UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
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Brenda Pedron Beltrame

# RELAÇÃO DA DELEÇÃO DO GENE *NKG2C* E HAPLÓTIPOS DE HLA-E COM A SUSCEPTIBILIDADE AO LÚPUS ERITEMATOSO SISTÊMICO

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Trabalho de conclusão de curso de graduação apresentado ao Instituto de Ciências Básicas da Saúde da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de Bacharela em Biomedicina.

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BANCA EXAMINADORA

Nadine Glesse

Fernanda Sales Luiz Vianna - UFRGS

José Artur Bogo Chies - UFRGS

## RESUMO

O lúpus eritematoso sistêmico (LES) é uma doença autoimune, caracterizada pela ativação excessiva da resposta imune inata que induz produção exacerbada de autoanticorpos e deposição de imunocomplexos. O processo inflamatório observado no LES é promovido por células como linfócitos T e linfócitos *Natural Killer* os quais expressam em sua superfície receptores pertencentes à família NKG2. O subtipo NKG2C desempenha função de ativação, induzindo a liberação de citocinas e citotoxicidade, quando ligado a moléculas HLA-E expressas por essas células. Sendo assim, infere-se que os receptores NKG2C e as moléculas HLA-E possuam um importante papel na susceptibilidade ao LES, já que são capazes de contribuir para o desenvolvimento do processo inflamatório. O objetivo desse estudo é avaliar se há relação entre a deleção do gene *NKG2C* e haplótipos de HLA-E com a susceptibilidade ao LES em uma população do sul do Brasil. A metodologia desse trabalho envolve a realização de PCR convencional e genotipagem. O PCR de *NKG2C* utiliza três pares de primers, o primeiro par amplifica a região do breakpoint da deleção, o segundo par amplifica o éxon 6 do gene *NKG2C* e o terceiro par atua como controle interno de amplificação e amplifica a região entre os éxons 3 e 4 do gene *NKG2A*. A genotipagem dos haplótipos de HLA-E baseia-se em múltiplas reações de PCR, as quais utilizam oito pares de primers para amplificação dos alelos *0101, *0103 (*01031 e *01032) e *0104, sendo sete pares para a identificação alélica e um como controle interno (gene *human growth hormone*). A genotipagem da deleção de *NKG2C* foi realizada em 326 indivíduos portadores de LES e 214 indivíduos controles saudáveis. A frequência dos genótipos encontrada no grupo de casos foi 0,72 wt/wt e 0,28 wt/del e no grupo controle foi 0,67 wt/wt e 0,33 wt/del. Não foram encontrados genótipos del/del em qualquer dos grupos, e as frequências dos genótipos da população estudada não estavam em equilíbrio de Hardy-Weinberg. Serão realizadas análises adicionais para confirmação dos genótipos de *NKG2C*. A genotipagem dos haplótipos de HLA-E está em andamento.



Palavras-chave: Lúpus eritematoso sistêmico. Gene NKG2C. Haplótipo. HLA-E.

## ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by excessive activation of innate immune responses that induces the production of autoantibodies directed against nuclear and cytoplasmatic antigens and leads to immunocomplexes deposition. The inflammatory process is mainly mediated by T and Natural Killer cells, which express NKG2C receptors on their surface. NKG2C receptors are involved with cytokine production and cytotoxicity when bound to HLA-E molecules expressed by other cells. Thus, it was hypothesized that NKG2C and HLA-E receptors can have an important role in SLE development, since these molecules can contribute to the development of an inflammatory process. The aim of this study is to evaluate the relationship between *NKG2C* gene deletion and HLA-E haplotypes with SLE susceptibility in a South Brazilian population. The methodology used was conventional PCR followed by genotyping. The *NKG2C* PCR reaction uses three sets of primers, the first amplifies the deletion breakpoint, the second amplifies the exon 6 of *NKG2C* gene and the third pair acts as an internal control and amplifies the region between exons 3 and 4 of *NKG2A* gene. HLA-E haplotype genotyping uses eight sets of primers, seven of them specific for the identification of alleles *0101, *0103 (*01031 and *01032) and *0104. The eighth pair amplifies the human growth hormone gene as an internal control. The genotyping was performed in 326 SLE patients and 214 control individuals. The genotypic frequencies observed were 0.72 wt/wt and 0.28 wt/del for the SLE individuals and 0.67 wt/wt and 0.33 wt/del for the control individuals. No del/del genotypes were found and the frequencies were not in Hardy-Weinberg equilibrium. Additional analyses will be performed to confirm the NKG2C genotypes. HLA-E genotyping is still in progress.



