Role of complement C4 in maintenance of B cell tolerance

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Abstract

Deficiency of early complement components can predispose individuals to lupus, a condition where balance between tolerance and autoimmunity is disrupted. Humoral autoimmunity is a hallmark of lupus and we use an Ig-transgenic mouse strain engineered to produce anti-self B-cells, termed 564Igi, to be able to dissect factors that allow self-reactive B cells to escape negative selection and become activated to produce autoantibodies. We find that most anti-self B-cells in 564Igi mice are deleted before reaching maturity and those that do enter the mature pool are anergic (non-responsive). Introduction of complement C4 deficiency in these mice, however, led to malfunction of a peripheral checkpoint in B-cell development, with greater frequency of anti-self B cells reaching maturity. These mature, anti-self B-cells were not anergic and formed germinal centers in higher propensity. Using mixed bone marrow chimeras, we found that the B-cell developmental errors observed in $C4^{-/-}$564Igi mice could be largely attributed to a dysfunctional myeloid compartment. Our current model holds that poor clearance and high load of apoptotic debris in $C4^{-/-}$564Igi mice chronically activates myeloid cells to release cytokines, like IFNα, in excess and reduce the stringency on anti-self B-cell maturation. Indeed, blocking IFNα action readily established negative selection in these mice.