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ORAL DISEASES

HLA-C/KIR GENOTYPES IN ORAL LICHEN PLANUS PATIENTS INFECTED OR NON INFECTED WITH HEPATITIS C VIRUS

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HLA-C/KIR GENOTYPES IN ORAL LICHEN PLANUS PATIENTS INFECTED OR NON INFECTED WITH HEPATITIS C VIRUS

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Running Title: OLP and HLA-C/KIR genotypes

Key words: KIR; Hepatitis C; Virus; Oral lichen planus

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Association of Oral Medicine. September 18-20, 2008 Salzburg, Austria

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5 **OBJECTIVES:** Oral Lichen Planus (OLP) is associated with hepatitis C virus (HCV) infection,
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7 and resembles graft-versus-host disease (GVHD) both clinically and histologically. The Killer Cell
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9 Immunoglobulin-like Receptor (KIR) genes encode a family of receptors expressed on NK and T
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11 cells and are supposed to play a significant role in GVHD and HCV infection. The aim of the present
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13 study was to analyze the association between OLP, HCV infection and variants in KIR gene
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15 expression.
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19 **METHODS:** 81 patients with OLP (36 HCV+ve and 45 HCV-ve) and 217 healthy controls (HCV-
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21 ve) were typed for the presence of eight KIR genes and of HLA-Cw* alleles by polymerase chain
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23 reaction-sequence specific primer.
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27 **RESULTS:** There were no significant differences in the frequency of the KIR genes and HLA-
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29 C1/C2 group alleles between cases and controls. We only found a significant difference in the
30
31 frequency of the gene KIR2DL2 between HCV +ve and HCV-ve OLP patients.
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34 **CONCLUSIONS:** The present data suggest that OLP is not associated with particular KIR genes or
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36 with HLA-Cw* alleles in patients without HCV infection. Contrarily, the role of those genes in
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38 OLP-HCV+ve patients is unclear and might warrant further researches.
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Introduction

Lichen Planus (LP) is a relatively common chronic inflammatory disorder affecting stratified squamous epithelia often involving predominantly or exclusively the oral cavity (Eisen *et al*, 2005; Scully and Carrozzo, 2008). LP results probably from an abnormal T-cell-mediated immune response in which basal epithelial cells are recognized as foreign because of changes in the antigenicity of their cell surface. In most of the cases the cause of this immune-mediated basal cell damage is still unknown (Lodi *et al*, 2005). There appears to be a genetic predisposition in some patients, as evidenced by frequent association of cutaneous idiopathic LP with the HLA-DR1 (DRB1*0101) allele (Powell *et al*, 1986; La Nasa *et al*, 1995).

Oral LP (OLP) resembles graft-versus-host disease (GVHD) both clinically and histologically (Thomas *et al*, 1996, Sato *et al*, 2006). OLP can be associated with hepatitis C virus (HCV) infection and this association seems to be the case in many, albeit not all, regions of the world. (Carrozzo, 2008; Shengyuan *et al*, 2009; Bigby, 2009; Lodi *et al*, 2010). Moreover the HLA-DR6 allele is significantly expressed in Italian patients with OLP and HCV (Carrozzo *et al*, 2001).

Natural killer (NK) cells represent a minor population of peripheral blood lymphocytes and major components of the innate immune system and are involved in both OLP and GVHD pathogenesis (Thomas *et al*, 1996; Parolini *et al*, 2007).

The function of NK cells in humans is regulated by a balance between opposite signals delivered by a set of HLA class I-specific inhibitory receptors and by a number of activating receptors and co receptors responsible for NK cell triggering (Lanier, 1998). By the combined use of these receptors, NK cells can discriminate between normal HLA class I⁺ cells and cells that have lost the expression of HLA class I molecules as a consequence of tumor transformation or viral infection (Lanier, 2005).

The Killer cell immunoglobulin like receptor (KIR) genes encode a family of inhibitory and activating receptors expressed on NK cells and on a subset of T cells (Moretta and Moretta, 2004). These receptors are transmembrane glycoproteins that have two or three extracellular Ig-like domains for binding MHC class I ligands, a stem region, and a signalling domain (the transmembrane region and cytoplasmic tail) for transducing either an inhibitory or activating signal. The KIR locus, containing a family of polymorphic and highly homologous genes, maps to chromosome 19q13.4 within the 1Mb leukocyte receptor complex (LRC). KIRs are likely to play a significant role in the control of the immune response: indeed, through their interaction with KIR isotypes that inhibit natural killer cell activity, certain HLA class I molecules are now known to protect healthy cells from spontaneous destruction by NK-cell-mediated cytotoxicity. In particular,

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3 within the HLA class I complex, the HLA-Cw* genes encode most of the inhibitory KIR ligands.
4 Binding with HLA-Cw antigens depend on the residue in position 80 and, on the basis of aminoacid
5 at this position (asparagine-N- or lysine-K), these antigens are considered respectively belonging to
6 C1 or C2 group (Moretta and Moretta, 2004; Carrington and Norman, 2003) (Table 1). However, on
7 the basis of the presence or absence of the KIR genes 2DL1, 2DL2, 2DL3, it was possible to outline
8 some different KIRhaplotypes: A, AB, B, C (Table 2).

