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POLYMORPHISMS IN CCL2&CCL5 CHEMOKINES/CHEMOKINE RECEPTORS GENES AND THEIR ASSOCIATION WITH DISEASES

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Background: Chemokines and chemokine receptors are major mediators of leukocyte trafficking into the sites of the immune response. They participate in defence against microbial infection, in Th1/Th2 polarization of the immune response, allograft rejection and angiogenesis/angiostasis as well as in tumorigenesis and metastasis. To date, several functional polymorphisms of chemokine and chemokine receptor genes have been discovered that are able to deregulate chemokine system and, therefore, they may interfere with the pathogenesis of a large number of inflammatory and other diseases. In this review we focus on the known polymorphisms of two chemokines: CCL2, CCL5 and their corresponding receptors (CCR2, CCR5) and we also discuss their associations with susceptibility and progression to selected immune-mediated diseases.

Methods And Results: Based on relevant literature this article gives a short overview of case-control and family studies regarding effect of the genetic factors on diseases such as coronary artery disease, systemic lupus erythematosus, diabetes mellitus, lung diseases and others.

Conclusion: Recent advance in the identification of chemokine genetic background of the diseases could provide opportunity for pharmacological treatment. However, we need more information about posttranscriptional events to understand functional relevance of polymorphisms and to discovery new avenues to blocking disease development.

INTRODUCTION

Chemokines are low-molecular-weight molecules characterized by the presence, as a common structural pattern, of four cysteine residues and are divided into four main families (CXC, CC, C and CX3C) according to the number of amino acids between the residues of the two most amino-proximal cysteines[1,2].

Chemokines are trophic molecules; that is, they signal leukocytes to move in a specific direction, along gradient of chemokine concentration. Besides this, they are also involved in various processes unrelated to leukocyte migration, including cell proliferation and direct activation of mast cells, basophils, fibroblasts and others. In addition, chemokines can affect Th1/Th2 polarization of the immune response[1,3]. Chemokine-induced signalling is mediated by a group of G protein-coupled receptors. Based on the sequence homology, two major chemokine receptor groups have been described: the CCR and the CXCR receptors.

Up- or down-regulation of chemokine and chemokine receptor expression has been observed in broad range of inflammatory and autoimmune diseases and is thought to be able to affect disease susceptibility, progression as well as severity. Recently, several polymorphisms have been shown to be responsible for the chemokine deregulation *in vitro* and *in vivo*[4,5,6,7].

DNA polymorphism is defined as a DNA sequence variation in the population with the frequency of the rare allele equal to 1 percent or higher. A single nucleotide polymorphism (SNP), originating from one nucleotide substitution, can increase or decrease transcription activity if it is located in the regulatory region of the gene. Nucleotide substitutions or insertions/deletions in the coding sequences of genes can cause qualitative changes of proteins. Accordingly, several polymorphisms in the genes encoding proteins important in the pathogenesis of particular diseases have been associated with disease susceptibility or severity. This review is focused on the known polymorphisms of two chemokines: CCL2, CCL5, their corresponding receptors (CCR2, CCR5) and their associations with diseases. Some of these associations are listed in Table 1.

1. CCL2/MCP-1 (Monocyte chemoattractant protein-1)

1.1 Biological function of CCL2

CCL2 is the member of the CC chemokine subfamily characterised by the absence of amino acid between conserved cysteines at amino-terminal end of the molecule. The concentration gradient of CCL2 is responsible for the movement of mononuclear cells, mainly monocytes/

Table1. CCL2, CCL5, CCR2 and CCR5 polymorphisms and their associations with particular diseases. The numbers in cells response studies of reference list.

Disease	Association	MCP-1-2518 and other# polymorphisms	CCR2V64I and others# polymorphisms of CCR2	CCL5 polymorphisms (RANTES -403*, -28+, others#)	CCR5 polymorphisms (CCR5Δ32*, others#)
Atherosclerosis	No	23	15, 56, 143		
Atherosclerosis in HIV-infected patients	Yes	144			
Coronary artery disease	Yes	15		16*	
	No	16	15	15*+	15*, 16*
Myocardial infarction	Yes	39	54, 143		55*
	No	18#	18, 55		108*
Stroke history	Yes	17			
Coronary Artery Calcification	Yes		56		109*
Abdominal aortic aneurysma	Yes				107*
Multiple sclerosis	Yes		61	78*+	62*110*, 111*, 112*, 114*
	No	23	62		113*
Systemic sclerosis	Yes	24			
Rheumatoid arthritis	Yes	25		99*+, 100*	115*, 116*, 117*
	No	26			
Asthma and atopy	Yes	20		80*, 81*, 82*+, 83+	119*
	No	145		20*+, 83*, 84*+	120*, 121*
Atopic eczema/dermatitis syndrome, atopic dermatis	No	21		21*+	
Pulmonary sarcoidosis	Yes		57, 59#		58*, 118#
	No	22	44#, 58	86*	
Type 1 diabetes	Yes				131*, 132*#
Type 2 diabetes	Yes	36		77*#	131*
		77		77+	
Diabetic nephropathy	Yes			92+#	133#
	No		133	92*	
Hepatitis C virus infection	Yes	40, 41		72*, 96*	71*, 72*, 134*, 135*
	No	72	71, 72	71*	96*
Kidney graft rejection	Yes	69			138#

Table 1. *Continues*

Liver graft rejection	Yes				139*
	No	39	68	39*+, 98*+	39*, 68#
Renal graft rejection	Yes		70		70#
	No		38		70*
Heart rejection	Yes			69*	137*, 69#
	No		69		
Systemic lupus erythematosus (SLE)	Yes	35		93+, 94*+	
	No	93	140	93*	140*
Lupus nephritis	Yes	34, 35			140*
Alzheimer's disease	Yes	42			
	No	42			
Dementia or neurocognitive impairment in HIV-1 infected patients	Yes	27			129*
Breast cancer	Yes	37	73		141*
	No			37*	73*#, 37*

macrophages, to sites of inflammation[1,2]. CCL2 is produced by a variety of cell types, including macrophages, lymphocytes[2], neutrophils[8], vascular endothelial cells[9], fibroblasts, keratinocytes[10] and several cancer cell lines[11]. These immune and non-immune cells produce CCL2 in response to stimulation by a broad area of mediators including cytokines[9], growth factors[10,12] and lipopolysaccharides[8] suggesting an CCL2 role in host defence against bacteria.

