Exp Oncol 2021
43, 3, 224–228

Experimental ONCOLOGY

ASSOCIATION OF LIPOPROTEIN LIPASE EXPRESSION WITH *TP53* GENE POLYMORPHISMS IN CHRONIC LYMPHOCYTIC LEUKEMIA CELLS

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***Background*: Expression of lipoprotein lipase (LPL) correlates with unmutated (UM) status of the variable region of the heavy chain of immunoglobulin (*IGHV*) genes, but the expression level of *LPL* in UM chronic lymphocytic leukemia (CLL) cases varies significantly. *Aim*: To study the association of *LPL* expression with the genetic variants of the *TP53* gene since both genes are involved in lipid metabolism. *Materials and Methods:* Expression of *LPL* mRNA was measured in peripheral blood mononuclears of 45 CLL patients with UM *IGHV* genes by real-time quantitative reverse transcription polymerase chain reaction. Mutational status of *IGHV* genes and *TP53* genotyping (rs1042522, rs1642785, rs17883323, rs2909430, rs145153611, rs113530090, rs12947788, rs12951053, and rs17878362) were performed by polymerase chain reaction amplification followed by direct sequencing. *Results*: Observed CLL patients were divided on groups with low (11.17 ± 2.66) and high (275.48 ± 39.37) *LPL* expression. In CLL patients with UM *IGHV* genes and low *LPL* expression we found an increased frequency of rs1042522 G ($p = 0.0036$), rs1642785 C ($p = 0.0001$), and rs17878362A2 alleles ($p = 0.0091$). The possible functional significance of these changes is discussed. *Conclusion*: Some polymorphic variants of *TP53* may be genetic modifiers for *LPL* expression level in CLL leukemic B-cells. Further research is required in a larger cohort to confirm these findings.**

***Key Words*: chronic lymphocytic leukemia, lipoprotein lipase, *IGHV* mutational status.**

DOI: 10.32471/exp-oncology.2312-8852.vol-43-no-3.16474

Chronic lymphocytic leukemia (CLL) is characterized by a heterogeneous course varying from indolent to highly aggressive [1]. A large number of CLL prognosis markers have been proposed, among them the mutational status of genes coding the variable region of the heavy chain of immunoglobulin (*IGHV*) remains the most reliable and universal to date [2, 3]. CLL patients with mutated (M) *IGHV* genes have a better prognosis than patients with unmutated (UM) *IGHV* genes.

The gene of lipoprotein lipase (*LPL*) was identified as a gene differentially overexpressed in patients with UM *IGHV* genes [4, 5] and is now considered to be a reliable RNA-based marker for CLL prognosis [6]. It is believed that the expression of *LPL* in patients with UM *IGHV* cases is a consequence of the demethylation of the CpG island involving the whole exon 1 and the first nucleotides of intron 1, whereas in cases with M *IGHV* genes, the promoter remains methylated [7]. As it was shown in the most studies, the expression level of *LPL* in CLL patients with UM *IGHV* genes cases varies significantly [8–13]. The reasons for this are not fully understandable.

One of the possible functions of the LPL in CLL cells is enzymatic, associated with lipolysis and subsequent fatty acid-mediated survival advantage [14–16]. McCaw *et al*. [17] found that different lipids, including free fatty acids, produced by the LPL activity, amplify cytokine-signaling in CLL cells that were not seen in normal lymphocytes. Numerous data indicate that the *TP53* gene is involved in the regulation of cellular metabolism, in particular, lipid metabolism. Some differences in metabolic processes depending on certain polymorphisms of the *TP53* gene have been established [18–21]. Therefore, the aim of this study was to determinate the association of the *LPL* expression as one of the key enzymes of lipid metabolism with the genetic variants of the *TP53* gene.