9
10 The possible role of KIR genes in HCV infection (Khakoo *et al*, 2004) and in the onset of GVHD
11 (Sun *et al*, 2005) has been reported in literature. Particularly, genes encoding the inhibitory NK cell
12 receptor KIR2DL3 and its human leukocyte antigen C group 1 (HLA-C1) ligand directly influence
13 resolution of HCV infection (Khakoo *et al*, 2004). On the other hand, mismatches of particular
14 activating KIRs such that the patient was negative and the donor was positive (P-D+) resulted in
15 increased risk of acute (KIR2DS1) and chronic (KIR2DS3) graft-versus-host disease (GVHD)
16 (Giebel *et al*, 2009).

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18 The aim of our study was to analyze the association between OLP, HCV infection and variants in
19 KIR gene expression.
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26 27 28 29 30 31 32 33 **Patients and methods**

34 35 *Patients*

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37 In our study the patient group included 81 Italian patients (48 women and 33 men; median age 58
38 years, range 27-80 years) recruited between January 2000 and January 2001 at the Oral Medicine
39 Section of the Department of Biomedical Science and Human Oncology of the University of Turin.
40 Clinical diagnosis was always confirmed histologically. No patient was suspected to have drug- or
41 restoration-related lichenoid lesions, and no patients presented histological signs of dysplasia.
42

43 Thirty-six consecutive patients had OLP with HCV infection (OLP-HCV+ve), whereas an age, sex
44 and clinical comparable disease control group of 45 OLP patients did not have HCV infection
45 (OLP-HCV-ve). Other causes of liver disease (such as autoimmune hepatitis, coinfection with
46 other hepatotropic viruses, drugs hepatotoxicity, etc.) were excluded, as described elsewhere
47 (Carrozzo *et al*, 1996).
48

49 The control group included 217 unrelated healthy (HCV-ve) Italian individuals randomly selected
50 from 22 immunogenetics laboratories located in northern, central and southern regions of Italy and
51 already comprised in another study about KIR genes typing in Italian Caucasic population
52 (Bontadini *et al*, 2006).
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3 Patients and controls were all Italian and their geographic origin had been carefully checked to
4 compare subjects from the same area. Patient's informed consent and approval from ethical
5 committee of the University of Turin were obtained.
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10 11 12 Virologic Assessments

13 The presence of serum anti-HCV antibodies (HCVAb) was determined by second or third
14 generation ELISA (Enzyme-Linked Immunoabsorbent Assay, Ortho Diagnostic Systems, Raritan,
15 NY, USA) and results confirmed with second or third generation RIBA (Recombinant Immunoblot
16 Assay; Ortho Diagnostic and Chiron Corp, Emeryville, CA, USA). Moreover, HCV-RNA was
17 detected by RT-PCR (Reverse Transcription Polymerase Chain Reaction; Amplicor, Roche
18 Diagnostic Systems, Branchburg, NY, USA).
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26 KIR typing and HLA-C1/C2 group determination

27 In order to analyse KIR/HLA-Cw* genes, DNA of our samples was previously extracted from
28 peripheral blood samples drawn in EDTA (ethylenediaminetetraacetic acid) anticoagulant tubes
29 using a micro salting-out procedure (Miller *et al*, 1988). The DNA concentration and the ratio were
30 evaluated.
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35 KIR typing and C1/C2 group determination of HLA-Cw* alleles were performed by the PCR-SSP
36 (Polymerase Chain Reaction-Sequence Specific Primers) method. Specific primer sequences for the
37 KIR genes 2DL1, 2DL2, 2DL3, 2DL4, 2DS1, 2DS2, 3DL1 were deduced from the literature
38 (Gomez-Lozano and Vilches, 2002), whereas for 3DL2 gene and HLA-Cw* alleles they were
39 designed following the Genbank protocol to design primers for cDNA.
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44 PCR products were transferred to the well of a 2% agarose gel. The DNA separation was performed
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46 photographed.
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49 All 81 patients were typed for KIR genes and analyzed for HLA-C1/C2 group determination; as
50 mentioned, all controls were previously typed for KIR genes within the Italian multicentre study,
51 whereas we recruited only 46/217 controls, whose DNA was available or isolated *de novo*, for
52 C1/C2 group determination.
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57 58 Statistical analysis

