Pathol. Oncol. Res. (2017) 23:165–171
DOI 10.1007/s12253-016-0132-z

ORIGINAL ARTICLE

Lipoprotein Lipase as a Prognostic Marker in Chronic Lymphocytic Leukemia

Zoltán Mátrai[1] · Hajnalka Andrikovics[2] · Anikó Szilvási[2] · András Bors[2] · András Kozma[1] · Emma Ádám[1] · Gabriella Halm[1] · Éva Karászi[1] · Attila Tordai[2] · Tamás Masszi[1,3]

Received: 12 January 2016 / Accepted: 12 October 2016 / Published online: 18 October 2016

Abstract The marked clinical heterogeneity of CLL makes early prognosis assessment important. Lipoprotein lipase (LPL) has been shown to confer adverse prognosis in CLL, recent data indicating it might also contribute to CLL cell survival and metabolism. We determined LPL mRNA expression in unselected peripheral blood of 84 CLL patients by RT PCR. Results were correlated with other prognostic markers and outcome. 30/84 (40 %) of cases were LPL positive based on the cutoff established by ROC analysis. In LPL positive patients significantly shorter median survival (136 vs 258 months, $p < 0.0001$) and time to first treatment intervals (36 vs 144 months, $p < 0.002$) were documented. LPL values correlated with male gender, higher stages, more treatment requirement, CD38 positivity and unmutated IgVH genes. Among cases with 13q deletion, LPL positivity identified a subcohort with poor outcome (median survival 108 months vs NR, $p < 0.0001$). In multivariate analysis, cytogenetic aberrations and LPL had significant impact on survival. Our results confirm that LPL is a strong predictor of outcome in CLL, able to improve prognostic accuracy in good risk cytogenetic subgroups. The relationship between its prognostic and functional role in CLL needs to be explored further.

✉ Zoltán Mátrai
matraiz1@gmail.com

[1] Department of Haematology and Stem Cell Transplantation, St. István and St László Hospital, Budapest, Hungary

[2] Laboratory of Molecular Diagnostics, Hungarian National Blood Transfusion Service, Budapest, Hungary

[3] Third Department of Internal Medicine, Semmelweis University, Budapest, Hungary

Key Words Lipoprotein lipase · CLL · Prognosis · IgVH mutation · 13q deletion · Survival

Introduction

Clinical heterogeneity is one of the distinctive features of CLL, some patients doing well for decades without intervention, others survive only a couple of years due to progressive disease. In the last decade, major efforts were made to explore the biological background of this diversity. Out of the numerous prognostic factors introduced in CLL, immunoglobulin gene mutation status has been established as one of the most reliable and informative prognostic factors. Representing an imprint of the cellular origin of the disease, the relative lack of somatic hypermutation in the IgVH genes is associated with progressiveness, poor-risk cytogenetics, CD38 positivity and short survival. Being stable over time, it is also used as reference when investigating new markers [1–3]. IgVH mutation status, genetic abnormalities and serum markers, optimally applied together provide complementary prognostic information [3, 4].

Microarray studies identified distinct sets of genes expressed differentially in mutated vs unmutated CLL [5, 6] and lipoprotein lipase (LPL) was one of several genes being overexpressed in unmutated cases. Based on these preliminary observations, together with ZAP-70 and other molecular markers, the role of LPL in CLL prognosis assessment was investigated by different groups. These studies indicated that LPL correlates closely with clinical course and survival [7–15]. Physiologically, LPL is expressed in muscle, adipose tissue, macrophages, but not in normal T and B lymphocytes [16]. Bound to capillary endothelium and released upon heparin, LPL catalyzes the hydrolysis of triacylglycerol of circulating chylomicrons and very-low-density lipoproteins. Remarkably, a growing body of recent data indicate that lipid utilization and LPL function play an

important role in the survival and metabolism of different tumors, including CLL [17–21].

