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CHRONIC LYMPHOCYTIC LEUKAEMIA: AN IMMUNOBIOLOGY APPROACH

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SUMMARY

B cell chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia that follows an extremely variable clinical course. Several important prognostic parameters defining pathogenic and clinical subgroups of CLL have been identified and validated recently. The biological significance of immunoglobulin (Ig) heavy chain variable region gene (IgHV) mutational status and associated ZAP-70 over-expression, CD38 and chromosomal aberrations have enabled to identify patients at high risk for early disease progression and inferior survival. Moreover, studies of the B cell antigen receptor (BCR) structure and receptor signalling have been most helpful in revealing some new aspects of the biology of this disease. In particular, the analysis of IG genes has revealed that the expressed IgHV/IgKV/IgLV gene repertoires of CLL cells differ from those of normal B cells. A further unique feature of the CLL IG repertoire is the existence of subsets of cases with "stereotyped" BCRs. Accumulating molecular and phenotypic data support the notion that CLL development and evolution is not a simple scholastic event and strongly indicates a role for antigen in driving the cell of origin for at least some subsets of CLL cases.

Key words: chronic lymphocytic leukaemia; clinical characterististics; molecular genetic aspects; immunoglobulin repertoire

INTRODUCTION

B cell chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia in Western countries. It is characterized by a progressive, monoclonal accumulation of small neoplastic B cells in the blood, bone marrow and lymphoid tissues. Most CLL cells express CD5, CD23, and low levels of surface immunoglobulin (Ig) [1, 2]. CLL follows an extremely variable clinical course with overall survival times ranging from months to decades [1, 2]. Recently, several important observations [3-9] related to the biological significance of immunoglobulin heavy chain variable region gene (IGHV) mutational status and associated ZAP-70 over-expression, CD38, and chromosomal aberrations have enabled identification of patients at high risk for early disease progression and inferior survival. Furthermore, studies of the structure and function of the B cell antigen receptor (BCR) used by these leukaemic cells have helped define the biology of this disease [10-12].

IMMUNOGLOBULIN DIVERSITY

The extraordinary capacity of the human immune system to cope with an immense variety of antigenic stimuli is attributed to the activity of three processes which alter the genomic sequence and structure at Ig loci of B cells: (1) somatic recombination; (2) somatic hypermutation (SHM); and, (3) class switch recombination (CSR) [13].

IGHV-IGHD-IGHJ recombination

The variable regions of both heavy and light chains contain three hypervariable areas (complementation determining regions, CDRs: CDR1, CDR2, CDR3) and four relatively invariant framework areas (FRs: FR1, FR2, FR3, FR4) [13]. At the genomic level, immunoglobulin variable region is encoded by separate genes that become joined together by the process called somatic recombination to make a functional gene [14]. In heavy chain genes, there are three distinct genes encoding for parts of the variable region: variable (V), diversity (D) and joining (J) genes [15]. Light chain variable regions comprise only two genes, V and J [16, 17]. Genes that can be recombined have specific sequence motifs adjacent to them, called recombination signal sequences, or RSS motifs [18, 19].

Somatic recombination takes place at the early stages of B cell differentiation within the bone marrow. Ig gene rearrangements usually start at the heavy chain locus (IgH) followed by similar rearrangements at the Ig light chain loci, first at the kappa locus (IgK) and, if failed, at the lambda locus (IgL) [20]. B cells which have completed functional recombination of both heavy and light chain variable region genes express IgM on the surface and migrate to secondary lymphoid organs. Cell surface expression of functional Ig molecules is necessary for the continued survival of early B cells.

Somatic hypermutation

Somatic hypermutation (SHM) of Ig variable genes forms a second cycle of diversification after somatic recombination which increases antibody diversity and produces antibodies with higher specificity [21]. During this process, mainly base substitutions and occasionally insertions/deletions are introduced into a region of 1-2 kb surrounding the antibody-coding sequence. In normal B cells, replacement mutations are preferentially clustered within the CDRs rather than the FRs. The current model for SHM describes the process as being divided into two phases: the first activation-induced deaminase (AID)-dependent phase creating substitutions at C•G pairs and the second phase creating substitutions at A•T pairs [22-25].

The SHM is classically considered to occur within the germinal centre following encounter with antigen. Cells expressing high affinity antibody molecules are positively selected and differentiate into either memory B cells or plasma cells [21, 22, 26]. Once selected, memory B cells no longer require surface immunoglobulin or antigen for continued long term survival. Mutated cells that produce low affinity antibody or fail to produce antibody, like the equivalent B cell precursors in the bone marrow, undergo apoptosis within the germinal centre. The consequence of the SHM is the selection of B cells that produce high affinity antibodies.

