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B CELL RESPONSES

Born to be (a bit) wild

> expression of FcγRIIb by activated B cells regulates germinal centre responses and can protect against the development of autoimmunity

Polymorphisms in the inhibitory Fc receptor FcγRIIb have been associated with the development of autoimmunity in both humans and mice. By engineering laboratory mice to express an *Fcgr2b* gene promoter that is most commonly associated with wild mice, Ken Smith and colleagues provide fresh insight into the immune functions of FcγRIIb. They show that the *Fcgr2b* promoter from wild mice prevents the upregulation of FcγRIIb expression in activated B cells. This leads to increased bystander activation of germinal centre B cells and predisposes these animals to the development of autoimmune disease.

Inbred mice can be divided into three distinct haplotypes based on genetic variation in the regulatory regions of *Fcgr2b*. Assessing *Fcgr2b* haplotypes in outbred mouse populations, the authors found that most wild mice carry haplotype I, which is characterized by two deletions in the promoter region of *Fcgr2b* and a deletion in intron 3. This haplotype is also carried by many autoimmune-prone laboratory mouse strains. By contrast, most commonly used laboratory strains, such as BALB/c and C57BL/6, do not carry deletions in the regulatory regions of *Fcgr2b*.

Neil Smith/NPG

To examine the functional relevance of these genetic variations, the authors generated 'knock-in' C57BL/6 mice (termed FcγRIIb$^{wild/H1}$ mice) that possessed the promoter and first three introns from a haplotype I mouse. Naive B cells from FcγRIIb$^{wild/H1}$ mice expressed similar levels of FcγRIIb to control B cells from C57BL/6 mice. However, when both mouse strains were immunized with the haptenated protein NP-KLH, only germinal centre B cells from C57BL/6 mice upregulated FcγRIIb expression. Using algorithm-based analyses, the authors identified a putative binding site for AP1 transcription factors in the promoter region of *Fcgr2b* in C57BL/6 mice that was not present in *Fcgr2b* haplotype I. Consistent with this, AP1 bound to the *Fcgr2b* promoter in activated B cells from C57BL/6 mice, but not in B cells from FcγRIIb$^{wild/H1}$ mice. Thus the genetic variations found in *Fcgr2b* haplotype I prevent B cells from upregulating FcγRIIb in response to AP1-activating stimuli.

The failure to upregulate FcγRIIb following activation led to an increase in the overall size of the germinal centre B cell pool in immunized FcγRIIb$^{wild/H1}$ mice. This appeared to be a result of enhanced signalling and survival in germinal centre B cells. The NP-specific antibodies produced by immunized FcγRIIb$^{wild/H1}$ mice were also of a higher affinity than those found in control mice. However, the overall number of NP-specific B cells in the germinal centre was not increased in FcγRIIb$^{wild/H1}$ mice, suggesting that FcγRIIb may be important for regulating bystander B cell responses in the germinal centre. In support of this, FcγRIIb$^{wild/H1}$ mice produced more autoantibodies specific for chromatin and double-stranded DNA following immunization than control mice, and showed spontaneous autoantibody production and increased deposition of immune complexes in the kidneys. Furthermore, in a model of collagen-induced arthritis, FcγRIIb$^{wild/H1}$ mice showed earlier disease onset and increased disease severity compared with control C57BL/6 mice.

These data show that the expression of FcγRIIb by activated B cells regulates germinal centre responses and can protect against the development of autoimmunity. It will be interesting to see what further insights into the immune system can be gained from studying wild mouse populations.

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ORIGINAL RESEARCH PAPER Espéli, M. *et al.* Analysis of a wild mouse promoter variant reveals a novel role for FcγRIIb in the control of the germinal centre and autoimmunity. *J. Exp. Med.* 29 Oct 2012 (doi:10.1084/jem.20121752)

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