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Review

Chemokine receptor gene polymorphisms and COVID-19: Could knowledge gained from HIV/AIDS be important?

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ABSTRACT

Emerging results indicate that an uncontrolled host immune response, leading to a life-threatening condition called cytokine release syndrome (also termed “cytokine storm”), is the major driver of pathology in severe COVID-19. In this pandemic, considerable effort is being focused on identifying host genomic factors that increase susceptibility or resistance to the complications of COVID-19 and translating these findings to improved patient care. In this regard, the chemokine receptor-ligand nexus has been reported as potentially important in severe COVID-19 disease pathogenesis and its treatment. Valuable genomic insights into the chemokine receptor-ligand nexus have been gained from HIV infection and disease progression studies. Applying that knowledge, together with newly discovered potential host genomic factors associated with COVID-19, may lead to a more comprehensive understanding of the pathogenesis and treatment outcomes in COVID-19 patients.

1. Introduction

The interactions between chemokine receptors and their ligands may affect susceptibility to a variety of infectious diseases as well as their clinical manifestations. In general, the chemokine receptor-ligand interactions mediate both the traffic of inflammatory cells and pathogen-associated immune responses. The role of the immune system in producing an uncontrolled and generalized inflammatory response (termed “cytokine storm”) in COVID-19 disease, caused by SARS-CoV-2 virus, is becoming increasingly clear (Qin et al., 2020; Mehta et al., 2020; Coperchiniet al., 2020). Although much is yet to be understood, based on current knowledge, the “cytokine storm” may manifest as one of the most dangerous and potentially life-threatening COVID-19-related events called acute respiratory distress syndrome (ARDS) (Qin et al., 2020; Mehta et al., 2020). Therefore, the immune response to SARS-CoV-2 infection and the role of the chemokine receptor-ligand system is being characterized with the final goal of identifying targeted therapeutic strategies (Sorbera et al., 2020; Ray et al., 2020; Chua et al., 2020). Here is a brief description of the studies showing that the chemokine receptor-ligand system is potentially important in severe COVID-19 disease pathogenesis and its treatment. In addition, presenting significant genomic characteristics of this system that we have learned from HIV infection and disease progression studies may be useful for future COVID-19 studies.

2. Role of chemokine receptor in COVID-19

2.1. Chemokine receptor-ligand interactions and COVID-19 severity

A study by Ray et al. (Ray et al., 2020) used a computational framework to test the hypothesis that SARS-CoV-2 infection drives changes in immune cell-derived factors that then interact with receptors expressed by the sensory neuronal innervation of the lung to further promote important aspects of disease severity, including ARDS. To test this hypothesis, the authors used published data from patients, existing RNA sequencing datasets from human thoracic dorsal root ganglion (hDRG) neurons and other sources, and a genome-wide ligand-receptor pair database curated for pharmacological interactions relevant for neuro-immune interactions. Their findings revealed a landscape of ligand-receptor interactions in the lung caused by SARS-CoV-2 viral infection and point to potential interventions to reduce the burden of neurogenic inflammation in COVID-19 pulmonary disease. In particular, genes upregulated in the COVID-19 patient samples include a multitude of genes that recapitulate clinical characteristics, such as increased cytokine signaling causing a “cytokine storm”, hypoxia, and inflammasome and sepsis-related genes. Many receptors for cytokines/
chemokines, identified as upregulated in COVID-19 patients, including C–C chemokine receptor (CCR) 1 (CCR1), CCR2, and CCR5 were also expressed in hDRG, suggesting a potential direct connection between those cytokines/chemokines and sensory neuron activation in the lung. Based on these findings, the authors claim, “our work highlights opportunities for clinical trials with existing or under development rheumatoid arthritis and other (e.g. C-C chemokine ligand 2 [CCL2], CCR5) drugs to treat high risk or severe COVID-19 cases.”

