Macedonian Journal of Medical Sciences. 2013 Sep 15; 6(3):285-295.
http://dx.doi.org/10.3889/MJMS.1857-5773.2013.0299
***Review Article***

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# *MICA* Polymorphism, Association with Diseases and the Role of Anti-MICA Antibodies in Organ and Stem Cell Transplantation

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**Citation:** Kirijas M, Spiroski M. MICA Polymorphism, Association with Diseases and the Role of Anti-MICA Antibodies in Organ and Stem Cell Transplantation. Maced J Med Sci. 2013 Sep 15; 6(3):285-295. http://dx.doi.org/10.3889/MJMS.1857-5773.2013.0299.

**Key words:** Major histocompatibility complex class 1 chain-related genes (MIC); MICA polymorphism; association with diseases; anti-MICA antibodies; organ and stem cell transplantation.

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**Received:** 12-Mar-2013; **Revised:** 27-May-2013; **Accepted:** 20-Jun-2013; **Online first:** 20-Jul-2013



**Competing Interests:** The authors have declared that no competing interests exist.

**Abstract**

Major histocompatibility complex class 1 chain-related genes (*MIC*) are part of the non-classical MHC genes located on the short arm of chromosome 6. *MICA* comprises of approximately 11 kb DNA and encodes polypeptide of 383 amino acids. The expression of MICA is limited to the surface of the epithelial cells, fibroblasts, keratinocytes and monocytes, but not on the surface of CD4+, CD8+ and CD19+ lymphocytes. It manifests its role by binding with the NK cell receptor NKG2D. There are 84 different alleles for MICA due to discovered polymorphisms in the exons 2 to 5. The aim of this review is to present the data known so far about the association of *MICA* with different diseases and the role of anti-MICA antibodies in organ and stem cell transplantation. The frequency of different MICA alleles and their association with different HLA-B alleles, as well as the association of MICA with different inflammatory diseases, infection diseases and tumors was determined. Post- and pre-transplant anti-MICA antibodies are associated with antibody-mediated rejection in kidney and heart transplantation. Patients with hematopoietic stem cell transplantation, which have MICA mismatch, have higher frequency of graft versus host disease episodes. In spite of lack of conclusive data about the role of anti-MICA antibodies in organ and stem cell transplantation, there is still clinical relevance for investigation of the polymorphisms of the *MICA* gene and anti-MICA antibodies.

## Introduction

Bahram et al.,1994 [1] described new group of non-classical *MHC* genes, which are highly divergent of all known MHC class 1 chains, called MHC class I chain-related genes (*MIC*). They probably separated early in the evolution from mammalian class 1 genes. Actually, in the search of the HLA-B region for other expressed genes, the *MICA* gene was identified. In the same time, another group of researchers found a group of nonclassical-MHC genes that they named PERB11, but it was soon realized that PERB11.1 is actually MICA, and PERB11.2 is MICB [2]. In the 2-kb MHC class 1 region of chromosome 6, 6 MIC loci were identified (The MHC Sequencing Consortium 1999) and in 2004 was updated to 7 *MIC* loci [3, 4]. *MICA* gene comprises of approximately 11kb DNA and is located around 46kb centromeric from *HLA-B*, whereas *MICB* is 89kb further centromeric from *MICA* (*MICC*, *MICD*, *MICE*, *MICF* and *MICG* are pseudogenes).

The organization of the exon-intron structure of the *MICA* gene is distinct from all known class 1 genes. These *MICA* characteristics are: the unique transmembrane and cytoplasmic tail sequences, 3 extra cystein residues in the α1 and α3 domains and several potential N-linked glycolysation sites. The *MICA* gene has 6 exons, which encode leader peptide, three extracellular domains (α1, α2 and α3), transmembrane segment and carboxy-terminal cytoplasmic tail [1]. *MICA* is highly polymorphic in all three alpha domains and has 15-36% sequence homology with the classical class 1 genes, and total 83% homology with *MICB* [5]. Unlike *MHC* class 1, *MICA* doesn't associate with beta-2 microglobulin [6].

