DERLEME REVIEW

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Importance of Non-HLA Antibodies in Solid Organ Transplantations

Solid Organ Transplantasyonunda Non-HLA Antikorlarının Önemi

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ABSTRACT The development of surgical techniques and the use of immunosuppressive agents can increase the lifespan of the graft in organ transplants. Nonetheless, donor specific and non-specific antibodies produced prior to transplantation cause both acute and chronic rejection and, consequently, graft damage. Non-HLA antibodies have started to attract attention as a result of the observation of rejections in patients whose cross match test results were negative and didn't have antibodies produced against donor specific and HLA panel. It has been determined that non-HLA antibodies cause both acute and chronic rejections, and may have different effects on the organ they target. These antibodies were first identified in 1995. Vascular receptors, adhesion molecules and intermediate filaments are among the targets of non-HLA antibodies. Many studies are available in literature investigating angiotensin type 1 receptor (AT1R), endothelin type A receptor (ETAR), collagen-V (Kol-V), K-alpha 1 tubulin (KA1T), perlecan (LG3) C-terminal fragment, associated with MHC class I polypeptide A and B. In addition, more non-HLA antibody targets can be identified and organ transplantation and graft survival studies can be developed. In this review, antigenic targets, treatment strategies and detection methods of non-HLA antibodies will be discussed.

Keywords: Transplantation; rejection; antibodies

ÖZET Cerrahi tekniklerin gelişmesi ve immünsupresif ajanların kullanımı, organ nakillerinde greftin yaşam ömrünü arttırılabilmektedir. Buna rağmen nakil öncesinde oluşmuş donöre özgü ve özgü olmayan antikorlar nakil sonrasında hem akut hem de kronik redde ve dolayısıyla greft hasarına sebep olmaktadır. Hem donöre özgü hem de belirli bir insan lökosit antijen (HLA) paneline karşı üretilen antikorları olmayan ve çapraz uyum testleri de negatif olarak belirlenen hastalarda da organ redlerinin gözlenmesi sonucunda, HLA dışı antikorları ilgi çekmeye başlamıştır. HLA-dışı antikorların hem akut hem de kronik redlere sebep olduğu, hedef aldıkları organa göre farklı etkilerinin olabileceği belirlenmiştir. Bu antikorlar ilk olarak 1995 yılında tespit edilmiştir. Vasküler reseptörler, adezyon molekülleri ve ara filamentler HLA dışı antikorlarının hedefleri arasındadır. Angiotensin tip 1 reseptörü (AT1R), endotelin tip A reseptörü (ETAR), kollajen-V (Kol-V), K-alfa 1 tubulin (KA1T), perlekan (LG3) C terminal fragmanı, MHC sınıf I polipeptidi ile ilişkili A ve B antijenlerine karşı tanımlanan antikorlarla ilgili birçok çalışma bulunmaktadır. Ayrıca daha fazla HLA dışı antikor hedefleri belirlenerek, organ nakli ve greft sağkalım çalışmaları geliştirilebilir. Bu derlemede, HLA dışı antikorların antijenik hedefleri, tedavi stratejileri ve tespit yöntemleri tartışılacaktır.

Anahtar Kelimeler: Transplantasyon; organ reddi; antikorlar

Organ transplantation is the definitive treatment that can be used in patients with end-stage kidney damage. However, antibodies generated by the recipient against human leukocyte antigens (HLA) of donor are the major risk factor, especially for antibody-mediated acute rejection.[1] Even if the targets of the humoral immune response are mainly

polymorphic HLA antigens, the investigations have shown that antibodies produced against non-HLA antigens also have effect on antibody-mediated rejection.[2] This result was achieved by determining the presence of increased antibody-mediated rejection in the kidney transplant from HLA-identical siblings. The detection of antibody-mediated rejection in the absence of donor-specific HLA antibodies has accelerated the research on antibodies developed against non-HLA antigens after cardiac, liver and renal transplantations. These antibodies can be produced against non-polymorphic or non-allelic proteins. Antibody development against non-polymorphic targets is due to inflammation, immunological response to graft, or proteins that spread to the immune system during graft damage. Transplanted tissue/organ (graft) microenvironment or rejection can destroy humoral tolerance to autoantigens.[3]

