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Efficacy of a mixture of synthetic peptides overlapping the conserved CBD1 epitope in gp41 of HIV-1 to protect against SHIV162P3 rectal challenge in cynomolgus macaques

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Abstract

The synthetic CBD1 peptide corresponding to the conserved caveolin-1 binding domain of HIV-1 glycoprotein gp41 (CBD1 epitope: CSLEQIWNNMTWMQWDK) elicits the production of antibodies in rabbits, mice, and macaques that inhibit infection of primary $CD4^+$ T lymphocytes by various primary HIV-1 isolates. In a detailed study in mice we then showed that peptides overlapping the caveolin-1 binding motif (CBM: IWNNMTWMQW) containing the N-terminal conserved isoleucine residue, when fused to a T helper epitope, induce high titered HIV-neutralizing antibodies. Interestingly, immune sera raised against a given peptide do not cross-react with related CBM-derived peptides, thus suggesting the existence of distinct neutralizing determinants, which probably reflect the dynamic conformational features of the CBD1 epitope in gp41. CBD1- and CBM-based peptides therefore provide specific immunogens for an efficient vaccine preparation against HIV/AIDS infection. In our current study, the efficacy of the CBD1-based peptide-cocktail vaccine-formulation was evaluated in cynomolgus macaques by challenging the vaccinated animals with a replication competent simian/human immunodeficiency chimera virus (SHIV) that expresses HIV-1 envelope glycoproteins. For this purpose, animals were vaccinated at week 0, 4, 10, and 16 with a preparation containing a mixture of CBM-based peptides fused to the $Gag_{298-312}$ epitope, the CBD1 peptide, the Tet_{A830} peptide, and adjuvants CpG and Montanide ISA 51. Once every two weeks, vaccinated aanimals were monitored for the humoral and cellular immune response, while during the SHIV challenge period they were also monitored for the plasma viral load using quantitative RT-PCR and analyzed for the average relative distribution of T-cell subsets. All immunized macaques responded by the production of high tittered and CBD1-based peptide specific antibodies. Six months after the fourth vaccine boost, six control and five vaccinated animals were challenged by repeated exposure to SHIV162P3 (NIH) via the mucosal rectal route. All of the six control animals were infected after 1-3 challenges with SHIV. Among the five vaccinated macaques, three became infected with a slight delay; one became infected only after nine weakly challenges, whereas one resisted nine weakly SHIV challenges. The protection of vaccinated compared to the control animals is significant; p=0.0564, Fisher's exact test. Analyses of CD4 and CD8 T cell dynamics indicated that whereas in non-vaccinated group CD4 T cell counts decrease at days 14 and 21, animals which received vaccine maintained CD4 T cell counts or even increase compared before infection. Thus, the peak of viral replication in days is positively correlated with the peak of CD4 T cell depletion in days. Analyses by flow cytometry of CD4 T cell subsets using the markers CD28 and CD95 demonstrated that CM memory cells (CD95+CD28+), which are considered to be assiocated with better protection are less depleted in vaccinated monkeys during the acute phase of infection. No difference was observed in Effector memory (CD95+CD28-) and naïve CD4 T cells (CD95-CD28+). Most importantly challenge with SHIV boosted at once the capacity of CD4 T cells in response to specific antigen stimulation.

Therefore, one week after SHIV challenge of vaccinated macaques, there is antigen specific memory T-cell response; i.e. there is a recall memory T cell response induced by the native CBD1 epitope presented by the input SHIV gp41 used as a challenge. The detection of specific CD4 T cells against the CBD1-based peptides revealed the potentiality of our vaccine strategy for HIV/AIDS. 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.