

Localized Gene-Specific Control of Accessibility to V(D)J Recombination Induced by E2A and EBF in Non-Lymphoid Cells

Peter Goebel and Ann J. Feeney
The Scripps Research Institute, La Jolla, CA

The rearrangement of Ig and TCR genes is a highly regulated process. The precise mechanisms by which this lineage-specific and temporal control of rearrangement is regulated are unknown, although the control is effected at the level of accessibility of the individual loci to recombination. Recent work has suggested that modulation of chromatin structure is a key factor in controlling accessibility for rearrangement. We have previously shown that ectopic expression of the transcription factors E2A or EBF with RAG induces rearrangement of IgH and IgL genes in a non-lymphoid cell line. V α I genes throughout the locus were induced to rearrange after transfection with E2A, suggesting that the entire V α locus was rendered accessible. However, our more recent data show that the Ig loci are not opened globally, but that recombination is localized. Genes from various families are interspersed in the D_H, V α and V α I loci, and certain families and individual genes undergo high levels of recombination upon E2A or EBF expression in BOSC cells, while other neighboring genes within the same locus are not induced to rearrange. We propose that accessibility occurs in a localized gene-specific manner, and that binding sites for factors facilitating accessibility may therefore be associated with individual gene segments. We hypothesized that E2A, which binds the SAGA complex containing histone acetyl transferase activity, might bind to the promoters of V α I genes, but not V α II genes, and would thus be able to recruit HAT to those sites and produce localized induction of histone acetylation for V α I genes. We used chromatin immunoprecipitation with antibodies reactive with acetylated histone H3 to test this hypothesis, and found that there was not a globalized induction of histone acetylation of V α I genes after transient transfection with E2A. However rearranged genes can be found in the DNA fraction associated with acetylated histones. We therefore propose that histones surrounding a small number of individual gene segments may become acetylated, and that those genes segments are preferentially allowed to undergo rearrangement.