RNA Processing Regulation of Immunoglobulin Gene Expression

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Mammalian genomes have been found to encode a surprisingly small number of genes. However, as many as 60% of all genes may be alternatively processed to generate a much greater diversity of proteins. Therefore, to fully understand gene expression and the generation of protein diversity, we must understand how the complex process of alternative RNA processing is regulated. From studying model RNA processing substrates, we know that this regulation is likely to be complex and the result of multiple protein-RNA and protein-protein interactions. In addition, it has become clear in recent years that RNA processing and transcription elongation are functionally coupled reactions and thus, factors that modulate transcription may also affect alternative RNA processing decisions. We have been studying the immunoglobulin M (Ig μ) gene, one of the first to be described to be alternatively processed, as a model system to better understand RNA processing regulation. This gene contains competing cleavage-polyadenylation and splice reactions which lead to the production of two different mRNAs whose abundance varies during B lymphocyte maturation. We have demonstrated that these two reactions are in direct competition and that their efficiencies must be balanced. Also, since another gene with a similar structure was regulated in cell lines and in a transgenic mouse, we have concluded that regulation must be mediated by factors that affect general cleavage-polyadenylation and/or splicing. We are currently using microarray analysis to identify genes whose expression changes when a B cell line is stimulated to differentiate. Some of the differentially expressed genes encode products relevant to RNA processing regulation and are candidate Ig μ expression regulators. Also, we have recently described a sequence element downstream from the internal poly(A) site that seems to be an RNA polymerase pause site. We are examining this pause site and the elongation properties of RNA polymerase on the μ gene to better understand Ig μ regulation as well as to gain insights into RNA polymerase elongation control in general.

Bruce, S.R., R.W.C. Dingle and M.L. Peterson (2003) B cell and plasma cell splicing differences: A potential role in regulated immunoglobulin RNA processing. *RNA* 9, 1264-1273.

Peterson, M.L., S. Bertolino, and F. Davis (2002) An RNA polymerase pause site associated with the immunoglobulin μs poly(A) site. *Mol. Cell. Biol*. 22, 5606-5615.