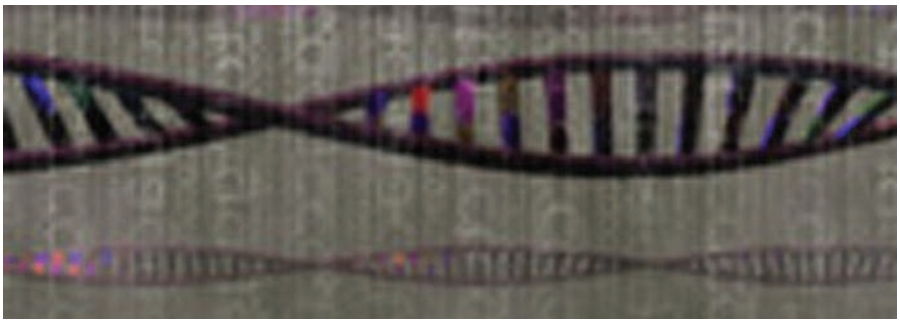
GENETICS

Do kallikrein genes protect against lupus nephritis?



In models of systemic lupus erythematosus (SLE), susceptibility to renal disease varies widely between strains of inbred mice. The underlying mechanism for this variability was previously unknown, but a recent study comparing nephritis-susceptible and nephritis-resistant strains implicates kallikrein genes as both protective agents and genetic determinants of renal disease.

Liu *et al.* used DNA microarrays to examine the renal cortex RNA from three strains of mice sensitive to anti-glomerular antibody-induced nephritis (AIGN) and two control strains. A subset of 50 genes were consistently differentially expressed between the disease-sensitive and control strains, which seemed to confirm the hypothesis that strain differences arise from renal-intrinsic differences.

"Interestingly," says Chandra Mohan, one of the senior authors of the study, "the nephritis-susceptible strains had reduced expression of a family of molecules called kallikreins in their kidneys." The kallikrein complex is located on a section of chromosome 7 associated with susceptibility to spontaneous lupus nephritis. Remarkably, 10 of the 50 genes downregulated in the kidneys of disease-susceptible mice belong to the kallikrein family.

Sequencing of five of the most differentially expressed genes revealed polymorphisms that reliably differentiated the disease-susceptible and disease-resistant mouse strains. However, the functional relevance of these polymorphisms remains unclear, and warrants further study.

Of note, genotyping of patients with lupus nephritis and healthy controls revealed differences in kallikrein gene sequences between the two groups. Studies comparing genotype data from several cohorts of healthy controls and patients with SLE and lupus nephritis suggested an association between kallikrein genes and human disease.

Are genetic differences responsible for the increased disease severity observed in nephritis-susceptible AIGN mice? In control mice, the investigators found a positive correlation between the upregulation of kallikrein genes in the kidneys and urine and reduced disease severity upon antibody challenge. Furthermore, the administration of drugs that increase activity in the kallikrein pathway ameliorated renal disease, whereas antagonists of this pathway induced worsening of nephritis. Together, the results suggest that kallikrein genes have a protective role.

"In total, these studies indicate that kallikreins may have an important role in lupus nephritis, both as protective agents and genetic determinants," says Mohan. "Researchers now have to ascertain whether these findings can be of clinical value in lupus nephritis." Differential expression of kallikrein gene polymorphisms or urinary kallikrein levels could prove to be useful markers of diagnosis or disease activity. In addition, new therapies could aim to elevate local levels of kallikreins in the kidneys.

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Original article Liu, K. *et al.* Kallikrein genes are associated with lupus and glomerular basement membrane-specific antibody-induced nephritis in mice and humans. *J. Clin. Invest.* **119**, 911–923 (2009).