Associations of MICA Polymorphisms with Inflammatory Rheumatic Diseases

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Abstract: Inflammatory rheumatic diseases are characterized by inflammation resulting from the immune dysregulation that usually attacks joints, skin and internal organs. Many of them are considered as complex disease that may be predisposed by multiple genes and/or genetic loci, and triggered by environmental factors such as microbiome and cellular stress. The major histocompatibility complex class I chain-related gene A (MICA) is a highly polymorphic gene that encodes protein variants expressed under cellular stress conditions, and these MICA variants play important roles in immune activation and surveillance. Recently, accumulating evidences from both genetic and functional studies have suggested that MICA polymorphisms may be associated with various rheumatic diseases, and the expression of MICA variants may attribute to the altered immune responses in the diseases. The objective of this review is to discuss potential genetic associations and pathological relevance of MICA in inflammatory rheumatic diseases that may help us to understand pathogenesis contributing to the development of these diseases.

Keywords: MICA, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, systemic lupus erythematosus, Behçet's disease, inflammatory bowel disease, ulcerative colitis and Crohn's disease.

INTRODUCTION

The major histocompatibility complex class I chain-related gene A (MICA) is a non-classic HLA gene [1]. Similar to classic HLA genes, its DNA sequence is highly polymorphic [2]. Two heavily investigated polymorphisms of the MICA are one single nucleotide polymorphism (SNP) at codon 129 leading to methionine (met) and valine (val) substitution, and a tri-nucleotide microsatellite (GCT)n starting at codon 293 named MICA-A(x), and an exceptional 5 repeats with an insertion of guanosine at codon 295 named MICA-A5.1. The former leads to a change of binding affinity to MICA receptor NKG2D [3], the latter causes structure alteration on MICA transmembrane (TM) domain [4]. In addition to individual polymorphisms, according to haplotypes of the exonic polymorphisms, about 100 MICA alleles have been identified [http://www.ebi.ac.uk/ipd/imgt/hla/]. Although, the functional significance of these polymorphisms has not been fully defined, some have been associated with immune-mediated diseases.

The MICA gene encodes a protein that expresses on the surface of selective cells such as gut epithelial, fibroblasts and endothelial cells [5, 6], and it plays unique roles in immune activation and surveillance [7, 8]. Under cellular stress conditions, such as infections, tissue injury, pro-inflammatory signals, and malignant transformation [9-15], MICA interacts with its receptor NKG2D found on natural killer (NK) cells, NK T cells, γδ T cells, αβ CD8+ T cells, and a minor immune-regulatory subset of CD4+ T cells [14-22]. Binding of MICA (membrane-bound MICA) with NKG2D triggers cell-mediated cytotoxicity and cytokine release from NK and T cells [13, 14, 23, 24]. On the other hand, the proteolytic cleavage of MICA proteins from expressing cells, termed MICA shedding produces soluble MICA that may control the immune process by down-modulating NKG2D expression [25, 26], and facilitate expansion of an immunosuppressive CD4+ T-cell subset [19]. In addition, MICA can be excreted in exosomes which can also down-regulate NKG2D activity [27]. Therefore, the balance between membrane-bound MICA and soluble MICA/exosomal MICA may control the outcome of immune function *via* NKG2D regulation.

Given its complex gene sequence and protein expression features, as well as unique functions in immune process, studies of MICA in order to understand pathogenesis of various immune-mediated diseases are important. Accumulating evidences have supported that MICA and its signaling pathway are useful biomarker for the measurement of disease susceptibility, evaluation of disease progression and/or development of therapeutic approaches. This review will focus on recent reports of MICA in association with inflammatory rheumatic diseases.

MICA IN RHEUMATOID ARTHRITIS (RA)

The first report of MICA in association with RA was based on a study of fifty-four Spanish families of affected son and daughter and 211 consecutive RA patients, in which MICA-A6 was suggested to be protective against RA in the shared epitope (SE) positive RA patients [28]. This result was immediately replicated by a small Caucasian

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case/control cohort (90/85) [29]. However, studies of a larger RA tri-families of French Caucasian along with an independent 100 RA trio families and a German Caucasian case-control (90/182) cohort did not confirm such an association. Instead, the evidence from the studies showed a MICA SNP rs1051794 corresponding to MICA codon 129 (MICA-129) in association with RA, and it was suggested that this SNP was in complete linkage disequilibrium (LD) with another functional SNP, rs1051792 that contributes differential binding affinity of MICA protein to its receptor NKG2D [30].

