THERAPY

TLR signaling interferes with the therapeutic activity of steroids in SLE

Patients with systemic lupus erythematosus (SLE) often require pulsed intravenous glucocorticoid therapy if oral glucocorticoids fail to control their disease. Why are doses of steroids that successfully control disease activity in other inflammatory conditions not effective in SLE? Research published in *Nature* indicates that persistent signaling downstream of Toll-like receptor (TLR)-7 and TLR9 in plasmacytoid dentritic cells (pDCs) might explain why glucocorticoids are less effective in this disease, a finding that could lead to a new steroid-sparing approach to SLE therapy.

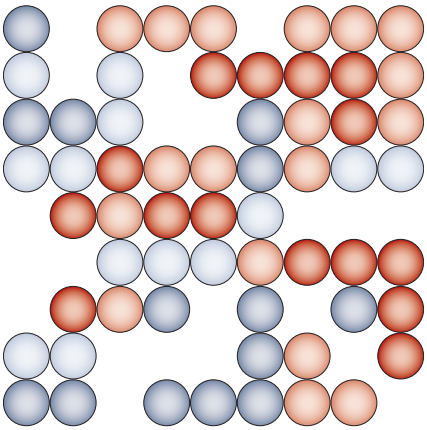
Key to the pathogenesis of SLE is the recognition of self nucleic acids by pDCs and B cells via TLR7 and TLR9, which leads to the generation of antinuclear antibodies, increased production of interferons (IFNs) and increased expression of IFN-regulated genes, the levels of which correlate directly with disease severity.

In this paper, scientists at Dynavax Technologies Corporation and the Baylor Institute for Immunology Research investigated the response of patients with SLE and healthy controls to glucocorticoid therapy, in terms of IFN response and effects on pDCs. Oral glucocorticoids (5–20 mg/day) failed to normalize the IFN signature in patients with SLE, or to reduce the levels of IFN-α produced by pDCs *in vitro* upon stimulation with TLR7 or TLR9 ligands including immune complexes from SLE patients. However, the addition of IRS (immunoregulatory sequence, a bifunctional TLR7 and TLR9 inhibitor developed by the team at Dynavax) to the steroids led to reduced levels of IFN-α production by pDCs. Pulsed intravenous glucocorticoids resulted in normalization of the IFN signature and a reduced number of pDCs in patients with SLE.

Given the key role for TLR7 and TLR9 in promoting the IFN pathway in SLE, and the inability of glucocorticoids to affect signaling by these two receptors, the authors concluded that "chronic activation of pDCs through TLR7 and TLR9 might account for the reduced ability of glucocorticoids to inhibit the IFN pathway in SLE patients," says Franck J. Barrat, a lead author on this paper.

To further investigate the signaling pathways involved, the researchers performed an analysis of the response of pDCs to steroids *in vitro*. Activation of TLR7 or TLR9 signaling protected pDCs (isolated from healthy controls) against glucocorticoid-induced cell death. Addition of IRS, which blocks TLR7 and TLR9 signaling, reversed this effect, resensitizing these cells to glucocorticoid-induced cell death.

The authors then studied the actions of glucocorticoids on pDCs in mouse models of lupus. pDCs from normal mice were considerably more sensitive to glucocorticoid-induced cell death than pDCs from lupus-prone mice.



Induction of TLR9 signaling (by a CpG-containing immunostimulatory sequence) provided pDCs from normal mice with some protection against cell death, and, conversely, addition of IRS increased the sensitivity of pDCs from lupus-prone mice to glucocorticoid-induced cell death.

"Our findings demonstrate that self nucleic acid recognition by TLRs is not only responsible for promoting the high IFN response in patients with SLE, but that this can also hamper the therapeutic activity of glucocorticoids in these patients," continues Barrat. "This obviously suggests that inhibitors of TLR7 and TLR9 signaling could prove to be effective corticosteroid-sparing drugs."

Jenny Buckland

Original article Guiducci, C. *et al.* TLR recognition of self nucleic acid hampers glucocorticoid activity in lupus. *Nature* **465**, 937–941 (2010)
Further reading Gilliet, M. *et al.* Plasmacytoid dendritic cells: sensing nucleic acids in viral infection and autimmune disease. *Nat. Rev. Immunol.* **8**, 594–606 (2008)

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