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Review Article

Pathogenesis of splenic marginal zone lymphoma

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ABSTRACT

Splenic marginal zone lymphoma (SMZL) is a distinct low grade B-cell lymphoma with an immunophenotype similar to that of splenic marginal zone B-cells. Like the normal splenic marginal zone B-cells, SMZLs also show variable features in somatic mutations of their rearranged immunoglobulin genes, with ~90% of cases harbouring somatic mutations but at remarkably variable degrees, suggesting that SMZL may have multiple cell of origins, deriving from the heterogeneous B-cells of the splenic marginal zone. Notably, ~30% of SMZLs show biased usage of *IGHV1-2*04,* with the expressed BCR being potentially polyreactive to autoantigens. Recent exome and targeted sequencing studies have identified a wide spectrum of somatic mutations in SMZL with the recurrent mutations targeting multiple signalling pathways that govern the development of splenic marginal zone B-cells. These recurrent mutations occur in *KLF2* (20–42%), *NOTCH2* (6.5–25%), NF-κB (*CARD11* ~7%, *IKBKB* ~7%, *TNFAIP3* 7–13%, *TRAF3* 5%, *BIRC3* 6.3%) and TLR (*MYD88* 5–13%) signalling pathways. Interestingly, the majority of SMZL with *KLF2* mutation have both 7q32 deletion and *IGHV1-2* rearrangement, and these cases also have additional mutations in *NOTCH2*, or *TNFAIP3*, or *TRAF3*. There is a potential oncogenic cooperation among concurrent genetic changes, for example between the IGHV1-2 expressing BCR and *KLF2* mutation in activation of the canonical NF-κB pathway, and between *KLF2* and *TRAF3* mutations in activation of the non-canonical NF-κB pathway. These novel genetic findings have provided considerable insights into the pathogenesis of SMZL and will stimulate the research in both normal and malignant marginal zone B-cells.

Contents

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1. Introduction

Splenic marginal zone lymphoma (SMZL) is a distinct low grade B-cell lymphoma, accounting for <2% of lymphoid neoplasm. Clinically, it is featured by splenomegaly, moderate lymphocytosis and sometimes autoimmune thrombocytopaenia or anaemia [1–3]. Histologically, SMZL is characterised by a neoplastic infiltrate composed of an inner zone of small lymphocytes that replace the normal mantle zone, and an outer zone of medium sized cells with clear cytoplasm in the location of the marginal zone where proliferation takes place [1,2]. The histological and immunophenotypic features of SMZL clearly separate it from nodal marginal zone lymphoma and extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma). More recent studies also reveal distinct genetic changes in SMZL, and interestingly many of these genetic changes affect the molecular pathways that govern the marginal zone B-cell development. This review summarises the recent advances in genetic characterisation of SMZL and discuss their potential role in the lymphoma pathogenesis.

2. Cell of origin of SMZL

The normal cell counterpart of SMZL is unclear [1], and the effort to define the differentiation stage of the B cells that give rise to SMZL is hindered by a lack of understanding in the development of human splenic marginal zone B-cells. Nonetheless, SMZL shares the immunophenotype ($CD27^+$ IgM^+ IgD^+) of human splenic marginal zone B-cells [1,2,4]. There are also similarities in the pattern of somatic hypermutation of the rearranged immunoglobulin heavy chain variable genes (*IGHV*) between SMZL and normal splenic marginal zone B-cells albeit limited studies in the latter. Somatic hypermutations of the rearranged *IGHV* are seen in the vast majority (~90%) of both SMZL and normal splenic marginal zone B-cells [5–10]. The extent of these somatic mutations is also similar between SMZL and normal splenic marginal zone B-cells, ranging from complete identity (100%) to the germline sequence, to minimally (97–99.9%) and significantly (<97%) mutated [5–10]. Finally, the characteristic mutation features of antigen selection are seen in a proportion of both SMZL and splenic marginal zone B-cells [5–9]. These findings suggest that SMZL may have multiple cells of origins, deriving from heterogeneous B-cells residing in the normal splenic marginal zone.

3. Marginal zone B-CELL development

The precise details on the generation of human splenic marginal zone B-cells, their migration to and retention in the splenic marginal zone are unclear. In light of the presence of somatic mutations of the rearranged *IG* genes in the vast majority of human splenic marginal zone B-cells, it is generally believed that these are IgM memory B-cells that exit the germinal centre reaction prior to isotype switch [4,11,12]. The splenic marginal zone B-cells without somatically mutated *IG* genes may derive from the T-cell independent pathway [4,11–13]. There are several molecular pathways or regulators that are known to play a critical role in marginal zone B-cell development (Fig. 1).

3.1. NOTCH2 signalling

The canonical NOTCH signalling is mediated by NOTCH ligand–receptor interaction between neighbouring cells. Upon binding by ligand DLL1, the surface receptor NOTCH2 undergoes two successive proteolytic cleavages: first to remove the extracellular domain by ADAM family protease, then to release the NOTCH intracellular domain (NICD) by γ-secretase [14,15]. The liberated NICD translocates to the nucleus, binds to the transcription factor RBPJ and transactivates its target genes [14,15]. During the transcriptional activation process, NICD is

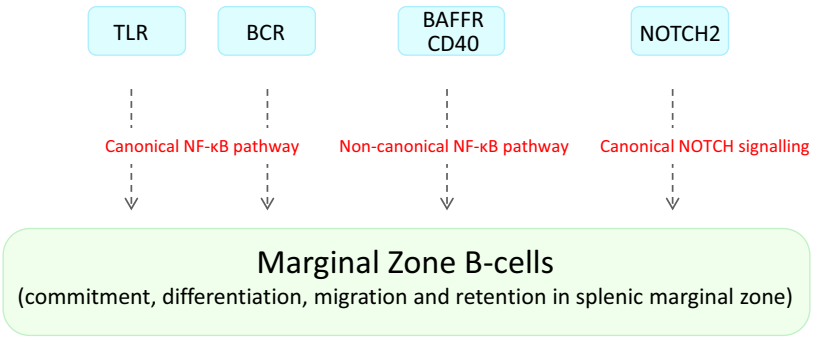

Fig. 1. Known surface receptors and their involved pathways critical for marginal zone B-cell development. A concerted action of these receptor signallings is thought to govern the commitment and differentiation of marginal zone B-cells, their migration to and retention in the splenic marginal zone although the precise role of these receptor signallings is not totally clear.