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CCR5: Established paradigms and new frontiers for a 'celebrity' chemokine receptor

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ABSTRACT

Because of the level of attention it received due to its role as the principal HIV coreceptor, CCR5 has been described as a 'celebrity' chemokine receptor. Here we describe the development of CCR5 inhibitory strategies that have been developed for HIV therapy and which are now additionally being considered for use in HIV prevention and cure.

The wealth of CCR5-related tools that have been developed during the intensive investigation of CCR5 as an HIV drug target can now be turned towards the study of CCR5 as a model chemokine receptor. We also summarize what is currently known about the cell biology and pharmacology of CCR5, providing an update on new areas of investigation that have emerged in recent research.

Finally, we discuss the potential of CCR5 as a drug target for diseases other than HIV, discussing the evidence linking CCR5 and its natural chemokine ligands with inflammatory diseases, particularly neuroinflammation, and certain cancers. These pathologies may provide new uses for the strategies for CCR5 blockade originally developed to combat HIV/AIDS.

1. CCR5 in sickness and in health

1.1. Chemokines in physiology and pathology

CCR5 belongs to the G protein-coupled sub-family of chemokine receptors, which consists of 19 signaling receptors and 4 atypical receptors in humans [1,2]. Chemokines are named according to their primary physiological role: eliciting the chemotactic trafficking of leukocytes from the blood to the tissues and around the lymphatic system, both under conditions of homeostasis and inflammation [3]. Certain chemokines are also involved in embryonic development [4], in particular during the formation of the central nervous system, where expression of certain chemokine receptors persists in the adult [5]. Outside of physiology, the chemokine/chemokine receptor network is of interest because of its implication in a number of pathologies, including a wide spectrum of inflammatory disorders, cancers and infectious diseases [3].

1.2. Physiological roles of CCR5

First identified in 1996 [6–8], CCR5 is expressed on a range of leukocytes, including macrophages, antigen presenting cells, activated T cells and natural killer cells [1,9]. CCR5 has a clear role in inflammation. At sites of infection or tissue damage, CCR5 ligands are released, leading to ingress and activation of effector cells which themselves release chemokines, further amplifying the signal [1,9]. CCR5 stimulation also modulates the behavior, survival and retention of immune cells in tissues [10]. This capacity, together with its involvement in the recruitment of regulatory T cells [11] indicates a role for CCR5 not only in inducing but also in resolving inflammation.

CCR5 is also implicated in the initiation of adaptive immune responses. While not expressed on circulating naïve T cells, CCR5 is upregulated upon their arrival in secondary lymphatic tissue [12], where it plays a role as a costimulatory molecule at the immunological synapse, responding to chemokines released by the partnering dendritic cell [13].

CCR5 is also expressed in non-immune system cells, most notably in the central nervous system, where it is found on microglia, astrocytes and neurons [14,15]. Its function in this context has not been fully elucidated, but there is evidence for roles in neuronal development, differentiation and survival [16].

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1.3. CCR5 and HIV

Following its discovery, CCR5 achieved almost immediate notoriety when it was identified as one of the HIV coreceptors used together with CD4 to enter and infect target cells [17–20]. Other chemokine receptors [21], notably CXCR4 [22], were implicated as HIV coreceptors at the same time, but it soon became clear that only CCR5 and CXCR4 are used to a significant extent by HIV [23]. Small changes in the coding sequence of the HIV envelope are sufficient to switch coreceptor use from CCR5 to CXCR4 and *vice versa*, and the mutagenic rate of replicating HIV means that both phenotypes are always likely to be present in an infected individual [24]. Despite this, CXCR4-using viruses are maintained at low levels in infected people under treatment, and transmission of virus from person-to-person is almost exclusively restricted to CCR5-tropic viruses [25].

The centrality of CCR5 in the HIV life cycle is underlined by the almost complete protection from HIV acquisition exhibited by people homozygous for a CCR5 null allele, CCR5Δ32, which encodes 32-base pair deletion in the CCR5 gene open reading frame, resulting in a truncated receptor that does not reach the cell surface [26–29]. Furthermore, the first and only example of a functional cure for HIV involved the 'Berlin patient', an HIV-positive individual who was treated for leukemia by ablation of his own leukocytes followed by grafting of hematopoietic stem cells from a compatible homozygous CCR5Δ32 donor: his reconstituted CCR5-negative immune system did not support replication and viremia was completely suppressed in the absence of any treatment [30].

The CCR5Δ32 allele emerged recently in human evolution [31,32], and is highly prevalent in certain groups (10% to 14% in populations of Northern European ancestry, with 1% homozygous) [33,34]. Individuals homozygous for CCR5Δ32 have not been reported to have any major health deficits [35], and CCR5 knock-out mice appear healthy and develop normally [36]. The apparent tolerance of this CCR5 deficiency is believed to be due to the promiscuity of the chemokine/chemokine receptor network, with other chemokine receptors and their ligands compensating for the lack of CCR5.

