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Is Chronic Lymphocytic Leukemia a Mistake of Tolerance Mechanisms?

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1. Introduction

Chronic Lymphocytic Leukemia (CLL) is a chronic lymphoproliferative disorder of the B lymphocytes. Small lymphocytic lymphoma (SLL) is considered to be the same disease in a non-leukemic form. CLL remains as an incurable tumour and clinical features have very variable presentation, course, and outcome. The progressive accumulation of monoclonal B lymphocytes leads to leukocytosis, lymphadenopathy, hepatosplenomegaly and marrow failure, and is sometimes associated with autoimmune manifestations.

It has been suggested that CLL cells are defective in apoptosis, which leads to the accumulation of malignant B cells. Furthermore, patients with proliferation rates greater than 0.35% per day have been found to have a more aggressive disease[18,19]. Proliferation of CLL cells is most prominent in proliferative centers that include specific areas in lymph nodes and bone marow[20,21]. Numerous CD4 T cells and dendritic cells are in close contact with CLL B cells [22], and micro environmental interactions like BM stromal cells are able to extend the survival of CLL upon direct contact[21]. Thus, the CLL population may originate from a clone with few or no V- domain mutations, or from a more mature clone whose V-domains have undergone the hypermutation process. This creates two separate pools of B cells, both of which originate from antigen-stimulated B lymphocytes. Additionally, IGHV unmutated CLL B cells expressing polyreactive antibodies whereas most IGHV mutated CLL´s did not. However, reversion of the IGHV mutated sequences to germline counterparts restored the polyreactivity (Herve et al 2005). Despite these features, the biological etiology of the divergent natural histories of IgVH unmutated vs mutated CLL and the origin of this type of leukemia/lymphoma remains unknown. For this reason we review the immunologic aspects that can help to understand this complex disease based in the findings that suggest that both unmutated and mutated subgroups of patients originally derive from autoreactive clones.

2. Diagnosis

The diagnosis of CLL requires the presence of at least 5000 B lymphocytes/μL in the peripheral blood (Hallek, et al 2008). CLL/SLL can be identified by the immunophenotype CD5+, CD10–, CD19+, CD20+, dim expression of surface immunoglobulin, CD23+, CD43 +/–, and cyclin D1– (Matutes, et al 2007). The absence of cyclin D1 is critical in distinguishing CLL/SLL from MCL. Bone marrow involvement is characteristically more than 30% of the nucleated cells in the aspirate are lymphoid.

Prognostic Markers and Genomic Aberrations

A favorable prognosis in CLL/SLL is associated with the presence of a mutated immunoglobulin heavy chain variable region, and low CD38 and zeta-chain–associated protein kinase 70 protein expression(Damle et al 1999;Kröber et al 2002;Hamblin et al 1999; Tobbin et al 2002; Crespo et al 2003). Chromosomal aberrations in CLL include del 6q, del 11q, del 13q, trisomy 12, and del 17p (Döhner et al 2000). Importantly, specific genomic aberrations have been associated with disease characteristics such better survival for patients with 12q trisomy and 13q deletion, poor survival and massive lymphadenopathy in 11q deletion and resistance to therapy in the group of patients with 17p deletion and p53 abnormalities (Döhrner et al 2000; Döhrner et al 1995; Döhrner et al 1997;Krober et al 2006). In addition, two miRNA (miR-15a and miR-16-1) were recently identified to be located in the critical region of the 13q14 deletion and their absence in CLL appears to be a major factor in preventing apoptosis and progression through the cell cycle (Aqeilan et al 2010; Cimmino et al 2005; Callin et al 2004; Mertens et al 2006).

Pathophysiology and cell of origin/normal counterpart of CLL

Different from other types of malignancies derived from mature B cells, the pathogenesis of B-CLL/SLL is much less understood. Notwithstanding extensive searching it is not known whether there is an equivalent normal cell in which the CLL arise. However, several cell types have been suggested as giving rise to chronic lymphocytic leukemia included memory, transitional, B1 and marginal zone B cells (Chiorazzi and Ferrarini 2011; Griffin et al 2011). In addition, it is not certain at what stage in lymphocyte maturation the CLL cell arises, since roughly equal numbers seem to come from pre-germinal center B lymphocytes (unmutated group) and post-germinal center B lymphocytes (mutated group). However, the comparison of CLL gene expression profiles with those of purified normal B cell subpopulations indicates that the common CLL gene expression profile is more related to memory B cells than to those derived from naïve B cells, CD5+ B cells, or germinal center centroblasts and centrocytes (Klein et al 2001; Rosenwald et al 2001, Klein and Dalla-Favera 2005). Interestingly, unmutated and mutated chronic lymphocytic leukemias derive from self reactive B cell precursors despite expressing different antibody reactivity (Herve et al 2005). This similar expression profile also suggest that the consequences or even the mechanism of transformation may be similar, irrespective of IGHV mutations status. This too suggests that rather than having a cellular origin or cellular subtype, CLL is originated by a coordinated normal immunologic tolerance mechanism to destroy self-reactive B cells and to avoid autoimmunity during their process of differentiation. This point of view is supported by the fact that some CLL mutated and unmutated cases derive from self-reactive B cells (Herve et al 2005) had evidence of multiple, related rearranged heavy and light chain immunoglobulin genes (Volkheimer et al 2007; Hadzidimitriou et al 2009, Stamatopoulos et

al 1996); some express more than one functional Ig heavy chain (Rassenti et al 1997), some had been anergized (Mockridge et al 2007; Muzio et al 2008), edited (Hadzidimitriou et al 2009, Stamatopoulos et al 1996), switched (Cerutti et al 2002) and/or had progressive immunoglobulin gene mutation (Volkheimer et al 2007; Roudier et al 1990; Ruzickova et al 2002).

Hypothesis: Autoimmunity as origin of CLL

The basic hypothesis of the origin of autoimmune disease depends of the emergence of a clone or a small number of clones of T and B lymphocytes capable of damaging interaction with normal cells of organ or tissue involved. Each clone is initiated from a cell which has developed an immune receptor adequately reactive with an accessible self antigen as a result of a V/D/J gene recombination in bone marrow (unmutated) or during somatic mutations in germinal centers (mutated). Importantly, this newly self-reactive cell ("forbidden clone") is anomalously resistant to inactivation by central and peripheral tolerance check points (Burnet 1972). Similar to an autoimmune disease, some lymphoproliferative diseases (marginal zone lymphomas and chronic lymphocytic leukemia) depends of the emergence of a clone capable of interact with an (auto) antigen and with other normal cells and an specific microenvironment to proliferate and survive. In a parallel way, newly malignant B cells are anomalously resistant to apoptosis and proliferate as result of acquisition of genetic damage during V/D/J gene recombination, somatic mutations, class switching and receptor edition/revision. Importantly, with the exception of class switching, the other mechanisms to increase the diversity of B cell receptors might induce both self-reactivity and/or DNA damage.

