7. W. J. Randel, F. Wu, *J. Clim.* **12**, 1467 (1999).
8. M. R. Schoeberl, P. K. Bhartia, E. Hilsenrath, O. Torres, *Geophys. Res. Lett.* **20**, 29 (1993).
9. X. Tie, G. P. Brasseur, B. Briegleb, C. Granier, *J. Geophys. Res.* **99**, 20545 (1994).
10. S. Solomon *et al.*, *J. Geophys. Res.* **101**, 6713 (1996).
11. A. M. Vogelmann, T. P. Ackerman, R. P. Turco, *Nature* **359**, 47 (1992).
12. A. Genin, B. Lazar, S. Brenner, *Nature* **377**, 507 (1995).
13. A. Robock, J. Mao, *Geophys. Res. Lett.* **19**, 2405 (1992).
14. _____, J. Mao, *J. Clim.* **8**, 1086 (1995).
15. G. Stenchikov *et al.*, in preparation.
16. D. W. J. Thompson, J. M. Wallace, *Geophys. Res. Lett.* **25**, 1297 (1998).
17. J. W. Hurrell, *Science* **269**, 676 (1995).
18. G. Stenchikov *et al.*, *J. Geophys. Res.* **103**, 13837 (1998).
19. I. Kirchner *et al.*, *J. Geophys. Res.* **104**, 19039 (1999).
20. A. Robock, *Science* **272**, 972 (1996).
21. M. Free, A. Robock, *J. Geophys. Res.* **104**, 19057 (1999).
22. R. D'Arrigo, G. Jacoby, M. Free, A. Robock, *Clim. Change* **42**, 663 (1999).
23. T. J. Crowley, *Science* **289**, 270 (2000).
24. J. T. Houghton *et al.*, Eds., *Climate Change 2001: The Scientific Basis* (Cambridge Univ. Press, Cambridge, 2001).

25. This work is supported by NASA grant NAG 5-9792 and NSF grant ATM-9988419.

PERSPECTIVES: IMMUNOLOGY

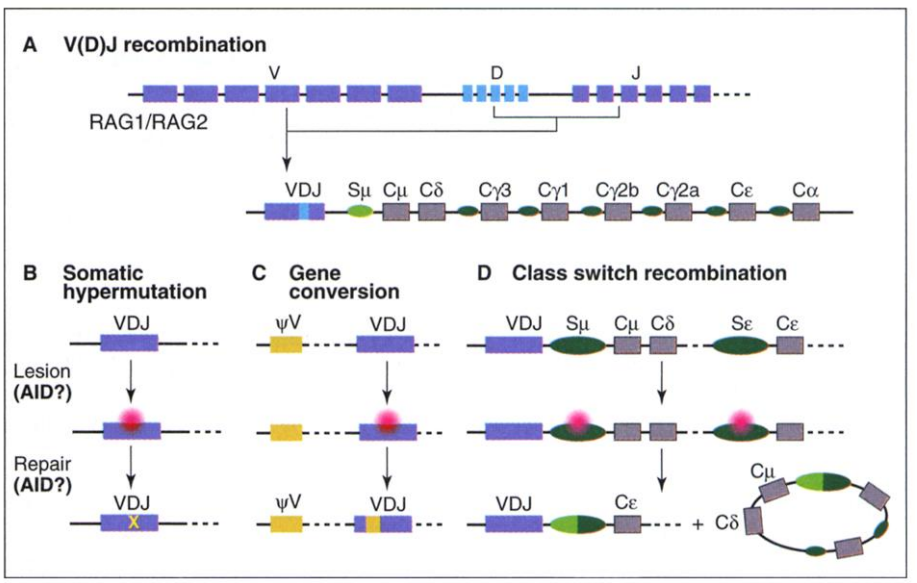
One AID to Unite Them All

Sebastian D. Fugmann and David G. Schatz

Immunoglobulin (Ig) genes, and the antibodies they encode, reign supreme in the realm of genetic diversity. These Ig genes are recombined, rearranged, and mutated by four different molecular processes in B lymphocytes as they develop and mature. Initially, Ig genes are assembled from scattered germline gene elements in a process called V(D)J recombination (see the figure, A). Thereafter, nucleotide changes can be introduced into the assembled variable exon, which encodes the portion of the antibody that makes contact with antigen, through somatic hypermutation (SHM) or gene conversion (GC) (see the figure, B and C). Finally, the constant region of the Ig gene, which determines antibody effector functions, can be swapped in a process known as class switch recombination (CSR) (see the figure, D). The molecular processes underlying SHM, GC, and CSR have proved difficult to delineate. Thus, the recent discovery that one gene, encoding an activation-induced cytidine deaminase (AID), is essential for SHM and CSR in both mice (*1*) and humans (*2*) has generated much excitement. On page 1301 of this issue, Arakawa *et al.* (*3*) neatly complete the picture by demonstrating that GC is also strictly AID-dependent. These authors show that disrupting the *AID* gene in the chicken B cell line DT40 results in a complete block of Ig gene conversion, and that this block can be reversed by reintroducing *AID* into the B cells. This finding is confirmed by Harris and colleagues in their work with DT40 cells, which have the advantages that GC is permanently switched on and that genes can be targeted efficiently (*4*). AID is therefore a pivotal player in the generation of antibody diversity and represents a fascinating point of convergence for the three disparate reactions that drive Ig gene assembly and modification.

