

IMMUNOLOGY IN JAPAN

IL-6: from its discovery to clinical applications

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Received 29 January 2010, accepted 5 March 2010

Abstract

In the late 1960s, the essential role of T cells in antibody production was reported. This led to our hypothesis that T-cell-derived soluble factors would have to be involved in the activation of B cells. The factor that induced B cells to produce immunoglobulins was initially named B-cell stimulatory factor-2. In 1986, we successfully cloned the complementary DNA encoding B-cell stimulatory factor-2, now known as IL-6. At the same time, IFN- β 2 and a 26-kDa protein found in fibroblasts were independently cloned and found to be identical to IL-6. Later, a hybridoma/plasmacytoma growth factor and a hepatocyte-stimulating factor were also proven to be the same molecule as IL-6. Now, we know that IL-6 is a pleiotropic cytokine with a wide range of biological activities in immune regulation, hematopoiesis, inflammation and oncogenesis. Since the discovery of IL-6, we have further clarified its activities, the IL-6R system and the IL-6 signal transduction mechanism. On the basis of the findings, a new therapeutic approach to block the actions of IL-6 by use of a humanized anti-IL-6R antibody has been proven to be therapeutically effective for rheumatoid arthritis, systemic juvenile idiopathic arthritis and Castleman's disease. In this review, I discuss the history of IL-6 research as a paradigm of progress from basic science to clinical applications.

Keywords: B-cell stimulatory factor-2, gp130, humanized anti-IL-6R antibody, IL-6, IL-6R

Introduction

IL-6 is a pleiotropic cytokine with a wide range of biological activities in immune regulation, hematopoiesis, inflammation and oncogenesis. Its activities are shared by IL-6-related cytokines such as leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF) and oncostatin M (1). The pleiotropy and redundancy of IL-6 functions have been identified by characterizing a unique receptor system comprising two functional proteins: a receptor specific for IL-6 (IL-6R) (2) and gp130, the common signal transducer of cytokines related to IL-6 (3, 4). Signal transduction through gp130 is mediated by two pathways: the JAK–STAT (Janus family tyrosine kinase–signal transducer and activator of transcription) pathway and the Ras–MAPK (mitogen-activated protein kinase) pathway (5, 6). The negative regulators of IL-6 signaling, SOCS (suppressor of cytokine signals), have also been identified (7–9). Furthermore, it has been shown that IL-6 is essentially required for the differentiation of T_H17 cells (10, 11).

Accumulating evidence indicates pathological roles for IL-6 in various disease conditions, such as inflammatory, autoimmune and malignant diseases (12). On the basis of the findings, a new therapeutic approach to block IL-6 signal using a humanized anti-IL-6R antibody for rheumatoid arthritis (RA), Castleman's disease and multiple myeloma has been attempted (13–15). For instance, the picture shown on

the left of Fig. 1 was taken 6 years ago and at that time this boy was 5 years old and suffering from juvenile idiopathic arthritis (JIA). He had a high fever every day, joint pain and swelling as well as hepatosplenomegaly. His growth had completely stopped when he became sick. However, 18 months after treatment with anti-IL-6R antibody, all symptoms had disappeared and his height increased by 18 cm. The question is why the blockade of IL-6 signals could have such a dramatic therapeutic effect. Here, I briefly review the history of the discovery of IL-6, its signaling mechanisms and autoimmune diseases caused by its overproduction.

T-cell factor(s) that help antibody production

In 1968, the role of T and B lymphocytes in antibody production was discovered by Miller and Mitchell (16) and Claman *et al.* (17). They found that B lymphocytes produce antibodies but not without the presence of T lymphocytes. I speculated that T cells must produce certain factors that induce growth and differentiation of B cells, such as B-cell growth factors and B-cell differentiation factors (18). In the early 1970s, I was a postdoctoral fellow in the laboratory of K. Ishizaka, who discovered IgE at Johns Hopkins University (19). Together, we discovered the presence of such activities in the culture supernatants of activated T cells (20–22).

Interestingly, our results also indicated the presence of distinct factors for IgE and IgG responses.