1.2 CCL2 gene and its polymorphisms

1.2.1 Localisation

Mehrabian *et al.* localized the gene for CCL2 on chromosome 17. By *in situ* hybridization, they localized the gene to 17q11.2–q21.1[13]. By a combination of *in situ* hybridization and a study of somatic cell hybrids, Rollins *et al.* assigned the gene to 17q11.2–q12[14]. They pointed out that CCL2 belongs to a family of cytokines which can be grouped into 2 subfamilies based on structure and chromosomal location, namely 17q and 4q[14].

1.2.2. Polymorphisms

In this study we summarise current data for seven MCP-1 polymorphisms that have been studied in relationship to disease susceptibility or severity. Four have been described in the distal regulatory region of the MCP-1 gene: –1811 A/G, –2136 A/T, –2518 A/G, –2835 C/A; one in promoter region: –927 G/C; one in the first intron: 764 C/G and one in the 3' flanking region: 3726 T/C. These seven CCL2 SNPs delineate 6 common haplotypes (H1 through H6)[4].

Four of the above mentioned SNPs (–2136*T, –2518*G, –2835*A, 764*G) in the CCL2 gene were found to be associated with increased levels of MCP-1 protein[4]. To our knowledge, the majority of case-control studies concentrated on the MCP-1-2518 SNP and, therefore, we will mainly focus on the relation of this polymorphism to disease pathophysiology.

1.3 Diseases associated with MCP-1-2518 SNP and other SNPs in the gene encoding CCL2 chemokine

1.3.1 Atherosclerosis and myocardial infarction (MI)

CCL2 is thought to play an important role in initiating and mediating atherosclerosis: circulating blood monocytes recruited to the cell wall serve as the precursors of the foam cells that form fatty streaks–the hallmark of early atherosclerotic lesions[3]. Moreover, CCL2 might also contribute to the thrombotic aspects of advanced atherosclerotic lesions, a late complication of atherosclerosis responsible for myocardial infarctions and strokes[3]. In addition, CCL2 expression is up-regulated in human atherosclerotic plaques[3] suggesting that genetic factors leading to deregulation of CCL2 production could affect development of atherosclerosis and atherosclerosis-associated diseases. In this context Szalai *et al.* found the frequency of the MCP-1-2518*G allele homozygotes significantly higher in coronary artery disease (CAD) patients than in healthy controls[15]. However, this association was not replicated in the subsequent larger study[16]. The higher prevalence of MCP-1-2518*G homozygotes was observed in patients with history of stroke[17] and myocardial infarction[4]. In agreement with the report of Simeoni[16],

MCP-1-2518 SNP was not associated with ischemic heart disease in an Irish population[18].

1.3.2 Lung diseases

In 1997 a genome-wide search found evidence for linkage of asthma to chromosome 17p11.1-q11.2 (CC chemokine cluster)[19]. Subsequently, several studies were conducted to explore possible association of MCP-1-2518 A/G SNP with asthma. In 2001 Szalai *et al.* showed higher prevalence of MCP-1-2518*G allele in asthmatic children than in controls and nonasthmatic atopic children[20]. In addition, the GG genotype correlated with asthma severity and the G allele was associated with increased blood eosinophil levels[20]. However, there was no association between MCP-1-2518 and atopic eczema/dermatitis syndrome or allergy in a cohort of Hungarian children[21].

In case of sarcoidosis, MCP-1-2518 does not play a substantial role in the disease susceptibility, but might be related to the recruitment of monocytes/macrophages to the alveolar spaces in Japanese patients with sarcoidosis[22].

1.3.3 Systemic sclerosis (SSc)

SSc is an autoimmune disease of the skin or internal organs and is characterized by increased synthesis of connective extracellular matrix. Karrer *et al.* found that homozygotes for MCP-1-2518*G allele were more common in SSc patients compared to controls[24].

1.3.4 Rheumatoid arthritis (RA)

MCP-1-2518 A/G polymorphism is associated with the susceptibility to RA in patients lacking the specific HLA epitope, which is the risk factor for RA acquiring[25]. When patients were not stratified according to the HLA status, distribution of MCP-1-2518 A/G polymorphism was similar in patients and healthy controls[26].

1.3.5 HIV infection

Associations of genetic polymorphisms with HIV-1 infection have been intensively studied predominantly for the chemokine receptors, but only a few studies on chemokine genes exist. Gonzalez *et al.* reported decreased risk of acquiring HIV-1 in homozygotes and heterozygotes for the MCP-1-2518*G allele[27]. The protective effect could be mediated through CCL2 overproduction[28] limiting HIV infection access to CCR2 that is a minor co-receptor for HIV[29]. On the other hand, homozygosity for MCP-1-2578*G was also associated with accelerated progression to AIDS and death[27]. Additionally, the association of higher CCL2 level with more advanced HIV disease was described[30]. Gonzalez *et al.* summarized that CCL2 can attract HIV infected macrophages that may disseminate the virus to different organs[27]. Thus, CCL2-mediated recruitment of macrophages and activation can also fuel HIV-1 pathogenesis. These findings indicated that the beneficial influence of MCP-1-2518 SNP does not occur once HIV-1 infection is established[27].