MATERIALS AND METHODS

The studied group consisted of 45 male patients with previously untreated CLL referred to the State Institution "National Research Centre for Radiation Medicine of the National Academy of Medical Sciences of Ukraine". The study was approved by the local Ethics Review Committee, all patients provided informed consent prior to participation. The diagnosis of CLL was based on clinical history, lymphocyte morphology and immunophenotypic criteria according to iwCLL guidelines [22]. Mutational status of *IGHV* genes was assessed as described previously [23]. Only patients with UM *IGHV* genes (⩾ 98% of homology to the germ line) were included in the study.

Genomic DNA and total RNA were extracted from peripheral blood mononuclear cells with the QIAamp Blood Mini Kit (Qiagen, United Kingdom) and TRI Reagent (Molecular Research Centre Inc., USA), respectively. The concentration and purity of RNA and DNA were assessed with NanoDrop Spectrophotometer (NanoDrop Technology, USA).

Expression of *LPL* was evaluated using real-time quantitative reverse transcription polymerase chain

Submitted: July 22, 2020.
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Abbreviations used: CI – confidence interval; CLL – chronic lymphocytic leukemia; HWE – Hardy – Weinberg equilibrium; *IGHV* – variable region of the heavy chain of immunoglobulin; LD – linkage disequilibrium; LPL – lipoprotein lipase; M – mutated; OR – odds ratio; PCR – polymerase chain reaction; SNP – single nucleotide polymorphism; UM – unmutated.

reaction (PCR) and CT ($2^{-\Delta\Delta Ct}$) method [24]. *LPL* expression in lymphocytes obtained from healthy donors was used as a calibrator for relative quantification.

TP53 genotyping was performed by PCR amplification followed by direct sequencing with the BigDye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems) as described earlyer [25]. Single nucleotide polymorphism (SNP) variants of the *TP53* gene with the minor allele frequency ⩾ 5% in the total European population were analyzed, namely: rs1042522, rs1642785, rs17883323, rs2909430, rs145153611, rs113530090, rs12947788, rs12951053, and rs17878362.

Hardy — Weinberg equilibrium (HWE) was evaluated by the chi–square (χ^2) test. SNPstats tool (http://bioinfo.iconcologia.net/snpstats/start.htm) was used for comparison of genotype and haplotype frequencies in groups of CLL patients with low and high *LPL* expression. Linkage disequilibrium (LD) between SNPs was estimated by calculating the *D'* and r^2 measures using CubeX online tool (http://www.oege.org/software/cubex/) and/or SNPstats tool. All tests were two-sided and considered statistically significant when $p \leqslant 0.05$. Statistical calculations were performed with SPSS for Windows (version 19.0; SPSS Inc., USA).

RESULTS

Relative *LPL* expression levels in observed CLL patients with UM *IGHV* genes ranged from 0.3 to 1024. As it was established earlier, the cut-off value of 17.0 showed the best degree of discrimination between the CLL cases with M and UM *IGHV* genes [9]. In 11 cases, *LPL* expression level did not exceed or was slightly above the cut-off value (mean 11.17 ± 2.66, median 13.7, range 0.1–24.3). These patients were included in the group with low *LPL* expression (I group). The remaining 34 patients with *LPL* expression levels ranging from 42.2 to 1024 (mean 275.48 ± 39.37, median 84.5) composed the group with high *LPL* expression (II group). Differences between groups were significant ($p = 0.016$).

The genotype frequencies of the most studied *TP53* gene polymorphisms corresponded to HWE. Only two SNPs (rs12947788 and rs12951053) exhibited the deviation from HWE ($p < 0.05$). Exonic rs1042522 was in LD with intronic rs1642785 ($D' = 0.9459$; $r^2 = 0.8884$; $p < 0.0001$); rs17883323 ($D' = 0.9972$; $r^2 = 0.2686$; $p = 0.0108$); rs17878362 and rs2909430 ($D' = 0.9993$; $r^2 = 0.6221$; $p < 0.0001$). Intronic rs1642785 was associated with rs17883323 ($D' = 0.9973$; $r^2 = 0.2686$; $p = 0.0073$), rs2909430 and rs17878362 ($D' = 0.9994$; $r^2 = 0.6223$; $p < 0.0001$); rs12951053 and rs12947788 ($D' = 0.7458$; $r^2 = 0.4517$; $p < 0.001$). Strong association was found between rs12951053 and rs12947788 ($D' = 0.9995$; $r^2 = 0.9995$; $p < 0.001$) (Figure).

