The study of cytokines by Japanese researchers: a historical perspective

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Abstract
Cytokines play vital roles in both innate and adaptive immunity, in which they regulate immune and inflammatory responses and maintain immunological homeostasis. In addition to the immune system, they also exert diverse functions in other cells. Cytokines have pleiotropic functions and thus the molecular identification of cytokines and their receptors has been fundamental for understanding their mechanisms of action in several physiological and pathological conditions. A number of Japanese scientists have made significant contributions to the identification of cytokines, their receptors and signalling pathways, and application of these novel observations to the clinic has made possible the development of novel therapies for various immune diseases and related disorders. Here we present an overview of cytokines and their receptors identified in recent years by Japanese researchers.

Keywords: chemokine, cytokine, cytokine receptor, interferon, IL

Introduction
The growth and differentiation of cellular components of systems such as the blood and immune systems are under the control of soluble mediators now known as cytokines. Cytokines bind to protein receptors on the cell surface and initiate signalling cascades that result in the transcription of specific sets of genes within the cell nucleus. Originally, cytokines had been categorized as soluble factors critical for cell-to-cell interactions during immune responses. However, it is now well known that functional pleiotropy is a characteristic feature of cytokines; for example, cytokines can exert a wide variety of different biologic functions on various cells, and several different cytokines can exert similar and overlapping functions. This functional pleiotropy and redundancy can now be explained at molecular levels by the properties of cytokine receptors. Many of these observations have been applied to the clinic where cytokines have been shown to be effective for the treatment of several immunological diseases.

A number of Japanese immunologists have contributed to the identification of cytokines and understanding their mechanisms of action. Here we briefly outline the history of the identification of cytokines and their receptors by Japanese scientists.
Before the cloning of IFNs, these molecules and other soluble factors had been the focus of much attention in the fields of biological sciences and medicine but their structure and function had remained elusive because of the difficulty in purifying IFNs. Tadatsugu Taniguchi made this possible. Japanese biologists should be proud of his pioneer work in this field of cytokine research. The availability of pure recombinant IFNs prepared through cDNA cloning made possible the rapid elucidation of pleiotropic functions of IFNs.

Identification of ILs and their receptors: milestone in cytokine research

IL-4, IL-5 and IL-6

In the late 1960s, the essential role of T cells in antibody production by B cells was reported. In 1968, the interactions between T and B cells that were essential for antibody production were clarified by J. F. Miller and H. N. Claman, implicating antigen-non-specific factors (now known as IL-4, IL-5 and IL-6) in antibody production besides cell-to-cell interactions (6, 7). In 1973, A. Schimpl and E. Wecker and Tadamitsu Kishimoto (Fig. 2) and Kimishige Ishizaka reported the presence of those factors released from T cells, which they called T-cell replacing factor (TRF) (8, 9). In the early 1980s, it was expected that at least two different kinds of factors derived from T cells were required for B-cell responses—one for the growth of activated B cells [B-cell growth factor (BCGF)] (10), and another for antibody induction in B cells [B-cell differentiation factor (BCDF)]. Several studies identified a number of factors regulating the B-cell responses in human and murine systems.

In 1983, during the International Congress of Immunology held in Kyoto, Tadamitsu Kishimoto from Osaka University and W. E. Paul organized a meeting to consider the nomenclature of these factors. Functionally and chemically well-characterized factors were given names such as B-cell stimulatory factor (BSF) followed by a consecutive number (11). However, at that time, none of them had been purified and their cDNAs were not yet cloned. Precise nomenclature and classification of these factors were possible only after the cloning of the cDNAs encoding cytokines.

In 1986, the cDNAs for three BSFs were cloned and identified; Japanese scientists made significant contributions to these investigations. Tasuku Honjo from Kyoto University, who had done beautiful work on Ig isotype switching in the 1970s, succeeded in the isolation of the cDNA encoding IL-4 (BSF-1/BCGF-1); this work was published in early 1986 (12). Thereafter, he and Kiyoshi Takatsu from Kumamoto University cloned the cDNA for IL-5 (BCGF-II), which was originally called TRF (13). Takatsu initially detected BCGF-II activities as TRF together with Toshiyuki Hamaoka in 1980 (14), and then Takatsu and Honjo cloned its cDNA (13).