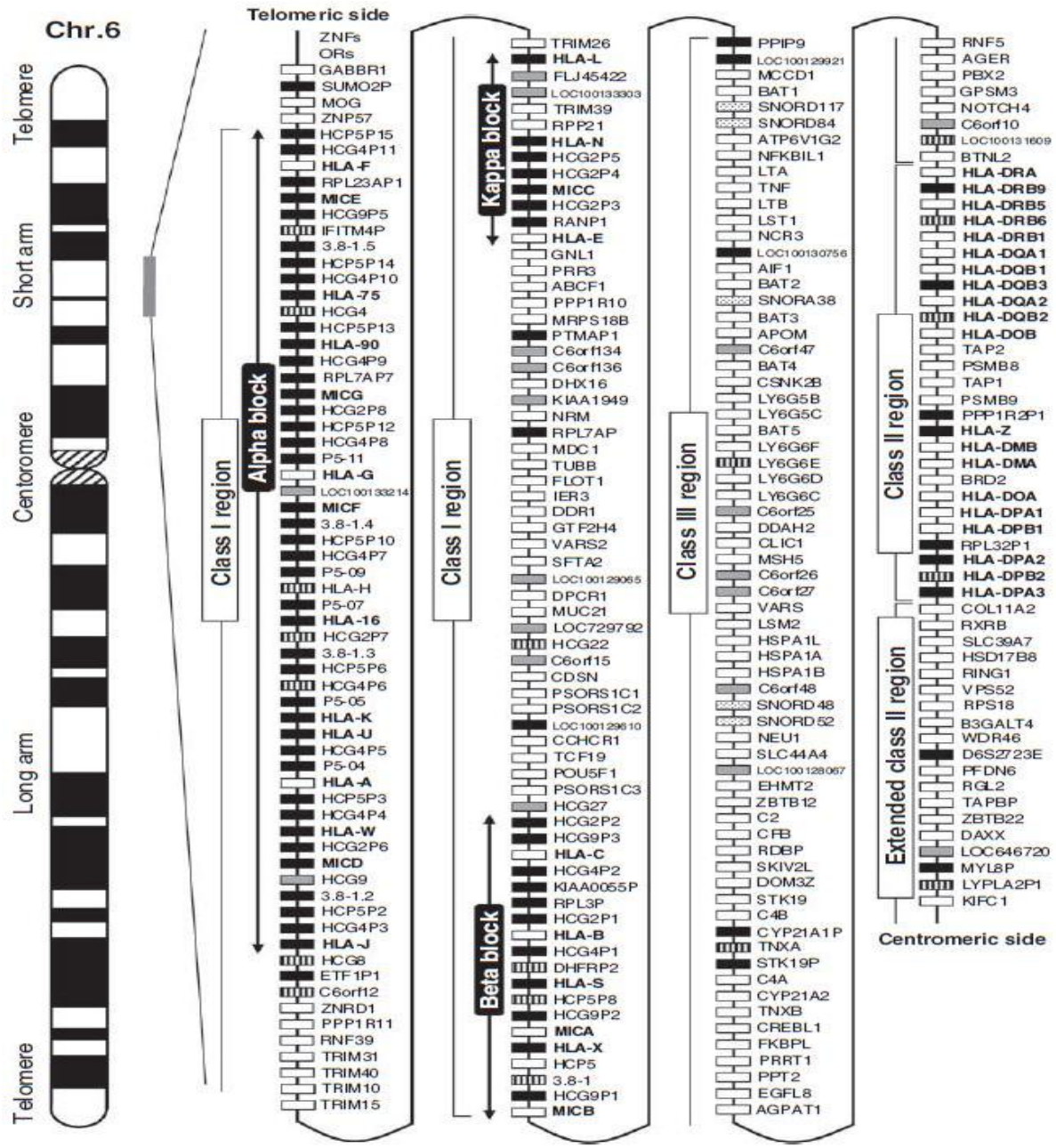


*Figure 1: Gene map of the human leukocyte antigen (HLA) region. The major histocompatibility complex (MHC) gene map corresponds to the genomic coordinates of 29677984 (GABBR1) to 33485 635 (KIFC1) in the human genome build 36.3 of the National Center for Biotechnology Information (NCBI) map viewer. The regions separated by arrows show the HLA subregions such as extended class I, classical class I, class III, classical class II and extended class II regions from telomere (left and top side) to centromere (right and bottom side). White, gray, striped and black boxes show expressed genes, gene candidates, non-coding genes and pseudogenes, respectively. The location of the alpha, beta and kappa blocks containing the cluster of duplicated HLA class I genes in the class I region are indicated [4].*

*MICA* encodes a polypeptide of 383 amino acids, which has *Mr* of approximately 42-44 kDa, but the mature protein has a *Mr* of ~65kDa. This difference is due to glycolisation at 8 potential N-glycosilation sites located along the 3 extracellular domains [6]. *MICA* encodes synthesis of a stress-induced protein which has limited pool of expression in the human tissues. It is thought that MICA plays a role in the humoral immunity through his interaction with NK cells receptor NKG2D, increasing NK cell response. They also interact with the γδ T cells and CD8+ αβ T cells [7]. MICA antigens are mostly found on the surface of the epithelial cells and fibroblasts [1], keratinocytes and monocytes, but not on the surface of CD4+, CD8+ and CD19+ lymphocytes [8]. PHA-activated CD4+ and CD8+ T cell blasts express MICA [9]. MICA are also present on the surface of the gastrointestinal tract [6], so GIT symptoms in GVHD are thought to be consequence of MICA antigen mismatch in donors and recipients of stem cells. However, a systemic transcriptional analysis of *MIC* genes with Northern blotting showed that both *MICA* and *MICB* are widely

transcribed in virtually every examined organ, with the exception of the central nervous system [10]. MICA antigens can be found on the surface of some melanomas and T cell leukemia's [11], which suggests that their expression can be related to the process of neotransformation. No difference was observed in the *MIC* transcription in healthy vs. tumours tissues in some types of solid organ tumors (colon, rectum, breast, uterus, kidney, lung, bladder, esophagus, liver, stomach) [10].