A study by Chua et al. (Chua et al., 2020) investigated the immune response and mechanisms associated with severe COVID-19 by performing single-cell RNA sequencing on nasopharyngeal and bronchial samples from 19 clinically well-characterized patients with moderate or critical disease. The chemokine and chemokine receptor expression of the different cell populations increased markedly in the critical compared to the moderate cases, suggesting an augmented recruitment of immune cells to the sites of inflammation. In particular, inflammatory macrophages showed high expression of the chemokine encoding genes CCL2 (encoding MCP1), CCL3 (encoding MIP1α), CCL20, C-X-C chemokine ligand 1 (CXCL1), CXCL3, and CXCL10, and pro-inflammatory cytokines. The authors state, “The transcriptional differences in critical cases compared to moderate cases likely contribute to clinical observations of heightened inflammatory tissue damage, lung injury and respiratory failure. Our data suggest that pharmacologic inhibition of the CCR1 and/or CCR5 pathways might suppress immune hyper-activation in critical COVID-19.”

2.2. A chromosome 3 gene cluster and respiratory failure in COVID-19 patients

A study by Ellinghaus et al. (Ellinghaus et al., 2020) has tested for association between > 8 million single nucleotide polymorphisms (SNPs) and the development of respiratory failure in COVID-19 patients (835 from Italy, 775 from Spain). The authors found the rs11385942 insertion-deletion GA/A SNP at chromosome 3p21.31 (association boundary chr3:45800446–46,135,604, Hg38) to be associated with COVID-19-induced respiratory failure, with genome-wide significance (P < 5 × 10−8) in the meta-analysis. The locus showed nominally significant association in both the Italian and Spanish sub-analyses. Furthermore, an age- and sex-corrected analysis corroborated these observations. The association signal at chromosome 3p21.31 comprised six genes including CCR9 and the C-X-C chemokine receptor 6 (CXCR6). The authors claim, “The preliminary results from the COVID-19 Host Genetics Consortium include suggestive associations within the same locus at chromosome 3p21.31, which lend considerable support to our findings….As such, it seems reasonable to conclude that the chromosome 3p21.31 locus is involved in COVID-19 susceptibility per se, with a possible enrichment in patients with severe disease. This latter interpretation is supported by the significantly higher frequency of the risk allele GA among patients who received mechanical ventilation than among those who received supplemental oxygen only as well as by the finding of younger age among patients who were homozygous for the risk allele than among patients who were heterozygous or homozygous for the nonrisk allele.”

The authors acknowledge that extensive genotype-phenotype elaboration of current findings could not be conducted and, therefore, a causative gene cannot be reliably implicated by the present data. Among the six genes included in the association signal, CXCR6 regulates the specific location of lung-resident memory CD8 T cells throughout the sustained immune response to airway pathogens, including influenza viruses. Flanking genes (e.g., CCR1 and CCR2) also have relevant functions, and further studies will be needed to delineate the functional consequences of detected associations (Ellinghaus et al., 2020).

2.3. CCR5 as a therapeutic target for COVID-19

A study by Patterson et al. (Patterson et al., 2020) has reported profound elevation of plasma IL-6 and CCL5 (also known as RANTES), a ligand for CCR5, decreased CD8+ T cell levels, and SARS-CoV-2 plasma viremia in 10 terminally-ill, critical COVID-19 patients. Following treatment with the CCR5-blocking antibody leronlimab, the authors observed complete CCR5 receptor occupancy on macrophage and T cells, rapid reduction of plasma IL-6, restoration of the CD4/CD8 ratio, and a significant decrease in SARS-CoV-2 plasma viremia. Consistent with reduction of plasma IL-6, single-cell transcriptomics showed that there were declines in myeloid cell clusters expressing IL-6 and interferon-related genes. The authors state, “These results demonstrate a novel approach to resolving unchecked inflammation, restoring immunologic deficiencies, and reducing SARS-CoV-2 plasma viral load via disruption of the CCL5-CCR5 axis, and support randomized clinical trials to assess clinical efficacy of leronlimab-mediated inhibition of CCR5 for COVID-19.”