In this work we evaluated the prognostic role of LPL in CLL as determined by RT PCR from unselected peripheral blood. Our results show that LPL accurately predicts outcome and is related closely to other prognostic markers in this disease.

Patients and Methods

CLL Patients

The study cohort included 84 patients attending the haematology clinic with available clinical history and LPL test results; no further pre-selection was applied. Clinical features, prognostic profiles and the incidence of various cytogenetic subgroups are presented in Tables 1 and 2, respectively. Diagnosis of CLL was established by standard morphological and immunophenotypic criteria. The median follow-up period was 102 (40–496) months. During this interval, 43 patients were treated for disease progression and 22 patients died. Blood samples were taken either at diagnosis after informed consent or later. The study has been approved by the Central Ethics Committe.

RT PCR Analysis of Lipoprotein Lipase mRNA

Peripheral blood samples of CLL patients and two healthy controls were used for total RNA isolation by Trizol extraction method followed by reverse transcription. Quantitative polymerase chain reaction (QPCR) was performed by LightCycler 480 real-time PCR System with Sybr-Green detection format. ABL1 (v-abl Abelson murine leukemia viral oncogene homolog 1) was used as housekeeping gene to normalize LPL expression. Primer sequences were adapted from van't Veer with modifications (LPL-F: 5′-CCG CCG ACC AAA GAA GAG AT-3′; LPL-R: CAA TGA CAT TGG AGT CTG GTT CTC TC-3′; and ABL-4F: 5′-GGG CTC ATC ACC ACG CTC CA-3′, ABL-6F: 5′-CTG CCG GTT GCA CTC CCT CA-3′ [10]. As LPL and ABL1 amplifications showed similar efficiency determined as the slope of linear calibration curves, the relative LPL to ABL1 expression level was calculated by the ΔCp method (ΔCp = CpLPL-CpABL1). LPL/ABL1 expression in patients were normalized to the expression found in healthy control samples.

IgVH Gene Mutation Status

IgVH mutation status was analysed by a multiplex PCR method and BIOMED-2 standardized primers [22, 23]. VH segment usage and the degree of sequence divergence from the nearest germline counterpart were identified using the National Institute of Health Ig Blast database. 95 % was used as a threshold to define IgVH mutation status positivity.

Interphase Fluorescence in Situ Hybridization

Dual-color interphase FISH analysis was performed on interphase nuclei of blood lymphocytes. The panel applied detected abnormalities at 11q22, 12 centromere, 13q14.3 and 17p13 using the following probes: Vysis LSI D13S319 (13q14.3) SpectrumOrange (SO) (30–190,045), Vysis LSI 13q34 SpectrumGreen (SG) (30–192,030); Vysis LSI ATM (11q22.3) SO (30–190,017), Vysis CEP12 SG (32–112,012); Vysis LSI TP53 SO (30–190,008), Vysis CEP17 SG (32–112,017) (Abbott Laboratories, Illinois, US). A minimum of 200 interphase nuclei were assessed from each hybridization using a Nikon E600 epifluorescence microscope. Images were captured and enhanced with the MacProbe 4.3 FISH software (Applied Imaging). Results were regarded clonal when the ratio of cells with any given abnormality exceeded the normal cutoff. Chromosome deletions or trisomy 12 were considered to be present when >8 % or >3 % of interphase cells showed one signal or three signals, respectively.

CD38 Measurement

For the diagnosis of CLL, three-colour immunostaining was used on peripheral blood samples using the following

Table 1 Clinical and laboratory features of CLL patients: comparison of LPL positive vs negative cohort

N		All 84	LPL+ 34	LPL- 50	
Male/female		46/38	22/12	24/26	p < 0.18
Median age (years)		70.5 (47–90)	69.9 (49–88)	70.8 (47–90)	p < 0.67
Stage	A + B C	44 40	8 26	36 14	p < 0.0001
CD38	positive (>7 %) negative (>7 %)	40 37	27 6	13 31	p < 0.0001
IgVH mutation	mutated (<95 %) unmutated (<95 %)	30 26	2 22	18 14	p < 0.0001
Treatment requirement	yes/no	43/24	23/5	20/19	*p* < 0.01

