CLONAL ORIGINS OF WALDENSTROM'S MACROGLOBULINEMIA

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Malignant B-cells can arise at any stage of normal B-cell differentiation, and knowledge of this stage of arrest will impact on disease classification and understanding underlying biology. Tumor cells retain in their genome an imprint of differentiation events likely to have occurred during clonal evolution, and which may continue to impact on tumor progeny. One particular locus, the rearranged immunoglobulin variable region (V) gene, can be particularly revealing in this regard. In fact, it has now become feasible to classify B-cell tumors in relation to the germinal center (GC), a site of somatic mutation, and define tumors as those of pre-GC origins, as those remaining in the GC, and as those with a post-GC origin, which traverse the GC and exit. Analysis of isotype switch events via V gene probes provides another tier of maturational status in tumor cells. The presence of tumor-derived isotype-switched transcripts can reveal whether tumor cells have activated switch mechanisms, at least at the RNA level. It is an assay of at least a log-scale greater sensitivity than Southern blotting to assess isotype switch.

For Waldenstrom's macroglobulinema (WM), early data on V_H gene status showed evidence for somatic mutation, and in one case demonstrated intraclonal heterogeneity. To extend these findings, we analyzed 7 cases of WM and 3 cases of IgM monoclonal gammopathy of undetermined significance (MGUS). In each case, V_H genes were somatically mutated with no evidence of intraclonal variation, including MGUS. Each case was further evaluated for evidence of isotpe-switch events using nested RT-PCR with patient-specific primers. No tumor-derived isotype switch variants could be identified in 7/7 WM and 3/3 MGUS cases, using a strategy that has successfully identified such transcripts in a number of other B-cell tumors in small cohort studies.

In contrast to IgM-secreting multiple myeloma, our results suggest clonal origins for IgM MGUS and WM from a mature IgM+ B-cell arrested at a stage preceding isotype switch. Tumor cells also do not appear to activate switch mechanisms during tumor maintenance. In IgM MGUS, these findings appear to indicate origins which differ from isotype-switched MGUS, some of which display intraclonal heterogeneity, but the number of cases need to be extended. The localization of IgM-secreting tumors to the bone marrow fits with the observation that normal IgM+ memory cells can be found there. Indeed, these memory cells retain the potential to mature to IgM-secreting cells. Tumorigenic arrest in IgM MGUS and WM could conceivably occur in such a cell at this site, with somatic mutation silenced and switch mechanisms not engaged.