Keywords: Lupus erythematosus systemic. NKG2C gene. NKG2C deletion. HLA-E haplotypes.

**SUMÁRIO**

# 1 INTRODUÇÃO COMPREENSIVA

Lúpus eritematoso sistêmico (LES) é uma doença autoimune, de etiologia multifatorial, que afeta aproximadamente 5 a cada 100.000 pessoas por ano no mundo, sendo dez vezes mais frequente em mulheres do que em homens. Essa doença é caracterizada pela ativação excessiva da resposta imune inata que induz produção exacerbada de autoanticorpos contra antígenos nucleares e citoplasmáticos, bem como pela deposição de imunocomplexos. As principais manifestações clínicas do LES são nefrite lúpica, trombocitopenia, vasculite, síndromes neuropsiquiátricas, complicações respiratórias e, em alguns casos pode haver sintomas gastrointestinais no início da doença (AHMADPOOR; DALILI; ROSTAMI, 2014; CARDOSO et al., 2008; LA PAGLIA et al., 2017). Além disso, LES está frequentemente associado a outras doenças autoimunes, como artrite reumatoide e síndrome de Sjögren (MANOUSSAKIS et al., 2004; SIMON et al., 2017). Indivíduos com LES também apresentam risco elevado de desenvolver infecções devido à própria atividade da doença e aos efeitos adversos causados pelos fármacos imunossupressores utilizados no tratamento. As infecções mais comuns são as urinárias, que são geralmente seguidas de Herpes Zoster, candidíase, tuberculose e pneumonia. Comorbidades cardiovasculares também estão frequentemente associadas ao lúpus, estando incluídas valvulopatias, aceleração da aterosclerose e trombose. A incidência de trombose em indivíduos portadores de LES é de vinte e cinco à cinquenta vezes mais comum se comparada à população em geral (LA PAGLIA et al., 2017).

O diagnóstico do LES é realizado de acordo com parâmetros estabelecidos pelo *American College of Rheumatology* (ACR), tais como presença de eritema malar e alterações renais, que são verificados a partir da anamnese, exame físico e laboratoriais. A solicitação de exames laboratoriais varia conforme manifestações clínicas da doença e dentre os exames destacam-se as dosagens de autoanticorpos, que em muitos casos não são específicas para o LES, mas auxiliam no estabelecimento do diagnóstico. Existem diversos autoanticorpos que podem ser avaliados, como o anti-DNA, anti-Sm, anti-Ro/SSa, anti-La/SSb, anti-Slc 70, anti-RNP, anticardiolipina IgM e IgG e anticoagulante lúpico. Além disso, pode ser solicitada a dosagem de fator antinuclear (FAN) que também auxilia no diagnóstico embora não seja um exame específico para LES. Para além do diagnóstico, o acompanhamento da progressão do LES também se faz importante, sendo assim, existem indicadores que auxiliam nesse processo, sendo esses o *Systemic Lupus Erythematosus Disease Activity Index* (SLEDAI) que

avalia a atividade da doença e o *Systemic Lupus International Colaborating Clinics* (SLICC) que indica o dano acumulado. Vale ressaltar que essas ferramentas de avaliação do LES são essenciais para o desenvolvimento de um esquema de tratamento efetivo (BRASIL, 2014).

A intensa ativação do sistema imune no LES, a qual resulta da interação de fatores genéticos e ambientais, é promovida por células como linfócitos T e linfócitos *Natural Killer* (NK), ocasionando inflamação em diversos órgãos e tecidos. Os linfócitos T e NK, quando ativados em situações de inflamação, expressam em sua superfície receptores denominados NKG2. Os receptores NKG2 são codificados por um cluster gênico presente no braço curto do cromossomo 12 e se subdividem conforme sua função e o modo em que são expressos na membrana celular. O subtipo NKG2A é um heterodímero expresso na membrana celular complexado à uma molécula CD94 e apresenta função inibitória. O subtipo NKG2D é um homodímero que apresenta função inibitória. Por sua vez, o subtipo NKG2C é um heterodímero expresso complexado à uma molécula CD94 e desempenha a função de ativar outras células do sistema imune, induzindo a liberação de citocinas e citotoxicidade. Sendo assim, infere-se que o receptor NKG2C possui um importante papel em doenças autoimunes, como o LES, já que é capaz de contribuir para a ativação e o desenvolvimento do processo inflamatório (IWASZKO; BOGUNIA-KUBIK, 2011; MIYASHITA et al., 2004).