## Polymorphisms of *MICA* and allele frequency

With the help of PCR-SSP, SSOP and SBT techniques, numerous *MICA* and *MICB* alleles have been identified. According to HLA nomenclature (http://hla.alleles.org/nomenclature/stats.html) there are 84 alleles and 71 protein for MICA and 40 alleles and 26 proteins for MICB published so far. The *MICA* gene polymorphisms are located along exons 2 to 5. Polymorphisms in exons 2 to 4 are nucleotide substitutions, which encode amino acid substitutions in the alpha1, alpha2 and alpha3 domains; whereas polymorphisms in exon 5 consist of different number of GCT repeats that encode for 4 to 10 Ala residues in the transmembrane domain (designated A4, A5, A5.1, A6 and A9) [12]. *MICA* extracellular alleles show certain association patterns with the transmembrane STR which are shown on Table 1 [13]. A change of the amino acid methionine (Met) to valin (Val) at position 129 of the alpha2-heavy chain domain classifies the MICA proteins into strong and weak binders of the NKG2D receptor, which in turn influences effector cell function [6].

**Table 1: Association of *MICA* extracellular allele with *TM-STR* [13].**

| *MICA* extracellular allele | *TM-STR* |
|---|---|
| *MICA*001* | *A4* |
| *MICA*002* | *A9* |
| *MICA*004* | *A6* |
| *MICA*007* | *A4* |
| *MICA*008* | *A5.1* |
| *MICA*009* | *A6* |
| *MICA*010* | *A5* |
| *MICA*011* | *A6* |
| *MICA*012* | *A4* |
| *MICA*016* | *A5* |
| *MICA*018* | *A4* |
| *MICA*019* | *A5* |

Most frequent *MICA* allele in North American Caucasoid [14] and in Western Europe [15] is *MICA*008* (5A5.1) which has shorter transmembrane domain and no cytoplasmic tail due to premature stop codon in exon 5. Despite that, it is efficiently expressed at the cell surface [6] where it can engage NKG2D. On Table 2 are shown the three most frequent *MICA* alleles in different regions according to the data on www.allelefrequencies.net. More detailed information about the frequency of different *MICA* alleles is available on the website.

**Table 2: The most frequent *MICA* alleles in different regions (data from www.allelefrequencies.net).**

| Region | MICA Allele | Allele frequency | Sample size | Reference |
|---|---|---|---|---|
| Asia | *A5* | 0.390 | 200 | [77] |
| | *MICA*010* | 0.390 | 41 | [78] |
| | *MICA*008* | 0.350 | 66 | [78] |
| Eastern Europe | *A5.1* | 0.443 | 108 | [79] |
| | *A6* | 0.407 | 27 | [80] |
| | *A9* | 0.232 | 108 | [79] |
| Middle East | *A6* | 0.500 | 18 | [80] |
| | *A5.1* | 0.222 | 18 | [80] |
| | *A5* | 0.167 | 18 | [80] |
| North Africa | *MICA*008:01* | 0.268 | 82 | [81] |
| | *MICA*004* | 0.232 | 82 | [81] |
| | *MICA*009:02* | 0.140 | 82 | [81] |
| North America | *MICA*008* | 0.550 | 242 | [82] |
| | *MICA*002:01* | 0.300 | 60 | [83] |
| | *MICA*004* | 0.295 | 39 | [83] |
| South & Central America | *MICA*002:01* | 0.641 | 174 | [84] |
| | *MICA*027* | 0.352 | 60 | [85] |
| | *MICA*010* | 0.341 | 89 | [84] |
| Sub-Saharan Africa | *MICA*002:01* | 0.424 | 46 | [83] |
| | *MICA*008:01* | 0.328 | 32 | [83] |
| | *MICA*004* | 0.270 | 74 | [83] |
| Western Europe | *MICA*008:01* | 0.530 | 166 | [15] |
| | *A5.1* | 0.370 | 154 | [86] |
| | *A6* | 0.370 | 158 | [27] |

Because of the closeness with *HLA-B,* it was found that *MICA* and *HLA-B* loci are in linkage disequilibrium. There are a lot of studies that show the association of different *MICA* and *HLA-B* alleles. The most frequent (>10%) are summarized on Table 3. More details are available on www.allelefrequencies.net. One *MICA* allele can be associated with different *HLA-B* alleles and vice versa [14].

