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The Role of Gene Polymorphisms rs1800629 TNFα and rs1800818 PDGFB in Relapses after Surgical Treatment of Diabetic Maculopathy

Роль полиморфизма гена rs1800629 TNFα и rs1800818 PDGFB в рецидивах диабетической макулопатии после хирургического лечения

Abstract

Analysis of the literature data indicated the possible role of gene polymorphisms rs1800629 (-308G/A) TNFα and rs1800818 PDGFB in the development of such complications of diabetes mellitus 2 type (DM2T) as diabetic retinopathy (DR) and maculopathy (DMP), which suggested the possibility of its connection to DMP relapses occurrence after surgery. The study included 313 patients with DMP (313 eyes) and initial (n=40), moderate or severe non-proliferative (n=92) and proliferative DR (n=181) stages. Patients underwent posterior subtotal vitrectomy (PSV) (n=78); PSV in combination with inner limiting membrane (ILM) peeling (n=85); PSV with ILM peeling and panretinal laser coagulation (n=81); and PSV with ILM peeling and panretinal laser coagulation and cataract phacoemulsification (n=69). Blood level of TNFα and PDGF-BB before surgical treatment was determined by enzyme immunoassay, polymorphisms – by polymerase chain reaction. For statistical procedures the Statistica 10 program (StatSoft, Inc., USA) was used. Our results and analysis of literature data suggest that the pathogenetic factor contributing to DMP relapses after surgery is a high content of TNFα in carriers of risk minor genotype A/A rs1800629. This genotype determined the development of DMP relapses in 96.9% of its carriers. Carriers of the G/A heterozygote also had an increased risk of relapses. The rs1800818 PDGFB was also associated with DMP relapses, but carriers of mutant genotypes (T/C and C/C) were less at risk than carriers of ancestral T/T genotype. The content of PDGF-BB was lower in the absence of relapses, which could explain the protective effect of this polymorphism. Thus, it can be assumed that both TNFα and PDGF-BB are potential targets for the development of targeted molecular therapy for DMP and its relapses after surgery.
Keywords: diabetic maculopathy, surgical treatment, recurrence, TNFα, PDGF-BB, rs1800629, rs1800818.

Резюме

Анализ литературных данных указывает на возможную роль полиморфизма гена rs1800629 (-308G/A) TNFα и rs1800818 PDGFB в развитии осложнений сахарного диабета 2-го типа (СД2) в виде диабетической ретино- (ДР) и макулопатии (ДМП), что дает возможность предположить

их участие и в развитии рецидивов ДМП после хирургического вмешательства. В исследование было включено 313 пациентов с ДМП (313 глаз) и начальной (n=40), умеренной или непролиферативной (n=92) и пролиферативной стадией ДР (n=181). Пациентам была проведена задняя субтотальная витрэктомия (ЗСВ) (n=78); ЗСВ с пилингом внутренней пограничной мембраны (ВПМ) (n=85); ЗСВ с пилингом ВПМ и этапом панретинальной лазерной коагуляции (n=81); ЗСВ с пилингом ВПМ, этапом панретинальной лазерной коагуляции ПСВ, факоэмульсификация катаракты (n=69). Уровень в крови TNFα и PDGF-BB до хирургического лечения определяли с помощью иммуноферментного анализа, полиморфизм – с помощью полимеразной цепной реакции. Для статистических исследований использовалась программа Statistica 10 (StatSoft, Inc., США).

Полученные нами результаты и анализ литературных данных позволяют предположить, что патогенетическим фактором развития рецидивов ДМП после хирургического лечения является высокий уровень содержания TNFα у носителей генотипа минорного генотипа A/A rs1800629. Этот генотип определил развитие рецидивов ДМП в 96,9% случаев. Носители гетерозигот G/A также имели повышенный риск развития рецидивов. Полиморфизм rs1800818 гена PDGFB также был связан с развитием рецидивов ДМП, но носители генотипов (T/C и C/C) были менее подвержены риску, чем носители T/T-генотипа. Содержание PDGF-BB было ниже у пациентов с отсутствием рецидивов, что могло бы объяснить защитное действие этого полиморфизма. Таким образом, можно предположить, что и TNFα и PDGF-BB являются потенциальными мишенями для разработки целевой молекулярной терапии ДМП и ее рецидивов после хирургического вмешательства.