Data on the distribution of *TP53* gene genotypes in both groups of patients are presented in the Table.

Table. Associations between *TP53* SNPs and relative *LPL* expression level

Model of inheritance	Genotype	Relative *LPL* expression level		OR (95% CI)	*p-value*
		Low	High		
rs1042522					
Codominant	C/C	1 (9.1%)	19 (55.9%)	1.00	
	G/C	9 (81.8%)	12 (35.3%)	**14.25 (1.60–47.16)**	0.012
	G/G	1 (9.1%)	3 (8.8%)	6.33 (0.31–30.75)	
Dominant	C/C	1 (9.1%)	19 (55.9%)	1.00	0.0036
	G/C – G/G	10 (90.9%)	15 (44.1%)	**12.67 (1.45–21.29)**	
Recessive	C/C – G/C	10 (90.9%)	31 (91.2%)	1.00	0.98
	G/G	1 (9.1%)	3 (8.8%)	1.03 (0.10–11.09)	
Overdominant	C/C – G/G	2 (18.2%)	22 (64.7%)	1.00	0.0058
	G/C	9 (81.8%)	12 (35.3%)	**8.25 (1.53–44.53)**	
Log-additive				**3.26 (1.03–10.35)**	0.034
rs1642785					
Codominant	G/G	1 (10.0%)	23 (67.6%)	1.00	
	G/C	7 (70.0%)	8 (23.2%)	**22.00 (2.36–44.71)**	0.0021
	C/C	2 (20.0%)	3 (9.2%)	**14.67 (1.00–35.27)**	
Dominant	G/G	1 (10.0%)	23 (67.6%)	1.00	0.0001
	G/C- C/C	9 (90.0%)	11 (32.4%)	**20.00 (2.26–76.76)**	
Recessive	G/G- G/C	8 (80.0%)	31 (90.8%)	1.00	0.43
	C/C	2 (20.0%)	3 (9.2%)	2.22 (0.32–15.43)	
Overdominant	G/G- C/C	3 (30.0%)	26 (76.5%)	1.00	0.0041
	G/C	7 (70.0%)	8 (23.5%)	**8.33 (1.77–39.16)**	
Log-additive		---	---	**4.25 (1.39–13.00)**	0.0057
rs2909430					
-	A/A	4 (36.4%)	27 (79.4%)	1.00	0.0091
	A/G	7 (63.6%)	7 (20.6%)	**6.75 (1.53–29.75)**	
rs17878362					
-	A1/A1	4 (36.4%)	27 (79.4%)	1.00	0.0091
	A1/A2	7 (63.6%)	7 (20.6%)	**6.75 (1.53–29.75)**	
rs17883323					
-	C/C	9 (81.8%)	33 (97.1%)	1.00	0.11
	C/A	2 (18.2%)	1 (2.9%)	7.33 (0.60–90.34)	
rs12947788					
-	C/C	9 (81.8%)	28 (82.3%)	1.00	
	C/T	1 (9.1%)	3 (8.8%)	1.04 (0.10–11.26)	0.97
	T/T	1 (9.1%)	3 (8.8%)	1.04 (0.10–11.26)	
rs12951053					
-	T/T	9 (81.8%)	28 (82.3%)	1.00	
	T/G	1 (9.1%)	3 (8.8%)	1.04 (0.10–11.26)	0.97
	G/G	1 (9.1%)	3 (8.8%)	1.04 (0.10–11.26)	

Significantly reduced frequency of C/C homozygotes (Arg72Arg) of rs1042522 ($p = 0.0036$), and, conversely, increased number of heterozygous C/G variants ($p = 0.0058$) and carriers of G allele ($p = 0.0036$) were found in patients of the group I.

