

## **Epigenetic dysregulation in Waldenstrom's Macroglobulinemia**

Antonio Sacco, Patricia Maiso, Salomon Manier, Steven P. Treon, Irene M. Ghobrial, Aldo M. Roccaro

Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

The term "epigenetics" has been first introduced by C.H. Waddington in 1939 as "the causal interactions between genes and their products, which bring the phenotype into being"; and subsequently used to define those heritable changes in gene expression that are not due to any alteration in the DNA sequence. The best-known epigenetic markers are histone acetylation and DNA methylation and histone acetylation. Moreover, all these phenomena are finely regulated in different manners, such as through microRNAs.

Waldenström's Macroglobulinemia (WM) is a low-grade B-cell lymphoma characterized by the presence of lymphoplasmacytic cells in the bone marrow (BM) and a monoclonal immunoglobulin M in the circulation. While WM cells showed minimal changes at cytogenetic studies and gene expression analysis, primary WM tumor cells present with a miRNA signature that differentiates them from their normal counterpart. Among deregulated miRNAs, miRNA-155 has been shown to play a pivotal role in the biology of this disease both in vitro and in vivo. Moreover, other miRNA changes in WM cells, such as the down-regulation of miRNA-9\*, has been proven to modulate the histone acetylation status in WM cells.

These findings demonstrate that epigenetic modifications are crucial in the pathogenesis of WM disease, thus providing the rationale for testing miRNA-based therapeutical approaches for the treatment of WM.