B cell development and autoimmunity

The current model of the pathogenesis of CLL suggest that stimulation by (self) antigens provides a pro-survival and possibly pro-proliferative advantage for CLL (precursor) cells, most likely leading initially to oligoclonal and subsequently monoclonal selection of malignant cells (Mertens et al 2011)

In humans, B cells develop from progenitors within the bone marrow (Fig1). The stages of B cell ontogeny from pro-B to pre-B to early B to mature B cells are marked by phenotypic changes, the most important of which is expression of the BCR for antigen on the cell surface at the early B cell stage of development (van Lochem et al 2004; Fuda et al 2009) . During the course of ontogenesis, B cells mature in the bone marrow according to the evolution of the Ig chain synthesis. Starting with the rearrangement of the V/D/J genes for the heavy chain at the pre-B stage, the recombination process continues through the VJ gene rearrangements for kappa light chain or for the lambda light chain at the immature stage. Thus, the resulting receptor (BCR) comprised of randomly selected heavy and light chains have an unpredictable specificity that could include ability to bind "self". However, there are tolerance check points at every stage of B cell activation and maturation (table 1 and 2). This tolerance mechanisms in bone marrow include receptor editing, clonal deletion, clonal anergy and differentiation to B1 cells (Goodnow et al 2005; Radic et al 1993; Tiegs et al 1993; Nemazee et al 2000; Luning Prak et al 2011) Notably, current evidence suggest that anergy, receptor edition and differentiation to B1 B cells could be implicated in the generation of CLL B cells (Herve et al 2005; Chu et al 2010; Mockridge et al 2007; Hadzidimitriou et al 2009, Stamatopoulos et al 1996; Ghia et al 2008a; Rassenti & Kipps 1997; Murray et al 2008;

Griffin et al 2011). Additionally , hematopoietic stem cells sorted from a CLL patient´s bone marrow produce CLL like disease when transplanted into immunosuppresed mice (Kikushige et al 2011). Importantly, autoreactive B cells may suffer receptor editing and anergy in bone marrow. At the same, recent evidence shows that L chain receptor editing occurs not only in bone marrow with a pre-B/immature B cell phenotype but also in immature/transitional splenic B cells. Nevertheless, editing at the H chain locus appears to occur exclusively in bone marrow cells with pro-B phenotype (Nakajima et al 2009).

Repertoire analyses of antibodies cloned from B cells derived from bone marrow and peripheral blood of healthy donors provide evidence for both a central tolerance check point in the bone marrow and a second peripheral checkpoint, as evidenced by a decrease in the frequency of autoreactive antibodies from 75% in bone marrow to 20% in the circulating naïve compartment (Yurasov, et al. 2005). Other tolerance mechanisms and peripheral check points include memory development check points (Tsuiji et al 2006) CD5+ expression (Morikawa et al 1993; Gary-Gouy et al 2002; Hillion et al 2005; Hippen et al 2000, Gary-Gouy et al 2002b, Dallou et al 2008), germinal centre exclusion (Cappione et al 2005; Pugh-Bernard et al 2001), receptor edition/revision (Luning Prack et al 2011), antibody feedback (Ravetch & Bolland 2001), anti-idiotypic network (Jerne 1974; Jerne 1984; Forni et al 1980) and all contribute to maintain tolerance and avoid autoimmune diseases.

The contribution of this mechanism in the development of CLL remain unknown, however, Ghia et al describe that CLL expressing IGHV3-21/IGVL3-21 most likely were derived from B cells that had experienced somatic mutation and germinal center maturation in an apparent antigen driven immune response previous to undergoing Ig receptor editing and after germinal-center leukemogenic selection (Ghia et al 2008b). This suggest that peripheral tolerance mechanism also contribute to the shape of self reactive CLL B cells generated and selected after somatic hypermutation. Other mechanisms as germinal centre exclusion, defects in antibody feedback and anti-idiotypic network in lymphoproliferative disorders remain unsolved, however some conjectures about their role have been proposed (García-Muñoz 2009a; García-Muñoz et al 2009b).

The fact that unmutated and mutated chronic lymphocytic leukemias derive from self reactive B cell precursors despite expressing different antibody reactivity (Herve et al 2005) suggest that this B cells escape from tolerance mechanisms. Even more Chiorazzi and Ferrarini suggest that CLL derives from competent B lymphocytes selected for clonal expansion and eventual transformation by multiple encounters and responses to (auto)antigen(s) (Chiorazzi and Ferrarini 2003). This two characteristics of CLL B cells guide us to think that CLL is the product of the selective pressure of tolerance check points in an auto-reactive B cell.

Development of Unmutated CLL B cells

Tumors displaying unmutated V genes have a shorter median survival, in one study of 99 months vs 293 months in the mutated cases (Hamblin et al 1999). Here, a cut-off of $\geq$98% homology to donor germline gene has been used to define unmutated tumor V genes to allow for a low degree of polymorphic allelic variation. There is an association between unfavorable cytogenetic aberrations (del 17p and del 11q) and unmutated CLL, although 13q- is more frequent in mutated CLL. However, there are discrepancies with many cases having some high-risk and other low-risk molecular features and more than 50% of IgVH

unmutated cases have no unfavorable cytogenetics (Krober et al 2006). Prominently unmutated CLL B cells are self reactive or polyreactive (Herve et al 2005) and seem that they are resistant to several tolerance mechanism.

Are unmutated CLL B cells invulnerable to anergy?