Although functional studies of these RA-associated MICA alleles have not been reported, MICA and NKG2D signaling appeared to be aberrant in RA patients [31]. In particular, substantial amount of synoviocyte-derived soluble MICA was observed in peripheral blood serum samples of RA patients [31]. However, it failed to induce down-modulation of NKG2D on T cells by overcoming opposing activity of tumor necrosis factor alpha (TNF-α) and IL-15 [31]. Increased NKG2D activity in RA patients was observed, and that may cause autoreactive T cell stimulation which may be responsible to the self-perpetuating pathology in RA [31].

MICA IN ANKYLOSING SPONDYLITIS (AS)

Studies of MICA in AS was first reported in a small case-control Caucasian cohort (48/50) [32], in which the four-repetition GCT of the MICA gene (MICA-A4) was found at significantly higher frequency in AS [32]. However, another study of AS case-control cohort (162/103) indicated that the frequency of the MICA-A4 allele was not significantly higher in the B27-positive and B27-negative patient groups, as compared to the B27-positive and B27-negative control groups, respectively [33]. Therefore, the MICA-A4 was considered in strong linkage disequilibrium (LD) with HLA-B27. This result was contradictive to a report from the studies of Sardinia AS (case/control: 82/139), in which a high frequency of MICA-A4 (80%) was found in HLA-B27-negative AS patients, and that was associated with AS [34]. Following MICA-A4 studies, Amroun *et al*. reported an association between MICA-129 met/met genotype and juvenile AS independent of HLA-B27 positivity in a case-control Algerian cohort (129/760) [35]. Recently, a sequencing study of the exonic haplotypes of the MICA alleles was performed in two large case-control cohorts of US Caucasian (1070/1003) and Chinese Han (473/536) [36]. From the studies, the haplotype allele MICA*007:01 was identified as a significant risk allele for AS in both Caucasian and Han populations, and MICA*019 was a major risk allele in Han AS patients. Conditional analysis of MICA alleles on HLA-B27 that unshielded LD effect supported independent associations of the MICA*007 and *019 with AS [36]. Of note, MICA*007 contains both MICA-A4 and MICA-129-met, MICA*019 with MICA-A5 and MICA-129-val compared to the common allele MICA*008 with A5.1 and MICA-129-val.

MICA IN PSORIATIC ARTHRITIS (PSA) AND PSORIASIS

Studies of MICA in PsA and psoriasis appeared more complex. A Spanish study of 65 patients with PsA, 5 psoriasis, and 177 healthy controls was the first to show MICA-A9 as a risk to PsA [37]. This observation was replicated in a case-control study (110/110) of another Spanish cohort [38]. Further studies in Jewish (Caucasian) cases and controls (52/73) suggested that a higher frequency of MICA-A9 in PsA patients is in LD with HLA-B alleles (B*5701, B*3801), but the latter were not increased in PsA [39]. Two studies of Chinese populations including each of the case-control studies of PsA (102/210) and psoriasis (105/160) indicated no association [40, 41].

Considering ethnic heterogeneity in genetics, Song *et al*. performed a meta-analysis using 10 studies involving 2,002 cases and 1,933 controls of European and Asian [42]. The results showed that MICA-A9 was significantly associated with PsA and psoriasis patients in the entire study population, and with PsA in Europeans and psoriasis in Asian populations [42].

In studies of the association between PsA clinical forms and MICA [43]. Two hundred and twenty-six patients were classified as asymmetric oligoarthritis (AO), symmetric poly-arthritis (PA) and spondylitis (SP), or combinations (PA/SP, OA/SP). Compared to 225 normal controls, only the combined PA/SP subset showed a significantly positive association with MICA-A9 [43]. Another study in Canadian Caucasian with 745 patients and 547 controls indicated that MICA-129-met/met was a marker of skin manifestations of PsA that was independent of HLA-B and -C [44].

A common concern of these genetic studies is relatively small sample sizes [45]. Recently, a large-scale fine-mapping study of psoriasis vulgaris (PsV) risk in the HLA region in 9,247 PsV patients and 13,589 controls of European descent was performed by imputing HLA-class I and II and MICA genes from SNP genotype data. HLA-C*06:02, *12:03, HLA-B amino acid positions 67 and 9, HLA-A amino acid position 95, and HLA-DQα1 amino acid position 53 showed significant association with PsV, but not MICA [46].