The non-HLA antibodies developed against donor antigens were first identified in 1995.[4] Terasaki et al. examined the immunologic and non-immunological factors involved in graft damage in HLA-matched and HLA-mismatched renal transplants, and emphasized the importance of clinical study and identification of non-HLA antibodies.[5] Following the first studies Collagen V (Col-V), Angiotensin type 1 receptor (AT1R), K-alpha 1 tubulin (KA1T), endothelin type A receptor (ETAR), bioactive C terminal fragment (LG3) of perlecan, MHC class I chain related protein A (MICA) and B (MICB) are determined as antigenic targets of non-HLA antibodies.[6] Non-HLA antibodies raised against these targets are usually autoantibodies and alloantibodies.[7]

Non-HLA antibodies can play a role in acute and chronic damage both as a complement fixing and non-HLA antibodies.[8] In two preliminary studies, the independent data were used and graft survival was detected to reduce when lymphocytotoxic antibodies existed before kidney transplantation that is performed between HLA-matched siblings. As a consequence, the importance of non-HLA immunity is underlined in chronic rejection.[9] Brasile et al. detected anti-endothelial antibodies (AECA) in a patient prior to transplantation from his mother and who had hyperacute rejection after transplantation. This patient was later transplanted from cadaver and had a hyperacute rejection again. Against both donors, the AECA was determined in the pre-transplant serum of the recipient. This suggests that these antibodies are important in the pathogenesis of antibody mediated rejection (AMR).[10]

The aim of this paper is to review the target antigens, therapeutic strategies and detection methods of non-HLA antibodies.

ANGIOTENSIN TYPE I RECEPTOR (AT1R)

The angiotensin type 1 receptor is a G protein-related receptor which is responsible for the regulation of blood pressure and water-salt balance. Overexpression of AT1R causes hypertension, vasoconstriction and vascular smooth muscle migration.[9] AT1R antibodies can bind to the AT1R molecules of the other organs of the recipient in addition to graft. This binding activates various cell signalling pathways as ERK signalling.[11] Antibodies against AT1R were first described in preeclamptic pregnancies.[9] In another study, these antibodies were identified as graft failure and acute rejection risk factors in renal transplantation.[12] It was reported that these antibodies can cause cell proliferation and vascular damage of kidney, increased levels of AT1R antibodies were detected in steroid refractory vascular rejection.[9,13] Banaisk et al evaluated the effect of non-HLA antibodies on kidney allograft by testing AT1R antibodies of 65 renal transplanted patients. The patient's CDC-XM results were detected negative.[14] It was reported that high-level AT1R antibodies may be related to enhanced graft loss. In this study Lee et al tested 12 renal transplanted patients who had no donor specific antibodies.[13] Dragun et al. have shown that antibodies binding to AT1R can mimic the behaviour of angiotensin II and induce endothelial and smooth muscle cell degeneration.[15]

Rejection is not seen in all renal recipients with AT1R antibody. Therefore it was thought that rejection can be influenced by additional cofactors like environmental conditions.[9] By detecting pre-

transplant AT1R antibodies, the risk for AT1R related AMR can be eliminated.

COLLAGEN AND K-ALPHA 1 TUBULIN (KA1T) ANTIBODIES

Collagen is a fibrous protein found in multicellular animals. They are the basic components of the skin and bones. It is secreted in high amounts in connective tissue cells and in very small amounts in other cell types. Approximately 40 collagen types have been described.[16] Collagen V is found in the epithelium of the trachea. After an injury of the lung, antigenic fragments of the collagen V releases and thus become a target for the T lymphocytes. After autoantibody production the transplant can be rejected.[17] Collagen IV is mainly found in glomerular extracellular matrix.[18] Angaswamy et al. showed the interaction between the transplant glomerulopathy and collagen IV and fibronectin antibodies.[19] Collagen antibodies have also been detected in cardiac transplant recipients. The development of collagen V antibodies in AMR patients and the correlation between them and DSA were noted.[9]

KA1T is a cytoskeletal intermediate filament protein and also expressed in respiratory epithelial cells. It was first discovered as a result of inducing the humoral response in lung transplants. Hachem et al detected KA1T and collagen V antibodies in 108 lung transplanted patients by ELISA method. According to their results, while 89% had antibodies to both K-α 1 tubulin and collagen V, 10% had antibodies only to K-α 1 tubulin, and 1% had antibodies only to collagen V. These antibodies can be a risk for bronchiolitis obliterans syndrome (BOS) and initiates the chronic allograft rejection process. It was also showed that a successful antibody depletion can decrease this risk.[20] Golocheikine et al. worked with 22 lung transplanted patients and analyzed the serum samples for the presence of collagen V and KA1T antibodies. The prevalence of DSA was detected more in non-HLA antibody positive group than negative group. Their findings also supported the results of the other studies in which KA1T antibodies can increase the BOS.[21] Immunization against major histocompatibility complex (MHC) class I antigens in pulmonary transplanted mice models has been shown to induce K-alpha1 tubulin and anti-collagen antibody responses to collagen.[22] The attachment of the pitched tubular epithelium of these antibodies results in an increase in the activation of the cell cycle signal, and fibroproliferation. Additionally the expression of fibrogenic growth factors also increase and all these events can cause BOS.[23]