At the same time, Tadamitsu Kishimoto and Toshio Hirano (Fig. 3) from Osaka University, who had discovered BSF-2 activity in 1970s, finally cloned its cDNA; it was later called IL-6 (15). IL-6 exhibited particular, unexpected pleiotropic functions that were not limited to B-cell biology. Cloning of IL-6 cDNA revealed that it had been previously studied under several different names including IFN-β2, plasmacytoma growth factor and hepatocyte-stimulating factor—names that described its distinct biological activities. Although it had
been named ‘IFN-β2’, later, a careful analysis of IL-6 revealed that it lacks direct anti-viral activity so it was renamed IL-6.

The cDNA cloning of IL-6 made possible a better understanding of the pathogenesis of several diseases and provided a potential tool for improving therapeutic approaches in several diseases. The earliest reports by Kishimoto and Hirano suggested a crucial role of IL-6 in inflammation and autoimmune diseases (16, 17). They found that cardiac myxoma cells produced a large amount of IL-6. Cardiac myxoma is a benign heart tumour that causes a wide variety of autoimmune and inflammatory symptoms that disappear after surgical removal of the tumours (18). They also discovered augmented IL-6 production by the synovium in rheumatoid arthritis and in other kinds of synovitis (16). Tadamitsu Kishimoto and the Chugai Pharmaceutical Co. developed a blocking antibody against IL-6R; the humanized antibody contained murine complementarity-determining region sequences. This antibody is now being used for the treatment of Castleman’s disease, rheumatoid arthritis and other immunological disorders, showing Kishimoto’s great contribution from bench to bedside (19, 20).

Japanese scientists also made significant contributions to identification of cytokine receptors and their signalling. Identification of cytokine receptors is essential for understanding the cytokine network. Tadamitsu Kishimoto together with Tetsuya Taga, discovered the IL-6R and its signal-transducing receptor component, gp130 (21–23). gp130 has been shown to be a common signalling component for the IL-6 family of cytokines, such as leukaemia inhibitory factor, ciliary neurotropic factor, oncostatin M, cardiotropin-1 and IL-11 (24). Subsequently, Kiyoshi Takatsu, who discovered IL-5, subsequently identified IL-5Ra, a unique component of the IL-5 receptor (25).

Common signal-transducing components were also identified in the IL-4 and IL-5 receptors. Ken-ichi Arai and Atsushi Miyajima made significant contributions regarding the common β component of the receptors for IL-3, IL-5 and granulocyte/macrophage-stimulating factor while they were working at DNA X in the USA (26–28). The common γ component of the receptors for IL-2, IL-4, IL-7, IL-9 and IL-15 was originally identified as a component of the IL-2 receptor and was discovered by Kazuo Sugamura (Fig. 4) from Tohoku University (29). It is worth noting that the γ chain of IL-2R is not only a common receptor component but is also encoded by the gene responsible for X-linked combined immunodeficiency (30).

Research on signal transduction is outside the scope of this review but some early work on cytokine signalling will be mentioned. Tadamitsu Kishimoto identified the signalling mechanisms that are mediated through gp130, including NF-IL-6, signal transducer and activator of transduction 3 (STAT3) and suppressor of cytokine signalling (SOCS) (21–23, 31–33). Shizuo Akira, who worked in Kishimoto’s laboratory, identified nuclear factor for IL-6 expression and STAT3 (31, 32). Akira is a well-recognized scientist in the field of innate immunity (34). In 1997, three groups including Tadamitsu Kishimoto and Akihiko Yoshimura reported the discovery of STAT-induced STAT inhibitor (SSI-I)/SOCS, an inhibitor of cytokine signalling (33, 35, 36).

IL-2

In addition to BCDF and/or BCGF, a T-cell growth factor (TCGF) was identified by Morgan et al. in 1976 (37); TCGF is now known as IL-2. Tadatsugu Taniguchi, who is now at Tokyo University (see his contribution to IFN research above), cloned the cDNA for IL-2 in 1983 in the midst of a tough international competition when he was working at the Tokyo Cancer Institute (38). This was the first time that a cDNA for an IL had been cloned.

