Genome-Wide DNA Methylation Analysis Reveals Epigenetic Influence on Intracellular and Cytokine Signaling Pathways in WM compared to IgM MGUS

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The role of DNA methylation in the immunoglobulin M (IgM) monoclonal gammopathy disease spectrum remains poorly understood. In recent work, a multi-omics prospective analysis was conducted integrating DNA methylation, RNA sequencing (RNA-seq), and whole-exome sequencing data in 34 subjects (23 with Waldenström macroglobulinemia [WM], 6 with IgM monoclonal gammopathy of undetermined significance [MGUS], and 5 normal controls). Analysis was focused on defining differences between IgM gammopathies (WM/IgM-MGUS) compared with controls, and specifically between WM and IgM-MGUS. Between groups, genome-wide DNA methylation analysis demonstrated a significant number of differentially methylated regions that were annotated according to genomic region. Next, integration of RNA-seq data was performed to identify potentially epigenetically deregulated pathways. We found that pathways involved in cell cycle, metabolism, cytokine/immune signaling, cytoskeleton, tumor microenvironment, and intracellular signaling were differentially activated and potentially epigenetically regulated. Importantly, there was a positive enrichment of the CXCR4 signaling pathway along with several interleukin (interleukin 6 [IL-6], IL-8, and IL-15) signaling pathways in WM compared with IgM-MGUS. Further assessment of known tumor suppressor genes and oncogenes uncovered differential promoter methylation of several targets with concordant change in gene expression, including CCND1 and CD79B. Overall, this research identifies how aberrant DNA methylation in IgM gammopathies may play a critical role in the epigenetic control of oncogenesis and key cellular functions.

Large-Scale Genome-Wide Association Study Illuminates Disease Aetiology for Waldenström Macroglobulinemia and Lymphoplasmacytic Lymphoma

Family history is a strong risk factor for Waldenström macroglobulinemia (WM)/ lymphoplasmacytic lymphoma (LPL). We previously identified two rare variants at 6p25.3 and 14q32.13 that were significantly associated with an increased risk of WM/LPL. However, the genetic basis for WM/LPL predisposition remains largely unknown. Here, we discuss new findings from the largest genome-wide association study (GWAS) of WM/LPL, including 1,707 cases and 58,328 controls with replication in four independent cohorts (570 cases and 771,770 controls). A total of twelve germline genetic variants were discovered to be associated with WM/LPL risk and replicated ($P< 5 \times 10^{-8}$). Interestingly, four of the discovered variants showed strong associations with WM/LPL risk with odds ratios greater than 10. Enrichment was observed for regulatory elements in CD19+ B-cells, and gene-based and colocalization analyses identified several potential biological pathways, including B-cell development and immune function. These findings provide deeper insight into disease aetiology and may be useful in identifying individuals at higher risk and suggesting new drug targets for treatment.