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

In a study of case-control cohort (48/158) of Italian population, the positive associations of MICA-A5 and MICA-A5.1 and negative association of MICA-A9 with SLE were observed, and which appeared independently from HLA-DR3 and DQ2 [47]. The increased MICA-A5.1 in SLE was also reported in Czech population (case/control: 123/96) [48]. Recently, a GWAS (case/control: 183/1288) of Central European population reported an association of cutaneous lupus erythematosus with SNP rs2844559 that is located 27 kb proximal of the MICA gene [49].

A Japanese study of cases and controls (SLE/RA/control: 716/327/351) indicated that the MICA129Met;A9 haplotype was associated with SLE, and there was an additive genetic effect between the MICA129Met;A9 haplotype and HLA-DRB1*15:01 [50]. However, the associations were not replicated in a Spanish study (case/control: 333/361) [51].

An increased expression of MICA was observed in SLE patients' kidneys [52]. The MICA 129Met;A9 was shown to suppress NK cell-mediated cytotoxicity, but it stimulated the release of IFNγ [50]. In addition, increased NKG2D(+) CD4(+) T cells were inversely correlated with disease

activity in juvenile-onset systemic lupus erythematosus (SLE) [53].

MICA IN BEHÇET'S DISEASE (BD)

Association between the MICA gene and BD appeared also controversial. Mizuki *et al*. first reported a significantly higher frequency of MICA-A6 in BD patients of Japanese cohort (case/control: 77/103) [54], which was independently supported by several other studies including a Greek (case/control: 38/40) [55] and a Korean cohort (108/204) [56], as well as a study of juvenile BD (jBD) of Italian cohort (18/20) [57]. However, the follow-up studies by Mizuki *et al.* indicated that the previously reported MICA-A6 association was due to LD effect of HLA-B51 [58-60], and this notion was in consistent with the studies of Spanish case-control cohort (58/194) [61] and Italian (69/130) [62].

An imputation with SNPs and meta-analysis of the extended HLA locus in 2 independent BD cohorts (case/control Turkish: 503/504 and Italian: 144/1270) showed that a SNP (rs116799036) between the HLA-B51 and the MICA was strongly associated with BD, and that influenced HLA-B*51 [63]. However, this observation was not replicated in a large case-control cohort (1,190/1,257), which instead verified HLA-B51 as a primary BA allele [64]. Recently, a study of Iranian BD reported that the HLA-B51 allele and the rs76546355/rs116799036 MHC SNP are independent genetic risk factors for BD [65].

While the association of single polymorphisms of the MICA with BD appeared inconsistent in different reports, increased haplotype alleles of the MICA*009 and/or *019 were associated with BD in two independent studies including case-control European Caucasian (56/90) and Spanish (42/165) cohorts [66, 67].

There are limited studies of pathological importance of MICA in BD. In a study with 27 patients and 21 controls, soluble MICA in serum and NKG2D expression on CD8+ T cells were not significantly increased in BD [68]. In another study, HLA-B51-restricted cytotoxic T lymphocytes autoreactive to MICA transmembrane peptides were detected in active DB patients [69].

MICA IN RHEUMATIC DISEASE ASSOCIATED INFLAMMATORY BOWEL DISEASE (IBD) INCLUDING ULCERATIVE COLITIS (UC) AND CROHN'S DISEASE (CD)

Although IBD is not categorized as rheumatic disease, strong association between IBD and spondyloarthropathy (SpA) is well documented [70-73]. About 10% SpA patients develop IBD in the follow-up studies [74-76], and 20-30% patients with IBD have rheumatic abnormality [77, 78]. Moreover, studies indicated that 20%-40% of patients with IBD fulfill the criteria for SpA [79, 80].

