Retrovirology

BioMed Central

Oral presentation

CCR5 and CXCR4 antagonist and agonist binding sites

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from 2006 International Meeting of The Institute of Human Virology
Baltimore, USA. 17–21 November, 2006

Published: 21 December 2006

Retrovirology 2006, **3**(Suppl 1):S39 doi:10.1186/1742-4690-3-S1-S39

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 their 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 and one CXCR4 antagonist have been crosslinked to their receptors 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 mass spectrometry of highly hydrophobic peptides initially developed using the rhodopsin GPCR system have been applied with some success to CCR5 and CXCR4, although these represent particular challenges due to the relative paucity of Met residue cleavage sites compared to rhodopsin and resistance to tryptic digestion. Nevertheless, peptides covering most of the extracellular and transmembrane regions of CCR5 that could interact with an antagonist can be identified, and affinity purification methods are being developed to isolate CXCR4 peptides crosslinked to derivatives of the antagonist T-140 that should facilitate the identification and localization of the crosslinking sites within the proteins.