According to the authors, leronlimab does not downregulate CCR5 surface expression or deplete CCR5-expressing cells, but does prevent CCL5-induced calcium mobilization in CCR5+ cells. This ability to specifically prevent CCL5-induced activation and chemotaxis of inflammatory CCR5+ macrophages and T cells suggests how leronlimab-mediated CCR5 blockade may be effective in resolving the hyperinflammatory state in COVID-19 and restoring more effective anti-viral immunity (Patterson et al., 2020).

3. Role of CCR5 in HIV/AIDS and other diseases

CCR5 is the main HIV-1 co-receptor involved in virus entry and cell-to-cell spread during acute and chronic infections: such CCR5-using and T cell-tropic viruses are adapted to and replicate in CD4+ memory T cells (Joseph and Swanstrom, 2018). Polymorphisms in CCR5 regulate CCR5 expression, which in turn influences HIV infection acquisition and subsequent disease progression. Among these polymorphisms, a 32 base pair deletion in the CCR5 open reading frame (ORF) (CCR5 Δ32, rs333) (McLaren and Carrington, 2015; Naranbhai and Carrington, 2017; Tough and McLaren, 2019) and a SNP in the promoter (~ 2459G/A, rs1799987) (Martin et al., 1998; McDermott et al., 1998) are the most well-characterized ones. CCR5 Δ32 provides partial to full protection against HIV infection, and therefore serves as a basis for gene deletion studies attempting to achieve a permanent HIV cure (Allen et al., 2018; Xu, 2020). Recent studies have discovered that certain SNPs in the CCR region, not within CCR5, also affect CCR5 expression, HIV infection, and disease progression (McLaren et al., 2015; Kulkarni et al., 2019).

3.1. CCR5 in other diseases

Beyond HIV, researchers have been investigating the involvement of CCR5 and the effects of CCR5 Δ32 on autoimmunity and inflammatory diseases, cancers, and other viral diseases (Jiao et al., 2019; Klein, 2008; Qidwai and Khan, 2016; Ellwanger et al., 2020a). Data suggest that there are varied impacts of CCR5 regulation and CCR5 Δ32 on human infections caused by the following non-HIV viruses: West Nile virus, Tick-borne encephalitis virus, Influenza virus, Human papillomavirus, Hepatitis B virus, Hepatitis C virus, Poliovirus, Dengue virus, Human cytomegalovirus, Crimean-Congo hemorrhagic fever virus, Enterovirus, Japanese encephalitis virus, and Hantavirus (Klein, 2008; Qidwai and Khan, 2016; Ellwanger et al., 2020a). The role of CCR5 in bacterial, parasitic, and fungal diseases has not been much studied (Klein, 2008; Qidwai and Khan, 2016; Ellwanger et al., 2020b).

3.2. CCR5 Δ32 and SARS-CoV-2 infection and death

In a study by Panda et al. (Panda et al., 2020) data of COVID-19
disease and mortality rate per million of inhabitants were obtained from the website (https://www.worldometers.info/coronavirus/), accessed on 29th June 2020). The prevalence of CCR5 Δ32 allele in healthy controls from 107 countries was obtained from an earlier publication (Solloch et al., 2017) and PubMed search. Spearman Rank Correlation tests ($\alpha = 0.0001$) were performed, and a significant positive correlation was observed between COVID-19 infection rate/million (Spearman $r = 0.4628$, $P < 0.0001$, $n = 107$) and mortality rate/million (Spearman $r = 0.5517$, $P < 0.0001$, $n = 107$) with the frequency of the Δ32 allele. In addition, a positive correlation was noticed between COVID-19 mortality rate and the Δ32 allele frequency in an African population (Spearman $r = 0.6261$, $P = 0.0045$). The authors state, “These data and findings are indicative of an association of CCR5 Δ32 with susceptibility to SARS-CoV-2 infection and mortality. However, the mechanism of CCR5 Δ32 allele offering predisposition to SARS-CoV-2 infection susceptibility and death of the patient is not known.”

