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THE ROLE OF TGF-β1 GENE POLYMORPHISMS IN THE DEVELOPMENT OF POST-TRANSPLANT COMPLICATIONS

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Transforming growth factor beta 1 (TGF-β1) is an immunosuppressive and profibrogenic cytokine capable of influencing the development of graft rejection and graft fibrosis in solid organ recipients. The TGF-β gene has a significant polymorphism that may cause individual protein expression levels and be associated with post-organ transplant complications. It is believed that three TGFB1 polymorphic variants (rs1800469, rs1800470 and rs1800471) may be associated with the development of graft rejection, graft fibrosis and chronic dysfunction of a heart, liver or kidney transplant. A review of current literature presents the results of studies on the relationship between TGF-β1 gene polymorphisms and post-transplant complications in solid organ recipients. The findings of various studies of TGF-β1 gene polymorphism in solid organ recipients are not always unambiguous, and their results are often difficult to generalize even with the help of meta-analysis. Samples included in studies vary in terms of ethnicity, gender, age, and underlying medical conditions, while results are highly dependent on sample structure or latent relatedness. Currently available data suggest that TGFB1 polymorphism may determine a predisposition to the development of graft rejection, graft fibrosis and graft dysfunction in solid organ recipients, but this is not conclusive and requires further, larger studies.

Keywords: single-nucleotide polymorphism, graft rejection, graft fibrosis, graft dysfunction.

Transplantation of vital organs is the only effective method of treatment for patients with end-stage chronic diseases leading to organ failure/irreversible loss of organ functions. Transplantation allows achieving long-term survival and rehabilitation. The post-transplant period may be accompanied by such complications as graft rejection, fibrosis and graft dysfunction. Prevention of these is an urgent task in transplantology [1].

The role of the major histocompatibility complex (MHC) in the occurrence of acute and chronic graft rejection is well studied. However, apart from MHC, other factors may influence the development of post-transplant complications. Today, there are a wide range of cytokines, including interleukins, interferons, various growth factors, and their receptors known to be important regulators of the immune response after organ transplantation [2].

Organ recipients can develop long-term post-transplant complications, including graft fibrosis, which can lead to structural and functional remodeling of the organ and subsequent dysfunction. Acute and chronic graft rejection, arterial hypertension, metabolic syndrome, diabetes mellitus, renal dysfunction, etc. contribute to fibrotic changes in the transplanted organ [3, 4].

Biopsy is mainly used to verify the pathology of transplanted organs. It is associated with all the risks of invasive interventions. The search for new molecular genetic markers and the development of minimally invasive techniques for detecting post-transplant complications based on these markers is a priority task that occupies an essential place in the concept of personalized medicine.

Transforming growth factor beta 1 (TGF-β1), a cytokine, an important component of the immune system that has immunosuppressive and profibrogenic effects, can have a significant impact on development of post-transplant graft rejection, graft fibrosis and infectious processes [5–8].

As studies by various authors, including the work by our laboratory have shown, cytokine levels correlate with liver transplant function and may have prognostic and diagnostic significance [9–12]. TGF-β1 content in the recipient's blood and tissues may depend on various factors, such as clinical, pharmacological, including genetic.

It is now known that the TGF-β1 gene has a significant genetic polymorphism that may cause individual levels of protein expression and be associated with various diseases [13–17] and post-transplant complications after organ transplantation [16, 18–22].

Cytokine TGFB1 is encoded by the TGFB1 gene, has sequence number 190180 in the Online Mendelian Inheritance in Man (OMIM) genetic database. The gene is located on the chromosome 19 long arm at locus 19q13.2, consists of 7 exons and 6 introns with a total length of about 23,000 base pairs. The size of the regula-

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tory part of the gene is about 3 base pairs and is located at positions –2665 to +423 in exon 1 (+1 is the translation start site) [23]. Currently, eight potentially significant single nucleotide polymorphisms (SNPs) and one deletion/insertion polymorphism (registered in gene databases as rs2317130, rs11466313, rs1800468, rs1800469, rs11466314, rs1800470, rs1800471 and rs11466316) that affect the TGF-β1 expression and regulate its transcription have been identified in the TGFB1 gene [24]. All of the single nucleotide substitutions studied are associated with characterization of human immune status and are on the list of those recommended by the 15th International Histocompatibility and Imunogenetics Workshop held in Brazil in 2008 for clinical diagnostic purposes.

