# Paleovirology and virally derived immunity

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BI Journal club
01.10.12

# Intro

Paleovirology and virally derived immunity. Aswad A, Katzourakis A., Trends Ecol Evol. 2012 Aug 14. [Epub ahead of print]

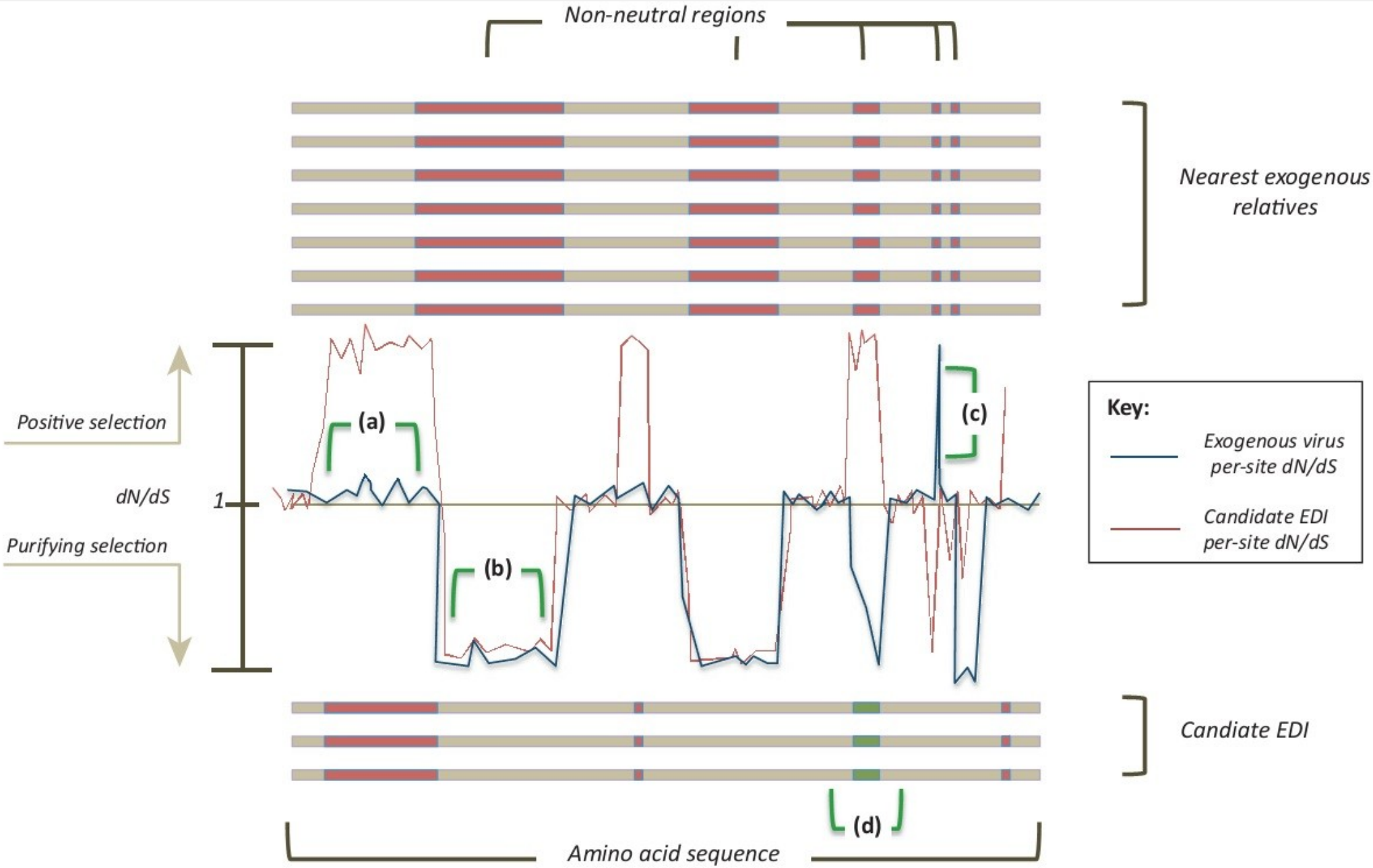
- Paleovirology – study of viruses on evolutionary timescales using information from endogenous viral elements (EVE)
- EDI – EVE derived immunity – immunity strategy that uses functional EVEs against viruses
- Intrinsic immunity – set of constitutively expressed inhibitors of viral pathogens (unlike adaptive and innate immunity)

