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Modeling the molecular evolution of SIV to HIV using humanized mice

Project Number
5R01AI123234-04

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Awardee Organization
COLORADO STATE UNIVERSITY

Description

Abstract Text

Project Summary / Abstract The AIDS **pandemic** caused by HIV-1 and to a lesser extent by HIV-2 resulted in more than 35 million deaths worldwide, with both these viruses now deeply entrenched in the human population. How these culprits arose during the 20th century from the long-preexisting benign ancient SIV viral strains is still a mystery. Several hypotheses have been put forward that include simple zoonotic transfer followed by spread, modern human migration spreading an otherwise isolated rural disease or inadvertent serial passage of the progenitor viruses in humans resulting in increased virulence. An experimental system that can test some of these hypotheses has been lacking until recently. With the advent of humanized mice (hu-mice) that harbor a transplanted human immune system, it has now become possible to address some key questions surrounding how a retrovirus native to non-human primates that existed through the millennia jumped the species barrier and evolved to give rise to the current human **pandemic**. Work in our laboratories and others have established a new generation of hu-mice that continuously generate human T cells, B cells, macrophages and dendritic cells de novo, and that are exquisitely sensitive to infection with HIV-1 and HIV- 2 giving rise to chronic viremia and CD4 T cell loss typical of AIDS. Thus, we are now in a unique position to directly evaluate the potential of ancestral SIV strains for human viral transmission, pathogenesis and evolution in a physiologically relevant in vivo human surrogate system. The primary aim of our studies is to exploit this unique in vivo model for serial passage of chimpanzee SIVcpz and sooty mangabey SIVsm viral strains, the progenitors of HIV-1 and HIV-2, respectively, and determine the genetic and phenotypic changes responsible for the emergence of the HIV viral strains. We recently derived promising preliminary data by successfully growing and adapting SIVsm and SIVcpz in hu-mice. Sequence data on the 2nd passage of SIVsm showed fixed mutations in gp41 and the 1st passage SIVcpz has shown sequence changes indicative of viral evolution. These emerging data point to the feasibility of our proposed studies and to reaching the exciting goal of understanding the genetic basis for emergence of both HIV types and thus shedding light on a long-standing mystery. In this work, we will serially passage SIVcpz and SIVsm in vivo in hu-mice to derive human adapted viruses that potentially represent fully evolved strains of HIV-1 and HIV-2 respectively, characterize the key pathogenic attributes, derive sequence data to identify adaptive sequence changes and assess the critical genomic changes in overcoming human restriction factors such as tetherin. To conduct these promising studies, we assembled an accomplished and enthusiastic team of collaborators Drs. Preston Marx (Tulane), Shelby O'Connor and David Evans (University of Wisconsin), Francoise Villinger (New Iberia Research Institute, Louisiana), Brandon Keele (NCI, Frederick), Mark Stenglein and Ramesh Akkina (Colorado State University) involved in complementary areas of work to synergize in this project.

Public Health Relevance Statement

Project narrative: The two viruses causing the AIDS, namely the HIV-1 and HIV-2 have arisen only in the recent century. The present consensus is that they both arose from their ancestor viruses that have been present in Chimpanzees and Sooty mangabeys. While the ancestral viruses have been around in their native species for millennia, it is a mystery that their successful transmission and adaptation occurred only recently. Several theories exist but experimental proof has been difficult to get due to the lack of a suitable animal model until recently. T

how the ancient SIVs became successful pathogens in the human, it is necessary to look at the gradual mutational changes that occurred in their genomes during the initial periods of zoonotic transmission and viral adaptation. Here we will use humanized mice that are susceptible to SIV and HIV infection to ascertain the evolutionary changes, both genotypic and phenotypic, in the SIVs when introduced into a human surrogate system. We believe that these studies are innovative, first of its kind and likely to shed light on how HIVs arose and gained fitness to spread in the human population. Results of these studies will be useful in determining how new pathogens arise and will help identify new candidate pathogenic SIVs in the wild that may have epidemic potential.

NIH Spending Category

HIV/AIDS Human Fetal Tissue Infectious Diseases Stem Cell Research

Stem Cell Research - Nonembryonic - Human

Project Terms

Acquired Immunodeficiency Syndrome Address Animal Model Area

B-Lymphocytes Back Benign CD4 Positive T Lymphocytes Cercocebus atys

Cessation of life Chronic Colorado Consensus Data Dendritic Cells

Disease Epidemic Evolution Generations Genetic Genome

Genomics Genotype Goals HIV HIV Infections HIV-1 HIV-2

Human Immune system In Vitro Infection Laboratories Light

Louisiana Modernization Molecular Molecular Evolution Mutation

Nucleotides Pan Genus Pathogenesis Pathogenicity

Peripheral Blood Mononuclear Cell Phenotype Physiological Population

Details

No information available for 5R01AI123234-04

Sub Projects

No Sub Projects information available for 5R01AI123234-04

Publications

No Publications available for 5R01AI123234-04

Patents

No Patents information available for 5R01AI123234-04

Outcomes

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