Higher vertebrates rely on an extremely diverse repertoire of antibodies to combat infectious pathogens. The initial "preimmune" antibody repertoire is generated during the assembly of Ig genes by V(D)J recombination. In many species, such as sheep, rabbit, and chicken, there is additional preimmune diversification after antibody gene assembly mediated by SHM and/or GC. An encounter between B cells and antigen drives further mutagenesis of Ig variable exons by SHM, and this, coupled with cellular selection events, allows the development of antibodies with very high affinity for the antigen. This "affinity maturation" process is a crucial component of our ability to resist reinfection by the same organism.

The molecular processes underlying V(D)J recombination are well established. First, DNA double-strand breaks are made by the RAG1-RAG2 enzyme complex, and then the broken ends are rejoined in a DNA repair process known as nonhomologous end joining. In contrast, remarkably little is known about SHM, GC, and CSR. It has long been assumed that these reactions, like V(D)J recombination, are initiated by DNA lesions and completed by DNA repair, but only recently has direct evidence for this begun to emerge. SHM has been linked to both DNA double-strand (*5, 6*) and single-strand (*7*) breaks, and does not seem to require nonhomologous end joining for lesion repair (*8*). The DNA double-strand breaks accumulate predominantly in the G_2 phase of the cell cycle (when chromosomes are in the form



Trading places. DNA rearrangements and nucleotide exchanges of the immunoglobulin heavy chain locus during B cell development and maturation. (**A**) In a process called V(D)J recombination, the exon encoding the antigen-binding domain of the antibody is assembled from V, D, and J gene elements (blue boxes). (**B**) During somatic hypermutation (SHM), point mutations (yellow X) are introduced into the VDJ exon through error-prone DNA repair. (**C**) During gene conversion (GC), stretches of nucleotide sequences (yellow boxes) are copied from pseudogene V elements (ψV) into the functional VDJ exon. (**D**) During class switch recombination (CSR), the exons encoding the constant region (C, gray boxes) of the antibody are swapped by recombination events between highly repetitive switch regions (S, green ovals). AID is required for SHM, GC, and CSR, but it is not clear whether this enzyme is involved in the creation or repair of the initial DNA lesion (red circles).

The authors are at the Howard Hughes Medical Institute and Section of Immunobiology, Yale School of Medicine, New Haven, CT 06510, USA. E-mail: david.schatz@yale.edu

of paired sister chromatids) and hence may be resolved by homologous repair (*6*). Although DNA lesions in GC have not yet been reported, lesion repair during GC is known to be strongly dependent on factors required for homologous repair but not on those for nonhomologous end joining (*9*). Thus, GC is likely to resemble SHM closely, both in its initiating strand lesion and in its lesion repair pathway (*9, 10*). CSR, in contrast, is thought to involve a pair of double-strand breaks, which in many (but perhaps not all) cases are repaired by the nonhomologous end joining machinery (*8*). Interestingly, the junctions formed in CSR are often flanked by point mutations (*8*), and a defect in the mismatch repair protein Msh2 has similar effects on SHM and CSR (*11*). It therefore seems possible that CSR, SHM, and GC have a common intermediate (perhaps a common type of DNA lesion) and share mechanistic similarities in the processing and repair of this intermediate.

How AID is involved in these three processes remains a mystery. The puzzle is made all the more tantalizing by the fact that the closest homolog of AID is the RNA-editing enzyme APOBEC-1 (*12*), which edits the mRNA of the *apoB* gene. The critical catalytic residues of APOBEC-1 are strictly conserved in AID, and like APOBEC-1, AID has the ability in vitro to convert a cytidine nucleotide to a uridine nucleotide through deamination (*12*). It is not yet known whether AID manifests deaminase activity in vivo—and if it does, what its targets might be.

Experiments thus far have sought to determine whether AID is essential for generating or repairing the DNA lesions of CSR, SHM, and GC. The results have not provided a single, clear answer. One study found that clusters, or "foci," of repair proteins form in the vicinity of the Ig heavy chain locus when B cells from normal, but not AID-deficient, mice are stimulated to undergo CSR (*13*). The simplest interpretation is that AID is required for the initial DNA lesions of CSR: no AID, no lesions, and hence no repair foci. Another study came to exactly the opposite conclusion concerning SHM. In the absence of the *AID* gene or AID activity, the double-strand breaks of SHM were not reduced in frequency (*14*).

