Mitophagy and HIV restriction

I. ABSTRACT

Mitophagy ‘eat-me’ tags identified in the TRIM5α interactome

Prohibitin 3 NIPSNAP1 NIPSNAP2 SAM50 TRAP1 MIC60 FKBP8 RHOT2 MTRAP VDAC1 ATAD3A

TRIM5α assemblies mitophagy machinery and protects cells from mitochondrial damage

II. WHY WE ARE INTERESTED IN TRIM5

HIV RESTRICTION

PATTERN RECOGNITION RECEPTOR

AUTOPHAGY REGULATOR

AUTOPHAGY SUBSTRATE

III. MULTIPLE ANTIVIRAL PROTEINS IDENTIFIED IN THE TRIM5 INTERACTOME

RhTRIM5-APEX2 prevents transduction with HIV-1 pseudovirus (as expected)

~350 proteins enriched in TRIM5-APEX2 versus APEX2 alone (log2 fold change > 1; P < 0.05)

Goals:

1) Identify TRIM5 interacting partners
2) Determine how retroviral capsid binding impacts TRIM5 interactions
3) Identify novel functions of TRIM5 in aid of antiretroviral defense

IV. TRIM5 INTERACTOME IS ENRICHED FOR MITOCHONDRIAL PROTEINS (SURPRISING)

Gene Ontology components

Nuclear membrane
Nucleolus
Cytoskeleton
Mitochondrion

TRIM5 interactome includes multiple mitophagy ‘eat-me’ proteins

‘Eat-me’ proteins are displayed on the outside of damaged mitochondria; have LC3 interacting regions (LIR); facilitate mitophagy

‘Eat-me’ proteins validated for TRIM5 interactions by coIP-NIPSNAP1, NIPSNAP2, Prohibitin 2

V. MITOCHONDRIAL DAMAGE RELOCALIZES TRIM5 TO MITOCHONDRIA PROXIMAL, CALnexin+ STRUCTURES

Mitochondria

Cytoplasm

Nuclear membrane

Mitochondrion

VI. TRIM5 AND AUTOPHAGY INITIATION MACHINERY COLocalize on DAMAGED MITOCHONDRIA

TRIM5 contributes to Parkin-dependent and Parkin-independent mitophagy

VII. TRIM5 BRIDGES EAT-ME TAGS WITH UPSTREAM AUTOPHAGY REGULATORS DURING MITOPHAGY

E1LR mutant of TRIM5:

1) deficient for binding E2 enzymes
2) loses E3 ligase activity
3) retains overall structure and HIV restriction

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IX. TRIM5 KNOCKOUT SENSITIZES CELLS TO MITOCOCHONDRIAL DAMAGE-INDUCED INFLAMMATION AND DEATH

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