Cellular Immunology 341 (2019) 103927

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Self-reactive IgG4 antibodies are associated with blocking of pathology in human lymphatic filariasis

Rashmi Mishra[a,1], Santosh K. Panda[a,b,*,1], Prakash Kumar Sahoo[a], Srilekha Mishra[a], Ashok Kumar Satapathy[a,*]

[a] Division of Immunology, ICMR-Regional Medical Research Centre, Chandrasekharpur, Bhubaneswar, Odisha, India
[b] Washington University, School of Medicine, St. Louis, MO, USA

ARTICLE INFO

Keywords:
Auto-antigens
Lymphatic filariasis
IgG subclass antibodies
Microfilaria

ABSTRACT

Lymphatic filariasis, a chronic disfiguring disease exhibits complex pathology. Based on different clinical manifestations, infected individuals are categorized into asymptomatic-carriers and chronic-patients. The mechanism behind differential clinical outcomes remains unclear. Roles of filaria-specific B cell responses in filariasis have been documented, whereas the contribution of B1 cell response and poly-specific IgG and IgA in the context of clinical filariasis is not deciphered. In this study, we measured the poly-specific IgG and IgA levels in different clinical categories of filariasis. Asymptomatic-carriers exhibited increased IgG4 antibodies against both filarial-antigens as well as auto-antigens compared to other clinical categories, although IgG against these auto-antigens remained lower. IgA levels against both filarial and auto-antigens were decreased in asymptomatic-carriers. A positive correlation between anti-filarial IgG4 and IgG4 against auto-antigens were observed, suggesting the synergistic role of poly-specific natural IgG4 with anti-filarial IgG4 in blocking the pathogenesis in asymptomatic microfilarial cases.

1. Introduction

Lymphatic filariasis is a major public health problem in tropical and subtropical countries, affecting about 120 million people worldwide [1]. This disease is caused by helminths such as *Wuchereria bancrofti (W. bancrofti)*, *Brugia malayi (B. malayi)* and *Brugia timori (B. timori)* and transmitted by mosquitoes. Based on the pathogenesis and disease manifestations, individuals are grouped into various clinical categories such as: (i) endemic normals (EN) – subjects residing in endemic areas but free of infection i.e absence of microfilaria (Mf), circulating filarial antigen (CFA) and other clinical symptoms of filarial disease; (ii) chronic (CH) – individuals with chronic elephantiasis/hydrocele or both for more than four years; and (iii) asymptomatic carriers (AS) – individuals with microfilaremia and antigenemia but without any clinical symptoms [2]. The protective immune mechanism responsible for this complex etiology remains unclear. Multiple components of the immune system have been implicated for the pathogenesis of filariasis. T cell hypo-response, apoptosis of T cells [3] and macrophages [4] and production of filaria specific antibodies by B cells have already been studied whereas, the role of natural antibody-producing B1 cells remains largely unknown.

B1 cells, a unique B cell population, produce low-affinity poly-reactive antibodies, viz; IgG, IgM, and IgA against an array of both self- and non-self-components such as actin, myosin, lipopolysaccharides (LPS), ss-DNA, etc [5]. Role of B1 cells in eliciting an immune response against various infections have been documented. Impaired B1 cell response resulted in increased mortality in mice infected with *Salmonella typhimurium (S. typhimurium)* and *Streptococcus pneumoniae (S. pneumoniae)* [6]. Transgenic mice expressing an increased level of B1 cells are resistant to *S. pneumoniae* infection [6]. These polyreactive antibodies also protect against viruses such as vesicular stomatitis virus, vaccinia virus, and influenza virus [7]. Role of these natural antibodies has been documented in helminth infections [8]. B1 cell-deficient mice are susceptible to *B. malayi* infection. B1 cells confer resistance to filarial infection in Rag1 knock out mice, even in the absence of conventional B cells and T cells.

Recently, we demonstrated that differential frequencies of B1 cells and IgM antibodies are associated with clinical outcomes of filariasis, whereas, the role of polyreactive IgG and IgA antibodies in clinical filariasis is not yet discovered. In this present study, we measured the

* Corresponding authors at: School of Medicine, Washington University in St. Louis, St. Louis, MO 63010, USA (S.K. Panda). ICMR-Regional Medical Research Centre, Bhubaneswar, Odisha 751023, India (A.K. Satapathy).
E-mail addresses: santoshrmrc@gmail.com (S.K. Panda), aksatapathy@gmail.com (A.K. Satapathy).
[1] These authors contributed equally.

https://doi.org/10.1016/j.cellimm.2019.103927
Received 30 March 2019; Received in revised form 11 May 2019; Accepted 21 May 2019
Available online 21 May 2019

profile of polyreactive IgG and IgA antibodies in different clinical categories of filariasis. Plasma level of IgG and IgA antibodies against actin, myosin, LPS and ss-DNA antigens, in AS cases were significantly less. Interestingly, we observed increased levels of IgG4 antibodies in AS cases against the panel of self-antigens indicating that natural IgG4 antibodies might play a role in blocking the development of the pathology in AS cases.

