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Editorial

Gene Expression Profiling of Waldenström's Macroglobulinemia vs. IgM Monoclonal Gammopathy of Undetermined Significance

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Editorial

Waldenstrom's Macroglobulinemia (WM) is an incurable B-lymphoproliferative disorder, characterized by the infiltration of Bone Marrow (BM) by a heterogeneous population of small B lymphocytes with variable plasmacytoid differentiation, as well as mature plasma cells, along with the presence of an IgM monoclonal gammopathy in the blood [1,2].

IgM Monoclonal gammopathy of undetermined significance (IgM-MGUS) is an asymptomatic condition determined only by the presence of a monoclonal immunoglobulin (M protein) [3,4]. Significantly, patients with IgM-MGUS show an increased risk of developing WM [5]. The rate of progression from IgM-MGUS to WM has been noted to be 1.5-2% a year [6].

WM (symptomatic and indolent) and IgM-MGUS can be identified based on two main features, the bone marrow infiltration and the existence of symptoms while the different biological and genetic characteristics need to be explored.

In this study we performed microarray analysis of WM and IgM-MGUS patients in order to define the molecular signature of WM B cells as well as plasma cells compared to their counterparts from IgM-MGUS. Our aim was to identify genes differently expressed and pathways distinguishing WM from IgM-MGUS in order to determine the molecular and biological mechanisms typical for each disorder.

We isolated BM CD19+ as well as CD138+ cells of 36 WM and 13 IgM-MGUS using Miltenyi Microbeads and we performed expression analysis with Affymetrix GeneChip HG U133 Plus 2.0 Array.

Data was processed using RMA and analyzed using SAM and a false discovery rate threshold of 5% to select the differentially expressed genes. To further select a subset of robust biomarkers, SVMs were used in a Monte Carlo bootstrap resampling schema with B=100 external training/test splits to discriminate between WM and IgM-MGUS.

No different genes were found from the comparison between WM vs. IgM-MGUS CD138+ cells.

641 probes were selected by SAM on CD19+ cells. SVMs permitted the selection of 66 robust biomarker genes with MCC accuracy on external samples equal to 0.87. Functional enrichment analysis demonstrated the involvement of the following pathways:

- Notch signaling pathway: *ADAM17* (promoting cell growth) was up regulated while *AGO1* and *AGO4* (negative regulation of translation) were down regulated in WM
- *CAPRIN1* and *SORT1* (pro-apoptosis) were under expressed while *CIAPIN1* (anti-apoptosis) was over expressed in WM
- Purine/pyrimidine metabolism (cell growth): *ENTPD5* (cell proliferation) was over expressed while *NT5E* (catabolic process) was under expressed in WM
- Sphingolipid pathway: *ACER3*, *COL4A3BP*, *GBA3* were down regulated in WM
- Rho-protein signal transduction: *FARP2* (cell survival) was over expressed in WM
- Transcription: *ITPRIPL2*, *L3MBTL4* were under expressed while *NFX1*, *LIMS1* (cell aging) *USF1* were over expressed in WM
- Immune system: *HLA-C* was up regulated in WM
- *PRKCA* was under expressed in WM and involved in 85 pathways (MAPK-NGF-EGF-VEGF-ErbB-Ras-HIF-1-mTOR-PI3K-Akt)
- *MIR1204///PVT1* (oncogene), *METTL3* (RNA-methylation), *MINA* (cell survival) were up regulated in WM

In conclusion, GEP of BM CD19+ cells demonstrated that 66 genes were robust biomarkers able to distinguish between WM and IgM-MGUS. The negative regulation of translation, pro-/anti-apoptotic processes, Notch signaling pathway, Purine/Pyrimidine metabolism, Sphingolipid metabolism and the regulation of transcription were mostly involved in the comparison between WM and IgM-MGUS.

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