection against parasites. However, new data indicates that eosinophils are much more intricate than previously suspected and that these white blood cells are pleiotropic and multi-functional. Eosinophils have now been shown to play a role in catalysing many different inflammatory responses within the body, as well as in modulating innate and adaptive immunity. The Rothenberg Laboratory is actively exploring the particulars and implications of the newly recognised roles of eosinophils in homeostatic functions and diseases.

FINDING A CAUSE

Research in the Rothenberg Laboratory largely focuses on eosinophilic esophagitis and other EGIDs. Eosinophilic esophagitis occurs when the wall of the esophagus becomes inflamed, filling with a large amount of eosinophils. The development of this condition is believed to be caused by allergic reactions, since an increase in eosinophils is often associated with allergies, such as asthma, hay fever, and food allergies. Patients with eosinophilic esophagitis typically suffer from allergic diseases, and specific food elimination induces disease remission, consistent with an allergic etiology.

Eosinophilic esophagitis appears in both children and adults with the most common symptoms being abdominal pain, nausea, vomiting, and coughing. The precise cause behind the allergic reaction leading to eosinophilic esophagitis is still unknown. It is on this subject that Rothenberg and his lab members have focused their attention. He is enthusiastic about his team’s success so far, both in gaining a greater understanding of the condition and in moving towards developing a treatment for it: “We have identified an eosinophilic esophagitis transcriptome, and this facilitates disease diagnosis, has prognostic value, and also determines responsiveness and exposure to specific therapy,” he remarks. “We have also used modern genetics (such as genome-wide association studies) to identify disease risk alleles, which has uncovered key pathways involved in disease pathogenesis and identification of disease risk. We have shown that the mechanism involves an IL-13-driven epithelial cell transcriptome involving eotaxin-3-driven eosinophilia.”

EGIDs are now emerging as a major form of chronic GI inflammatory problems. Like eosinophilic esophagitis, these conditions are brought on by an increase in the amount of eosinophils without a specific identifiable cause and are characterised by eosinophil infiltration in one or more areas of the GI tract and a lack of eosinophils in other organs. These conditions appear in both children and adults, but most commonly affect patients prone to allergic reactions, and food allergies in particular, and bring about abdominal pain and abnormal GI symptoms.

Datasets gathered from fundamental studies for EGIDs are being further tested in translational research models, which could result in improved clinical treatments for these diseases. “Fortunately, we have moved basic findings through translational studies (in vivo modelling in mice and ex vivo human systems),” Rothenberg reveals, “and now onto clinical usage. Some of the prospective therapies that we have developed are at the stage of ongoing clinical trials, and some have already been adapted in clinical practice.” When translating the lab’s research to clinic, Rothenberg states that it is always a challenge to conclude which findings can be applied to human usage. However, if the project members are able to uncover the underlying causes behind these conditions for translation into clinical treatments and an eventual cure, it would be a major success for researchers and offer promising hope for patients.