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LUPUS NEPHRITIS

Targeting Bcl-2 prevents nephritis in mice

> ABT-199 produced dose-dependent protective effects on the kidneys

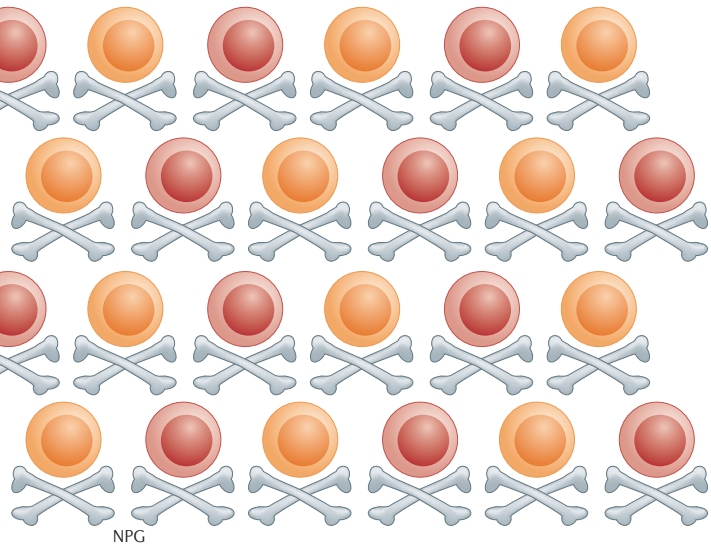
Inhibition of the anti-apoptotic factor Bcl-2 by a selective oral inhibitor, ABT-199, prevents the development of tubulointerstitial inflammation (TII) in lupus-prone mice, according to a study published in *Arthritis & Rheumatology*. Kichul Ko and colleagues found that inhibition of Bcl-2 was also able to prolong survival and prevent proteinuria in the mice, suggesting Bcl-2 is an attractive therapeutic target.

Failure to regulate apoptosis in the lymphocytes of patients with systemic lupus erythematosus (SLE) leads to the survival of autoreactive immune cells that contribute to SLE-related complications such as lupus nephritis. By examining tissue from the kidneys of patients with lupus nephritis, Ko and colleagues discovered that kidney-infiltrating B cells and T cells expressed high levels of Bcl-2 in comparison to activated lymphocytes from the germinal centres of healthy secondary lymphoid tissues.

The researchers used a new high-throughput technique called automated cell phenotyping (ACP) to assess Bcl-2 expression in the cells of kidney tissue slices viewed by confocal laser scanning multicolour microscopy. "This technique was adopted as it is difficult to assess the frequency of specific cells expressing particular cytosolic or surface markers in human tissue," says Ko. ACP showed that Bcl-2 was expressed by both B cells and T cells, and that these Bcl-2-expressing lymphocytes were found predominantly in the tubulointerstitial space, and at a lower frequency the glomerulus; these findings were then verified at the mRNA level by laser-capture microdissection and qPCR.

Next, the researchers turned to the *NZB/W* F_1 mouse model of lupus, where they found a similar pattern of Bcl-2 expression in B-cell and T-cell infiltrates in the tubulointerstitial space of the kidneys. Treating these mice with ABT-199 produced dose-dependent protective effects on the kidneys, markedly reducing TII, but having less of an effect on glomerular nephritis. These results were similar to those obtained by treatment with mycophenolate mofetil, a therapy currently in use for patients with SLE. "ABT-199 has been shown to be well tolerated in a phase 1 trial in SLE," says Ko, adding, "additional studies will be needed to see whether Bcl-2 inhibition will improve renal survival in patients with lupus nephritis."

Joanna Collison



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ORIGINAL ARTICLE Ko, K. *et al.* BCL-2 as a therapeutic target in human tubulointerstitial inflammation. *Arthritis Rheumatol.* http://dx.doi.org/10.1002/art.39744 (2016)