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Review

The clinical course of patients with chronic lymphocytic leukemia (CLL) is highly heterogeneous. Gene expression analyses have revealed that leukemic cells with unmutated immunoglobulin heavy chain genes (IgV_H) differ from CLL cells with mutated IgV_H in the expression level of some genes, i.e. encoding kinase ZAP-70 and antigen CD38. Recently, additional markers in CLL, including the expression level of apoptosis-regulating genes/proteins (Bcl-2, Mcl-1) and microRNAs, have been suggested. In this review, we attempt to provide data concerning the properties of lipoprotein lipase (LPL), as well as to present its prognostic value in CLL. LPL mRNA expression level was able to predict mutational status in a high percentage of CLL cases and high LPL expression was associated with shorter treatment-free survival. Importantly, since LPL activity is low (or absent) in other blood cell types, its expression can be determined by PCR technique in peripheral blood mononuclear cells or in lysed blood samples.

Key words: chronic lymphocytic leukemia, prognostic factors, lipoprotein lipase, IgV_H mutational status.

Lipoprotein lipase: a new prognostic factor in chronic lymphocytic leukaemia

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Introduction

Chronic lymphocytic leukemia (CLL) is a cancer of elderly people since the average age of patients is over 60 years, although 10% to 15% of patients are under 50 [1]. The neoplastic lymphocytes, mainly of lineage B, are characterized by the expression of at least one of the pan-B antigens (most often CD19) that is co-expressed with the T-cell marker CD5, the expression of CD23, weak expression of CD20 and CD79b, as well as hardly detectable expression levels of surface immunoglobulins with one of the light chains – κ or λ [2, 3]. In clinical practice, two prognostic tools are used, based on Rai's or Binet's classifications, further extended by a recently suggested modified system [3]. Since the course of CLL is heterogeneous, these classifications are of limited use and are insufficient to predict the disease outcome at the early stages of the cancer. In the last years, some new parameters have been introduced besides the so-called standard prognostic factors such as Rai/Binet's classifications, lymphocyte doubling time, atypical morphology, bone marrow infiltration, increase in β2-microglobulin concentration, soluble antigen CD23 (sCD23) and increased activity of thymidine kinase and lactic dehydrogenase [3, 4]. Among these parameters, the most important prognostic value is attached to the mutational status of immunoglobulin genes (IgV_H), the expression of tyrosine kinase ZAP-70 and antigen CD38, as well as cytogenetic aberrations in leukemic cells [5–9]. For a few years, somatic mutations of *I* IgV_H have been considered as a crucial factor determining the course of CLL and the responsiveness to therapy [5, 10]. It is widely accepted that neoplastic lymphocytes pass through the germinal centers where they mutate and enter the blood in the state of anergy. Owing to these events, the mutated type of CLL (in which B lymphocytes show less than 98% similarity to the IgV_H genes in the germ line) is characterized by a milder course, longer survival period and higher efficacy of therapy [11]. On the other hand, a lack of mutations in IgV_H is related to faster progress of the disease, worse prognosis and chemoresistance [5, 10, 12, 13]. Nevertheless, it has been revealed that mutation of the IgV_H3-21 region does not confirm the correlation with favorable outcome and it is associated with an aggressive type of CLL [14]. In the assessment of CLL prognosis, different sensitive techniques such as polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH) and DNA microarray are used. Genetic aberrations are detected in more than 80% of patients with CLL cases and these are mostly deletions of chromosomes 13 (13q14), 11 (11q22-23), 17 (17p) and 7 (7q), as well as trisomy of chromosome 12 [4, 9, 15]. Moreover, a significant prognostic value has been attached to the high expression of tyrosine kinase ZAP-70 (Zeta-Associated Protein-70), a mediator of the T-cell receptor signaling pathway, and CD38 glycoprotein on the leukemic lymphocyte surface [6, 7]. Up-regulated expression of ZAP-70 and CD38 is related to CLL cases with unmutated IgV_H [4, 16]. The multi-factorial analyses (IgV_H mutational status, CD38 and ZAP-70) of more than 1,000 patients with CLL revealed that ZAP-70 expression had the strongest prognostic value, especially for the time when the therapy should be applied [16].

