Retrovirology

Poster presentation

CCR5 Antagonist and Agonist Binding Site Structures

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Several small molecule antagonists of the HIV co-receptors CCR5 and CXCR4 are being developed as HIV entry inhibitors, but side effects have been observed in clinical trials that are likely due to agonist activity and/or cross-reactivity with closely related receptors. In order to develop high resolution maps of the binding sites for these antagonists that can be exploited to improve the activity and specificity, we are synthesizing derivatives of CCR5 and CXCR4 antagonists which contain photo-crosslinking groups at a variety positions in the molecules and that retain high affinity and activity against the receptors. Derivatives of two CCR5 antagonists have been crosslinked to affinity-purified CCR5 or CCR5 expressed on cells, and the interaction sites are being mapped by mass spectrometry. Techniques for purification, crosslinking, CNBr and/or trypsin digestion, and LC/MS/MS and MALDI-TOF mass spectrometry of highly hydrophobic peptides initially developed using the rhodopsin GPCR system have been applied with some success to CCR5. The peptide photo-crosslinked to a derivative of the antagonist TAK-779 has been identified, and modeling of the interaction with CCR5 suggests that it binds within the transmembrane region of the receptor and is oriented parallel to the transmembrane helices – in striking contrast to the perpendicular orientation expected for GPCR agonists.