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CCR5 gene editing – Revisiting pros and cons of CCR5 absence

CCR5 gene editing in human embryos was recently announced, leading to significant debate in the scientific community regarding the ethical aspects and biological implications of this procedure (Cyranoski and Ledford, 2018). The announced genetic intervention was a supposedly CRISPR-mediated *CCR5* gene deletion. Discussing the ethical aspects of *CCR5* editing is not the focus of this article. Importantly, ethical concerns are being raised out by other authors elsewhere (Wang et al., 2018; Zhang et al., 2018). We further stress that different articles bring valuable information on the ethical aspects of genetic interventions in human embryos (Cartier-Lacave et al., 2016; Hildt, 2016; Krishan et al., 2016; Rossant, 2018). Actually, the precise consequences of this gene edition are unknown. However, previous studies that evaluated the absence or low expression of CCR5 through different approaches may bring us valuable information about the potential effects of *CCR5* gene editing.

CCR5 is a chemokine receptor with seven transmembrane domains (Parmentier, 2015), encoded by *CCR5* gene, and expressed primarily on the surface of leukocytes (Raport et al., 1996; Rottman et al., 1997; Wu et al., 1997; Lederman et al., 2006). CCR5 and its ligands (MIP-1α/CCL3, MIP-1β/CCL4, CCL5/RANTES, among others) mediate the migration of leukocytes to inflamed tissues and specific inflammatory sites (Lederman et al., 2006; Jones et al., 2011). More recently, the participation of CCR5 in different cellular processes and pathological conditions has been evidenced (Brelot and Chakrabarti, 2018; Scurci et al., 2018). Besides, CCR5 is a co-receptor necessary for HIV-1 infection (Parmentier, 2015; Brelot and Chakrabarti, 2018).

CCR5 gene has various polymorphisms that affect CCR5 expression, and these variants are found in different human populations (Ansari-Lari et al., 1997; Mummidi et al., 1997; Zhang et al., 2003; Barmania et al., 2013; Parmentier, 2015). Among *CCR5* polymorphisms, CCR5Δ32 is the most studied due to its association with protection against HIV infection. CCR5Δ32 is a 32-base pair deletion in *CCR5* coding region, found mainly in Caucasoid individuals and genetically admixed populations (Martinson et al., 1997; Solloch et al., 2017; Ellwanger et al., 2018). In homozygosis, CCR5Δ32 promotes the formation of a truncated protein, showing only four transmembrane domains. This truncated protein is not expressed on the cell membrane. Therefore, individuals with a homozygous genotype for CCR5Δ32 have a strong (but not complete) protection against HIV-1 infection, once they lack CCR5 expression. This lack of expression avoids HIV-CCR5 interaction and consequently the virus-cell fusion. On the other hand, the heterozygous genotype for CCR5Δ32 causes a reduced CCR5 expression on the cell surface, a condition associated with a slower progression of HIV infection/AIDS (Dean et al., 1996; Liu et al., 1996; Samson et al., 1996; Balotta et al., 1997; Wu et al., 1997; Venkatesan et al., 2002; Brelot and Chakrabarti, 2018).

Considering that the absence of CCR5 expression was associated with a relative resistance against HIV infection, different approaches aiming the blockade or deletion of this molecule were performed. A study published in 2009 described the first and so far single case of long-term control of HIV infection as a result of non-pharmacological medical intervention. This result was obtained after a leukemic HIV-infected patient received an allogeneic hematopoietic stem cell transplant derived from a CCR5Δ32 homozygous donor (Hütter et al., 2009). The patient submitted to this procedure is popularly known as “the Berlin patient” (Brown, 2015). Currently, CCR5 blockers are used for HIV therapy and are already being tested for the treatment of other diseases, including cancer (Brelot and Chakrabarti, 2018; Vangelista and Vento, 2018).

Nevertheless, sometimes much attention is given to one single aspect of a given molecule, and the complex network of interactions behind it is somehow neglected. For example, although the relationship between CCR5 and HIV infection has been extensively studied, many biological aspects of CCR5 are still unknown. Considering this, here we highlight some potential pros and cons of CCR5 manipulation (Table 1), based on studies addressing the CCR5Δ32 allele, pharmacological CCR5 blockade, animal models, *in vitro* tests, and *CCR5* gene editing. In 2009, a similar discussion was held by our group by approaching the association of several pathological conditions and the potential effects of a null *CCR5* allele (Vargas et al., 2009). However, much was uncovered in recent years regarding the interactions of CCR5 in both healthiness and disease, and therefore, this issue should be revisited in light of the emerging gene editing technologies.