2. Materials and methods

2.1. Ethics statement

The study was approved by the Institutional Ethical Committee of the Regional Medical Research Centre (Indian Council of Medical Research), Bhubaneswar, Odisha, India, and informed consent were obtained from the study subjects for the collection of blood samples.

2.2. Collection of human blood samples

Blood samples, for this study, were collected from inhabitants of Tirumala village of Bhubaneswar, Odisha, India, after informed consent was obtained from all individual participants. This area is highly endemic for *W. bancrofti* infection. About 5 ml of nocturnal blood was collected in heparinized vials from the study population as per the ethical guidelines of Regional Medical Research Centre, Bhubaneswar, Odisha, India. The plasma was separated from the collected blood samples and stored at −80 °C until further use. Both male and female subjects, within 15–50 years, were selected for this study. Based on antigenemia, microfilaremia and clinical manifestations the study population was categorized into different clinical groups [9,10].

2.3. Chemicals and antibodies

The anti-human antibodies (IgG, IgA, IgG1, IgG2, IgG3, and IgG4) with appropriate conjugates, LPS from *Escherichia coli (E. coli)*, ss-DNA derived from calf-thymus, actin from porcine muscle, and myosin from porcine heart, BSA, and PBS were procured from Sigma Chemical Co., USA. Polystyrene 96-well ELISA plates were purchased from (NUNC-Maxisorp, Sigma-Aldrich, St. Louis, MO, USA).

2.4. Preparation of native filarial antigen

Setaria digitata (S. digitata) is a bovine filarial parasite which is having mitochondrial genomic similarity with human filarial parasites like *W. bancrofti* and *B. malayi* [11]. Somatic extracts of *S. digitata* and *B. malayi* exhibit similar antigenicity. Plasma levels of IgA and IgG are similar against both the antigens [2,12]. So, we have used *S. digitata* antigen in this study and further referred as filarial antigen. Filarial parasites were collected from bovine peritoneum, in phosphate-buffered saline (PBS), supplemented with 1% glucose, from a local butchery. Freshly collected adult female parasites of *S. digitata* were used for the preparation of filarial antigens by the method described elsewhere [13]. The parasites were washed thoroughly in PBS, grounded in a glass homogenizer and then ultrasonicated (Artek sonic dismembrator; Bio-Logics, Inc., Manassas, VA, USA) for 15 minutes. The extracts were centrifuged at 1500 RPM for 10 minutes, and the soluble supernatants were aliquoted and stored at −20 °C for further use. The protein content was measured by Bradford calorimetry method.

2.5. Circulating filarial antigen (CFA) assay

CFA levels in plasma samples were measured using commercially available Trop Bio ELISA kit for the quantification of antigens according to the manufacturer's instructions (Tropical Biotechnology Pvt. Ltd, Townsville, Australia) and expressed as antigen units.

2.6. ELISA

Levels of IgA, IgG, IgG1, IgG2, IgG3, and IgG4 against several auto-antigens (ss-DNA, actin, myosin, LPS) and filaria antigens were measured by ELISA by the method described elsewhere [14]. 96-well ELISA plates were coated with 1 μg/well antigens diluted in PBS and incubated at 37 °C for 4 hrs followed by overnight incubation at 4 °C. Plates were blocked with 1% BSA-PBS. The plates were washed thoroughly, and human plasma samples diluted 1:200 in BSA-PBS containing 0.01% Tween-20 (BSA-PBS-T) were incubated. After 2 hrs the plates were washed and, were incubated with optimally diluted mouse monoclonal anti-human subclass reagents at the following dilutions: IgG, 1:4000; IgA, 1:1000; IgG1, 1:2000; IgG2, 1:2000; IgG3, 1:1000 and IgG4, 1:4000. IgG4 (1:4000) to filarial native antigen, IgG4 (1:1000) to actin and myosin, IgG4 (1:2000) to LPS and ss-DNA were added. The plates were thoroughly washed and probed with anti-mouse IgG peroxidase (1:1000). Enzyme activity was measured using tetramethylbenzidine (TMB) (Sigma-Aldrich), and absorbance was recorded at 450 nm using an ELISA reader. We have used the standard laboratory procedure to calculate the ELISA unit. A pool of 30 plasma samples (10 from each category i.e. EN, AS, CH) was used as the internal standard. This plasma pool was used in every ELISA plate along with the samples. The O.D. value of this pool plasma was considered as 100 ELISA units and accordingly, the ELISA units of other samples were calculated as follows:

$$(\text{O.D. of the sample}/\text{O.D. of the pool standard}) \times 100.$$

The results were expressed as arbitrary ELISA units using this internal standard.

2.7. Data analysis

Graph Pad Prism V-5 (Graph Pad Software, Inc., San Diego, CA, USA) was used for statistical data analysis. Two-tailed unpaired Students *t*-test was used for comparison of two experimental groups. Coefficients of correlation were determined by the Pearson correlation test. P values < 0.05 were considered as significant.

3. Results

3.1. Study population

The status of infection was evaluated by the examination of blood smear for Mf, and the plasma samples were also tested by Og4C3 ELISA kit (Trop Bio) for the presence of the circulating filarial antigen (CFA). The EN and CH individuals exhibit no circulating Mf whereas the AS category has 15.3 mean Mf density. Fifty patients in each clinical group were recruited for this study and the antibody levels against filarial antigens and auto-antigens were evaluated from the collected plasma samples. This study population is free from other chronic diseases and also free from other common helminth infections.