# Paleovirology

- Direct paleovirology examines viral integration within host genomes to deduce evolutionary history of EVEs
- Querying genomes with viral proteins using sequence similarity tools
- Identified EVEs are compared to known related exogenous viruses and to syntenic regions of related organisms to determine age of integration and selection pattern
- Indirect paleovirology

  extinct viruses, TRIM5, APOBEC3H

# Selection patterns



# Endogenous viral elements

- Virally derived genes discovered in several species.
- Promoters, transcriptional regulators, LTR
- Most EVEs are passive
- Some EVEs have intact ORF and dN/dS indicates purifying selection
- Of these only few EDI genes (that act as inhibitors of viral infection) have been confirmed
- EVEs are present and relatively abundant in variety of hosts, some probably have similar function

# EDI genes

| EDI | Viral origin/host genome | Function(s) |
|---|---|---|
| *Fv4* | Retroviral *env*/mouse | Receptor interference |
| endogenous JSRV | Betaretroviral gag; *env*/sheep | Heteromultimerization, receptor interference |
| endogenous FeLV | Retroviral *env*/cat | Receptor interference |
| endogenous ALV | Avian leukosis virus *env*; *whole*/chicken | Receptor interference, immune tolerization |
| IRIS | *env*/fruit fly | Unknown |
| *Rmcf1, 2* | *env*/mouse | Receptor interference |
| *Fv1* | Retroviral *gag*/mouse | Capsid interaction |
| *Gypsy*-like LTR retrotransposons | Retroviral *gag*/vertebrates | Unknown |
| endogenous MMTV | Mouse mammary tumor virus *sag*/mouse | T cell deletion |
| EBLN | Bornavirus-like *NP*/mammalian | Unknown |
| NIRVs | Ebolavirus-like *VP35*; *NP*/Bats | Unknown |
| CGIN1 | Retroviral RNase/mammalian | Unconfirmed ubiquitination mechanism |
| APOBEC3 | Retroviral regulatory element | Up regulation of viral inhibition by APOBEC |
| IAPV | Picornavirus | Unknown |