In the course of CLL, leukemic B-cells meet multiple interferences in the apoptotic signal transduction. In CLL cells, the expression of proteins such as regulators of apoptosis, belonging mainly to the Bcl-2 family, is different from that observed in normal B-cells. The prognostic significance of the Bcl-2 proteins, and the polymorphisms of their genes, in CLL patients have been recently reviewed in *Contemporary Oncology* [17].

Moreover, the expression profiles of small, non-coding RNA – microRNA (miR) – can be used to distinguish between normal and leukemic B-cells, and in CLL prognosis, as well as in the evaluation of disease progression [18–20]. Researchers from Carlo M. Croce's laboratory [19] published results indicating that the expression of 13 out of 190 analyzed miRs can be useful for differentiating aggressive from benign CLL. Importantly, their expression is in close relation with the mutational status of IgV_H and the level of ZAP-70. miR-15a and miR-16-1 have been further characterized, and their genes are located on chromosome 13 (13q14.3), which is the most often deleted (in about 68% of cases) in patients with CLL. It is suggested that the deletion of chromosome 13 leads to the silencing of miR-15a and miR-16-1 expression, which causes an increase in the synthesis of anti-apoptotic protein Bcl-2 [20].

The alterations in lipid metabolism are observed in a large number of cancers that result from e.g. their increased hydrolysis. Researchers' attention has been drawn to lipolytic enzymes, whose activity can be a valuable marker in CLL prognosis. Lipoprotein lipase belongs to the group of such enzymes [21–25].

Lipoprotein lipase

Lipoprotein lipase (LPL) is an enzyme belonging to the hydrolase class (*EC* 3.1.1.34) that participates in lipid metabolism [26]. The human *LPL* gene, which spans about 30 kbp,