**Table 3: Frequency of MICA-HLA association from different studies (data from www.allelefrequencies.net)**

| Haplotype | Frequency (%) | Sample size | Reference |
|---|---|---|---|
| MICA*008-B*08:01 | 20.6 | 242 | [82] |
| MICA*027-B*40:02 | 20.4 | 42 | [85] |
| MICA*002:01-B*40:35 | 20.0 | 42 | [85] |
| MICA*004-B*42:01 | 18.0 | 39 | [83] |
| MICA*002:01-B*53:01 | 16.7 | 39 | [83] |
| MICA*002:01-B*53:01 | 15.2 | 46 | [83] |
| MICA*010-B*46:01 | 14.7 | 255 | [87] |
| MICA*008:01-B*15:03 | 14.1 | 32 | [83] |
| MICA*019-B*15 | 13.1 | 255 | [87] |
| MICA*002:01-B*53:01 | 12.8 | 74 | [83] |
| MICA*002-B*53 | 12.4 | 201 | [88] |
| MICA*004-B*44 | 12.1 | 165 | [89] |
| MICA*008-B*07:02 | 12.0 | 242 | [82] |
| MICA*002:01-B*53:01 | 11.7 | 60 | [83] |
| MICA*004-B*44 | 11.5 | 199 | [90] |
| MICA*008:01-B*40:01 | 11.5 | 100 | [91] |
| MICA*004-B*49:01 | 10.9 | 32 | [83] |
| MICA*004-B*44:03:01 | 10.6 | 82 | [81] |
| MICA*008-B*07 | 10.6 | 165 | [89] |
| MICA*008-B*44:02 | 10.6 | 242 | [82] |
| MICA*010-B*15:01 | 10.4 | 139 | [92] |
| MICA*010-B*40 | 10.3 | 199 | [90] |
| MICA*002-B*38 | 10.0 | 95 | [89] |
| MICA*008-B*08 | 10.0 | 103 | [93] |
| MICA*027-B*40 | 10.0 | 199 | [90] |

## *MICA* and inflammatory diseases

The proximity of the HLA locus, its polymorphism and the interaction with the NKG2D receptor, make the *MICA* gene target for many association studies. The polymorphism of *MICA* exon 5 microsatellite (TM) was determined in a group of 226 patients with different clinical forms of psoriatic arthritis in a Italian study [16]. They found significant positive association between MICA-A9 and the peripheral symmetric polyarthritis form combined with spondilitis and negative association of the MICA-A5, A4 genotype with psoriatic arthritis. Another group studied the frequency of extracellular polymorphisms of the *MICA* alleles in 128 Tai psoriasis patients [17]. *MICA*010* and *MICA*017* were associated with Type 1 psoriasis and *MICA*010* with Type 2. The haplotype analysis showed that MICA*008-HLA-B*13-Cw*0602 and MICA*010-HLA-B*4601-Cw*01 were significantly increased in both Type 1 and Type 2, while MICA*002-HLA-B*38-Cw*07(01-03) and MICA*017-HLA-B*57-Cw*0602 were elevated only in Type 1. Most of the associations of MICA with psoriasis and psoriatic arthritis are dependent on linkage disequilibrium with *HLA-B* and *HLA-C* risk alleles. Independently of HLA, *MICA**016 influences the risk of developing psoriasis without arthritis, while homozygocity for *MICA**00801 increases the risk of developing psoriatic arthritis in patients with psoriasis [18].

Stress-inducible MICA is aberrantly expressed in rheumatoid arthritis synoviocytes and stimulate autologous CD4+CD28- T cell cytokine and proliferative responses [19]. This was the reason why *MICA* polymorphisms were analyzed in patients with rheumatoid arthritis. The non-synonymously coding SNP *MICA-250* (rs1051794, Lys196Glu) was associated (P=0.014) with rheumatoid arthritis in a study of 300 French Caucasian individuals (negative for *HLA-DRB1* risk alleles) belonging to 100 RA trio families [20].

The association of *HLA-B27* with ankylosing spondilitis is well documented. Su H. et al. [21] found that *MICA**007 was more frequent in patients with ankylosing spondilitis than controls with dominance of the haplotype MICA*007-B27. It's suggested that the higher frequency of MICA is due to its strong linkage disequilibrium with HLA-B27, and MICA alone is not associated with ankylosing spondilitis [22].

Goto et al. analyzed the association of *MICA* A4 allele and acute anterior uveitis. *MICA* A4 (microsatellite allele with four repetitions of GCT/AGC) was present with statistically higher frequency in the group of patients with HLA-B27 positive acute anterior uveitis and was in linkage disequilibrium with HLA-B27 [23].

*HLA*-B*51 is known to be associated with Behcet's disease and Hughes EH et al. [24] analyzed the association of *MICA* with the disease. *MICA**009 was more frequent in the group of patients with Behcet's disease and was in linkage disequilibrium with *HLA*-B*51. Same results were obtained from Munoz-Saa I. et al. [25]. MICA might influence the pathogenesis of Behcet's disease through its interaction with NK and gammadelta T cells.