Table 2 Differential expression of LPL in various cytogenetic subgroups

FISH abnormality	13q-	normal	11q-	complex	17p-
n	40	16	5	17	1
LPL positive	8/40	8/16	5/5	10/17	1/1
LPL negative	32/40	8/16	0/5	7/17	0/1

antibodies: anti-CD5 FITC (clone: L17F12), anti-CD19 PerCP-Cy5.5 (clone: SJ25C1), anti-CD23 PE (clone: EBVCS-5). CD38 was measured by dual staining for anti-CD19 FITC (clone 4G7)/anti-CD38 PE (clone HB-7), all monoclonal antibodies from Becton Dickinson. Measurements were performed on a FACSCalibur flow cytometer and data analysed by the CellQuest software (BD). CD38 expression was evaluated within the CD19 positive B-cell population and expressed as percentage of CD38/19 dual positive cells. CLL clones with CD19/CD38 dual positive cells equal or greater than 7 % were considered CD38-positive.

Statistical Analysis

Descriptive statistics were performed by the GraphPad Prism 5 software. ROC analyses [24] and Fisher's exact test were carried out with the Medcalc 10.2. program. For Kaplan-Meier and Cox multivariate survival analyses, the SPSS 15.0 software was employed. Statistical significance was accepted at $p < 0.05$.

Results

Distribution of LPL Values

LPL values normalized to healthy controls showed assymetrical distribution with a median of 0.66 (range 0–48) (Fig. 1). The optimal cutoff separating LPL positive and negative cases could be identified as 1.77 by ROC analysis. Applying this threshold, 34 patients were classified as LPL positive, 50 as LPL negative.

Correlation of LPL with Clinical Features and Other Prognostic Markers

Comparison of the LPL positive vs negative patient cohort showed association of LPL positivity with higher stages, CD38 positivity, unmutated IgVH genes and more treatment requirement. No differences were found between different genders or age groups (Table 1). A close linear relationship was found between LPL and CD38 ($p < 0.0001$). Analysis of LPL expression in various cytogenetic subgroups revealed overrepresentation of LPL positive cases in adverse prognostic subgroups (11q-, 17p- or complex aberrations), whereas 80 % of those with 13q deletion were LPL negative (Table 2).

Survival Analysis

Overall Survival

Kaplan-Meier curves revealed markedly reduced survival in LPL positive vs negative patients (median survival 136 vs 258 months, $p < 0.0001$) (Fig. 2a). In univariate analysis, IgVH mutation status, ($p < 0.007$), CD38 positivity ($p < 0.001$), clinical stage ($p < 0.009$) and cytogenetic aberrations ($p < 0.001$) were found to have impact (Table 3). In the multivariate model, only cytogenetic aberrations (HR 3.64, $p < 0.03$) and LPL positivity (HR 4.21, $p < 0.02$) remained significant (Table 4).

Treatment-Free Survival

Time to first treatment (TTFT) was significantly shorter in LPL positive vs negative cases (36 vs 144 months respectively, $p < 0.002$) (Fig. 2b.). Univariate analysis identified the same variables being significant in overall survival with the addition of age (Table 3). In the multivariate test, cytogenetic aberrations, IgVH mutation status and stage remained significant (Table 4).

