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MicroRNA layer of MHC in infectious diseases

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ABSTRACT

The Major Histocompatibility Complex (MHC) harbors key genes of the immune response that are likely useful as biomarkers for infectious diseases. However, little is known about their microRNAs and what role they play in infections. The present study aimed to describe the miRNA genes in the MHC (MHC-miRNA), their variability and associations with infectious diseases. Additionally, MHC-miRNA host and target genes were also evaluated in associations with infectious diseases. Surveys in several databases and literature reviews identified 48 MHC-miRNA genes, with high SNP and CNV variability able to disrupt MHC-miRNA expression and putatively under selective pressure. Eight MHC-miRNAs were found inside or close regions of classical MHC rearrangements (RCCX and DRB genome organization). The proportion of MHC-miRNAs associated with infections (23%) was higher than the proportion found for the 1917 hsa-miRNA (4%). Additionally, 35 MHC-miRNAs (57%) have at least one of their target genes associated with infectious diseases, while all nine MHC-miRNA whose host genes were associated with infections have also their target genes associated with infections, being host and target genes of five MHC-miRNAs reported to be associated with the same diseases. This finding may reflect a concerted miRNA-mediated immune response mechanism triggered by infection.

1. Introduction

The major histocompatibility complex (MHC) in humans is one of the densest regions of the genome, with approximately one gene per 16 kb [1]. Moreover, MHC shows the highest levels of polymorphisms in the genome [2], likely due to natural selection [3,4].

It is noteworthy that the MHC is one of the most studied regions of the genome due its wide association with common and complex diseases like cancer, autoimmunity and infectious diseases [5]. Hence, the MHC is always considered as a major source of candidate genes for a large number of diseases, in particular, infectious diseases [6], mainly because of the involvement in antigen presentation during the immune response [7].

More recently, a new topic in the understanding of gene expression control and gene-environment interaction, called epigenetics, arose and has provided more insight on how the host promptly reacts to infections [8,9]. MicroRNAs (miRNA) are a class of such epigenetic markers that have been described as involved in different kinds of infections, including viruses, bacteria and even helminths [10–14]. Additionally, miRNAs have been found to regulate several key genes of the immune response [15,16], playing a key role in fighting infections.

The mechanism of silencing genes by using short antisense RNA to inhibit protein translation or degrade mRNA is highly conserved across the majority of organisms. miRNAs belong to this group of RNAs, which are about 22 nucleotides long, derived from hairpin molecules and have imperfect complementarity to mRNA targets, likely causing repression of translation [17].

Thus, an interesting focus is to comprehensively explore the epigenetic component of the MHC in terms of miRNA genes harbored in the MHC (MHC-miRNA). In primary databases 13 miRNA loci were known inside MHC, but this number was expanded recently to 89 putative novel miRNA transcripts, where only 48 of them undergo Dicer-dependent biogenesis and are loaded onto the Argonaute silencing complex [18]. Thus, the present study consolidates both database and recently published miRNA loci, investigating their variability and if it would impact their expression. Moreover, the profile expression of MHC-miRNAs, their target genes and eventual host genes were also approached in the context of association with infectious diseases, providing an integrated view of MHC-miRNAs features in infectious diseases.

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Table 1
Major approaches of the study and their respective database sources, survey and analysis strategies.

