DPP9 directly sequesters the NLRP1 C-terminus to repress inflammasome activation

Graphical abstract

DPP9 checkpoints the decision between life and death based on the balance of full-length NLRP1 (FL-NLRP1) to NLRP1-CT.

**Background**

**NLRP1**

Pro-caspase-1

Caspase-1

IL-1β

Mature

GSDMD

Positive

Negative

Sensor

Proteins

DAMP

PAMP

(+ASC)

DPP9

Activates

Mature

IL-1β

Pyroptosis

**Inflammasome**

Sensor

Proteins

GSDMD

DPP9

Activates

Mature

IL-1β

Pyroptosis

**Loss-of-DPP9 interaction causes pyroptosis**

**FL-NLRP1 rescues NLRP1-CT via DPP9 interaction**

**VbP displaces NLRP1-CT**

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**Fig. 1.** Inflammasome pathway overview. NLRP1 is an inflammasome sensor that activates in response to diverse damage- (DAMPs) and pathogen-associated molecular patterns (PAMPs). **Fig. 2.** NLRP1 domain structure. FIIND autoprocessing at S1213 splits full-length NLRP1 (FL-NLRP1) into noncovalently associated NLRP1-NT and NLRP1-CT. **Fig. 3.** NLRP1 NT-degradation activates the inflammasome. **Fig. 4.** a, Cryo-EM map the ternary NLRP1 αNLRP1 β-DPP9 dimeric complex. b, A schematic diagram of a single monomeric unit denotes the entire NLRP1 and DPP9 molecules versus the ordered, resolved portions of the proteins (red circle). **Fig. 5.** DPP9 captures FL-NLRP1 and NLRP1-CT. **Fig. 6.** VbP displaces NLRP1-CT from the DPP9 active site. **Fig. 7.** a, Schematic of three interfaces involved in DPP9-NLRP1 interactions. b, Lactate dehydrogenase (LDH) release. Interface I and II mutations result in NLRP1 autoactivation in the absence of the activator VbP, while interface III (UPA A-UPA B) mutations kill inflammasome activity. **Fig. 8.** a, Schematic of the dTAG method for dTAG13-induced NLRP1 NT-degradation. b–c, ASC speck formation and rescue of specks through co-expression of FIIND-SA (binds DPP9 site A).