Systemic lupus erythematosus (SLE) is a disease with unknown etiology, but with predisposing genetic background. DRB1*03-DQA1*0501-DQB1*0201-B8 haplotype has the strongest genetic association identified so far with SLE (26). Gambelunghe et al. [27] found that MICA5/5.1 genotype was positively associated (OR=28.9, corrected P<0.0015) and MICA9 was negatively associated with SLE (OR=0.2, corrected P<0.0005). DR3-DQ2-MICA5.1 and DR3-DQ2-MICA5 haplotypes was more frequent in patients with SLE (P<0.011). However, in a Japanese study [28], *MICA* $^{129}$Met;A9 haplotype was positively associated with SLE patients who were negative for *HLA-DRB1*15:01*, whereas simultaneous presence of *MICA* $^{129}$Met;A9 and *HLA-DRB1*15:01* showed highest likelihood of association (OR 2.4) in the patients.

Celiac disease is an autoimmune disease that affects the small intestine in genetically predisposed people. There is strong MICA expression on the surface of the cells in the gut in patients with active celiac disease [29]. This effect is mediated by IL-15 and triggers direct activation and costimulation of intraepithelial T lymphocytes, which can damage the enterocytes through NKG2D/MICA interaction after gliadin-induced expression of MICA on gut epithelium [29]. Positive association for MICA allele A4 and negative for A9 was determined in Basque families with celiac disease. The haplotype A5.1-DRB1*0301 was associated with risk of disease, but the stratification analysis didn't show independent contribution of MICA alleles to risk of celiac disease [30]. In another Spanish study, positive association of MICA A5.1 with celiac disease, independently of CD-predisposing DQ2 haplotype, was found (31). MICA9 has protective role in autoimmunity [32].

Few studies analyzed the association of different MICA polymorphisms and type 1 diabetes mellitus, autoimmune disease that results from destruction of the insulin-producing beta cells. There is statistically significant positive association of *MICA A5* and *A5.1* and type 1 diabetes mellitus [33-37] and negative for *MICA9* [36] and *A6* [35]. OR of 54 was obtained for the haplotype DRB1*04-DQA1*0301-DQB1*0302-MICA5 [33].

Another autoimmune disease associated with MICA is alopecia areata (AA), organ specific autoimmune disease caused by T-cell infiltrates surrounding hair follicles. The patchy AA was significantly associated with *MICA**5.1, whereas *MICA**6 was associated with all types of AA. They are part of extended haplotypes associated with AA HLA-DQ1-DR6-MICA*5.1 and HLA-DQB1*0201-DR3-MICA*5.1 [38].

## *MICA* and tumors

There are many studies that confirm the MICA expression in different types of tumors, like of the lung, breast, kidney, liver, ovary, prostate, colon, melanomas and some types of leukemias [12]. The exact role of MICA in tumor transformation is not yet defined, but it regulates the immune response through binding with the NKG2D receptor on the NK cells and mediates the lysis of epithelial and non-epithelial tumors. Hepatocellular carcinoma is a lung cancer who develops, in most of the cases, after chronic hepatitis B and C infection. Single nucleotide polymorphism (SNP) rs2596542 located in the *MICA* promoter region is significantly associated with the risk of HCV- and HBV-induced hepatocellular carcinoma [39]. The patients with hepatocellular carcinoma have higher serum level of soluble MICA [39, 40] and high value for sMICA is associated with poorer prognosis of HCC. *MICA-A5.1* allele is associated with HCC (P=0.036) in a South China Han population [41].

Luo et al. [42] analyzed the role of different *MICA* polymorphisms in leukemia. They found positive association for *MICA A5* (P<0.0005) and negative association for *MICA A5.1* and *MICA*008* (P=0.0235 and P=0.0329, respectively) with leukemia. Increased risk for leukemia was found for *MICA* A5 and *MICA**010 homozygotes, whereas heterozygotes for *MICA**008 and *MICA* A5.1 were linked with decreased risk for leukemia.

MICA expression is undetectable in normal skin, primary nevi (intradermic, junction, mixed, lentigo and congenital samples), benign lesions (seborrheic keratosis), premalignant lesions (actinic keratosis) and benign basocellular cancer, whereas in melanoma there is high expression of MICA. Thus, analysis of MICA expression in different skin samples can help differentiate between benign and malignant nevi [43].

## *MICA* and infection

The up-regulation of MICA expression on the surface of dendritic and epithelial cells after microbial infection, like with Mycobacterium tuberculosis [44], led to investigation of the polymorphisms of *MICA* alleles in patients with tuberculosis. Significant negative association for *HLA*-A*02 and *HLA*-B*18 and for the haplotype HLA-B*18-MICA*018 was found in a Brazilian study, which suggests protective role for *HLA-A**02 and *HLA-B**18 (in a linkage disequilibrium with *MICA**018) [45]. Negative association, and protective role, was also found in patients with leprosy for the *MICA**027, and *MICA**010 and *MICA**027 were negatively associated with multibacillary leprosy [46]. In a study of 230 sib pairs with paucibacillary leprosy in South India, *MICA**5A5.1 was associated with susceptibility to leprosy [47]. *MICA**5A5.1 allele has a single G insertion occurring in a background of five alanine repeats, causes frameshift mutation which results in a premature stop codon and a truncated transmembrane domain. It's importance is still unknown.