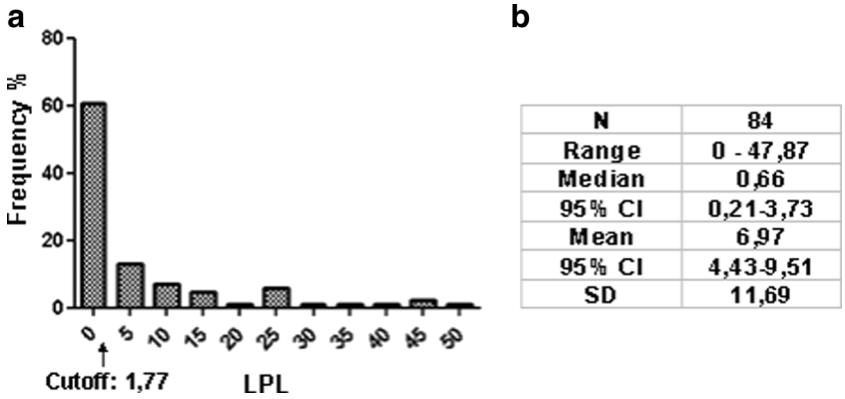

Fig. 1 Distribution (**a**) and descriptive parameters (**b**) of LPL mRNA expression in blood samples of CLL patients

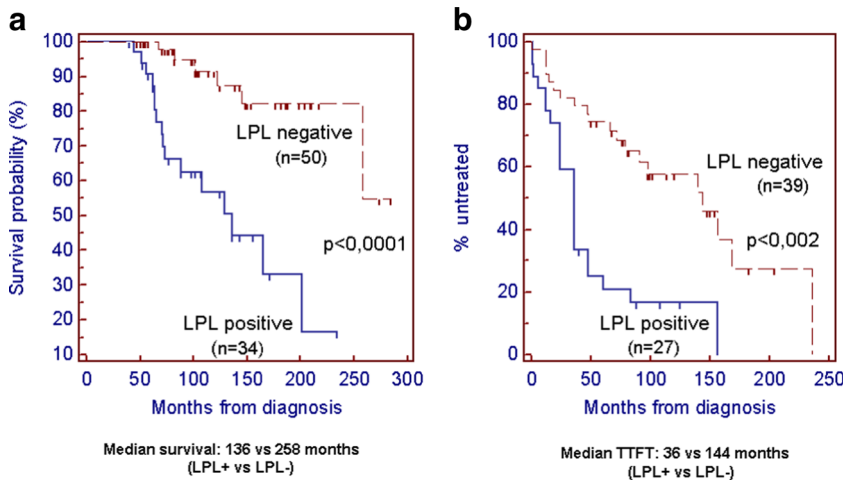

Fig. 2 (**a**) Overall and (**b**) treatment-free survival of LPL positive vs negative patients

LPL Expression in Good Prognosis Cytogenetic Subgroups

To explore whether LPL expression could dissect further prognostic subcohorts in this cytogenetic subgroup, cases with 13q deletion as the sole abnormality or with normal FISH results were assessed depending on concurrent LPL expression. Out of 40 patients with 13q deletion, 8 were LPL positive and 32 LPL negative (Table 2). During a median follow-up of 104 (40–496) months, 4 patients (50 %) died in the LPL positive group in contrast to 2 patients (6 %) in the LPL negative cohort. LPL positive patients had markedly reduced survival (median survival 108 months vs not reached, $p < 0.001$) (Fig. 3a). Similar results were obtained when cases with 13q- and normal FISH results were evaluated together (Fig. 3b).

Concurrent Use of LPL and CD38

To test whether applying LPL and CD38 together could provide further prognostic information. LPL/CD38 dual positive patients were found to have reduced survival (129 months) in contrast to dual negatives (median survival not reached). Discrepant cases had intermediate outcome (Fig. 4).

Discussion

Our results are consistent with previous reports that LPL expression is related closely to CLL progression and outcome. Patients with LPL values above the cutoff had markedly reduced overall and treatment-free survival. The association of LPL positivity with higher clinical stages, poor risk cytogenetics, unmutated IgVH genes, more treatment requirement and CD38 positivity are in agreement with earlier observations [9, 10, 12, 13] reflecting the connection between LPL and aggressive course. Its close correlation with CD38, a marker of cell proliferation and activation in this disease [25, 26] is especially remarkable. The fact that both CD38 and LPL can localize to lipid rafts [27] can add further functional link between these two molecules. Moreover, our results show that the combined use of LPL and CD38 can improve prognostic accuracy, confirming the findings of Kaderi et al. [14].

