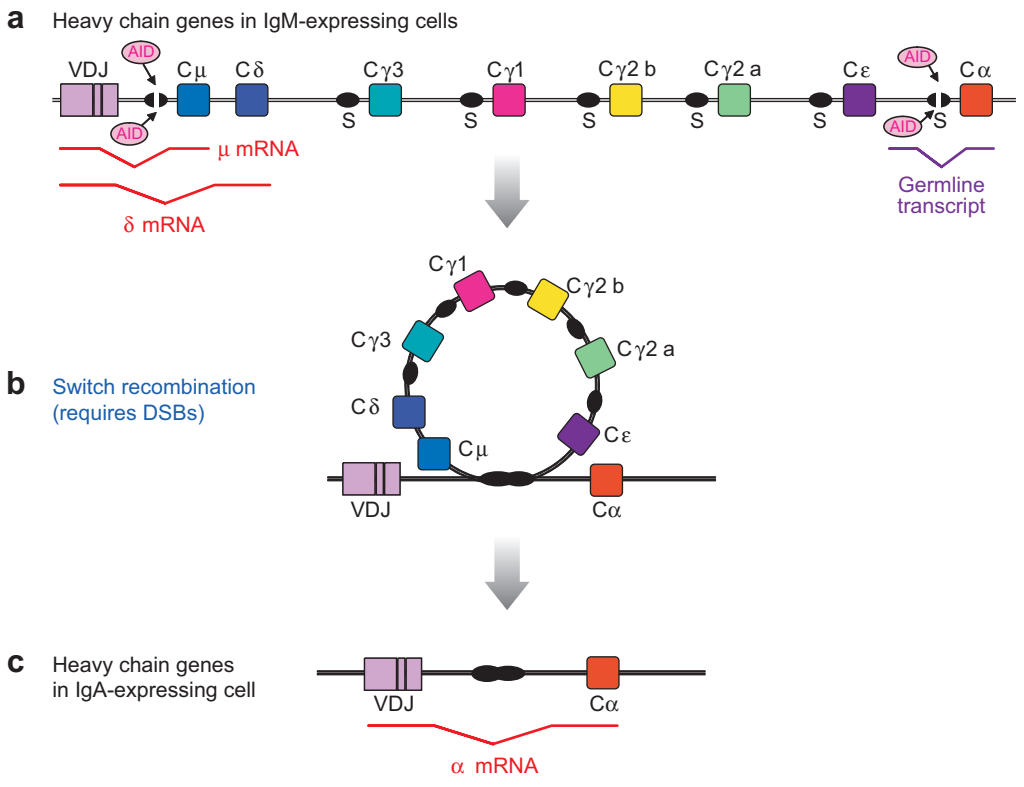

Figure 1

Diagram of Ig class switch recombination (CSR) to IgA. (*a*) The mouse IgH locus in B cells expressing IgM and IgD (by alternative RNA transcription/processing). During CSR, activation-induced cytidine deaminase (AID) deaminates dC residues in the top and bottom strands of transcriptionally active S regions (Sμ and Sα in the diagram shown), initiating a process (described in the text) that results in double-strand DNA breaks (DSBs) in both S regions and CSR by intrachromosomal deletion (*b*). (*c*) The IgH locus after CSR to IgA. Splicing diagrams of the μ, δ mRNAs and the germline α transcript are indicated below the diagram of the locus. Similar germline transcripts are induced from unrearranged Cγ, Cε, and Cα genes, depending on the cytokine stimulation received by the B cell.

(22–25). This requirement appears to be at least partly due to the requirements for induction of AID expression (25). Transcription of AID mRNA is induced synergistically by IL-4 and CD40 signaling via induction of Stat6 and NF-κB transcription factors (26). However, these signals are very rapid. Pax5 is also essential for AID mRNA transcription, and Pax5 binds to the AID promoter in LPS+IL-4-treated splenic B cells (27). Most interestingly, binding of Pax5 to the AID promoter is not detected until two days after addition of the activators, suggesting that the kinetics of Pax5 binding might be important for explaining the requirement for cell division for AID induction. Furthermore, AID function is regulated by active export from the nucleus (28–30), which might also contribute to the delay in CSR.

Naive B cells have the potential to switch to any isotype, and cytokines secreted by T cells and other cells direct the isotype switch (reviewed in 7, 31, 32). Although there is more to be discovered, the predominant mechanism for regulating isotype specificity is by regulation of transcription through S regions,