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The study of allergy by Japanese researchers: a historical perspective

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Abstract

It has been over a hundred years since Shibasaburo Kitasato and Emil Adolf von Boehringer's finding of a serum component that neutralizes bacterial toxins and the subsequent development of antiserum therapy. Over that time, many Japanese researchers have greatly contributed to our understanding of the molecular mechanisms for allergic and inflammatory diseases. This article is aimed at introducing such individual work and how these areas have contributed to our understanding of the mechanisms of allergic reactions.

Introduction

The term 'allergy' initially emerged at the start of the 20th century but its meaning has evolved to describe immediate hypersensitive immune responses (also known as reagenic reactions or anaphylaxis) to allergens by predisposed (or atopic) individuals. Nowadays allergy is recognized as a complicated and still incompletely characterized variant of normally protective immune mechanisms. As we discuss below, many elements involved in the pathogenesis of allergy—for example antibodies, cytokines, cell surface receptors and various cell types—have emerged along with our evolving understanding of more general immune responses.

As with other aspects of immunology, our current understanding of allergy relies on scientific breakthroughs and conceptual insights by a number of brilliant researchers over many decades. This article describes the role of many such researchers, especially those from Japan. We also highlight some of the recent and ongoing studies that have built on the work of these pioneers.

Antibodies and their role in allergy

Pioneering work on antisera

Shibasaburo Kitasato (1853–1931; Fig. 1) was born in Kumamoto, Japan and studied under Robert Koch at the University of Berlin, Germany, from 1886 to 1891, where he helped to break new ground in bacteriology and immunology. Among this work, it is particularly noteworthy that he devel-

oped a pure culture system to grow tetanus bacilli and in 1890 found that serum contained a neutralizing activity against tetanus toxoid. This work was in collaboration with Emil Adolf von Boehringer, who was also Koch's disciple and performed the studies on anti-diphtheria toxin that became the subject for von Boehringer's Nobel Prize in 1901—the first Nobel Prize to be awarded in Medicine and Physiology. Since these findings by Kitasato and von Boehringer, antisera—which are serum preparations containing antibodies that neutralize bacterial toxins and pathogens—have been utilized for treatment of many infectious diseases.

Kitasato, now known as 'the Father of Bacteriology in Japan', also later dedicated his efforts to the establishment of the Institute for Study of Infectious Diseases in 1892 (which is now the Institute of Medical Science at the University of Tokyo), the Kitasato Institute in 1914 and the Keio University School of Medicine in 1917. Kitasato and von Boehringer's pioneering work opened new avenues to dissecting the function of antibody-producing cells, antibody structure and the mechanisms for antibody production and regulation, which have also been the basis for studies on allergy by Japanese researchers.

The discovery of IgE and its role in allergy

Soon after the work of Kitasato and von Boehringer, at the beginning of the 20th century, several brilliant findings emerged in the field of allergy. In 1902, Charles R. Richet and Paul J. Portier, a French physiologist and a French zoologist,



Fig. 1. Shibasaburo Kitasato. Courtesy of the Kitasato Institute.

respectively, recognized a novel immune response—for which Richet and Portier created the neologism ‘anaphylaxis’ to signify ‘non-protection’—in a dog that developed severe systemic symptoms in response to a second injection of sea anemone toxin (1): the Nobel Prize in Medicine/Physiology for 1913 was awarded to Richet for his studies on anaphylaxis. In 1921, Carl Willy Prausnitz and Heinz Küstner (2), a German bacteriologist and a German gynecologist, respectively, demonstrated the transferability of local hypersensitivity by the intradermal injection of serum from an allergic person into a normal person, which is now called the ‘P–K reaction’.

Kimishige Ishizaka (Fig. 2) and his wife, Teruko Ishizaka, were inspired by Kitasato and von Boehring’s achievements and by the exciting progress in the field of allergy described above and dedicated their efforts to the elucidation of the mechanism for toxin-induced anaphylaxis; they worked at the National Institute of Health (now the National Institute of Infectious Diseases) in Tokyo during the mid 1950s. A series of epoch-making studies by Teruko and Kimishige Ishizaka during 1959–89, first at the California Institute of Technology, Pasadena, USA, then at Johns Hopkins University, Baltimore, USA and in particular at the Children’s Asthma Research Institute and Hospital, Denver, CO, USA, established that IgE



Fig. 2. Kimishige Ishizaka at Yamagata University Hospital. Courtesy of Kimishige Ishizaka.

is a key element for provoking immediate-type hypersensitivity in mammals.

