Lecture 1

Origin and progression of HIV-1

Adelajda Zorba
HIV is the causative agent of AIDS

- 60 million infected people
- 25 million deaths
- 14 million orphaned children in South Africa alone

UNAIDS 2009 report
AIDS does not develop in monkeys where HIV originated from.

How come?
HIV is a zoonotic (can be transmitted from non-human animals to humans) lentivirus (lt. lenti=slow, virus=poison)

Found in chimpanzees today is SIVcpz (<-misnomer)

http://www.avert.org/hiv-types.htm
HIV-1 origin: chimpanzee

HIV-2 origin: Sooty mangabey

http://www.prn.org/index.php/progression/article/origin_of_the_aids_pandemic_58
http://monkeysphotos.blogspot.com/2008/10/white-collared-mangabey.html
Humans acquired HIV-1 from chimpanzees:
Evolutionary relationship of SIVcpz and HIV-1 based on envelope protein sequence analysis

Four chimpanzee subspecies based on mtDNA sequence differences
Two important observations

1. Three separate introductions of SIVcpz in the human population

2. Three separate introductions of SIVcpz in the human population

Humans acquired HIV-1 from cross-species transmission of SIVcpz from chimpanzees

Chimpanzees acquired SIVcpz from:

Red-capped mangabeys

Spot-nosed monkeys

http://cercopan.wildlifedirect.org/tag/red-capped-mangabey/
How to go about studying chimpanzees?

Gombe National Park (Tanzania)

How to go about studying chimpanzees?

Gombe National Park (Tanzania)

- non-invasive (urine and fecal-based Western blots assays)
- RT PCR

AIDS does not develop in monkeys where HIV originated from.

How come?

Did it really?

Yes!
Not only SIVcpz but also HIV-1 infected chimpanzees do not develop AIDS

Which model system should be used to research AIDS?
A new model system: Rhesus Macaques
(develop AIDS-like symptoms when infected with SIVcpz not HIV-1)
An infectious, even-closer mimic of HIV-1: SHIV

(contains HIV-1 envelope glycoproteins)

Chimpanzees | Rhesus Macaques | Humans
---|---|---
SIVcpz = harmless | SIVcpz = harmful | SIVcpz = ?
HIV-1 = harmless | **HIV-1 = harmless** | HIV-1 = harmful
SHIV = harmful

Why?
1. Viral Entry Level: An incompatible receptor in the Old World Monkey cells?

**SHIV**

No, because SHIV can replicate at a high titer in rhesus macaques
2. Post-Entry Events: A block that targeted the viral capsid prevented permanent infection?

cDNA from rh.mac. into HeLa cells → Infect cells with pseudotyped HIV-1-GFP → VSV (vesicular stomatitic virus) envelope proteins

-look for GFP-negative colonies
-check for infection with SIVcpz
TRIM5α_{rh} inhibits HIV-1 infection but not SIVcpz or SHIV-based infection 2004

(it must not work on the particle-recognition level, but at an even more atomistic level)

Although rhesus macaque TRIM5α_{rh} inhibits HIV-1, human TRIM5α_{hu} does not inhibit HIV-1

Why not?
Study the infectivity of chimeric TRIM5α proteins
Removal of Arginine 332 Allows Human TRIM5α To Bind Human Immunodeficiency Virus Capsids and To Restrict Infection

Yuan Li,¹ Xing Li,¹ Matthew Stremlau,¹ Mark Lee,¹ and Joseph Sodroski¹,²*
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What we know so far..

1. Humans contracted HIV-1, the virus responsible for AIDS, from chimpanzees and sooty mangabeys.

2. Both SIVcpz and HIV-1 are harmless to chimpanzees.

3. SIVcpz is harmful to rhesus macaques, but HIV-1 is harmless.

4. TRIM5α could explain why this is the case.

5. We need to understand what capsids are...
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What are those?

…to be continued in Lecture 2