DNA Repair and Autoimmunity

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A recent large-scale replication study of a previous genome-wide association study (GWAS) suggested that a single nucleotide polymorphism (SNP) linked to the POLB gene is associated with systemic lupus erythematosus (SLE). Importantly, this SNP is correlated with decreased POLB expression (Pol β). To determine if decreased Pol β activity results in SLE, we constructed a mouse model of a hypomorphic allele of POLB that encodes an enzyme with slow DNA polymerase activity. Pol β is a key enzyme in the base excision repair (BER) pathway that prevents accumulation of intermediate DNA repair substrates that lead to genomic instability. Here we show that knock-in mice expressing this hypomorphic POLB allele develop autoimmune pathology strongly resembling SLE. As in SLE, the POL B mutant mice exhibit dermatitis, renal disease, and have high levels of antinuclear antibody (ANA). Of note, the immunoglobulin heavy chain junctions from the POL BY265C/C mice have shorter lengths, and somatic hypermutation is dramatically increased. These results demonstrate that decreased Pol β activity during the generation of immune diversity leads to lupus-like disease in mice and suggest that decreased expression of Pol β in humans is an underlying cause of SLE, likely by a similar mechanism.

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Marine Sciences Building Room 150 (MSB-150) – BBC (via Polycom)