There is evidence implicating the MCP-1-2518*G allele as a critical factor in the pathogenesis of various diseases accompanying HIV infection. Thus, the study by Alonso- Alonso-Villaverde *et al.* showed that HIV-infected patients with the MCP-1-2518*G allele have a 5-fold increased risk for atherosclerosis[144]. Furthermore, GG homozygotes had 4.7-fold higher likelihood of developing HIV-associated dementia[27]. Higher levels of CCL2 chemokine in cerebrospinal fluid[27, 28] can increase the capacity of HIV-infected leukocytes to transmigrate through the blood-brain barrier[31]. By contrast, Singh *et al.* failed to find any association of MCP-1-2518 A/G SNP with neuropsychological impairment in HIV patients[32]. In addition, Modi *et al.* studied two other CCL2 SNPs (-2136 A/T located in the promoter region and 767 C/G located in intron 1) and described elevated H7 haplotype (MCP-1-2136*T and 767*G with -1385*A in the Eotaxin promoter) in uninfected European-Americans repeatedly exposed to HIV-1 through high-risk sexual behaviour or contaminated blood products[33].

1.3.6 Systemic lupus erythematosus (SLE)

Two papers have reported an association of MCP-1-2518 A/G polymorphism with clinical manifestation of SLE in terms of renal involvement toward lupus nephritis[34, 35]. In addition, Tucci *et al*. suggest that an A/G or G/G genotype may predispose to the development of SLE[35].

1.3.7 Other diseases

Tumor infiltrating lymphocytes and tumor associated macrophages are thought to play a crucial role in tumour immune surveillance and development. In breast cancer patients, Ghilardi *et al* found no differences in the distribution of MCP-1-2518 A/G variants compared with controls[37]. However, the authors observed a correlation between the presence of at least one G allele and the presence of metastasis[37]. Considering involvement of leukocyte infiltration in allograft rejection, detection of genetic markers for CCL2 upregulation could also be helpful for predicting the outcome of transplantation. In this context, Kruger *et al.* showed that MCP-1-2518 GG genotypes of kidney graft recipient reduce long-term graft survival[38]. On the other hand, Schroppel *et al.* genotyped liver transplant recipients for MCP-1-2518 SNP and failed to show any association with the incidence of acute rejection episodes or long-term liver graft survival[39].

Muhlbauer *et al.* investigated the correlation of MCP-1-2518 A/G SNP with hepatic CCL2 expression and disease outcome in patients with hepatitis C. MCP-1-2518*G allele carriers were more common in hepatitis C virus (HCV) infected patients with more advanced fibrosis and severe inflammation[40]. In contrast, subsequent study showed that the frequency of the G allele and the G allele carriers were decreased in chronic HCV infection and the differences were not observed when compared to patients with or without cirrhosis[41].

In an Italian population, MCP-1-2518 GG genotype and G allele were associated with Alzheimer's disease[42], but this data was not confirmed in Spanish population[42].

2. CCR2

2.1 Biological function of CCR2

CCR2 is a promiscuous CC chemokine receptor with an affinity for CCL2, CCL7, CCL8 and CCL13 ligands[1,43]. CCR2 is mainly expressed by memory T lymphocytes, monocytes, dendritic cells, B cells and basophils. Neutrophils also can express CCR2 but only under specific conditions[1,43].

CCR2 has two isoforms, CCR2A (360 amino acids) and CCR2B (374 aa), which differ only in their terminal carboxyl tails. These amino acid sequences located in the terminal carboxyl tail determine good CCR2B transportation to the cell surface, whereas the major part of CCR2A is located in the cytoplasm. CCR2B is the predominant isoform in monocytes and the levels of both CCR2A and CCR2B decrease as the monocytes differentiate into the macrophages.

2.2. CCR2 gene and its polymorphisms

2.2.1 Localisation

The CCR2 gene is located on chromosome 3p21-p24 in a CC chemokine receptor cluster in proximity to the CCR1, CCR3, CCR4, and CCR5 genes[43].

In this review we discuss in total nine biallelic CCR2 SNPs, in which relationship with varied disease susceptibility or severity was studied. They are located in the CCR2 gene at the following nucleotide positions: -6928 G/T, -6752 A/G, 190 G/A, 840 C/T, 3000 A/G, 3547 T/C, 3610 A/G, 3671 C/G, 4385 T/A. Apart from SNP 840 C/T, the remaining eight SNPs form nine haplotypes (haplotypes 1–9)[59]. In addition, a complete linkage disequilibrium between 840 C/T and 4385 A/T variants has been shown by Valentonyte *et al*.[44].