The pros and cons listed in Table 1 certainly do not exhaust the potential effects linked to CCR5 absence, reduced CCR5 expression, or those associated with the functional blockade of this molecule. The literature is full of examples showing different effects of both CCR5 absence and low expression in various pathological situations. These findings must be taken into consideration in future discussions regarding *CCR5* gene editing. The few examples listed here cover a broad spectrum of distinct conditions, ranging from infections, cancer, and autoimmune diseases to even pregnancy disorders, highlighting the complexity and extension regarding the effects of CCR5 absence. Moreover, those effects will depend on population-associated features, such as the ethnic/genetic background of a specific human population as well as to the presence of pathogens and environmental-related disease triggers. Of note, two major points must be highlighted. First, the absence of CCR5 due to gene-editing techniques may lead to different physiological consequences as compared to those observed in individuals homozygous for CCR5Δ32. The truncated form of CCR5 will not be present in such gene-edited individuals. Evolutionary forces may have influenced the selection of distinct genetic variants which eventually “compensate” the lack of CCR5 expression due to Δ32 allele and, within this same reasoning, a role of truncated CCR5 protein itself - even in the resistance against the HIV infection - has not been ruled out (Barmania and Pepper, 2013). Second, chemokine-ligand systems are classically considered as redundant, and although the absence of CCR5 molecule should be compensated by other chemokine receptors

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Table 1
Potential pros and cons of *CCR5* gene editing based on different lines of evidence.

Pros and cons	Approach	Some findings and methodological aspects	References
Pros			
Protection against HIV infection	*CCR5* gene editing	*CCR5* edition using CRISPR/Cas9 system promoted protection against HIV infection *in vitro* and *in vivo* (study using human cell lines and mice)	Kang et al. (2015); Xu et al., 2017
Protection against enteroviral cardiomyopathy	*CCR5* polymorphism (CCR5Δ32 cohort data)	CCR5Δ32 was associated with spontaneous myocardial enterovirus clearance and better outcomes (study in humans)	Lassner et al. (2018)
Reduced risk for autoimmune diseases	*CCR5* polymorphism (CCR5Δ32 cohort data)	CCR5Δ32 was associated with reduced risk for rheumatoid arthritis and multiple sclerosis (studies in humans)	Toson et al. (2017); Troncoso et al. (2018)
Better prognosis in colorectal cancer	Pharmacological CCR5 blockade	CCR5 blockade promoted better clinical responses in colorectal cancer patients (study in humans and *in vitro* tests)	Halama et al. (2016)
Low risk for preeclampsia development	*CCR5* polymorphism (CCR5Δ32 cohort data)	CCR5Δ32 was associated with protection against preeclampsia (studies in humans)	Gurdol et al. (2012); Telini et al. (2014)
Cons			
Worst outcome in West Nile virus infection	*CCR5* polymorphism (CCR5Δ32 cohort data)	CCR5Δ32 was associated with severe and fatal outcomes of symptomatic West Nile virus infection (study in humans)	Glass et al. (2006)
Increased heart dysfunction in Chagas disease	Low CCR5 expression	Low CCR5 expression was correlated with severe chronic chagasic cardiomyopathy (study using human cells)	Talvani et al. (2004)
Increased risk for worst outcome in colorectal cancer	Low CCR5 expression	Low CCR5 expression was associated with lymphatic dissemination of colorectal cancer (study using tissue samples from human patients and *in vitro* tests)	Zimmermann et al. (2010)
Impaired brain function	Low CCR5 expression and KO mice	CCR5 absence/low expression (using CCR5 knockout mice and *in vitro* tests) induced astrocyte activation, astrogliosis, amyloid-β deposit, and memory dysfunction	Lee et al. (2009); Hwang et al. (2016)

(Mantovani, 1999), it is possible that CCR5 performs unique functions not yet clarified (Chen et al., 2018).

CCR5 gene editing seems to be a double-edged sword: there are advantages and disadvantages, and we should be aware of such behavior. It is too early to conclude the actual effects of a procedure that abolishes the expression of a component of the immune system seemingly involved in so many different situations. The conclusions could only appear from the follow-up of individuals submitted to *CCR5* editing.

Conflicts of interest

The authors declare no conflicts of interest.

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