Existem dois artigos na literatura relacionando receptores NKG2 com susceptibilidade à LES. Nesses trabalhos é relacionada a presença de polimorfismos de nucleotídeo único (em inglês *single nucleotide polymorphism*; SNP) nos genes que codificam esses receptores com o desenvolvimento da doença, já que algumas alterações no DNA podem impactar na síntese proteica do receptor e por sua vez interferir em sua função. O estudo publicado por Kabalak et al. (2010) demonstrou que há relação entre o genótipo GG do SNP rs2255336, presente no gene NKG2D, com o LES em uma população alemã. Já o trabalho desenvolvido por Piotrowski et al. (2012) avaliou o mesmo polimorfismo em população polonesa e seus resultados confirmam os obtidos por Kabalak et al. (2010).

Além dos SNPs, também é interessante avaliar a deleção do gene *NKG2C,* visto que a deleção do gene impede a expressão da proteína correspondente (GAMAZON; NICOLAE; COX, 2011). O estudo publicado por Miyashita et al. (2004) determinou que a deleção do gene *NKG2C* é decorrente da perda de um fragmento de 16kb, cujo ponto de início foi mapeado distante 1,5-1,8 kb da região 3'UTR do gene *NKG2A*. Entretanto, nesse estudo desenvolvido em populações holandesa e japonesa, não foi identificada associação entre a deleção do gene *NKG2C* e a susceptibilidade ao LES. Ademais, há também artigos relacionando SNPs do gene *NKG2C* com outras doenças autoimunes. No estudo desenvolvido

por Park, Park & Song et al. (2008) em indivíduos coreanos portadores de artrite reumatoide, foi observado que o genótipo Ser/Ser do polimorfismo *NKG2C* c.305C>T (Ser102Phe) está relacionado à artrite reumatoide. Por fim, o trabalho publicado por Zeng et al. (2013) identificou que há relação entre a deleção do gene *NKG2C* e a baixa expressão do alelo *0101 do HLA-E com a susceptibilidade à psoríase em indivíduos caucasianos provenientes dos Estados Unidos.

Os receptores NKG2C são reconhecidos pela molécula de MHC (do inglês *major histocompatibility complex*) não clássica Ib HLA-E (do inglês *human leukocyte antigens-E*), em humanos. A partir da ligação com o HLA-E, expresso por diversos tipos celulares, o NKG2C exerce sua função sobre a citotoxicidade e liberação de citocinas, induzindo inflamação. Além de reconhecer os receptores NKG2C, o HLA-E também interage com proteínas virais, bacterianas e sinalizadoras de estresse. Sendo assim, o HLA-E apresenta importante função na proteção contra infecções e manutenção da integridade celular (LAUTERBACH et al., 2015). O HLA-E é caracterizado pela presença reduzida de polimorfismos e padrão restrito de expressão celular. O HLA-E, assim como outros HLA de classe I, possui duas subunidades: uma cadeia pesada e uma cadeia leve. O gene que codifica a cadeia leve, que não é polimórfica, está presente no cromossomo 15, enquanto que o gene codificante da cadeia pesada, que é polimórfica, está inserido em um cluster no braço curto do cromossomo 6 (IWASZKO; BOGUNIA-KUBIK, 2011). Segundo alguns artigos, o HLA-E apresenta cinco alelos (*0101, *0102, *01031, *01032 e *0104), no entanto, um trabalho recente identificou apenas três alelos (*0101, *01031 e *01032) em populações japonesa e afro-americana, bem como em vinte e oito linhagens celulares (GRIMSLEY et al., 2002). Vale ressaltar que polimorfismos de HLA-E já foram associados com outras doenças autoimunes, como psoríase e Doença de Behçet, sendo que os alelos mais comumente estudados são o *0101 e o alelo *0103 (ZENG et al., 2013; SEO et al., 2007). Considerando que a interação entre NKG2C e HLA-E é necessária para a liberação de citocinas e citotoxicidade das células NK, é importante avaliar se diferentes alelos dos genes de HLA-E podem estar envolvidos com a inflamação característica do LES, por esse motivo, nesse estudo o gene HLA-E foi haplotipado dos indivíduos participantes. Potencialmente, a expressão de diferentes alelos pode prejudicar a interação do HLA-E com o NKG2C e assim impactar na inflamação.