2.2.2 CCR2V64I polymorphism and its functional consequence

The mostly studied CCR2 SNP is 190 G/A located in exon 1. It has been shown that its distribution is strongly dependent on ethnicity[45,46,47,48]. Its mutation leads to the substitution of valine by isoleucine (V64I) in the transmembrane region of the protein. Data on the influence of this SNP on the expression of CCR2 are controversial. In the literature there are both evidence for CCR2V64I function[49] as well as lack of effect on CCR2 expression[50]. Nakayama *et al.* observed up-regulation of CCR2A-64I compared to CCR2A without substitution[49]. Accordingly, a chemotaxis assay showed that cells expressing CCR2A-64I migrated more efficiently than those expressing CCR2A-64V, in spite of the fact that CCR2A mostly localized in cytoplasm and only a small portion observed on the cell surface. By contrast CCR2B expression was not affected by this mutation. Furthermore, pulse–chase experiments have revealed that higher expression of CCR2A-64I was due to increased stability of CCR2A-64I[49]. Although these data suggest an association of CCR2V64I with increased CCR2A expression on the cell surface, it does not seem to be a unique property of this SNP. In parallel, the authors also measured CCR5 surface expression that was more severely blocked by co-expression of CCR2A-64I than by CCR2A-64V. Furthermore, this negative effect of CCR2A on CCR5 expression was shown to arise from the possibility of heterodimer formation between CCR2A and CCR5. CCR2A has been even suggested to recognise CCR5 in immature form and may interfere with the maturation process of CCR5 molecules in the cytoplasm. Similarly, HIV-1 co-receptor activity of CCR5 was more dramatically reduced by co-expression of CCR2A-64I than by co-expression of CCR2A-64V. Taken together, the authors concluded that CCR2A-64I polymorphism modulates CCR5 surface expression[49]. By contrast, a previous study showed that CCR2V64I mutation does not affect the surface expression or co-receptor activity of CCR5 on co-transfected cell lines[50]. Although CCR2V64I slightly decreased CCR5 expression levels in CD4+T and peripheral blood mononuclear cells, this difference was not statistically significant[50,51]. Nakayama *et al.* speculated that the negative effect of CCR2V64I on CCR5 expression could be limited to specific cell types[49]. Moreover, one study suggested that surface CCR5 expression appears to be a poor predictor of either its internalization or reexpression. In this context, CCR2V64I polymorphism was indicated to decrease CCR5 reexpression after ligand-induced internalization in $CD4^+$ T cells[52].

2.3 Diseases associated with CCR2 polymorphisms

2.3.1 Atherosclerosis and MI

Ortlepp *et al.* studied CCR2V64I SNP distribution in patients with MI and atherosclerosis[53]. The authors found that CCR2 VI/II genotypes were significantly associated with MI in patients younger than 65 years[53]. Similarly, the relationship of VI genotype with an early onset of MI in females was reported[54]. In both studies, age limitation is in agreement with the recent hypothesis that genetic factors may have impact on MI patients with onset only before the age of 65 years[53,54]. In contrast, no association of this SNP with MI was found in Spanish or Icelandic cohorts[18,55].

Additionally, patients with the rare allele CCR2-64I have less coronary artery calcification[56], but there was no association of the CCR2 genotype with coronary atherosclerosis[53].

2.3.2 Lung diseases

To date, four reports studying the CCR2 gene in association with sarcoidosis exist. In Japanese patients, CCR2-64I reduced the risk of sarcoidosis[57], but this observation was not confirmed in Czech or Dutch patients[44,58]. Valentonyte *et al*. also found no association with other CCR2 SNPs (190 G/A, 840 C/T or 4385 A/T) and sarcoidosis[44]. Association of CCR2-haplotype 2 (A at nucleotide position -6752, A at 3000, T at 3547, and T at 4385) was observed in patients presenting with Löfgren's

syndrome, an acute form of sarcoidosis[59]. To date there are no data of possible association of CCR2V64I SNP with pulmonary fibrosis or asthma.

2.3.3 Multiple sclerosis (MSc)

In vitro studies have shown that CCL2/CCR2 interaction induces efficient transmigration of mononuclear cells across the microvascular endothelial layers of the brain[60]. The most frequently studied CCR2V64I SNP could, therefore, affect the inflammatory process of MSc. CCR2-64I/64I genotype was shown protect against the development of MS in a Japanese population[61]. However, the authors found no association between genotypes and age at disease onset, disease progression index or clinical course such as relapse-remission or secondary progressive course. They speculate that this protection may be through intracellular interactions of mutant proteins with other chemokine receptors, such as CCR5, which influence MSc pathogenesis[61]. It is also possible that a mutation in another region of CCR2 may be directly responsible for the protective effect, because there was no association of CCR2V64I with MSc in a family-based study of Canadian patients[62]

2.3.4 HIV infection

CCR2 is utilized as a minor HIV co-receptor with no exactly established tropism. CCR2-64I variant is thought to provide protection against progression to AIDS, but it does not influence the acquisition HIV-1 infection[45, 63, 64, 65, 66]. A recent study even reported CCR2V64I SNP association with HIV-1 infection susceptibility[67].

2.3.5 Other diseases

CCR2V64I mutation had no effect on kidney, liver or heart graft failure[38, 68, 69]. However a significant reduction in the risk of acute renal transplant rejection was found in recipients who possessed the CCR2-64I allele[70]. Further, CCR2V64I was explored in patients infected with hepatitis C virus (HCV) and negative results were reported[71, 72]. Furthermore, current findings suggest that CCR2V64I polymorphism might have a protective role against breast cancer development[73].

2 CCL5/RANTES (RANTES, Regulated upon Activation, Normal T cell Expressed and Secreted)

3.1 Biological function of CCL5 chemokine

CCL5 is a potent chemoattractant for memory T lymphocytes, monocytes and eosinophils[1], its function is not only mediated by CCR5 but also CCR1, CCR3 and other receptors[1]. CCL5 was found to be highly expressed in activated T lymphocytes, macrophages, fibroblasts, platelets, mesangial cells, epithelial cells, megakaryocytes and some tumours[1].

3.2 CCL5/RANTES gene and its polymorphisms

The CCL5 gene is located on the short arm of chromosome 17(17q11.2-q12)[1].

This part of the review combines data on seven SNPs within the CCL5 gene: four SNPs located in the promoter region: -28 C/G, -109 C/T, -105 C/T, -403 G/A; two SNPs in the first intron: Int1.1 T/C and Int1.2 G/A and one SNP in an Alu-related repeat area of the 3' untranslated region: 3' 222 T/C. Four of the above mentioned SNPs (-403 G/A, -28 C/G, In1.1 T/C, and 3'222 T/C) form 5 common haplotypes with the most frequent being the haplotype 1 with the common alleles at positions -403, -28, In1.1, and 3'222[6]. It should be noted that the haplotype distribution is dependent on ethnicity[5, 76].

The functional effect of RANTES-403 G/A, -28 C/G and In1.1 T/C SNPs was confirmed in several reporter assay systems[5, 6].