At that time, we could not explain this phenomenon on a molecular basis but later the presence of T_H1 and T_H2 T-cell subsets for IgG and IgE responses was discovered by Mosmann *et al.* (23). Fortunately, we identified a B-lymphoblastoid cell line called 'CESS', which produces IgG upon stimulation with T cells or T-cell-derived factors (24). By employing this cell line, we, together with Hirano *et al.* (25), isolated the complementary DNA (cDNA) for one of the B-cell-stimulating factors that is now known as IL-6.

The pleiotropic activity of IL-6

Surprisingly, the use of a cDNA, recombinant IL-6 and anti-IL-6 antibodies has made it clear that this molecule had been studied under many different names as depicted in Table 1. One of these names was hybridoma/plasmacytoma growth factor in mice and, in fact, the E μ -IL-6 transgene (i.e. a translocation of the Ig μ -chain enhancer to the IL-6 locus to enhance IL-6 expression) caused polyclonal growth of plasma cells in spleen and lymph nodes in a BL6 strain (26). When we introduced a Balb/c genetic background in these transgenic mice, monoclonal and transplantable plasmacytomas were induced (27). This confirmed seminal studies performed by Potter and Boyce (28) in which intra-peritoneal injection of paraffin oil in Balb/c mice (which are more susceptible than most other strains) generated inflammatory granulomas producing plasmacytoma growth factor and typical plasmacytomas (28).

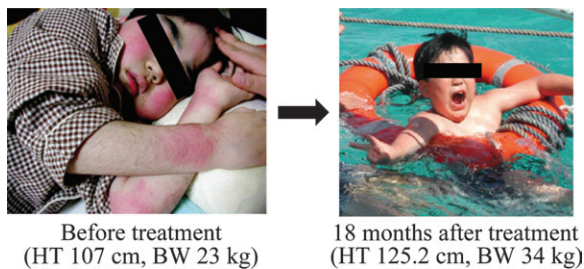


Fig. 1. Humanized anti-IL-6R mAb therapy for JIA. This 5-year-old boy with JIA was treated with tocilizumab. He was previously treated with acetylsalicylic acid, prednisolone, methylprednisolone, lisdex-amphetamine, cyclosporin A and azathioprine but suffered from this disease with symptoms such as fever, joint pain, growth retardation, compression fracture of the thoracic spine due to osteoporosis and hepatosplenomegaly. All symptoms were improved and his height increased by 18 cm during 18 months of tocilizumab treatment. BW, body weight; HT, height.

Table 1. Different names assigned to the IL-6 molecule

IL-6
B-cell stimulatory factor-2
IFN- β 2
26-kDa protein
Hybridoma/plasmacytoma growth factor
HSF

IL-6 had also been studied under the name of hepatocyte-stimulating factor (HSF), which induces various acute-phase proteins including C-reactive protein (CRP), β 2-fibrinogen, amyloid protein, haptoglobin, hemopexin and so on (29, 30). In specially prepared IL-6-gene-deficient mice, a significant reduction was observed in the acute-phase reaction induced by the intramuscular injection of turpentine oil, which confirmed that IL-6 functions as HSF (31).

The IL-6R system and gp130

The next question was how the signal from IL-6 could be transduced into cells and stimulate pleiotropic activities. We first isolated the receptor for IL-6 in 1988 (2), but this did not have any unique sequence to account for the signal transduction. During the following couple of years, however, most cytokine receptors were isolated, including those for IL-2, IL-4, IFN, erythropoietin, growth hormone and others, and it was found that all these cytokine receptors showed a similar tertiary structure and formed a family, the so-called cytokine receptor family. Our study of the IL-6R revealed a unique cytokine receptor organization. Binding of IL-6 with the 80-kDa IL-6R was seen to induce the interaction of another cell surface polypeptide chain; this chain has a molecular mass of 130 kDa and is thus called gp130 (3, 4).

Interestingly, subsequent studies performed by several laboratories including ours revealed that gp130 functioned as a receptor component for several cytokines other than IL-6, such as CNTF in brain, LIF, oncostatin M, IL-11, IL-27, neupoeitin and cardiotrophin in heart (32–36). gp130 was expressed in almost all tissues and cells, some of which did not express the 80-kDa IL-6R; this explains the pleiotropy and redundancy of the IL-6 family of cytokines. Later, it was shown that the unique structure of the IL-6R system, consisting of the specific 80-kDa receptor and a 130-kDa common signal transducer, was found in most cytokine receptor systems, such as the common γ -chain for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, and the common β -chain for IL-3, IL-5 and granulocyte macrophage colony-stimulating factor. The discovery of gp130 established the concept of a unique cytokine receptor system consisting of a specific receptor and a common signal transducer, which is the mechanism for the redundancy and pleiotropy found among many cytokine functions (37).

