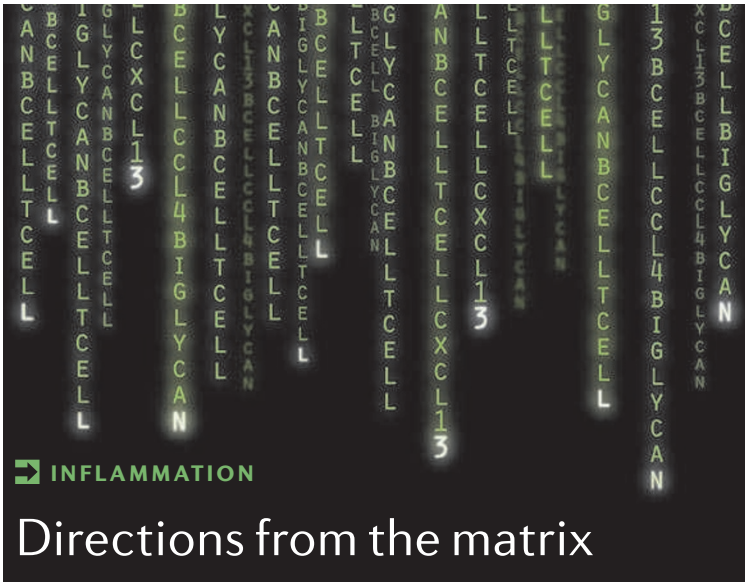

INFLAMMATION

Directions from the matrix

Emerging evidence reveals that components of the extracellular matrix can directly regulate inflammatory processes. Now, researchers have identified a role for the matrix component biglycan in the pathogenesis of lupus nephritis through its ability to induce expression of the B cell chemoattractant CXC-chemokine ligand 13 (CXCL13).

Biglycan, which exists in the extracellular matrix and as a soluble molecule, has previously been shown to act as an endogenous danger signal by activating Toll-like receptor 2 (TLR2), TLR4 and the NLRP3 (NOD-, LRR- and pyrin domain-containing 3) inflammasome. This activity led the authors to investigate whether biglycan is involved in renal inflammation associated with systemic lupus erythematosus (SLE). They first observed that biglycan levels are increased in the plasma and kidneys from patients with lupus nephritis, as well as from MRL–*lpr* mice and NZB/W F1 mice (mouse models of SLE). Moreover, plasma biglycan levels in MRL–*lpr* mice increased progressively over time, coinciding with the initiation and progression of disease.

In keeping with a role for biglycan in the pathogenesis of lupus nephritis, biglycan-deficient MRL–*lpr* mice did not develop the enlarged kidneys, high albuminuria and high serum immunoglobulin levels that occurred in wild-type MRL–*lpr* mice with disease. Furthermore, transient overexpression of soluble human biglycan increased albuminuria and worsened renal pathology in MRL–*lpr* mice owing to a large influx of mononuclear cells, including macrophages and T cells. This increase in immune cell infiltration was associated with higher renal and plasma levels of the macrophage and T cell chemoattractants CC-chemokine ligand 2 (CCL2), CCL5 and CCL3. Greater numbers of B cells, mainly B-1 cell populations, also infiltrated the kidneys of mice that overexpressed biglycan compared with the numbers in control mice. Finally, biglycan was also found to promote the production of active caspase 1 and mature interleukin-1β (products of NLRP3 inflammasome activation) in diseased MRL–*lpr* mice.

Of particular interest to the authors was the finding that CXCL13 levels were increased in diseased mice and reduced in biglycan-deficient MRL–*lpr* mice. CXCL13 recruits B cells that express CXC-chemokine receptor 5 and has previously been described as a marker of disease activity in SLE. Importantly, *in vitro* incubation of peritoneal macrophages and splenic dendritic cells from wild-type mice with biglycan triggered CXCL13 production, and this was shown to depend on their expression of TLR2 and TLR4 and not on activation of the inflammasome. Finally, *in vivo* experiments using mice deficient in TLR2, TLR4 or both TLRs confirmed that biglycan acts through these TLRs to induce the production of pro-inflammatory mediators and CXCL13, which drive the infiltration of immune cells into the kidneys.

These data identify a new biglycan-mediated mechanism of immune regulation, one that could be involved in other B cell-mediated renal diseases, as suggested by the observation that biglycan and CXCL13 levels are increased in plasma and renal biopsies from patients with acute renal allograft rejection.

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ORIGINAL RESEARCH PAPER Moreth, K. *et al.* The proteoglycan biglycan regulates expression of the B cell chemoattractant CXCL13 and aggravates murine lupus nephritis. *J. Clin. Invest.* **120**, 4251–4272 (2010)