Novel Pharmacological Sites within the MHCI-Nef-µ1 Complex

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Basic Biomedical Sciences
2013

Human immunodeficiency virus type-1 (HIV-1) produces a protein called Nef when it infects host cells. Nef is a non-enzymatic protein, and it is abundant in the early stage of the viral replication cycle. This protein has two major functions: downregulation of major histocompatability complex-I (MHC-I) and CD4, both important proteins for the proper function of the immune system, from the surface of infected cells. These two functions of Nef contribute to the progression of AIDS. Nef associates with cellular proteins called adaptor protein complex-1 (AP-1) to downregulate MHC-I. MHC-I presents antigenic viral peptides on the cell surface, which allows the detection and killing of virus-infected cells by immune cells called cytotoxic T-lymphocytes (CTLs). But when the HIV-1 Nef protein is present, it downregulates MHC -I with the help of AP-1, and this enables HIV-1 infected cells to evade this detection and killing. This whole process involves assembly of a complex between these three proteins: the cytoplasmic domain (CD) of MHC-I, HIV1-Nef, and medium-sized (µ) subunit of AP1 (µ1). Our recently published three-dimensional structure of this complex has shown us how these molecules interact with each other at the atomic level. Therefore, we propose to identify new sites of pharmacological importance present at the interactive interfaces of these proteins. We are particularly interested in a narrow groove formed by two of the proteins (Nef and µ1) that cradles the third (the CD of MHC-I). We plan to accomplish our goals by introducing mutations into the complex, and by designing and testing peptides (very short pieces of protein) that can block the complex-assembly. These goals will be achieved using laboratory techniques that we have in hand. If we can successfully validate new sites on this complex as drug targets, then we hope to invigorate the discovery of novel drugs against HIV1 that can empower the host immune system to clear the infection.