

The achilles heel in HIV-1: The conserved caveolin-1 binding domain in the transmembrane envelope glycoprotein gp41 is a B- and T-cell epitope target for vaccine development

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Abstract

Generation of a broadly effective vaccine against HIV-1 is complicated due to the extremely fast level of mutation of its genomic sequence, and the high degree of variability between various viral clades. Consequently, a conserved functional sequence in the HIV genome may represent the "Achilles' heel" of HIV for the development of an efficient vaccine. In 1997-1998 we discovered that nucleolin also exists at the cell surface where it serves as a low affinity receptor for various growth factors and microorganisms including HIV-1. Further studies using equilibrium density fractionation using sucrose gradient of Triton X-100 extracts from freshly HIV-1 infected cells, revealed the coexistence of viral matrix, gp41, reverse transcriptase, and newly synthesized HIV-1 DNA with components of lipid raft microdomains containing also caveolin-1 and surface nucleolin. Caveolin-1 is constitutively expressed in cells but being cholesterol binding protein it is insoluble in non-ionic detergents. Consequently the presence of caveolin-1 with the HIV-1 replication complex indicates its Triton X-100 solubilisation during the HIV-1 entry process. We identified a distinct caveolin-1 binding motif in the ectodomain of gp41 which is conserved in every single HIV-isolate, ⁶²³WNNMTWMEW⁶³¹. This strong conservation as well gp41 binding to caveolin-1, suggest that there is a constant selective pressure to preserve this sequence for a specific function in the HIV infectious cycle. By a series of studies, we demonstrated that the synthetic CBD1 peptide (SLEQIWNNMTWMQWDK), corresponding to the consensus caveolin-1 binding domain of HIV-1 gp41, is characterized by a distinct structure that accounts for its capacity to penetrate the cell membrane, bind caveolin-1 present at the internal side of the plasma membrane, thus suggesting that the CBD1-epitope could be functional for translocation of gp41 within the plasma membrane. Importantly, the CBD1 peptide is capable of eliciting the production of broadly neutralizing antibodies in rabbits, mice, and macaques. Further studies in mice indicated that HIV-neutralizing antibodies against CBD1 react with multiple conformational epitopes that overlap the highly conserved caveolin-1 binding motif (CBM: IWNNMTWMQW) with the N-terminal conserved isoleucine residue. The CBM-based peptides IWNNMTWMQW and IWNNMTW when fused to a T helper epitope are immunogenic by inducing high titer CBM-specific antibodies capable of neutralizing HIV-1 infection. In our final study, the efficacy of the CBD1-based peptide-cocktail vaccine-formulation was evaluated in cynomolgus macaques to resist SHIV challenge via the mucosal rectal route. Among the five vaccinated macaques, three became infected with a slight delay compared to the controls; and two resisted eight weakly SHIV challenges. Interestingly, vaccinated animals maintained CD4 T cell counts, and CM memory cells (CD95+CD28+) were not depleted during the acute phase of infection. Most importantly challenge with SHIV boosted at once antigen specific memory T-cell response.

The initiation of a recall memory T cell response induced by the native CBD1 epitope presented by the input challenge SHIV gp41 enforces the potentiality of our vaccine strategy. Moreover, as immune responses against the CBD1-epitope are not detectable in HIV-infected individuals; CBD1-based vaccines could have applications as a therapeutic vaccine in AIDS patients.

Biography

Ara Hovanessian (Director of Research 1, CNRS; "Chevalier dans l'Ordre National du Mérite") did his Ph.D. at the University of London and at the NIMR in Mill Hill. Then as a senior investigator and 'Chef d'Unité', he spent 26 years at the 'Institut Pasteur' in Paris in close collaboration with Luc Montagnier. Since 2004, he is at CNRS-Université Paris Descartes where he conducts two major projects: 1) on the development of a synthetic vaccine for AIDS, and 2) on the development of synthetic peptides for cancer therapy. His research discoveries include the interferon-induced 2'-5' oligoadenylate synthetases (1512 PubMed articles) and the protein kinase PKR (3132 PubMed articles). He has more than 40 patents on the diagnosis of HIV-2 and HIV-2 envelope glycoproteins, Inhibitors of HIV entry, synthetic vaccines against HIV, surface-nucleolin as a target in cancer therapy. He has published > 190 papers (PubMed) 75% of which he is the first or the last author.