## 1.1 JUSTIFICATIVA

O LES apresenta grande impacto na qualidade de vida dos indivíduos afetados devido à sua fisiopatologia e também pelo tratamento realizado com fármacos corticoides e outros imunossupressores. Devido à vasculite desencadeada pela deposição de imunocomplexos, os pacientes podem apresentar eritema cutâneo, lesões edemaceadas e dolorosas nas regiões palmar e plantar, mialgia, cefaleia, astenia entre diversos outros sintomas, que afetam de maneira substancial seu bem-estar físico (REIS; COSTA, 2010). Além disso, há diversos relatos na literatura de comprometimento psicológico associado ao LES, tais como depressão, ansiedade, distúrbios do humor e psicose (ROBINSON et al., 2010; POPESCU; KAO, 2011). Em vista desses sintomas impactantes, o desenvolvimento de estudos que caracterizem as bases genéticas da susceptibilidade ao LES é essencial para a descoberta de novas possibilidades de tratamento e diagnóstico preciso. Ademais, não há estudos que relacionem a deleção do gene *NKG2C* e haplótipos de HLA-E com a susceptibilidade ao LES na população brasileira e existem poucos estudos avaliando os mesmos parâmetros em outras populações humanas. Sendo assim, os resultados descritos na literatura devem ser confirmados em diferentes populações.

## 1.2 OBJETIVOS

O objetivo desse estudo é avaliar se há relação entre a deleção do gene *NKG2C* e haplótipos de HLA-E com a susceptibilidade ao lúpus eritematoso sistêmico, bem como investigar se há relação dessas variantes com as manifestações clínicas e gravidade da doença.

## 2 ARTIGO CIENTÍFICO

# "RELATIONSHIP OF *NKG2C* GENE DELETION WITH SUSCEPTIBILITY TO SYSTEMIC LUPUS ERYTHEMATOSUS"

Brenda Pedron Beltrame, Maria Cristina Cotta Matte, José Artur Bogo Chies

Immunobiology and Immunogenetics Laboratory, Post-Graduation Program in Genetics and Molecular Biology, Genetics Department, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

ABSTRACT: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by excessive activation of innate immune responses that induces autoantibodies synthesis against nuclear and cytoplasmatic antigens and immunocomplexes deposition. The inflammatory process is mainly promoted by T and Natural Killer cells, which express NKG2C receptors on their surface. NKG2C receptors are involved in cytokines production and cytotoxicity, processes that may contribute to SLE development. The aim of this study was to evaluate the relationship between *NKG2C* gene deletion and SLE susceptibility in a South Brazilian population. The methodology used was conventional PCR followed by genotyping. The genotyping was performed in 326 SLE patients and 214 control individuals. The genotypic frequencies observed were 0.72 wt/wt and 0.28 wt/del for the SLE individuals and 0.67 wt/wt and 0.33 wt/del for the control individuals. No del/del genotypes were found and the frequencies were not in Hardy-Weinberg equilibrium. Additional analyses will be made to confirm the *NKG2C* genotypes.

KEYWORDS: lupus erythematosus systemic; NKG2C gene; NKG2C deletion.

## 1. INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects approximately 5 per 100,000 people per year in the word, being ten times more frequent in women as compared to men. This disease is characterized by excessive activation of innate immune responses which induce exacerbated production of autoantibodies against nuclear and cytoplasmic antigens and deposition of immune complexes (Ahmadpoor, Dalili & Rostami, 2014; La Paglia et al, 2017). The intense activation of the immune system observed in SLE is promoted by T lymphocytes and Natural Killer cells (NK), leading to inflammation in several organs. These cells, when activated in inflammatory situations, express on their surface receptors called NKG2. NKG2C receptors are codified by a gene cluster on chromosome 12 and are classified according to their function and structure. The NKG2C subtype is an activation receptor that is present on T and NK cells surfaces complexed with a CD94 molecule and that induces cytokine synthesis and cytotoxicity mediated by other immune cells. Thus, NKG2C receptor probably has an important role on autoimmune diseases pathogenicity, such as SLE, contributing to the establishment of an inflammatory process (Iwaszko & Bogunia-Kubik, 2011; Miyashita et al, 2004). Besides some GWAS studies, there

