Receptor Editing as a Mechanism of B Cell Tolerance
Selvakumar Sukumar and Mark S. Schlissel

J Immunol 2011; 186:1301-1302; doi: 10.4049/jimmunol.1090129
http://www.jimmunol.org/content/186/3/1301

References
This article cites 31 articles, 17 of which you can access for free at:
http://www.jimmunol.org/content/186/3/1301.full#ref-list-1

Subscription
Information about subscribing to The Journal of Immunology is online at:
http://jimmunol.org/subscription

Permissions
Submit copyright permission requests at:
http://www.aai.org/About/Publications/JI/copyright.html

Email Alerts
Receive free email-alerts when new articles cite this article. Sign up at:
http://jimmunol.org/alerts
Receptor Editing as a Mechanism of B Cell Tolerance
Selvakumar Sukumar and Mark S. Schlissel

Acquired immunity relies upon a prolific but non-discriminating mechanism to generate an Ag receptor repertoire of innumerable specificities with the investment of a minimal amount of the genome’s coding capacity. This strategy, however, requires a mechanism to address the generation of lymphocytes whose Ag receptors recognize self molecules. For this reason, the adaptive immune system has evolved several checkpoints to purge the immune repertoire of elements that react toward self, collectively referred to as immune tolerance (1, 2). The genes that encode the H and L chains of the BCR or its secreted counterpart, the Ab molecule, are assembled in developing B lymphocytes by rearranging individual gene segments through a process termed V(D)J recombination (3). A vast number of B cells specific for self Ags are indeed generated by this process and are eventually removed from the pool of mature cells by mechanisms that act either during the development of B cells in the bone marrow (central tolerance) or after they enter the circulation and secondary lymphoid tissues (peripheral tolerance). The two Pillars of Immunology articles highlighted in this issue from the Nemazee and Weigert laboratories report the discovery of a novel mechanism of B cell self tolerance, termed “receptor editing,” that purges self-reactive receptors from the B cell repertoire and replaces them with innocuous receptors (4, 5).

Goodnow, Basten, and coworkers (6, 7) published the first genetically manipulated model of B cell tolerance, using transgenes encoding an anti-hen egg lysozyme Ab and either soluble or membrane-associated hen egg lysozyme. This work established that self-specific B cells can be tolerated upon exposure to a self Ag either by elimination of these cells (clonal deletion) or by rendering them functionally nonresponsive (clonal anergy) (8). These authors failed to detect what is perhaps the most important mechanism of B cell tolerance, however, receptor editing.

The Nemazee and Weigert groups discovered receptor editing independently through the analysis of elegant but distinct transgenic models of B cell tolerance. Nemazee’s group generated a transgenic mouse in which the B cells express H and L chain genes encoding an anti–H-2Kko or β Ab. As expected, when they bred these mice with mice expressing either the H-2k or the H-2b MHC haplotype, most, if not all, idiotype-positive B cells were absent from the periphery. Surprisingly, a significant number of idiotype-positive cells were present in the bone marrow, however. They observed that idiotype-positive (and thus slgM⁺) cells in the bone marrow continued to express high levels of the V(D)J recombinase and displayed ongoing κ and λ rearrangement. As a consequence, significantly higher numbers of λ⁺ cells were present in the periphery than when the same transgenic mouse was analyzed on an H-2d (nonselecting) background. None of these findings were present in mice in which H-2k expression was restricted to peripheral tissues, prompting the authors to infer that developing B cells with self-reactive BCRs that encounter their cognate self Ags were inactivating their κ-chains by secondary rearrangements and generating λ L chains de novo to replace them, such that the BCRs were no longer self reactive.

The Weigert laboratory had reported previously on their own very successful model to study the suppression of self-reactive Abs. These investigators introduced by transgenesis recombined H (μ) and L (κ) chain genes that encoded an anti-dsDNA Ab of the type observed in systemic autoimmune diseases such as lupus. Gay et al. reported that these self-reactive B cells continued to productively rearrange endogenous κ or λ L chains in the presence of the functional transgenic κ L chain. B cells that successfully paired an endogenously rearranged L chain with the transgenic H chain and lost their specificity for dsDNA were spared from deletion. These papers established that by continued expression of the recombinase and rearrangement of other L chain alleles, self-reactive B cells were able to edit their receptor specificities and escape clonal deletion.