One area in which CCR5 deficiency is clearly disadvantageous, however, is in controlling infection by West Nile virus. People homozygous for CCR5Δ32 were found to be overrepresented in a two cohorts of patients with symptomatic West Nile virus, particularly for the subset of patients that had fatal complications [37]. A further study demonstrated that homozygosity for the CCR5Δ32 allele does not increase the likelihood of infection by West Nile virus, but confirmed its association with a higher risk of complications post-infection [38]. Similarly, CCR5 knockout mice experimentally infected by West Nile virus showed strongly increased mortality compared to wild-type controls [39].

In summary, CCR5 is crucial to HIV for infection and spread, yet almost completely dispensable for human health. As such it is a highly attractive drug target for therapy, prevention, and even cure of HIV.

1.4. CCR5 and HIV therapy

The pharmaceutical industry invested heavily on targeting CCR5 for HIV therapy [40], leading to the progression of severally promising orally available small molecule inhibitors through clinical development. Of these, aplaviroc was discontinued in 2008 after evidence of hepatotoxicity was observed in clinical trials [41], and vicriviroc was discontinued after clinical studies failed to demonstrate sufficient efficacy compared to standard treatment in Phase 3 clinical studies [42]. Only maraviroc [43], which was licensed in 2007, has entered clinical use so far, although cenicriviroc, a dual CCR2/CCR5 inhibitor, is progressing through clinical development [44]. In addition, two anti-CCR5 monoclonal antibodies have been developed for HIV therapy. One of these, CCR5mAb004, completed a Phase 1 study in 2006 [45], but no research has been published since. The other, PRO-140 [46], is currently in Phase 2/3 studies, with results anticipated in 2017 [47].

1.5. CCR5 and HIV prevention

For HIV prevention, maraviroc is being developed both in tablet form for an oral pre-exposure prophylaxis strategy [48] and as a component of topical delivery strategies (e.g. vaginal and rectal gels [49,50], intravaginal rings [51]) to block the sexual transmission of HIV. Another class of compounds that have been extensively evaluated as HIV prevention agents are analogs of RANTES/CCL5, one of the native ligands of CCR5. Native CCR5 ligands have relatively weak intrinsic anti-HIV activity [52], but certain chemokine analogs that have been described are many orders of magnitude more potent. Starting with the discovery that attaching a short hydrophobic extension to the N-terminus of RANTES/CCL5 strongly enhanced anti-HIV potency [53], a program of further optimization using chemical synthesis approaches led to the identification of a further enhanced compound, PSC-RANTES [54]. PSC-RANTES was used in a highly stringent macaque vaginal challenge model to demonstrate that topical application of a CCR5 inhibitor is sufficient for full protection against vaginal viral challenge [55]. However, relatively large doses of PSC-RANTES were required for full protection, and since it is a protein requiring chemical synthesis steps in manufacture, PSC-RANTES was considered to be too expensive for development for use as an HIV prevention agent, given that the populations most in need live in the poorer regions of the world [56]. PSC-RANTES was subsequently reversed engineered into a series of fully recombinant chemokine analogs using a phage display approach [57]. This led to the identification of 5P12-RANTES, a chemokine analog as potent [57] and efficacious [58] as PSC-RANTES, but (i) amenable to low-cost production by microbial fermentation [59] and (ii) lacking the CCR5 signaling activity exhibited by PSC-RANTES [57], which was considered a risk owing to the possibility of inducing inflammatory responses at the site of administration. 5P12-RANTES has been taken forward into clinical development as a medicine for HIV prevention. Together with the group of other highly potent anti-HIV chemokine analogs that were generated during its discovery, 5P12-RANTES also represents a valuable tool to probe the cell biology and pharmacology of CCR5 (see Section 4).

1.6. CCR5 and curing HIV

Finally, HIV cure strategies involving CCR5 attempt to replicate the success obtained with the 'Berlin patient'. Progress has been limited by the challenges involved in grafting heterologous stem cells [60], however, and an alternative focus is on taking the patients own stem cells and modifying them to create a phenotype analogous to that of CCR5Δ32 homozygotes [61,62].

2. CCR5 structure and activation

Understanding of the biology and pharmacology of CCR5 has aided in the development of strategies to discover new inhibitors, and helped to elucidate their inhibitory mechanisms. In this section we summarize what is known about the structure of CCR5, and its activation mechanism.

2.1. CCR5 structure

Chemokine receptors, including CCR5, are members of the superfamily of G-protein coupled receptors (GPCRs). GPCRs comprise approximately 4% of the total number of coded proteins in the human genome [63] and are targeted by approximately 30% of currently licensed medicines [64]. As such they have been extensively studied at both the structural and functional level. Structurally, GPCRs are comprised of (i) seven transmembrane helices, which together form a hydrophobic transmembrane domain, (ii) the N-terminal domain plus