ENGINEERING CHEMOKINE-BASED CCR5 BLOCKERS TO TACKLE INFECTIOUS AND INFLAMMATORY DISEASES

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The C-C chemokine receptor type 5, CCR5, is expressed on various cell types and is involved in a large number of pathophysiological conditions. In recent years, CCR5 gained a huge attention, as it was found to play a central role in several infectious (e.g., HIV-1and *Staphylococcus aureus*), inflammatory and autoimmune diseases, and in major pathologies such as cancer and atherosclerosis. Most importantly, CCR5, the major HIV-1cellular co-receptor and the exclusive one in primary infections, is the molecular portal for HIV-1entry and transmission. Interestingly, the CCR5 Δ32gene deletion encodes for a truncated nonfunctional protein, providing resistance to HIV-1infection in homozygous individuals. Consequently, CCR5 and its ligands present a great potential for targeted therapies based on the development of high-affinity receptor antagonists and CCR5 gene editing. Gene editing of CCR5 to introduce the naturally occurring Δ32mutation has the aim to provide protection from HIV-1infection and possibly eradication of the virus from infected individuals. However, individuals naturally carrying the Δ32mutation may have adjusted their chemokine system to compensate for CCR5 absence, hence the *de novo* introduction of this mutation might bring some pathophysiological burden. Besides gene editing, biochemical CCR5 blockade *via* the development of potent CCR5 antagonists is a seemingly more realistic large scale therapeutic approach. Significant efforts are under way to understand the fine structural details of the interaction between CCR5 and its ligands and maraviroc, a small chemical drug, has been developed and FDA-approved as HIV-1entry inhibitor acting as CCR5 antagonist. CCL5 is a natural chemokine ligand for CCR5, a small globular protein with a very stable fold. Previous research from my group produced the engineered CCL5 mutant CCL5 5p125m, the most potent *in vitro* CCR5 antagonist HIV-1inhibitor reported to date (1000 fold more potent than maraviroc). My ongoing research at NU is aimed at the 3D structure rational design and production of even more potent CCL5 derivatives and their investigations as inhibitors in the expanding therapeutic perspective of CCR5 blockade for a growing number of pathological conditions.