Fig. 3. Toshio Hirano. Courtesy of Toshio Hirano.

Fig. 4. Kazuo Sugamura. Courtesy of Kazuo Sugamura.
The IL-2 receptor contains three components—α, β and γ. IL-2Rα was identified as the Tac antigen by T. Uchiyama from Kyoto University, when he was working in Waldmann's laboratory (39), and the IL-2Rα cDNA was isolated by three groups including Tasuku Honjo's in 1984 (40–42). The cytoplasmic tail of IL-2Rα is very short, and thus it was believed that there should be other signalling components. In 1989, Tadatsugu Taniguchi cloned the IL-2Rβ using anti-β-chain antibody prepared by Masayuki Miyasaka (43, 44), when he was working at Osaka University. Kazuo Sugamura also discovered and characterized the γ chain of IL-2R as described above (29).

IL-18 and other ILs

IL-18 was originally identified by Haruki Okamura from Hyogo College of Medicine as a potent IFN-γ-inducing factor in the serum and the liver of mice that had been sequentially administered Propionibacterium acnes and LPS (45). The source of IL-18 has been demonstrated to be Kupffer cells. Kenji Nakashima, who is also from Hyogo College of Medicine, further identified and characterized the biological activities of IL-18 (46). This cytokine induces cytokine production, amplifies T1,1 and T1,2 responses (dependent on the cytokine milieu) and promotes cytotoxic activity and development of NK cells. IL-17 is produced by T1,17 cells, which are a newly discovered CD4+ helper T-cell subset playing a critical role in allergic responses. The pioneering work of Y. Iwakura from Tokyo University demonstrated the crucial role that IL-17 plays in the pathogenesis of murine arthritis (47).

Identification of chemokines: IL-8 and SDF-1 (C–X–C chemokine ligand 12)

Inflammation is a host response to a wide variety of tissue injury and is characterized by migration of leukocytes and leakage of fluids from the blood into extravascular tissues. Accumulating evidence indicates that tissue injury induces the production of several mediators, such as C5a, leukotrienes and platelet-activating factor, which mediate the migration of leukocytes. In addition, selective recruitment of leukocytes is mediated by specific factors. Matsushima et al. (48) reported on one of these factors, named monocyte-derived neutrophil chemotactic factor. It was isolated from LPS-stimulated human monocyte culture supernatants. This chemokine is now called IL-8 and is the prototype CXC chemokine.

Another significant contribution was made in the field of hematopoietic stem cell research. Takashi Nagasawa identified stromal cell-derived factor-1 (SDF-1) (C–X–C chemokine ligand 12) as a pre-B-cell stimulating factor when he was working with Kishimoto's group at Osaka University (49). Tasuku Honjo independently cloned the cDNA for SDF-1 by using his new ‘signal trap method’ (50). Takashi Nagasawa confirmed the essential role of SDF-1 in B lymphopoiesis by developing gene-deficient mice (51). Nagasawa also isolated the receptor for SDF-1 [C–X–C chemokine receptor 4 (CXCR4)] (52). During receptor identification, he was surprised to notice that the sequence of the receptor was a murine homolog of the HIV I entry co-receptor. The CXCR4-deficient mice uncovered a role of SDF-1 and CXCR4 in organ vascularization during embryogenesis, which is the first evidence that chemokines can also function as pleiotropic cytokines (53).

Conclusions

As described here, Japanese immunologists have made significant contributions to the identification of cytokines and their receptors, clarifying a number of mechanisms in the immune system. In addition to the immunologists mentioned above, a large number of Japanese and foreign immunologists have also contributed to the progress of cytokine research. Unfortunately, it is impossible to refer to all contributors in this short review. Friendship, cooperation and sometimes sound competition have encouraged the international community of immunologists to pursue new findings to advance science. We know that we have much more to learn and hope that Japanese scientists will continue to make important and exciting discoveries in the cytokine field in collaboration with colleagues from all over the world in the search for novel discoveries and hopefully new and effective therapies.

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