MICA has been extensively studied in IBD. MICA-A5.1 was identified as a protective allele to CD and extensive form of UC in two independent case-control studies including Tunisian (36 cases/123 controls) and Spanish (121/116) cohorts, respectively [81, 82]. On the other hand, MICA-A5 was correlated with worse progression of UC [82], and was associated with late age of onset of CD [81]. MICA-A6 also was associated with UC in Tunish and Japanese (case/control: 36/12 and 83/132, respectively) studies [81, 83]. A higher frequency of MICA-129met/met was reported in IBD patients of Murcians (case/control: 88/154) [84]. A haplotype study showed that allele MICA*007 was associated with UC of North European Caucasian (141 cases *vs* 118 controls) [85]. However, these associations were not in agreement with several other reports. Two Chinese studies presented contradictory results by showing an increase of MICA-A5.1 in UC patients [86, 87]. The frequencies of MICA-129-val was significantly higher in UC patients of a Chinese cohort (case/control: 272/560) [88]. A later report of Japanese case-control (64/236) cohort of UC patients indicated that MICA-A6 association attributed to LD with HLA-B52 [89]. Two study of Caucasoid origin with CD (n=94 and 248), UC (n=94 and 329) and controls (n=154 and 354) could not find any associations of particular alleles of the MICA gene [90, 91]. Taking together, like other genetic association studies, in addition to sample size as an important factor, the incidence of MICA variants in patients with IBD may vary between different racial and ethnic populations.

The intestinal epithelial cell (IEC) is a major MICA expression cell type. Increased MICA expression was found on IECs in CD. Correspondingly, an increased subset of CD4(+) T cells expressing NKG2D was also found in the lamina propria from patients with CD, along with an increased Th1 cytokine profile and perforin in the periphery and in the mucosa in CD [92, 93]. These findings highlight the role of MICA-NKG2D in the activation of a unique subset of CD4(+) T cells with inflammatory and cytotoxic properties in CD [92].

SUMMARY AND PERSPECTIVE

Multiple polymorphisms of the MICA gene have been extensively examined in rheumatic diseases. Although some results are inconsistent, which are mainly conflicted in primary susceptibility verses secondary effect from the HLA class I or II genes. There seems to be an agreement that significantly increased frequencies of specific MICA alleles occur in various rheumatic diseases. The discrepancies of the genetic association of the MICA gene with the diseases may be largely caused by sample size and heterogeneity of study populations (Table **1**). It is particularly concerned that the numbers of study subjects in most of the reports were relatively small with low statistical power.

In addition, genotyping methods and disease subtypes may also be important factors. Therefore, much research remains to be done on the genetics of MICA in rheumatic diseases.

MICA has been attributed to play important roles in immune surveillance. However, the evidence of functional MICA variants contributing to pathogenesis of many rheumatic diseases is still unconvincing. MICA polymorphism and/or haplotype alleles encode unique protein structures, and/or exhibit specific functions. For instance, MICA-A5.1 contains an insertion of guanine at codon 295 that results in a premature stop codon at position

Table 1. Summary of associations between inflammatory rheumatic diseases and MICA.

