EPIGENETICS

Demethylation of IFN-regulated genes in SLE neutrophils

An analysis of the DNA methylome of neutrophils and low-density granulocytes (LDGs) from patients with systemic lupus erythematosus (SLE) has revealed a pattern of demethylation in interferon-signature genes, which, the investigators suggest, could contribute to SLE pathogenesis via Toll-like receptor (TLR)-9 stimulation during NETosis.

Using a genome-wide approach, the researchers quantified DNA methylation levels at >485,000 methylation sites in neutrophils from female patients with SLE ($n=15$) and healthy women ($n=15$) with the Infinium® HumanMethylation450 BeadChip array (Illumina, USA). Of the 293 CpG sites that were differentially methylated in SLE neutrophils, 199 (68%) were hypomethylated, which corresponding author Amr Sawalha highlights as indicative of a qualitative difference in the DNA of these cells. “This suggests that DNA externalized

by SLE neutrophils during NETosis is more pathogenic than DNA from healthy neutrophils, as hypomethylated DNA is more capable of stimulating dendritic cells via TLR-9,” explains Sawalha.

Notably, interferon-signature genes were consistently hypomethylated in SLE neutrophils. “This robust demethylation suggests that these genes are more transcriptionally accessible in lupus neutrophils,” adds Sawalha, “which could also have a pathogenic role in the disease.”

The investigators also explored whether epigenetic differences could explain findings from previous studies that LDGs are more prone to NETosis and produce more type I interferon, TNF and IFN- γ than normal-density neutrophils in SLE.

Despite being distinct cell populations, however, LDGs and neutrophils were

near-identical in terms of their DNA methylation patterns. The exception was hypomethylation of the cytoskeleton-related gene *RAC1* in LDGs, but whether *RAC1* hypomethylation contributes to LDGs being more prone to NETosis—a process that involves extensive cytoskeletal remodelling—remains unclear. Sawalha concludes, “Future studies would have to focus on mechanistic understanding of what causes the demethylation of interferon-regulated genes in lupus neutrophils, and if the qualitative DNA difference observed in lupus neutrophils in this study alters TLR-9 responses.”

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