Low BCR signaling induced by weak reactivity to self antigens induce B cells to enter a tolerized but alive state referred to as anergy (Gauld et al 2006; Getahun et al 2009) . In most cases, anergic B cells are characterized by chronic low level BCR signaling and exhibit reduced surface IgM levels but can express high levels of IgD (Getahun et al 2009; Goodnow et al 1998; Dolmetsh et al 1997). Interestingly, anergy depends on the degree of BCR occupancy and require constant transduction of a BCR signal (Goodnow et al 1989; Benshop et al 2001;Gauld et al 2005). Although it is clear that stimulation through the BCR occurred during the natural history of all types of CLL, it is quite peculiar that unmutated CLL cells retain the capacity to transmit signals through the BCR via surface IgM (Lanham et al 2003). The low expression of the BCR is the hallmark of CLL cells and anergic B cells, and appears to contribute towards producing poorer responses to BCR stimulation. Despite low levels of surface expressed immunoglobulin, signalling through the B cell receptor is possible. ZAP-70 expression has shown to augment signalling via IgM ligation in CLL cells as measured by phosphorylation of downstream mediators such as Syk, BLNK and PLC and calcium influx (Chen et al 2005) This increased signalling might lead to enhanced proliferation or survival of the leukemic cell (Bernal et al 2001). Significantly, a number of studies have shown a strong association between ZAP-70 expression and unmutated IGHV genes. This findings could imply that if an immature self-reactive B cell recognize an auto-antigen and also express ZAP-70 survival and activating signals prevail over anergy. In this case a self reactive CLL B cell selected by a self-antigen during B cell development in bone marrow might mature despite they undergo an anergy process and likely to progress to transitional and mature B cell.

Unmutated CLL cases are more frequently CD38 (66-77%) and ZAP-70 (93%) positive, exhibit IgM+ and IgD+ surface immunoglobulin, express higher amounts of BCR and response better to stimulation compared with mutated CLL´s (Wiestner et al 2003, Hamblin et al 2002; Thumberg et al 2001; Döhner et al 2000; Mockridge et al 2007; Guarini et al 2008). This characteristics suggest that this unmutated CLL B cells where resistant to anergy and progress to mature autoreactive naive B cells.

Receptor editing be unsuccessful to avoid self-reactivity and might induce polyreactive BCR in unmutated CLL B cells

Immature B cells expressing self-reactive IgM antibodies may undergo repeated rounds of light chain rearrangement to lessen the self specificity of the antibody, a process termed receptor editing (Nemazee et al 2000; Luning Prak et al 2011). Evidence of receptor editing in CLL is provided by the fact that a number of CLL´s have multiple light chain rearrangements (Hadzidimitriou et al 2009). B cell receptor of CLL B cells react with recurrent self antigens in vitro including IgG, thyroglobulin, DNA, actin, cardiolipin and others as well as microbial antigens and epitopes exposed on cell surface as a result of apoptosis and also could be stimulated by stroma-derived antigens (Sthoeger et al 1989; Dighiero et al 1991; Chiorazzi et al 2005; Lanemo Myhrinder et al 2008). Sustained or repetitive BCR signaling promotes survival in CLL cells (Petlickovsky et al 2005; Bernal et al

2001). Notably, unmutated CLL B cells are self reactive or polyreactive (Herve et al 2005). Interestingly, 79.3% of unmutated CLL antibodies are polyreactive (Herve et al 2005), and reactivity with a particular form of apoptotic cells is a common feature of this subset (Chu et al 2010). Even more, recently Rozcova et al revealed that Toll like receptor 9 (TLR-9) agonists are a potent stimulus from CLL B cells and induce proliferation, expression of CD38 and secretion of cytokines (Rozcova et al 2010). Outstandingly, TLR-9 recognition of self-molecules (nucleic acids in apoptotic cells) of the host, which are not easily distinguishable from those of no-self (infectious organisms) has the potential to provoke autoimmune diseases. Intriguingly, the unmutated CLL subset expresses antibodies with long heavy and light chain CDR3 (Herve 2005) and some cases of unmutated CLL with 100% of IGHV identity have multiple light chain rearrangements (Hadzidimitriou et al TS25 2009), associated with receptor edition. This suggest that receptor editing mechanisms could be not working well in this subset, even more is possible that increase polyreactivity (Luning Prak et al 2011; Binder et al 2010) and promote survival of self-reactive (Sandel et al 1999) CLL B cells. Consequently, BCRs that react with diverse epitopes may be more prone to sustained signaling. As a result, some unmutated CLL B cells expressing multireactive BCR have a more aggressive course than CLLs expressing less reactive BCRs (Binder et al 2010).

Are unmutated CLL B cells insensitive to CD5 action?

Induction of CD5 by autoantigen might be a mechanism by which the production of autoantibodies is avoided and also maintains tolerance in anergic B cells (Berland et al 2002; Hippen et al 2000). Recently, a very interesting observation was made that many CLL leukemia antibodies recognize non-muscle myosin heavy chain IIA exposed apoptotic cells (MEACs) and that natural antibodies from human serum also react with MEACs. In this study 15 of 16 MEAC-reactive CLL mAbs carried unmutated IGVH genes (Chu et al 2010). Several mechanisms are involved in the tolerance associated with expression of CD5. Likewise, CD5 expression prevents B lymphocytes from uncontrolled self reactivity increasing the BCR signalling threshold[51], and is associated with reexpresion of RAG, receptor edition/revision, and lack of responsiveness to BAFF in some cells outside bone marrow and germinal centres (Lee et al 2009; Hippen et al 2000, Hillion et al 2005). Along this line, the fact that anergic autoreactive B cells may express CD5+ and that immunoglobulin secreted by unmutated B-CLL cells is often autoreactive and react with a variety of autoantigens (including Fc portion of IgG, DNA, histones, cardiolipin, cytoskeletal proteins and insulin) support the notion that unmutated self-reactive B CLL cells are under check to avoid pathogenic autoimmunity (Broker et al 1988; Caligaris-Cappio et al 1996; Morbach et al 2006). We speculate that the expression of ZAP-70 and CD38 could encourage the stimulation of unmutated CLL B cells and overcome the inhibition induced by CD5. In addition, CD5 does not inhibit properly the BCR mediating signalling in leukemic B cells and in some cases provide viability signals or/and promote CLL B cell survival (Perez-Chacon et al 2007; Perez-Chacon 2007b; Gary-Gouy et al 2007; Gary-Gouy et al 2002; Gary-Gouy et al 2002).

Are unmutated CLL B cells transformed human B1 cells?

Similarities between normal human B1 cells and malignant chronic lymphocytic leukemia (CLL) cells, include that both are CD20+CD27+CD43+CD70-; most normal B1 cells express CD5, as do malignant CLL cells; and, both express relatively nonmutated IGHV. In addition,

normal human B1 cells are ZAP-70+ like unmutated CLL cells. As a final point, in respect to pathophysiology, Griffin et al propose that the chronically activated phenotype of normal B1 cells may predispose to malignant transformation (Griffin et al 2011).

Are unmutated CLL naïve self-reactive B cells efficiently excluded by germinal centres?