Signal transduction from the cell surface to the nucleus

Stimulation of cells with IL-6 induced tyrosine phosphorylation of intra-cytoplasmic proteins, which indicated that a certain unknown tyrosine kinase was activated, although gp130 does not possess a kinase domain in its intra-cytoplasmic portion. We found a conserved sequence known as box1 in the intra-cytoplasmic portion of most cytokine receptors including gp130 (38, 39). A novel family of tyrosine kinases designated as the JAK family was identified by Ihle and his colleagues (40–42). We also isolated a new transcription factor, initially called APRF (acute-phase responsive factor) (6), now known as Stat3 (43), which was activated by Jak, formed a dimer and translocated into the nuclei. Thus, the whole picture of IL-6 signal transduction, from cell surface to gene expression, was identified (Fig. 2).

Negative regulation of the IL-6 signals by SOCS

Cytokines such as IL-6 are essential for life but its constitutive overproduction is often involved in various diseases, which accounts for negative regulatory mechanism in the IL-6 signaling system. We discovered a molecule initially called SSI (STAT-induced STAT inhibitor) (8), now known as SOCS (7–9). SOCS is one of the target genes of the JAK–STAT signaling pathway; SOCS binds with JAKs to inhibit their activity and thus negatively regulates the signals.

Overproduction of IL-6 in disease

In spite of the presence of such a negative feedback mechanism, constitutive overproduction of IL-6 is responsible for the pathogenesis of various inflammatory diseases. Just after isolation of the IL-6 gene in 1986 (25), we noticed that cardiac myxoma, a benign heart tumor, often produced a large amount of IL-6 and realized that this could explain various inflammatory symptoms of patients (44, 45). We also noticed that the synovial tissues of the joints of patients with RA constitutively produced a large amount of IL-6 (Fig. 3) (46). Patients with Castleman's disease showing multiple lymph node swellings with massive infiltration of mature plasma cells suffered from severe inflammatory symptoms, such as high fever, anemia, increased levels of acute-phase proteins and hyper- γ -globulinemia. We detected constitutive production of IL-6 in the affected lymph nodes of the patients, while their sera showed high concentrations of IL-6, which could explain the inflammatory symptoms of the patients (47).

Treatment with anti-IL-6R antibody: from cDNA to clinic

Not only IL-6 but also soluble IL-6R levels are enhanced in patients with such inflammatory diseases, so that the complex of IL-6 and soluble IL-6R stimulates gp130 and induces inflammatory signals. For treatment of these patients, we therefore attempted to block the IL-6 signals induced by the interaction of IL-6 with cell surface IL-6R as well as the

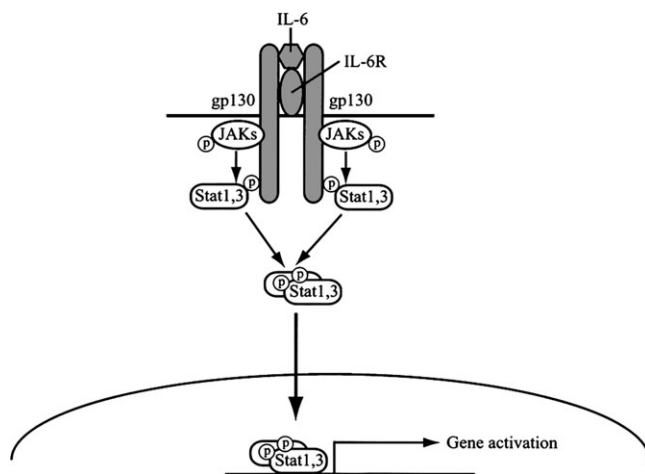


Fig. 2. IL-6 signal transduction. IL-6-mediated stimulation induces homodimerization of gp130, activating (phosphorylating) JAKs, and Stat1 and Stat3. Activated Stat1 and Stat3 form homodimers or heterodimers, which induce activation of various genes.

neutralization of the soluble receptors by establishing an antibody against the receptors, known as the anti-IL-6R antibody (Fig. 4) (13).

