Abstract  Class switch recombination (CSR) has been the least well understood of the Ig gene DNA rearrangements. The discovery that activation-induced deaminase (AID) is a pivotal player in CSR as well as somatic hypermutation (SHM) and its variant, gene conversion, represents a sea change in our understanding of these processes. The recognition that AID directly deaminates ssDNA has provided a springboard toward the emergence of a model that explains the initiation of these events. Nonhomologous end joining (NHEJ), the main pathway for the repair of double-strand breaks in mammalian cells plays a key role in the resolution of CSR transactions. Mediators of general double-strand break repair are also involved in CSR and
are mutated in several immunodeficiency diseases. A global picture of the mechanism of CSR is emerging and is providing new insights toward understanding the genetic events that underlie B cell cancers.

1 Introduction

Humoral immunity is dependent on the expression of immunoglobulin (Ig) to fend off pathogenic challenges. The humoral immune system has evolved to produce Ig with a broad repertoire of binding specificities and to avoid expression of autoreactive antibodies by using positive and negative selection strategies. Ig molecules are composed of two heavy (H) and light (L) chains, each with two functionally distinct domains. The highly diverse variable (V) domains bind to antigens, whereas effector functions are mediated by the constant (C) regions. Individual Ig molecules are remarkably specialized with highly restricted antigen-binding capacities. To attain the diversity of antigen binding required by the immune system, V genes are assembled from multiple gene segments, thereby parlaying a limited complement of genetic material into a vast potential for antigen binding through the process of V(D)J joining (reviewed in Hesslein and Schatz 2001). During the primary immune response, infectious agents stimulate and cause clonal expansion of a few B cells bearing Ig with low-affinity antigen. To produce effective immunity, Ig must have high-affinity antigen-binding specificity and be located in the appropriate tissues. Ig undergoes two additional genetic alterations, class switch recombination (CSR) and somatic hypermutation (SHM), which serve to refine and increase the specificity of the humoral immune response.

Successful V(D)J joining leads to assembly of H and L chain V regions and the expression of low-affinity Ig. These antibodies form the repertoire of the primary immune response and can bind antigen but cannot carry out all effector functions efficiently. Upon antigenic challenge, activated B cells undergo CSR to produce new effector functions and migrate to germinal centers, where their V regions become substrate for mutational events. SHM results in affinity maturation of the Ig repertoire, which increases the effectiveness of the humoral immune response. In chickens and rabbits, V regions are diversified by gene conversion that permits templated acquisition of sequences copied from parts of upstream pseudogenes. Although the molecular machineries which carryout CSR, SHM and gene conversion are quite different, exci-