Approaches	Survey and analysis strategies.
Identification of miRNA coding genes in MHC	● Survey in MIRBASE (http://www.mirbase.org/search.shtml), considering that MHC is located between positions 28,510,120 and 33,480,577 in the short arm of chromosome 6, according to GRCh38.p11 (https://www.ncbi.nlm.nih.gov/grc/human/regions/MHC?asm=GRCh38.p11) ● miRNAs of a recent paper were also included [18]. From a total of 89 putative novel miRNA transcripts, we considered only those 48 of which undergo Dicer-dependent biogenesis and are loaded onto the Argonaute silencing complex
Evaluation of the variability in MHC-miRNA genes	● Each MHC-miRNA gene was surveyed for SNPs in the database variation viewer (https://www.ncbi.nlm.nih.gov/variation/view), as reported in dbSNP source database. The same procedure was used to compute the number of SNPs of the MHC region and entire chromosome 6 ● The proportion of polymorphic sites was computed as the pooled number of SNPs/pooled size of MHC-miRNA genes. This proportion was compared with that for 1917 miRNA genes in humans listed in miRDB (http://mirdb.org/FuncMir.html), excluding the MHC ones. Statistical analysis was performed by Chi-square test ● The proportion of polymorphic sites MHC-miRNA genes was compared with those for the entire MHC and for entire chromosome 6, excluding MHC-miRNA regions. Statistical comparison was performed by the exact Chi-square test □ CNVs (deletions) harboring MHC-miRNA genes were surveyed in the Database of Genomic Variants (http://dgv.tcag.ca/dgv/app/home?ref=GRCh38/hg38) ● Classical MHC rearrangements, RCCX in class III [34], located at Chr6: 31971091–32115334, and DRB genome organization in class II [35,36] located at Chr6: 32459820–32589848, were also investigated for the presence of MHC-miRNA genes within these regions
Target and host genes of MHC-miRNA genes	● Putative target genes for those MHC-miRNA genes were surveyed in mirDB (http://mirdb.org/), considering scores higher or equal to 98 ● Host genes of MHC-miRNA were identified according MIRIAD database (http://bmi.ana.med.uni-muenchen.de/miriad/) [19]
MHC-miRNAs associations with infectious diseases	● MHC-miRNAs and their target and host genes were surveyed for associations with infectious diseases in GeneRIF (Gene References into Functions), by querying the Gene database (https://www.ncbi.nlm.nih.gov/gene), NCBÍs Phenotype-Genotype Integrator (https://www.ncbi.nlm.nih.gov/gap/phegeni) and PubMed ● To determine if MHC-miRNAs are more or less associated with infectious diseases than other genomic miRNAs, the total list of 1917 human miRNAs (http://www.mirbase.org/cgi-bin/mirna_summary.pl?org=hsa; accessed in December 2018) was also reviewed in the same way as the MHC-miRNA. ● Statistical comparison was performed by the Chi-square test

Abbreviations used: MHC (major histocompatibility complex), miRNA (microRNA), MHC-miRNA (miRNA in MHC region), SNP (single nucleotide polymorphism), CNV (copy number variation).

2. Methods

The major methodological approaches included (i) the identification of miRNA genes in the MHC and their main features; (ii) the evaluation of the variability of MHC-miRNA genes and how structural variation in the MHC can disrupt these miRNA genes and iii) a literature review of these miRNA genes, in terms of their expression, host and target genes. Table 1 shows these approaches and their respective database sources, strategies for survey and analyses. All databases were accessed between December 2018 and January 2019.

3. Results

3.1. MHC-miRNA polymorphisms and MHC structural variation impacting miRNA expression

The list of all 13 MHC-miRNA genes found in databases and the 48 putative miRNA reported by Clark et al. [18] is presented in Table 2, along with their features and variability.

The proportion of polymorphic sites relative to the pooled MHC-miRNA genes sizes was 0.114 (1.14 SNPs each ten bp) and differs from the estimated for the 1917 hsa-miRNAs (0.17; Chi-square 1799; $p < 0.0001$). The MHC-miRNA proportion of polymorphic sites is similar to the observed for the entire chromosome 6 (0.11; Chi-square 1.28; $p = 0.26$), but higher than for the entire MHC (0.077; Chi-square 101.3; $p < 0.0001$).