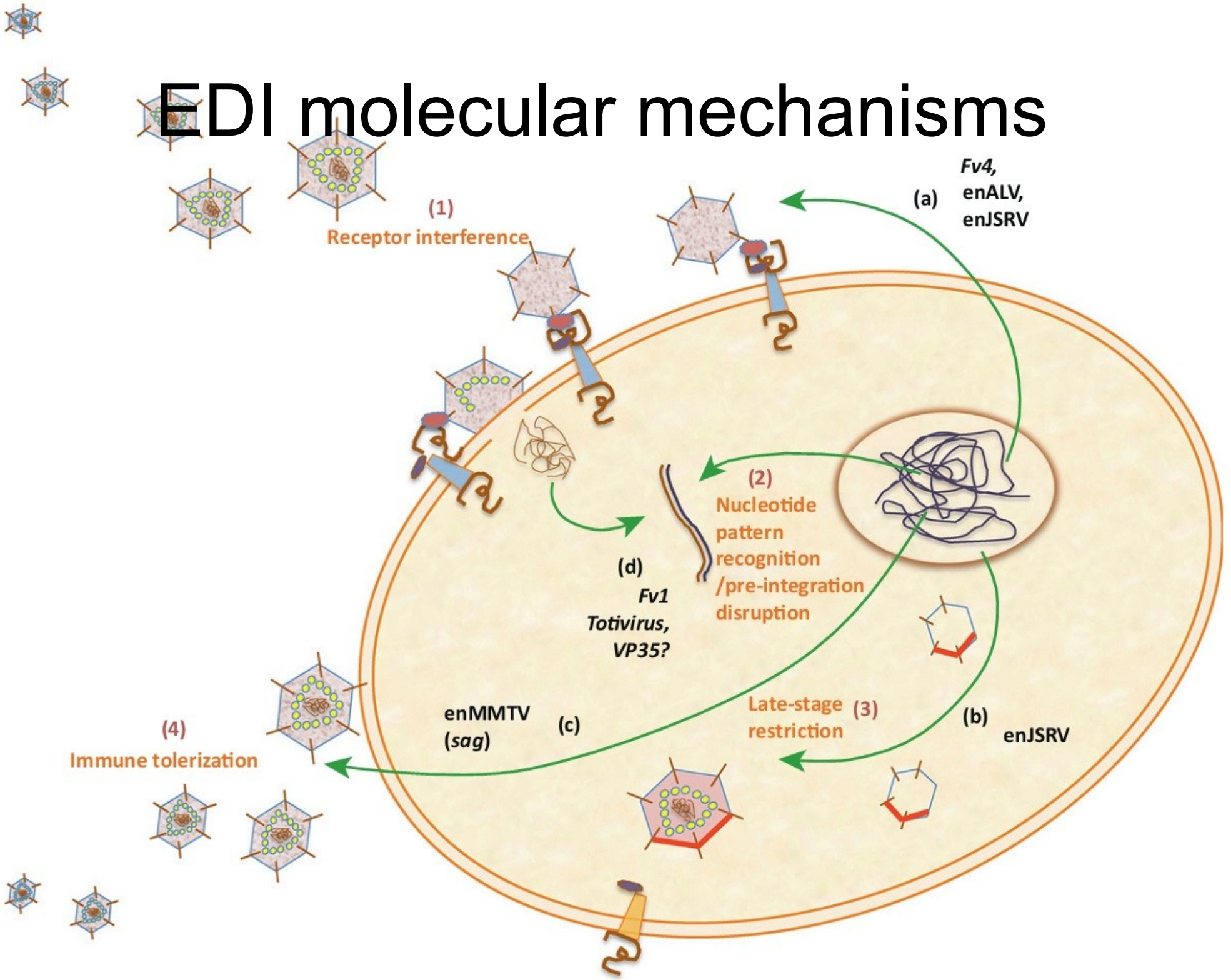
# Molecular strategies of EDIs

- Blocking cell entry (saturating receptors that mediate viral entry)

  *Fv4* in mice is defective endogenous retrovirus with intact *env* capsid gene 90% similar to MuLV
- *Rmcf and Rmcf2* are indepentently derived EVE genes that offer resistance to different strain of MuLV by same mechanism
- Disrupt viral replication after cell entry

  *Fv1* contains *gag* group-specific antigen gene that interacts with viral capsid protein after entry and restricts replication
- Anticipatory strategy

# EDI molecular mechanisms



# Anticipatory EDI strategy

- In chicken endogenous avian lekosis virus (ALV) tolerizes host against exogenous virus and reduces debilitating immune reaction (although increasing viral replication)
- In mice mouse mammary tumor virus (MMTV) uses super-antigen *sag* to promote division of infected cells via activation of T-cells.

