Does the mutational landscape change with evolution of IgM-MGUS to active WM?

Cristina Jiménez, Miguel Alcoceba, Sara Alonso, Marcos González, Ramón García Sanz

Patients with IgM-MGUS have a risk of progression to WM or to other lymphoproliferative disorders of 1.5-2% per year. This process probably implies multiple steps and the acquisition of genetic alterations, but the mechanisms involved are not well established yet.

MYD88 L265P mutation, the hallmark of WM, has been shown to be also present in 50-80% IgM-MGUS, suggesting that it may be an early driver mutation that confers a competitive advantage to the clone and predisposes it to further genetic alterations that are responsible for progression to WM. However, little is known about other mutations described with lower frequency in this disease. We studied 12 of these genes (ARID1A, CD79A, CD79B, TP53, MYBBP1A, TRAF2, TRAF3, RAG2, HIST1H1B, HIST1H1C, HIST1H1D, and HIST1H1E) in a series of 61 patients, distinguishing between IgM-MGUS (n=14), asymptomatic WM (n=23), and symptomatic WM (n=24), in order to see if these abnormalities were present from the beginning of the pathogenesis.

Overall, there were 23/61 patients with alterations, corresponding to 3/14 (21%) MGUS, 8/23 (35%) asymptomatic and 12/24 (50%) symptomatic WM. The mean number of mutations per patient also increased progressively according to the disease stage (0.2, 0.4 and 0.7, respectively). This would suggest an association between the clinical behavior and the number of mutations, being higher as the disease progresses during the clone evolution.

Interestingly, patients with a wild MYD88 gene (n=5), showed no additional mutations in any of the genes here studied. The most frequently mutated were CD79B (n=5, 8%), HIST1H1E (n=4, 7%), and MYBBP1A, ARID1A and TRAF3 (n=3, 5% for each of them), showing no differences between disease stage. Finally, we found no correlation between any mutation and the clinical outcome of the patients.

Following this concept, we decided to study WM transformation to aggressive lymphoma by performing WES in four WM patients who progressed to DLBCL, and we compared germline, and tumor DNA at diagnosis and transformation. Analysis revealed that the most frequently mutated genes at WM diagnosis (MYD88, CXCR4 and CD79B) were constantly present throughout the course of the disease. However, there were additional mutated genes at transformation, being especially frequent TP53, CARD11, PIM1 and KMT2D (MLL2).