From the 61 MHC-miRNA considered, 52 (85%) are localized in regions where copy number variation (CNV) deletions were reported, putatively disrupting miRNA expression (Table 2). Interestingly, considering both classical regions of rearrangement in MHC, the class III RCCX and DRB genome organization in class II, only RCCX harbor one MHC-miRNA gene (CHOP_60). Thus, RCCX rearrangements can delete and affect CHOP_60 expression. However, since these rearrangements could encompass miRNA genes close to their boundaries, seven miRNA genes are highlighted because they are < 200 kb from these limits: hsa-mir-1236, hsa-mir-6721, hsa-mir-6833 and CHOP_64, close to RCCX region, and hsa-mir-3135b, CHOP_52 and CHOP_43, close to the class II DRB region. Table 2 also indicates these MHC-miRNA localization and proximity to RCCX and DRB regions.

3.2. MHC-miRNA and their host and target genes

The percentage of intragenic MHC-miRNAs (54%) was slightly lower than for the entire genome (61.5%) [19], being statistically not significant (Fisher exact test; $p = 0.28$). The MHC-miRNAs with their respective host genes are presented in Table 3.

The evaluation of target genes revealed that 51 MHC-miRNA genes target 82 different genes, and eleven genes are targets for two or more different MHC-miRNAs. The number of target genes per MHC-miRNA ranged from zero to 52, considering our 98–100 score criteria (Table 3).

3.3. MHC-miRNAs association with infectious diseases

The literature review of revealed studies where three MHC-miRNAs (23%) were directly associated with infectious diseases, including hsa-miR-4646 upregulated in hepatitis B [20] and latent tuberculosis [21], hsa-miR-877 upregulated in tuberculosis-infected individuals [22] and hsa-miR-1236, which seems to inhibit the infection of monocytes by HIV-1 [23]. Clark et al recently published miRNAs do not allow yet the identification of direct miRNA-infectious diseases associations in literature.

In contrast, a survey of association with infectious diseases was also carried out in the complete list of 1917 human miRNA genes and demonstrated that only 4% of these genes were associated with infectious disease (Chi-square Test; $p = 0.014$).

Both target genes and host genes, in case of intragenic miRNAs, are functionally related to miRNA effects and it would be interesting to expand the infectious diseases association analysis to target and host genes.

The expression of miRNAs may be regulated in different ways, and one of them is, in the case of intragenic miRNAs, the co-expression with host genes [24]. In this context, 33 from 61 MHC-miRNAs were intragenic, being nine of these host genes (27%) reported to be associated with infectious diseases (Table 3).

Table 2
List of MHC-miRNA genes and their respective gene locations, gene size in bp, number of polymorphic sites (SNPs), proportion of polymorphic sites (SNP/SIZE) and copy number variation deletions (CNVs) that include MHC-miRNAs loci.

