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Review

Unlocking the secrets of immunoglobulin receptors in mantle cell lymphoma: Implications for the origin and selection of the malignant cells

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ABSTRACT

Immunogenetic analysis of mantle cell lymphoma (MCL) has offered important evidence helping to decipher the immune pathways leading to its development and also prompting a reappraisal of the views about its ontogeny. In particular, older and more recent studies have demonstrated that MCL is characterized by a highly distinctive immunoglobulin gene repertoire with remarkable predominance of the *IGHV3-21* and *IGHV4-34* genes; restricted associations of *IGHV*, *IGHD* and *IGHJ* genes, culminating in the creation of quasi-identical ("stereotyped") heavy complementarity-determining region 3 sequences in roughly 10% of cases; and, very precisely targeted and, probably, functionally driven somatic hypermutation, ranging from minimal (in most cases) to pronounced. Furthermore, comparison to other entities, in particular CLL, revealed that several of these immunogenetic features are "MCL-biased". On these grounds, an antigen-driven origin of MCL could be envisaged, at least for subsets of cases.

1. Introduction

Mantle cell lymphoma (MCL) is an aggressive B cell malignancy, which represents 5–10% of non-Hodgkin lymphomas [1–3]. Most patients present at a late clinical stage with widespread lymph node involvement, while leukemic disease, involvement of the gastrointestinal tract, bone marrow and spleen also frequently occur [1]. The median overall survival is 3–5 years and, at present, conventional treatment is not curative [1,3]. However, MCL is not clinically homogeneous, as subsets of patients show a more favorable clinical course with a relatively long period of stable disease [1,4]. Furthermore, MCL is histologically heterogeneous with several variants defined on the basis of cytologic appearances [2].

Mounting evidence suggests that the clinical and phenotypic heterogeneity of MCL is linked to an underlying genetic heterogeneity. The cytogenetic hallmark of MCL is the chromosomal translocation t(11;14)(q13;q32) which results in the juxtaposition of the *CCDN1* locus on chromosome 11 to the *immunoglobulin heavy chain* (*IGH*) locus on chromosome 14 [5]. At the molecular level, this aberration leads to constitutive over-expression of cyclin D1 causing gross cell-cycle deregulation [3,6–8]. Although the up-regulation of this cell cycle regulatory protein contributes to the pathogenesis of MCL, it is not sufficient by itself for tumor progression, supporting early findings in mice studies [9]. MCL is also characterized by a large number of recurrent genomic aberrations, implying that cyclin D1 over-expression must be accompanied by other genetic abnormalities to promote lymphomagenesis [3,10–12]. Notably, candidate genes have been identified in some of these regions, where many of them are involved in important aspects of cell cycle regulation and DNA response (e.g. *ATM*, *BCL2*, *MYC*, *TP53*) [10,13]. Finally, it is relevant to note that a minor fraction of MCL cases do not over-express the *CCND1* gene and lack any translocation affecting chromosome 11q13 locus, though still exhibiting similar gene expression profiles and similar secondary genetic alterations to t(11;14)-positive MCL, arguing that they share a common genetic origin [1,3–4,14–15].

Studies over the last two decades have proven beyond doubt that immunogenetic analysis can offer important insight into the ontogeny and evolution of B cell lymphomas [16,17]. In particular, the presence of somatic hypermutation (SHM) in the clonotypic immunoglobulin (IG) receptors is widely considered as evidence of affinity maturation within the context of antigen encounter [18,19], while restrictions in the IG gene repertoire are regarded as a "molecular signature" of selection by antigen [20]. Hence, the

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study of IG receptors may assist in both tracing the developmental stage at which lymphomatous transformation occurred and understanding the cross-talk between the neoplastic clones and their microenvironment.

MCL constitutes no exception in this respect. Here we provide an overview of earlier and recent immunogenetic studies of MCL; relate the molecular findings about the IG receptors to the pathogenesis and evolution of this lymphoma; and, finally, discuss potential clinical and prognostic implications.

2. Mantle cell lymphoma exhibits a biased IGHV gene repertoire

Similar to other B cell malignancies, the study of the IG gene repertoire in MCL has focused mainly on *IGH* gene rearrangements. A consistent finding in all relevant studies of MCL was the strong bias to the usage of the certain *IGHV* genes. In particular, preferential use of the *IGHV4-34*, *IGHV3-21* and *IGHV3-23* genes has been reported, though their relative frequencies differed between studies [21–26].

We recently published a large study of the IGHV-IGHD-IGHJ gene rearrangements from 807 patients with MCL, by far the largest yet conducted [27]. Our results confirm and significantly extend previous observations that the *IGHV* gene repertoire in MCL is remarkably biased, since only four genes (*IGHV3-21*, *IGHV4-34*, *IGHV1-8*, and *IGHV3-23*) collectively accounted for almost half of the cohort (Fig. 1). On these grounds, we proposed that selective forces may have been critical in shaping the IG gene repertoire and, by extension, that a limited set of antigens and/or super antigens may be specifically involved in MCL development [27]. Additional evidence in support of this notion is provided by the comparison of the IG gene repertoire in MCL versus either normal B cells, including naïve B cells [28], or other B cell malignancies, namely chronic lymphocytic leukemia (CLL) [29] and splenic marginal zone lymphoma (SMZL) [30], which revealed significant differences, especially regarding the usage of the *IGHV3-21* and *IGHV1-8* genes (Fig. 2). Therefore, the immunogenetic evidence is compatible with distinct immune pathways to lymphoma development: whether this implies selection of different progenitor cells, or different selecting elements or both remains to be established.