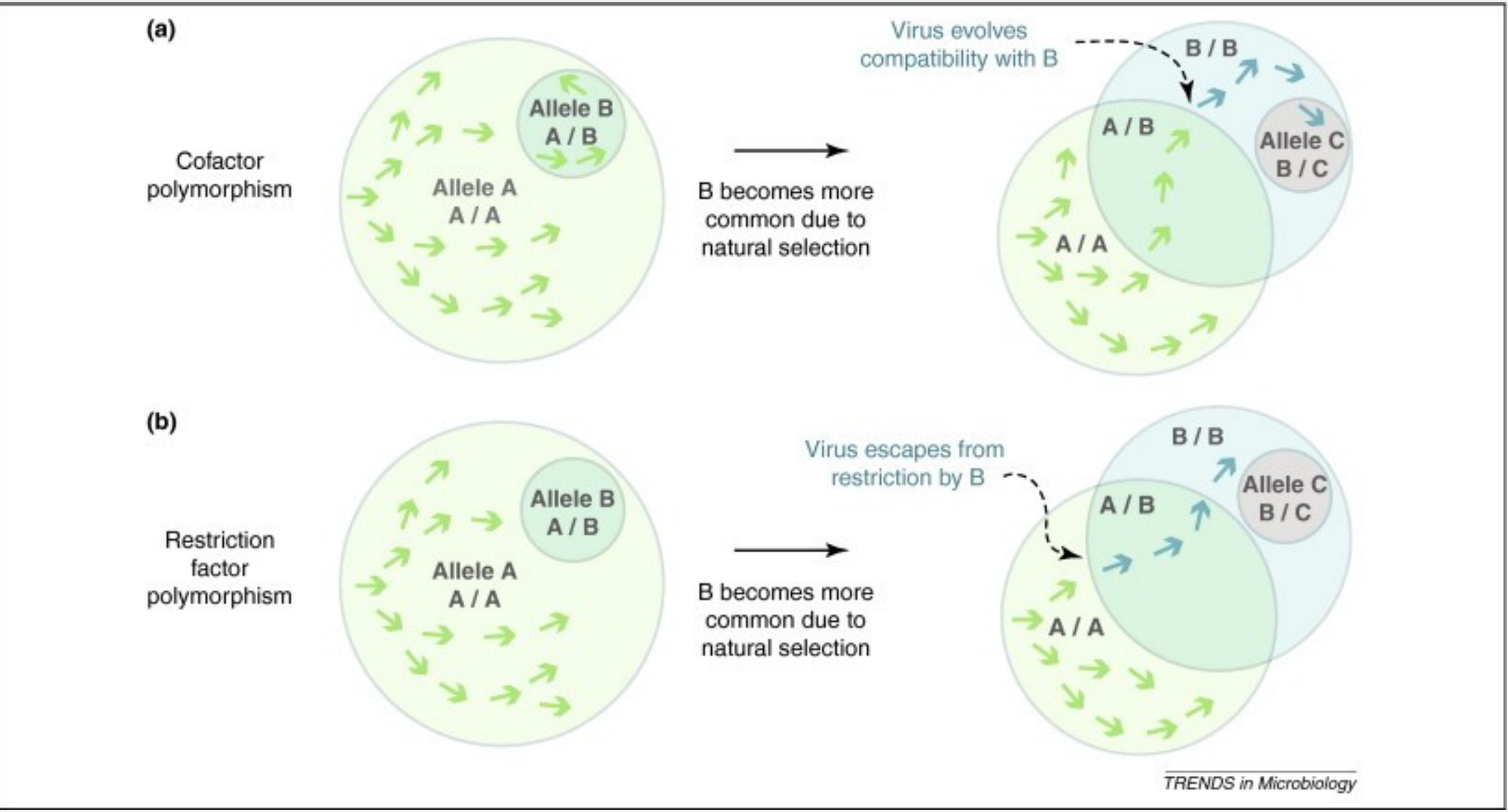
  Endogenous MMTV expresses *sag* during host development which results in deletion of specific *sag*-responsive T-cells. This reduces ability of MMTV to spread

# Evolutionary arms race

- Viruses have short generation times
- Low-fidelity replication allows them to adapt to response faster that host can adapt.
- Host cannot compete by evolutionary adaptation alone, uses different methods (adaptive immunity)

Human and macaque APOBEC3 proteins disrupt HIV infection, but only strains without Vif protein.
SAMHD1 protein is HIV-restriction factor, effect of which is counteracted by viral auxiliary protein VPx