miRNA	Localization	Size	SNPs	SNP/SIZE	CNVs
CHOP_83	chr6:226217–226295	79	13	0.165	6
CHOP_77	chr6:270979–271049	71	11	0.155	21
CHOP_80	chr6:2413252–2413318	67	8	0.119	0
CHOP_76	chr6:2662534–2662620	87	18	0.207	1
CHOP_86	chr6:3089988–3090066	79	11	0.139	0
CHOP_78	chr6:3229400–3229470	71	10	0.141	0
CHOP_79	chr6:3379533–3379601	69	12	0.174	0
CHOP_72	chr6:3394317–3394387	71	7	0.099	0
CHOP_84	chr6:3413207–3413277	71	6	0.085	0
CHOP_81	chr6:3497783–3497853	71	6	0.085	0
CHOP_87	chr6:4297806–4297894	89	24	0.270	9
CHOP_82	chr6:4650556–4650630	75	9	0.120	0
CHOP_70	chr6:4739873–4739953	81	11	0.136	0
CHOP_55	chr6:28709145–28709227	83	1	0.012	3
CHOP_18	chr6:28719694–28719776	83	10	0.120	3
CHOP_67	chr6:28752429–28752507	79	0	0.000	3
CHOP_59	chr6:28827416–28827494	79	0	0.000	3
CHOP_1	chr6:28869349–28869431	83	0	0.000	3
CHOP_58	chr6:28934513–28934599	87	0	0.000	3
CHOP_41	chr6:29188931–29189015	85	0	0.000	9
CHOP_20	chr6:29597099–29597169	71	0	0.000	5
CHOP_34	chr6:29983639–29983717	79	0	0.000	13
CHOP_13	chr6:30111222–30111296	75	10	0.133	5
CHOP_38	chr6:30243415–30243491	77	10	0.130	5
hsa-mir-877	chr6:30584332–30584417	86	18	0.209	6
CHOP_57	chr6:30648625–30648695	71	6	0.085	8
CHOP_35	chr6:30726532–30726608	77	12	0.156	9
CHOP_42	chr6:30773501–30773577	77	10	0.130	8
hsa-mir-4640	chr6:30890883–30890972	90	18	0.200	7
CHOP_47	chr6:30902270–30902350	81	0	0.000	7
CHOP_19	chr6:30955647–30955713	67	7	0.104	10
CHOP_25	chr6:30984488–30984566	79	7	0.089	11
hsa-mir-6891	chr6:31355224–31355316	93	47	0.505	16
CHOP_39	chr6:31527950–31528030	81	15	0.185	7
CHOP_2	chr6:31533661–31533735	75	0	0.000	7
CHOP_32	chr6:31595059–31595149	91	6	0.066	6
hsa-mir-6832	chr6:31633787–31633858	72	14	0.194	9
CHOP_61	chr6:31651475–31651545	71	5	0.070	9
CHOP_4	chr6:31686084–31686168	85	0	0.000	7
hsa-mir-4646	chr6:31701029–31701091	63	12	0.190	6
CHOP_48	chr6:31703910–31703982	73	7	0.096	6
CHOP_65	chr6:31719620–31719704	85	10	0.118	5
hsa-mir-1236[A]	chr6:31956839–31956940	102	18	0.176	7
CHOP_60[B]	chr6:32078492–32078566	75	11	0.147	8
CHOP_64[A]	chr6:32124871–32124953	83	7	0.084	8
hsa-mir-6721[A]	chr6:32170030–32170116	87	17	0.195	8
hsa-mir-6833[A]	chr6:32179816–32179876	61	10	0.164	9
CHOP_52[C]	chr6:32326294–32326374	81	4	0.049	7
CHOP_43[C]	chr6:32441274–32441344	71	16	0.225	8
hsa-mir-3135b[C]	chr6:32749912–32749979	68	8	0.118	12
CHOP_45	chr6:32878435–32878515	81	7	0.086	5
CHOP_44	chr6:32885544–32885618	75	2	0.027	6
CHOP_15	chr6:32981887–32981957	71	15	0.211	5
CHOP_54	chr6:33160492–33160564	73	0	0.000	4
hsa-mir-219a-1	chr6:33207835–33207944	110	24	0.218	6
hsa-mir-6873	chr6:33287227–33287289	63	16	0.254	6
hsa-mir-6834	chr6:33290245–33290325	81	13	0.160	5
CHOP_22	chr6:33368155–33368233	79	2	0.025	5
CHOP_5	chr6:33373716–33373786	71	0	0.000	5
CHOP_30	chr6:33381575–33381661	87	0	0.000	5
hsa-mir-5004	chr6:33438331–33438437	107	16	0.150	6

[A] Less than 200 kb from RCCX region; [B]inside RCCX region; [C]less than 200 kb from DRB region. The nomenclature published by Clark et al [18] was maintained.

Additionally, 33 MHC-miRNAs (54%) have at least one of their respective target genes reported to be associated with infections (Table 3), mainly viral and bacterial, but some fungi, protozoans and a trematode parasite were also reported.

Table 3
Reported gene associations with infections of MHC-miRNA host genes and target genes.