Table 3 Univariate Cox proportional hazard analysis of overall and treatment-free survival

			Overall survival			Treatment-free survival		
			HR	95 % CI	*p*-value	HR	95 % CI	p-value
Cytogenetic aberrations	11q–17p-12+ or complex	13q- or normal	**4.61**	1.87–11.35	**<0.001**	**3.05**	1.65–5.66	**<0.0001**
Gender	male	female	1.57	0.65–3.78	0.32	1.09	0.60–1.98	0.79
CD38	>7 %	<7 %	**5.58**	1.97–16.7	**<0.001**	**2.55**	1.31–4.99	**<0.006**
LPL	>1.77	<1.77	**5.22**	2.04–13.39	**<0.001**	**2.50**	1.35–4.61	**<0.003**
Stage	C	A or B	**3.78**	1.38–10.33	**<0.009**	**3.56**	1.90–7.00	**<0.0001**
Age	<70 years	>70 years	1.43	0.60–3.41	0.42	1.85	0.97–3.50	0.06
IgVH mutation	>95 %	<95 %	**7.96**	2.04–16.93	**<0.007**	**3.89**	3.10–20.66	**<0.005**

Bold numbers represent covariates with statistical significance

Table 4 Multivariate Cox proportional hazard analysis of overall and treatment-free survival

			Overall survival			Treatment-free survival		
			HR	95 % CI	HR	95 % CI	HR	95 % CI
Cytogenetic aberrations	11q–17p-12+ or complex	13q- or normal	**3.64**	1.14–11.59	**0.03**	**2.25**	0.99–5.07	**0.05**
CD38	>7 %	<7 %	0.05		0.82	0.50		0.48
LPL	>1.77	<1.77	**4.21**	1.31–13.54	**0.02**	**1.65**		0.20
Stage	C	A or B	0.06		0.80	**2.89**	1.21–6.88	**0.02**
Age	<70 years	>70 years	0.31		0.58	0.99		0.32
IgVH mutation	>95 %	<95 %	1.08		0.30	**2.88**	0.99–8.38	**0.05**

Bold numbers represent covariates with statistical significance

Most clinical studies on LPL recognize an association with cytogenetic abnormalities [8, 9, 13, 14]. In our material, correlations with 13q, 11q-, 17p- and complex aberrations were found. Particularly interesting is the relationship with 13q deletion, regarded to confer the best outcome in CLL [28]. Within this FISH subcategory, LPL expression could dissect a patient subcohort with extremely shortened survival. The fact that half (4 of 8) of LPL positive patients died during the follow-up in contrast to 2 of 32 LPL negatives indicates that LPL expression implies an aggressive, proliferative form of the disease able to offset the indolent course of CLL with 13q deletion. On the other hand, LPL negative cases with 13q deletion had extremely favourable outcome. These findings reinforce earlier observations [9, 11, 12, 14] and support the simultaneous testing of LPL and cytogenetics routinely since 13q deletion itself does not seem to be robust enough to identify progressive cases correctly. The results also fit into reports showing remarkable heterogeneity of CLL with 13q deletion, progressiveness associated with larger fragment deletions [29], mono- vs biallelic deletions [30] or percentage of cells harbouring the abnormality [31]. It remains to be seen whether earlier treatment could improve the otherwise dismal outcome of these patients.

Clinical studies of LPL are heterogeneous regarding the method how the optimal cutoff separating positive and negative values is defined. Some investigators apply a threshold fitted to IgVH mutation status [8], employ Youden index [12] or ROC analysis of survival results [9, 11] as in this work. That our cutoff stands closest to Nuckel et al's [9] might relate to the fact that both include a normalizing step to healthy controls. To improve inter-study comparisons, these aspects of data analysis require further standardization.