Teruko and Kimishige Ishizaka found a novel antibody isotype that normally occurs in very small amounts in the γ globulin component of serum and which Ishizaka and colleagues initially termed erythema-inducing γ globulin (γ E). They discovered it by developing rabbit antibodies that neutralized the ‘reaginic component’ (i.e. what triggers allergic symptoms when allergen is encountered) in human serum (3–5); the rabbit antibodies were thus found to neutralize human antibodies that in turn recognized allergen. Later, γ E was found to be identical to an atypical protein that was found in some patients with myeloma in Uppsala, Sweden (6, 7) and that is now termed IgE. The discovery of IgE and the excellent work of Teruko and Kimishige Ishizaka on its role in allergic responses via mast cell and basophil activation opened a new avenue not only for understanding how allergy is induced but also for analyzing how immune responses are provoked and regulated, of which we currently know the basic scenario.

At Ishizaka’s highly productive laboratories in Baltimore, Denver and the La Jolla Institute for Allergy and Immunology, USA (where Kimishige Ishizaka was the president of the institute during 1989–96), a large number of Japanese

researchers were trained. In particular, Tomio Tada (8), Kiyoshi Takatsu (9) and Tadimitsu Kishimoto (see upcoming articles by Kumanogoh and Ogata and by Kishimoto in this journal's 'Immunology in Japan' series) have made exceptionally prominent contributions to the advancement of immunology. In addition, Ishizaka trained Hirohisa Saito (now at the National Center for Child Health and Development, Tokyo), Makoto Iwata (now at Tokushima Bunri University), Junji Yodoi and Toshiaki Kawakami, some of whose work is introduced below.

Cytokines with a role in allergy and other immune responses

The discovery of a cytokine, IL-5, that is pivotal for allergy

Takatsu (Fig. 3), who was also inspired by Kitasato and von Boehring, was very interested in how tubercle bacilli can provoke robust immune responses. In 1980, Takatsu, supervised by Masayasu Kitagawa and Toshiyuki Hamaoka at Osaka University, discovered a novel B-cell-stimulating factor, which he called T-cell-replacing factor (10–12) but which is now termed IL-5, in an assay system where B cells are activated by the supernatant of T cells stimulated with purified protein derivatives prepared from killed tubercle bacilli.

This discovery by Takatsu and his colleagues (including those at Kumamoto University and the Institute of Medical Science, the University of Tokyo) and its impact on immunology are discussed in depth in the accompanying review article by Kouro and Takatsu in this issue (9). Particularly, the



Fig. 3. Kiyoshi Takatsu. Courtesy of Kiyoshi Takatsu.

pivotal roles of IL-5 and its receptor in B-cell development and function and in eosinophil chemotaxis and its maturation have been established particularly well in allergy. Recently, anti-IL-5R antibody therapy has been actively applied to human allergic patients and is yielding a partially satisfactory effect (9).

Events downstream of cytokine signaling

The work on cytokines and T-cell subset differentiation in allergy by Toshinori Nakayama (at Chiba University) and by Akihiko Yoshimura (at Kurume University, Kyushu University and now at Keio University) will now be emphasized in the more general context of T_H1/T_H2 balancing and of negative feedback regulation in the immune responses, respectively.

Nakayama, who had studied under Tada at the University of Tokyo and Alfred Singer at the National Cancer Institute, Bethesda, MD, USA, has revealed the basic regulation of T_H1/T_H2 cell differentiation by signaling molecules such as the Ras/mitogen-activated protein kinase cascade (13). He is now examining the control of T_H2 differentiation by transacting nuclear factors such as polycomb group gene products (14).

Yoshimura and colleagues identified CIS1 (cytokine-inducible Src-homology 2-protein 1) (15–17), which is a target gene of, and then targets to, signal transduction and activator of transcription (STAT) 5 and the JAB (Janus kinase 2-binding protein) (18). JAB is identical to STAT-induced STAT inhibitor 1 identified by Kishimoto and colleagues (19) and also to suppressor of cytokine signaling (SOCS)-1 identified by Douglas J. Hilton and colleagues at the Walter and Eliza Hall Institute for Medical Research, Australia (20). These findings have established a family of a SOCS-box-containing molecules termed the CIS/JAB/SOCS family that are critical elements for maintaining immune homeostasis and other physiological events involving cytokine signaling.

