

## Response to: 'Serum complement factor C5a in IgG4-related disease' by Fukui *et al*

We appreciate the interest shown by Dr S Fukui and colleagues<sup>1</sup> in our recent paper, 'How to diagnose IgG4-related disease (IgG4-RD)'.<sup>2</sup>

IgG4-RD is characterised by increased serum IgG4 concentrations and number of IgG4-positive plasma cells in affected lesions.<sup>3</sup> However, its diagnosis can be difficult, because clinical signs vary depending on the organs affected.

A Japanese team established comprehensive diagnostic criteria for IgG4-RD, 2011 focusing on the concentration of serum IgG4 (>135 mg/dL), numbers of IgG4-positive cells (>10 cells/HPF) and ratio of IgG4-positive to IgG-positive cells (>40%) in affected tissues.<sup>4</sup>

However, many cases of IgG4-RD with low levels of IgG4 and mimickers of IgG4-RD with increased serum IgG4 have been reported and the concept of IgG4-RD has become blurred. Therefore, new specific markers or new criteria for IgG4-RD are required.<sup>5</sup>

Human IgG4 has a unique structure distinguished from the other IgG subclasses by lack of interaction with the complement system and inability to activate the classical complement pathway.<sup>6,7</sup> However, hypocomplementaemia has been observed in IgG4-RD ever since the concept was first established<sup>8</sup> and is in particular more frequent and sometimes severe in IgG4-related kidney disease.<sup>9</sup> A recent study showed that non-IgG4 IgG such as IgG1, which can activate complement, might be involved in the activation of complement in IgG4-RD.<sup>10</sup>

Fukui *et al* reported the significant increase of C5a in IgG4-RD and suggested it for a therapeutic target.<sup>1</sup> However, serum C5a elevation is also a very important feature of active systemic lupus erythematosus (SLE). Since elevated C5a levels in IgG4-RD are much lower than in active lupus cases<sup>11</sup> and only some groups of patients with IgG4-RD have hypocomplementaemia, the production of C5a in SLE and IgG4-RD likely exhibits significant differences in both underlying mechanism and pathogenetic role.

Although the details of the pathogenesis of IgG4-RD are unclear at present, recent basic studies have implicated the toll-like receptor (TLR) signalling pathway.<sup>12</sup> Activation of C5aR in macrophages inhibits TLR-4 signals resulting in reduction of IL-12, IL-23 and IL-27 production by inflammatory macrophages.<sup>13</sup> Thus, the role of cross-talk between innate and acquired immunity through the complement pathway and TLR system is attracting attention in the pathogenesis of IgG4-RD.<sup>14</sup>

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### REFERENCES

- 1 Fukui S, Fujita Y, Origuchi T, *et al*. Serum complement factor C5a in IgG<sub>4</sub>-related disease. *Ann Rheum Dis* 2018;**78**:e65.
- 2 Umehara H, Okazaki K, Kawano M, *et al*. How to diagnose IgG4-related disease. *Ann Rheum Dis* 2017;**76**:e46.
- 3 Umehara H, Okazaki K, Masaki Y, *et al*. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. *Mod Rheumatol* 2012;**22**:1–14.
- 4 Umehara H, Okazaki K, Masaki Y, *et al*. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012;**22**:21–30.
- 5 Umehara H, Okazaki K, Nakamura T, *et al*. Current approach to the diagnosis of IgG4-related disease - Combination of comprehensive diagnostic and organ-specific criteria. *Mod Rheumatol* 2017;**27**:381–91.
- 6 Schuurman J, Perdok GJ, Gorter AD, *et al*. The inter-heavy chain disulfide bonds of IgG4 are in equilibrium with intra-chain disulfide bonds. *Mol Immunol* 2001;**38**:1–8.
- 7 van der Neut Kolfschoten M, Schuurman J, Losen M, *et al*. Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. *Science* 2007;**317**:1554–7.
- 8 Masaki Y, Dong L, Kurose N, *et al*. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis* 2009;**68**:1310–5.
- 9 Kawano M, Saeki T, Nakashima H, *et al*. Proposal for diagnostic criteria for IgG4-related kidney disease. *Clin Exp Nephrol* 2011;**15**:615–26.
- 10 Yamada K, Yamamoto M, Saeki T, *et al*. New clues to the nature of immunoglobulin G4-related disease: a retrospective Japanese multicenter study of baseline clinical features of 334 cases. *Arthritis Res Ther* 2017;**19**:262.
- 11 Sakuma Y, Nagai T, Yoshio T, *et al*. Differential activation mechanisms of serum C5a in lupus nephritis and neuropsychiatric systemic lupus erythematosus. *Mod Rheumatol* 2017;**27**:292–7.
- 12 Watanabe T, Yamashita K, Sakurai T, *et al*. Toll-like receptor activation in basophils contributes to the development of IgG4-related disease. *J Gastroenterol* 2013;**48**:247–53.
- 13 Hawlisch H, Belkaid Y, Baelder R, *et al*. C5a negatively regulates toll-like receptor 4-induced immune responses. *Immunity* 2005;**22**:415–26.
- 14 Umehara H, Nakajima A, Nakamura T, *et al*. IgG4-related disease and its pathogenesis-cross-talk between innate and acquired immunity. *Int Immunol* 2014;**26**:585–95.