Ключевые слова: диабетическая макулопатия, хирургическое лечение, рецидив, TNFα, PDGF-BB, rs1800629, rs1800818.

■ INTRODUCTION

One of the main complications of type 2 diabetes mellitus (DM2T) is visual organ damage, in particular diabetic retinopathy (DR) and diabetic maculopathy (DMP) [1–3]. Moreover, DMP does not develop in all cases of DR: the frequency of DMP increases according to the severity of DR. Thus, in non-proliferative DR (NPDR) the development of DMP occurs in 3–38% of patients, in preproliferative – in 20–63%, and in proliferative DR (PDR) – in more than 70%.

The importance of pro-inflammatory cytokines and, in particular, tumor necrosis factor-alpha (TNFα) for insulin resistance formation is well-known [4]. The molecular basis of this effect is the role of TNFα in signal transduction from the insulin receptor, namely, – inhibition of insulin receptor substrate (IRS-1) phosphorylation and, accordingly, tyrosine phosphorylation, which prevents further activation of PI3K/Akt- and Erk/MAP pathways of glucose uptake [5, 6].

Genetic factors, in particular the polymorphic state of genes, contribute to the emergence of DM2T and its complications [7–10]. Thus, a meta-analysis conducted in Chinese Han population, which included 10 studies (1425 patients with DM2T and 1116 controls), established the association of minor allele A rs1800629 TNFα (OR=1.63; 95% CI 1.17–2.25) and genotypes according to the dominant model of inheritance (OR=1.47; 95% CI 1.17–1.85) [8]. A Brazilian study (745 patients with DM2T, including 331 people without DR, 246 with NPDR and 168 with PDR) showed that the frequency of allele

A rs1800629 TNFα was significantly higher in patients with PDR than in patients without DR (p=0.035), and had an association with its development (OR=1.82; 95% CI 1.11–2.98) [9]. A systematic review of publications from 2000 to 2016 by G.I. Luna and al. (2016), drew attention to the contradictory results of determining the association of rs1800629 TNFα with DM2T in different populations, which, according to the authors, is related to their ethnic differences, and justifies the need for such studies in each population separately [10].

Also, the regulatory polypeptide – platelet-derived growth factor (PDGF), which is a transmembrane glycoprotein with mitogenic properties – plays an important role in DMP development [11–13]. The source of PDGF in blood is α-granules of platelets, and in tissues – fibroblasts, smooth muscle cells, astrocytes [14, 15]. PDGF-BB is produced by activated macrophages and neoangiogenic endothelium and, unlike other isoforms that are rapidly excreted from the cell, remains associated with it [16]. In hypoxia and ischemia, PDGF-BB stimulates endothelial cell proliferation and neoangiogenesis, increases capillary permeability [17]. Hyperglycemia can induce postreceptor resistance to PDGFB by activating C-delta protein kinase (PKC-delta), MAP-kinase and protein tyrosine phosphatase (SHP-1) and thus dephosphorylating PDGFB receptor [18]. The latter phenomenon is associated with diabetic intraretinal microvascular abnormalities (IRMA) [3].

The rs1800818 PDGFB (gene localization 22q13.1; Chr.22: 39244698 on GRCh38) is located in the intron of the five-bar-untranslated region (5'-UTR Variant). It has been shown that in carriers of this polymorphism, that have viral fever with thrombocytopenia syndrome, the blood PDGF-BB level and mRNA expression were significantly reduced (p=0.015) [19]. It was also determined that rs1800818 PDGFB was associated with three-year and overall survival in patients, operated on colorectal cancer metastases and having anti-VEGF therapy, which, according to the authors, is associated with angiopoiesis and pericyte proliferation [20]. Significant activation of PDGF-BB in DR, especially in its proliferative form, as well as analysis of numerical experimental data with models of DR and DMP in knockout mice on PDGFB genes or its receptor, suggest that this gene for DMP is of great value [21, 22]. We have previously shown the determining role of PDGF-BB for the formation of DMP relapses after surgery [11, 12].