Studies of the genetic polymorphism of the TGFB1 gene in solid organ transplantation have been carried out mainly in kidney and liver recipients [25–28], and considerably less in heart recipients, due to the number of heart transplants performed [29–31]. As a rule, the outcomes studied included acute and chronic rejection, mid-term graft function, tacrolimus levels, new-onset diabetes after transplantation, development of graft fibrosis, and incidence of infectious diseases.

The greatest interest to researchers in the field of solid organ transplantation comes from 3 polymorphic variants in the TGFB1 gene: rs1800469, which is a cytosine to thymine substitution C(–509)T in the promoter region, localized in exon 1 in codon 10 (T+869C), rs1800470, leading to leucine to proline substitution, and rs1800471 in codon 25 (C+915G), leading to arginine to proline substitution in the protein product. Presumably, the above SNPs can lead to different levels of TGF-β1 production and may be associated with graft rejection, fibrosis, and chronic graft dysfunction [20, 27, 30].

In heart recipients, two TGFB1 gene polymorphisms have been mainly investigated: rs1800470 and rs1800471. A number of studies have found an association between rs1800471 and acute cellular rejection and/or development of coronary heart disease after heart transplantation [32–34]. However, other studies have failed to find a reliable association between acute cellular rejection and rs1800471 [35, 36], and this polymorphism has not been found to be associated with chronic rejection either [37]. Data on association of rs1800471 with kidney function after transplantation are also inconsistent [38, 39]. For the rs1800470 polymorphism, it has been shown that it may be associated with accelerated development of CHD [37] and impaired renal function after heart transplantation [40].

Linkage analysis of TGF-β1 gene polymorphism in liver recipients showed predisposition of a certain genotype to liver fibrosis and kidney failure after transplantation [41, 42]. D. Eurich et al [42] investigated two types of polymorphism and their relationship with the development of liver fibrosis in 192 liver recipients. It was shown that the C allele substitution at codon 25 was associated with liver fibrosis. On the other hand, a study by H. Xie et al. [26] could not find an association between TGF-β1 polymorphism and acute rejection or recurrent hepatitis B virus infection in liver recipients.

Results and conclusions from various studies of TGFB1 genetic polymorphism in solid organ recipients are not always unambiguous, which may be due to the insufficient number of cases studied, ethnic heterogeneity of the sample, as well as differences in definition of the studied phenotypes and application of different analysis techniques. Meta-analyses and systematic reviews are often used to summarize heterogeneous studies, which are conducted according to certain standards and are thought to bring disparate data to a common denominator [18, 28, 43].

For example, a meta-analysis of 18 studies looking for an association between the TGF-β1 + 869 T/C and TGF-β1 + 915 G/C gene polymorphisms are not associated with acute rejection susceptibility in kidney recipients [28].

A meta-analysis of 23 case-control studies with 795 acute kidney rejection cases and 1,562 non-rejection controls also sound no significant association between the TGF-β1 codon 10 polymorphism (rs1982073) and an increased risk of acute kidney rejection in the general population [44]. Moreover, stratified analysis revealed no significant association between TGF-β1 polymorphism and susceptibility to acute rejection depending on the ethnicity of the recipient and donor. The researchers concluded that TGF-β1 polymorphism rs1982073 was not significantly associated with increased susceptibility to rejection. However, the authors conclude that studies with a large number of subjects from different ethnic groups are required to further validate the results.