3.2. Asymptomatic carriers have less plasma IgG and IgA antibody levels against auto-antigens

Previously, we have demonstrated that, during human lymphatic filariasis, microfilaremic carriers (AS) exhibited a significant decrease in frequency of B1 cells as well as decreased levels of IgM antibodies to various auto-antigens and filarial antigens as compared to other categories of filariasis such as endemic normal (EN) and chronic pathology (CH) [15]. Since IgA and IgG autoantibodies are also produced by B1 cells [16,17], we measured the profile of IgA and IgG antibodies against several auto-antigens (such as actin, myosin, LPS, and ss-DNA) in plasma of different clinical categories (i.e. EN, AS and CH). The titer of IgG and IgA antibodies against auto-antigens in AS cases were significantly lower than EN and CH cases (Fig. 1A and B), whereas IgG

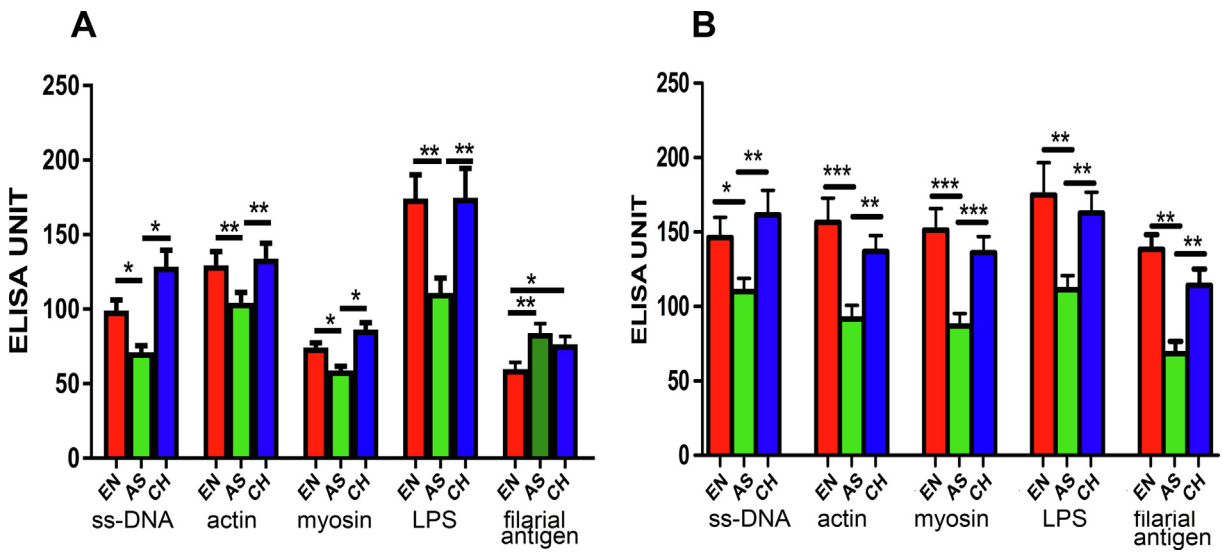

Fig. 1. Plasma level of IgG and IgA antibodies to filarial antigens and various auto-antigens in different clinical categories (EN, CH and AS) of filariasis were measured by ELISA. (A) Level of IgG antibodies to ss-DNA, actin, myosin and LPS were significantly low in plasma of AS individuals as compared to EN and CH. N = 50, * P < 0.001, and ** P < 0.03. (B) There are significantly low levels of IgA antibodies to all auto-antigens in plasma of AS individuals compared to other clinical categories. N = 50, * P < 0.05, ** P < 0.01, *** P < 0.001.

levels against filarial antigens were significantly higher in infected cases (AS, CH) as compared to endemic normals (Fig. 1A). In agreement with a previous study [2], we have observed that AS cases exhibit lower levels of IgA against filarial antigens as compared to EN and CH cases (Fig. 1B). Above data suggested that differential IgG and IgA antibody profile against filarial antigens and auto-antigens might play a role in the clinical outcome of filariasis.

3.3. Profile of IgG isotypes against different auto-antigens and filarial antigens

It has been demonstrated that anti-filarial IgG isotype antibodies contribute to the outcome of filarial pathogenesis [18]. So, we measured titers of IgG isotypes in plasma of filarial patients against filarial antigens and different auto-antigens. Differential levels of IgG subclasses against auto-antigens among different categories of filariasis were observed. Increased levels of anti-filarial IgG4 was found in AS cases as compared to EN and CH. Interestingly, IgG4 levels against different auto-antigens were also increased in AS cases whereas, a definitive correlation between IgG1, IgG2, and IgG3 antibodies and clinical outcome of filariasis was not observed (Fig. 2).