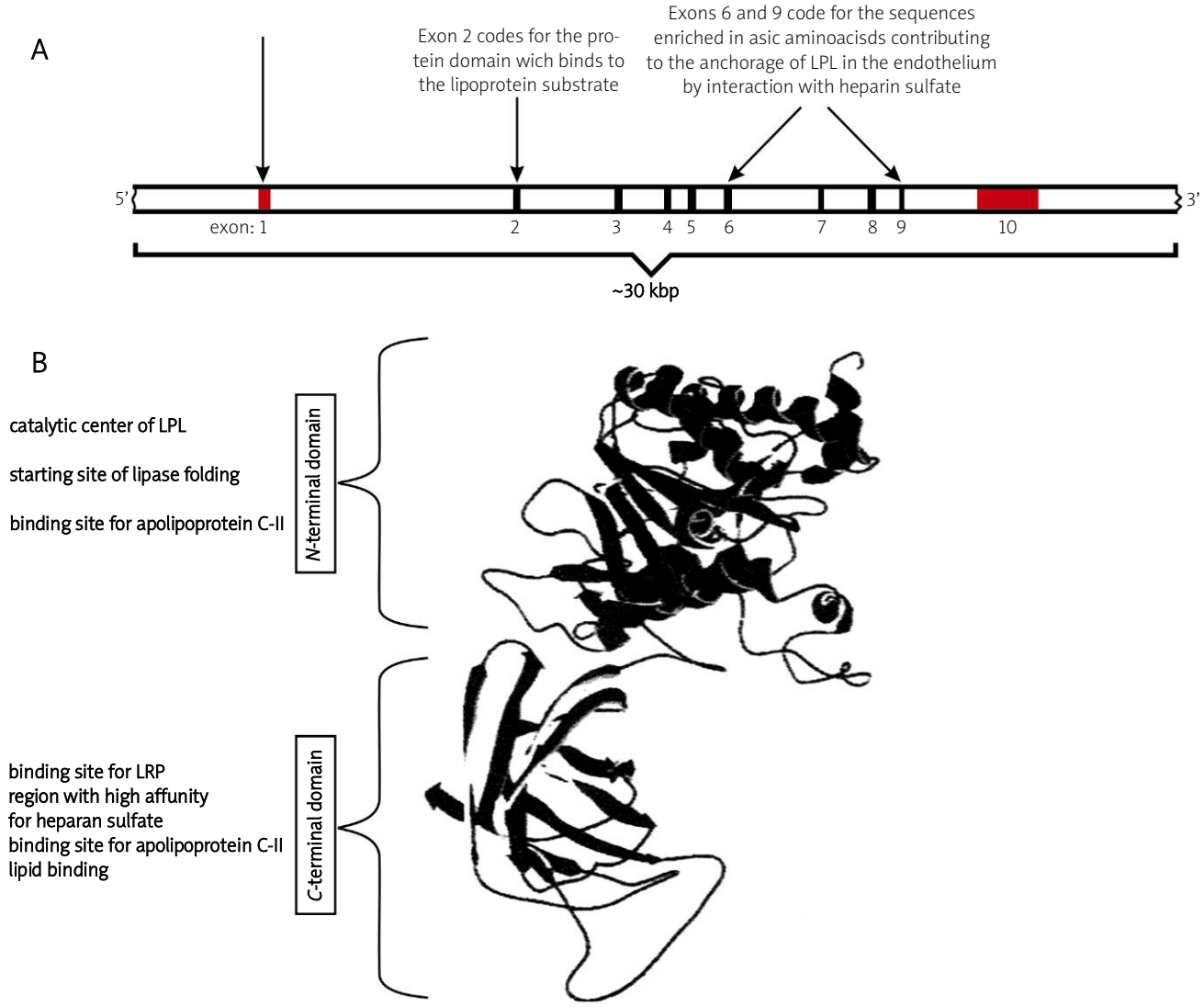

Fig. 1. A) Structure of the LPL gene. Untranslated regions are highlighted in red (based on [27]). B) Three-dimensional structure of the lipoprotein lipase monomer. The amino-terminal domain (amino acids from 1 to 310), the carboxy-terminal domain (amino acids from 311 to 448), as well as the most significant functions of depicted fragments are shown in the picture (based on [28, 30, 32]).

was identified on chromosome 8 (8p22) and contains 10 exons (Fig. 1A) It has an intron : exon ratio ~9, characteristic for a mammalian gene [27]. This enzyme hydrolyzes triglycerides (TGs) present in circulating lipoproteins, such as chylomicrons, very low density and intermediate density lipoproteins (VLDL and IDL, respectively) into free fatty acids (FFA). Their release supplies the cells with important energetic substrates [29, 30]. To some extent, the aforementioned lipase functions also as phospholipase A_1 [31]. A low molecular weight apolipoprotein C-II (apo C-II) is a main activator of lipoprotein lipase [31], whereas its activity is inhibited by apolipoprotein C-III (apo C-III) [28].

