LETTER

DC-SIGN and α2,6-sialylated IgG Fc interaction is dispensable for the anti-inflammatory activity of IVIg on human dendritic cells

Intravenous immunoglobulin (IVIg) is widely used to treat autoimmune diseases. Several mutually nonexclusive mechanisms are proposed to explain the beneficial effects of IVIg in patients (1, 2). Lately, Ravetch and colleagues (3) demonstrate that anti-inflammatory activity of IVIg is mediated mainly by antibodies that contain terminal α2,6-sialic acid linkages at the Asn297-linked glycan of Fc region.

Anthony et al. (4) recently demonstrate that SIGN-R1, a C-type lectin receptor on mouse splenic macrophages, recognizes and mediates anti-inflammatory effects of sialylated IgG Fc. In addition, the authors report that sialylated IgG Fc proteins also bind to DC-SIGN, the human orthologue of SIGN-R1. However, it is important to note that DC-SIGN and SIGNR1 differ significantly in their cellular and tissue distribution. Because DC-SIGN is expressed specifically on human dendritic cells (DC), we sought to explore whether DC-SIGN and α2,6-sialylated IgG Fc interaction is indispensable for the anti-inflammatory effect of IVIg in the context of human DC.

Interestingly, we found that both intact IVIg and F(ab′)$_2$ fragments of IVIg that lacks the Fc region, and hence lacking terminal α2,6-sialic acid linkages, inhibit TLR-mediated activation of DC as assessed by phosphorylation of ERK1/2 (Fig. 1), an intracellular signaling molecule that mediates inflammatory response of DC upon interaction with TLR agonists. The results suggest that DC-SIGN and α2,6-sialylated IgG Fc interaction is dispensable for the anti-inflammatory activity of IVIg on human DC. In fact, we found that IVIg also targets CD40 on human DC (5). Therefore, caution should be exercised while translating results from murine models to patients.

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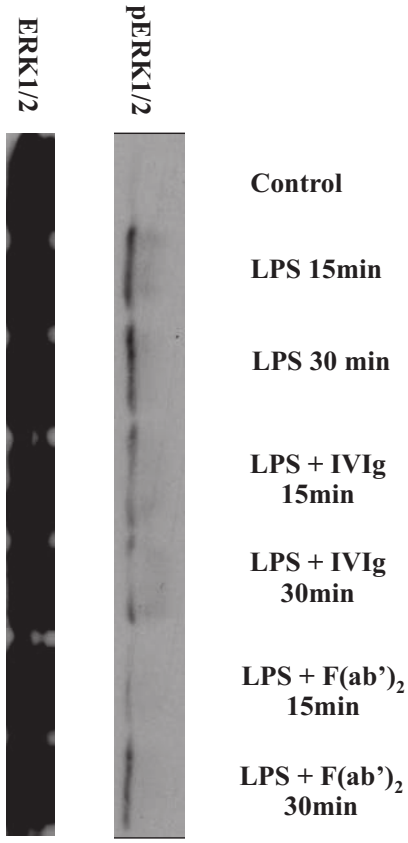

Fig. 1. IVIg and F(ab′)$_2$ fragments of IVIg mediate anti-inflammatory effect on human dendritic cells. Six-day-old monocyte-derived DC were cultured in the presence of 0.15 mM IVIg or F(ab′)$_2$ fragments of IVIg for 12 h. The cells were then exposed to TLR-4 agonist lipopolysaccharide (1 μg) for 15 and 30 min. The activation of ERK1/2 was monitored by immunoblotting with antibody to phospho-ERK1/2 (*Right*). An equal amount of protein loaded in each lane was confirmed with immunoblotting by using antibody to the nonphosphorylated form of ERK1/2 (*Left*).

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