3.4. Levels of anti-filarial IgG4 and IgG4 antibody levels against auto-antigens are correlated

High IgG4 titers are associated with asymptomatic infection and are positively correlated with microfilaremia [19]. Since, increased IgG4 antibody levels against auto-antigens were found in AS cases and these antibodies are having low affinity and poly-specific in nature [18], we analyzed the correlation between levels of anti-filarial IgG4 and levels of IgG4 against auto-antigens. Anti-filarial IgG4 levels were found to be positively correlated with auto-antigen specific IgG4 levels in AS cases, (Fig. 3), indicating a role of natural IgG4 in blocking the development of immunopathology.

4. Discussion

Genetic traits, the intensity of parasite infection, collateral bacterial and fungal infections, and complex interplay between parasite and host-immune response contribute to the etiology of lymphatic filariasis [20]. Filarial parasite skewed inflammatory response towards anti-inflammatory Th2 type response characterized by IL-4, IL-13 production, which ultimately induce immunosuppressive TGF-β and IL-10 [10,21]. Suppression of inflammatory response allows the parasite to establish a chronic infection without significant tissue damage [22,23]. Other than the cellular response, the humoral response also has been implicated for the differential manifestation of the filarial disease. Higher IgE and IgA antibody levels found in chronic patients whereas increased IgG4 is associated with AS groups [24–26]. Other than filarial specific classical B cell response, the role of B1 cells in nematode infection has been documented. Poly-specific low-affinity auto-antibodies produced by B1 cells facilitates parasite clearance in experimental helminth infections [8], whereas its role in clinical filariasis remains unclear. Here in this study, we found increased levels of IgG4 against an array of auto-antigens (actin, myosin, LPS, ss-DNA) in AS cases as compared to other clinical groups. The titer of IgG4 antibody against auto-antigens also positively correlated with anti-filarial IgG4 levels.

Elevated level of IgG4 is, however, a hallmark of hypo-immune response such as helminth diseases [16,27]. IgG4 antibodies are normally formed due to long-term exposure or repeated exposure to antigens in a non-infectious condition. Several studies reported elevated levels of IgG4 antibodies in AS cases of helminth infections such as filariasis and schistosomiasis [28–31]. Individuals infected with *W. bancrofti* were having higher levels of both total and filarial-antigen specific IgG4 antibodies [32–35]. High IgG4 expression was found in individuals with *Loa. loa* microfilaremia [36]. The response to auto-antigens at the IgG4 subclass level had not been previously characterized for different groups of lymphatic filariasis.

IgG4 is a prominent isotype of IgG antibodies which play an important role in the initiation of the immune response in allergic as well as parasitic diseases. IgG4 is different from the other three isotypes by exhibiting anti-inflammatory response [37]. High levels of IgG4 antibodies are present in the plasma of AS individuals as compared to other clinical groups. Although the precise mechanism of this association is yet to be explained, the anti-inflammatory and functional mono-valency property of IgG4 might help the parasite for evasion of host immune response. Natural IgG4 antibodies might play a role synergistically with filarial specific IgG4 in the maintenance of immune suppressive state in AS cases and support the survival of the parasite.

Filarial infection induces alternate activation of macrophages and escapes from the inflammatory immune response [13,38]. Furthermore, induction of apoptosis in macrophages by APC mediated filarial antigen