Up-regulation of MICA expression was found also in viral infections, i.e. CMV infection induces up-regulation of the MICA expression in vitro on cultured fibroblasts and endothelial cells and in vivo in interstitial pneumonia [48]. However, another study showed down-regulation of full-length MICA expression after CMV infection in a U373 astrocytoma cell line and not for the truncated form [49]. Fibroblasts with decreased MICA were protected from NK cell killing, whereas the virus-infected cells with truncated form of MICA were destroyed. Moenkemeyer et al. [50] found positive association of *MICA5.1* with CMV reactivation in HIV-1-infected patients (p=0.032).

Dendritic cells from Hepatitis C virus-infected patients couldn't up-regulate MICA expression after IFN-alpha stimulation and failed to activate NK cells [51, 52]. This effect contributed to prolonged HCV infection due to poor dendritic cell-NK cell cross-talk and lower NK cell activation [12]. *MICA**015 was associated with recovery from HCV infection and chronic hepatitis B infection [53], but because it was detected in a small fraction of persons, additional studies are necessary.

## Anti-MICA antibodies

After the discovery of MICA antigens on the surface of endothelial cells and their polymorphism, the question about the ability of the human organism to create anti-MICA antibodies was raised. Zwirner and his colleagues created three recombinant MICA proteins, which consisted of the alpha 1, alpha 2 and alpha 3 domains and with the help of enzyme-linked immunosorbent assay tried to analyze if MICA can be target for specific antibodies in the sera of transplanted patients [54]. In the sera samples collected in different periods after organ transplantation, the presence of specific anti-MICA antibodies was detected. Although with this finding was raised the question of how this persons were immunized, the fact that these polymorphic, HLA-similar MICA molecules, expressed on the surface of endothelial cells, were recognized by specific antibodies in the sera from transplanted patients suggests that MICA can be target molecule in allograft rejection.

## Methods of antibody identification

With the aim to discover if people can create anti-MICA antibodies and their meaning, Zou Y. and his colleagues developed a method for detection with the use of Luminex beads. They created recombinant MICA antigens in insect cells comprised of signal peptide, extracellular domains of MICA*001,

MICA*002, MICA*004, MICA*008 and MICA*009, six-his tag sequence and a biotinylation peptide. These proteins were expressed on HighFive insect cells, they were purified with nickel affinity agarose and were attached to Luminex beads [55]. In the next period, a few modifications were done to make the detection of these antibodies more specific. This modifications included use of Sf9 insect cells instead of HighFive, the conjugation of the MICA proteins with carboxilated Luminex beads was done with carbodiimide hydrochloride and two steps of purification were used, first based on his-tag with nickel agarose, and the second included immuno-absorption with anti-MICA monoclonal antibody 6B3, attached to sepharose beads [56]. In order to determine which polymorphisms can be identified with anti-MICA antibodies, Zou Y. and colleagues created soluble MICA recombinant proteins, which represent 11 common alleles, two hybrid alleles and two single amino acid mutated alleles. The procedure included first determination of the pattern of a serum on MICA-conjugated Luminex beads, than absorption of the serum with transfected cells, which express only one defined MICA allele, and at the end eluation of the antibodies with acid. With this experiment, they identified 14 patterns of reactivity: antibodies that recognize single alleles, small groups consisting of 2, 3 or 4 alleles and larger groups called MICA-G1 and MICA-G2 [56]. The identification of target epitopes for antibody binding helps in the understanding of the development of MICA antibodies, which are mainly, result of donor-specific allo-immunization. Similar results were obtained from Dequesnoy and colleagues. They tested 6 sera from patients, who had been sensitized after transplantation, with Luminex panels of single MICA alleles and the HLAMatchmaker program to analyze serum antibodies pattern. The HLAMatchmaker analysis revealed generally consistent antibody reactivity patterns, which correlate with the presence of specific eplets [57].

## Mechanisms of MICA antibodies-induced allograft injury

Complement-mediated and antibody-dependent cell-mediated cytotoxicity are the mechanisms by which donor-specific anti-HLA alloantibodies initiate renal allograft rejection [58]. Apparently, MICA can't fix complement because C4d positivity is rare in anti-MICA antibodies positive patients [59]. However, Zou Y. and colleagues in order to determine whether MICA is a target for complement-dependent cytotoxicity, produced monoclonal antibodies by immunization of mice with recombinant MICA*008 and also investigated human alloantibodies and observed the patterns of reactivity with ELISA, Western blot and flow cytometry. Their results suggested that MICA alloantigens may be more immunogenic than previously suspected and that they may contribute to the pathogenesis of antibody-mediated response (AMR) through complement-mediated injury [60]. Furthermore, Alvarez-Marques A. and colleagues investigated two groups of patients with AMR, one with C4d deposition in renal biopsies and the second patients with graft dysfunction negative for C4d. Anti-MICA donor-specific antibodies were more frequent in the C4d+ group (21%) than in the C4d- group (7.7%, p=0.15). Although the investigated groups were not large, the detection of DSA anti-MICA antibodies suggested their role in the antibody-mediated allograft immune response after kidney transplantation [61].