Chemokine receptors and their ligands, including CCR5 and CCL5, have been found to play important role in inflammatory response, which most commonly involve the recruitment of leukocytes to eliminate infectious agents. Differential expression of chemokine receptor and ligand may contribute to variations in inflammatory pattern, which in turn may have distinct effects on the course or establishment of infections. As CCR5 is a primary entry receptor for HIV, it is appreciable that expression variations of CCR5 due to CCR5 polymorphisms may influence the acquisition of HIV infection as well as the disease progression. However, the impacts of CCR5 polymorphisms on the replication and infection of non-HIV viruses and other pathogens are complex and may not be generalized (Klein, 2008; Qidwai and Khan, 2016; Ellwanger et al., 2020a; Ellwanger et al., 2020b). These impacts could be disease-specific and/or population-specific.

4. Genetic variation, CCR5, and HIV/AIDS outcomes

4.1. CCR5 Δ32 and promoter SNP −2459G/A

A variety of studies conducted in the 1990s examined the associations between CCR5 polymorphisms Δ32 and −2459G/A (also known as 59029G/A and 303G/A) and HIV-1 infection and disease progression. In those studies, the Δ32 allele, compared with the wild-type (wt) allele, was associated with protection against HIV infection and/or delayed disease progression (Martin et al., 1998; Dean et al., 1996; Zimmerman et al., 1997). The −2459G allele, compared with the −2459A allele, was associated with delayed HIV disease progression (Martin et al., 1998; McDermott et al., 1998). In a number of studies, the Δ32 and −2459G alleles were associated with significantly reduced in vitro promoter activity, CCR5 expression, and HIV propagation, compared with the ORF wt and −2459A alleles, respectively (McDermott et al., 1998; Hladik et al., 2005; Kawamura et al., 2003; Mummidii et al., 2000; Salkowitz et al., 2003; Shieh et al., 2000). Recent studies have provided insight into the molecular mechanisms regarding the association between CCR5 promoter polymorphisms and transcriptional regulation of the promoter, and how this association correlates with CCR5 cell surface expression as well as HIV disease phenotype (Jiang et al., 2011; Goralnusse et al., 2015; Joshi et al., 2017).

The CCR5 Δ32 allele is found predominantly in European populations, with rare occurrences in Asians and native populations from Africa, the Americas, and Oceania (Solloch et al., 2017) (see Table 1). On the other hand, allele frequency of CCR5 −2459G ranges from 32% to 66% in most populations (see Table 1). In Papua New Guinea, an Oceania country, this allele frequency was much higher, 85% in one study (Clark and Dean, 2004) and 98% in another (Mehlotra et al., 2015).

The CCR5 haplotype nomenclature system consists of a total of nine polymorphisms, which include CCR5 ORF wt/Δ32 and −2459G/A. CCR5 haplotypes are organized into nine evolutionarily distinct human haplogroups (HH) designated HHA, −B, −C, −D, −E, −F, −G, −H, and −G'. In turn, may have distinct effects on the course or establishment of infections. As CCR5 is a primary entry receptor for HIV, it is appreciable that expression variations of CCR5 due to CCR5 polymorphisms may influence the acquisition of HIV infection as well as the disease progression. However, the impacts of CCR5 polymorphisms on the replication and infection of non-HIV viruses and other pathogens are complex and may not be generalized (Klein, 2008; Qidwai and Khan, 2016; Ellwanger et al., 2020a; Ellwanger et al., 2020b). These impacts could be disease-specific and/or population-specific.

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4 out of 5 super populations, the A_A haplotype frequencies range from 14% to 37% (see Table 2). A_A may be considered a “risk” haplotype, as it may be associated with higher CCR5 expression compared with rs1799987A or rs1015164A (Mehlotra, 2020).

