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# Is negative regulation by CD45 involved in lupus?

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## Keywords

Autoimmunity, CD45, lupus, lymphocytes

# Context

CD45 is a receptor-like transmembrane protein tyrosine phosphatase (RPTP) expressed on all nucleated hematopoietic cells that is required for signal transduction. In particular, CD45 has been shown to be an important proximal antigen receptor signalling molecule for optimal effector responses in T and B cells, as well as for lymphocyte development. Naive T cells predominantly express $CD45RA^{+}$ isoforms and switch to the expression of CD45R0 upon activation. Most recently, the effects of dimerization of the intracytoplasmic domain of CD45 have suggested that CD45 is negatively regulated by dimerization. The biological relevance of this effect *in vivo*, however, is not known.

# Significant findings

This study reports on the phenotype of C57BL/6 mice with a single point mutation, glutamate 613 to arginine, termed CD45 E613R, which inactivates the inhibitory wedge of CD45. T and B lymphocyte development in CD45 E613R mice appeared to proceed normally (normal CD4/CD8 profile of thymocytes and IgM/IgD splenocytes), with no increase in the numbers of activated lymphocytes, based on the expression of CD69 in 4-week-old mutant mice. Older mutant mice developed progressive lymphadenopathy and splenomegaly, in contrast to young mutant mice and wild-type mice. Both T and B cells in lymph nodes were activated, as shown by the frequency of $CD69^{+}$ cells without evidence of clonal expansions (analyzed by V? TCR and V?). No increase in CD25/CTLA4 T cells was found. RNAse protection assays revealed raised levels of interleukin-10 and interferon-? transcripts in CD45 E613R mice only. Strikingly, homozygous mutant mice produced 35-fold elevated serum IgA but no total IgG or IgM. Most notably, these CD45 E613R mice developed interstitial nephritis and glomerulonephritis with proteinuria in association with the production of anti-dsDNA autoantibodies (25% heterozygous, 63% homozygous), symptoms seen in human lupus. Homozygous mice, and to a lesser degree heterozygous mice, died prematurely when compared to wild-type littermates.

# Comments

This study extends our knowledge of the effects of inhibiting CD45 dimerization as a result of manipulating the symmetrical interactions of the structural wedge. Since previous studies demonstrated that CD45 deficiency of T and B cells led to severely impaired immune responses, it appears that CD45 is involved not only in early activation but also in deactivation of immune responses to an extent that has not been fully appreciated. Whereas the CD45 E613R mutation appears to have no effect on T and B lymphocyte development, it causes a severe autoimmune syndrome similar to lupus. Whether these findings are relevant to the pathogenesis of lupus (interstitial nephritis is less pronounced, while glomerulonephritis predominates) or lymphoproliferative syndromes in man remains to be determined.

# Methods

CD45 dimerization assay, CD45 E613R mutant mice, RNAse protection assay

## References

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