CONNECTIVE TISSUE DISEASES

The *MECP2/IRAK1* locus modulates SLE risk via epigenetics

Polymorphisms in several genetic loci have been linked with systemic lupus erythematosus (SLE), but the mechanisms by which they influence disease development are poorly understood. Now, new research has characterized the effect of a known risk variant in the *MECP2/IRAK1* locus.

“The study was done to try to understand how the SLE-risk variant in this genetic locus can increase SLE susceptibility”, explains lead author Amr Sawalha. To achieve this aim, the investigators first analysed the expression of *IRAK1* and the two splice isoforms of *MECP2* (*MECP2A* and *MECP2B*) in primary human T cells obtained from healthy individuals who were homozygous for either the SLE-risk or the non-risk haplotype. Interestingly, they found that levels of *MECP2B* mRNA were increased in stimulated T cells with the risk haplotype.

MECP2 is a key regulator of the expression of methylation-sensitive genes and also recruits

DNA methyltransferase 1 during DNA replication. Exploring the effects of the *MECP2/IRAK1* risk variant on genome-wide DNA methylation in stimulated T cells, the investigators found that although the average level of methylation was not altered, 245 CpG sites were differentially methylated in T cells homozygous for the risk haplotype. Many of these sites were in genes associated with antigen presentation (particularly HLA class II genes) and the interferon response, suggesting that the *MECP2/IRAK1* risk variant can affect immune responses through epigenetic mechanisms.

To further investigate the impact of high *MECP2* levels, the researchers used transgenic mice overexpressing human *MECP2*. Gene expression profiling of stimulated T cells from transgenic and control mice identified 109 differentially expressed genes. Notable among these was *Eif2c2*, which

modulates the expression of miR-21, a microRNA known to be upregulated in CD4⁺ T cells from patients with SLE.

Moreover, pathway analyses suggested that the activity of the IL-6, IL-17 and CD40 signalling pathways, which have important roles in immune responses, might be modified by these expression changes.

But is autoimmunity induced by these effects? Intriguingly, the researchers showed that *MECP2*-transgenic mice have substantially higher serum levels of anti-nuclear antibodies than wild-type mice. The next step will be “to look for the effect of this SLE-associated genetic variant in other cell types”, proposes Sawalha.

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