Thus, these data indicated the possible role of polymorphisms rs1800629 (-308G/A) TNFα and rs1800818 PDGFB in the development of DM2T complications, in particular, DR and DMP, and indicated the need to study the possible relationship of these polymorphisms with DMP relapses after its surgical treatment in patients from the Ukrainian ethnic group.

■ PURPOSE

To determine the association of rs1800818 PDGFB and rs1800818 PDGFB with DMP relapses after surgery.

■ MATERIALS AND METHODS

The study included 313 patients with DM2T (313 eyes) with DMP and initial (1st group; n=40), moderate or severe non-proliferative DR (NPDR; 2nd group; n=92) and proliferative DR (PDR; 3-rd group; n=181), who were treated at the Kyiv City Clinical Ophthalmological Hospital "Center for Eye Microsurgery",

which is the clinical base of the Ophthalmology Department of the Shupyk National Medical Academy of Postgraduate Education (Kyiv, Ukraine). All patients underwent conventional ophthalmological examinations. The severity of DR and DMP was established according to the International Clinical Scale of the American Academy of Ophthalmology (2002) [3]. In this study, patients received four types of surgical treatment. 78 patients underwent three-port closed subtotal vitrectomy 25+. 85 patients underwent additionally internal limiting membrane peeling during vitrectomy. In 81 patients, in addition to these procedures, a stage of panretinal laser coagulation (PRLK) was performed. In addition to all these interventions, cataract phacoemulsification (PhEC) was performed in 69 patients.

The blood level of TNFα (Bender Medsystems, Austria) and PDGF-BB (Human PDGF-BB Quantikine ELISA Kit; R&D Systems; USA) was determined before surgery in all patients by enzyme-linked immunosorbent assay. The color intensity of enzymatic reaction product was quantified on Multiscan EX photometer, Thermo Electron Corp. (Finland). Analysis of genetic polymorphisms was performed by real-time polymerase chain reaction (PCR). In the first stage of the study, genomic DNA was isolated from whole venous blood using standard reagents "PureLink® Genomic DNA Kit For Purification of Genomic DNA"; manufacturer INVITROGEN (USA). In the second stage, real-time PCR was performed using unified test systems "TaqMan Mutation Detection Assays" Life-Technology (USA) in the automatic amplifier Gene Amp® PCR System 7500 (Applied Biosystems, Inc., USA). As control, 95 people of the same sex and age who did not have any visual pathology, were involved.

Patients were examined at 1, 3, 6 months and 1 year after surgery. All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki (as amended in 1964) and with the permission of the Bioethics Committee. All patients gave informed consent to participate in the study.

Statistica 10 (StatSoft, Inc., USA) was used for statistical processing of the obtained data. To determine the nature of data distribution, Kolmogorov – Smirnov and χ-square tests were performed. The median (Me) and the first and third quarters (Q1; Q3) of the variation series were used for descriptive statistics of quantitative data. Comparison tables and Pearson's nonparametric criterion χ-square were used to compare categorical variables. In all cases, statistical evaluation of $p<0.05$ was considered plausible.

■ RESULTS AND DISCUSSION

The DMP relapses frequency in general was 29.7%, by groups: in the 1st – 27.5%, in the 2nd – 22.8% and in the 3rd – 33.7% (p=0.180). According to the literature, in patients with DM2T there was an increase in TNFα blood level, which corresponds to the severity of the disease and its complications, in particular – DR [23]. According to our data, blood level of cytokine before surgery increased as the stage of DR progressed (Table 1).

In the 1st group of patients the content of TNFα exceeded the control 1.2 times (p=0.005). In groups 2 and 3, the cytokine level was 2.0 and 3.4 times higher than in controls, respectively ($p<0.001$). The maximum level of TNFα was observed in patients of the 3rd group who had PDR, the minimum – in patients of the 1st group with the initial NPDR.

Table 1
The content of TNFα in the control and patient groups; Me (Q1; Q3)

Marker	Control, n=95	1st, n=40	2nd, n=92	3rd, n=181
TNFα, pg/ml	15.95 (9.95; 21.54)	19.52 (16.30; 22.61)	31.20 (25.39; 37.01)	53.99 (42.31; 66.27)
	H=315.79; p<0.001			
PDGF-BB, ng/ml	27.55 (20.18; 33.47)	27.81 (22.09; 33.13)	45.28 (38.99; 50.78)	61.72 (56.85; 72.89)
	H=321.09; p<0.001			

Notes: H – intergroup differences according to the Kruskal – Wallis criterion (multiple comparisons); p – is the probability of differences between intergroup comparisons (accepted if p<0.05).

