A HUMAN-SPECIFIC CARD8 MOTIF PERMITS INFLAMMASOME ACTIVATION AFTER HIV-1 INFECTION

0228

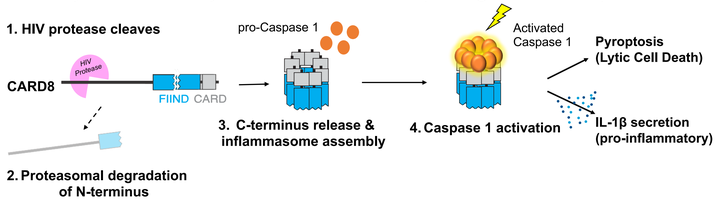
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BACKGROUND

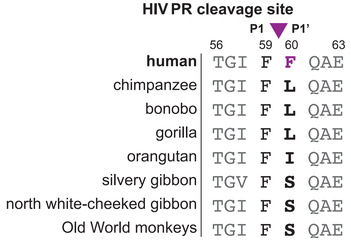
- Inflammasomes are cytosolic innate immune complexes that can sense/respond to pathogens, and promote inflammation
- The CARD8 inflammasome is activated by recognizing the enzymatic activity of HIV-1 protease (Wang et al 2021)



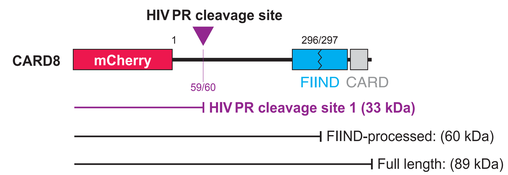
RESULTS

Figure 1: A human-specific motif allows CARD8 to detect protease activity from multiple HIV strains

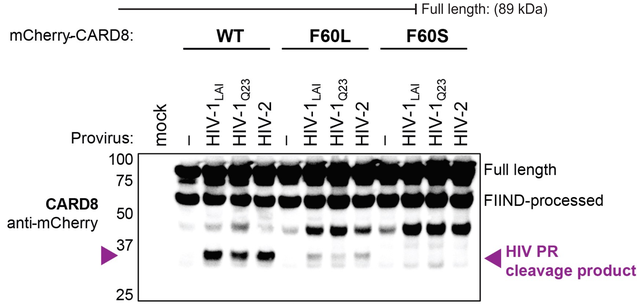
A *Alignment of primate CARD8 protein sequences*



B *mCherry-CARD8 used in cleavage assays in C)*



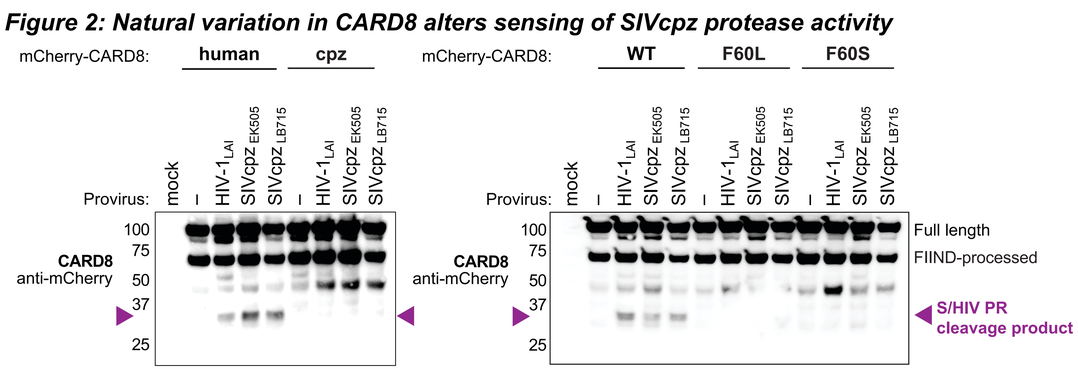
C



HEK293T cells were transfected with a construct encoding N-terminally mCherry-tagged WT, F60L, or F60S CARD8 and indicated HIV proviral constructs. Immunoblotting was carried out for CARD8 cleavage.

