The HIV virus is a growing epidemic in the world that is responsible for the cause of death of millions of individuals. Modern medicine has not found a cure and the high mutations that occur make the virus even harder to suppress once inside the body. The HIV virus is made of key domains: the inner core and viral membrane. The purpose of this poster was to follow point mutations that occur in the V3 loop on the gp120 and CD4 counts of 2 needle using patients in Baltimore MD who have contracted the viral membrane. A non-progressor, the CD4 count did not drop throughout the study, and a rapid-progressor, the CD4 count dropped drastically through the study, patients V3 loop of the gp120 on the viral membrane were studied to find a reason as to why one patient died from HIV and the other did not die. The V3 loop binds to CCR5 and CXCR4 receptors for the T-cell in the body. Research has shown that HIV can utilize the V3 loop to bind to CCR5 and CXCR4 is the most lethal combination for the destruction of the host T-cells. The V3 loop binds to the receptors through specific and nonspecific binding techniques and allows for the virus to enter into the T-cell leading to death of that T-cell. In this study it was possible to see as to why the rapid-progressor did indeed die from the actions of the HIV virus where as the non-progressor lived with a high CD4 count. These reasons all relate back to point mutations along the V3 loop and the structural alignment between the V3 loop when interacting with the CCR5 and CXCR4 receptors.

Background

The V3 loop of gp120 and its role in the cause of death of millions of individuals. Modern medicine has not found a cure and the high mutations that occur make the virus even harder to suppress once inside the body. The HIV virus is made of key domains: the inner core and viral membrane. The purpose of this poster was to follow point mutations that occur in the V3 loop on the gp120 and CD4 counts of 2 needle using patients in Baltimore MD who have contracted the viral membrane. A non-progressor, the CD4 count did not drop throughout the study, and a rapid-progressor, the CD4 count dropped drastically through the study, patients V3 loop of the gp120 on the viral membrane were studied to find a reason as to why one patient died from HIV and the other did not die. The V3 loop binds to CCR5 and CXCR4 receptors for the T-cell in the body. Research has shown that HIV can utilize the V3 loop to bind to CCR5 and CXCR4 is the most lethal combination for the destruction of the host T-cells. The V3 loop binds to the receptors through specific and nonspecific binding techniques and allows for the virus to enter into the T-cell leading to death of that T-cell. In this study it was possible to see as to why the rapid-progressor did indeed die from the actions of the HIV virus where as the non-progressor lived with a high CD4 count. These reasons all relate back to point mutations along the V3 loop and the structural alignment between the V3 loop when interacting with the CCR5 and CXCR4 receptors.

Rapid-progressor

Patient 10

Patient 10 was considered to be a rapid-progressor in the study done in Baltimore MD. This patient appears to have survived to the end of the study although with an extremely low CD4 count of 15 on visit 6. Looking at the CD4 count of this patient between visit 2 and visit 3 there was a significant drop in the patients CD4 count. The overall sequences of visits 1 and 2 were combined as well as the sequences from visits 3 and 4 which all represent similar V3 sequences. Comparing the sequences from visit 1 & 2 to the sequence from 3&4 there are point mutations that occur that shift the binding affinity from the CCR5 receptor the favor binding to the CXCR4 receptor. The V3 loop is found on the gp120 protein and has a specific 3 dimensional structure that facilitates the HIV virus to binding to CCR5 and CXCR4 receptors on T-cells. The V3 loop is found on the gp120 protein and has a specific 3 dimensional structure that facilitates the HIV virus to binding to CCR5 and CXCR4 receptors on T-cells. There are two different sequences of the V3 loop: R5 and X4. For the purposes of this poster the RS will only be considered. The V3 loop consists of 36 amino acids and has 2 stem and 1 crown domain as seen in the sequences below. The V3 loop begins with a disulfide bond between C1 and C36. The N-terminal stem consists of a conserved N-terminal loop and a small section of the β strand. The C-terminal stem is a conserved nescent hairpin. The crown region consists of a variable β strand, a conserved β hairpin turn, and a variable ridged loop. The β hairpin turn consists of a highly conserved GP1 sequence that is seen in all HIV isolates. The stem regions are believed to bind to the N-terminal domains of the CCR5 and CXCR4 receptors through salt bridges and nonspecific binding. The crown region of the V3 loop binds more specifically to the ECL2 of CCR5 and CXCR4 receptors utilizing the variable regions surrounding the β hairpin turn motif. Research has shown that the variable regions can undergo rapid point mutations that favor the binding of CCR5 or CXCR4. The ribbon diagram above show the conformation change that the V3 loop undergoes when it is in a water solution (Left) to a more polar solution (Right) that is typically seen upon binding to the different receptors. The correct 3 dimensional structure is necessary for aligning the crown region to the ECL2 allowing for viral binding.

Patient 12

Patient 12 was considered to be a non-progressor in the study done in Baltimore MD. This patient was considered a non-progressor by not observing a CD4 count drop throughout the duration of the study. After transcribing all of the mutant gp120 V3 loops that were obtained from the study, there were no point mutations that occurred within the overall sequences. For the purposes of this poster the V3 loop was examined. The amino acid sequence closely resembled that of the RS sequence. Looking closely at the sequence, the selected amino acids appear to be specific for CCR5 binding and not CXCR4 binding. Looking at the point mutation study done in figure 4 the amino acids that appear to significantly affect the binding of V3 loop to CCR5 are still conserved (R11 and I26). Although a point mutation that is present throughout the entire study for this patient is a change from R11 to P13. This amino acid is located in the middle of a β strand. The phi and psi angles needed to form a correct β strand are not able to be obtained creating a hydrophobic pocket for the F20 to interact. The two receptors are very similar in function and structure although there are subtle differences that allow the V3 loop to be specific to either the CCR5 or CXCR4 receptor.

Non-progressor

Patient 12

Patient 12 was considered to be a non-progressor in the study done in Baltimore MD. This patient was considered a non-progressor by not observing a CD4 count drop throughout the duration of the study. After transcribing all of the mutant gp120 V3 loops that were obtained from the study, there were no point mutations that occurred within the overall sequences. For the purposes of this poster the V3 loop was examined. The amino acid sequence closely resembled that of the RS sequence. Looking closely at the sequence, the selected amino acids appear to be specific for CCR5 binding and not CXCR4 binding. Looking at the point mutation study done in figure 4 the amino acids that appear to significantly affect the binding of V3 loop to CCR5 are still conserved (R11 and I26). Although a point mutation that is present throughout the entire study for this patient is a change from R11 to P13. This amino acid is located in the middle of a β strand. The phi and psi angles needed to form a correct β strand are not able to be obtained creating a hydrophobic pocket for the F20 to interact. The two receptors are very similar in function and structure although there are subtle differences that allow the V3 loop to be specific to either the CCR5 or CXCR4 receptor.

References


V3 Loop Binding to CCR5 and CXCR4 of Rapid and Non Progressor HIV Patients in Baltimore MD