When analyzing the relationship of TNFα content with the presence or absence of DMP relapses in groups of patients, it was found that in the 1st and 2nd groups in the presence of relapses the cytokine level was significantly higher, especially in patients with initial NPDR (Table 2).

In group 2, the difference was less significant, while in group 3, the situation changed: the median TNFα level was higher in the absence of relapses. Analysis of the sample showed that the data distribution did not differ significantly (p=0.062), and their ranges actually overlapped. Thus, the increase in blood TNFα level is associated with the relapses presence only in NPDR, in PDR there was no such connection.

Such preconditions determined the main task of the study – to establish the connection of rs1800629 TNFa with the DMP relapses development after surgical treatment (Table 3).

It was found that in patients with relapses the frequency of ancestral genotype G/G was significantly lower than in patients without relapses

Table 2
The level of TNFα (pg/ml) depending on DMP relapses; Me (Q1; Q3)

Relapses	1st	2nd	3rd	H; p
present	24.09 (22.49; 25.32) (n=11)	34.89 (29.46; 40.22) (n=21)	49.24 (39.77; 65.56) (n=61)	H=45.89; p<0.001
absent	17.76 (15.12; 20.28) (n=29)	29.98 (23.17; 36.89) (n=71)	57.39 (43.62; 67.08) (n=120)	H=152.04; p<0.001
U; p	U=25.00; p<0.001	U=498.0; p=0.022	U=3038.0; p=0.062	

Notes: H – differences by Kruskal – Wallis criterion (multiple comparisons); U – differences according to the Mann – Whitney criterion (pairwise comparisons); p – is the probability of differences between intergroup comparisons (accepted if p<0.05).

Table 3
The effect of rs1800629 TNFα genotypes on the DMP relapses development

Genotype	The presence of relapses, n (f)		χ^2	p	OR	95% CI
	present	absent				
G/G	5 (0.054)	154 (0.700)	139.7	<0.001	0.02	0.01–0.06
G/A	57 (0.613)	65 (0.295)			3.76	2.27–6.27
A/A	31 (0.333)	1 (0.005)			109.50	14.65–818.23

Notes: n (f) – number and frequency; χ^2 – Pearson's chi-square criterion; p – is the probability of intergroup comparisons by the criterion χ^2 (accepted at p<0.05).

(p<0.001). At the same time, the frequency of risky rs1800629 variants (heterozygote G/A and minor homozygote A/A) under relapse conditions was significantly increased (p<0.001).

Also a very interesting fact should be mentioned: among the studied cohort of patients there were 32 with minor homozygous genotype A/A, and almost all of them (31 people; 96.9%) in the postoperative period had DMP relapses. This directly indicated the determinant of the minor genotype A/A rs1800629 TNFa in the development of DMP relapses. The risk of DMP relapses in carriers of the G/A heterozygote was 3.8 times increased (OR 3.76; 95% CI 2.27–6.27); in carriers of the protective ancestral homozygote G/G this risk was significantly reduced – 50 times (OR 0.02; 95% CI 0.01–0.06). Therefore, the obtained results directly indicated the important role of rs1800629 TNFa for DMP relapses formation after surgical treatment, regardless of the DR severity.

The level of PDGF-BB in the groups also increased (see Table 1): the maximum values were observed in patients with PDR, the minimum – in the initial NPDR. The blood level of PDGF-BB in patients with PDR (3rd group) exceeded the control value by 2.2 times (p<0.001). It was shown that the level of PDGF-BB was significantly increased in the serum and vitreous of patients with PDR compared with the control [21]. These data coincide with ours, which proves the pathogenetic role of increasing the content of this marker in DR.

Analysis of the relationship between PDGF-BB level before surgical treatment with the presence or absence of DMP relapses showed (Table 4) that in the presence of relapses, the PDGF-BB level in each group was statistically significant (p<0.001 by Mann – Whitney test) higher than in the absence of relapses (1.3–1.4 times).

