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Letter to the Editor

Pros and cons of a missing chemokine receptor—Comments on "Is the European spatial distribution of the HIV-1-resistant CCR5-Δ32 allele formed by a breakdown of the pathocenosis due to the historical Roman expansion?" by Eric Faure and Manuela Royer-Carenzi (2008)

Dear Editor,

We read with interest the recent article by Faure and Royer-Carenzi (2008). While reading this article, we were amazed by the two-edged sword behaviour exhibited by the CCR5-Δ32 allele in face of the pathogens. Since its description as a natural HIV-1-resistant variant, the human CCR5-Δ32 allele was widely investigated both in healthy populations (in order to characterize populations with different ethnic origins) as well as in pathological conditions (in efforts to associate this variant with resistance against other pathogens). As pointed out by Faure and Royer-Carenzi (2008), a quite interesting picture of the CCR5-Δ32 allele distribution among human populations has emerged from these studies, characterized by the absence of such variant among native populations from Americas and Oceania, an almost complete absence among native populations from Africa and Asia, and an intriguing north–south gradient on Caucasoid populations in Europe.

Given that the CCR5-Δ32 mutation was discovered as a protective variant against a viral infection, it was first supposed that it might induce resistance to a set of infectious diseases. Several authors have tried to explain the unusual pattern of distribution of this null variant as an advantage provided by the CCR5-Δ32 allele against infections. Considering that HIV-1 has too recently become a human pathogen to influence any allele frequency, candidates to act as selective agents for the CCR5-Δ32 included *Yersinia pestis* and the smallpox virus. Nevertheless, here Faure and Royer-Carenzi (2008) depart from the most currently accepted views. In their article, they propose that the CCR5-Δ32 might have been an ancient allele, widely distributed and with relatively high frequencies in early European populations. Then, a negative selection event (and the authors suggest this negative selection was the spread of pathogens principally during Roman expansion) shaped the current map of frequency distribution for the CCR5-Δ32 allele through the resident European populations. Finally, they conclude that zoonoses might account for such distribution, although the nature of the specific parasite remains currently unknown.

The CCR5 molecule has strong influences on the immune system. Besides its pro-inflammatory role, it is also a regulatory molecule (de Kleer et al., 2004; Ruprecht et al., 2005), having been reported to be involved in the T-cell memory compartment at both the levels of cell recruitment and cell differentiation (Chiesa et al., 2004; Gattorno et al., 2005). We may, therefore, hypothesize that the absence of such an important molecule could, directly or indirectly, impair the establishment of effective immune responses in certain situations, in spite of being protective against some infections as previously stated. We would like to add to this discussion highlighting some situations where the CCR5-Δ32 allele was described to be associated with deleterious symptoms, or negative outcomes, in inflammatory or infectious diseases and even in cancer development.

In our laboratory, we study the role of the CCR5-Δ32 allele on inflammatory diseases. For instance, although a protective role for this variant was suggested in the context of rheumatoid arthritis (Gómez-Reino et al., 1999; Pokorny et al., 2005), data from our group have showed a correlation between disease severity and high CCR5-Δ32 frequency in juvenile idiopathic arthritis (Scheibel et al., 2008). An age-dependent contrasting behaviour was also observed by Srivastava et al. (2003) with an association of CCR5-Δ32 with reduced risk of childhood but not adult asthma. Furthermore, Gade-Andavolu et al. (2004) associated high frequencies of the CCR5-Δ32 allele to early death in multiple sclerosis patients. We also observed a higher CCR5-Δ32 frequency among sickle cell disease (SCD) patients, which present a chronic inflammatory condition (Chies and Nardi, 2001), as compared to healthy controls from the same ethnic group (Chies and Hutz, 2003). It is important to point out that, in another study from our group, we observed a tendency for the development of severe clinical course in SCD patients that carry the CCR5-Δ32 allele (Vargas et al., 2005). Linking inflammation and infection, it is interesting to mention that SCD patients are prone to recurrent infections, especially respiratory infections, and that it was shown that CCR5 knockout (KO) mice infected with a mouse-adapted strain of influenza A virus displayed increased mortality rates associated with acute, severe pneumonitis (Dawson et al., 2000). Therefore, we can argue that the presence of an intact pool of $CCR5^+$ cells is important to efficiently deal with such infections.

