High-level replication allows SHIVs to overcome the macaque interferon response

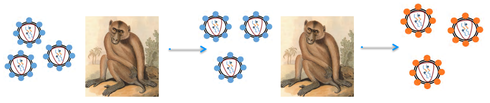
Abstract # 280
Session P-C3

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Background

- Type-I interferon (IFN) is an innate immune factor that induces multiple host restriction factors that could restrict replication, especially early in infection. Some of the IFN-induced factors are species-specific and could contribute to poor replication of HIV-1 in macaques.
- SHIVs are generally derived by serial passage and adaptation in macaques. Most SHIVs based on circulating HIV-1 variants do not replicate in macaques and those in common use were generally derived from HIV-1 isolates that were first adapted in culture.

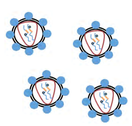


- The process of serial passage in macaques could lead to adaptive mutations that allow SHIVs to evade or antagonize the IFN response.
- **OBJECTIVE**: Determine whether macaque-passaged SHIVs are resistant to type-I IFN and how their IFN-sensitivity compares to SHIVs based on circulating HIV-1 envelopes

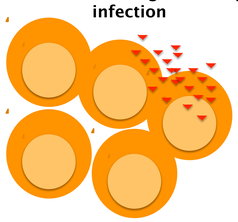
Methods

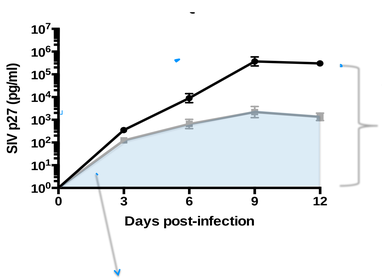
Viral replication time course in immortalized **pig-tailed macaque CD4+ cells** (Muñoz J Med Primat 2009)

Spinoculate at starting MOI of 0.02



Continuous treatment with IFNα-2a starting at 5 hrs post-initial infection





Measure of IFN-induced inhibition of replication

Area-under-curve (AUC)

$$\text{AUC ratio} = \frac{\text{AUC IFN+}}{\text{AUC IFN-}}$$

Measure of replication kinetics → Fit replication curve days 0 – 6 days post-infection to best-fit straight line

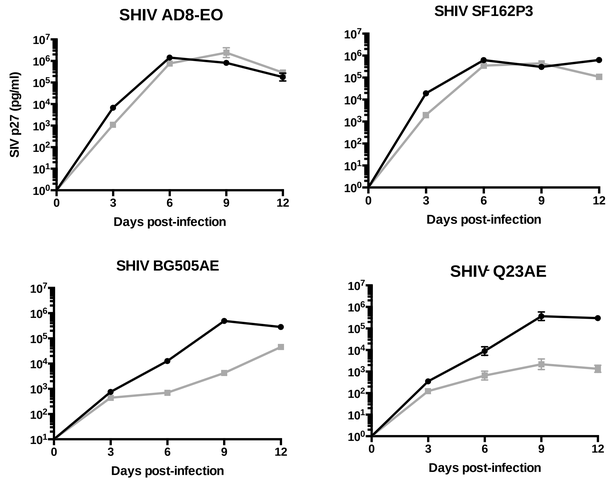
Replication Kinetics and IFN Sensitivity of SHIVs in Macaque Cells

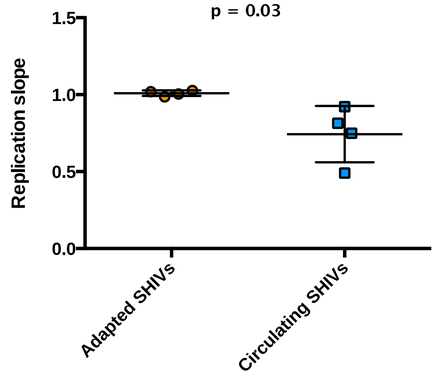
A panel of SHIVs was tested for replication kinetics and IFN sensitivity in macaque cells:

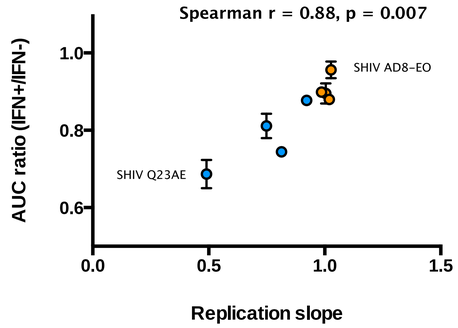
3 pathogenic SHIVs (AD8-EO, SF162P3, 1157ipd3N4)
1 culture-adapted SHIV (AD8)
4 SHIVs based on circulating HIV-1 Envs (QF495AE, MG505GV, BG505AE, Q23AE)

Untreated **IFN treated (1000U/ml)**

The SHIVs tested exhibited a range of replication kinetics and sensitivities to IFN treatment





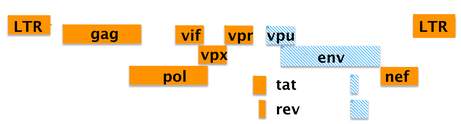


SHIVs adapted in culture or by passage in macaques exhibited significantly higher replication kinetics compared to SHIVs based on circulating HIV-1 envelopes.

Replication kinetics predict the ability of SHIVs to overcome the macaque IFN response.

Mapping Determinants of IFN Resistance

Generated chimeras introducing partial or full HIV-1 genes from SHIV AD8-EO to SHIV Q23AE and tested IFN sensitivity

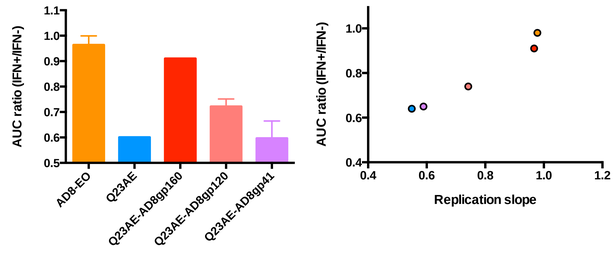


SHIV AD8-EO and SHIV Q23AE are isogenic except for HIV-1 genes (*vpu, env* and partial *tat* and *rev*)

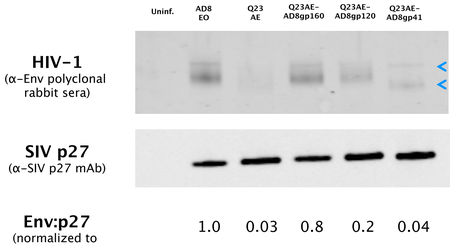


Mapping Determinants of IFN Resistance

Determinants in both Env gp120 and gp41 likely contribute to increased replication kinetics and resistance to IFN treatment.



Tested virions produced from infected macaque cells for Env content by western blot



SHIV AD8-EO and SHIV Q23AE have different levels of virion-associated Env content that could contribute to differences in replication kinetics.

Conclusions

- For the SHIVs tested, lab-cultured and macaque-passaged SHIVs exhibited higher replication kinetics and greater resistance to IFN treatment compared to SHIVs based on circulating HIV-1 Env variants.
- Determinants in both gp120 and gp41 of HIV-1 Env contribute to increased replication kinetics of SHIVs in macaque cells.
- Adaptations in Env, either in culture or in macaques, may contribute to replication kinetics that allow SHIVs to saturate or antagonize an IFN-induced host factor.

Acknowledgments

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