MYD88 L265P in WM and related disorders

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Following the discovery of karyotypic translocation signatures in certain B cell lymphoma subtypes such as t(8;14) with greater expression of bcl2 in FCL or t(11;14) and bcl1 in MCL, it was speculated that such molecular signatures would be identified in WM. As a result of an international effort, deletion 6q was identified in approximately 50% of WM, hardly convincing for a driver genomic alteration, and never delivered any significant proof of its clear impact in the physiopathology of WM, e.g. either identification of key genes or a clear role in disease progression. In the mean time, a BRAF V600E mutation was described in hairy cell leukemia, where no clear karyotypic signature was known of besides a complex display of genetic features, anticipating that a molecular signature, likely playing a key role in the physiopathology of the disease, might be identified for each entity of low grade NHL. The progress was only made possible with the discovery of new techniques with greater sensitivity and the opening era of deep sequencing of the genome. Here we are, in WM, with the groundbreaking discovery of the MYD88 L265P mutation, saluted as the most important progress made in WM since the early characterization of WM as part of the lymphoplasmacytic low grade B cell NHL group in the WHO classification.

Several studies have then confirmed that MYD88 locus is altered in approximately 90% of Waldenstrom's macroglobulinemia (WM), mainly through the L265P mutation, but other alterations were described as gain on chromosome 3 at 3p22 locus that included MYD88 gene. MYD88 L265P mutation appears to be the most frequent mutation described to date in WM, appears to be highly specific of WM, and one might consider that this mutation might act as a molecular signature of WM, at least could be part of the diagnostic armamentarium of WM. MYD88 L265P may be considered as the first genetic hit in WM that promotes NF-kB and JAK-STAT3 signalling, and subsequently initiates alteration of major pathways, such as apoptotic pathways. WM cells may acquire additional genetic hits over time, mediated through loss of heterozygosity, gene amplification or epigenetic changes that may potentially contribute to further deregulation of the WM clone and promote tumour progression.

Several issues remain to be solved, including that MYD88 L265P mutation was described in IgM MGUS questioning on whether it is related to presence of IgM secreting clones or to the malignant features of some of these clone, e.g. WM/lymphoplasmacytic-related clones. Furthermore, the mutation was observed in MZL although rarely, the main differential diagnosis of WM, questioning on the histopathology definition of WM as compared to MZL. In other words, when MZL is diagnosed on a histopathology report of a BM or lymph node sample and harbour MYD88 L265P mutation, should this be considered MZL or WM/LPC. Other questions the use of MYD88 as a target for therapeutic, or as a marker of response, and more importantly minimal residual disease.

We have entered a new era in WM since the discovery of the MYD88 L265P mutation, the world of WM is on motion, the promise is great, and this discovery will unleash a wave of discoveries that will certainly ultimately benefit to the patients and their family.