are two studies specifically approaching *NKG2* single nucleotide polymorphisms (SNP) in SLE. Kabalak et al (2010) identified a relationship between SLE and the GG genotype of SNP rs2255336, present in *NKG2D* gene, in a German population. Piotrowski et al (2012) evaluated the same polymorphism in the Polish population and also found a relationship with SLE. Furthermore, there are some studies correlating *NKG2C* SNPs with other autoimmune diseases. For example, in the study developed by Park, Park & Song (2008) in Korean individuals, the Ser/Ser genotype of c.305C>T(Ser102Phe) polymorphism in the *NKG2C* gene was correlated with rheumatoid arthritis development. In addition, the deletion of the *NKG2C* gene was also investigated in the context of the receptor expression. Nevertheless, in a study developed in Dutch and Japanese populations, no relationship was found between *NKG2C* gene deletion and SLE susceptibility (Miyashita et al, 2004). Since ethnical differences may impact in the deletion frequency, more studies are required in different populations to clearly establish the role of this molecule in SLE. Thus, the aim of this study was investigated the relationship of *NKG2C* deletion with susceptibility to systemic lupus erythematosus in a South Brazil population.

## 2. MATERIAL AND METHODS

For this study, 326 SLE and 214 healthy individuals were recruited. All patients were under medical care at the Rheumatology Service of Hospital de Clínicas de Porto Alegre, the capital of the southernmost state of Brazil. The control group includes healthy individuals without prior history of autoimmune disease. All patients were diagnosed with SLE according to the American College of Rheumatology (ACR) Criteria and all participants signed written informed consent. Clinical and demographic features of SLE and healthy individuals are described at Table 1. Total DNA extraction of peripheral blood samples were performed using a salting out method (Lahiri & Nurnberger, 1991). Genotyping of *NKG2C* deletion was performed according to the PCR protocol design by Miyashita et al (2004). The PCR reaction uses three sets of primers, the first amplifies the deletion breakpoint at 3'UTR of *NKG2A* and results in a 411pb fragment when *NKG2C* gene is absent; the second pair amplifies the exon 6 and results in a 363pb fragment when the gene is present; the third pair acts as an internal control and amplifies a 780pb fragment from exon 3 to exon 4 of *NKG2A* gene. Statistical analyses were performed with IBM SPSS Statistics, version 25.0 (IBM Corp, Armonk, NY). Hardy-Weinberg equilibrium was calculated according to the chi-squared test (Rodriguez & Day, 2009).

## 3. RESULTS AND DISCUSSION

The *NKG2C* gene deletion has been associated with increased susceptibility to several diseases, both considering autoimmune conditions such as psoriasis, as well as infectious diseases, in the case of cytomegalovirus and HIV infections (Zeng et al, 2013; Vietzen et al, 2018; Thomas et al, 2012). In this study, we analyzed the relationship between a *NKG2C* deletion and susceptibility to SLE. In our sample, the frequency of women was significantly elevated in the group of individuals with SLE as it would be expected since the disease is more prevalent in women.

The calculated genotypic frequencies amongst the SLE patients were 0.72 for the wild-type homozygous and 0.28 for the heterozygous genotypes. Amongst controls, the frequencies were 0.67 and 0.33 respectively for wild-type homozygous and heterozygous. No homozygous for the deletion were observed along the study and the genotypic frequencies

were not in Hardy-Weinberg equilibrium and this may result from a sample bias, such as the selection of non-random samples, or problems in genotyping technique, for example due to non-specific amplification that masks the homozygosis of the del allele. However, it is worth mentioning that studies in the literature use distinct methodologies for allelic determination.

For comparison, the frequencies of the del/del genotype in other populations are shown in Table 2 and it can be observed that the frequencies can vary between 0.66% in Mexican population and 13.1% in African population.

The results obtained do not corroborate a correlation of the *NKG2C* gene deletion and susceptibility to lupus erythematosus systemic. More tests will be performed to confirm the genotypes. Further studies in different populations should be conducted to evaluate the importance of *NKG2C* deletion on SLE development.

## 4. ACKNOWLEDGEMENTS

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## 6. TABLES

Table 1. Clinical and demographic features of SLE patients and controls.

| Features | Patients n (%) | Controls n (%) |
|---|---|---|
| Women | 437 (92) | 172 (40.5) |
| Age (mean ± sd) | 47.50 ± 14.81 | 42.74 ± 10.25 |
| European-derived | 352 (74.4) | 322 (75.1) |
| African-derived | 121 (25.6) | 107 (24.1) |
| Nephritis | 203 (42.7) | |
| Anti-DNA | 226 (48) | |
| Anti-Sm | 96 (20.5) | |
| Anticardiolipin | 130 (28) | |
| Lupus anticoagulant | 41 (8.8) | |
| False-positive VDRL | 24 (5.2) | |
| Anti-Ro | 188 (41.9) | |
| Anti-La | 60 (13.4) | |
| Anti-RNP | 144 (32.1) | |
| Anti-Scl 70 | 13 (2.9) | |
| Active smoker | 181 (38.8) | |
| Ex-smoker | 106 (22.8) | |
| Alcoholism | 11 (2.4) | |
| LES history | 63 (13.8) | |
| Sjögren | 39 (8.7) | |
| SLICC* | 1 (0-2) | |
| SLEDAI* | 1 (0-4) | |

SLEDAI systemic lupus erythematosus disease activity index, SLICC systemic lupus international collaborating clinics, VDRL venereal disease research laboratory test. *Median (minimum - maximum).

