IFITM3 REDUCES RETROVIRAL ENVELOPE ABUNDANCE AND FUNCTION AND IS COUNTERACTED BY GLYCOGAG

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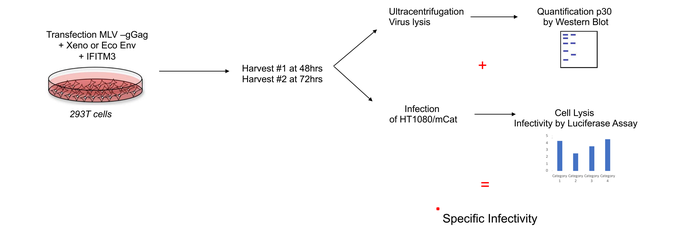
BACKGROUND

The interferon-induced transmembrane (IFITM) proteins are known for inhibiting the entry of a wide array of viruses into host cells. Furthermore, when IFITM3 is present in virus-producing cells, it reduces the fusion potential of HIV-1 virions, but the mechanism is poorly understood.

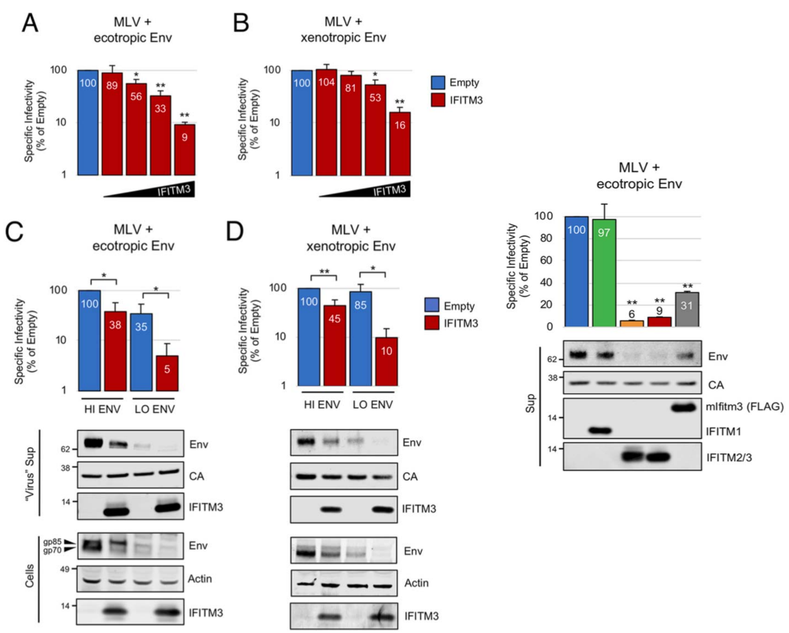
METHODS

To describe the antiviral mechanism of IFITM3 and to discover modes of viral evasion, we took advantage of a murine leukemia virus (MLV)-based pseudotyping system.