Thus, it was shown, that, first of all, there is an increase in the blood level of PDGF-BB in DMP in the presence of moderate and severe NPDR and, to a greater extent, – PDR; and second of all, there is an association of DMP surgical treatment relapses with the blood level of PDGF-BB before surgery.

The connection of rs1800818 PDGFB with the relapses DMP development was further clarified (Table 5).

The frequency of ancestral homozygous T/T genotype in patients with DMP relapses was significantly higher than that in patients without relapses (3.0 times), while the frequencies of heterozygotes (T/C) and minor homozygotes (C/C) were significantly lower (in 5.8 and 3.6 times,

Table 4
The level of PDGF-BB (ng/ml) depending on DMP relapses; Me (Q1; Q3)

Relapses	1st	2nd	3rd	H; p
Present	34.40 (32.75; 40.35) (n=11)	59.71 (56.57; 64.02) (n=21)	76.46 (72.89; 82.96) (n=61)	H=64.73; p<0.001
Absent	24.56 (21.32; 28.07) (n=29)	41.40 (38.34; 46.92) (n=71)	58.66 (54.96; 61.71) (n=120)	H=269.32; p<0.001
U; p	U=14.00; p<0.001	U=23.00; p<0.001	U=12.00; p<0.001	

Notes: H – differences by Kruskal – Wallis criterion (multiple comparisons); U – differences according to the Mann – Whitney criterion (pairwise comparisons); p – is the probability of differences between intergroup comparisons (accepted if p<0.05).

Table 5
The effect of rs1800818 PDGFB genotypes on DMP relapses development

Genotype	The presence of relapses, n (f)		χ^2	p	OR	95% CI
	present	absent				
T/T	80 (0.860)	62 (0.282)	88.43	<0.001	162.1	59.4–442.3
T/C	9 (0.097)	124 (0.564)			0.03	0.01–0.07
C/C	4 (0.043)	34 (0.154)			0.17	0.06–0.50

Notes: n (f) – number and frequency; χ^2 – Pearson's chi-square criterion; p – is the probability of intergroup comparisons by the criterion χ^2 (accepted at $p<0.05$).

respectively). According to Pearson chi-square criterion, such shifts had a high degree of significance ($p<0.001$).

In our opinion, such results showed the importance of the minor allele C for prevention of DMP relapses after surgical treatment. The risk of relapses in C allele-carriers (genotypes C/C and C/T) were significantly reduced. According to the obtained data, only in the studied cohort of patients, 38 people were the carriers of minor genotype C/C and almost all of them (34 people; 89.5%) in the postoperative period had no DMP relapses. The risk of DMP relapses in minor homozygote C/C carriers was significantly reduced (5.9 times; OR 0.17; 95% CI 0.06–0.50).

The results showed an association of rs1800818 PDGFB with DMP relapses after surgical treatment and were consistent with the study that showed that in rs1800818 minor allele carriers the blood level of PDGF-BB and mRNA expression were significantly reduced ($p=0.015$) [19]. Therefore, it could be assumed that rs1800818 PDGFB, which is located in the intron of the five-bar-untranslated region (5'-UTR), reduces mRNA expression and PDGF-BB levels, which is manifested in minor allele C carriers. Given the established protective role of this polymorphism for the occurrence of DMP relapses, we can assume that C allele carriers have lower risk of relapses due to relatively low content of PDGF-BB. The pathogenetic role of the latter for the occurrence of DR and DMP is indicated by experimental and clinical data, as well as the results of our previous studies [11, 12, 17, 21, 22].

Thus, it can be assumed that both TNFα and PDGF-BB are potential targets for the development of targeted molecular therapy for DMP and its relapses after surgery.

■ CONCLUSIONS

1. Our results and analysis of literature data suggest that pathogenetic factor that contributes to the DMP relapses after surgery is the high level of TNFα in carriers of risk minor genotype A/A rs1800629 TNFα. This genotype determined the development of DMP relapses in 96.9% of its carriers. Carriers of the G/A heterozygote also had an increased risk of relapses.
2. The rs1800818 PDGFB was also associated with DMP relapses, but carriers of mutant genotypes (T/C and C/C) were less at risk than ancestral T/T genotype carriers. The PDGF-BB level was lower in absence of relapses, which could explain the protective effect of this polymorphism.

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