Germinal centres (GCs) have long been considered as the only sites capable of sustaining a high rate of somatic hypermutation [26]. Contrary to this idea, it has recently been found that splenic autoreactive B cells in autoimmune MRL/Faslpr mice proliferated and underwent active somatic hypermutation at the T zone–red pulp border rather than in GCs [27]. These results implicate this region as an important site for hypermutation. Because somatic mutations can create autoreactive B cells from the innocuous ones [28], mechanisms that censor autoreactive mutants are likely to be important in the GC. These protective mechanisms may be the reason why mutation is normally restricted to the GC. However, when the antigenic stimulus is chronic and the antigens involved may stimulate through unique pathways, B cells may mutate elsewhere and thereby escape the mechanisms that normally censor autoreactive B cells in the GC environment.

Class switch recombination

The IgH locus consists of an ordered array of five constant region (IgHC) genes: mu, delta, gamma, epsilon and alpha. Class switch recombination (CSR) replaces the IgHC gene to be expressed from mu to gamma or epsilon or alpha, resulting in switching of antibody isotype from IgM to IgG, IgE, or IgA, respectively, without changing antigen specificity. Each isotype determines the manner in which captured antigens are eliminated or the location where the IG is delivered and accumulated [13, 29].

CSR is induced in vivo by both T-dependent (TD) and T-independent (TI) antigens [30]. B-cell activation by TD antigens requires interaction of the CD40 ligand expressed on activated T cells and CD40 on the surface of B cells. T-independent antigens can activate B cells in the absence of direct T- and B-cell interactions. Recent studies have shown that is possible to mimic *in vitro* TD antigen stimulation by culturing B cells in the presence of anti-CD40 along with specific cytokines, and TI activation by treatment with LPS plus or minus the addition of specific cytokines. In concert with antigen-dependent activation, cytokine-induced signalling provides specificity to CSR [31].

CLL SUBGROUPS: CLINICAL IMPLICATIONS

One of the most important molecular genetic parameters defining pathogenic and prognostic subgroups of CLL is the mutational status of the IGHV genes [1, 3, 4, 8, 32-35]. Other surrogate markers such as ZAP-70 and CD38 have also been identified and validated [3, 8, 9, 36, 37]. Moreover, genomic aberrations, telomere length and BCR signalling have been shown to be of pathogenic and clinical relevance in CLL [1, 2, 5, 8, 38].

Mutational status of immunoglobulin genes and surrogate markers in CLL

CLL cells are CD5+ cells and express IgM/IgD [1, 10, 11]. This phenotype could be reported as a mantle zone-like phenotype of naive cells, which express unmutated Ig genes. In this concept, CLL was initially thought to carry little, if any, somatic mutation. This idea was modified in 1999 when two groups of investigators demonstrated a strong correlation between mutational status and disease prognosis [3, 4].The analysis of IgHV gene mutations revealed two distinct categories of CLL, with and without somatic mutations. In these studies IgHV gene sequences with differences of > 2% from the most similar germline gene were considered as "mutated" to avoid the possibility that some of these differences might represent unknown allelic polymorphisms in the IGH locus [34]. IgHV sequences that exhibited <2% difference from the germline gene were considered as "unmutated".

Somatic mutations do not appear to occur uniformly among IgHV gene subgroups, rather they display a hierarchy of mutations (IgHV3> IgHV4> IgHV1) [6, 39]. Differences appear even more striking when considering individual IgHV genes, with IgHV1-69 carrying very few mutations as opposed to IgHV3-07, IgHV3-23 and IgHV4-34, which show a high load of mutations. These differences may indicate that the CLL precursors received contrasting stimulations by distinct types of antigen prior to leukaemic transformation or that the precursors were transformed into leukaemic cells at distinct maturation stages [1, 10, 11].

CD38 is a membrane protein that marks cellular activation and maturation and has signalling activity [8, 32, 36]. CD38 expression is associated with neoplastic cells showing atypical morphology, diffuse bone marrow infiltration, high peripheral blood lymphocytosis and a less favourable overall prognosis. Further studies have revealed that CD38 and IgHV mutation status often overlap, although not always, but CD38 may perhaps vary over time [40]. CD38 is now viewed as an independent prognostic marker of outcome, with its own biological and clinical value [36, 41].

In a pioneering gene-expression profiling study in CLL, a panel of genes has been identified in which the expression of a small subgroup of genes, including those encoding ZAP-70, IM1286077, and C-type lectin, correlated with the mutational status of IgVH genes [42]. ZAP-70 (zeta-associated protein 70) is a receptor-associated protein tyrosine kinase originally found in T cells. Recent data have shown that the expression of ZAP-70 protein is strongly associated with CLL cells carrying unmutated IgVH genes [9, 37]. The immunofluorescence method for identifying ZAP-70+ cells in CLL is not fully standardized amongst different laboratories, and it remains to be determined whether this parameter is amenable to the routine clinical workup of patients with CLL. Therefore, knowing both ZAP-70 level and IgHV mutational status provides more useful prognostic information than knowing only one.