ANTI-LG3 ANTIBODIES

Perlecan is one of the largest proteoglycans which consists of about 500 kDa core protein and each side chain of 65 kDa. The core protein is composed of many structural regions and provides biofunctional diversity of perlecan.[24] Proteoglycans are particularly involved in morphogenesis and tissue remodelling processes.[25] It is one of the major components on the surfaces of vascular membranes.[26] LG-3 is the C-terminal fragment of the perlecan.[27] Pilon et al. showed the increased circulatory and urinary LG3 levels in mice with renal dysfunction, acute rejection and chronic vascular injury.[28] Riesco et al. studied with 11 hypersensitized kidney transplantation patients and LG3 antibodies were detected in 52% of them. Four out of 11 patients presented AMR and LG3 antibodies. The authors reported that detection of the non-HLA antibodies can decrease the risk of humoral rejection.[29]

Cardinal et al. compared acute vascular injury and acute tubule interstitial rejection. According to their results increasing levels of anti-LG3 titers were associated with acute vascular rejection. Their data showed that anti-LG3 antibodies are the elevators of immune-mediated vascular injury.[30] However Padet et al. observed no association between the LG3 antibody levels and transplantation outcomes.[31] Therefore further studies with larger samples are needed to evaluate LG3 antibody levels and transplantation outcomes.

MIC ANTIBODIES

MHC class I related chain A (MICA) and MHC class I related chain B (MICB) are important non-

HLA antibody target molecules. The *MICA* and *MICB* genes are localized to the HLA-B locus and encodes 62-kDa cell surface proteins.[32,33] They have similar homology to HLA class I molecules. Many cell types, including endothelial cells and monocytes, express MICA (except lymphocytes).[34] MICA antibodies have been identified in acute renal and cardiac allograft rejections.[35] In particular, *MICA* expression is induced in T lymphocytes by cytokines such as IL-2, IL-4 and IL-15. Li et al. noted that a cytokine storm occurred during the rejection challenge in the inflamed graft and *MICA* expression was induced on the surface of the infiltrating lymphocytes. This group determined that MICA antibody levels were much higher in humoral rejections than in cellular rejections.[35] Mizutani et al. reported increased levels of MICA and MICB antibodies in serum samples from patients with renal allograft rejection. They were produced in patients who had rejection episode more than the patients with stable grafts function.[36] Terasaki et al reported a close association between MICA antibodies and chronic renal rejection.[37] There are studies on the importance of these antibodies in heart transplants.[32]

As shown above, studies mainly focused on MICA antibodies. This could be because of unknown mechanism of MICB antibodies and MICB expression and effect on transplantation outcomes. Further studies are needed to highlight the role of MICB antibody in transplantation.

ANTI-VIMENTIN, ANTI-MYOSIN ANTIBODIES

Vimentin is an intermediate filament protein found in mesenchymal originated cells.[38] Like other intermediate filament proteins, vimentin also plays a role in the stabilization of the structure of the cytoplasm. It has been determined that mouse models that have no vimentin expression had a normal phenotype, however in some special cases the absence of vimentin causes phenotypic abnormalities. This suggests that vimentin has an important function in dynamic cellular processes.[39]

It is expressed in the cytosol of mature leukocytes, in fibroblasts, on the surface of apoptotic T cells and neutrophils, and in endothelial cells. Autoantibodies against vimentin are produced in autoimmune diseases such as lupus and rheumatoid arthritis.[40] However in solid organ transplantation vimentin antibodies has been also detected. Vimentin is not expressed by adult cardiomyocytes and healthy kidney tubular cells. However during rejection some tubular epithelial cells can express vimentin.[38]

These antibodies were first identified in 2001 as anti-vimentin antibodies of the IgM type in heart transplant patients.[38] Vimentin is expressed in high levels in intima and coronary arteries. High titres of anti-vimentin antibodies are observed in cardiac transplant recipients with chronic arterial vasculopathy.[38] Whether this relationship is independent of HLA sensitization is unclear.[22]

