Clonal complexity in Waldenstrom macroglobulinemia and potential therapeutic options

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Most B lineage cancers, including Waldenstrom macroglobulinemia (WM), are monoclonal, with only one productive immunoglobulin IgH VDHJ gene rearrangement. However next generation sequencing and single cell analysis reveals that for some WM patients, as well as for some chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) patients, inter-clonal diversity exists with one or more additional clones. WM and MM have mutated CDR3, while CLL subdivides into unmutated CDR3 (uCLL) and mutated CDR3 (mCLL). Allelic exclusion ensures that only one productive IgH rearrangement is permitted in each B cell. Sequencing IgH VDJ allows determining the developmental process undergone by parent B cells that gave rise to B lineage cancers. If a parent B cell succeeds in its first try, its clone will harbor one productive allele and one germline allele (monoallelic). If the parent B cell failed its first attempt at IgH rearrangement, its clone will harbor one non-productive IgH and one productive IgH (biallelic). B cells from healthy donors include both patterns. In unmutated CLL, biallelic clones occur at about the same frequency as for healthy B cells. However, for WM, MM and mCLL, which are likely to arise from antigen-experienced memory B cells, nearly all are monoallelic, including the additional clones that make up inter-clonal diversity. This might suggest that biallelic parent B cells may be negatively selected during transformation to WM, MM or mCLL.

B lineage cancers are also subject to strong clonal dominance. Given that new clones can emerge however, it becomes important to ensure that treatment does not inadvertently facilitate escape of additional clones. Clonal dominance appears to be strong in most WM, MM and uCLL, all of which have a poor outcome. Dominance appears to be weak in mCLL, which has a relatively good prognosis. Strong clonal dominance may correlate with more aggressive disease, and more effective immune blockade. However, inter-clonal diversity may also contribute to T cell blockade by abnormal clones which might otherwise have no clinical impact. Evaluation of PD-1/PDL-1 immune checkpoint inhibitors as immunotherapeutics in WM (abstract by Chu et al.) appears justified for controlling both clinical and cryptic clones.