59 Frequencies of KIR genes and HLA-C alleles were determined by direct counting. In this study we
60 compared the frequency of the single KIR genes and HLA-C alleles between the cases and the

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3 control group and, within the cases, between the following different subgroups: HCV+ve/HCV-
4 ve;erosive OLP/non-erosive OLP; just oraloral/mucocutaneous LP as previously defined (Carrozzo
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8 *et al*, 2001). We also compared the frequency of the different KIR haplotypes (A, B, AB, and C)
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10 between the same groups. Differences in frequency between different groups were compared by the
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12 Chi-square test using the Statistical Package for Social Sciences (spss) software program (version
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14
15 12, Chicago, IL, USA). Corresponding P-values were considered significant at values < 0.05.
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18 **Results**

19 Single KIR genes frequency

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23 There were no significant difference in the frequency of KIR genes between the OLP subjects and
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25 the healthy controls (Table 3). Similarly no significant difference was found comparing erosive
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27 OLP with non-erosive OLP (data not shown) or comparing exclusive oral LP patients with
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29 mucocutaneous LP patients (Table 3). We only found a significant difference ($p = 0.0326$) in the
30
31 frequency of KIR2DL2 and a trend towards significance in the frequency of 2DS2 ($p = 0.0655$)
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33 between HCV seronegative OLP and HCV seropositive OLP patients (Table 3).
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39 HLA-C alleles frequency

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42 We did neither find any significant differences in the frequency of HLA-C1/C2 alleles between
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44 cases and controls nor between any of the subgroups compared (Table 4).
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49 KIR haplotypes frequency

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52 There was neither significant difference in the frequency of KIR haplotypes between OLP patients
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54 and the controls nor in the subgroups (data not shown).
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Discussion

The aetiology of OLP has not been fully elucidated. Studies have suggested the presence of a genetic predisposition to the development of OLP (Scully *et al*, 1998). Most idiopathic cutaneous LP world-wide is in fact related to the HLA-DR1 (DRB1*0101 allele), whereas in Italy HCV-related OLP appears to be particularly associated with the HLA class II allele HLA-DR6. Moreover a significant association was found between erosive OLP and HLA-DR3 allele (Carrozzo *et al*, 2001; Jontell *et al*, 1987).

NK cells are important components of the innate immune response (Williams *et al*, 2005). NK cells are regulated in part by inhibitory receptors that recognize MHC class I molecules on normal cells. In humans, inhibitory receptors that recognize classical MHC class I molecules belong to the KIR family. The reason for KIR diversity and the contribution of individual KIRs to signalling in NK cells and T cells are not fully understood, but their importance has been underscored by several recent genetic studies which have linked combinations of KIR and HLA genes with the outcome of various diseases (type I diabetes, psoriatic arthritis, HCV infection and others). Associations with different KIR-HLA combinations, involving activating KIR or inhibitory KIR genes to different extents, have been described. These data suggest that diseases can be modified by specific KIR-ligand interactions, rather than by global responsiveness of NK cells or T cells (Rajagopalan and Longo, 2005). In particular, many studies suggest the presence of an association between KIR genes (especially activating KIR genes) and diseases characterized by an alteration of the immune response like rheumatoid arthritis, scleroderma, lupus erythematosus, psoriasis, type I diabetes (Williams *et al*, 2005; Yen *et al*, 2006; van der Silk *et al*, 2003; Momot *et al*, 2004; Pellet *et al*, 2007). It is probable that activating KIR may synergize with TCR-mediated signals to cause aberrant immune activation and autoimmune reactions. Moreover, activating KIR would stimulate cytokine production by NK cells, which contributes to inflammation. (Rajagopalan and Longo, 2005).

A possible role of KIR genes in the pathogenesis of LP has not been investigated so far. However an association appears to be present between KIRs and GVHD (Sun *et al*, 2005) whose aspect is very similar to OLP, both clinically and histologically (Sato *et al*, 2006). Moreover KIR genes appear to be involved in the pathogenesis of diseases often associated with OLP, such as HCV infection and diabetes mellitus (Khakoo *et al*, 2004; van der Silk *et al*, 2003), and an altered activity of NK cells in LP patients has been suggested (Hunyadi *et al*, 1986).

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3 In our study we did not find any significant differences in the KIR genes frequency between OLP
4 cases and healthy controls. We only found a significant difference in the frequency of the gene
5 KIR2DL2 between HCV+ve and HCV-ve OLP patients. However this significant result is probably
6 just due to the chronic HCV infection. In fact the low frequency of KIR2DL2 observed in HCV+ve
7 OLP patients has been yet correlated with a persistent HCV infection (Montes-Cano *et al*, 2005).