3.3 Diseases associated with CCL5 polymorphisms

3.3.1 Atherosclerosis

When Simeoni *et al.* explored distribution of RANTES-403 G/A in coronary artery disease (CAD), -403*A variant was associated with increased risk of CAD and it remained significant after multivariate adjustment[16]. Furthermore, Boger *et al.* reported an association of cardiovascular events as main cause of mortality in patients with type 2 diabetes with carriage of RANTES-403*A or In1.1*C alleles[77].

3.3.2. Multiple sclerosis (MSc)

A case-control study showed that RANTES-403 G/A polymorphism is associated with more than double higher risk of susceptibility to MSc. RANTES-28 G/C is associated with both early onset and longer survival of MSc patients[78].

3.3.3 Lung diseases

The airway inflammation characteristic for asthma involves CCL5 up-regulation leading to associated tissue eosinophilia. Furthermore, the genome-wide search for asthma and atopy susceptibility genes points to the CCL5 gene[79]. In this context, a case-control study found that RANTES-403*A allele increases disease susceptibility to both atopy and asthma in Caucasian subjects[80]. In agreement with this, a recent study reported that the RANTES-403*A allele is transmitted with atopy and atopic asthma, although its contribution appears to relate more to atopy than to asthma[81]. By contrast, RANTES-403 G/A polymorphism did not influence asthma susceptibility in Chinese or Hungarian children and in a Japanese population[20, 82, 83] or atopy susceptibility in Chinese children[82] or allergy in Hungarian children[20].

Along with RANTES-403 C/G SNP, the effect of RANTES-28 C/G SNP on asthma susceptibility has also been studied. RANTES-28 C/G SNP correlates with the numbers of peripheral eosinophils and with asthma

severity in a Chinese population[82]. On the other hand, one study reported an association of RANTES-28*G allele with late-onset asthma in a Japanese population[83] and others observed the absence of RANTES-28 C/G association with asthma in Hungarian children[20] or with atopy[82,84]. Yao *et al.* further analysed haplotype distribution of *RANTES*-403G/A and -28C/G and observed that the haplotype 3 (-403*G, -28*G) was more common in a near-fatal asthma group compared to mild-moderate asthma, atopy or a healthy control group[84].

Furthermore, CCL5 over-production correlates with pulmonary sarcoidosis, particularly in patients with more advanced disease[85]. In agreement with this, Takada *et al.* suggested an association of RANTES-403 G/A polymorphism with the number of organs involved and CD4/CD8 rate, but not with susceptibility to sarcoidosis as a whole[86].

3.3.4 HIV infection

There are 5 common CCL5 SNPs (-403 G/A, -109 T/C, -28 C/G, In1.1 T/C, and 3'222 T/C) that have been studied either separately or as 4 common haplotypes regarding HIV infection.

3.3.5 Susceptibility to HIV infection

Gonzalez *et al.* explored the distribution of RANTES-403 G/A, -28 C/G SNPs and RANTES haplotype pairs in HIV positive and HIV negative individuals in worldwide populations[87]. This study and others have showed that the evolutionary histories of human populations have had a significant impact on the distribution of variation in these genes, and that this may be responsible, in part, for the heterogeneous nature of the epidemiology of the HIV-1 pandemic[5,87,88,89,90].

In European Americans, it has been observed that the ancestral haplotype pair AC/AC of RANTES-403 G/A and -28 C/G SNPs is associated with higher risk of acquiring HIV-1[87]. Further common haplotype pairs among European Americans (AC/GC GC/GC, and GC/AG) decrease susceptibility to HIV infection compared to the ancestral haplotype pair. However this association was not found in African Americans[87]. Furthermore, the haplotype pair AC/GC of RANTES-403/-28 SNPs was more common in seroconverter versus exposed-uninfected participants of Multicenter AIDS Cohort Study (MACS)[89]. In contrast, the haplotype pair GC/GC was more common in exposed-uninfected versus HIV positive individuals [89]. These data suggest that the *RANTES*-403*A allele is a risk factor for acquiring HIV, but may produce different phenotypes in distinct populations[87,89].

By contrast to the MACS study Zhao *et al.* observed that the haplotype 1 (-403G, -28C) and -403*G allele are over-represented in Chinese HIV positive patients, whereas -403 A/A genotype was associated with lower susceptibility to HIV infection[88]. In a Hispanic population the haplotype ACT of three RANTES SNPs (-403 A/G, intron 1 C/T, 3' UTR 222 T/C) has protective effect, but this does not apply to African-American populations or other populations of North Americans with HIV-1 infection[90]. A Japanese study failed to find any effect of -403 A/G or -28 G/C on acquiring HIV infection[5].

3.3.6 Susceptibility to AIDS progression

McDermott *et al.* studied the distribution of RANTES-403 G/A and -28 C/G SNPs and their compound genotypes in exposed-uninfected participants of the Multicenter AIDS Cohort Study (MACS)[89]. Here the haplotype pair RANTES-403 G/A and -28 C/C correlated with slower progression to AIDS compared to the haplotype pair RANTES-403 G/G and -28 C/C among seroconverters lacking CCR5Δ32. These data imply that RANTES-403*A allele may be a protective factor for HIV progression. Haplotype pair AC/AC was associated with disease progression in European Americans, but not African Americans[87]. Furthermore, RANTES SNPs at positions -28 C/G, -109 T/C, and -403 G/A were not associated with long-term nonprogressive HIV-1 infection in a Spanish white population[91].

A Japanese case-control study found that haplotype 3 (-403*A, -28*G) correlates with slower rates of CD4+ lymphocyte depletion, suggesting that haplotype 3 may play a role in delaying AIDS progression[5,87]. By contrast, Chinese symptomatic HIV positive patients had a higher frequency of the -28*G alelle and haplotype 3 (-403*A, -28*G) compared to asymptomatic patients suggesting an effect on disease progression[88].

