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(Un-)Braiding the genome

This month's issue of *Nature Immunology* includes a special focus on Chromatin Dynamics in the Immune System. A comprehensive overview and four review articles demystify the molecular mechanisms that underlie lymphocytes' unique recombination events and the gene expression programs that specify cellular identity and function. Our Chromatin Dynamics focus website (http://www.nature.com/ni/special_focus/chromatin_dynamics/), free until September, contains additional features and online-only links, contributed by immunology experts on chromatin. On the website readers can delve further into the historical background of remodeling or recombination to gain additional understanding of this field.

The fiftieth anniversary of the Watson-Crick DNA structure and the successful execution of the human and mouse genome sequencing projects has riveted the attention of scientists and the public. After 1953, biologists became focused onto DNA and the huge problem it presented. How could all proteins, indeed, the entire blueprint of an organism, be encoded within its bases? The nascent field of immunology was making tremendous conceptual advances in understanding the extent of diversity and adaptability of immune responses. With the emergence of DNA as the genetic material, an immediate question posed by immunologists was how a genome of finite size could encode the diversity of antibody molecules that were known to be produced by the immune system. The genome could not possibly contain enough antibody genes.

The discovery of split immunoglobulin genes made by Tonegawa and colleagues in 1976 revolutionized the field and ushered in the modern genomic era of immunology. This work was followed by the discovery that T cells use the same mechanism to encode their antigen receptors. Subsequent study has identified the key genetic targets for recombination, components of the recombination machinery and the receptor signaling pathways that are required to initiate events at target genetic loci. Cellular machinery for V(D)J recombination follows precise temporal- and lineage-specific rules, and when recombination is successfully executed, the resulting protein signals a halt to further recombination by the process of allelic exclusion. Thus, questions addressing target specificity morph into questions about what regulates gene accessibility. The review by Krangel illuminates our current understanding of the gene-selection mechanisms that are activated during V(D)J recombination.

These advances leave us a new dilemma. Instead of trying to explain how the multitude of antibodies are encoded in our genomes, we need to explain how a cell manages to express only a tiny fraction of the genome at any one time. We have gone from too few to too many genes. Chromatin is a topologically complex nucleoprotein structure, with distinct histone modifications that correlate with the accessibility of genetic loci for transcription or recombination. In his review, Smale discusses how genes are silenced as maturing lymphocytes choose lineages and what elements and factors are needed to maintain this inaccessible genetic state. Rao and colleagues then review how, in response to external signals, self-reinforcing networks of genetic expression are established in differentiating lymphocytes and are then stably passed onto their daughter cells.

Because lymphocytes are the only somatic cells that undergo regulated genetic recombination as part of their developmental program, these cells face unique challenges in maintaining their chromatin integrity. Although this concern might not be a great problem for site-specific recombinases, such as the RAGs, antigen-activated B lymphocytes undergo additional, potentially mutagenic, recombination events that are targeted, albeit imprecisely, to their immunoglobulin loci. In 2000, Honjo and colleagues made the seminal discovery of the activation-induced cytidine deaminase (AID) enzyme, which is absolutely required for both immunoglobulin class switch recombination and somatic hypermutation. Weill and colleagues review our current knowledge of what AID might be doing to target the immunoglobulin genes and how the ensuing DNA lesions are then resolved by repair enzymes.

As noted by Alt and colleagues in their overview, accessibility to transcription and recombination work hand-in-hand in generating antigen receptor diversity. Although we have learned much about local constraints and rules that govern gene expression and lymphocyte recombination, we know little about the long-range chromosomal interactions needed to activate or juxtapose distant genetic loci for recombination. Thus, despite having sequenced our genes, we have much to learn about how cells manage their genomic database.