Species-Specific APOBEC3 Splicing and Variations in Viral Mutagenesis

Armando Mendez[1,2], Rachael Rodriguez[1], Azad Khosh[1], Kathryn Jackson-Jones, Margarita Rzhetskaya, Nadeen Abdallah, Judd Hultquist, Diako Ebrahimi[1]
[1]Texas Biomedical Research Institute, San Antonio, TX, USA, [2]University of Texas San Antonio, San Antonio, TX, USA, [2]Northwestern University, Chicago, IL, USA

BACKGROUND

- The DNA of humans and nonhuman primates (NHPs) codes for up to seven APOBEC3 (A3) enzymes, capable of packaging into HIV/SIV particles and causing viral GG>AG and GA>AA mutations. These mutations can inhibit the virus, confer drug resistance, or facilitate immune evasion, depending on their extent and sequence context.
- A3G predominantly induces GG>AG mutations, while other A3 enzymes primarily induce GA>AA changes.
- A recent study suggest that a splicing defect is A3G from macaque species lead a reduced level of GG>AG mutations in SIV, compared to HIV (PMID: 31776266)

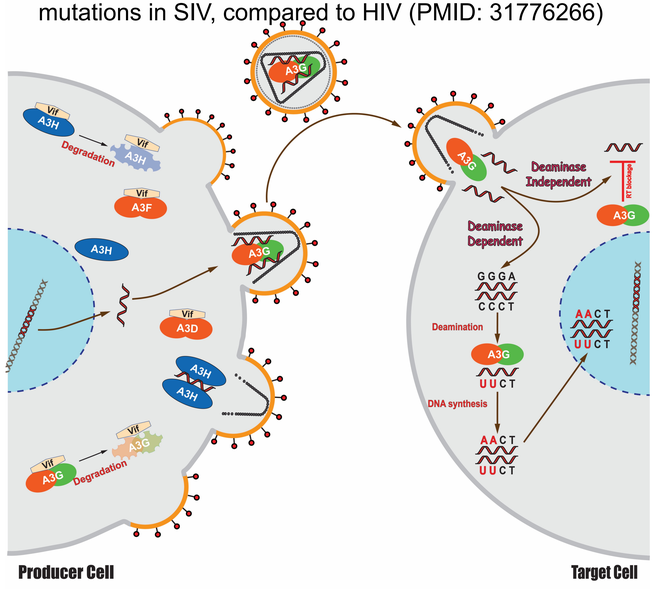

Fig 1. Mechanism of A3-induced HIV/SIV mutagenesis

APPROACH

To determine the source, prevalence, and functional impact of A3G splicing defect, we analyzed over 200K HIV/SIV sequences, over 400 long-read and short-read RNAseq datasets, as well protein mass spectrometry data across human and diverse NHP species. Additionally, we conducted a series of experiments including infectivity and oligo-based deaminase assays.