### 6. Conclusions

Hyperimmune activation and “cytokine storm” are present in cases of severe COVID-19. In this pandemic, the goal is to identify host genomic factors that increase susceptibility or resistance to the complications of the disease, and to translate these findings in a timely manner to improved patient care (Murray et al., 2020). As various approaches are being taken to uncover biological networks underlying host-pathogen (SARS-CoV-2) interactions and common variants therein, it may be important to consider that common variants occur in some of those networks, which have been characterized to play functionally significant roles in other global epidemic diseases. In this regard, the role of certain polymorphisms within as well as outside CCR5 in HIV/AIDS may be worth considering. CCR5 receptor and a nearby gene cluster, where many other chemokine receptor genes are located, may be potentially involved in COVID-19 treatment (Patterson et al., 2020) and may contribute to susceptibility to the complications of the disease (Ellinghaus et al., 2020; Panda et al., 2020). In other words, the 1.5 Mb CCR region on chromosome 3 (chr3:45.5–47, Hg19) may be playing roles in both HIV/AIDS and COVID-19. This region contains CCR5 and several functionally significant SNPs including rs1015164 (McLaren et al., 2015; Kulkarni et al., 2019). It also includes the 335 kb region (chr3:45800446–46,135,604, Hg38 [chr3:45841938–46,177,096, Hg19]) containing the rs11385942 insertion-deletion GA/ASNP, which was found to be associated with COVID-19-induced respiratory failure (Ellinghaus et al., 2020). Therefore, further characterization of this chromosomal region in COVID-19 patients seems warranted.

In addition, as the studies targeting CCR5 for COVID-19 treatment are performed, and such a treatment starts becoming increasingly available, it is imperative to include ORF wt/Δ32, −2459G/A, and rs1015164G/A polymorphisms in the treatment outcome analyses. Given the significance of Δ32, even when present as a single allele, the ORF wt/Δ32 genotype information ought to be included in such studies.

| Polymorphism | Alleles | Location | Overall frequency (range) | European | South Asian |
|--------------|---------|----------|---------------------------|----------|-------------|
| rs1799987<sup>a</sup> | G/A | Chr 3:46370444 | 40% (32–49%) | 57% (50–66%) | 41% (35–52%) |
| rs333 | wt/Δ32 | Chr 3:46373453 | 0 (0–3%) | 3% (2–4%) | 0 |
| rs1015164 | G/A | Chr 3:46410189 | 5% (2–8%) | 22% (19–25%) | 19% (14–24%) |
| rs4317138 | T/C | Chr 3:46420653 | 5% (2–8%) | 23% (19–26%) | 19% (14–26%) |

* Phase 3 populations (26 populations, 2504 samples).
* Known as −2459G/A, 59029G/A, and 303G/A.
* Ancestral allele/Mutant allele; wt = wild-type, Δ32 = 32 bp deletion.
* GRCh38 coordinate.
* Mutant allele.

### Table 1

Certain functional polymorphisms within and around CCR5 in 1000 Genomes populations.<sup>a</sup>

| Polymorphism | Alleles | Location | Overall frequency (range) | African | American | East Asian | European | South Asian |
|--------------|---------|----------|---------------------------|---------|----------|------------|----------|-------------|
| rs1799987<sup>a</sup> | G/A | Chr 3:46370444 | 40% (32–49%) | 57% (50–66%) | 41% (35–52%) | 54% (47–57%) | 39% (38–41%) |
| rs333 | wt/Δ32 | Chr 3:46373453 | 0 (0–3%) | 3% (2–4%) | 0 | 11% (7–16%) | 1% (0–3%) |
| rs1015164 | G/A | Chr 3:46410189 | 5% (2–8%) | 22% (19–25%) | 19% (14–24%) | 32% (28–37%) | 28% (21–32%) |
| rs4317138 | T/C | Chr 3:46420653 | 5% (2–8%) | 23% (19–26%) | 19% (14–26%) | 33% (28–38%) | 29% (23–33%) |