Lipoprotein lipase is synthesized mainly in the adipocytes and myocytes (including cardiomyocytes), but its relatively high expression is also detected in macrophages, lactating mammary glands, pancreatic islets, several areas of the nervous system, spleen, testicles, ovaries, kidneys, lungs, liver and adrenal glands [28, 29, 32–35]. After biosynthesis, the enzyme is secreted into the blood vessels where it anchors by binding to heparan sulfate residues, a component of the endothelial proteoglycans. In the presence of heparin, LPL can be released to the blood, where it exists mainly as inactive monomers metabolized by the liver [26, 29]. The N-glycosylated homodimer is an active form of enzyme in which the subunits (55 kDa each) interact non-covalently. Dimerization takes place in the endoplasmic reticulum (ER). Also the glycosylation of asparagine residues, Asn^{43} and Asn^{359}, takes place in the ER, and the modification of Asn^{43} is both necessary and sufficient for the activation and release of LPL from this cellular compartment. The process of folding an appropriate LPL conformation requires the participation of chaperone proteins (calnexin and calreticulin), as well as Ca^{2+} ions, and begins from its *N*-terminal domain [32, 33]. Apart from the catalytic activity, the described enzyme contributes to lipoprotein uptake by the cell that is possible thanks to its participation in the interaction with the LDL receptor-like protein (LRP) or the proteoglycans of target cells. LDL receptor-like protein molecules can bind to either the active or inactive form of lipoprotein lipase. The binding site of LRP is situated in the C-terminal region of the LPL molecule (Fig. 1B) [33, 34]. In this domain, there is a fragment of 24 amino acids (from 415 to 438) that intermediates the binding between LPL and a lipid substrate, and is responsible for stabilization of the active homodimer [35].

Expression of lipoprotein lipase in CLL cells

The analyses of gene expression in leukemic cells have revealed that many genes are expressed differentially when compared with the normal ones [18, 21, 22, 36–38]. In the described cases, these changes are in close relationship with the presence or lack of mutations in the IgV_H genes. In the so-called unmutated type of CLL, the overexpression of at least several dozen genes that make leukemic cells similar to myocytes or adipocytes is claimed. Some genes encode proteins involved in lipid metabolism. In this group, *LPL* encoding lipoprotein lipase plays a pivotal role [21, 36, 37].

Since 2005, numerous studies on the expression of lipoprotein lipase in leukemic cells and the evaluation of this parameter as an independent prognostic marker in CLL have been conducted. The patients who underwent the assessments formed a heterogeneous group with respect to the stage of the disease, age, gender, the presence of genetic aberrations and applied therapies. Simultaneously, the correlation between the level of LPL and other prognostic factors (e.g. ZAP-70, CD38), including mutations of IgV_H genes, was evaluated [22–25, 38–45]. The most important results of the published studies are summarized in Table 1.

With few exceptions, patients with unmutated type of CLL are characterized by significantly higher expression of the *LPL* gene measured at the mRNA level that correlates with more complex course of the disease and worse prognosis. On the other hand, the expression of LPL at a lower level in patients with mutations in IgV_H genes is associated with favorable patient outcome [22–25, 38–40, 42–45]. This correlation was also confirmed at the level of intracellular protein, although this assay had a less significant differentiating value. The complex mechanisms of regulation of *LPL* gene expression and protein stability may underlie these observations. For that reason, estimation of mRNA level seems to be a more informative analysis [22, 44]. Moreover, LPL expression on the cell surface does not correlate with its mRNA level inside the cell [22].

Lipoprotein lipase can be not only an independent factor mirroring the stage of the disease, but also a valuable prognostic marker correlating with treatment-free survival (TFS) and overall survival (OS). A considerable number of published results indicate that high LPL expression is related to shorter TFS and OS [22, 24, 25, 38–40, 42, 44, 45]. So far, the application of a specific chemotherapy option has not caused an increase in OS so the results obtained in the experiments with treated patients probably did not influence the association between LPL expression and OS [40]. Furthermore, the expression of LPL mRNA does not change significantly during the course of the disease so that the level of LPL relates both to possible cancer progression in low-risk patients and the patients with more advanced disease (stage B and C according to the Binet classification) [23, 38]. Moreover, the high expression of LPL in patients with Binet's stage A suggests the need for applying treatment and predicts a poor prognosis even in the case of presence of favorable prognostic parameters [24, 25]. Recently published results have also supported the pivotal role for LPL as a prognostic factor in patients with cancer remission, after application of therapy [42].

It should be emphasized that LPL expression is not a differentiating parameter between patients with mutated type of CLL (with favorable prognosis) and those who have mutated V_H3-21 segments (with poor prognosis). In both cases, the LPL level was similar [44, 45]. For that reason, the assessment of ZAP-70 expression seems to be a better marker.

