What mutations accompany disease transformation in WM?

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Patients with Waldenström's macroglobulinemia (WM) may experience histological transformation to more aggressive lymphoma subtypes, such as diffuse large B-cell lymphoma (DLBCL). Although this is an uncommon event (the 5-year cumulative incidence rate is 1%), it represents a real problem since these patients have worse prognosis and lower survival from the moment of transformation than the newly diagnosed lymphomas. Understanding the biological causes and mechanisms of this process may allow to identify patients in high risk for disease transformation. However, no biological studies have been carried out in patients with transformed WM until now.

We have performed a whole-exome sequencing study in a cohort of eight WM patients who transformed to DLBCL. Two of them were *MYD88* wild-type. Time to transformation ranged from 0 months (one patient was diagnosed with both diseases at the same time) to 153 months. Our results showed that WM transformation was driven by the acquisition of many novel alterations whose total number may be associated to the suddenness of the event (the higher the mutation number, the shortest time to transformation). However, what ultimately prompts the transformation process would not be the amount of alterations or the elapsed time, but the acquisition of specific alterations. Accordingly, we could identify three kinds of alterations:

First, mutations present at both stages in a high proportion of tumor cells, like *MYD88* or *CXCR4*, which are thought to be early drivers of the malignant process. Within this group, we identified alterations in *CD79A*/*B* in a higher frequency (5/8 patients, 63%) than what has been reported in conventional WM (15%).

The second group would include recurrent mutations gained at transformation (e.g. *PIM1*, *FRYL*, *HNF1B*), which may represent cooperating events participating in the selection of the clones responsible for disease progression.

Finally, the third group would be the passenger mutations, those that were present at diagnosis or acquired during the WM progression, but that eventually disappeared and

were no longer detected at transformation. This is well illustrated in one patient who had an initial response and subsequent symptomatic progression of WM before transformation. There were common alterations in all samples (diagnosis, progression and transformation), but some of the variants detected in the intermediate event (such as two *TP53* mutations) had not been observed at diagnosis and were not either maintained at transformation. This suggests that the whole transforming process results from a branching pattern of tumor evolution.

In conclusion, WM transformation to high-grade lymphoma involves complex and heterogeneous mechanisms in which a common leading cause cannot be identified for all patients. Nevertheless, the high incidence of *CD79A*/*B* mutations within this particular cohort of transformed patients compared to conventional WM, suggests a potential role as biomarkers for predicting the risk of transformation.