* Table 2

| Population | Description | rs1799987-rs1015164 | D' (r²) | haplotype frequency<sup>a</sup> |
|-----------|-------------|---------------------|---------|-------------------------------|
| African | Gambia | 1 | 8% |
| | African | 1 | 6% |
| | Ancestry | Gambian | 0.86 (0.10) | 6% |
| | L.setSelection(As | 1 | 6% |
| | in | 1 | 2% |
| | Western | 0.75 (0.05) | 4% |
| | | Lyuba in | 3% |
| | | Weuye, | 3% |
| | | China (LYW) | 3% |
| | | Eza in | 3% |
| | | Nigeria (ESN) | 3% |
| American | Colombian | 1 | 21% |
| | in Medellin, | 1 | 24% |
| | Colombia (CLM) | 1 | 18% |
| | Mexican | 0.85 (0.09) | 18% |
| | | Ancestry | 1 | 25% |
| | in Los Angeles, | 1 | 25% |
| | CA (MXL) | 1 | 25% |
| East Asian | Chinese D | 1 | 16% |
| | ai in Xiu | 1 | 14% |
| | | Xiangba, China (CDX) | 1 | 21% |
| | Han Chinese in | 0.94 (0.26) | 24% |
| | Beijing, | 0.94 (0.35) | 17% |
| | | China (CHB) | 0.94 (0.35) | 16% |
| | Japanese in | 0.94 (0.35) | 17% |
| | Tokyo, Japan (JPT) | 0.94 (0.26) | 24% |
| | | in Ho Chi Minh | 0.94 (0.35) | 17% |
| | | City, Vietnam (KHV) | 0.94 (0.35) | 17% |
| European | Utah residents with | 1 | 21% |
| | Northern | 0.95 (0.33) | 1% |
| | | and Western | 0.95 (0.33) | 32% |
| | | European Ancestry | 0.95 (0.33) | 32% |
| | | (CEU) | 0.95 (0.33) | 32% |
| | British in | 0.95 (0.33) | 32% |
| | | England and | 0.95 (0.33) | 32% |
| | | Scotland (GRR) | 0.95 (0.33) | 32% |
| | Iberian | 1 | 29% |
| | | population in | 1 | 29% |
| | | Spain (IBS) | 1 | 37% |
| | Toscana | 1 | 25% |
| | in Italy (TSI) | 1 | 25% |
| South Asian | Bengali in Bangladesh (BBB) | 1 | 22% |
| | Gujarati Indian in | 0.94 (0.57) | 30% |
| | Houston, TX (GHI) | 0.94 (0.57) | 30% |
| | Indian Telugu in the | 0.97 (0.64) | 31% |
| | UK (ITU) | 0.97 (0.64) | 31% |
| | Punjabi in Lahore, | 0.87 (0.49) | 26% |
| | Pakistan (PL) | 0.87 (0.49) | 26% |
| | Sri Lankan Tamil in | 1 | 28% |
| | the UK (STU) | 1 | 28% |

* Data not available.
* haplotype rs1799987A_rs1015164A.
Also, –2459G/A and rs1015164G/A polymorphisms should be included because they regulate CCR5 expression and are prevalent worldwide, the latter in American, East Asian, European, and South Asian populations. Moreover, the potential “risk” haplotype A-A of these polymorphisms is also quite prevalent. If A-A is associated with higher CCR5 expression, it may affect CCR5-based treatment outcomes in COVID-19 patients. Knowing whether an individual receiving such an immunologic or chemotherapeutic intervention is carrying two, one, or no A-A haplotype would enable a better understanding of the response to the intervention.

It is acknowledged that direct information on the influence of CCR5 polymorphisms on COVID-19 disease severity is very limited at the moment. Moreover, mechanistic studies providing plausible explanations on how polymorphisms in CCR5 and other related genes would correlate with the disease severity and clinical manifestations of COVID-19, including the recruitment of immune cells/inflammatory cells to the infection sites, are needed. Nevertheless, with the discovery of potential host genomic factors associated with COVID-19 and knowledge already gained from other global infectious diseases, there is now a greater potential to improve clinical management and foster better patient outcomes.