Biases in V gene use and Stereotyped BCRs

The expressed IgHV/IgKV/IgLV gene repertoires of CLL cells differ from those of normal B cells [1, 6, 7, 10, 11, 39]. CLL cells use predominantly IgHV1, IgHV3 and IgHV4 subgroup genes in a distribution that is different from that reported for normal peripheral blood CD5+ B lymphocytes [6, 39]. Specifically, the IgHV1 family is overexpressed and the IgHV3 subgroup is underexpressed in relation to the circulating CD5+ repertoire.

The mature normal Ig repertoire is dominated by few genes without evidence for preferential pairings of Ig heavy/light chain genes or subgroups [43, 44]. No associations exist between heavy/light chain CDR3 lengths and sequences or between IGHV/IGHD/IGHJ genes [45]. In contrast, as recently shown by several groups, a unique feature of the CLL IG repertoire is the existence of subsets of cases with "stereotyped" BCRs [1, 6, 7, 46-55]. Along these lines, we have recently demonstrated that stereotyped HCDR3 sequences may be identified in >20% of CLL cases [55]. Importantly, the comparison of CLL sequences to non-CLL sequences from B cells of diverse sources has revealed that HCDR3 restriction is "CLL-biased" [55]. Considering the extremely low probability (10^{-12}) of co-expression of identical BCRs, the aforementioned findings further support the notion that CLL development and evolution is not a simple scholastic event and indicates a role for antigen in driving the cell of origin for at least some subsets of CLL cases.

BCR signalling

The preceding molecular and phenotypic data suggest that antigenic stimulation of the CLL precursor cells is likely to have occurred prior to or during leukaemic transformation [1, 10, 11]. However, it is also possible that antigenic stimulation exerts a promoting effect on the growth of certain CLL clones following leukaemic transformation [1, 10, 11]. This is supported by evidence that a number of CLL cases have an intact BCR-initiated signal transduction pathway. These cases are particularly frequent among the unmutated and CD38+ B-CLL subgroups [56]. It has been shown that the majority of unmutated (UM) CLL cases are able to signal via sIgM. In contrast, the majority of mutated (M) CLL cases fail to signal via sIgM *in vitro*. Approximatelly 50% of M-CLL cases unable to signal via sIgM were able to signal via sIgD [1, 11, 3]. A further smaller subset was competent to signal only via Ig-α [57]. The ability to signal via other molecules in the BCR indicates that downstream signal transduction pathways are operative in CLL. Therefore, failure to signal is a membrane-proximal event characteristic of anergic cells. The distinctive anergic status in the majority of M-CLL, and in proportion of UM-CLL, is more likely the result of prior signalling events, which have rendered the cell membrane resistant to further stimulation.

CONCLUSION

A large body of evidence suggests that CLL development and evolution is not a simple scholastic event and indicates a role for antigen in driving the cell of origin for at least a proportion of CLL cases. It would not be unreasonable to speculate that stimulation through the BCR may occur at different time-points in the natural history of the disease, depending upon the nature of the antigenic element(s). The message is clear: let´s try to find the antigens.

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ХРОНИЧНА ЛИМФНОЦИТНА ЛЕУКЕМИЈА – ИМУНОБИОЛОШКИ ПРИСТУП

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КРАТАК САДРЖАЈ

Хронична лимфоцитна леукемија која потиче од Б-ћелија (Б-ХЛЛ) је најчешћи облик леукемије код одраслих особа. Она се одликује изузетно променљивим клиничким током. Недавно је утврђено неколико патолошких и клиничких параметара Б-ХЛЛ важних за прогнозу ове болести. Приказан је преглед савремених приступа клиничко-патолошкој прогнози тока Б-ХЛЛ, као и резултати савремених молекуларногенетских анализа овог обољења. Откривена су нова сазнања о биолошком значењу мутационог статуса гена променљивог региона тешких ланаца (*IgHV*) имуноглобулина (*Ig*), као и значај повезаности с прекомерном експресијом *ZAP-70*, експресијом *CD38* и аберацијама хромозома, која омогућавају препознавање болесника код којих постоји висок ризик за рани развој болести и краће преживљавање. Истраживања која су проучавала структуру рецептора антигена Б-ћелија (*BCR*) и начин преношења регулаторних сигнала помогла су у откривању нових биолошких аспеката болести. Детаљна анализа *Ig* показала је да се репертоар манифестованих *IgHV/IgKV/IgLV* гена код Б-ХЛЛ разликује од репертоара нормалних Б-лимфоцита. Додатна јединствена одлика имуноглобулинског репертоара Б-ХЛЛ је постојање подгрупа стереотипних рецептора. Резултати истраживања молекуларних и фенотипских одлика ове болести подржавају став да настанак и развој Б-ХЛЛ није искључиво последица једноставног стохастичког догађања, већ наглашавају и важну подстицајну улогу антигена у предодређивању матичне клоногене ћелије која потиче од болести бар код неких подгрупа болесника са Б-ХЛЛ.

Кључне речи: хронична лимфоцитна леукемија; клиничке одлике; молекуларна генетика; имуноглобулински репертоар

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