More attention should be paid to the co-analyses of lipoprotein lipase expression and the product of *ADAM29* (disintegrin and metalloproteinase domain 29-containing protein) gene expression. This gene is localized on chromosome 4 and codes the described enzyme that participates in the cell-cell interactions and between a cell and the extracellu-

Table 1. Lipoprotein lipase as a new prognostic factor in chronic lymphocytic leukemia

References	Number of patients	Correlation with mutations in IgV_H	Statistically insignificant correlation		Statistically significant correlation[4]
Oppezzo *et al.*[1] [23]	127	76%		EFS	ZAP-70
Heintel *et al.*[2] [22]	104	84%	Rai and Binet's stage	TFS OS	del11q, del17p
Nückel *et al.*[1] [38]	133	not determined		TFS	ZAP-70, CD38
Van't Veer *et al.* [39]	130	84%	gender, age, del11q	OS	ZAP-70
Van Bockstaele *et al.*[3] [24]	50	80%		TFS OS	ZAP-70, karyotype abnormalities
Nikitin *et al.* [40]	134	88%	karyotype abnormalities	OS	LDT, Rai's or Binet's classifications
Saad *et al.* [41]	25	not subjected to verification	ZAP-70	LDH, karyotype abnormalities, poor response to therapy	
Maloum *et al.*[2] [42]	119	76%		EFS OS	
Xu *et al.* [43]	58	not determined	gender, age	ZAP-70, CD38, Binet's stage, karyotype abnormalities	
Mansouri *et al.*[2] [44]	148	not determined	age, Rai's stage	TFS OS	
Kienle *et al.* [45]	222	76%		OS	
Kaderi *et al.* [25]	252	not determined		OS	CD38, karyotype abnormalities

EFS – event-free survival, TFS – treatment-free survival, OS – overall survival, LDT – lymphocyte doubling time, LDH – lactic dehydrogenase
[1]Additionally, the index LPL/ADAM29 (L/A index) was determined.
[2]The LPL expression was evaluated at the mRNA and protein levels (in other studies LPL expression was measured only at the level of mRNA).
[3]The whole blood lysate was used.
[4]Apart from mutations in IgV_H, for which a statistically significant correlation was found in each study (except for [41]).

lar matrix [46]. It should be noted that *ADAM29* is expressed in CLL cells at different levels, with respect to mutational status of IgV_H, but it is not expressed in normal B lymphocytes. In patients with unmutated CLL type, a lower level of ADAM29 expression is observed – reversely than for LPL. It seems that the LPL/ADAM29 (L/A) ratio is a more sensitive parameter that highly correlates with the mutations of IgV_H compared with the estimation of these factors separately. It was determined that, in comparison with ZAP-70 expression, the L/A ratio was the only one that positively correlated with event-free survival. Nevertheless, according to Nückel *et al.* [38], the evaluation of each of these enzymes can be an independent prognostic factor in the course of CLL.

Recently published results have provided, apart from the usefulness ensured by the analysis of *LPL* expression, some practical advantages. Firstly, the analysis can be performed using a quite easy and widely accessible technique, quantitative real-time polymerase chain reaction (qRT-PCR) [22–25, 38–45]. Secondly, the comparison of *LPL* expression in CLL cells with its level in the peripheral blood mononuclear cells from healthy donors provided the information that *LPL* expression is highly specific for leukemic cells. In normal blood cells, *LPL* mRNA was absent or very low, and the presence of monocytes that express *LPL* did not significantly influence the final results. For that reason, the lymphocyte isolation procedure can be omitted without affecting the reliability of the results. This method can be much more simplified because the whole blood lysates can be successfully used to maintain comparative results [24]. Taken together, the methodology of LPL identification predominates over the analysis of mutations in the IgV_H genes or ZAP-70 expression because the presence of other cells (T lymphocytes, natural killers) interferes significantly with the results among others due to high expression of kinase ZAP-70 in these cells [22–25, 38–45].

