Antigen Reduction, a New Approach for the Treatment of Subsets of MGUS and Multiple Myeloma?

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Editorial

There is mounting evidence that chronic antigen stimulation as an early pathogenic mechanism in the development of B-cell malignancy concerns significant numbers of patients. It is now established that about 50% of cases of chronic Lymphocytic Leukemia (CLL), leukemic clones display somatically-mutated Immunoglobulin (Ig) Heavy (H) Chain Variable (IGHV) genes, an observation consistent with antigen-driven disease [1]. Because of distinct disease presentation and evolution, it has become important to recognize antigen-driven B-cell malignancies: for instance, patients with somatically-mutated (antigen-driven) CLL have a more favorable clinical course than other CLL patients [2,3]. Evidence in favor of chronic antigen stimulation has also been reported in Monoclonal Gammapathy of Undetermined Significance (MGUS) and in Multiple Myeloma (MM) [4-8]. Myeloma patients whose monoclonal immunoglobulin targets Epstein-Barr virus (EBV) EBNA-1 protein i.e. (who likely have EBV-driven MM) may present with a more severe form of disease [6]. The antigens associated with the development of CLL, MGUS or MM are far from being all identified, yet the current literature suggests that they may differ in CLL and in MGUS/MM. CLL-associated antigens appear to be mostly autoantigens, notably cytoskeleton components (non-muscle myosin heavy chain IIA, vimentin, coflin-1, filamin B) and auto-antigens typically found in apoptotic cells and in bacteria [9-11]. Evidence of virus (Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV))-driven CLL has been less reported [12-14]. The targets of monoclonal Igs from MGUS and MM patients reported so far include viruses (> 25% cases, predominantly EBV, and to a lesser degree, HCV and other Herpesviruses), glucoolipids (notably Lysoglucosylceramide (LGL1)) and a glucocerebrosidase-associated enzyme (saposin C) [4-8]. Altogether, about half of MGUS and MM patients may present with a monoclonal Ig specific for EBV, HCV, another virus, or LGL1. To summarize, CLL-associated antigens seem to be mostly autoantigens that relate predominantly to bacterial infections and/or apoptotic cell removal, whereas the presently identified targets of MGUS and MM monoclonal Igs seem to be associated with viral infection or with LGL1.

These new findings support a pathogenic model of antigen-driven disease valid not only for about half of CLL cases, but also for MGUS and MM. In this model, represented in the figure below, a latent viral infection normally leads to the production of polyclonal Igs directed at the virus, then for subsets of patients, Ig production becomes oligoclonal and overtime, monoclonal (MGUS stage). Chronic inflammation is already present at these early stages: indeed, similar levels of inflammation cytokines were reported at the MGUS and MM stages [15]. Over the years, the repeated acquisition by the plasmacytic clone of multiple genetic alterations of increasing severity allows the disease to eventually progress toward smoldering myeloma, then to overt MM. Importantly, this new pathogenic model offers new therapeutic approaches for both MM and MGUS: in addition to eliminating the malignant plasma cells, the objective of current MM therapeutic protocols, one can envision to suppress, or at least reduce the amount of antigen responsible for the disease, i.e. the target of the patient’s monoclonal Ig, once identified.

Identification of antigen-initiated MGUS and MM cases can now be done, via the determination of the target of the patient’s monoclonal Ig (infectious pathogen, LGL1, other self-antigen), and the relevant assays could become useful new diagnostic tests for MGUS and MM [6,16,17]. MGUS patients, who are not treated presently, could benefit from antigen-reduction treatments, and this approach would contribute to prevent evolution toward overt MM [18,19]. Applied to antigen-
driven MGUS, if one could clear the underlying chronic infection early on, it may be possible to prevent the development of MM. Whenever possible, a reduced amount of autoantigen responsible for the chronic stimulation of the plasmacytic clone should be similarly beneficial. In support of this approach, the addition of anti-viral drugs to classic MM treatments resulted in disease regression and/or improved response to chemotherapy for HCV-associated MM cases [20,21]. Regarding Herpesviruses and particularly EBV, different anti-viral drugs already exist and new drugs as well as vaccines are being developed [22-24]. Drugs that target BCR signaling, already used successfully in CLL, may also be considered [25-28]. Regarding myeloma patients with a LGL1-specific monoclonal Ig, reduction of LGL1 levels may be envisioned as a complementary treatment: in Gaucher patients, LGL1 reduction has been successfully achieved for years now, and in murine models, LGL1 reduction has been shown to prevent B-cell malignancy [29-33].

In conclusion, target antigen reduction deserves consideration as a new therapeutic option to be tested in MGUS and as a complementary treatment in MM protocols.

References