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Membrane permeabilisation is mediated by distinct epitopes in mouse and human orthologs of the necroptosis effector, MLKL

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Necroptosis is a lytic programmed cell death pathway with origins in innate immunity that is frequently dysregulated in inflammatory diseases. The terminal effector of the pathway, MLKL, is licensed to kill following phosphorylation of its pseudokinase domain by the upstream regulator, RIPK3 kinase. Phosphorylation provokes the unleashing of MLKL's N-terminal four-helix bundle (4HB or HeLo) domain, which binds and permeabilises the plasma membrane to cause cell death. The precise mechanism by which the 4HB domain permeabilises membranes, and how the mechanism differs between species, remains unclear. Here, we identify the membrane binding epitope of mouse MLKL using NMR spectroscopy. Using liposome permeabilisation and cell death assays, we validate K69 in the α3 helix, W108 in the α4 helix, and R137/Q138 in the first brace helix as crucial residues for necroptotic signaling. This epitope differs from the phospholipid binding site reported for human MLKL, which comprises basic residues primarily located in the α1 and α2 helices. In further contrast to human and plant MLKL orthologs, in which the α3-α4 loop forms a helix, this loop is unstructured in mouse MLKL in solution. Together, these findings illustrate the versatility of the 4HB domain fold, whose lytic function can be mediated by distinct epitopes in different orthologs.

Level of Expertise

Early Career <5 Years

Presenter Gender

Man

Pronouns

Which facility did you use for your research

National Deuteration Facility

Students Only - Are you interested in AINSE student funding

Do you wish to take part in the Student Poster Slam

Condition of submission

Yes

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