

Correspondence

Fc-sialylated IgGs in intravenous immunoglobulins are not responsible for induction of regulatory T cells

To the Editor:

High-dose but not low-dose intravenous immunoglobulins (IVIGs) induce potent anti-inflammatory effects that have proven beneficial in the treatment of various inflammatory and autoimmune diseases. Several distinct mechanisms of action have been proposed, including most recently dependence on IgGs terminally sialylated with α 2,6-linked sialic acid on Asp297 in the IgG Fc domain (sIgG) that by binding SIGN-R1 (specific intracellular adhesion molecule-grabbing nonintegrin receptor 1), the murine homolog of DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3 grabbing non-integrin), elicit anti-inflammatory responses.¹ An attractive feature of this mechanism is that it explains the need for high-dose IVIGs for the treatment of autoimmune and inflammatory diseases because sIgGs are present in limited amounts in IVIGs.

We previously reported the novel finding that *low-dose* IVIGs exerted potent anti-inflammatory effects, including induction of regulatory T (Treg) cells and IL-10-secreting ICOS⁺CD4⁺ T cells to protect against herpes simplex virus 1 encephalitis in a mouse model. Importantly, we showed that only the nonsialylated IVIG component of IVIGs induced Treg cells and ICOS⁺CD4⁺ T cells and mediated protection, whereas the sIgG component did not protect or induce Treg cells.² There are several reports that IVIGs augment the expansion and suppressive functions of Treg cells, which were correlated with improved outcomes in autoimmune disease models such as EAE (experimental autoimmune encephalomyelitis) and patients with autoimmune diseases.^{3,4} However, the specific component in IVIGs involved was not identified in these studies. Massoud et al⁵ now report that the sIgG fraction of IVIGs binds the dendritic cell immunoreceptor (DCIR) to induce Treg cells in a mouse model of allergic airways disease, resulting in marked improvement in airway hyper-responsiveness (AHR). However, our article was deliberately not cited in this report presumably because it is contradictory. Likewise, several recent reports contesting the operation of the sIgG anti-inflammatory mechanism in various autoimmune disease models were also not cited likely because this would further detract from the article.^{6,7}

Several methodologic issues detract from the veracity of the conclusions drawn in the article. *Sambucus nigra* agglutinin (SNA)-lectin affinity columns were used to purify sIgGs from IVIGs, which the authors appear to equate with IgGs sialylated on Fc Asp297, ignoring published reports that most of the highly sialylated IgGs obtained by SNA fractionation of IVIGs are sialylated on the Fab⁸; hence, their data do not support a role for Fc-sIgG in Treg-cell induction. The authors assert that sIgG binding to DCIR is responsible for Treg-cell induction and protection

against AHR. However, no data showing specific binding to DCIR expressed on Chinese hamster ovary (CHO) cells are presented. Furthermore, flow cytometry cannot be used to show colocalization or internalization of sIgG and DCIR (Fig 2, E, and Fig 3, B) and, in this regard, it is notable that DCIR is still expressed on the surface of sIgG-treated cells (Fig 2, B, and Fig 3, B), which is inconsistent with the internalization of sIgG-DCIR complexes. Further complicating the interpretation of these data is a recent report that DCIR expressed on CHO cells fails to bind the natural glycan ligands Lewis^b or Man³ because of steric hindrance stemming from the glycosylation of the DCIR carbohydrate recognition domain.⁹ Finally, in the absence of depletion or adoptive transfer experiments,² a role for IVIG-induced Treg cells in protection against AHR remains speculative. Overall, the major conclusions in this article, namely, that sIgGs specifically bind the DCIR expressed on dendritic cells to induce Treg cells that protect against AHR, are not rigorously supported by the data.

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