# Evolutionary arms race



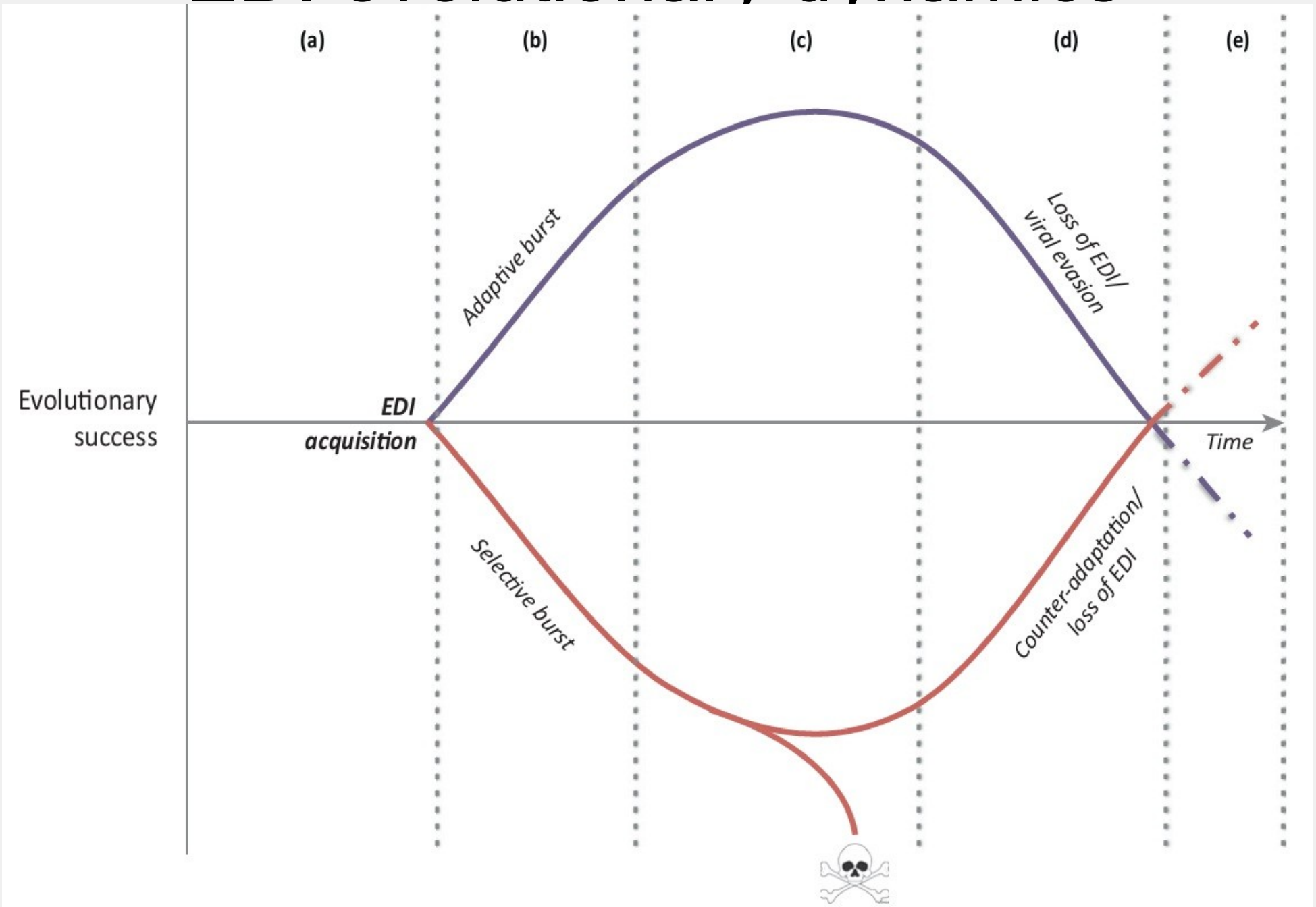
# Cost to host

- Intrinsic immunity allows evolutionary shortcuts but come with fitness cost
- Adaptive strategy allows virus to spread but reduces damage to host and potentially leaves host vulnerable to other pathogens
- Receptor blocking hampers normal functions of the receptor
- Fitness advantage of EDI competes with selective cost of viral infection is higher than EDI drawbacks, depending on population structure, genomics, disease ecology

# EDI dynamics

- Virus integration (frequency depends on patterns of viral infection, effect of integration event and type of virus)
- EVE fixation (if new EVE is neutral it may drift in population before gaining beneficious mutation for EDI function) and is subject to positive selection
- EDI loses advantage (if EDI succeeds against virus or if virus counter-adapts) and negative selection dives its extinction

# EDI evolutionary dynamics



# EDIs are transient

- Population structure might result in heterogenous localized EDI acquisitions and extinctions that never reach species-wide fixation
- In most cases the lifetime of EDI will be shorter than it takes to reach fixation
- Thus examining genomes of single individuals will fail to identify most EDIs

  In honeybees IAPV insertion is found in third of tested populations, offers resistance to infection

  In koala active ERV is variably prevalent in some populations

# Co-option

- Exaptation – the process of functional co-option from different source of origin
- EVE-host gene fusion to create novel function
- Immunomodulatory EVE: syncytin takes part in formation of ephitelial layer of placental villi – syncytiotrophoblast (protection from maternal immune attack). Repeated co-option
- CCR5Δ32 allele offers resistance against HIV with spatially heterogenous frequencies (maintained in Europeans). HIV emerged too recently ro be responsible for purifying selection. Probabe ancestral EDI against other virus.

# Conclusion

- Paleovirology allows study of endogenous viral elements
- Some EVEs are co-opted as cellular genes, often as antiviral inhibitors
- EDI is strategy of evolutionary shortcut that uses genetic material originated from virus against virus itself
- Study of EDIs reveals evolutionary history and significance of host-virus interaction