In order to prevent autoimmunity, censoring mechanisms, including anergy and sequestration into the marginal zone, ultimately forbid the participation of mature autoreactive B cells in productive germinal centres reactions, thereby precluding their expansion into the long-lived IgG memory and plasma cell compartments. Importantly, most self reactive and polyreactive IgG antibodies originate from non self-reactive B cells that acquired reactivity by somatic hypermutation (Tiller et al 2007). Significantly, somatic hypermutation does not appear to occur uniformly among CLL IGHV genes(Chiorazzi et al 2005; Fais et al 1998; Tobin et al 2002; Ghia et al 2005) and might suggest the effect of germinal centre exclusion and tolerance mechanisms to maintain the self-reactive BCR in a germ line state and avoid the participation of unmutated CLL cases in germinal centres reactions.

Development of Mutated CLL B cells

Fifty percent of CLL patients have undergone somatic hypermutation in IGHV, and these patients have a more indolent clinical course and longer survival than those without somatic hipermutation (Hamblin et al 1999; Damle et al 1999). The majority of cases of mutated CLL fail to signal via IgM in vitro (Lanham et al 2003; Chen et al 2002). Interestingly, CLL B cells that express only IgD+ are linked to mutated IGHV genes, negative or low CD38 expression, and 50% of mutated CLL cases unable to signal via IgM were able to signal via IgD (Stevenson et al 2004). Muzio et al, showed that CLL B cells (typically IGH-mutated cases) that do not respond to BCR ligation show activation cellular pathways that suggest anergy (Muzio et al 2008). Essentially, mutated CLL cases derive from B cells with self-reactive receptors that were anergized, edited or regulated to avoid autoimmunity. This is supported by the fact that when mutated non autoreactive immunoglobulin sequences of mutated CLL cases were reverted to their germline counterparts, they encoded polyreactive and autoreactive antibodies (Herve 2005). Despite somatic hypermutation had been proposed as a mechanism to change original BCR self reactivity (germ line) towards some non-self BCR (Murray et al 2008), this is an eccentric mode to loss self reactivity because, self reactive naive B cells are efficiently excluded from germinal centres (Tsuji et al 2006; Cappione A 3rd et al 2005; Pugh-Bernard et al 2001) and if this check point is bypassed B cells progress to plasmatic cells that produce auto-antibodies. Still, a significant fraction of self-reactive BCR fail to be edited or trigger deletion in primary lymphoid tissues, either because the self-antigen are bound with only low avidity or because they are not sufficiently abundant in primary lymphoid organs. For receptors with intermediate avidity for self antigens, the risk they pose for autoimmunity may not overshadow their potential use in fighting infection. B cells with receptors that fall into this zone undergo a conditional type of clonal deletion that is extrinsically regulated through competition with B cells bearing less self reactive BCR (Cyster et al 1994; Lanemo Myhrinder et al 2008). This also can explain that unmutated CLL cases and mutated CLL cases express different antibody repertoires and different VH genes (Fais et al 1988; Johnson et al 1997). Current data support that CLL cells are in active (auto) antigen driven receptor editing, presumably by keeping away from autoreactivity

associated with preferential autoimmune linked IGHV gene utilization in CLL patients like IGHV3-21, IGHV4-34, IGKV1-17 (Foreman et al 2007; Hadzidimitruiou et al 2009) and also IGHV5-51 and IGHV1-69 in unmutated IgVH genes (Chapal et al 2000; Vanura et al 2008). Interestingly, highly polyreactive antibodies are expressed frequently by unmutated CLL, but only rarely by mutated cases, supporting the view that the receptor editing mechanism is significantly active to try to elude autoimmunity in CLL.

In mutated CLL cases quite a lot of cellular strategies are used to regulate self-reactive receptors at different points during B cell differentiation.

1. The receptor is edited to one that is less self reactive by V(D)J recombination (Hadzidimitriou et al 2009; Rassenti et al 1997 Ghia et al 2008b; Kalinina et al 2011).
2. Regulation by BCR downregulation and anergy (Muzio et al 2008).
3. Induction of inhibitory receptors as CD5 by self-reactive BCR (Hippen et al 2000; Morikawa et al 1993; Dallou et al 2008; Hillion et al 2005).

Table 1. BCR tolerance mechanisms in central lymphoid organs (bone marrow) include receptor edition, anergy and induction of inhibitory receptors as CD5.

Regulation of self reactive receptor in follicles

Each of the checkpoints described above deal with self-reactive receptor generated by V(D)J recombination in the primary lymphoid organs; however, self-reactive BCRs are also generated in a second wave of receptor-gene-diversification through somatic hypermutation in germinal centre follicles of peripheral lymphoid tissues (Shiono et al 2003; Radic et al 1994; Ray et al 1996). Despite somatic hypermutation could produce modifications in BCR to ablate self-reactivity (Murray et al 2008) also might produce new self-reactive BCR. In addition somatic hypermutation poses a particular severe threat of autoimmunity for the reason that increase the affinity of antibodies for self-antigens, the follicular pathway of B cell differentiation generates long lived plasma and memory cells and numerous apoptotic cells be present in germinal centres with self components that are trapped and displayed as immune complexes on follicular dendritic cells. For these reasons the immune system contain a number of mechanisms to elude the maturation of self-reactive B cells that encourage an autoimmune disease. Self-reactivity of mutated CLL cases may derive from immature self-reactive B cells that suffer somatic hypermutation or by non-self reactive B cells that acquire self-reactive BCR during somatic hypermutation in germinal centres. In humans two types of memory B cells have been described: IgM+ memory B cells and class-switched memory B cells (Agematsu et al 1997; Klein et al 1998; Tangye et al 1998). Transition from naive B cells into circulating IgM+ memory B cells is accompanied by efficient counter selection against self reactive naive B cells before the onset of somatic hypermutation and that self reactive IgM+ memory B cells present in the circulation of healthy humans gain self-reactivity as a result of somatic hypermutation (Tsuji et al 2006).

The increase in self-reactivity during transition between mature naive and IgG+ memory B cells might be due to selective advantage for pre-existing self-reactive cells, or selection for cells with self reactive antibodies produced by somatic hypermutation. (Tiller et al 2007) This mechanisms could contribute to generate the IgG+ CLL cases (Ghiotto F, et al 2004).

1. Germinal centre exclusion (Tsuji et al 2006; Cappione A 3rd et al 2005; Pugh-Bernard et al 2001).
2. The receptor is modified to one that is less self reactive by BCR hypermutation (Murray et al 2008, Tiller et al 2007).
3. Receptor edition/revision (Hadzidimitriou et al 2009; Kalinina et al 2011; Rochas et al 2007)
4. CD5 expression (Hillion et al 2005).
6. Absence of T cell help (Shokat et al 1995)
7. Competition for follicular niches (Cyster et al 1994)

Table 2. Tolerance mechanisms in peripheral lymphoid organs.