Similar data were obtained regarding the distribution of rs1642785 polymorphic variants: a significant decrease in the number of homozygotes of dominant allele (G/G) and an increase in the number of heterozygous genotype (G/C) in the group of patients with low *LPL* expression. In this group, an increased number of heterozygotes of rs2909430 and rs17878362 was revealed as well.

No associations of *LPL* expression level with rs17883323, rs12947788, and rs12951053 were found. SNP rs145153611 and rs113530090 were monomorphic and presented only by homozygotes of dominant allele in both groups of patients.

According to data of SNPstats tool analysis, haplotype G–C–G–A2 (odds ratio (OR) = 9.69; 95% confidence interval (CI) 1.74–54.0; $p = 0.013$) was associated with significantly increased risk of low *LPL* expression when compared with the reference haplotype C–G–A–A1 (rs1042522/rs1642785/rs2909430/rs17878362, respectively).

DISCUSSION

The *TP53* gene encodes p53 protein, which plays a central role in the arrest of cell cycle and apoptosis following DNA damage [26, 27]. At present, over 200 SNPs in *TP53* have been identified (http://www-p53.iarc.fr/). The association of *TP53* SNPs with the susceptibility to different types of cancer has been most widely studied [28–31]. Recently, however, much attention was paid to the participation of p53 in the development of metabolic disorders and diseases, associated with atherosclerosis [18–21].

There is evidence that the frequencies of G allele of rs1042522 increased in disorders that are often accompanied by abnormalities of the serum lipid spectrum and LPL activity [32]. Elevated frequencies of carriers of G allele of rs1042522 were found among obese people [33], coronary heart disease [34, 35], type II diabetes [36, 37]. Therefore, our results on reduced *LPL* expression in patients with CLL in the presence of the G allele of rs1042522 are in the context of previously obtained data and may reflect the general mechanisms of the effect of *TP53* on lipid metabolism in different cell types.

Two intron SNPs (rs17878362 in intron 3 and rs1642785 in intron 2) are in close LD (according to our data D' = 0.9994; $r^2 = 0.6223$; $p < 0.0001$). A region of intron 3, containing rs17878362, forming G-quadruplex structures in p53 pre-mRNA is involved in the alternative splicing of *TP53* intron 2. Differential splicing of intron 2 leads to the generation of mRNAs that encode canonical suppressor p53 protein and the Δ40p53 isoform, which lacks the transactivation domain and acts as a negative regulator of p53 activity [38]. In experiments with lymphoblastoid cell

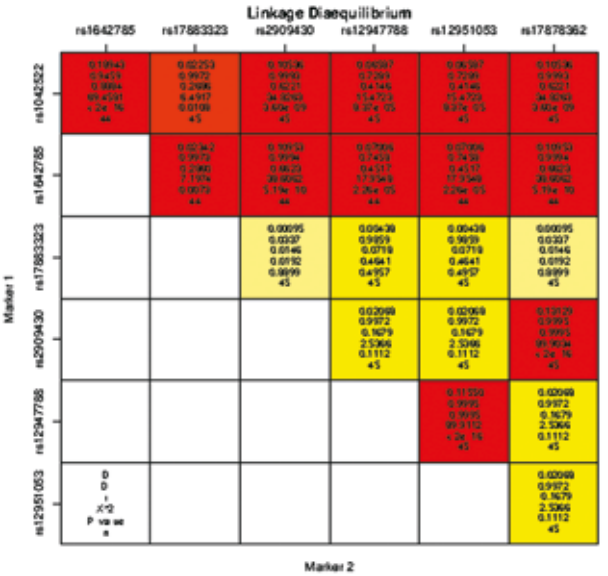

Figure. Graphical representation of D' and r^2 values for *TP53* polymorphisms. Linkage disequilibrium (LD) plots was generated using SNPstats tool

