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IRF5 promoter usage and response to toll-like receptor stimulation

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Abstract

Interferon regulatory factor 5 (IRF5)is proapoptotic and has polymorphisms that confer risk for autoimmune disease. IRF5 has four first exon choices: 1D, 1A, 1B, and 1C respectively and the promoter region of exon 1A contains a CGGGG indel which is a risk factor for: Systemic lupus erythematosus, Sjögrens disease, Multiple Sclerosis, Crohns disease, and ulcerative colitis as determined by genome wide association studies (GWAS). The presence of this indel changes transcription factor binding in the promoter and correlates with higher levels of IRF5 as transcription levels are dependent on a gene's first exon. Additionally, based on mRNA testing the 1A exon is also translated most efficiently. Thus the 1A risk indel may contribute to an increase in apoptosis through upregulation of IRF5 by increased transcription and efficient translation.

To determine which transcription factors would bind to IRF5's promoter, we used ChIP-sequencing data (ENCODE database).This data was used in conjunction with the FactorBook database to define where conserved genomic sequences where transcription factors are likely to bind in the promoter regions of IRF5. Exons 1A and 1D were found to contain putative PU.1 and NFkB binding sites. IRF5's four promoters were cloned into luciferase plasmids to determine promoter activity for each exon using immune and epithelial cells. Imiquimod, a Toll-like receptor 7 ligand, and etoposide were used to activate the promoters. As a result of imiquimod treatment IRF5 levels were doubled ($p<0.001$), due to increased expression of exon 1A (2.2 fold, $p=0.03$) and 1D (2.8 fold, $p=0.03$), although when untreated there is less exon 1D usage in cells with the risk indel. IRF5 itself is a transcription factor for CCR7, one of its downstream targets, yet the risk indel is more likely to turn down CCR7 which suggests that it may be acting as a repressor.

Understanding polymorphisms in the promoter regions of IRF5 and the effect that transcription factors play in the activity of these promoters is critical to determining how IRF5 is regulated in those with risk factors for autoimmune disease.