Lopez-Soler et al showed the association between anti-vimentin antibodies and interstitial fibrosis-tubular atropy (IFTA) in 97 renal transplanted patients by using Luminex method. They detected that increasing levels of vimentin antibodies (>15 ug/ml) can be a risk of elevated levels of IFTA and graft loss.[41] On the other hand, Gunasekaran et al studied with 24 patients who had biopsy-proven transplant gromerulopathy after kidney transplantation. They observed increased levels of anti-vimentin antibodies of IgG isotypes in TG patients, while in stable kidney transplanted patients anti-vimentin IgM isotype was detected. Therefore it can be suggested that the isotype switching of anti-vimentin antibodies can affect the transplantation outcome.[42]

Carter et al. investigated the presence of anti-vimentin antibodies in 51 kidney transplanted patients who had graft loss. Interestingly they've noticed that the patients who was HLA-DQ2 positive, form more vimentin antibodies than negatives ($p=<0.001$). Also they investigated the association between vimentin antibodies and cytokine production and they found that while in stable conditions vimentin can regulate the immune response, vimentin can activate Th-2 immunity if there is a condition that activates immune response.[43]

Myosin is an intracellular protein which has a coiled alpha-helix conformation, located in atrial myocytes, ventricular myocytes and skeletal muscle fibers. The association of anti-myosin antibod-

ies and several heart diseases has been described.[44] O'Donohoe et al described the anti- myosin antibodies in 43 patients with myocardial infarction. They've noticed that anti-myosin antibodies are formed in patients following myocardial infarction and IgG levels persist beyond 6 months.[45] Studies have shown that T cells of the recipient recognizes cardiac myosin proteins and induces cardiac allograft rejections in the absence of alloimmune response to MHC class II molecules.[46] It has been determined that the life span of anti-myosin antibodies seen before the onset of the disease is less than 2 years in heart transplanted patients.[47]

MINOR TISSUE COMPATIBILITY ANTIBODIES (MIHA)

Genes that are not associated with MHC and cause a slower rejection are called minor tissue compatibility genes. The first hypothesis on the relationship between the results of the MiHA in bone marrow transplants was suggested in female patient who had been transferred from his brother. Peripheral bloodstream cytotoxic T cells were isolated, which were found to be counteracted by antigens presented in HLA-unrelated donor cells.[48]

MiHAs are polymorphic peptides of 9-12 amino acids. MiHAs that bind to the antigen binding site of HLA-class I or II molecules are recognized by T lymphocytes. Thus, it has been determined that MiHAs are specific for HLA antigens.[48] Differences between MiHAs are the result of amino acid polymorphisms, gene deletions or many intracellular mechanisms. The MiHA diversity recognized by the TCR can result from single or multiple amino acids.[48]

MiHAs expressed by normal recipient tissues become the target of donor T cells. This immunological response causes graft-versus-host-disease (GVHD) and post-transplant mortality. Recent studies have shown that MiHAs are expressed in hematopoietic tumor cells. When donor T cells target MiHAs expressed in leukemia cells, autoimmunity causes graft versus leukemia (GVL) and after transplantation malign cells can be killed.[49]

Minor HLAs are well-defined in HLA-identic stem cell transplantations. However, the effect is not completely known in solid organ transplantations.[50]

DETECTION METHODS OF NON-HLA ANTIBODIES

After the description of the first lymphocytotoxicity assay by Patel and Terasaki in 1969, high throughput methods were developed to increase sensitivity and specificity. The sensitivity of these methods varies and can affect the interpretation of the results. The clinical consequences of sensitization to non-HLA antibodies cannot be determined well because non-HLA targets cannot be identified sufficiently. To increase the studies on non-HLA antibodies, screening and identification methods should be developed. It was shown that antigens expressed mainly on endothelial and epithelial cells are the primary target of humoral responses in organ transplantation. Insufficient standardized protocols limit the crossmatch tests in which endothelial cells are used. Different assays have been used to detect and identify anti-endothelial cell antibodies as complement dependent crossmatch, flow cytometry and immunofluorescence. These methods had different sensitivity, specificity and can detect distinct immunoglobulin types.[51] As a source of donor antigens endothelial cells are difficult to isolate. Therefore a new technique called XM-ONE was developed that depends on the isolation of the endothelial cell precursors from peripheral blood. In the same assay the antibodies against T and B lymphocytes, and endothelial cells can be tested.[52]

IgG from patient sera can be used for the identification of AECA by immunoblotting.[53] Otherwise by using immunoblotting, there are several studies that identify non-HLA targets as vimentin, AT1R, tubulin, myosin, collagen.[6,47,54-56]