The CCR5 KO mice is an interesting model to observe how the absence of the CCR5 molecule affects immune responses. Thus, besides the above-mentioned example with influenza A virus, CCR5 KO mice were shown to be less efficient at controlling the progression of virus replication following herpes simplex virus-1 (HSV-1) infection (Carr et al., 2006) and displayed a significant reduction in cumulative survival following infection with HSV-2, in comparison to wild-type controls (Thapa et al., 2007). They also develop significantly higher levels of parasitemia and cardiac parasitism during acute *Trypanosoma cruzi* infection, which correlate with reduced survival (Hardison et al., 2006); they are more susceptible to infection with the intracellular protozoan parasite *Toxoplasma gondii* (Khan et al., 2006); and they have inefficient migration of $CD4^+$ regulatory T cells to sites of *Leishmania major* infestation (Yurchenko et al., 2006). Nevertheless, these impaired responses, in some situations, can act in a favorable way by reducing the inflammatory state associated with the pathological condition. Barr et al. (2005), found that CCR5 KO mice present a diminished capacity to clear *Chlamydia trachomatis* infection, as compared to normal mice. However, the fertility of

1567-1348/$ – see front matter
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infected CCR5 KO mice was only mildly affected in the short term, and unaffected in the long term, in comparison to wild-type animals. Furthermore, translational studies in humans revealed that among patients with positive anti-chlamydial IgG responses, tubal pathology correlated with a low incidence of CCR5-Δ32, while women without tubal pathology had higher incidence of the CCR5 deletion, as compared to controls. This study clearly illustrates the two sides of missing a functional CCR5 molecule, considering just one pathological situation.

Other studies, considering susceptibility to infectious diseases in humans, have showed a higher CCR5-Δ32 allele frequency in Lithuanian patients with tickborne encephalitis (TBE) as compared to patients with non-TBE aseptic meningoencephalitis, or with healthy TBE-virus negative controls (Kindberg et al., 2008). Higher frequencies of the variant allele were also observed in Greek patients with brucellosis (Skendros et al., 2002) and in symptomatic West Nile virus (WNV) infection cases (Glass et al., 2005, 2006, reviewed by Lim et al., 2008), as compared to healthy volunteers or asymptomatic cases, respectively.

Besides its involvement in autoimmune and inflammatory diseases, the CCR5 molecule also has crucial roles on tumoral immunity. Srivastava et al. (2008) shown that the CCR5-Δ32 allele was associated to gallbladder cancer susceptibility. Duell et al. (2006) observed an elevated Odds Rate for current active smoking and CCR5-Δ32 genotypes in relation to pancreatic cancer risk and suggested that intact CCR5 may offer pancreatic cells some protection from the damaging effects of tobacco smoking. Also, data from a primary breast cancer clinical series showed that disease-free survival was shorter in individuals bearing the CCR5-Δ32 allele than in CCR5 wild-type patients, but only for those whose tumors expressed wild-type p53 (Mañes et al., 2003).

In conclusion, it seems that the maintenance, as well as fluctuations on the frequency, of the CCR5-Δ32 allele in human populations obey an intrincated net of genetic and environmental factors. These environmental factors (more specifically, the exposition to pathogens) suffer changes over time and, therefore, the presence of this variant might be advantageous or disadvantageous depending on the situation (or pathogen). Considering that, we could state that the antagonism of CCR5 (which is currently being evaluated to fight certain infections) may be advantageous in certain circumstances, but disadvantageous in others. It sounds awfully primitive, but amazingly true, that we will not be able to determine the outcome of the use of CCR5 antagonists in any other way but empirically, as suggested by Klein (2008). Furthermore, as pointed out by Faure and Royer-Carenzi (2008), only an approach combining various fields of investigation will enable us to fully understand the complex interrelations between pathogens and the CCR5-Δ32 allele.

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