Tolerance induced by absence of T-cell help:

A substantial portion of the activated B cells migrate to germinal centers where they undergo the process of somatic hypermutation. These B cells first remove the BCR from their surface, then undergo several rounds of division, and finally re-express mutated immunoglobulin receptors. The cells then undergo a negative selection process similar to that of transitional B cells. The antigen is provided from antigen-antibody complexes on follicular dendritic cells. Survival requires the receptor to be of high enough affinity to out-compete the already circulating antibody and allow B cell uptake and processing of antigen For display peptides to primed helper T cells, which have also moved into the germinal centers (Kearneay et al 1994). If the B cell receives T cell-help it survives and is stimulated to undergo another round of expansion and differentiation. If T cell help is not received, the B cell can become anergized or die by apoptosis (Shokat, et al 1995).

We suggest that in CLL with mutated Ig genes, the proliferating B cells is likely to have traversed a germinal center and acquire "*de novo* self-reactivity" originated in the process of somatic hypermutation mechanism or by receptor editon revision. After this "*de novo* autoreactivity" a normal CD5- B cell can theoretically be transformed into a "*de novo* autoreactive memory B cell" that express CD5+ (increase the threshold for BCR activation), suffer receptor revision (change light chains to evade autoimmunity), down regulate surface Ig (to avoid activation), and remain under check by germinal center exclusion (to diminish the chance to progress in the maturation and become plasma cells that produce autoantibodies). Finally, all this tolerance mechanism converts this B CD5- B cell into an "anergic-edited-CD5+CD27+ memory B cell" excluded from germinal centres. These "*de novo* autoreactive" memory B cells could retain a process of "self-renewal", a specificity that changes (receptor editing-revision) and/or that can not be activated because this "new malignant cell" is an "anergic cell" excluded from germinal centres**.** This speculation could

explain why mutated IGVH CLL susbsets ("anergic cells") have an indolent course related to the absence of BCR signalling activation.

IGVH gene usage in CLL is highly selective, and often associated with autoantibody reactivity (Oscier et al 1987). The fact that almost 30 % of CLL patients share BCRs with restricted, quasi-identical immunoglobulins sequences should aid the understanding of the functional interplay between CLL cells and the microenvironment. On the one hand, unmutated IGVH CLL subsets recognizes apoptotic cells in bone marrow and spleen and express a functionally competent BCR, as shown by the fact that most of it can be stimulated following Ig ligation *in vitro*. On the other hand, CLL mutated that has acquired "*de novo*" autoreactivity induced by somatic hypermutation recognizes apoptotic cells in germinal centres; however they become anergic and are unresponsive throughout BCR stimulation. In a CLL mutated subset the "memory-anergic" B cell returns to bone marrow in the same way that normal memory B cells.

Other immunologic alterations that theoretically might predispose the lost of CLL clone control: Impaired immunologic synapses

CD4 and CD8 T cells of patients with CLL show impaired immunological synapse formation with antigen presenting cells (APC)(Ramsay et al 2008). This dysfunction is in part induced by the CLL B cells. This impaired immunological synapse within T cells and APC could contribute to the failure to mount an effective immune response in patients with CLL. Moreover, it may also add other immunological abnormalities like hipogammaglobulinemia (impaired T cell – B cell interactions), autoimmunity (impaired regulatory T cell control), and second tumours (diminished immunosurveillance mediate by NK and CD8 T cells). Interestingly, lenalidomide, an immunomodulatory drug, could repair this synapses with an enhancement of immune cell function. This effect is clinically observed during treatment of CLL patients with this agent because lenalidomide probably induces a strong activation of the immune system complicated by swelling of involved lymph nodes and fever named tumour flare reaction (Chanan-Khan et al 2006; Aue et al 2009)

Antibody mediated immunoregulation:

The antigen-antibody complexes are also likely to be responsible for the phenomenon known as original antigenic sin, in which memory B cells, generated during a prior exposure to a cross-reacting antigen, present or down-regulate the response to these unique new determinants on the antigen[70]. Memory B cells seem to have an advantage for rapid activation and this produces antibodies that feed back to inhibit the priming of naïve B cells possessing receptors that are specific to unique determinants of the second immunogen. This feedback mechanism is most likely mediated through antigen-antibody complexes that interact with FcγRIIb on the naïve B cells and inhibit signal transduction through their IgM receptors (Ravetch et al 2001). In patients with hipogammaglobulinemia this feedback mechanism is impaired and might contribute to expansion of autoreactive B cells (García-Muñoz 2009b) , and in patients with CLL it may add an additional risk to uncontrolled proliferation of CLL clones.

Anti-idiotypic B cell regulation: In 1974 Jerne proposed that antibody production could be regulated by other antibodies that recognized unique idiotypic determinants in the V regions of the first antibody. He postulated that an increase in the production of the first antibody could negatively regulate the production of anti-idiotypic antibodies, and vice

versa. Because of the interconnected pathways in such a network, perturbation of one segment would be dampened by the presence of others segments and thus the original steady state would be buffered (Jerne 1984; Jerne 1970; Forni et al 1980).

Patients with CLL have an increased proportion of autoimmune haemolytic anemia (AIHA) and idiopatic autoimmune thrombocytopenia (ITP) and infections. It is probable that the idiotypic network is disrupted in CLL patients and that this could lead to an increased risk of autoimmunity on one hand and immunodeficiency on the other. Treatment with intravenous immunoglobulins (IVIg) could in theory restore idiotypic network and antigen-antibody-complexes feedback in CLL B cells. Remarkably, patients with AIHA treated with IVIg experiment a reduction of the size of lymph nodes and spleen (Diehl et al 1998). This suggests that immune-complexes feedback and idiotypic network could contribute indirectly in the control of CLL.