Cytokines involved in a novel type of allergy

Kenji Nakanishi at Hyogo College of Medicine, Nishinomiya, has found a novel type of allergic reaction, in which IgE does not play a major role but the cytokines IL-18 and IL-33 do, in the induction and exacerbation in the inflammatory disease (21, 22). Such non-IgE-mediated non-atopic allergic reactions are proposed to be provoked by 'super T_H1 ' cells, which are induced from typical T_H1 cells by IL-18 and go on to produce T_H2 -type cytokines IL-13 and IL-3, which then activate mast cells and basophils. Thus, infections will trigger dendritic cells, epithelial cells in the airway and in skin tissues and endothelial cells to produce IL-18.

Cell surface receptors with a role in allergy and other immune responses

Fc receptors on mast cells and B cells in allergy

Although an intriguing role for basophils in allergic reactions is emerging (23, 24), which will be discussed in a later section, mast cells are the primary effector cells in the overall reactions. In particular, Stephen Galli (Stanford University, USA) and Henry Metzger and their colleagues have made significant contributions to the elucidation of these aspects of the significance of mast cells and their molecular machineries (25–29).

There are two types of receptors for the Fc portion of the IgE molecule (Fcε); these are termed FcεRI, which has relatively high affinity, and FcεRII. Chisei Ra, in collaboration with Metzger and Jean-Pierre Kinet at National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, USA, identified the FcεR γ-subunit as a critical component for the cell-surface expression and signaling of the high-affinity IgE receptor, FcεRI (30, 31); interestingly, the FcεR γ-subunit is also found in macrophage receptors for the Fc portion of the IgG molecule (FcγR; also see below) (32). Ra and colleagues, now at Nihon University, have been testing the efficacy of clinical application of anti-IgE therapy for allergy. Kawakami (33, 34), who—as mentioned above—is a former member of Kimishige Ishizaka's laboratory in La Jolla and who is still working there, is identifying several important issues, such as IgE-mediated FcεRI up-regulation on mast cells.

IgE can also bind to its low-affinity receptor, FcεRII (CD23). Kishimoto and Hitoshi Kikutani, at Osaka University, identified for the first time that the B-cell-specific differentiation antigen CD23 could bind IgE (35, 36) and found that its deletion in mice resulted in the impairment of antigen-specific IgE-mediated enhancement of antibody responses (37). Yodoi, at the Immunology Institute, Kyoto University, cloned human FcεRII in collaboration with Tasuku Honjo's group (38) and made significant contributions to our understanding of the generation and functions of the receptor (39) and the 'IgE-binding factor', a soluble form of FcεRII (40). These distinguished studies by Kikutani, Yodoi and their colleagues have made a basis for our current understanding on CD23 as an important modulator for IgE responses (41).

From a historical perspective, IgE-specific regulatory factors have been enthusiastically studied by several groups in Japan, including those of Kishimoto at Osaka, Tada at Chiba and Yodoi at Kyoto. It is interesting to note that a series of studies on IgE-regulatory factors by Kishimoto and Masaki Suemura (42–44) during the late 1970s and early 1980s described several modulatory molecules for IgG or IgE production, some of which led to the identification of IL-4 and IFN-γ later.

Stimulatory and inhibitory Fcγ receptors in allergy and other immune responses

Jeffrey V. Ravetch, first at the Sloan–Kettering Institute (New York, NY, USA) and currently at Rockefeller University (New York, USA), has brought up many young researchers including several who came from Japan, whilst conducting his series of excellent studies on Fc receptors and immune regulation (45, 46). Tomohiro Kurosaki, now at Osaka University and the Riken Research Center for Allergy and Immunology in Yokohama but previously the first Japanese postdoctoral scientist in Ravetch's laboratory, elucidated signaling mechanisms for stimulatory ('activating') FcγRs (47, 48); currently his efforts are been focused on B-cell signaling (49).

Toshiyuki Takai from Okayama University joined Ravetch's laboratory and generated mutant mice with deletions of the common γ chain of Fc receptors (see above) (50). Then, in collaboration with Ravetch (51), he identified the physiological significance of a unique inhibitory FcγR, FcγRIIB, and later performed analyses on inhibitory immune receptors (52) at Tohoku University, Sendai.

