Nature Reviews Rheumatology | Published online 7 Jul 2016; doi:10.1038/nrrheum.2016.116

LUPUS NEPHRITIS

NRF2, a novel target in steroid-refractory LN?

> DMF, an NRF2 activator … suppressed renal disease in mice with pristane-induced LN

Activation of NRF2 (nuclear factor erythroid 2-related factor 2) has organ-protective effects in mice with pristane-induced lupus nephritis (LN), and might be especially useful to treat glucocorticoid-resistant LN, according to new work by Shin Ebihara and colleagues. "NRF2 activators showed stronger effects than glucocorticoids in the kidney *in vitro* and *in vivo*," points out Ebihara, the study's corresponding author.

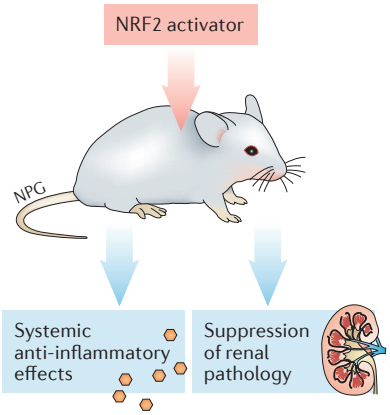
Although glucocorticoids reduced autoantibody production in mice with pristane-induced LN, their renal pathology (which strongly resembles human lupus glomerulonephritis) did not improve, suggesting that LN in this model is glucocorticoid-resistant. "It is very important for therapy against LN to directly prevent the kidney disease and not necessarily to inhibit the autoantibody production," Ebihara explains.

The researchers found that TNF-stimulated healthy human renal mesangial cells are similarly resistant to the anti-inflammatory effects of glucocorticoids; this resistance was associated with increased expression of the glucocorticoid receptor β-isoform, which acts as a dominant-negative inhibitor of the α-isoform.

Dimethyl fumarate (DMF) is an NRF2 activator approved to treat multiple sclerosis and psoriasis. Ebihara's team showed that DMF not only suppressed renal disease in mice with pristane-induced LN, but also attenuated production of inflammatory cytokines in TNF-stimulated healthy human renal mesangial cells. Of note, *NRF2* polymorphisms confer an increased risk of LN in humans, and previous preclinical studies have reported beneficial effects of targeting NRF2 in other mouse models. "NRF2 activators also suppress renal disease in spontaneous lupus models, such as NZB/W F1 or MRL/lpr mice, which are strongly glucocorticoid-sensitive," notes Ebihara.

His team is now planning further translational studies in collaboration with clinicians. "We would like to evaluate the effect of NRF2 activators on the development of glucocorticoid-resistant diseases, for example focal segmental glomerulosclerosis and steroid-resistant nephrotic syndrome," Ebihara says.

Caroline Barranco



ORIGINAL ARTICLE Ebihara, S. *et al.* Nuclear factor erythroid 2-related factor 2 is a critical target for the treatment of glucocorticoid-resistant lupus nephritis. *Arthritis Res. Ther.* **18**, 139 (2016)