## The role of anti-MICA antibodies in kidney transplantation

Anti-HLA antibodies formed before the kidney transplantation can produce immediate reaction, whereas the antibodies formed post-transplantation are not associated with immediate reaction, but rather initiate process of damage and repair in the endothelium, resulting in the characteristic construction of the blood vessels, commonly found in chronic rejection. In order to determine the role of post-transplant anti-HLA and anti-MICA antibodies in chronic allograft rejection after kidney transplantation, Mizutani et al. [62] tested 679 postoperative serial serum samples from 39 patients who rejected their grafts and 26 with functioning grafts. Patients who rejected transplants more frequently had anti-HLA and anti-MICA antibodies compared to patients without rejection (95% vs. 58%, p<0.01). The peak PRA, determined with Luminex, was 19.6% in rejected transplants and 6.7% in functioning transplants (p<0.05). Not all of these antibodies were donor-specific and some of them appeared and then were lost before graft rejection occurred. Mizutani et al. think that donor-specific antibodies are often absorbed in the organ and fixed onto the antigenic sites of the donor kidney vasculature. But when they saturate the endothelium, they spill out into the circulation. Martin et al., who showed that donor-specific antibodies, which couldn't be found before the nephrectomy, were noted after removal of the graft [63], confirmed this. Similar results were obtained from Ozawa et al. [64], 93% of 266 kidney recipients with graft failure had anti-HLA antibodies and 21% had anti-MICA antibodies, in comparison with 46% and 7% patients with functioning grafts who had anti-HLA and anti-MICA antibodies, respectively.

Zou Y. et al. determined the presence of anti-MICA antibodies in kidney recipients before the transplantation [65]. They found that 217 out of 1910 patients (11.4%) had anti-MICA antibodies with 1-year graft survival rate of 88.3 ± 2.2% as compared to 93.0 ± 0.6% among patients in the MICA antibody-negative group (p=0.01). According to Zou Y. et al. MICA antigens are significantly associated with and might play a role in rejection, in the absence of previous sensitization against HLA, like in recipients of first

transplants, patients who received grafts from well-HLA-matched donors and recipients not previously sensitized against HLA. The role of anti-HLA and anti-MICA antibodies in graft failure was confirmed in several studies [66-68].

**Table 4: Studies of major histocompatibility complex class I chain-related gene A antibodies in kidney transplant recipients.**

| Authors | Year | Time of serum | Method | Anti-MICA | Number Or % | p |
|---|---|---|---|---|---|---|
| Mizutani et al.[62] | 2005 | PostTx | CDC | + | 28 | <0.05 |
| | | | | - | 37 | |
| Ozawa M. et al.[64] | 2006 | PostTx | Luminex | + | 12% | |
| | | | | - | 88% | |
| Zou Y. et al.[65] | 2007 | PreTx | Luminex | + | 217 | =0.01 |
| | | | | - | 1693 | |
| Terasaki et al.[66] | 2007 | PostTx | Luminex | + | 52 | <0.01 |
| | | | | - | 1872 | |
| Zhang Ming et al. [67] | 2011 | PostTx | Luminex | + | 15 | |
| | | | | - | 37 | |
| Zuowei Li et al.[68] | 2012 | PostTx | Luminex | + | 11 | >0.05 |
| | | | | - | 57 | |
| Anne Lemi et al.[69] | 2012 | PostTx | Luminex | + | 42 | |
| | | | | - | 737 | |

However, Lemy A. at al. in a study of 779 kidney transplant recipients in 2012 [69], obtained different results from the ones mentioned before. They found no statistical significance in the four-year death-censored graft survival between MICA+ and MICA- patients (97% vs. 94%, P = 0.28) and also the rates of acute rejection (AR) and chronic antibody-mediated rejection (CAMR) were compatible between the two groups (AR: 6.3% vs. 3.8%, P=1.0; CAMR: 18.8% vs. 15.4%; P=1.0). By multivariate analysis, graft loss was associated with HLA DR mismatches, AR within the 1$^{st}$ year, serum creatinin at 1 year ≥ 1.5 mg/dL and presence of HLA antibodies, but not MICA antibodies. Although they do not rule out the pathological effect of anti-MICA antibodies, there are certain methodological limitations (low prevalence, confounding by HLA antibodies) that are likely to prevail in any study looking at the role of MICA in graft failure.

Recently, consensus guidelines on the testing and clinical management issues associated with HLA and non-HLA antibodies in transplantation, was published [70] and comprehensive list of recommendations were provided covering the technical, pretransplantation and posttransplantation monitoring of HLA antibodies in solid organ transplantation. It was emphasized that the presence of preexisting antibodies to MICA has been shown to correlate with kidney graft outcome in some studies and not in others (Table 4). Although the data support the association of anti-MICA antibodies with allograft failure, the hypothesis that MICA antibodies are causal has not been proven.