Disease	MICA Variant	Population or Ethnicity	Case/Control or Family	Association (Risk or Protective)	References
RA	MICA--A6	Spanish	54 families and 211 cases	yes (protective)	[28]
RA	MICA--A6	Caucasian	90/85	yes (protective)	[29]
RA	MICA--A6	French Caucasian (FC) and German Caucasian (GC)	100 families (FC) and 90/182 (GC)	none	[30]
RA	MICA--129	French Caucasian (FC) and German Caucasian (GC)	100 families (FC) and 90/182 (GC)	yes (unknown)	[30]
AS	MICA--A4	Caucasian	48/50	yes (risk)	[32]
AS	MICA--A4	Caucasian	162/103	none due to LD with HLA--B27	[33]
AS	MICA--A4	Sardinia	82/139	yes (risk)	[34]
AS	MICA--129 met/met	Algerian	129/760	yes (risk)	[35]
AS	MICA*007:01	US Caucasian	1070/1003	yes (risk)	[36]
AS	MICA*007:01	Chinese Han	473/536	yes (risk)	[36]
AS	MICA*019	Chinese Han	473/536	yes (risk)	[36]
PsA	MICA--A9	Spanish	65/177	yes (risk)	[37]
PsA	MICA--A9	Spanish	110/110	yes (risk)	[38]
PsA	MICA--A9	Jewish	52/73	yes (risk)	[39]
PsA	MICA--A9	Chinese	102/210	none	[40, 41]
PsA	MICA--A9	mixed populations with meta--analysis	2002 /1933	yes (risk)	[42]
PsA	MICA--129--met/met	Canadian Caucasian	745/547	yes (risk)	[44]
psoriasis	MICA--A9	mixed populations with meta--analysis	2003 /1933	yes (risk)	[42]
psoriasis	MICA--A9	Chinese	105/160	none	[40]
psoriasis	MICA--A9	European	9247/13589	none	[46]
SLE	MICA--A5	Italian	48/158	yes (risk)	[47]
SLE	MICA--A5.1	Italian	48/158	yes (risk)	[47]
SLE	MICA--A9	Italian	48/158	yes (protective)	[47]
SLE	MICA--A5.1	Czech	123/96	yes (risk)	[48]
SLE	MICA129Met;A9	Japanese	716/351	yes (risk)	[50]
SLE	any of MICA variants	Spanish	333/361	none	[51]
BD	MICA--A6	Japanese	77/103	yes (risk)	[54]
BD	MICA--A6	Greek	38/40	yes (risk)	[55]
BD	MICA--A6	Korean	108/204	yes (risk)	[56]
jBD	MICA--A6	Italian	18/20	yes (risk)	[57]
BD	MICA--A6	Iranian	84/87	none due to LD with HLA--B51	[58]
BD	MICA--A6	Spanish	58/194	none due to LD with HLA--B51	[61]
BD	MICA--A6	Italian	69/130	none due to LD with HLA--B51	[62]
BD	MICA*009	European Caucasian	56/90	yes (risk)	[66]
BD	MICA*019	Spanish	42/165	yes (risk)	[67]
CD	MICA--A5.1	Tunisian	36/123	yes (protective)	[81]
CD	MICA--A5	Tunisian	36/123	late age of onset	[81]
CD	any of MICA variants	Caucasian	94/154	none	[90, 91]

(Table 1) contd…..

Disease	MICA Variant	Population or Ethnicity	Case/Control or Family	Association (Risk or Protective)	References
CD	any of MICA variants	Caucasian	248/354	none	[90, 91]
UC	MICA--A5.1	Spanish	121/116	yes (protective)	[82]
UC	MICA--A5.1	Chinese	86/172 and 124/172	yes (risk)	[86, 87]
UC	MICA--A5	Spanish	121/116	worse progression	[82]
UC	MICA--A6	Tunisian	36/12	yes (risk)	[81]
UC	MICA--A6	Japanese	64/236	none due to LD with HLA--B52	[89]
UC	MICA--A7	Japanese	83/132	yes (risk)	[83]
UC	MICA--129--val	Chinese	272/560	yes (risk)	[88]
UC	MICA*007	European Caucasian	141/118	yes (risk)	[85]
UC	any of MICA variants	Caucasian	94/154	none	[90, 91]
UC	any of MICA variants	Caucasian	329/354	none	[90, 91]
IBD	MICA--129met/met	Murcians	88/154	yes (risk)	[84]

304, which in turn encodes a truncated MICA protein lacking part of the transmembrane domain and the whole cytoplasmic tail [2]; The proteins encoded by MICA-129-met possess stronger binding affinity to NKG2D than MICA-129-val [3]; Among MICA*008, *007 and *019, MICA*008 expresses less on the surface of human fibroblasts, but can be excreted in exosomes that down-regulate NKG2D activity [27, 94], MICA*019 highly expressed on the surface of the fibroblasts whereas expression of MICA*007 was the lowest in the soluble form, which may suggest a predominant up-regulation on NKG2D by both alleles. From its functional point of view, no matter contributing to primary or secondary disease susceptibility, changes of frequencies of MICA variants may impact cellular functions and subsequent immune responses or inflammatory process in the diseases. Therefore, a possible change of NKG2D signaling caused by high affinity of MICA to NKG2D may present in AS, PsA, SLE and IBD that were reported in association with MICA-129met [35, 36, 44, 50, 84], and a potentially predominant up-regulation of NKG2D may occur in AS, BD and UC that were associated with MICA*007 and/or *019 [36, 67, 85].

In fact, altered expression of MICA and activity of NKG2G, and/or its downstream signals have been reported in RA, SLE, BD and IBD [31, 52, 53, 69, 92, 93]. Further research may be focused on how MICA variants are associated with MICA/NKG2D signaling that contributes to pathogenesis in rheumatic diseases.

CONFLICT INTEREST

The authors confirm that this article content has no conflict of interest.

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