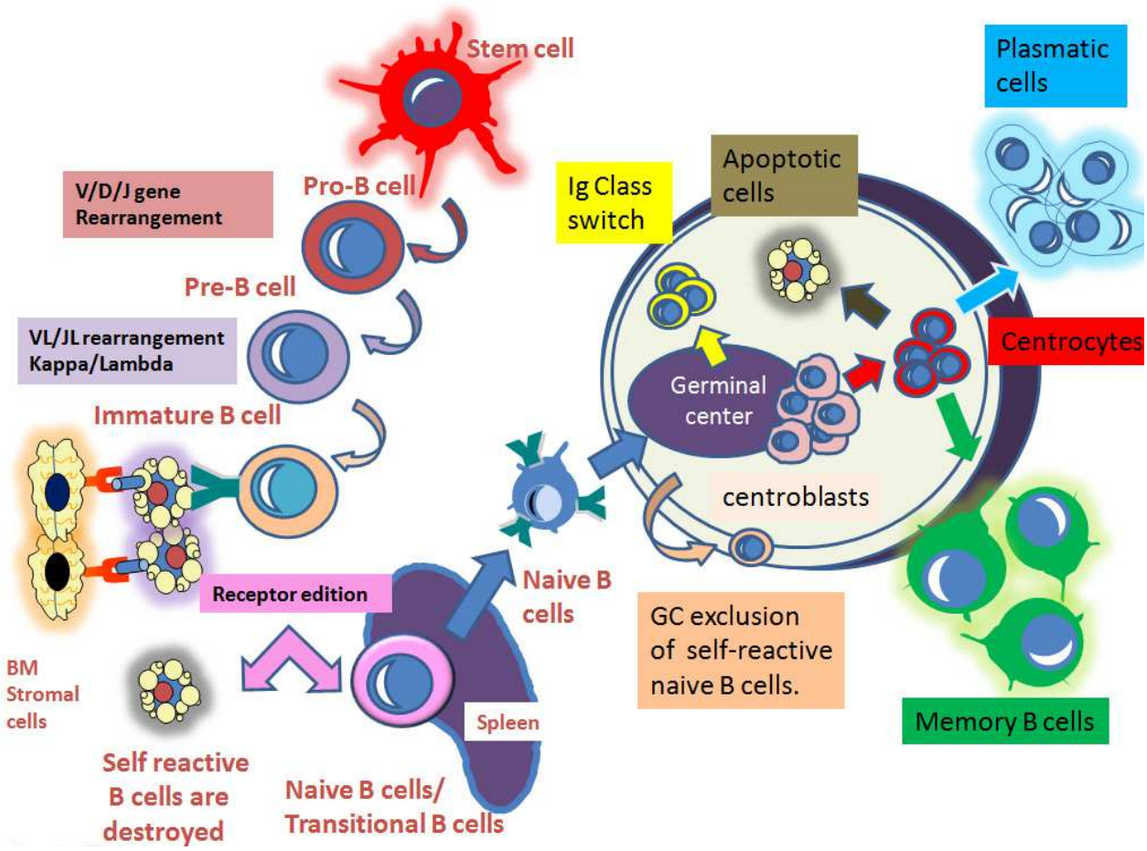
MYD88 Mutation

Interestingly, mutations in MYD88 and KLHL6 genes have been reported recently in patients with mutated CLL patients (Puente et al 2011). Significantly, similar to CLL patients, patients with MYD88-deficiency do not secrete autoantibodies (Isnardi et al 2008). We speculate that if mutations in MYD88 gene were acquired during germinal center reaction, is possible that self-reactive B cells cannot progress to plasmatic cells but retain some features or memory B cells. Even more, TLR-9 acts via MYD88 and might induce proliferation of CLL B cells. However, mutations in MYD88 might disturb the function of this TLR-9 and contribute to the biology and better prognosis of mutated CLL cases.

IGHV gene usage in CLL is highly selective, and often associated with autoantibody reactivity. The fact that almost 30 % of CLL patients share BCRs with restricted, quasi-identical immunoglobulins sequences should aid to the understanding of the functional interplay between CLL cells and the microenvironment. On the one hand, unmutated *IGHV* CLL subsets recognizes apoptotic cells in bone marrow and spleen and express a functionally competent BCR, as shown by the fact that most of it can be stimulated following Ig ligation *in vitro*. On the other hand, CLL mutated that has acquired "*de novo*" autoreactivity (¿mutations in MYD88?) induced by somatic hypermutation recognizes apoptotic cells in germinal centres; however they become anergic and are unresponsive throughout BCR stimulation. In a CLL mutated subset the "memory-anergic" B cell returns to bone marrow in the same way that normal memory B cells.