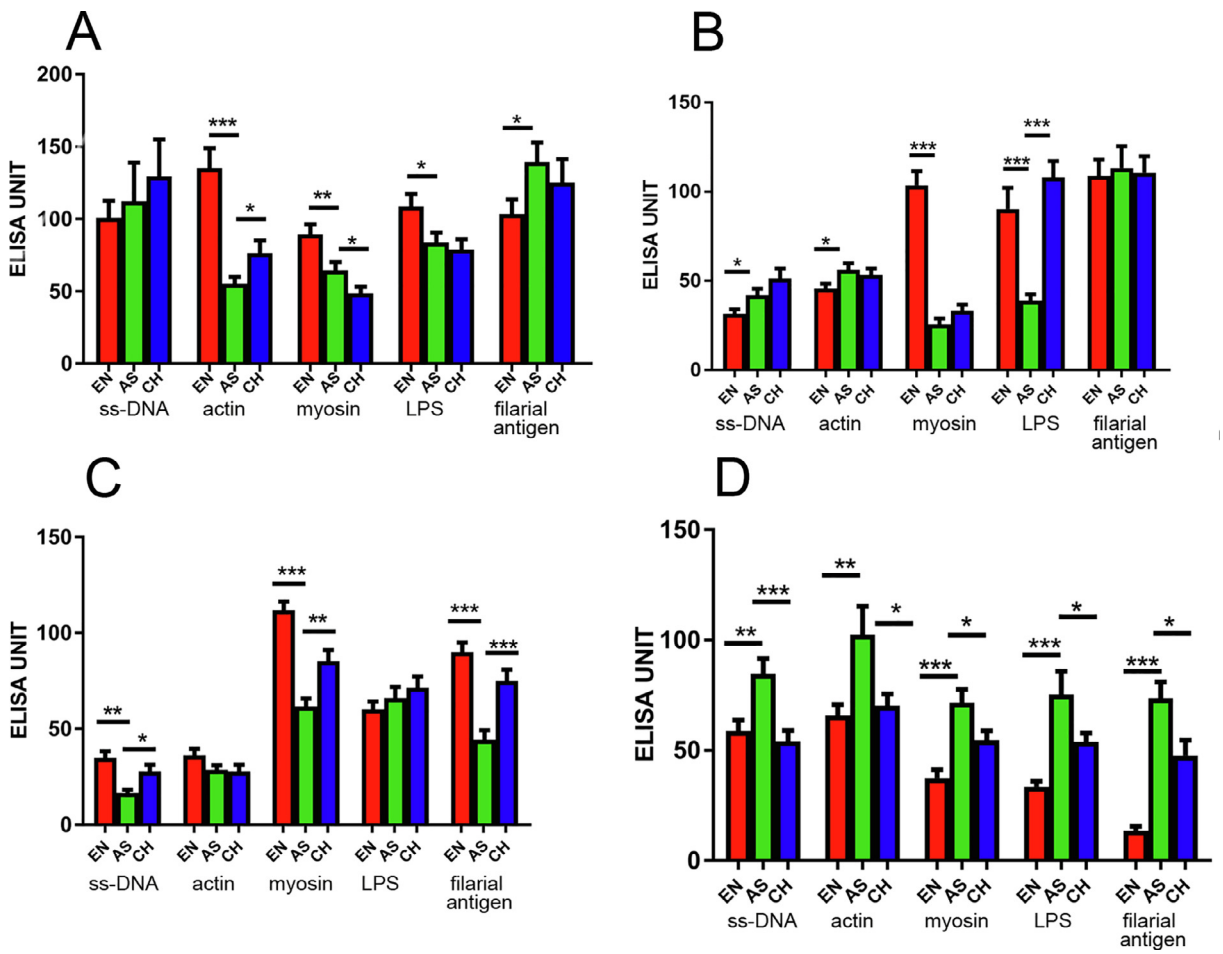

Fig. 2. Plasma levels of IgG subclasses against filarial antigens and auto-antigens in different clinical categories. Profile of IgG1 (A), IgG2 (B), IgG3 (C) and IgG4 (D) antibodies against different auto-antigens (ss-DNA, actin, myosin, LPS) and filarial antigens in plasma of EN, AS and CH groups. N = 50 (EN, CH), N = 40 (AS), * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$.

and inhibition of T cell proliferation demonstrates the cause of defective and ineffective innate immune response against filarial parasites [4,39]. B1 cells might play a role before the adaptive response come into the picture and decide the fate of parasitemia and clinical outcomes in filariasis. Further investigations might specifically decipher how stage-specific immune response against filarial parasites regulate the degree of infection.

Advances in the field of allergy and autoimmunity demonstrate that incidence of these inflammatory diseases is negatively correlated to helminth infection [40]. High titers of IgE which contribute to parasite clearance is associated with autoimmune response [41,42]. Recently Prodjinotho et al., demonstrated that IgG4 inhibits IgE induced release of elastase and histamine [16]. Further, it was demonstrated that IL-10 inhibits IgE production and promotes IgG4 production [43,44]. Moreover, IL-10 induced the differentiation of IgG4 secreting plasma cells from IgG4 switched B cells [45]. In case of lupus patients, IgG4 and complement deposition are negatively correlated and it was hypothesized that IgG4 may dampen the inflammatory cascade in lupus pathogenesis by forming non-pathogenic immune-complexes. Previously, we have demonstrated that AS individuals have increased plasma levels of IL-10 [15]. Here, we have demonstrated that high titers of self-reactive IgG4 are associated with AS cases. So, the commitment of B1 cells to produce IgG4 might block the production of other pathogenic IgG isotype and skew the development of autoimmune response, which in turn induce allergy and autoimmune disorder. Secondly, IgG4 in association with nuclear antigens might form non-pathogenic immune complex (ICs) and blocks the formation of pathogenic lCs. Further research on the dynamics of B1 cells and polyreactive antibody production in the context of helminth infection and autoimmune response may open of new avenues for therapy of both the diseases.

Declaration of Competing Interest

The authors have no conflict of interest.

Acknowledgments

We would like to thank Dr. Alok Das Mohapatra for the nice feedback. The authors are also thankful to anonymous volunteers who participated in this study. We are thankful to the Indian Council of Medical Research, India for providing the funds and resources.

Data and materials availability

All data pertaining to this study is published in the paper or included in the Supplemental Materials.

Authors contribution

RM and AKS designed the experiments. RM: performed all the experiments. SM: helped in the experiments. PKS: collected the samples. SKP, PKS, and AKS analyzed the data. RM and SKP wrote the manuscript.