One possible, albeit inelegant, conclusion is that AID acts in different ways in CSR and SHM. Perhaps AID edits two different RNA molecules: one encoding a factor involved in generating CSR strand lesions, and the other encoding a protein that operates in the repair phase of SHM and GC. It is tempting to think, however, that AID does not have a split personality. One possibility is that AID is required for the strand lesions of all three processes, although this would imply that the abundant double-strand breaks associated with SHM are neither intermediates of, nor derived from intermediates of, the SHM reaction. Perhaps most appealing is the notion that AID is essential for the processing and repair phase of all three reactions. In SHM and GC, this could involve shunting homologous repair into an "atypical" pathway, for example, by recruiting error-prone polymerases or facilitating the use of a pseudogene donor rather than the sister chromatid. Recent experiments have demonstrated that "perversion" of error-free homologous repair can indeed induce nucleotide changes that closely resemble those observed in SHM (*9*). For CSR, one could imagine that AID acts to prevent rapid, nonproductive resealing of the initial DNA lesions, which in turn allows processing of the breaks and the engagement of the two switch partners (and the formation of repair foci).

Whatever turns out to be the case, one thing is certain: Determining the function of AID—and, if it is an RNA editing enzyme, the identity of its RNA targets—will cast a great deal of light on what is currently a rather murky situation. The results of Arakawa, Harris, and their colleagues tell us that when this happens, not only CSR and SHM but also GC will be under the spotlight.

References

1. M. Muramatsu *et al.*, *Cell* **102**, 553 (2000).
2. P. Revy *et al.*, *Cell* **102**, 565 (2000).
3. H. Arakawa, J. Hauschild, J.-M. Buerstedde, *Science* **295**, 1301 (2002).
4. R. S. Harris *et al.*, *Curr. Biol.*, in press.
5. L. Bross *et al.*, *Immunity* **13**, 589 (2000).
6. F. N. Papavasiliou, D. G. Schatz, *Nature* **408**, 216 (2000).
7. Q. Kong, N. Maizels, *Genetics* **158**, 369 (2001).
8. J. P. Manis, M. Tian, F. W. Alt, *Trends Immunol.* **23**, 31 (2002).
9. J. E. Sale *et al.*, *Nature* **412**, 921 (2001).
10. N. Maizels, *Cell* **83**, 9 (1995).
11. M. R. Ehrenstein, M. S. Neuberger, *EMBO J.* **18**, 3484 (1999).
12. M. Muramatsu *et al.*, *J. Biol. Chem.* **274**, 18470 (1999).
13. S. Petersen *et al.*, *Nature* **414**, 660 (2001).
14. F. N. Papavasiliou, D. G. Schatz, *J. Exp. Med.*, in press.

PERSPECTIVES: ECOLOGY

Species Diversity—Scale Matters

Katherine J. Willis and Robert J. Whittaker

As predictions of the loss of global biodiversity grow increasingly pessimistic, identifying the factors that determine species richness has become a hot topic. The best-known pattern in species diversity is the gradient ranging from low at the poles to high at the equator. This pattern is so general across so many taxa that it suggests the existence of an equally general explanation. Much attention, therefore, has been given to finding *the* mechanism that explains patterns of species richness, with the underlying assumption that whatever scale the relationship is measured at can be scaled up or down in simple fashion. If this were so, a model that successfully accounts for local patterns in richness could be scaled up to account for variations seen at a coarser regional or even global scale. This reasoning resembles that used to explain evolutionary change, where variations manifest over decades or centuries can be scaled up to describe the more dramatic patterns of macroevolutionary change over geological time. But, as some evolutionists have argued (*1*), biological and environmental systems are more complex than this. It is becoming increasingly apparent that the factors best accounting for patterns of biodiversity seem to be delimited by scale. This finding needs to be taken into account when assessing present or predicting future worldwide patterns of species richness.

Enhanced online at www.sciencemag.org/cgi/content/full/295/5558/1245

The authors are in the School of Geography and the Environment, University of Oxford, Oxford OX1 3TB, UK. E-mail: kathy.willis@geography.oxford.ac.uk

Rahbek and Graves (*2*) have examined the geographic range of 2869 species of birds breeding in South America. By analyzing the same species data set over 10 spatial scales, ranging from 12,300 to 1,225,000 km^2, the authors were able to make direct comparisons of patterns of numbers of species as a function of scale. The number of species was statistically analyzed against a suite of environmental variables including climate, ecosystem diversity, topography, and latitude. The investigators found that the order in which the explanatory variables entered the statistical models varied with scale: Whereas precipitation was the most influential fac-