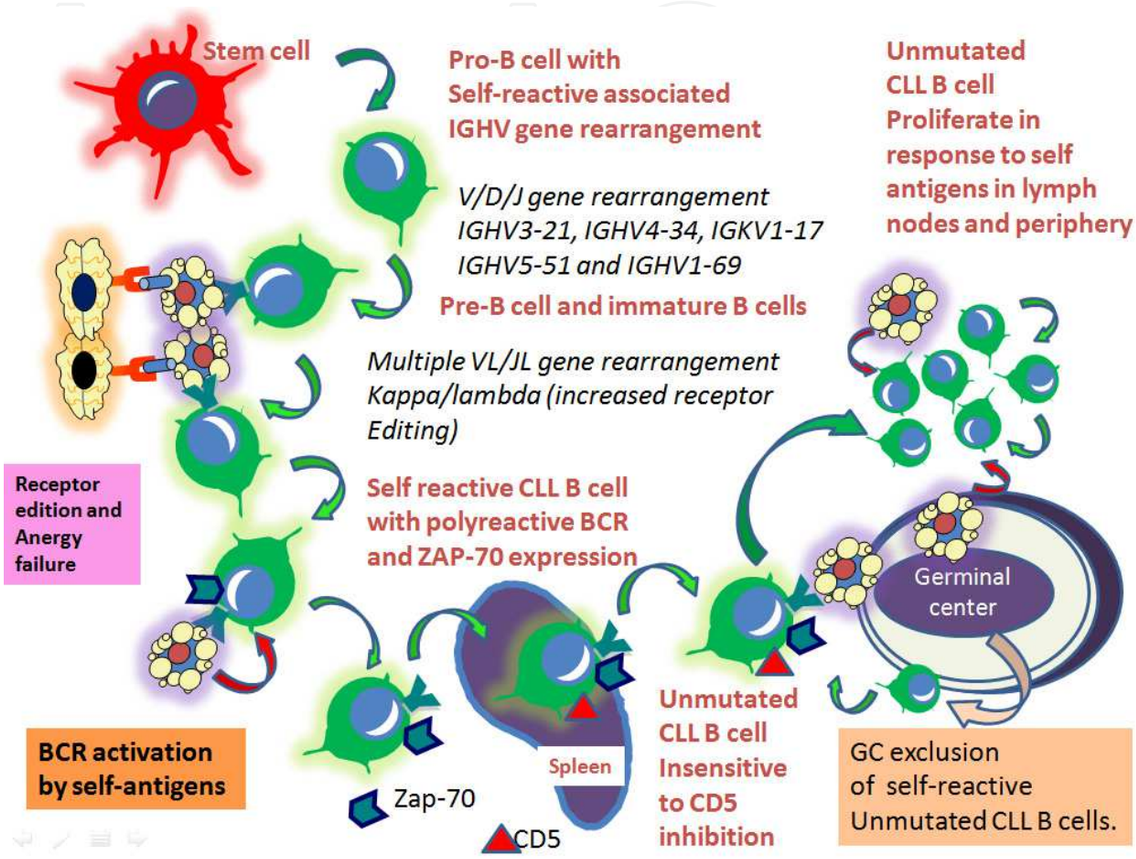
3. Conclusion

Chronic lymphocytic leukemia can be separated into cases that harbour somatic mutation in their IGVH genes, or cases without somatic mutations. IGVH gene usage in CLL is highly selective, and often associated with autoantibody reactivity. Despite the fact that the cell surface markers and gene expression of CLL cells suggest that both subsets originate from a precursor cell of the same developmental stage, these findings could be only the result of several immunologic mechanisms that try to destroy or avoid the persistence of self-reactive CLL B cells. CLL is characterized by multiple immune deficiencies and autoimmune phenomena associated with persistent tolerance mechanism trying to control self-reactive CLL B cells growth.



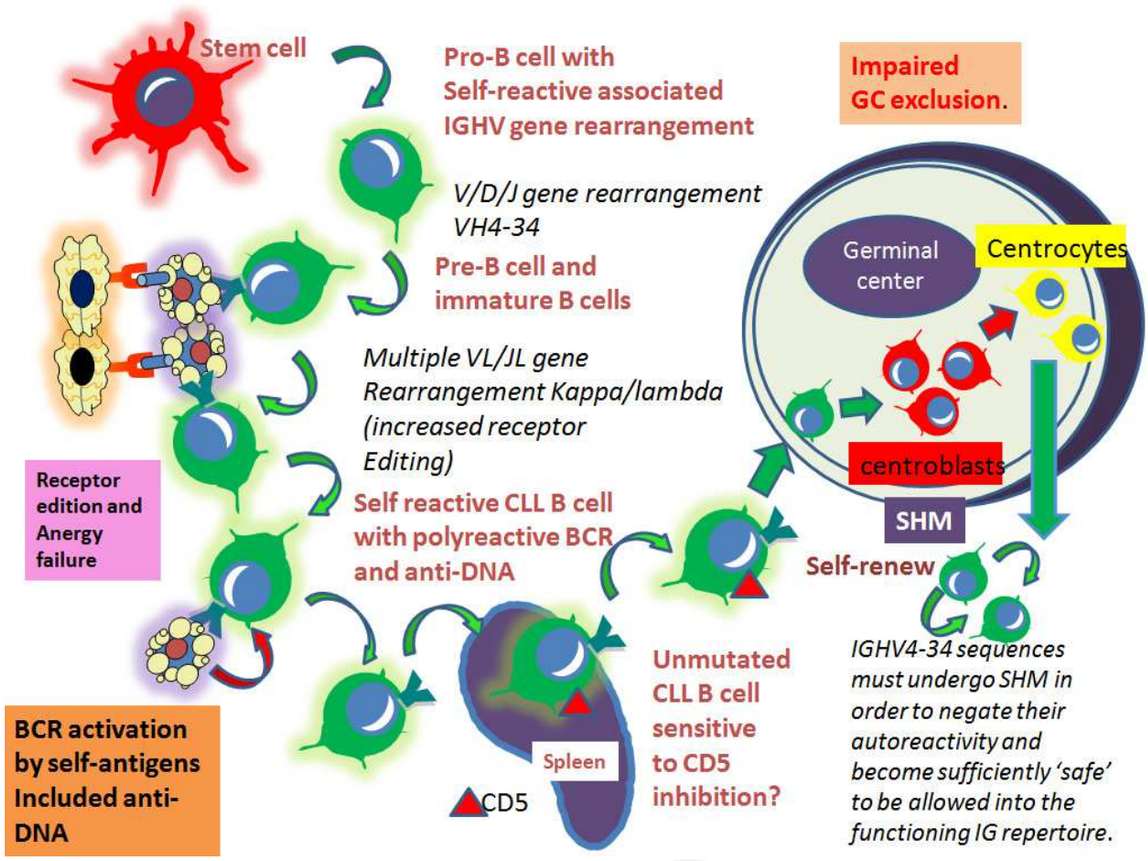
B-cell development occurs initially in the bone marrow and subsequently in lymphoid organs. In bone marrow, hematopoietic progenitor cells (HSC) differentiate into the earliest identifiable cell type committed to the B-cell lineage, the pro-B cell. The pro-B cell undergoes a rearrangement of its immunoglobulin (Ig) heavy chain genes and is called a pre-B cell. Subsequent rearrangement of the light chain enables the cell to express surface IgM and the cell becomes an immature transitional B lymphocyte. These cells leave the bone marrow and are called naïve B cells. They are arrested in the G0 phase of the cell cycle. These naïve B cells enter the lymphoid tissue, where they are exposed to antigen-presenting cells, become activated and differentiate into plasma cells or memory B cells. Through activation by an antigen, B cells differentiate into centroblasts, resulting in Ig isotype switching and somatic mutations in the variable region of the Ig with the generation of high-affinity antibodies. Centroblasts then progress to the centrocyte stage and re-express surface Ig. The centrocytes with high-affinity antibodies differentiate into either memory B cells or plasmablasts, which subsequently move to the bone marrow and terminally differentiate into plasma cells.

Fig. 1. Normal B cell development.



