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Effects of an IRF 5 lupus risk allele on apoptosis, splicing, and promoter usage

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Autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis and others affect millions of americans. The polymorphism rs2004640, found in the Interferon regulatory factor 5 (IRF5) promoter has been found to be a risk factor for several autoimmune diseases. We sought to define functional molecular effects due to this risk factor in cells from healthy individuals with the risk factor compared to those without. In cells with this polymorphism, we found >2-fold higher levels of IRF5 mRNA and protein ($p<0.05$). IRF5 is proapoptotic, so we expected higher levels of IRF5 would lead to increased apoptosis. Apoptosis levels were found to be 2.1 fold higher in risk cells ($p=0.012$). Since the polymorphism allows use of the IRF5 alternate first exon 1B, we analyzed four potential IRF5 promoters using ChIP-Seq data (ENCODE database) and the FactorBook database to define transcription factor binding sites. From this analysis, a p53 binding site was found only on the promoter for exon 1B. Further analysis measured the proportion of usage of each exon using qPCR. Usage of exon 1C was 2.3-fold lower ($p=0.013$) and 1D was 3.6-fold lower ($p=0.017$) in risk cells. We discovered 5 new splice variants of IRF5 mRNA, three of which used the exon 1B promoter. Each new variant was missing part of an instability domain, which may affect protein stability. These changes in expression, apoptosis and splicing help to explain how this polymorphism affects cellular and molecular processes and contributes to the development of autoimmune disease.

Biography

Brian Poole is extremely dedicated to researching lupus, due both to inherent interest in the biological problems and a family member afflicted with the disease. He completed Ph.D. at Pennsylvania State University College of Medicine, and post-doctoral training at the Oklahoma Medical Research foundation, where he examined the role of Epstein-Barr virus in the development of lupus. Since obtaining his current position at Brigham Young University, he has enjoyed supervising his research lab focused on the role of genetic risk factors, specifically IRF5, in the development of lupus, and mentoring multiple undergraduates.

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