

EXPRESSION OF ACTIVATION-INDUCED CYTIDINE DEAMINASE IS REGULATED BY CELL DIVISION, PROVIDING A MECHANISTIC BASIS FOR DIVISION-LINKED CLASS SWITCH RECOMBINATION.

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Class switch recombination (CSR) is the process by which B cells alter the effector function properties of their immunoglobulin (Ig) molecules. The decision to switch to a particular Ig isotype is determined primarily by the mode of B cell activation and cytokine exposure. More recent work indicates that the likelihood or probability of switching increases with successive cell divisions and is largely independent of time. We have analyzed different molecular events associated with CSR using cell division as a reference point in an attempt to gain insight into the mechanism of division-linked switching. Our results indicated that the accessibility of C_H regions targeted for CSR was established after the cells had undergone a single cell division and did not vary significantly with subsequent cell divisions. In contrast, expression of both AID mRNA and protein was found to increase with successive divisions, exhibiting a striking correlation with the frequency of CSR. Levels of AID in a given division remained constant at different time-points, strongly suggesting that the regulation of AID expression was division-linked and independent of time. In addition, constitutive AID expression from a transgene accelerated division-linked CSR. Consequently, we propose that the division-linked increase in AID expression provides an underlying molecular explanation for division-linked CSR.