Carter et al. tested vimentin antibodies in 44% of the patients that had graft failure by flow cytometry assay in which recombinant vimentin was bound to polystyrene microspheres.[40] Fhied et al. developed a bead-based immunoassay using Lu-

minex technology. The data presented in this study demonstrates by using this method and performing epitope mapping antibodies can be detected in different disease conditions. More investigations should be done for the clinical validation of the assay.[57] Riesco et al. assessed anti-MICA and anti-perlecan antibodies by Luminex method in serum samples while AT1R antibodies were analysed by ELISA since it was not included in Luminex assay.[58]

Dragun et al. used a sandwich ELISA for detection of AT1R-Abs in serum to detect antibody mediated rejection.[59] O'Donohoe also used ELISA to detect anti-myosin antibodies in patients with myocardial infarction.[45] Lemy and Cox tested MICA specificity by using LUMINEX LSA-MIC assay. They evaluated that immunosuppressive therapy could affect the MICA antibody levels and the harmful effect.[60] Therefore it has been seen obviously that immunosuppressive treatment could have an impact on the test results.

THERAPEUTIC STRATEGIES

Standardized therapy for the treatment of the non-HLA antibody-related rejections may vary and in general specific to the clinical protocols. The aim of the therapy is removing antibodies and decreasing the level in circulation. However, the results of the therapies are not certain. Data is limited to case reports and randomized therapies were trying to investigate for a longer patient survival and to prevent graft failure. Various therapies were reported for the treatment of AT1R-mediated AMR. The combination of AT1R antagonists, plasmapheresis, intravenous immunoglobulin (IVIG) was reported in several studies.[61-63] Jobert et al. used corticosteroids, anti-thymocyte globulins, plasmapheresis and oral candesartan and had successful results on AT1R antibodies.[64] Bortezomib which is a proteasome inhibitor and plays an important role in apoptosis of plasma cells was found to be effective on AT1R antibodies. However it was reported that it has short-term effect. Therefore it is mainly effective on early-onset AMR than late-onset AMR.[65] In another study, plasmapheresis, IVIG and rituximab were used in anti-MICA antibody treatment in a renal transplant patient and three fold decrease of MICA mean fluorescence intense (MFI) levels was detected.[66] Scornik et al. estimated that de novo formed AT1R antibodies in patients who received AT1R blockers or ACE inhibitors with combination of tacrolimus, Mycophenolate mofetil (MMF) and steroids were detected not to develop features of AT1R antibody related pathology.[67] MMF was also found effective on anti-vimentin antibodies in a study which includes 86 patients. When the authors compared the use of MMF instead of azathioprine, less antibody levels were detected by using MMF.[68] More studies on targeted therapies for non-HLA antibodies in different solid organ transplantations can lead to a standardized treatment protocol.

CONCLUSION

Antibodies against HLA antigens are known to cause many problems in organ transplants, such as acute and chronic rejections resulting in the loss of the organ. There are also many studies on treatment strategies applied to prevent these problems. However, non-HLA antibodies have begun to attract interest as a result of observation of organ rejections in patients who have negative cross-match test results. It has been determined that non-HLA antibodies also cause both acute and chronic rejections and may have different effects depending on the organ they target. The response of non-HLA antibodies to treatment strategies applied to transplant patients has not been fully determined. The studies continue to identify the pathogenicity and immunological mechanisms of non-HLA antibodies with modern genomic and proteomic platforms used in the identification of antibody repertoires. It is expected that the results of these studies will contribute to the development of new treatment strategies and to the extension of graft survival after transplantation.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mustafa Soyöz, Tülay Kılıçaslan Ayna, İbrahim Pirim;* ***Design:*** *Mustafa Soyöz, Tülay Kılıçaslan Ayna;* ***Control/Supervision:*** *Mustafa Soyöz, Tülay Kılıçaslan Ayna;* ***Data Collection and/or Processing:*** *Burcu Çerçi, Mustafa Soyöz;* ***Analysis and/or Interpretation:*** *Burcu Çerçi, Mustafa Soyöz;* ***Literature Review:*** *Burcu Çerçi;* ***Writing the Article:*** *Burcu Çerçi, Mustafa Soyöz;* ***Critical Review:*** *Mustafa Soyöz, Tülay Kılıçaslan Ayna;* ***References and Fundings:*** *İbrahim Pirim;* ***Materials:*** *Mustafa Soyöz, Tülay Kılıçaslan Ayna.*

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