AIM2 inflammasome is activated by pharmacological disruption of nuclear envelope integrity

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Inflammasomes are critical sensors that convey cellular stress and pathogen presence to the immune system by activating inflammatory caspases and cytokines such as IL-1β. The nature of endogenous stress signals that activate inflammasomes remains unclear. Here we show that an inhibitor of the HIV aspartyl protease, Nelfinavir, triggers inflammasome formation and elicits an IL-1R-dependent inflammation in mice. We found that Nelfinavir impaired the maturation of lamin A, a structural component of the nuclear envelope, thereby promoting the release of DNA in the cytosol. Moreover, deficiency of the cytosolic DNA-sensor AIM2 impaired Nelfinavir-mediated inflammasome activation. These findings identify a pharmacologic activator of inflammasome and demonstrate the role of AIM2 in detecting endogenous DNA release upon perturbation of nuclear envelope integrity.
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