Human and animal lentiviruses: from pathogenesis to vaccine development.

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Emergence of human immunodeficiency virus (HIV) has caused near 80 million infections and killed half of these infected persons worldwide. HIV is a member of the lentivirus genus of the Retroviridae family that are single-stranded positive enveloped RN viruses. Lentiviruses were found in primates (human and monkeys), feline (cats, lion, puma...), Bovine (cattle), equine (horses) and small ruminants (goats and sheep). The reason why HIV infection is associated with exacerbated pathogenesis compared to the naturally attenuated goat lentivirus CAEV is not well understood. We hypothesized that increase of CAEV genome complexity by adding SIV/HIV genes will result in increased pathogenicity of the virus. We investigated this hypothesis by generating chimeric CAEV/SIV genomes and demonstrated that indeed they were associated with increased pathogenic properties. We then looked for the key elements in the genome of CAEV that are associated with the lack of severe pathogenesis and persistence in the great majority of CAEV-infected goats. We found that in contrast to primate lentiviruses (SIV & HIV) the called Tat protein of CAEV has no transactivation function of CAEV LTR and this latter has a constitutive promoter. We demonstrated that the called Tat of CAEV was indeed structurally and functionally a Vpr like protein. These properties associated with the attenuated CAEV were used to develop a novel chimeric CAEV/SIV/HIV genome that was used as a prototype HIV DNA vaccine. This DNA vaccine was designed to produce viral proteins that assemble into viral particles able to undergo a single cycle of replication in absence of integration of the vaccine genome. We evaluated this vaccine in the mouse model and provided the proof of the concept that it induces potent antigen specific T cell responses in humanized NOD/SCID mice compared to BALB/C. We then immunized macaques with a single dose of our DNA vaccine and studied the induced immunogenicity during 18 months. We found that all (6/6) vaccinated animals developed potent T cell responses specific to all expressed antigens by the vaccine, but the highest were against Gag and Nef, and these responses persisted the whole 18 months period of the study. These responses contained both polyfunctional CD4+ and CD8+ T cells. Furthermore the responses contained primary and memory effector cells as well as central memory T cells. More interestingly, we found that the memory responses contained also precursor memory T cells that have high capacity of proliferation (PHPC). Although all animal developed humoral responses, the antibodies were not associated with any neutralizing activity in the in vitro serum neutralization test. Eighteen months post immunization all vaccine and control animals were challenged by the mucosal route with a highly pathogenic heterologous strain of SIV.

Interestingly, 3 months post challenge the preliminary results of the ongoing experiment show: 1) 5/6 animals in each group (Vaccine and Control) were infected, 2) 5/5 animals from the vaccine group controlled totally their virus infection by the weeks 6-10 post-infection to an undetectable level of viremia as tested by a sensitive real-time RT-PCR, 3) in contrast 4/5 controls animals were persistently infected showing positive RT-PCR results 4) the ongoing experiment will establish how stable is the induced control of the pathogenic virus and whether this control is associated with the clearance of infectious virus.

Conclusion: this is the first HIV DNA vaccine that induces this type of protection in 100% of vaccinated macaques with a single immunization dose.