RESULTS

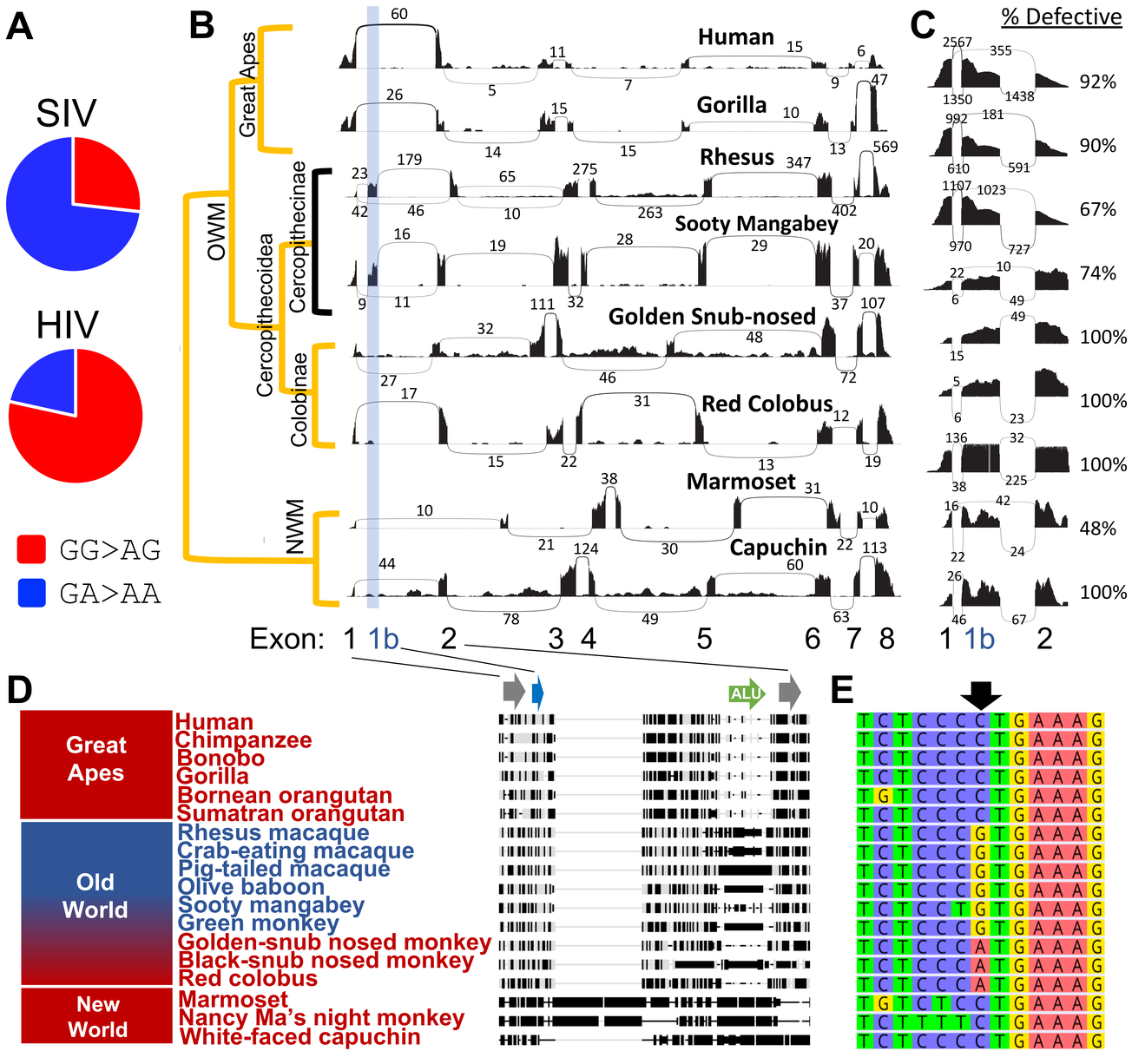

Fig 2. Role of *A3G* mRNA splicing in differential HIV/SIV mutagenesis.
A) HIV/SIV hypermutation profiles; B) *A3G* RNAseq profiles across species; C) Prevalence of A3G splicing defect across rhesus diverse macaques; D&E) Potential genomic determinants of aberrant A3G splicing in Old-World monkeys.

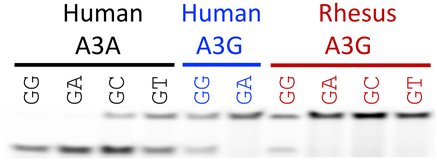

Fig 3. Oligo-based cleavage assay
Rhesus macaque A3G expressed *in vitro* is able to induce GG>AG mutations, indicating that any reduction in GG>AG mutations is likely due to a splicing defect.

CONCLUSION

- A3G experiences a splicing defect in most Old-World monkeys, including macaques, which are commonly used as HIV models.
- This defect is likely responsible for the decreased occurrence of GG>AG mutations (a signature of A3G) in SIV genomes.
- Studies aiming to elucidate A3G's role as a barrier to cross-species transmission of SIV/HIV must be reassessed to account for this splicing defect.
- Future investigations into viral mutagenesis, drug resistance, and immune evasion using rhesus macaques should consider this splicing anomaly.

FUNDING

R56 AI174877
Texas D-CFAR

National Institute of Allergy and Infectious Diseases