lines established from the peripheral blood of breast cancer patients, it was found that transcripts containing the C allele of rs1642785 had lower stability than that containing the G allele. The highest basal and radiation-induced p53 and Δ40p53 levels were associated with combined rs1642785-GG/rs17878362-A1A1 alleles, whereas the presence of rs1642785-C with either rs17878362 allele was associated with lower p53 pre-mRNA [39]. Morten *et al*. [40] have shown that Δ40p53: p53 ratio was significantly lower in samples of human breast cancer that were homozygous for the polymorphic allele of rs17878362 (A2/A2 genotype) compared with heterozytotes (A1/A2) and especially low compared with homozygous for the dominant allele (A1/A1). The authors suggest that a low Δ40p53:p53 ratio is associated with better disease-free survival of patients carriers of the rs17878362 A2 allele. Δ40p53 lacks the first 39 amino acids contained by full-length p53 that encode the first transcriptional activation domain and can alter p53 target gene expression [41, 42].

Thus, in CLL patients with UM *IGHV* genes and low *LPL* expression, we found an increased frequency of rs1642785 C and rs17878362-A2 alleles, which are associated with lower stability of *TP53* mRNA gene and, possibly, with an altered Δ40p53:p53 ratio. These preliminary data suggested that in the leukemic B cells of CLL patients there was some association between *LPL* expression level and the functional state of the *TP53* gene, the mechanisms of which have not been elucidated to date. One of such mechanisms may be a changed content of miR29, which is under the strict transcriptional control from p53 [43] and, in turn, influence on the transcription of the *LPL* gene [44].

In conclusion, some *TP53* SNP may be genetic modifiers for *LPL* expression level in CLL leukemic B-cells. Further research is required in a larger cohort of patients to confirm our findings.

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АСОЦІАЦІЯ МІЖ ЕКСПРЕСІЄЮ ЛІПОПРОТЕЇНЛІПАЗИ ТА ПОЛІМОРФІЗМАМИ ГЕНА *TP53* У ХВОРИХ НА ХРОНІЧНУ ЛІМФОЦИТАРНУ ЛЕЙКЕМІЮ

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Стан питання: Експресія ліпопротеїнліпази (ЛПЛ) корелює з немутованим статусом варіабельної ділянки генів важких ланцюгів імуноглобуліну (*IGHV*), однак рівень експресії ЛПЛ у хворих на хронічну лімфоїдну лейкемію (ХЛЛ) з немутованою варіабельною ділянкою *IGHV* значно різниться. ***Мета***: Дослідити асоціацію між експресією ЛПЛ та генетичними варіантами гена *TP53*, оскільки обидва гени залучені до метаболізму ліпідів. ***Матеріали та методи***: Експресію мРНК ЛПЛ визначали в мононуклеарах периферичної крові 45 хворих на ХЛЛ з немутованою варіабельною ділянкою *IGHV* методом кількісної зворотнотранскриптазної полімеразної ланцюгової реакції у реальному часі. Для визначення мутаційного статусу генів *IGHV* та генотипування *TP53* (rs1042522, rs1642785, rs17883323, rs2909430, rs145153611, rs113530090, rs12947788, rs12951053, та rs17878362) виконували ампліфікацію за допомогою полімеразної ланцюгової реакції з наступним прямим секвенуванням. ***Результати***: Залежно від низької (11,17 ± 2,66) або високої (275,48 ± 39,37) експресії ЛПЛ виділяли групи хворих на ХЛЛ. У хворих з немутованою варіабельною ділянкою *IGHV* та низьким рівнем експресії ЛПЛ виявили підвищену частоту алелів rs1042522 G (p = 0,0036), rs1642785 C (p = 0,0001) та rs17878362A2 (p = 0,0091). Обговорюється можливе функціональне значення цих змін. ***Висновки***: Деякі поліморфні варіанти *TP53* можуть модифікувати рівень експресії ЛПЛ у лейкемічних клітинах В-ХЛЛ. Для підтвердження цих даних необхідні подальші дослідження із залученням більшої когорти хворих.

Ключові слова: хронічна лімфоцитарна лейкемія, ліпопротеїнліпаза, мутаційний статус *IGHV*.