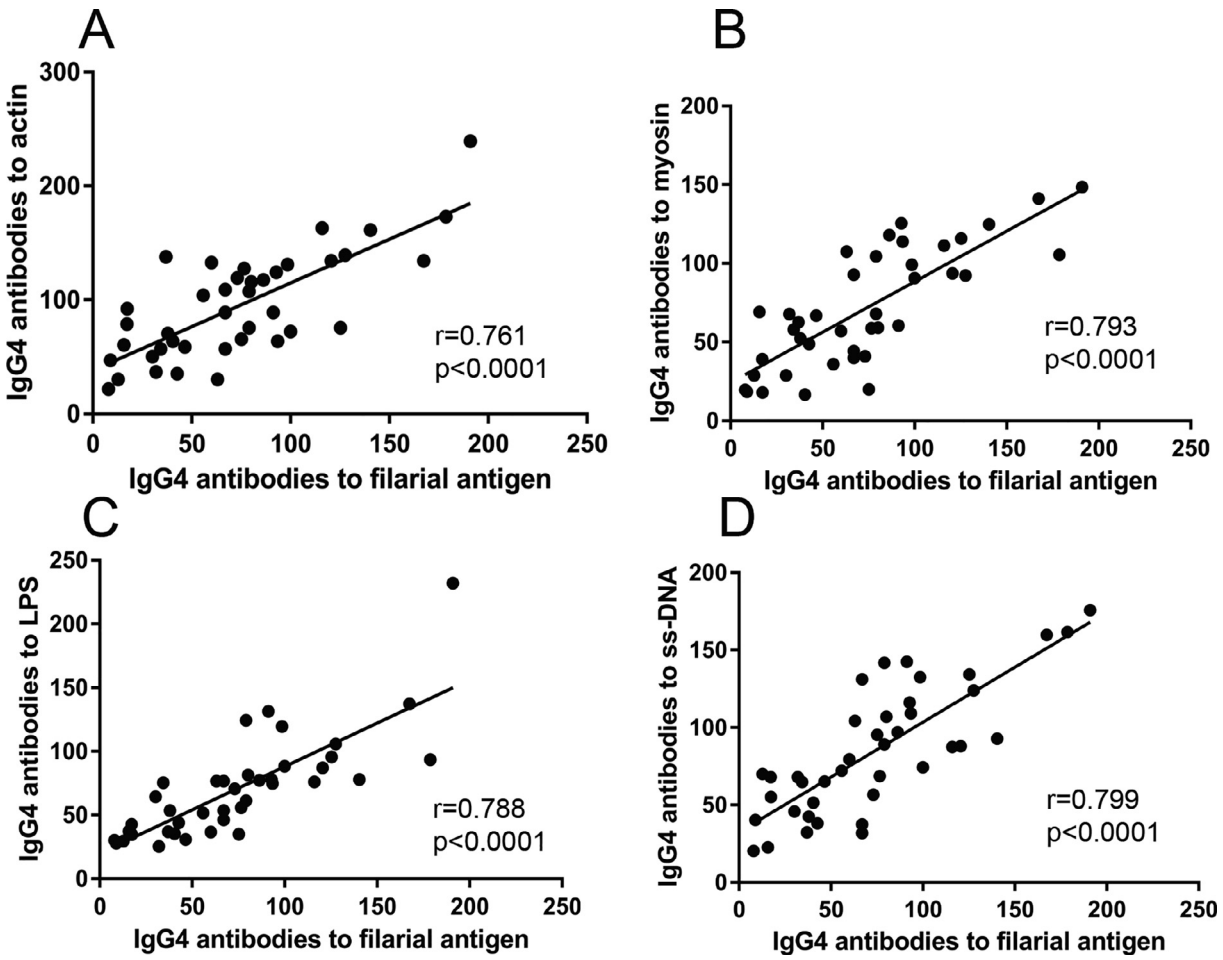

Fig. 3. Correlation between plasma level IgG4 antibodies to filarial antigens and IgG4 antibodies to various auto-antigens such as ss-DNA, actin, myosin and LPS in AS cases of human filariasis. (A) Levels of anti-filarial IgG4 antibodies were positively correlated with anti-actin IgG4 antibodies in the plasma of AS individuals ($r = 0.761$, $P < 0.0001$, $N = 40$). (B) A positive correlation was observed between levels of IgG4 antibodies against the filarial antigens and IgG4 antibodies to myosin ($r = 0.793$, $P < 0.0001$, $N = 40$) in AS individuals. (C) Levels of anti-filarial IgG4 to IgG4 against LPS ($r = 0.788$, $P < 0.0001$, $N = 40$) and (D) A similar correlation between anti-filarial IgG4 antibody and IgG4 antibody against ss-DNA ($r = 0.799$, $P < 0.0001$, $N = 40$) was observed.

References

[1] R.K. Shenoy, Clinical and pathological aspects of filarial lymphedema and its management, Korean J. Parasitol. 46 (2008) 119–125.

[2] B.R. Sahu, M.C. Mohanty, P.K. Sahoo, A.K. Satapathy, B. Ravindran, Protective immunity in human filariasis: a role for parasite-specific IgA responses, J. Infect. Dis. 198 (2008) 434–443.

[3] R. Mishra, S.K. Panda, P.K. Sahoo, M.S. Bal, A.K. Satapathy, Increased Fas ligand expression of peripheral B-1 cells correlated with CD4(+) T-cell apoptosis in filarial-infected patients, Parasite Immunol. 39 (2017).

[4] A. Das Mohapatra, S.K. Panda, A.K. Pradhan, B.K. Prusty, A.K. Satapathy, B. Ravindran, Filarial antigens mediate apoptosis of human monocytes through Toll-like receptor 4, J. Infect. Dis. 210 (2014) 1133–1144.

[5] A.F. Popi, I.M. Longo-Maugeri, M. Mariano, An overview of B-1 cells as antigen-presenting cells, Front. Immunol. 7 (2016) 138.