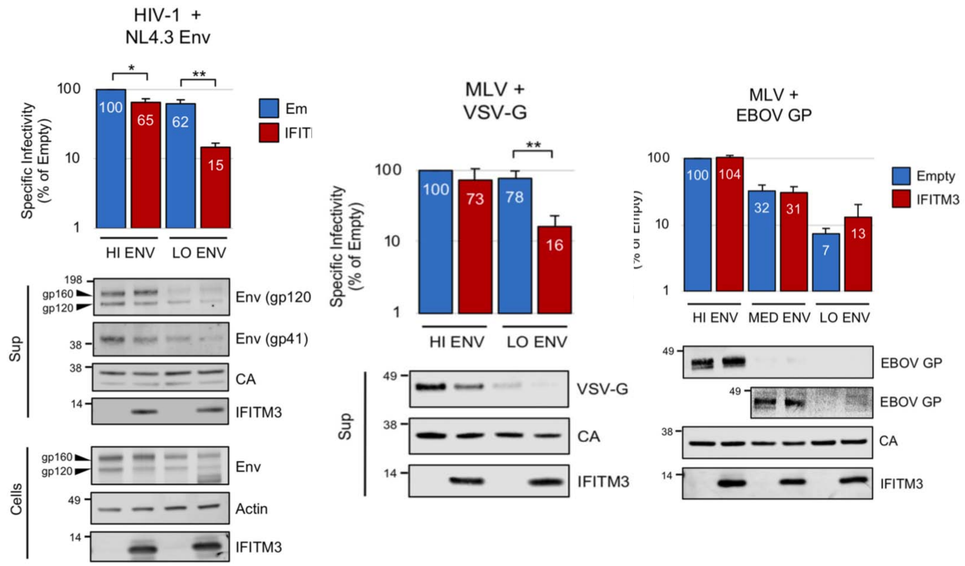


RESULTS

IFITM2/3 inhibits MLV infectivity by altering Env quantity and quality



IFITM3 selectively inactivates HIV-1 and VSV-G pseudotypes but not Ebola

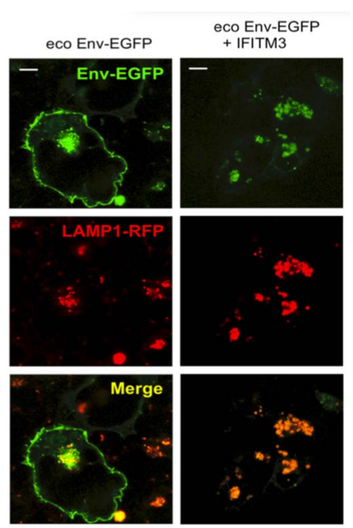


Just as with MLV, restriction of HIV-1 infectivity by IFITM3 was maximal when small amounts of HIV-1 Env were used to pseudotype particles

Inhibition of VSV-G-mediated infectivity at low doses of VSV-G is accompanied by a reduction in the level of VSV-G incorporation

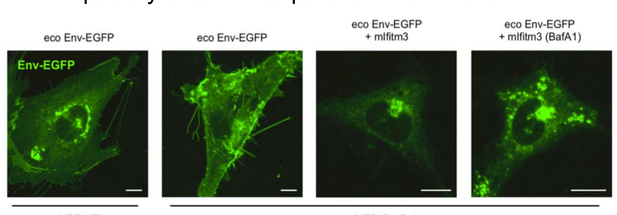
In contrast, IFITM3 showed no ability to inactivate EBOV GP

IFITM3 interferes with Env trafficking and promotes its degradation in endolysosomes



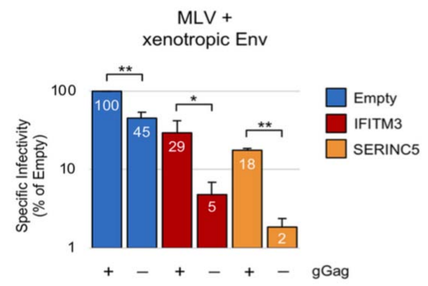
Ectopic IFITM3 interferes with
- MLV Env processing and trafficking
- Which leads to Env degradation in endolysosomes,

→ paucity of Env incorporation into virions.

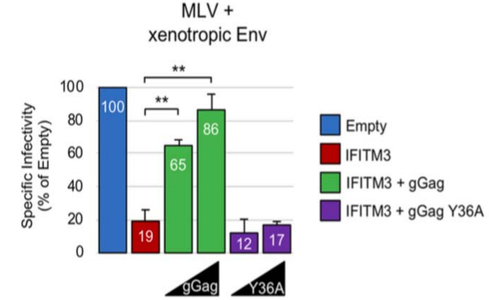


Endogenous human and murine IFITM3/Ifitm3 are both negative regulators of MLV Env proteins.

GlycoGag rescues infectivity in the presence of IFITM3



GlycoGag in *trans* is capable to overcome restriction by IFITM3



GlycoGag mutated in its AP-2 recognition motif (Y36A) does not counteract IFITM3
→ endocytosis of glycoGag is necessary for the function

CONCLUSIONS

Overall, we demonstrate that IFITM3:

- impairs virion infectivity by decreasing Env quantity and Env function,
- glycoGag confers virions with resistance to IFITM3 and,
- the antiviral activities of IFITM3 and SERINC3/5 may be linked.

We are now testing whether the antiviral function of IFITM3 is maintained in SERINC5 knockout cells and whether other retroviral accessory proteins, such as HIV-1 Nef and EIAV S2, also exhibit the capacity to counteract IFITM3.