Table 2. Frequencies of *NKG2C* del/del genotype in patients and controls.

| Population | Healthy n (%) | SLE n (%) |
|---|---|---|
| Japanese (Hikami et al, 2003) | 210 (4.3) | 114 (6.1) |
| Japanese (Miyashita el al, 2004) | 245 (4.1) | 155 (5.2) |
| Dutch (Miyashita el al, 2004) | 105 (3.8) | 89 (5.6) |
| North American (Zeng et al, 2013) | 493 (2.2) | |
| Mexican (Rangel-Ramírez et al, 2013) | 300 (0.66) | |
| West-African, Gambia (Goncalves et al, 2016) | 313 (13.1) | |
| East-African, Tanzania (Goncalves et al, 2016) | 244 (5.3) | |

## 3 CONCLUSÕES E PERSPECTIVAS

Lúpus eritematoso sistêmico é uma doença autoimune grave, cujos mecanismos fisiopatológicos ainda não estão completamente elucidados. O objetivo desse trabalho foi identificar se há relação entre a deleção do gene *NKG2C* e haplótipos de HLA-E com a susceptibilidade ao LES visando ampliar o conhecimento sobre essa doença e assim possibilitar novos meios de diagnóstico e tratamento. A genotipagem da deleção do gene *NKG2C* foi realizada em 326 indivíduos portadores de LES e 214 indivíduos controles saudáveis. Tendo em vista que as frequências genotípicas observadas não se encontravam em equilíbrio de Hardy-Weinberg, serão realizadas mais análises a fim de esclarecer esse resultado e não foram feitas correlações entre as frequências genotípicas com os sintomas e gravidade da doença.

Não foi possível a conclusão das genotipagens dos haplótipos de HLA-E, por se tratar de uma metodologia bastante complexa, que engloba múltiplas reações de PCR (as quais utilizam oito pares de primers, sendo sete pares para a identificação dos alelos e um par que atua como controle interno de amplificação [gene *human growth hormone*]). Sendo assim, as perspectivas desse trabalho incluem a genotipagem de HLA-E nesta mesma população. Os resultados das análises adicionais de *NKG2C* e da genotipagem dos haplótipos de HLA-E serão publicados nos próximos trabalhos produzidos pelo grupo de pesquisadores do Laboratório de Imunobiologia e Imunogenética.

O panorama atual dos estudos sobre lúpus eritematoso sistêmico compreende diversas pesquisas cujo objetivo é avaliar a interação entre os receptores NKG2C e HLA-E. Neste contexto, Lauterbach et al. (2015) observaram que a expressão de níveis basais de HLA-E não é capaz de ativar o NKG2C de maneira suficiente, a ativação ocorre somente quando o HLA-E está complexado ao peptídeo líder do HLA-G. Hagberg et al. (2015) identificaram a presença de anticorpos anti-NKG2C em indivíduos portadores de LES, sendo que estes anticorpos interferem tanto na interação do NKG2C com HLA-E quanto na função das células NK e induzem depleção de alguns subtipos dessas células.

Além disso, Joseph et al. (2018) observaram que há relação entre hipometilação de locais específicos do genoma com o índice de atividade da doença (SLEDAI) e etnicidade em pacientes portadores de LES. Há também estudos recentes relacionando deficiências do sistema complemento com o LES (HIRAKI; SILVERMAN, 2018) e identificação de miRNAs presentes no soro como biomarcadores para a doença (ZENG et al., 2018).

Em suma, muitos estudos têm sido realizados para elucidar o mecanismo fisiopatológico do lúpus eritematoso sistêmico. Sendo assim, a identificação de uma potencial relação entre a deleção do gene *NKG2C* e haplótipos de HLA-E com a susceptibilidade ao lúpus é uma abordagem experimental que poderá vir a contribuir de maneira substancial para a compreensão da doença.

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