The role of LPL in CLL cells remains elusive, including the fact that normal B lymphocytes do not possess this enzyme. It seems pivotal to determine whether the expression of this lipolytic enzyme is the effect of the alterations in neoplastic cells or whether it is connected with CLL pathogenesis [40]. The results reported by Pallasch *et al.* [37] seem to support the second hypothesis. These researchers suggest that LPL expression in CLL cells is a result of BCR (B-cell receptor) activation. The stimulation of CLL cells *in vitro*, both with somatic mutations in the IgV_H genes and without them, resulted in lipoprotein lipase expression. Taking into consideration the genesis of both cell types in two CLL types, this mechanism could clarify the high LPL expression in the unmutated

type of this leukemia. CLL lymphocytes are more sensitive to BCR stimulation. Treatment with a lipase inhibitor, orlistat (tetrahydrolipstatin), resulted in the apoptotic death of leukemic cells, suggesting that changes in expression of lipases (including lipoprotein lipase) underlay this cancer development. Interestingly, the cytotoxic effects of orlistat on primary CLL cells was enhanced by their simultaneous exposure to fludarabine, a purine analog commonly used in CLL treatment. It seems that both drugs used together acted synergistically in apoptosis induction in leukemic cells [37]. Accepting this point of view, LPL can be not only an important prognostic marker, but also a therapeutic target. The involvement of LPL in lipid metabolism suggests its role in supplying the neoplastic lymphocytes with high-energy substrates. In this context, it could be decisive for the 'well-being' of leukemic cells, influencing their survival and proliferation [25]. This is supported by studies that confirmed high activity of the fatty acid degradation pathway in CLL cells [39]. However, including the significant differences between LPL expression with respect to the mutated or unmutated type of CLL, it can be presumed that the nature of these cells should be highly perceived. CLL cells without mutations in the IgV_H genes are characterized by higher sensitivity to activation through surface receptors. For that reason, it is suggested that LPL can contribute to the creation of lipid rafts that participate in B lymphocyte activation [26]. On the other hand, in the CLL cells heparin sulfate is synthesized and contributes to stabilization of the described enzyme on the cell surface, and it may be involved in tumor cell migration [24]. The role of the microenvironment of the lymphocytes in chronic lymphocytic leukemia development and progression is undeniable [47]. Interactions with appropriate factors and cells are indispensable in evasion of apoptosis by neoplastic B lymphocytes [12]. The surface expression of LPL associated with its ability to create a 'bridge' between other molecules supports its participation in the interaction with dendritic and stromal cells. Supporting this, it was noted that surface LPL molecules in patients with unmutated type of CLL had lower lipolytic activity although its expression level was higher. It provides a rationale that this enzymatic protein is involved in a process other than lipid metabolism [44].

Summary

Lipoprotein lipase is a promising candidate to be an important prognostic factor in chronic lymphocytic leukemia. Owing to the feasibility of its detection, in the near future LPL is expected to become a substitute for DNA sequencing in order to evaluate the presence or lack of mutations in the IgV_H genes, simultaneously providing the equivalent information. For the time being, LPL seems to be as good a prognostic marker as kinase ZAP-70, or, according to some researchers, even better [24, 39]. An open issue is to define the cut-off value and the standardization of the method used for the detection of LPL expression. The changes in the expression of genes involved in lipid metabolism are probably related to their participation in the development of chronic lymphocytic leukemia, and undoubtedly contribute to CLL cell survival. Uncovering the reason for LPL expression in leukemic lymphocytes, whilst LPL is absent in normal cells, would make this knowledge applicable for the new therapeutic options. The novel findings with the lipase inhibitor orlistat [37] provide the rationale for this approach and allow one to speculate that drugs targeting lipid metabolism might be new compounds for the therapy of this leukemia.

The authors declare no conflict of interest.

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