The two most frequent *IGHV* genes in the MCL repertoire, namely *IGHV3-21* and *IGHV4-34* (with frequencies peaking at 16.5% and 14.5%, respectively [27]), are intriguing from both an immunological and an ontogenetic perspective. In the case of the former, among all human *IGHV* genes, *IGHV3-21* along with its closest relatives, i.e. the *IGHV3-48* and *IGHV3-11* genes, exhibit the highest homology scores (85–89%) to a certain mouse *IGHV* gene (*IGHV5-17*) [31]. Although the nature of the selective forces driving the evolution of the *IGH* locus among different species is still a matter of controversy, it has been argued that the distinct evolutionary directions taken by the human and mouse IG genes will be in part induced through selection by the antigens produced in the different environments that humans and mice have encountered over the past 70 million years of evolution [32–34]. Therefore, the remarkable phylogenetic conservation of *IGHV3-21* and its mouse homolog can justifiably be considered as strong evidence for conservation by some functional constraint.

The *IGHV4-34* gene encodes antibodies, which are intrinsically autoreactive by virtue of universal, and largely light chain-independent, recognition of the N-acetyllactosamine (NAL) residues expressed by the blood group I/i antigens and many other self-glycoproteins, including CD45/B220 [35,36]. In addition, they may bind other self-antigens such as DNA, gangliosides, IgG (rheumatoid factor activity), and neutrophil cytoplasmic antigens (ANCA activity) [36,37].

IGHV4-34 B cells account for a large fraction of the pre-immune repertoire and expand after certain infections (e.g. by EBV or *Mycoplasma pneumoniae*) [37]. Intriguingly, a large fraction of mouse peritoneal B-1 cells that react with anti-phosphatidylcholine/red blood cells is encoded by the *VH12 gene* [38], the closest mouse homolog to the human *IGHV4-34* gene [31]. Similar to what has been observed for human IGHV4-34 B cells, autoreactive VH12 mouse B-1 cells are positively selected and appear to play a protective antimicrobial role [38]. Hence, it has been suggested that the *IGHV4-34* gene has been selected over evolutionary time for the ability to offer protection against a broad range of pathogens and also for providing functions crucial for the regulation of homeostasis [39], e.g. removal of debris produced by the daily turnover of apoptotic cells. Likely due to these properties, however, autoreactive IGHV4-34 cells are strictly censored in the peripheral repertoire of healthy individuals, perhaps explaining why IGHV4-34-encoded antibodies are infrequent in the sera of normal individuals [40], suggesting an anergic status of IGHV4-34 B cells.

The relevance of these observations to MCL ontogeny is currently unknown. However the striking overuse of these highly conserved genes in the MCL repertoire raises the possibility that the progenitors of at least a major fraction of MCL cases are perhaps constrained to express particular *IGHV* genes, which would render them selectively responsive to (a range of) certain antigens.

3. Restricted associations of IGHV, IGHD and IGHJ genes in mantle cell lymphoma lead to the creation of distinctive antigen-binding sites

Sequence diversity among IG receptors is not evenly distributed but highly concentrated in the antigen-binding site. This skewing of diversity is mainly attributed to the highly diverse complementarity-determining region 3 (CDR3) sequences which are the principal determinant of specificity in antigen recognition, at least in the primary repertoire [41]. This fact has also prompted extensive studies into the molecular and structural features of the CDR3s (especially those of the heavy chains, VH CDR3s) in IG receptors of both normal and malignant B cell clones, which have yielded a vast amount of information concerning the potential mechanics and dynamics of the antigen-binding site with implications for antigen selection [42–44]. In the field of human lymphomas, this research activity has culminated in the recognition of cases of CLL with highly similar to virtually identical IGs in their B cell receptors ("stereotyped" BcRs), collectively accounting for an amazing one-third of all CLL [29,31]. Notably, emerging data suggests that the grouping of CLL cases into subsets based on IG stereotypy can be reflected in a similar antigen reactivity profile and a similar clinical outcome, at least for selected subsets [45–51].

Biases in the *IGHD* and *IGHJ* gene repertoires and other distinctive VH CDR3 features were already apparent in the early immunogenetic studies of MCL. Consistent results have been reported in almost all relevant publications [21–26], including our recent study [27]. In particular, *IGHD3* genes predominate, especially the *IGHD3-3* gene, whose frequency in our series exceeded 10%. Regarding *IGHJ* genes, the majority of cases utilized either the *IGHJ4* or the *IGHJ6* gene [27].

Far more interesting, though, than individual gene frequencies, is the restricted association of specific *IGHV* genes with certain *IGHD* or *IGHJ* genes. For instance, we found that more than 30% of *IGHV3-21* rearrangements utilized the *IGHD3-3* gene. Similar, though less pronounced biases were seen for *IGHV1-8* and *IGHV4-34* rearrangements, which frequently utilized the *IGHD2-2* or the *IGHD2-15* gene, whereas, in contrast, no such bias was