The mechanism by which LPL mRNA can predict outcome as well as the significance of LPL enzyme function in CLL are still under investigation. The importance of lipid utilization in cancer cell viability has been shown in other cancer cell types [17] and lymphomas including diffuse large cell lymphoma and Burkitt's lymphoma [18, 32]. Malignant cells are capable of both de novo lipid biosynthesis and fatty acid metabolism, both of which represent potential therapeutic targets [19]. Although previous reports indicated that LPL in not active functionally in CLL [33, 34], recent work from Rozovski et al. showed that unlike normal B-cells, CLL cells are capable to store lipids like adipocytes or monocytes and metabolize free fatty acids in an LPL-dependent manner with the transciption factor STAT3 initiating LPL transcription

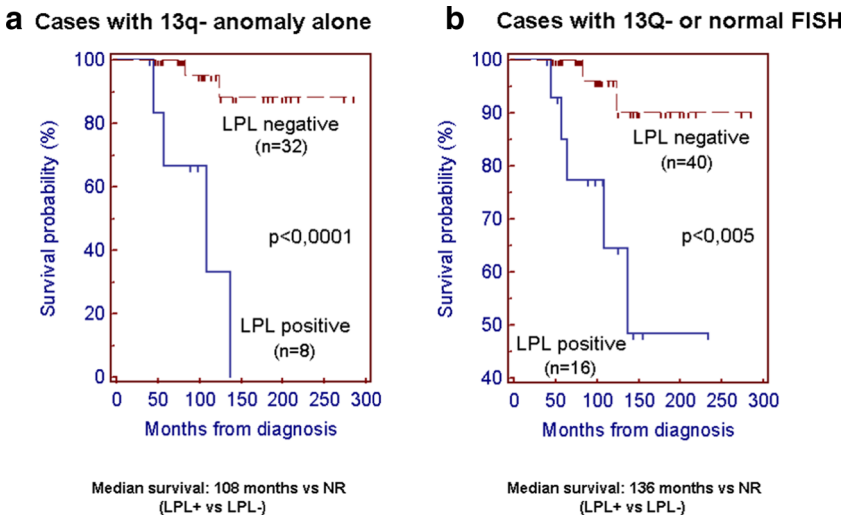

Fig. 3 Survival of LPL positive vs negative patients with good prognosis FISH abnormalities. (**a**) Cases with 13q deletion alone (**b**) cases with either 13q deletion or normal FISH

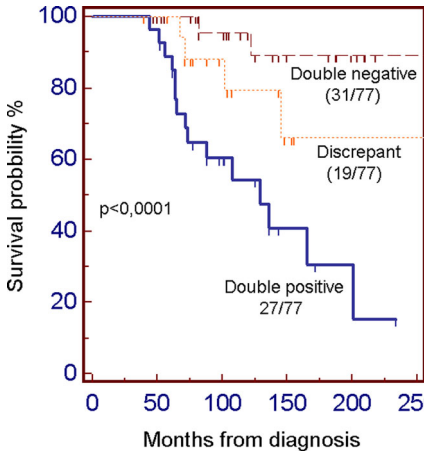

Fig. 4 Prognostic efficacy of evaluating LPL and CD38 simultaneously

[20]. Interestingly, the same study also found that LPL activation renders survival advantage for CLL cells. Moreover, BCR stimulation of CLL, but not normal CD5+ B-cells were shown to induce LPL expression, a process inhibited by the lipase inhibitor orlistat [35]. Altogether, these data support the idea that lipid metabolism is required for the function and survival of actively signalling CLL cells, a process in which LPL plays a crucial role [21]. They might also explain why high LPL expression is associated with progressive clinical course and short survival.

In summary, our results confirm that LPL expression is a strong predictor of outcome in CLL, indicating a progressive course with poor survival. Its presence can identify aggressive cases in good risk cytogenetic subgroups, thereby improving prognostic accuracy. These advantages and its relatively straightforward applicability make it an attractive candidate for regular clinical use.