MHC-miRNA	Host Genes		Target Genes	
	Name	Associations	Number	Associations
CHOP_1			5	Yes
CHOP_2	ATP6V1G2-DDX39B/ DDX39B	Yes	3	Yes
CHOP_4	LOC105375019	No	3	Yes
CHOP_5			10	Yes
CHOP_13	TRIM31/ TRIM31-AS1	No	4	Yes
CHOP_20			9	No
CHOP_25	MUC21	No	49	Yes
CHOP_30			20	Yes
CHOP_32			13	Yes
CHOP_38	HCG17	No	11	Yes
CHOP_39			4	No
CHOP_41			1	No
CHOP_42	HCG20		20	Yes
CHOP_43	HLADRA	Yes	21	Yes
CHOP_48			8	Yes
CHOP_52	LOC101929163/ C6orf20/ HNRNPA1P2	No	4	Yes
CHOP_55			2	No
CHOP_58			19	Yes
CHOP_60	TNXB/ RNA5SP206	No	3	No
CHOP_64	ATF6B	No	21	Yes
CHOP_65	LY6G6C	No	47	Yes
CHOP_67			13	Yes
CHOP_70	CDYL	No	22	Yes
CHOP_72	SLC22A23	No	12	Yes
CHOP_76			5	Yes
CHOP_77	LOC102723922	No	1	No
CHOP_78			2	Yes
CHOP_79	SLC22A23	No	1	No
CHOP_81			4	No
CHOP_82			9	Yes
CHOP_84	SLC22A23/ LOC105374890	No	1	Yes
CHOP_86	RIPK1	Yes	49	Yes
hsa-mir-877	ABCF1	Yes	6	Yes
hsa-mir-4640	DDR1	Yes	0	No
hsa-mir-6891	HLA-B	Yes	4	Yes
hsa-mir-6832	PRRC2A	Yes	10	Yes
hsa-mir-4646	ABHD16A	No	3	Yes
hsa-mir-1236	NELFE	Yes	6	Yes
hsa-mir-6721	AGPATI	No	18	Yes
hsa-mir-6833	RNF5	Yes	51	Yes
hsa-mir-3135b			4	No
hsa-mir-219a-1			10	Yes
hsa-mir-6873	WDR46	No	52	Yes
hsa-mir-6834	PFDN6	No	1	No
hsa-mir-5004	SYNGAP1	No	7	No

Associations with infectious diseases, according to a literature survey in the PubMed and GeneRIF (Gene References into Functions) databases. The detailed description of diseases, target genes and references are shown in Supplementary Table 1. The nomenclature published by Clark et al [18] was maintained.

Moreover, eight MHC-miRNAs have associations with infectious diseases reported for both host and target genes. More interestingly is the fact that host and target genes of five MHC-miRNAs: hsa-mir-1236 (HCV), hsa-mir-877 (retrovirus), hsa-mir-6891(HBV), CHOP_43 (HCV) and CHOP_86 (HEV and HIV) share associations with the same infectious agents. The complete description of host and target genes with their respective associations with infectious diseases and bibliography is presented in Supplementary Table 1.

4. Discussion

Based on the proportion of polymorphic sites MHC-miRNAs presented levels of variability lower than miRNAs located outside the MHC (0.114 versus 0.17). The same trend seems to not be found if we

compare the proportion of polymorphic sites from the entire MHC region with the entire chromosome 6 excluding MHC (0.077 versus 0.11). However this low proportion of polymorphic sites from MHC region seems to be restricted to intergenic regions, since classical genes, like HLA-A, -B, C and -DRB1showed proportion of polymorphic sites over five times higher (0.41, 0.44, 0.38, 0.38, respectively), in agreement with the higher degree of polymorphisms in MHC genes than in other regions of the genome frequently highlighted in literature [25].

Moreover, miRNA genes within and outside the MHC present higher variability than for general MHC and chromosome 6, similar to the pattern observed for HLA genes and MHC region that is likely maintained by balancing selection. Hence, although miRNA-mediated silencing of genes is very widespread and conserved, their sequences seem to tolerate the accumulation of mutations well.