In hindsight, a number of clues pointing to the existence of an editing mechanism were present at the time these key papers were published. The Selsing and Leder laboratories had observed that Vκ gene segments in λ⁺ B cells had often recombined with a downstream recombination element, deleting the Cκ region in a process termed RS recombination. They hypothesized that the κ locus had attempted to recombine in λ⁺ B cells and that any resultant κ-chain, productive or otherwise, had been actively deleted (9–11). In addition, the Yamagishi laboratory had reported that circulating DNA excised from the κ locus owing to deletional recombination contained pre-existing κ rearrangements that were sometimes in-frame and thus capable of coding for a functional κ-chain (12). These results were puzzling at the time, as they conflicted with the previously established notion that expression of a complete Ig results in permanent inactivation of the recombinase machinery, leading to allelic exclusion (13, 14). The Nemazee and Weigert papers showed, heretically, for the first time that ongoing gene rearrangement can edit a self-reactive BCR and...
change its specificity, thus rescuing these cells from clonal deletion. Nemazee and colleagues intelligently argued that this receptor selection, as opposed to clonal selection, may be an important mechanism in maintaining tolerance.

Recent reports estimate that at least 50% of developing B cells are initially self reactive (15, 16). Although self-reactive B cells can be deleted in the bone marrow (17, 18) or rendered anergic in the periphery (6), several studies indicate that receptor editing in developing B cells is the predominant mechanism that maintains B cell tolerance (18–20). These papers also raised the possibility that B cells can express multiple BCRs with at least a small difference in their specificities, especially if they are self reactive. Recently, the presence of such allelically included cells that continue to express the self-specific receptor in conjunction with the innocuous receptor generated by editing, as well as their potential contribution to the secretion of natural autoantibodies, have been confirmed (21, 22).

Receptor editing may play an additional role in mature B cells. Recombinase gene expression (23), L chain gene rearrangement (24), and, rarely, H chain Vh hybrids (generated via receptor revision) (25, 26) have been observed in peripheral or germinal center B cells. B cells that express various developmental markers and contain dsDNA breaks indicative of ongoing recombination have been reported outside the bone marrow (23, 24), but it remains to be seen if these cells are recent bone marrow emigrants or genuine mature B cells that reactivate V(D)J recombination. The purpose of receptor editing in the periphery may be either to rescue cells that have become self reactive (27) or to enhance diversification during affinity maturation (28, 29).

Interesting parallels exist between receptor editing in B cells and sequential TCRs locus rearrangements observed during positive selection in developing T cells. Double positive T cells expressing functional surface TCR fail to downregulate recombinase expression or inactivate further TCRs rearrangement until their TCR can recognize self MHC–peptide complexes at a threshold affinity (30). This ongoing rearrangement edits TCRα-chains and results in their successive replacement. However, this TCR engagement must be non-stimulatory, as a strong TCR signal during these developmental stages causes clonal deletion. In yet another remarkable example of T and B cells sharing similar mechanisms, experiments using certain transgenic models indicate that developing T cells receiving a stimulatory signal through their TCRs continue to express the recombinase and rearrange the α-chain in an attempt to edit the offending receptor (31), implicating receptor editing as one of the mechanisms responsible for T cell tolerance.

These Pillars articles ushered in an era of controversy over the relative contributions of receptor editing, clonal deletion, and clonal anergy to B cell tolerance, but several ensuing papers have firmly established receptor editing as the key mechanism of B cell tolerance. The discovery of receptor editing changed the way workers in this field thought about clonal selection, allelic exclusion, and the regulation of the V(D)J recombinase. Future research will determine the full scope of receptor editing and the precise nature of its regulation.

Disclosures
The authors have no financial conflicts of interest.

References