References

1. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK (1999) Unmutated Ig VH genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood 94(6):1848–1854
2. Damle RN, Wasil T, Fais F et al (1999) IgV Gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood 94:1840–1847
3. Chiorazzi N (2012) Implications of new prognostic markers in chronic lymphocytic leukemia. Hematology 2012:76–87
4. Kröber A, Seiler T, Benner A, Bullinger L, Brückle E, Lichter P, Döhner H, Stilgenbauer S (2002) VH mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia. Blood 100:1410–1416
5. Rosenwald A, Alizadeh AA, Widhopf G et al (2001) Relation of gene expression phenotype to immunoglobulin mutation genotype in B cell chronic lymphocytic leukemia. J Exp Med 194(11):1639–1647
6. Klein U, Tu Y, Stolovitzky GA, Mattioli M, Cattoretti G, Husson H, Freedman A, Inghirami G, Cro L, Baldini L, Neri A, Califano A, Dalla-Favera R (2001) Gene expression profiling of B cell chronic lymphocytic leukemia reveals a homogeneous phenotype related to memory B cells. J Exp Med 194(11):1625–1638
7. Oppezzo P, Vasconcelos Y, Settegrana C et al (2005) The LPL/ADAM29 expression ratio is a novel prognosis indicator in chronic lymphocytic leukemia. Blood 106(2):650–657
8. Heintel D, Kienle D, Shehata M et al (2005) High expression of lipoprotein lipase in poor risk B-cell chronic lymphocytic leukemia. Leukemia 19(7):1216–1223
9. Nückel H, Hüttmann A, Klein-Hitpass L, Schroers R, Führer A, Sellmann L, Dührsen U, Dürig J (2006) Lipoprotein lipase expression is a novel prognostic factor in B-cell chronic lymphocytic leukemia. Leuk Lymphoma 47(6):1053–1061
10. van't Veer MB, Brooijmans AM, Langerak AW et al (2006) The predictive value of lipoprotein lipase for survival in chronic lymphocytic leukemia. Haematologica 91(1):56–63
11. Van Bockstaele F, Pede V, Janssens A, Callewaert F, Offner F, Verhasselt B, Philippé J (2007) Lipoprotein lipase mRNA expression in whole blood is a prognostic marker in B cell chronic lymphocytic leukemia. Clin Chem 53(2):204–212
12. Nikitin EA, Malakho SG, Biderman BV et al (2007) Expression level of lipoprotein lipase and dystrophin genes predict survival in B-cell chronic lymphocytic leukemia. Leuk Lymphoma 48(5):912–922
13. Xu W, Li JY, Shen QD, Wu YJ, Yu H, Fan L (2009) Expression level of lipoprotein lipase in Chinese patients with chronic lymphocytic leukemia and its correlation with other prognostic factors. Int J Lab Hematol 31(5):552–559
14. Kaderi MA, Kanduri M, Buhl AM et al (2011) LPL is the strongest prognostic factor in a comparative analysis of RNA-based markers in early chronic lymphocytic leukemia. Haematologica 96(8):1153–1160
15. Kristensen L, Kristensen T, Abildgaard N et al (2015) LPL gene expression is associated with poor prognosis in CLL and closely related to NOTCH1 mutations. Eur J Haematol . doi:10.1111/ejh.1270017 Dec
16. Mead JR, Irvine SA, Ramji DP (2002) Lipoprotein lipase: structure, function, regulation, and role in disease. J Mol Med 80(12):753–769
17. Kuemmerle NB, Rysman E, Lombardo PS et al (2011) Lipoprotein lipase links dietary fat to solid tumor cell proliferation. Mol Cancer Ther 10(3):427–436
18. Dashnamoorthy R, Abermil N, Behesti A et al (2014) The lipid addiction of diffuse large B-cell lymphoma and potential treatment strategies with novel fatty acid synthase (FASN) small molecule inhibitors. Blood 124:4490
19. Zaidi N, Lupien L, Kuemmerle NB, Kinlaw WB, Swinnen JV, Smans K (2013) Lipogenesis and lipolysis: the pathways exploited by the cancer cells to acquire fatty acids. Prog Lipid Res 52(4):585–589
20. Rozovski U, Grgurevic S, Bueso-Ramos C et al (2015) Aberrant LPL expression, driven by STAT3, mediates free fatty acid metabolism in CLL cells. Mol Cancer Res 13:944–953
21. Rozovski U, Hazan-Halevy I, Barzilai M, Keating MJ, Estrov Z (2015) Metabolism pathways in chronic lymphocytic leukemia. Leuk Lymphoma 8:1–8
22. van Dongen JJ, Langerak AW, Brüggemann M, Evans PA, Hummel M, Lavender FL et al (2003) Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 concerted action BMH4-CT98-3936. Leukemia 17(12):2257–2317
23. Matthews C, Catherwood M, Morris TC, Alexander HD (2004) Routine analysis of IgVH mutational status in CLL patients using BIOMED-2 standardized primers and protocols. Leuk Lymphoma 45(9):1899–1904

