Session III: Genetic Basis and Pathogenesis of WM and IgM Related Disorders

Abstract 114

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High-throughput microRNA profiling: Identification of miRNAs with a potential pathogenetic role in Waldenström's macroglobulinemia. Adamia S.[1], Amin S.[1], Patterson C.[1], Moreau P.[3], Minvielle S.[3], Li C.[1], AvetLoiseau H.[3], Anderson K.C.[1], Munshi N.C.[1,2] and Treon S.P.[1] [1]Dana-Farber Cancer Institute, and [2]Boston VA Healthcare System, Harvard Medical School, Boston, MA, USA; [3]Hematology Department, Hopital de Nantes, Nantes, FRANCE.

MicroRNAs that are small noncoding RNAs regulate expression of protein-coding genes by inducing cleavage of targeted transcripts or inhibiting translation. Despite intense research efforts true genetic basis of Waldenström's Macroglobulinemia (WM) is unclear. To better understand distinct mechanism WM-genesis and to identify markers for diagnosis and/or novel targets for treatment we evaluated expression of 384 microRNAs in WM patients as compared to healthy donors (HD), as well as CD138+ cells from myeloma (MM) patients. miRNA profiling, using miRNA array, were conducted in 13 WM and 79 MM patients, and 13 HDs. Data obtained from microRNA array were analyzed using SDS, RQ manager, R and dChip softwares according to the recommendations. MiRNA profiling demonstrtes significant (p=0.001) upregulation of miRs -192, -125b, -21, -155 and downregulation of miRs-181c, -572, and -650 in CD19+WM cells from patients compared to their counterpart from HDs. Analysis of bone marrow derived CD138+ cells of WM patients as compared to CD138+ cells from HDs demonstrated modulated expression of 40 microRNAs that includes upregulation of miR-192, -193b, -17-3p, -585, -148b, and downregulation of miR-29c, -155, -126, -148a, -125a, -181d, -30a-3p, let-7b, let-7c, and others. Comparison analysis of WM CD138+ cells to MM CD138+ cells identified 17 miRNA that are upregulated and 4 that are downregulated. Unsupervised hierarchical clustering of filtered microRNAs, based on their DCt values, identified two major groups within the WM and MM population (groups A and group B). Samples of Group A includes WM samples along with MM. Cells from these MM patients appears to have higher proliferative nature as they cluster with MM cell lines. Within B group, a second degree node group B, clusters with normal plasma cells indicating more indolent course. Our further analysis demonstrates that the microRNAs that are significantly modulated in patients with WM targets critical signaling pathways including apoptosis, hematopoietic cell differentiation and proliferation and survival through modulation functions of HOX, c-myc, and Bcl-2. Thus, this study demonstrated significant modulation of the micoRNA with respect of their expression in WM cells as compared to their counterparts from HDs and identified miRNAs targeting those genes that encode proteins involed in B cell differentiation, growth and survival. Also, our analysis demonstrated existence of similarities between CD138+WM and MM cells from patients.