This antibody has been humanized and was given the name tocilizumab and the trade name Actemra. It was approved in April 2008 in Japan, in January 2009 in Europe and in January 2010 in the USA. More than 10 years ago, this antibody was first used for the treatment of a patient with Castleman's disease. After its administration to a patient suffering from high fever, the fever went down, CRP levels dropped to zero and hemoglobin levels increased. A phase II clinical study with 30 patients in Japan confirmed its effectiveness for Castleman's disease. All laboratory test results including CRP, serum amyloid A, hemoglobin, albumin, IgG and cholesterol showed normalization.

In an experimental animal model of RA, IL-6-gene-deficient mice did not show any significant inflammation in

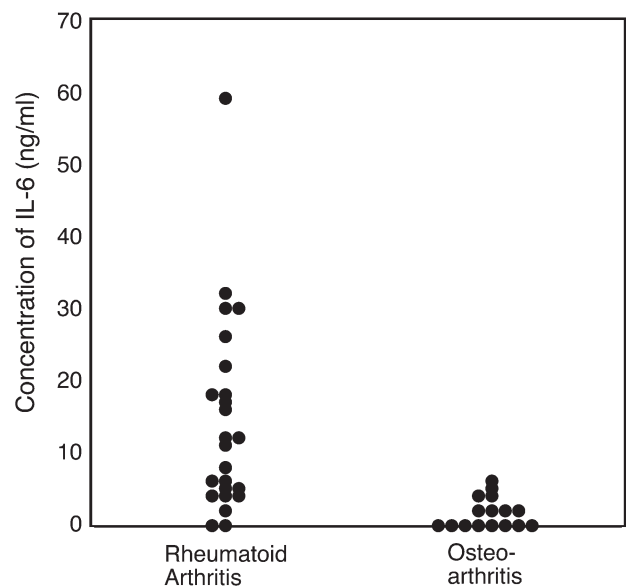


Fig. 3. Concentrations of IL-6 in synovial fluids of patients with RA and osteoarthritis. IL-6 concentrations were determined using a solid-phase radioimmunoassay (46).

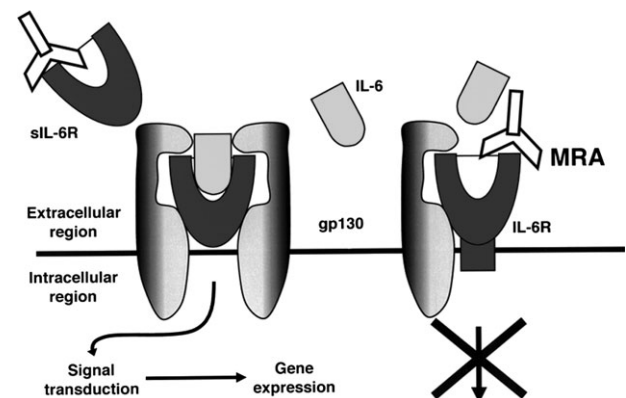


Fig. 4. Blockade of IL-6 signals by an anti-IL-6R antibody (tocilizumab). Tocilizumab binds both cell surface IL-6R and soluble IL-6R (sIL-6R) (55).

the joints, indicating that IL-6 was an essential effector molecule for induction of arthritis (48). As a follow-up to these basic studies, a phase III trial involving RA patients was completed in Japan in September 2005. As shown in Fig. 5 (14), the patients showed significant improvement of symptoms and ACR (American College of Rheumatology) improvement scores ACR20, ACR50 and ACR70 were 89, 70 and 47%, respectively. As shown in Fig. 5, an important point in this trial was that this was monotherapy without the use of any other anti-rheumatic drugs such as methotrexate. The most important point of this therapy was that bone absorption and joint destruction could be completely prevented. The culture of the synovial cells from the patients combined with their peripheral mononuclear cells demonstrated that multinuclear osteoclast generation was completely inhibited by the addition of the anti-IL-6R antibody.

Interestingly, a phase III clinical trial with a group of anti-tumor necrosis factor (TNF)-unresponsive patients showed a significant positive response to the anti-IL-6R antibody, suggesting that the mechanism of the therapeutic effect of anti-IL-6R and TNF inhibitors may be different (15).

