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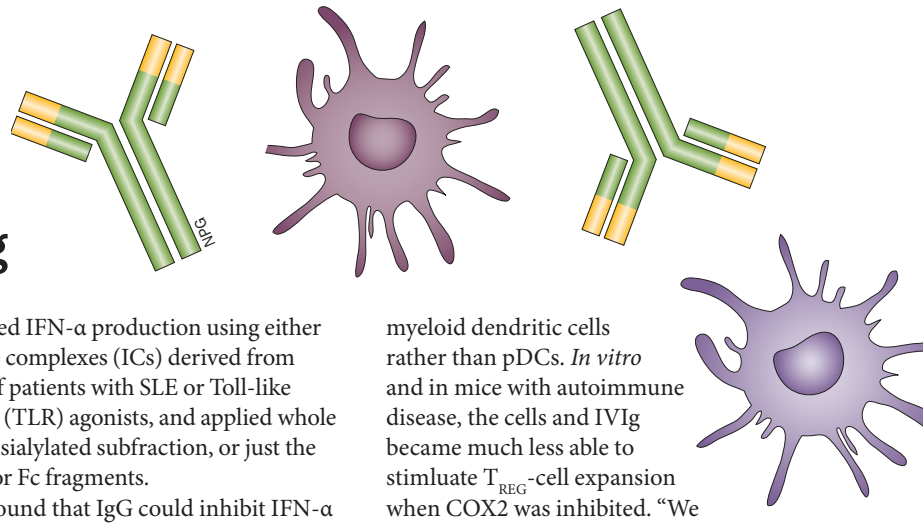

THERAPY

New mechanisms of IVIg

Two studies revealing mechanisms by which intravenous immunoglobulin (IVIg) therapy modulates dendritic-cell functions suggest that improved understanding and application of this therapy could increase its efficacy. "These reports are two breakthroughs that advocate harnessing IVIg in the era of biological therapies for autoimmune rheumatic diseases," enthuses Yehuda Shoenfeld, head of the Zabludowicz Center for Autoimmune Diseases, Israel, who was not involved in the work.

IVIg preparations contain mostly IgG, from numerous donors, and are used off label in several rheumatic diseases, including systemic lupus erythematosus (SLE). Evidence of optimum regimens and precisely how the treatment works is, however, lacking. Jagadeesh Bayry, Srini Kaveri and colleagues chose to probe how IVIg can cause expansion of regulatory T (T_{REG}) cells, whereas Keith Elkon and co-workers were intrigued by its effect on IFN-α production and the potential role of sialylation. Both groups identified mechanisms involving prostaglandin E2 (PGE2).

In human peripheral blood mononuclear cells and isolated plasmacytoid dendritic cells (pDCs), Elkon and colleagues stimulated IFN-α production using either immune complexes (ICs) derived from serum of patients with SLE or Toll-like receptor (TLR) agonists, and applied whole IgG, the sialylated subfraction, or just the F(ab')2 or Fc fragments.

"We found that IgG could inhibit IFN-α by two mechanisms," reports Elkon. "First, Fc fragments, regardless of their sialylation status, blocked the binding of ICs to the Fcγ receptor on pDCs, thereby inhibiting IC internalization and IFN-α stimulation." The effect of such blockage on uptake of ICs was known, but monomeric IgG had not previously been shown to achieve it. The second mechanism applied to TLR-induced IFN-α production, which circumvents Fc receptors. "We found that F(ab')2 fragments of IgG could inhibit this response," continues Elkon. "Surprisingly, it was the sialylated subset that was the more potent inhibitor." Furthermore, the investigators identified IgG-mediated stimulation of PGE2 production by monocytes (a mediator known to suppress IFN-α production by pDCs) as the mode of inhibition.

Bayry and colleagues also identified PGE2 production, by cyclo-oxygenase 2 (COX2), as a suppressive mechanism induced by IgG, but in antigen-presenting myeloid dendritic cells rather than pDCs. *In vitro* and in mice with autoimmune disease, the cells and IVIg became much less able to stimluate T_{REG}-cell expansion when COX2 was inhibited. "We observed that IVIg-mediated COX2 induction and T_{REG} expansion are F(ab')2-dependent," notes Bayry, whose group also identified a role for IVIg engagement of the receptor DC-SIGN.

Both groups are eager to probe the clinical relevance of their data. "IVIg may be a useful therapy for patients in which IFN-I or pDCs are implicated," says Elkon, adding that the PGE2 pathway could be a target in SLE. Serum PGE2 level might also be a biomarker for response to IVIg therapy, suggests Bayry.

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Original articles Wiedeman, A. E. *et al.* Contrasting mechanisms of interferon-α inhibition by intravenous immunoglobulin after induction by immune complexes versus Toll-like receptor agonists. *Arthritis Rheum.* doi:10.1002/art.38082 | Trinath, J. *et al.* Intravenous immunoglobulin expands regulatory T cells via induction of cyclooxygenase-2-dependent prostaglandin E2 in human dendritic cells. *Blood* doi:10.1182/blood-2012-11-468264