Two studies explored the influence of four RANTES SNPs (-403 G/A and -28 C/G, In1.1 T/C and 3` 222 T/C) and their haplotypes related to HIV infection progression. An *et al.* found that haplotype 3 (which contains In1.1*C) correlates with AIDS accelerating in African-Americans and European-Americans[6]. Weaker association of the In1.1*C-containing haplotype 4 carriage with rapid AIDS progression was also evident in African-Americans, but not in European-Americans[6]. In African Americans, subsequently, Duggal *et al.* observed that homozygotes for the haplotype 1 (-403*G, -28*C, In1.1*T, and 3222*T) have lower viral load than individuals carrying at least one R2, R3, or R4 haplotype[76]. Additionally, after adjusting for potential confounders, including the CCR5Δ32, CCR2 V64I, and CCR5 P1 promoter haplotypes, the strength of the association was even stronger for the R1 haplotype[76].

3.3.7 Diabetes mellitus

The RANTES promoter -28*G genotype may be a risk factor for diabetic nephropathy in patients with type 2 diabetes mellitus[92]. Boger *et al.* studied the effect of the functional polymorphisms in the RANTES gene on mortality in a collective of type 2 diabetes hemodialysed patients. Patients carrying the RANTES-403*A or In1.1*C alleles had 81% and a 46% higher risk for all-cause mortality, mainly due to cardiac events. Similar data were obtained by haplotype analysis[77].

3.3.8 Systemic lupus erythematosus (SLE)

In the Chinese population, children with RANTES-28 C/G or G/G genotypes have more than double the risk

of SLE compared to those with the C/C genotype[93]. Subsequently, another Chinese study found that a compound genotype -403 G/G and -28 C/C correlated with a risk of SLE and -403*G allele is probably related with renal damage[94].

3.3.9 Other diseases

CCL5/CCR5 interaction is likely to be important during hepatitis C virus infection, where T cells are recruited to the liver parenchyma to mediate clearance of HCV-infected hepatocytes[95]. Consistent with this hypothesis, RANTES-403 G/A SNP was observed to decrease risk of severe inflammation in Hepatitis C virus–seropositive patients heterozygous or homozygous for the *RANTES* promoter alleles -403*A[96, 72]. By contrast, a recent study found no association of RANTES polymorphisms with disease outcome or severity of hepatitis C virus infection[71].

Fleury *et al*. suggested a favourable role for anti-RANTES therapy in heart transplantation reducing graft infiltration by monocytes/macrophages[97]. Accordingly, the carriers of RANTES-403*A allele are at higher risk of developing "late" outcome of acute heart transplant rejection, if they are carriers of CCR5 haplotype E at the same time[69]. On the other hand, RANTES-28 C/G and -403 G/A neither influenced the incidence of acute rejection nor affected allograft survival after liver transplantation[39, 98]. Five years allograft survival, however, involved 61.3% liver recipients with the GG genotype of RANTES-403 G/A against 58.8% recipients with the GA and AA genotypes[98]. This difference was also not statistically significant[98].

Recent results indicate that RANTES-403 G/A SNP is associated with susceptibility to rheumatoid arthritis and polymyalgia rheumatica[99, 100]. In addition, Wang *et al.* also reported compound genotype RANTES-403 A/A, -28 C/G more common in Chinese patients with rheumatoid arthritis[99]. On the other hand, RANTES-403 A/G SNP affects neither the susceptibility to breast cancer nor presence of metastases[37].

3 CCR5

3.1 Biological function of CCR5

The CC receptor 5 mediates chemotaxis after the interaction with its ligands CCL3, CCL4, CCL5 and CCL8[1, 64]. CCR5 is presented by activated/memory Th1 lymphocytes, macrophages, peripheral blood-derived dendritic cells, endothelial cells, epithelium, vascular smooth muscle, and fibroblasts. CCR5 expression was also reported in $CD34^+$ hematopoietic progenitor cells, Langerhans' cells, neurons, astrocytes, and thymocytes[1, 43].

4.2 CCR5 gene and its polymorphisms

CC chemokine receptor 5 is localized on chromosome 3p21.3-p24[99]. In the CCR5 gene, open reading frame (ORF) 32 base pair deletion CCR5Δ32 creates a truncated protein that fails to reach the cell surface. This most studied polymorphism is present in various Caucasian populations at a frequency of about 9%, while it is almost absent in some African, Japanese and Chinese ethnic groups[101, 102]. Among European white populations there is a north to south gradient of the prevalence of the deletion allele, with allelic frequencies highest in Denmark and Northern France and lowest in Corsica[103].

CCR5 expression may be regulated by the broad spectrum of polymorphisms located in either upstream promoter or downstream promoter, which includes the "intronic" region between exons 1 and 3. In this context, sequence analysis of CCR5 *cis*-regulatory region (-2761 to -1835) revealed 32 variable sites that define 27 unique human haplotypes. Based on 7 polymorphisms (-2733 A/G, -2554 G/T, -2459 G/A, -2135 T/C, -2132 C/T, -2086 A/G, and -1835 C/T) 7 distinct clusters of these haplotypes were designated as CCR5 human haplogroups (HH)-A, -B, -C, -D, -E, -F, and -G[104]. The CCR5 haplogroups also involve haplotype P1 (208*G, 612*A, 626*C, 627*C, 630*C, 647*C, 676*A, 684*T, 714*C, 811*G) that is in linkage disequilibrium with CCR5Δ32 and CCR2-64I[106]. Similarly CCR5 haplotypes in haplogroups F (HHF*2) and G (HHG*2) are associated with CCR2-64I and CCR5Δ32 polymorphisms, respectively[104].