[6] K.M. Haas, J.C. Poe, D.A. Steeber, T.F. Tedder, B-1a and B-1b cells exhibit distinct developmental requirements and have unique functional roles in innate and adaptive immunity to S. pneumoniae, Immunity 23 (2005) 7–18.

[7] Y.S. Choi, N. Baumgarth, Dual role for B-1a cells in immunity to influenza virus infection, J. Exp. Med. 205 (2008) 3053–3064.

[8] N. Paciorkowski, P. Porte, L.D. Shultz, T.V. Rajan, B1 B lymphocytes play a critical role in host protection against lymphatic filarial parasites, J. Exp. Med. 191 (2000) 731–736.

[9] L.J. Wammes, F. Hamid, A.E. Wiria, H. Wibowo, E. Sartono, R.M. Maizels, H.H. Smits, T. Supali, M. Yazdanbakhsh, Regulatory T cells in human lymphatic filariasis: stronger functional activity in microfilaremics, PLoS Negl. Trop. Dis. 6 (2012) e1655.

[10] S. Babu, T.B. Nutman, Immunology of lymphatic filariasis, Parasite Immunol. 36 (2014) 338–346.

[11] S.N. McNulty, A.S. Mullin, J.A. Vaughan, V.V. Tkach, G.J. Weil, P.U. Fischer, Comparing the mitochondrial genomes of Wolbachia-dependent and independent filarial nematode species, BMC Genomics 13 (2012) 145.

[12] A.N. Perumal, Y.I. Gunawardene, R.S. Dassanayake, Setaria digitata in advancing our knowledge of human lymphatic filariasis, J. Helminthol. 90 (2016) 129–138.

[13] S.K. Panda, S. Kumar, N.C. Tupperwar, T. Vaidya, A. George, S. Rath, V. Bal, B. Ravindran, Chitohexaose activates macrophages by alternate pathway through TLR4 and blocks endotoxemia, PLoS Pathog. 8 (2012) e1002717.

[14] S.K. Panda, V. Facchinetti, E. Voynova, S. Hanabuchi, J.L. Karnell, R.N. Hanna, R. Kolbeck, M.A. Sanjuan, R. Ettinger, Y.J. Liu, Galectin-9 inhibits TLR7-mediated autoimmunity in murine lupus models, J. Clin. Invest. 128 (2018) 1873–1887.

[15] R. Mishra, P.K. Sahoo, S. Mishra, K.G. Achary, B. Dwibedi, S.K. Kar, A.K. Satapathy, Bancroftian filariasis: circulating B-1 cells decreased in microfilaria carriers and correlate with immunoglobulin M levels, Parasite Immunol. 36 (2014) 207–217.

[16] U.F. Prodjinotho, C. von Horn, A.Y. Debrah, L. Batsa Debrah, A. Albers, L.E. Layland, A. Hoerauf, T. Adjobimey, Pathological manifestations in lymphatic filariasis correlate with lack of inhibitory properties of IgG4 antibodies on IgE-activated granulocytes, PLoS Negl. Trop. Dis. 11 (2017) e0005777.

[17] A.F. Cunningham, A. Flores-Langarica, S. Bobat, C.C. Dominguez Medina, C.N. Cook, E.A. Ross, C. Lopez-Macias, I.R. Henderson, B1b cells recognize protective antigens after natural infection and vaccination, Front. Immunol. 5 (2014) 535.

[18] T. Adjobimey, A. Hoerauf, Induction of immunoglobulin G4 in human filariasis: an indicator of immunoregulation, Ann. Trop. Med. Parasitol. 104 (2010) 455–464.

[19] T.H. Dafa'alla, H.W. Ghalib, A. Abdelmageed, J.F. Williams, The profile of IgG and IgG subclasses of onchocerciasis patients, Clin. Exp. Immunol. 88 (1992) 258–263.

[20] K.T. Cuenco, E.A. Ottesen, S.A. Williams, T.B. Nutman, C. Steel, Heritable factors play a major role in determining host responses to Wuchereria bancrofti infection in an isolated South Pacific island population, J. Infect. Dis. 200 (2009) 1271–1278.

[21] A. Kwarteng, S.T. Ahuno, Immunity in filarial infections: lessons from animal models and human studies, Scand. J. Immunol. 85 (2017) 251–257.

[22] T.B. Nutman, V. Kumaraswami, Regulation of the immune response in lymphatic filariasis: perspectives on acute and chronic infection with Wuchereria bancrofti in South India, Parasite Immunol. 23 (2001) 389–399.

