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Human MLKL is maintained by RIPK3 in an inactive conformation prior to disengagement and cell death by necroptosis

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Necroptosis is a caspase-independent form of programmed cell death that results in the compromise of plasma membranes and release of inflammatory cellular contents. Dysregulated necroptosis has been shown to play a role in a range of different human pathologies, including ischemia-reperfusion injury, inflammatory diseases, and inflammatory bowel disease. Phosphorylation of MLKL by the RIPK3 kinase leads to MLKL oligomerization, translocation to, and permeabilization of, the plasma membrane to induce necroptotic cell death. The precise choreography of MLKL activation remains incompletely understood. Here, we used Monobodies, synthetic binding proteins, that bind the pseudokinase domain of MLKL to detect endogenous protein interactions within human cells. We showed that MLKL is stably bound by RIPK3 prior to their disengagement upon necroptosis induction. Crystal structures of MLKL pseudokinase domain in complex with two different monobodies or RIPK3 kinase domain identified two distinct conformations of MLKL pseudokinase domain. These structures support that human RIPK3 maintains MLKL in an inactive conformation prior to the induction of necroptosis. These studies provide further evidence that MLKL undergoes a large conformational change upon activation and identify MLKL disengagement from RIPK3 as a key regulatory step in the necroptosis pathway.

Level of Expertise

Student

Presenter Gender

Man

Pronouns

He/Him

Which facility did you use for your research

Australian Synchrotron

Students Only - Are you interested in AINSE student funding

Yes

Do you wish to take part in the Student Poster Slam

Yes

Condition of submission

Yes

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