Considering CCR5 expression, Hladik *et al.* reported reduced CCR5 densities on both T-helper cells and monocytes with haplotypes CCR5Δ32/CCR5-2459*A (in complete linkage disequilibrium) and CCR5 wt/CCR5-2459*G[7]. Further CCR5-2459*A homozygosity correlates with increased number of CD4+ cells expressing CCR5 in individuals without CCR5Δ32 and CCR2-64I. Furthermore CCR5-2459*A allele is in complete linkage disequilibrium with CCR5-59653*T[105].

4.3 Diseases associated with CCR5 polymorphisms

4.3.1 Atherosclerosis and myocardial infarction (MI)

CCR5Δ32 increases the risk for abdominal aortic aneurysm (AAA)[107]. In addition, it could be a useful factor that differentiates AAA from both peripheral arterial occlusive disease and carotid stenosis as well as from ruptured AAA. In this context, the homozygotes for rare deletion have more than four-fold higher risk for ruptured AAA than electively repaired AAA[105]. On the other hand, Gonzalez *et al*. found that Spanish males carrying the CCR5Δ32 allele are protected against an early episode of MI[55]. In agreement with this, Szalai *et al.* suggested that the homozygotes for CCR5Δ32 are protected against heart disease because they found no homozygotes for CCR5Δ32 in CAD patients but six in the control group[15]. However, there was no difference in CCR5Δ32 allele distribution between patients and controls. This relationship between CAD and CCR5Δ32 was not observed in a German study[16] as well as in Czech males, who had their first MI before the age of 55 years[108]. In addition, CCR5Δ32 can increase the degree of calcification in specific conditions[109].

4.3.2 Multiple sclerosis (MSc)

T cells expressing CCR5 are increased in the blood of patients with multiple sclerosis[1]. More importantly, perivascular space and nearby microglia are also infiltrated by CCR5 positive cells. In addition, antagonists to this receptor could be useful for treating of MS[60]. These findings suggest that altered CCR5 expression could modulate MS.

This is in agreement with an immunogenetic study that reported, approximately, 3 years later MSc onset in patients carrying CCR5Δ32[62]. CCR5 deletion allele may also be considered as a favourable prognostic factor in MS, based on percentage of patients who reached EDSS (Expanded Disability Status Scale)[110]. Furthermore, Sellebjerg *et al*. found that CCR5Δ32 is associated with lower risk of recurrent clinical disease activity[111]. In other studies, however, the deletion affected neither disease severity[112, 113], nor age of MSc onset[110, 113]. In some cases, indeed, CCR5Δ32 was associated with earlier age of MSc onset[111, 112]. CCR5Δ32 mutation was observed to be also associated with MSc in HLA-DR4-positive Russians[114]. A more recent study only admitted that CCR5Δ32 has a dose effect on CCR5 expression in the central nervous system, because CCR5Δ32 homozygotes contained no CCR5 positive T-cells in lesions and periplaque white matter, whereas heterozygous patients had reduced CCR5 expression compared to wild type patients. On the other hand, there was no difference in the density of macrophages/microglia stratified according to CCR5Δ32 genotype and demyelinating stage[113]. These data indicate that CCR5 expression is not essential for the development of MS.

4.3.3 Rheumatoid arthritis (RA) and related diseases

The CCR5Δ32 is a genetic marker related to the severity of RA[115]. Recent study provides further evidence for a protective effect of the CCR5Δ32 variant on rheumatoid arthritis in a New Zealand cohort[116]. In Slovak Caucasians, carrier status for the CCR5Δ32 allele may also contribute to protection from the development of primary Sjogren's syndrome[117].

4.3.4 Lung diseases

Petrek *et al.* reported that CCR5Δ32 allele is associated with susceptibility to sarcoidosis in the Czech population[58]. In addition, because it was present in 39 % of patients requiring corticosteroids but only in 17 % patients who did not need therapeutic intervention, the authors related this CCR5 deletion allele to the more advance disease[58]. Besides CCR5Δ32 polymorphism, a recent study explored the distribution of a further seven SNPs (at positions -2459, -2135, -2086, -1835, -5663, -3900, and -3458) in Dutch and British patients with sarcoidosis. In both populations, CCR5 haplotype HHC was overrepresented among sarcoidosis patients with radiographic stages II and higher versus stages 0 and I. Furthermore, the carriers of CCR5 haplotype HHC were associated with a lower number of pulmonary function tests and BAL neutrophilia[118].

CCL5/CCR5 mediated chemotaxis may favourably affect the bias of Th2 immune response of asthma by induction Th lymphocytes with Th 1 phenotype. By contrast, Hall *et al.* found that individuals carrying CCR5Δ32 are at reduced risk of developing asthma[119]. Subsequently two studies failed to show any association of this polymorphism with asthma or disease severity[120, 121]. Furthermore, a transmission disequilibrium test showed similar results for susceptibility to atopy or wheeze[120].

4.3.5 HIV infection

Along with the CD4 receptor, CCR5 is utilized as a major HIV co-receptor for entry of macrophage-tropic, non-SI (NSI) HIV-1 variants (called R5) into the cells[122]. According to current hypotheses, the homozygotes for CCR5Δ32 have nearly complete resistance to HIV-1 infection despite repeated exposure, and HIV-1 infected heterozygotes for CCR5Δ32 delay the onset of acquired immunodeficiency syndrome (AIDS)[123]

By contrast to the above-mentioned CCR5Δ32 deletion, homozygotes for the haplotype P1 are associated with rapid progression to AIDS in both Caucasian and African-American populations[106, 123, 124, 125]. Both CCR5Δ32 and *CCR5* P1 have a strong influence early in HIV-1 infection [126]. When homozygosity for haplotype P1 occurs in individuals that are also heterozygous for protective CCR5Δ32 and CCR2-64I, their effects are offset by each other[106]. Further, the haplotype P1 was found to be in a complete linkage disequilibrium with CCR5-2459*A allele (CCR5-2459 A/G SNP)[124, 125]. CCR5-2459 A/A individuals progress to AIDS faster than G/G individuals in the absence of the CCR5Δ32 and CCR2-64I[7, 127, 128, 129]. In addition, recent results indicate that inheritance of the CCR5Δ32/wt plus CCR5-2459 A/G genotype combination may reduce target cell susceptibility to HIV-1[7]. Furthermore, P1 haplotype and CCR5-2459*A allele form part of the haplogroup HHE (-2459*A and -2135*C but lacking -2733*G and -1835*T) that has been reported to be associated with rapid AIDS progression[130].