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Author contributions
R.K.M. wrote the manuscript.

Declaration of Competing Interest
None.

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References
Allen, A.G., Chung, C.-H., Atkins, A., et al., 2018. Gene editing of HIV-1 co-receptors to prevent and/or cure virus infection. Front. Microbiol. 9, 2940.
Chua, R.L., Lukassen, S., Trump, S., et al., 2020. COVID-19 severity correlates with airway epithelial-immune cell interactions identified by single-cell analysis. Nat. Biotechnol. 38, 970–979.
Clark, V.J., Dean, M., 2004. Haplotype structure and linkage disequilibrium in chemokine and chemokine receptor genes. Hum Genom. 1, 255–273.
Copechini, F., Chiovato, L., Groce, I., Magri, F., Rotondi, M., 2020. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 53, 25–32.
Dean, M., Carrington, M., Winkler, C., et al., 2019. Genetic restriction of HIV-1 infection in patients with CD4+ T cell depletion complex childhood HIV. J. Health Care Poor Underserved 22, 73–90.
Jiao, X., Nawab, O., Patel, T., et al., 2019. Recent advances targeting CCR5 for cancer and its role in immune-oncology. Cancer Res. 79, 4801–4807.
Joseph, S.B., Swanstrom, R., 2018. The evolution of HIV-1 entry phenotypes as a guide to changing target cells. J. Leukoc. Biol. 103, 421–431.
Joshi, A., Punke, E.B., Sedano, M., et al., 2017. CCR5 promoter activity correlates with HIV disease progression by regulating CCR5 cellular surface expression and CD4 T cell infections. Sci. Rep. 7, 7792.
Kawamura, T., Goldin, F.O., Suyaga, M., et al., 2003. HIV-1 productively infects Langerhans cells, and infection levels are regulated by compound CCR5 polymorphisms. Proc. Natl. Acad. Sci. U. S. A. 100, 8401–8406.
Klein, R.S., 2008. A moving target: the multiple roles of CCR5 in infectious diseases. J. Infect. Dis. 197, 183–186.
Kulkarni, S., Lied, A., Kulkarni, V., et al., 2019. CCR5ASNRNA variation differentially regulates CCR5, influencing HIV disease outcome. Nat. Immunol. 20, 824–834.
Li, Z., Zhang, Z., He, Z., et al., 2009. A partition-ligation-combination-subdivision EM algorithm for haplotype inference with multilocus markers: update of the SHEsis software. Mol. Genet. Genomic. 282, 75–86.
Martin, M.P., Dean, M., Smith, M.W., et al., 1996. Genetic acceleration of AIDS progression by a promoter variant of CCR5. Science 282, 1907–1911.
McDonald, D.H., Zimmerman, P.A., Guignard, F., Kleeberger, C.A., Leitman, S.F., Murphy, P.M., 1998. CCR5 promoter polymorphism and HIV-1 disease progression. Multicenter AIDS Cohort Study (MACS). Lancet 352, 866–870.
McLaren, P.J., Carrington, M., 2015. The impact of host genetic variation on infection with HIV-1. Nat. Immunol. 16, 577–582.
McLaren, P.J., Coulouges, C., Bartha, I., et al., 2015. Polymorphisms of large effect explain the majority of the host genetic contribution to variation of HIV-1 virus load. Proc. Natl. Acad. Sci. U. S. A. 112, 14658–14663.
Mehlotra, R.K., 2019. CCR5 promoter polymorphism – 2459G/A: forgotten or ignored? Cells 8, 651.
Mehlotra, R.K., 2020. New knowledge about CCR5, HIV infection and disease progression: is “old” still valuable? AIDS Res. Hum. Retrovir. (In press).
Mehlotra, R.K., Hall, N.B., Bruse, S.E., et al., 2015. CCR2, CCR5, and CXCL12 variation and HIV/AIDS in Papua New Guinea. Infect. Genet. Evol. 36, 165–173.