[23] S. Babu, C.P. Blauvelt, V. Kumaraswami, T.B. Nutman, Cutting edge: diminished T cell TLR expression and function modulates the immune response in human filarial

infection, J. Immunol. 176 (2006) 3885–3889.
[24] E. Lobos, T.B. Nutman, J.S. Hothersall, S. Moncada, Elevated immunoglobulin E against recombinant Brugia malayi gamma-glutamyl transpeptidase in patients with bancroftian filariasis: association with tropical pulmonary eosinophilia or putative immunity, Infect. Immun. 71 (2003) 747–753.
[25] E. Mitre, T.B. Nutman, IgE memory: persistence of antigen-specific IgE responses years after treatment of human filarial infections, J. Allergy Clin. Immunol. 117 (2006) 939–945.
[26] S.K. Joseph, S.K. Verma, M.K. Sahoo, A. Sharma, M. Srivastava, M.V. Reddy, P.K. Murthy, IgG subclass responses to proinflammatory fraction of Brugia malayi in human filariasis, Indian J. Med. Res. 135 (2012) 650–655.
[27] Y.L. Lont, L.E. Coffeng, S.J. de Vlas, A. Golden, T. de Los Santos, G.J. Domingo, W.A. Stolk, Modelling anti-Ov16 IgG4 antibody prevalence as an indicator for evaluation and decision making in onchocerciasis elimination programmes, PLoS Negl. Trop. Dis. 11 (2017) e0005314.
[28] R. Iskander, P.K. Das, R.C. Aalberse, IgG4 antibodies in Egyptian patients with schistosomiasis, Int. Arch. Allergy Appl. Immunol. 66 (1981) 200–207.
[29] A. Jassim, K. Hassan, D. Catty, Antibody isotypes in human schistosomiasis mansoni, Parasite Immunol. 9 (1987) 627–650.
[30] B. Evengard, L. Hammarstrom, C.I. Smith, S.G. Johansson, E. Linder, Subclass distribution and IgE responses after treatment in human schistosomiasis, Clin. Exp. Immunol. 73 (1988) 383–388.
[31] I. Ljungstrom, L. Hammarstrom, W. Kociecka, C.I. Smith, The sequential appearance of IgG subclasses and IgE during the course of Trichinella spiralis infection, Clin. Exp. Immunol. 74 (1988) 230–235.
[32] E.A. Ottesen, F. Skvaril, S.P. Tripathy, R.W. Poindexter, R. Hussain, Prominence of IgG4 in the IgG antibody response to human filariasis, J. Immunol. 134 (1985) 2707–2712.
[33] M.C. Mohanty, A.K. Satapathy, P.K. Sahoo, B. Ravindran, Human bancroftian filariasis – a role for antibodies to parasite carbohydrates, Clin. Exp. Immunol. 124 (2001) 54–61.
[34] R. Noordin, R.K. Shenoy, R.A. Rahman, Comparison of two IgG4 assay formats (ELISA and rapid dipstick test) for detection of brugian filariasis, Southeast Asian J. Trop. Med. Public Health 34 (2003) 768–770.
[35] C. Jiraamonnimit, S. Wongkamchai, J. Boitano, H. Nochot, S. Loymek, S. Chujun, S. Yodmek, A cohort study on anti-filarial IgG4 and its assessment in good and uncertain MDA-compliant subjects in brugian filariasis endemic areas in southern Thailand, J. Helminthol. 83 (2009) 351–360.
[36] J.P. Akue, T.G. Egwang, E. Devaney, High levels of parasite-specific IgG4 in the absence of microfilaremia in Loa loa infection, Trop. Med. Parasitol. 45 (1994) 246–248.
[37] M. van der Neut Kolfschoten, J. Schuurman, M. Losen, W.K. Bleeker, P. Martinez-Martinez, E. Vermeulen, T.H. den Bleker, L. Wiegman, T. Vink, L.A. Aarden, M.H. De Baets, J.G. van de Winkel, R.C. Aalberse, P.W. Parren, Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange, Science 317 (2007) 1554–1557.
[38] S. Babu, V. Kumaraswami, T.B. Nutman, Alternatively activated and immunoregulatory monocytes in human filarial infections, J. Infect. Dis. 199 (2009) 1827–1837.
[39] R.T. Semnani, M. Law, J. Kubofcik, T.B. Nutman, Filaria-induced immune evasion: suppression by the infective stage of Brugia malayi at the earliest host-parasite interface, J. Immunol. 172 (2004) 6229–6238.
[40] A.K. Panda, B.K. Das, Absence of filarial infection in patients of systemic lupus erythematosus (SLE) in filarial endemic area: a possible protective role, Lupus 23 (2018) 1553–1554.
[41] R. Ettinger, J.L. Karnell, J. Henault, S.K. Panda, J.M. Riggs, R. Kolbeck, M.A. Sanjuan, Pathogenic mechanisms of IgE-mediated inflammation in self-destructive autoimmune responses, Autoimmunity 50 (2017) 25–36.
[42] S.K. Panda, R. Kolbeck, M.A. Sanjuan, Plasmacytoid dendritic cells in autoimmunity, Curr. Opin. Immunol. 44 (2017) 20–25.
[43] A.A. Lin, A.F. Freeman, T.B. Nutman, IL-10 indirectly downregulates IL-4-induced IgE production by human B cells, Immunohorizons 2 (2018) 398–406.
[44] R.C. Aalberse, S.O. Stapel, J. Schuurman, T. Rispens, Immunoglobulin G4: an odd antibody, Clin. Exp. Allergy 39 (2009) 469–477.
[45] J.S. Satoguina, E. Weyand, J. Larbi, A. Hoerauf, T regulatory-1 cells induce IgG4 production by B cells: role of IL-10, J. Immunol. 174 (2005) 4718–4726.