The above examples show that it is difficult to generalize the results of heterogeneous studies even with meta-analysis. The samples included in the studies vary in terms of ethnicity, gender, age, and underlying diseases, while the resulting evidence may be highly dependent on sample structure or latent relatedness. It is possible that larger studies involving genome-wide genetic variation could uncover new loci and confirm known genetic variations associated with organ transplant outcomes.

Independence from the physiological state, immutability and one-time test represent some of the important advantages of gene diagnostics over other laboratory methods of analysis. The results of such a study provide information about a patient's weaknesses and allow targeted prevention of diseases by selecting medications according to the individual characteristics of the patient's body. Meanwhile, complex conditions such as acute and chronic graft rejection or dysfunction can be influenced by multiple genetic polymorphisms, which individually contribute only a small proportion to the overall risk and whose significance is difficult to assess when analyzing small groups. Various pathogenetic pathways are

involved in the development of these conditions, and in many cases, it is unclear which processes are involved or how important a particular pathway is. Therefore, studies on candidate genes based on prior knowledge of gene function do not always lead to identification of genetic variants associated with clinical outcomes of organ transplantation.

Analysis of stable combinations of several polymorphisms composing a haplotype (a cluster of alleles inherited together) may be more informative than single polymorphisms and help identify the genetic basis of susceptibility to gene-associated diseases [24]. For the TGFB1 gene, co-carriage of several polymorphisms is assumed, which can lead to cumulative association that is determined by unidirectional changes in protein levels [45]. However, the study of more than one polymorphism requires multivariate analysis of a large sample, otherwise the study may lead to false-positive results.

TGF-β1 levels may be determined not only by the polymorphism of a single gene, but also by genetic variants of other factors included in the cellular pathways of the cytokine, such as binding proteins and its receptors. For example, it has been shown that in liver recipients, the risk of developing hepatitis C is associated with the frequency of rs868 single-nucleotide polymorphism in the TGFBR1 gene of TGF-β cytokine receptor gene, which is located in the untranslated region of the gene [46].

Interactions between different genes may also be of clinical importance. For example, in patients with type 1 diabetes, which is a multifactorial autoimmune disease where the interaction and polymorphism of the HLA and insulin genes are important, an interaction between the HLA genes and various cytokines, particularly TGF-β1, has also been found [47].

In addition, predisposition to various polygenic diseases may depend on the ethnic origin of the individual, which necessitates studies in genetically homogeneous groups. It should be noted that, at present, there are virtually no studies on the role of gene polymorphism outside the MHC system in the development of post-transplant complications in solid organ recipients in the Russian population.

Genome-wide association studies (GWAS), which include millions of genetic variants, are considered the most appropriate research design for polygenic diseases. Importantly, such studies use an agnostic approach, meaning that there is no bias, unlike candidate gene studies based on prior knowledge of gene function. Whole-genome studies require large sample sizes, which are necessary to ensure statistical power and significance of the result, but are limited by the number of transplants performed [29]. To solve the problem, an international network of genetic and translational research in transplantation (www.igenetrain.org) was established, which currently conducts about 30 genomics studies. Whole-genome studies in transplantology are aimed at improving transplant outcomes through more accurate dosing and individual selection of immunosuppressive drugs and/or possible stratification of the risk of adverse organ transplant outcomes. It has been shown that the use of genetic typing data of recipient and donor polymorphisms in prognostic models can improve the accuracy of calculating the risk of graft fibrosis following liver transplantation [48].

CONCLUSION

Presented evidence suggests that in organ transplantation, TGF-β1 levels in blood may be genetically determined and may determine the predisposition to fibrosis, graft dysfunction and infectious diseases in solid organ recipients. However, currently available evidence on the role of TGFB1 polymorphism in post-transplant complications is not enough to draw unequivocal conclusions; further, more extensive research is required [18, 42].

Finding out the role of polymorphism of genes encoding the activity of pro- and anti-inflammatory cytokines, including TGF-β, in the pathogenesis of post-transplant complications is an important task that, on one hand, will allow to predict the risk of developing a pathology or its severity and, on the other hand, will allow to individually select a specific therapy for a particular patient.

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