Mehta, P., McAuley, D.F., Brown, M., et al., 2020. On behalf of the HLA across specialty collaboration, UK: COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 395, 1033–1034.
Mummidi, S., Bamshad, M., Abjoua, S.S., et al., 2000. Evolution of human and non-human primate CC chemokine receptor 5 gene and mRNA. Potential roles for haplotype and mRNA diversity, differential haplotype-specific transcriptional activity, and altered transcription factor binding to polymorphic nucleotides in the pathogenesis of HIV-1 and simian immunodeficiency virus. J. Biol. Chem. 275, 18946–18956.
Murray, M.F., Kenny, E.E., Ritchie, M.D., et al., 2020. COVID-19 outcomes and the human genome. Genet. Med. 22, 1175–1177.
Naranbhai, V., Carrington, M., 2017. Host genetic variation and HIV disease: from mapping to mechanism. Immunogenetics 69, 489–498.
Panda, A.K., Padhi, A., Prusty, B.A.K., 2020. CCR5 Δ32 minor allele is associated with susceptibility to SARS-CoV-2 infection and death: an epidemiological investigation. Clin. Chim. Acta 510, 60–61.
Patterson, B.K., Seethamraju, H., Dkhoy, K., et al., 2020. Disruption of the CCL5/ RANTES-CCR5 pathway restores immune homeostasis and reduces plasma viral load in critical COVID-19. medRxiv. https://doi.org/10.1101/2020.05.22.20108673. preprint. (Posted May 05, 2020, Revision under review).
Qudwai, T., Khan, M.Y., 2016. Impact of genetic variations in C-C chemokine receptors and ligands on infectious diseases. Hum. Immunol. 77, 961–971.
Qin, C., Zhou, L., Hu, Z., et al., 2020. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin. Infect. Dis. 71, 762–768.
Ray, P.R., Wangzhou, A., Ghneim, N., et al., 2020. A pharmacological interactome between COVID-19 patient samples and human sensory neurons reveals potential drivers of neurogenic pulmonary dysfunction. Brain Behav. Immun. (Online ahead of print).
Salkowitz, J.R., Bruse, S.E., Meyerson, H., et al., 2003. CCR5 promoter polymorphism determines macrophage CCR5 density and magnitude of HIV-1 propagation in vitro. Clin. Immunol. 108, 234–240.
Sheib, B., Liu, Y.E., Hsieh, B., Fan, Y.P., Wang, S.T., Li, C., 2000. Influence of nucleotide polymorphisms in the CCR2 gene and the CCR5 promoter on the expression of cell surface CCR5 and CXCR4. Int. Immunol. 12, 1311–1318.
Solloch, U.V., Lang, K., Lange, V., Bohme, I., Schmidt, A.H., Sauter, J., 2017. Frequencies of gene variant CCR5Δ32 in 87 countries based on next-generation sequencing of 1.3 million individuals sampled from 3 national DKMS donor centers. Hum. Immunol. 78, 710–717.
Sorbera, I., Graz, A.L., Dulact, C., 2020. Taking aim at a fast-moving target: watching for SARS-CoV-2 and COVID-19. Drugs Future 45, 1–6.
Tough, R.H., McLaren, P.J., 2019. Interaction of the host and viral genome and their influence on HIV disease. Front. Genet. 9, 720.
Xu, M.M., 2020. CCR5Δ32 allele, gene editing, and warnings for the future of CRISPR-Cas9 as a human and humane gene editing tool. Cell Biosci. 10, 48.
Zimmerman, P.A., Buckler-White, A., Alkhatib, G., et al., 1997. Inherited resistance to HIV-1 conferred by an inactivating mutation in CC chemokine receptor 5: studies in populations with contrasting clinical phenotypes, defined racial background, and quantified risk. Mol. Med. 3, 23–36.