Session II: Genetic Basis and Pathogenesis

of WM and IgM Related Disorders

Abstract 109

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CD27 in defining B-cell memory origins in WM. Surinder S. Sahota, Gavin Babbage, Nicola Weston, Bell Cancer Sciences Division, School of Medicine, University of Southampton, Southampton, UNITED KINGDOM.

CD27 is a transmembrane glycoprotein which belongs to the tumor necrosis factor receptor family, and functions to regulate B-cell activation via its ligand, CD70. Seminal studies identified CD27 as an apparently robust marker for memory B-cell status in normal human B-lymphocytes. However, the imprint of somatic mutation (SM) in immunoglobulin variable (V) region genes remains the gold standard for defining memory status, and encounter with antigen. In Waldenström's macroglobulinemia (WM), early small cohort studies reported a high level of SM in all tumor V_H genes, with no intraclonal variation at the bulk population level, suggesting origins from a post-follicular B-cell. More recently, a few WM cases have been reported which display unmutated (UM) V_H genes. In mutated (MUT) WM, the major subset of disease, we observed that when V_H mutation patterns are evaluated at the single cell level, there is evidence for substantial intraclonal variation, revealing that at least some of the tumor progeny is engaged in on-going mutations. These cases also express activation induced cytidine deaminase (*AID*), a pre-requisite for SM. Furthermore, we also observed a low level of *in-vivo* isotype switching in WM, implicating *AID* and indicating intraclonal diversification. Importantly, we were able to confirm that WM cells could be traced in CD27+ve and CD27-ve fractions, questioning whether MUT WM arises from conventional CD27 memory B-cells. Recently, we evaluated a distinct IgM+CD27-ve population in normal peripheral lymphocytes which lacks ABCB1 transporter activity associated with naïve B-cells. Analysis of V_H3/V_H5 genes in this IgM+CD27-ve pool revealed a low level of mutation, delineating a novel memory population. Such a cell could give rise to WM, with on-going mutations generating high levels seen in tumor cells. Consequently, in MUT WM it is the imprint of V gene mutation, not CD27 expression, which is the definitive marker of origins from a memory B-cell, derived either from the new CD27- memory pool or from CD27+ memory B-cells which then shed expression as tumor evolves. UM WM defines a separate minor pathway of origin from naïve B-cells. In WM, V_H gene mutational status clearly reveals divergent clonal pathways of origin of disease.