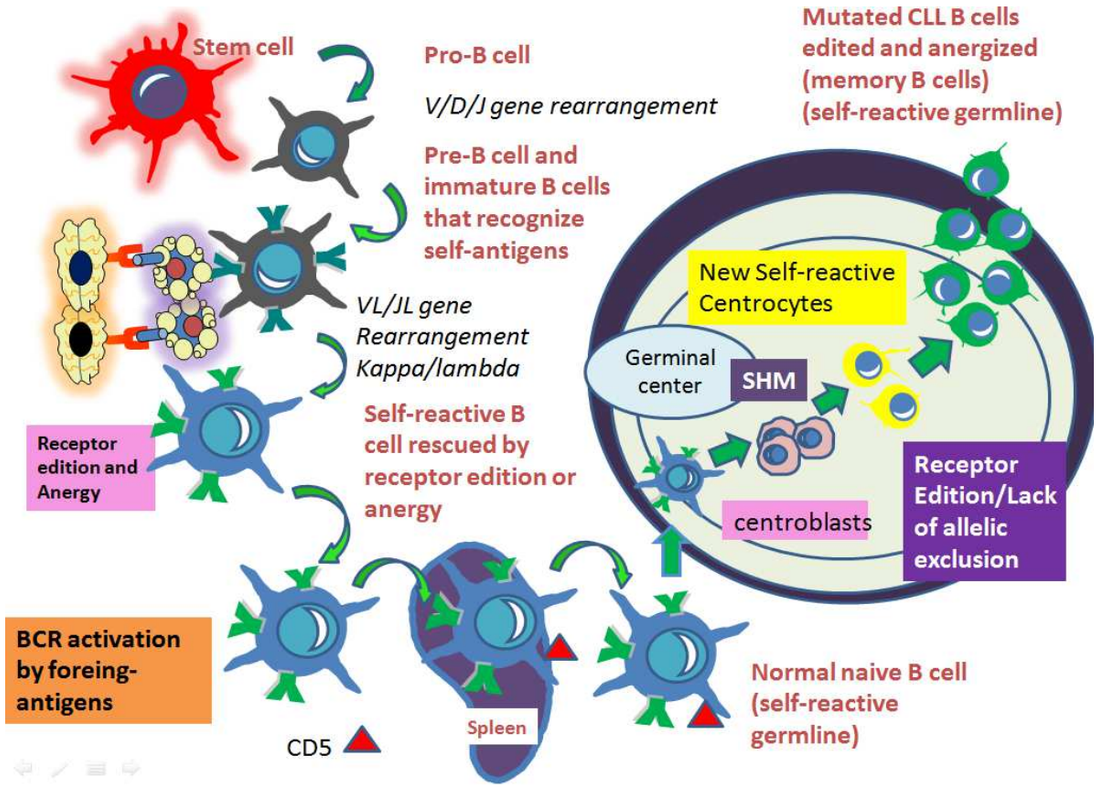
Unmutate CLL B-cell development occurs initially in the bone marrow and subsequently in lymphoid organs. In bone marrow, hematopoietic progenitor cells (HSC) differentiate into the pro-B cell that use IGHV genes related with autoimmunity. The pro-B cell undergoes a rearrangement of its immunoglobulin (Ig) heavy chain genes and is called a pre-B cell. Subsequent rearrangement of the light chain enables the cell to express surface self reactive BCR that fail to be corrected by several rounds of receptor edition. This self-reactive B cells acquire Zap-70 or other alterations that induce increased BCR activation. This is the way in which this self-reactive CLL B cells pass up tolerance mechanisms as anergy and inhibition exerted by CD5. These cells leave the bone marrow as unmutated polyreactive CLL B cells. These unmutated polyreactive CLL B cells enter in the lymphoid tissue, where they are exposed to antigen-presenting cells and self-antigens, however, they cannot be converted into plasma cells or memory B cells with mutations because they are efficiently excluded by germinal centers.

Fig. 2. Hypothesis about generation of unmutated B cells (García-Muñoz et al. Ann Hematol. Accepted).



Mutated CLL B-cell development occurs initially in the bone marrow and subsequently in lymphoid organs. In bone marrow, hematopoietic progenitor cells (HSC) differentiate into the pro-B cell that use IGHV genes related with autoimmunity. The pro-B cell undergoes a rearrangement of its immunoglobulin (Ig) heavy chain genes and is called a pre-B cell. Subsequent rearrangement of the light chain enables the cell to express surface self reactive BCR that fail to be corrected by several rounds of receptor edition. This self-reactive B cells enter in germinal centres and undergo somatic hypermutation in order to negate their autoreactivity. This is the way in which this self-reactive CLL B cells pass up tolerance mechanisms as germinal centre exclusion, however, fortunately they suffer some mutations to reverse their self reactivity and avoid autoimmune diseases as SLE. These cells leave the germinal center as mutated CLL B cells memory like cells.

Fig. 3. "Impaired Germinal Centre exclusion model for development of mutated CLL cases wiht VH4-34.



Mutated CLL B-cell development occurs initially in the bone marrow and subsequently in lymphoid organs. In bone marrow, hematopoietic progenitor cells (HSC) differentiate into the pro-B cell that use IGHV genes related with autoimmunity. The pro-B cell undergoes a rearrangement of its immunoglobulin (Ig) heavy chain genes and is called a pre-B cell. Subsequent rearrangement of the light chain enables the cell to express surface self reactive BCR that succeed to be corrected by several rounds of receptor edition. This ex-self-reactive B cells acquire CD5 or other alterations that induce lesser BCR activation. This is the way in which this ex-self-reactive CLL B cells suffer tolerance mechanisms as receptor edition, anergy and inhibition exerted by CD5. These cells leave the bone marrow as unmutated normal naïve B cells. These naïve ex-self reactive B cells enter in germinal centres and suffer somatic hypermutation (SHM) and acquire a new self-reactive BCR, however, again tolerance mechanisms as receptor edition/revision and CD5 expression make this cells in an anergic memory ex-self-reactive B cells. Importantly, reversion of the IGHV mutated sequences to germline counterparts restored the polyreactivity and self-reactivity.

Fig. 4. Mutated CLL B cells generated by somatic hypermutation (García Muñoz et al. Ann Hematol. Accepted).

4. Acknowledgment

The authors declare that a review paper on immunological aspects in CLL is actually accepted in Ann of Hematology.

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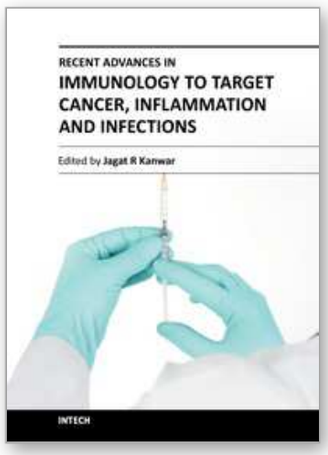

Recent Advances in Immunology to Target Cancer, Inflammation and Infections

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Immunology is the branch of biomedical sciences to study of the immune system physiology both in healthy and diseased states. Some aspects of autoimmunity draws our attention to the fact that it is not always associated with pathology. For instance, autoimmune reactions are highly useful in clearing off the excess, unwanted or aged tissues from the body. Also, generation of autoimmunity occurs after the exposure to the non-self antigen that is structurally similar to the self, aided by the stimulatory molecules like the cytokines. Thus, a narrow margin differentiates immunity from auto-immunity as already discussed. Hence, finding answers for how the physiologic immunity turns to pathologic autoimmunity always remains a question of intense interest. However, this margin could be cut down only if the physiology of the immune system is better understood. The individual chapters included in this book will cover all the possible aspects of immunology and pathologies associated with it. The authors have taken strenuous effort in elaborating the concepts that are lucid and will be of reader's interest.

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