24. Metz CE (1978) Basic principles of ROC analysis. Semin Nucl Med 8:283–298
25. Matrai Z, Sherrington PD, Pettitt AR, Zuzel M, Cawley JC (2003) CD38 expression in CLL is a marker of cell cycling activity. Blood 102(11):671a
26. Damle RN, Temburni S, Calissano C, Yancopoulos S, Banapour T, Sison C, Allen SL, Rai KR (2007) Chiorazzi N. CD38 expression labels an activated subset within chronic lymphocytic leukemia clones enriched in proliferating B cells. Blood 110:3352–3359
27. Zubiaur M, Fernández O, Ferrero E, Salmerón J, Malissen B, Malavasi F, Sancho J (2002) CD38 is associated with lipid rafts and upon receptor stimulation leads to Akt/protein kinase B and Erk activation in the absence of the CD3- immune receptor tyrosine-based activation motifs. J Biol Chem 277:13–22
28. Dohner H, Stilgenbauer S, Benner A, Leupolt E, Krober A, Bullinger L et al (2003) Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 343:1910–1916
29. Strefford JC, Parker H, Parker A, Robinson H, Chaplin T, Chen X et al (2009) 13q deletion size predicts disease progression and response to treatment in patients with chronic lymphocytic leukaemia. Blood 114:671
30. Pettitt AR, Emmens CJ, Lin K, Harris RJ (2005) Chronic lymphocytic leukaemia patients with a biallelic deletion of 13q14 have a more favourable profile of prognostic factors compared with cases that have a monoallelic 13q14 deletion. Blood 106:5019
31. Hernández JA, Rodríguez AE, González M et al (2009) A high number of losses in 13q14 chromosome band is associated with a worse outcome and biological differences in patients with B-cell chronic lymphoid leukemia. Haematologica 94:364–371
32. Ambrosio MR, Piccaluga PP, Ponzoni M, Rocca BJ, Malagnino V, Onorati M et al (2012) The alteration of lipid metabolism in Burkitt lymphoma identifies a novel marker: adipophilin. PLoS One 7(8): e44315. doi:10.1371/journal.pone.0044315
33. Porpaczy E, Tauber S, Bilban M et al (2013) Lipoprotein lipase in chronic lymphocytic leukaemia - strong biomarker with lack of functional significance. Leuk Res 37(6):631–636
34. Mansouri M, Sevov M, Fahlgren E, Tobin G, Jondal M, Osorio L, Roos G, Olivecrona G, Rosenquist R (2010) Lipoprotein lipase is differentially expressed in prognostic subsets of chronic lymphocytic leukemia but displays invariably low catalytical activity. Leuk Res 34(3):301–306
35. Pallasch CP, Schwamb J, Konigs S, Schulz A, Debey S, Kofler D et al (2008) Targeting lipid metabolism by the lipoprotein lipase inhibitor orlistat results in apoptosis of B-cell chronic lymphocytic leukemia cells. Leukemia 22:585–592