8
9 These data may suggest that in the patients with OLP and HCV infection the virus persistence could
10 exert a chronic immunological pressure which could contribute to the onset of the OLP lesions.
11 However, this hypothesis is entirely speculative because in the present study no HCV+ve controls
12 without OLP have been included.

13
14 Contrarily, the analysis of the HLA-Cw* genes has not pointed out any significant results,
15 suggesting that the onset of OLP is not correlated with particular HLA-Cw* ligands.

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17 In conclusion, the results of the present study suggest that KIR and HLA-Cw* genes are not
18 involved in the pathogenesis of OLP without HCV infection whereas the role of those genes in OLP-
19 HCV+ve patients is unclear and might warrant further researches.

20 21 22 23 24 25 26 27 28 29 30 31 **Acknowledgements**

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33 Sciences and Human Oncology, University of Turin

34 35 36 37 **Author Contributions**

38 M Carrozzo and A Amoroso have designed the study. A Elia, R Broccoletti and M Carrozzo
39 collected the blood samples. V Mereu, E Dametto and ME Fasano made the laboratory
40 investigations. S Rendine made the statistical analysis. A Elia and M Carrozzo wrote the paper.

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Table 1- HLA-Cw alleles according to C1 and C1 grouping

Group HLA	HLA- Cw Alleles
C1 group *	01, 03, 0411, 0429, 0611, 07, 08, 12, 14, 1507, 16
C2 group **	0114, 02, 0307, 0310, 0315, 0329, 0345, 04, 05, 06, 0707, 0709, 0810, 1204, 1205, 1209, 1221, 15, 1602, 1609, 17, 18

* Ligands to KIR: 2DL2, 2DL3, 2DS2

**Ligands to KIR: 2DL1, 2DS1

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Table 2. KIR haplotypes

Haplotypes	KIR Genes		
	2DL1	2DL2	2DL3
A	+	-	+
B	-	+	-
AB	+	+	+
C	+	+	-
C	-	+	+
C	-	-	+
C	-	-	-

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Table 3. Difference in the frequency of KIR genes between the OLP group and Controls and in OLP subgroups

KIR	Observed Frequency		P
	OLP N=81 (%)	Controls N=217 (%)	
2DL3	67 (82.72)	192 (88.48)	0.189
2DS2	43 (53.09)	115 (53)	0.989
2DL2	40 (49.38)	115 (53)	0.579
2DL1	77 (95.06)	208 (95.85)	0.766
2DL4	81 (100)	216 (99.54)	0.540
3DL1	74 (92.5)	210 (96.77)	0.110
2DS1	31 (38.27)	79 (36.41)	0.766
3DL2	81 (100)	217 (100)	-
	OLP HCV+ve N=36 (%)	OLP HCV-ve N=45 (%)	
2DL3	31 (86,11)	36 (80)	0,4698
2DS2	15 (41,67)	28 (62,22)	0,0655
2DL2	13 (36,11)	27 (60)	0.0326
2DL1	33 (91,67)	44 (97,78)	0,2072
2DL4	36 (100)	45 (100)	-
3DL1	34 (94,44)	40 (90,91)	0,5503
2DS1	12 (33,33)	19 (42,22)	0,4134
3DL2	36 (100)	45 (100)	-
	Mucocutaneous LP N=17 (%)	Pure OLP N=64 (%)	
2DL3	13 (76.47)	54 (84.38)	0.444
2DS2	11 (64.71)	32 (50)	0.280
2DL2	9 (52.94)	31 (48.44)	0.741
2DL1	15 (88.24)	62 (96.88)	0.144
2DL4	17 (100)	64 (100)	-
3DL1	15 (88.24)	59 (93.65)	0.4519
2DS1	9 (52.94)	22 (34.38)	0.1615
3DL2	17 (100)	64 (100)	-

Table 4- Frequencies of HLA- C1/C2 antigens in cases and controls and in the subgroups analysed

HLA-Cw	Observed Frequency		P
	OLP N=81 (%)	Controls N=46 (%)	
Group 1	30 (37,04)	16 (34,78)	0,3686
Group 2	10 (12,35)	10 (21,74)	
Group 1/2	41 (50,62)	20 (43,48)	
	OLP HCV+ve N=36 (%)	OLP HCV-ve N=45 (%)	0.9301
Group 1	13 (36.11)	17 (37.78)	
Group 2	5 (13.89)	5 (11.11)	
Group 1/2	18 (50)	22 (51.11)	
	Mucocutaneous LP N=17 (%)	Pure OLP N=64 (%)	0.7553
Group 1	6 (35.29)	24 (37.5)	
Group 2	3 (17.95)	7 (10.94)	
Group 1/2	8 (47.06)	33 (51.56)	