Tatsushi Muta and Masao Ono, who were also trained by Ravetch but are currently at Tohoku University, found tyrosine phosphorylation of FcγRIIB and the recruitment of Src-homology 2 domain-containing inositol phosphatase, respectively, upon B cell receptor stimulation (53, 54). These contributions have established a significant mechanism for positive/negative regulation of immune responses and diseases, including allergy and autoimmune disorders, and have also generated the basis for the finding of a specific receptor for IgG in intravenous Ig (55), which is used to treat many immunodeficiencies and inflammatory or autoimmune diseases.

Receptors for inflammatory mediators in allergy

Two Japanese biochemists, Shu Narumiya at Kyoto University and Takao Shimizu at the University of Tokyo, both of whom have studied under the biochemist Osamu Hayaishi at Kyoto University, have made significant contributions to our understanding of prostaglandin receptors (56, 57) and of leukotrienes and their receptors (58–61) in allergy, respectively.

Cell types with newly identified roles in allergy

Mast cells, T_H2 cells and eosinophils have long been studied in association with allergy. Recent studies have introduced other types of cells, including natural killer T cells (NKT cells), basophils and regulatory T cells (Treg cells), as novel players in allergic responses. A novel role for the cytokine-signaling molecule STAT3 has also emerged.

A role for NKT cells in allergy

NKT cells express characteristics of both NK cells and conventional T cells and produce large quantities of T_H2 cytokines and IFNγ in response to various stimuli. Dale T. Umetsu uncovered a crucial role for NKT cells in the development of allergen-induced airway hyper-reactivity (62), in collaboration with Masaru Taniguchi who had studied under Tada at Chiba University and has successfully established NKT cell-deficient mice (63). Taniguchi's group at the Riken Research Center in Yokohama further narrowed down the responsible cells and identified a novel subset of NKT cells expressing IL-17RB that induce IL-25-dependent airway hyper-reactivity (64).

Novel roles for basophils in allergy and other immune responses

Basophils, the least common granulocyte in the blood, have long been neglected in immunological analysis. Recent studies have defined previously unrecognized roles for basophils in both allergic responses and immune regulation. Hajime Karasuyama, who had studied under Tada at the University of Tokyo and is now at Tokyo Medical and Dental University, demonstrated crucial roles for basophils in IgE-mediated chronic allergic inflammation and IgG-mediated systemic anaphylaxis (65, 66), and Nakanishi at Hyogo College of Medicine identified basophils as antigen-presenting cells that preferentially augment T_H2 immune responses (67).

Immunodeficiencies reveal a role for Treg cells and STAT3 in allergy

Highly elevated serum IgE is the hallmark of many allergic disorders. Intriguingly, some primary immunodeficiencies also

display this feature, including immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) and hyper-IgE syndrome (Job's syndrome).

Forkhead box P3 (Foxp3) was identified as the disease-causing gene in IPEX, which is characterized by autoimmune disease, inflammatory bowel disease and severe allergy. Shimon Sakaguchi at Kyoto University, a pioneer of Treg cells, subsequently demonstrated Foxp3 as a critical regulator of Treg cell development and function (68), highlighting the importance of Treg cells in controlling the development of allergic disorders in line with the original concept of suppressor T cells presented by Tada at Chiba University.

Hyper-IgE syndrome is characterized by the susceptibility to bacterial infections, severe atopic dermatitis with high levels of serum IgE and skeletal abnormalities. Yoshiyuki Minegishi at Tokyo Medical and Dental University identified a dominant-negative mutation in the STAT3 gene as the major cause of hyper-IgE syndrome, demonstrating that a deficiency in signal transduction for multiple cytokines is the pathogenesis of this disorder, which includes allergic manifestations (69).

Concluding remarks

In addition to those issues introduced in this article, Japanese researchers have been making enormous contributions in the treatment of allergic disorders. Examples include: exploiting the beneficial effects of innate immunity and of Treg cells as discussed in the previous articles by Kaisho and Takeda (70) and by Arase and Seino (8), respectively; and the potential manipulation of NKT cells, basophils and immunoregulatory receptors introduced in this article. During the next decade, we will surely see further prominent achievements in therapeutic aspects of allergy.

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Abbreviations

γ E	erythema-inducing γ globulin
Fc ϵ	the Fc portion of the IgE molecule
Fc γ	the Fc portion of the IgG molecule
Foxp3	Forkhead box P3
IPEX	immune dysregulation polyendocrinopathy enteropathy X-linked syndrome
JAB	Janus kinase 2-binding protein
NKT cells	natural killer T cells
SOCS	suppressor of cytokine signaling
STAT	signal transducer and activator of transcription
Treg cell	regulatory T cell

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