As shown in Fig. 1, anti-IL-6R treatment had a dramatic therapeutic effect on a patient with JIA. In phase II trials with 14 patients (49), CRP levels and the erythrocyte sedimentation rate went down and fever episodes were stabilized, while all laboratory test findings became normalized. A double-blind, placebo-controlled phase III trial reported in the *Lancet* in 2008 confirmed the efficacy of this antibody for JIA (15). Systemic onset of JIA is not responsive to TNF inhibitors.

In RA patients undergoing anti-IL-6R therapy, serum IL-6 levels gradually decreased to normal. Anti-IL-6R antibody can block the IL-6 signal but not neutralize IL-6, which strongly suggests that a blockade of the IL-6 signal could normalize the immune disorders present in these autoimmune diseases. Recently, IL-6 has been found to be essential for the induction of one of the T_h subsets, T_h17 (10, 11), which may be involved in the pathogenesis of autoimmune diseases (Fig. 6). Further basic as well as clinical studies on IL-6 and anti-IL-6R antibody can be expected in the near future to contribute to the elucidation of the pathogenesis of various autoimmune diseases including RA and JIA.

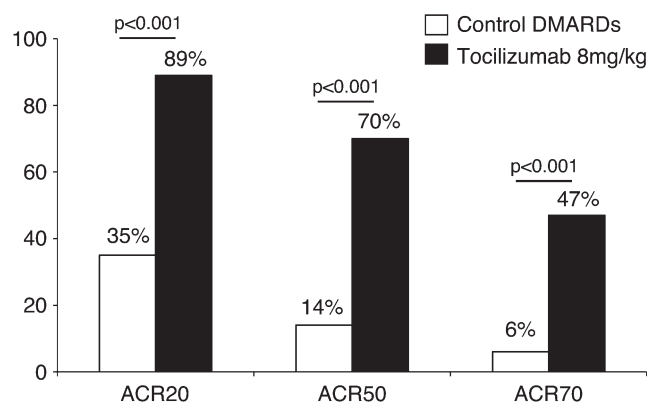


Fig. 5. ACR response rate at week 52. There were significantly more ACR20, ACR50 and ACR70 responses in the tocilizumab group than in the control DMARDs (disease-modifying anti-rheumatic drugs) group ($P < 0.001$).

Aryl hydrocarbon receptor: a novel player in T_h17 cells and macrophages

Because IL-6, together with transforming growth factor (TGF)- β , induces T_h17 cell differentiation from naive T cells, we tried to demonstrate the mechanism of IL-6-induced T_h17 cell differentiation. Consequently, we found that aryl hydrocarbon receptor (Ahr) is specifically induced in naive T cells under T_h17 -polarizing conditions such as TGF- β plus IL-6 and participates in T_h17 cell differentiation (50–52). T_h17 differentiation is positively regulated by IL-6 in combination with TGF- β and negatively regulated by IFN- γ , IL-27 or IL-2.

Positive T_h17 regulation is controlled by Stat3, whereas negative regulation is controlled by Stat1 and Stat5. Kimura *et al.* (50) found that Ahr binds to Stat1 and Stat5, but not to other members of the STAT family, in T_h17 cells (50), suggesting that Ahr may regulate the generation of T_h17 cells by modifying the activation of Stat1 and Stat5, which negatively regulate T_h17 generation. Indeed, Ahr deficiency prolonged Stat1 activation 24 h after stimulation with TGF- β plus IL-6, whereas its activation was relatively transient and returned to the basal level in wild-type naive T cells during the same period. In contrast, Stat3 activation was equally maintained in both Ahr wild-type and knockout naive T cells.