Based on current evidence, the pretransplantation and posttransplantation group in the consensus recommendations, does not recommend routine pretransplantation testing for non-HLA antibodies [70]. In the section Future directions and research, it was mentioned that future studies are required to define the role of preexisting non-HLA antibodies on the outcome of solid organ and cellular transplantations.

## Anti-MICA antibodies in heart transplantation

The role of anti-MICA antibodies, in absence of anti-HLA antibodies, in acute heart allograft rejection was investigated by Suarez-Alvarez et coworkers [71]. They examined 190 pre- and post-transplant serum samples from 44 patients collected during the first year after transplantation. Anti-MICA antibodies were significantly higher among the ones with severe acute rejection (AR) than those without rejection were (60.7% vs. 14.3%, p = 0.0038 by complement-dependent cytotoxicity (CDC); 55.5% vs. 5.7%, p = 0.0020 by Luminex). They observed wider specificity of anti-MICA antibodies by Luminex than CDC assay and all patients developed anti-MICA antibodies against three or more alleles, which can suggest possible cross reactivity among alleles. All patients who had positive MICA Ab post-transplantation and developed AR had donor-specific antibodies (DSA), which can suggest that the appearance of anti-MICA antibodies before the episodes of rejection can contribute to the development of the rejection. The level of expression of MICA in endomyocardial biopsies was examined with quantitative RT-PCR from 10 cardiac transplant recipients within the first year after transplantation and found that MICA mRNA expression levels were higher in biopsies with rejection (grade 3A/3B or 2R/3R) than in biopsies without rejection (grade <3A or 2R). There was absent MICA staining in heart biopsies not showing rejection. Thus, the monitoring of anti-MICA antibodies in heart transplantation may be useful marker for early detection of AR. Kauke T. and colleagues [72] in a group of 159 patients screened for anti-MICA Ab after the transplantation confirmed these findings. Thirty six (22.6%) of them were positive for anti-MICA Ab and they found statistical significance between the presence of post-transplant specified anti-MICA Ab in patients sera and acute rejection and cardiac allograft vasculopathy.

However, a study done by J.D. Smith and colleagues [73] found no correlation between the presence of anti-MICA antibodies and graft survival following heart transplantation. Their study included pretransplant serum from 491 and posttransplant serum from 196 adult cardiac allograft recipients who were negative for anti-HLA antibodies. They found no effect of pretransplant or posttransplant production of MICA antibodies on the number of AR episodes in the first year, or cardiac allograft vasculopathy assessed the third and fifth year. Furthermore, the immunochemistry of cardiac biopsies from 11 patients did not demonstrate presence of MICA antigen. This data suggest that anti-MICA Ab alone have small

effect on graft survival unlike anti-HLA antibodies whose effect on graft survival after heart transplantation and increased incidence of acute rejection is well documented [74].

## Association of mismatching for MICA with graft versus host disease after stem cell transplantation

One of the major causes of mortality after allogeneic hematopoietic stem cell transplantation (HSCT) is graft-versus-host disease (GVHD). It was hypothesized by Parmar S. et al. [75] that MICA antigens can be recognized as transplantation antigens and may cause GVHD after HSCT in a cohort of 236 patients with myeloid leukemia. 73% of them had 10/10 matches in HLA-A, B, C, DR and DQ and only 8.4% were MICA mismatched. They observed higher rate of grade II-IV acute GVHD in the MICA mismatched patients (80% vs. 40%, P=0.003) and higher occurrence of gastrointestinal acute GVHD due to the expression of MICA antigens on the gastrointestinal epithelium and the fact that they can be induced on dendritic cells that play an essential role in antigen presentation processes that initiate GVHD [52]. The effect of anti-MICA Abs was investigated in the same year by another group of researchers who came to similar results [76]. They found that patients bearing MICA-129 val/val genotype were at higher risk of developing chronic GVHD (63% vs. 45% at 3 years; P=0.03) in a group of 211 patient and donor pairs typed for MICA-129 alleles. They also determined the level of soluble MICA in the sera of 116 patients and found highly significant association between posttransplantation sMICA higher than 80 pg/mL and the incidence of cGVHD. However, the presence of anti-MICA antibodies before transplantation correlated with low levels of sMICA after transplantation and thus low incidence of cGVHD, which strongly suggests neutralizing effect of MICA antibodies on sMICA.

## Conclusion

The major histocompatibility complex class 1 chain-related gene A (*MICA*) polymorphisms are associated with different inflammatory diseases, infections diseases and tumors. Many studies confirm their role in the pathogenesis of these diseases. Anti-MICA antibodies are important risk factors for antibody-mediated rejection after kidney and heart transplantation, thus their analysis is important in patients follow up after transplantation. GVHD after HSCT is more frequent in patients who were mismatched for MICA.

In spite of lack of conclusive data about the role of anti-MICA antibodies in organ and stem cell transplantation, there is still clinical relevance for investigation of the polymorphisms of the *MICA* gene and anti-MICA antibodies, especially meta-analysis of all published studies.

## Acknowledgements

Ss Cyril and Methodius University of Skopje PhD School covered publication fee for this review article.

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