Some additional evidence agrees with this idea. First, the miRNA silencing mechanism is due to imperfect complementarity of miRNA with the 3′ UTR target regions of mRNA [17]. A second fact is that miRNAs have been found to be involved in signaling between the host and their pathogens [26], thus being high levels of variability advantageous in the same way observed for immune response genes like HLA [27]. In this context, the higher variability of miRNA genes could only reflect a co-evolutionary interplay between miRNAs and their targets, in agreement with the study of Saunders et al. [28] that found high variability at 3'UTR target sequences and suggested signatures of positive selection.

Despite that only one miRNA is inside RCCX region seven other were located close to the boundaries of RCCX and DRB regions that where large gene rearrangements are frequently observed generating different haplotypes. Thus the presence and expression of some miRNAs can be haplotype-specific, as pointed by Clark et al [18]. Moreover, a large number of CNVs is presently reported as being able to delete and disrupt the expression of 85% of MHC-miRNAs.

Indeed, some studies already described how mutations in miRNA genes affect the expression of their target genes, like mutations in hsa-miR-146a and hsa-miR-27a contributing to breast cancer susceptibility and promote disease susceptibility, like SNPs in miRNA genes predisposing to breast cancer [29] and the role of a insertion/deletion polymorphism in hsa-mir-184a loci in the expression of its target gene, HLA-C, modulating HIV control and the risk of Crohn disease [30]. Additionally, miRNAs harbored in the CNVs regions as potential functional variants putatively related to diseases have been recently discussed in 22q11.2 deletion syndrome [31] and become important since 85% of MHC-miRNA are CNV-harbored. In this context, the age acquirement of somatic CNVs [32] could be related to decreasing miRNA levels in aging [33]. These results suggest that miRNA polymorphisms need to be considered in the understanding of their full role in diseases.

The results highlight that the proportion of MHC-miRNA genes associated with infectious diseases was higher than the association with hsa-miRNA genes outside the MHC. Noteworthy is also that 34 (56%) of the MHC-miRNA genes have either their host genes or their target genes reported as associated with infectious diseases. Also remarkable was the fact that all eight MHC-miRNA whose host genes were associated with infectious diseases have also their target genes associated with infections, and host and target genes of five MHC-miRNAs were reported to be associated with the same infectious agents.

Since MHC genes are well known to be related to infectious diseases, these results may not be a coincidence. An important regulatory mechanism of miRNA expression is the co-expression of them with their host genes or clusters of genes [24], which is regulated and expressed in a concerted way.

Hence, it is plausible to accept the predominance of miRNAs associated with infections in MHC as a clue of a coupled mechanism in response to infections, where the same triggers that demand response from MHC genes also regulate MHC-miRNA expression to some extent, whose actions would regulate target genes also related to response to infections.

Associations of MHC-miRNAs with infectious diseases were revealed to be impressive, considering both direct association studies and associations found with their most probable target genes. Moreover, the role of many host genes in the immune response against infections and their putative co-expression with the MHC-miRNA they harbor should also be considered in an integrated manner during infection processes. Along with the expression profiles in blood tissues, a new epigenetic layer of the MHC is now unraveled, which is relevant for the understanding of MHC-miRNA role in infectious diseases.

Thus, it is plausible to evaluate miRNA association with infectious diseases considering not only candidates such as MHC-miRNAs but also expression of their main target and host genes as well, along with their variability that may disrupt miRNA expression.

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Author contributions statement

All authors were actively involved in the surveys and analysis by handling the several databases used. SNF, EJMS and ALSS were involved in data analysis and manuscript preparation and all other steps, EFS, MML and MSLS were involved in data mining from databases and reviews of literature.

Conflict of interest statement

The authors declare that there were no personal, professional or financial relationships that could potentially be construed as a conflict of interest during any phase of the present study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humimm.2019.02.006.

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