These results indicate that IL-6-mediated activation of Ahr negatively regulates Stat1 activation in T_h17 cells. The mechanism by which Ahr interacts with Stat1 and Stat5 in these circumstances is not yet understood. Given that Ahr serves both as a transcription factor and as a ligand-dependent

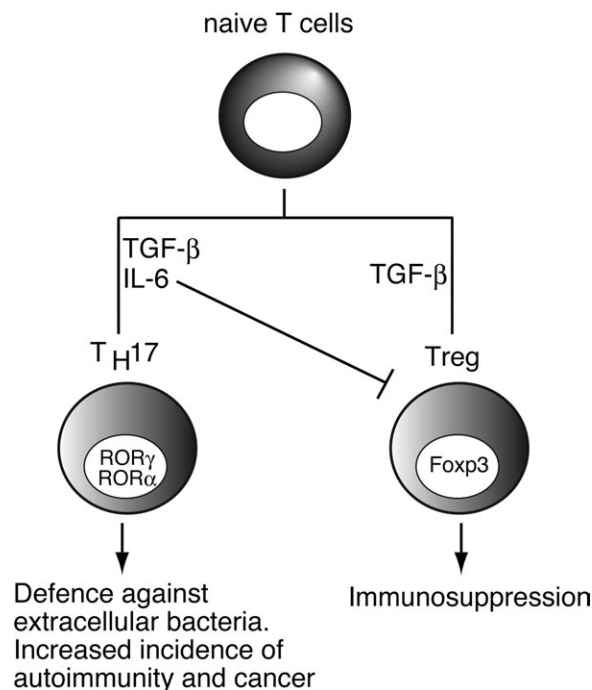


Fig. 6. T_h17 and Treg differentiation. IL-6, together with TGF- β , induces T_h17 cell differentiation from naive T cells. In contrast, IL-6 inhibits regulatory T-cell (Treg cell) differentiation induced by TGF- β . Retinoic acid receptor γ (ROR γ) and ROR α are transcription factors typically expressed in T_h17 cells; forkhead box p3 (Foxp3) is typically expressed in Treg cells.

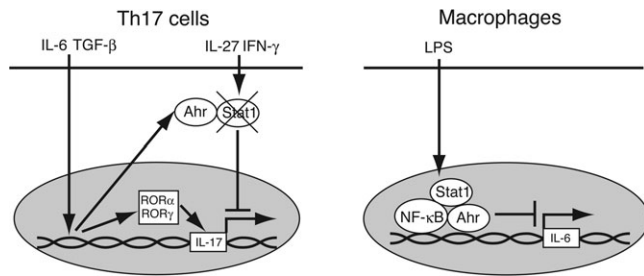


Fig. 7. Ahr functions in T_H17 cells and macrophages. Ahr is induced under T_H17 -polarizing conditions and participates in T_H17 cell differentiation by inhibiting Stat1 activation; Stat1 suppresses T_H17 cell development. In macrophages, Ahr is induced by LPS. Ahr, in combination with Stat1, regulates LPS-induced inflammatory responses. ROR, retinoic acid receptor.

E3 ubiquitin ligase (53), it is possible that Ahr marks activated Stat1 for degradation via its ubiquitin ligase function in T_H17 cells.

More recently, we found that Ahr negatively regulates lipopolysaccharide (LPS)-induced inflammatory responses in macrophages (54). It has been shown that Ahr forms a complex with Stat1 and nuclear factor- κ B (NF- κ B) in macrophages stimulated by LPS, which leads to inhibition of the promoter activity of IL-6. It thus appears that Ahr plays an essential role in the negative regulation of the LPS signaling pathway through interaction with Stat1. We have also provided evidence that Ahr differentially regulates Stat1 activation and NF- κ B transcriptional activity in T cells and macrophages, respectively (Fig. 7). This suggests that Ahr, which is under regulation of IL-6, may control immune responses and inflammation through the regulation of T cells and macrophages and be involved in several autoimmune diseases.

Conclusions

As described, IL-6 participates in a broad spectrum of biological events, such as immune responses, hematopoiesis and acute-phase reactions. In contrast, de-regulation of IL-6 production has been implicated in the pathogenesis of a variety of diseases, including plasmacytoma/myeloma and several chronic inflammatory proliferative diseases. Future studies on the regulation of IL-6 expression and clarification of the molecular mechanisms of IL-6 functions, as well as of inhibitors of IL-6 signals, should provide information critical to a better understanding of the molecular mechanisms of these diseases and the development of new therapeutic methods including antibody therapy.

Funding

Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation; Chugai-Roche Pharmaceutical Co. Ltd, Tokyo, Japan.

Acknowledgements

I thank hundreds of my collaborators for their tremendous contribution, for sharing data and for their helpful discussion for more than

40 years. I also thank A. Kumanogoh and A. Kimura for their help in the preparation of the manuscript.

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