4.3.6 Diabetes mellitus

CCR5Δ32 predispose to later onset of type 1 diabetes mellitus [131]. A subsequent study found the relationship of both CCR5Δ32 and CCR5-2459*G allele with developing diabetic nephropathy, but only in males. In addition, the haplotypes with at least one risk allele (CCR5Δ32 or CCR5-2459*G allele) remained associated with diabetic nephropathy, whereas the haplotype containing CCR5-2459*A and lack of CCR5Δ32 allele had protective effects on disease susceptibility[132]. By contrast, CCR5-2459*A allele was suggested to be an independent risk factor for diabetic nephropathy in patients with type 2 diabetes[133].

4.3.7 Hepatitis C and hepatitis B infection

Promrat and Liang outlined the role of polymorphisms of the genes for CCR5, CCR2 and their ligands in HCV susceptibility and disease prognosis[96]. In this context, they discussed the relevance of studies that reported higher frequency of CCR5Δ32 in HCV infected haemophiliacs[134] or in a subgroup of HIV exposed non-positive individuals[135]. A subsequent study failed to find any association of CCR5Δ32 with HCV infection[96]. On

the other hand, heterozygotes for CCR5Δ32 were shown to be associated with spontaneous hepatitis C viral clearance and lower hepatic inflammation scores in women[71]. In agreement with this, Hellier *et al.* found an association between CCR5Δ32 and reduced portal inflammation and milder fibrosis in large European cohort[72]. Considering HBV infection, the CCR5-2459*A allelic genotype was associated with an increased risk of chronic infection rather than spontaneous clearance, and the presence of the CCR5-2459*G allele was associated with the spontaneous clearance of HBV[136].

4.3.8 Transplantation

There are two studies that investigated the influence of CCR5 polymorphisms on outcome of cardiac transplantation. Fildes *et al.* found that CCR5Δ32 in cardiac graft donor is associated with favourable effects on survival following heart transplantation in patients transplanted for a non-ischemic condition[137]. However, they found no correlation between recipient genotype and outcome of transplantation. On the other hand, Simeoni *et al*. reported that subjects with transplanted heart carrying both the CCR5 haplotype E and the RANTES-403*A allele are at increased risk of developing of delayed heart graft rejection[69]. Consistently, the renal graft recipients with CCR5-2459 A/A genotype were found to have reduced risk of acute renal graft rejection[70]. On the other hand, the CCR5-2459*A allele is more prevalent in donor kidney that experienced acute cellular rejection, acute rejection or biopsy/proven chronic allograft nephropathy[138]. Furthermore, CCR5-2459 A/G influences neither the incidence of acute liver rejection nor long-term allograft survival after liver transplantation[39]. There were no differences in the incidence of acute renal graft rejection among patients stratified as with or without CCR5Δ32[70]. CCR5Δ32 is a risk factor for the development of ischemic-type biliary lesions after liver transplantation and leads to the reduction in 5-year survival[139]. This relationship between CCR5Δ32 and liver graft survival or risk for liver acute rejection was not reported in previous study[68].

4.3.9 Systemic lupus erythematosus (SLE)

CCR5Δ32 was not involved in susceptibility to SLE in a Spanish population, although this polymorphism correlates with the development of lupus nephritis in Spanish patients with SLE[140].

4.3.10 Other diseases

Singh *et al.* showed that the heterozygotes for CCR5Δ32 have less neurocognitive impairment in cohort of children with symptomatic HIV-1 infection[129].

In a Turkish population heterozygotes for CCR5Δ32 are at higher risk for the development of breast cancer as well as laryngeal, thyroid and brain carcinomas[141]. Another study fail to find any association between CCR5Δ32 or CCR5-2459 A/G and breast cancer[73]. By contrast, CCR5Δ32 is protective factor against AIDS related non-Hodgkin's lymphoma, but it is not associated with risk for Kaposi's sarcoma[142].

In 2001 Hampe *et al.* suggested the existence of inflammatory bowel disease (IBD) susceptibility gene on the proximal part of chromosome 3p[74]. However, it is unlikely that the CCR5Δ32 allele is an important marker for predisposition to IBD[74, 75].

CONCLUSION

Several studies provide evidence of the susceptibility of gene profile of CCL2/CCL5 and CCR2/CCR5 that promotes deregulation of leukocyte trafficking leading to disease progression or higher risk of disease onset. Furthermore, both chemokine receptors are utilised by HIV as co-receptors for cell entry and their several variants have been showed to modulate susceptibility to HIV infection. Recent data also suggest that screening for CCL2/CCL5 and CCR2/CCR5 polymorphisms can be useful for forecasting transplantation outcome and the process of metastasis. However, further work is needed to explain inconsistent results among similarly designed studies. For example, recent advances in the identification of linkage disequilibrium between gene variants provide opportunity for other large case-control studies. However, rare incidence or suboptimal definition of some diseases remain restrictive factors. Further challenges arise from the heterogeneity of disease progression markers. We also need more information about posttranscriptional events to understand functional relevance of polymorphisms and to discovery new avenues to blocking disease development.

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