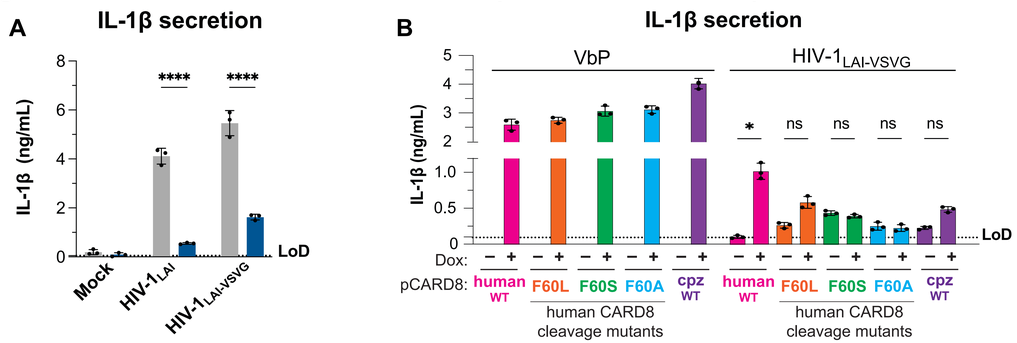
Humans are uniquely susceptible to CARD8 inflammasome activation after HIV-1 infection

Figure 2: Natural variation in CARD8 alters sensing of SIVcpz protease activity



*HEK293T cells were transfected as in **Fig1.** with either A) human or chimpanzee (cpz) or B) WT, F60L, or F60S CARD8 and indicated provirus constructs.*

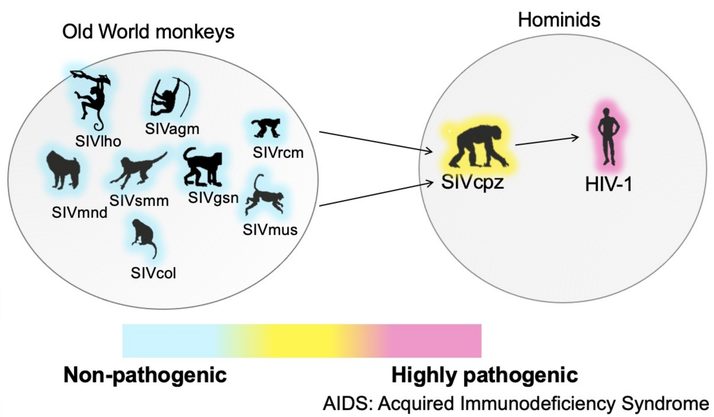
Figure 3: HIV-1 inflammasome activation is dependent on a human-specific motif in CARD8



A) WT or CARD8 KO THP-1s were primed with Pam3CSK4 and either treated with mock, HIV-1_{LAI} or HIV-$1_{LAI\text{-}VSVG}$ and probed 24 hours post-infection for IL-1β levels. B) Complemented CARD8 KO lines were left uninduced or induced then primed with Pam3CSK4 and treated with either 10 μM VbP (known CARD8 inflammasome agonist) or HIV-$1_{LAI\text{-}VSVG}$ then assessed for IL-1β secretion.

CONCLUSIONS

- Human CARD8 is uniquely susceptible to HIV/SIV proteases
- SIVcpz protease was poised to activate human CARD8 prior to cross-species transmission
- CARD8 inflammasome activation occurs during HIV infection and is dependent on human-specific motif in CARD8
- Could this partially explain increased pathogenesis of HIV-1 in humans relative to other primates?



FUTURE DIRECTIONS

- Explore CARD8 inflammasome activation in primary cells infected with HIV/SIV

SUPPORT

- CMB Training Grant -T32GM007270
- NIH DP1 DA051110-03
- NIH DP2 AI 154432-01
- CROI New Investigator Scholarship

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CROI Conference on Retroviruses and Opportunistic Infections