B CELL RESPONSES

Regulating receptor editing

> …NF-κB … does seem to have a role in preventing the development of self-reactive B cells by modulating receptor editing.

PHOTOALTO

When the B cell receptor (BCR) on an immature B cell recognizes self antigen, receptor editing occurs during which immunoglobulin light chain rearrangements continue in order to change the BCR specificity. Previous studies addressing the role of nuclear factor-κB (NF-κB) in B cell development have yielded conflicting results. Now, the results of a study by Cadera *et al.* point to a possible role for NF-κB in receptor editing.

The authors took advantage of the fact that NF-κB directly regulates the activity of inhibitor of NF-κBα (IκBα). So, they looked at the activity of NF-κB using a targeted mutant mouse in which β-galactosidase (β-gal) expression reports the activity of IκBα ($I\kappa B\alpha^{+/lacZ}$ mouse). Having first confirmed that known activators of NF-κB also induced β-gal expression, the authors looked at β-gal expression during B cell development from bone marrow cells. Stage-specific β-gal expression was observed, with a peak of expression in pre-B cells. Using real-time reverse transcription PCR to quantify various light chain locus transcripts, they found that $\beta\text{-gal}^+$ pre-B cells had increased light chain replacement or editing gene rearrangements compared with $\beta\text{-gal}^-$ pre-B cells. Furthermore, retroviral infection of an IκBα super-repressor (which inhibits the activation of NF-κB through the classical pathway) in primary bone marrow cell cultures resulted in diminished immunoglobulin light λ-chain (Igλ) rearrangements and reduced Igκ accessibility, suggesting that inhibiting NF-κB can downregulate immunoglobulin light chain gene rearrangement. Various markers of receptor editing, including recombining sequence gene rearrangements (which are considered a hallmark of receptor editing) and secondary Igκ gene rearrangements, were observed in $\beta\text{-gal}^+$ pre-B cells and not $\beta\text{-gal}^-$ pre-B cells, showing that IκBα expression correlates with receptor editing.

To confirm that NF-κB has a role in receptor editing, $I\kappa B\alpha^{+/lacZ}$ mice were crossed with various BCR knock-in mice to generate mice expressing either a self-specific BCR or an innocuous BCR. In the two mouse lines expressing a self-specific BCR, in which the developing B cells are almost all undergoing receptor editing, most of the B cells expressed IκBα, as measured by β-gal expression. By contrast, most of the B cells from the mice expressing an innocuous BCR, in which receptor editing was not needed, did not express the β-gal reporter gene.

So, how might NF-κB mediate the regulation of receptor editing? Transcripts of many NF-κB target genes were quantified using reverse transcription PCR. This showed a fourfold increase in interferon-regulatory factor 4 (IRF4) transcripts in $\beta\text{-gal}^+$ pre-B cells compared with $\beta\text{-gal}^-$ pre-B cells. This implies that NF-κB could be acting through IRF4, which has previously been shown to have a role in pre-B cell development and receptor editing.

This study shows that although NF-κB may not have an essential role in B cell development *per se*, it does seem to have a role in preventing the development of self-reactive B cells by modulating receptor editing.

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ORIGINAL RESEARCH PAPER Cadera, E. J. *et al.* NF-κB activity marks cells engaged in receptor editing. *J. Exp. Med.* 6 Jul 2009 (doi:10.1084/jem.20082815)