CHEMOKINE RECEPTOR GENE STRUCTURE AND FUNCTION: IMPLICATIONS FOR HIV 1 PATHOGENESIS

Nelson L. Michael, M.D., Ph.D.*
Walter Reed Army Institute of Research
Bethesda, Maryland

Abstract

Cellular entry of human immunodeficiency virus type 1 (HIV 1) requires binding to both CD4 and to one of the chemokine receptors which act as co-receptors. Viruses which infect T-cell lines are frequently found in late-stage HIV disease and utilize the chemokine receptor CXCR4 while viruses which can infect macrophages and are present throughout disease utilize CCR5. While these are the major co-receptors, several minor co-receptors have also been identified to include CCR2b, CCR3, Bonzo, BOB, APJ, CCR8, CCR9, GPR1, CX3CR1, US28, and V28. The CC chemokines RANTES, MIP-1, and MIP-1 and MCP-1 through -4 are natural ligands for CCR5 and CCR2b, resepctively. The CXC chemokine stromal cell-derived factor-1 (SDF-1) is the exclusive ligand for CXCR4.

Genetic defects in CCR5 and polymorphisms in CCR2b and SDF1 are associated with delayed disease progression (and reduced transmission risk for CCR5 gene defects) in many, but not all, studies. The association of the CCR5 gene defect 32 is mitigated when the viral quasispecies evolves away from CCR5 utilization. Polymorphism studies for CXCR4 required elucidation of its genomic organization which we have recently published. CXCR4 contains a single intron interrupting the coding sequences and is regulated by the transcription factors NRF-1 and Sp1. Single-strand conformational polymorphism analysis and limited DNA sequence analysis of CXCR4 from the promoter through the 3. untranslated region revealed a rare (allelic frequency 0.0075), silent C3952 T change at isoleucine 261. This stands in striking contrast to the presence of common polymorphisms in CCR2b, CCR5, and SDF-1 and likely reflects the relative importance of these genes to normal physiology.

Polymorphisms in the CCR5 promoter region are in strong linkage disequilibrium with both CCR264I and CCR532 and , thus, cannot explain the mechanism of action of either allele. One CCR5 promoter allele, P1, is associated with differences in expression of or signaling through any recognized co-receptor nor susceptibility to HIV 1 infection. The complex interplay between host and viral factors that mediate HIV 1 pathogenesis remains an area of intense investigation suffused with considerable enigma.

*Paper not available.